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EDITORIAL

Diabetes, diabetic complications, and blood pressure targets

Cristiana Catena, GianLuca Colussi, Francesca Nait, Gabriele Brosolo, Leonardo A Sechi

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Abstract

Association of diabetes with hypertension is frequent and it well known that high blood pressure potentiates the probability of diabetic patients to develop macrovascular and microvascular complications. Strong evidence obtained in a number of large scale prospective studies indicates that adequate blood pressure control in diabetic patients is highly beneficial for prevention of cardiovascular events. Nonetheless, only a limited proportion of hypertensive-diabetic individuals included in studies on anti-hypertensive treatment has met the predefined blood pressure goal. The optimal blood pressure goal to be pursued in diabetic patients with hypertension to guarantee effective protection from cardiovascular outcomes is still under intense debate and recommendations of current guidelines on hypertension treatment are still inconsistent. We comment here on the most important studies and conclude that current evidence does not conclusively support the need to reach a blood pressure target in hypertensive patients with diabetes different from nondiabetic hypertensive individuals.

Key words: Diabetes; Hypertension; Cardiovascular events; Guidelines; Randomized controlled trials; Evidence based medicine

Core tip: Hypertension potentiates the probability of diabetic patients to develop macrovascular and microvascular complications and prospective studies demonstrate that adequate blood pressure control in diabetic patients is highly beneficial for prevention of cardiovascular events. Blood pressure targets in diabetic patients with high blood pressure are under debate and are discussed in this editorial.

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INTRODUCTION

Diabetes mellitus and arterial hypertension are important modifiable risk factors for cardiovascular mobidity and mortality. Association of diabetes with hypertension is frequent and if, on one hand, incidence of hypertension in patients with type-2 diabetes is two times higher than in matched subjects without diabetes[1], on the other hand risk of patients with hypertension to develop diabetes is three-fold that of patients with normal blood pressure (BP)[2]. The frequent association between diabetes and hypertension may depend from a variety of mechanisms. These mechanisms include primarily aging, increased body weight, and insulin resistance[3,4], although a contribution of vasoconstriction and vascular rarefaction has also been suggested[5].

Presence of hypertension potentiates the probability of diabetic patients to develop macrovascular and microvascular complications and this is why these two conditions have been often identified as "the bad companions" (Figure 1). In addition to mechanisms that are peculiar of each disease such as effects of hyperglycemia, advanced glycation products, and polyols on the side of diabetes, and increased shear stress on the side of hypertension, these two conditions share many pathophysiologic mechanisms that contribute to cardiac and vascular damage. These mechanisms include endothelial dysfunction, activation of the renin-angiotensin system, proinflammatory and prothrombotic mechanisms, lipoprotein abnormalities, and changes in arachidonic acid metabolites levels. Type-2 diabetic patients with hypertension are at increased risk of coronary heart disease, stroke, heart failure, and renal insufficiency and association with additional comorbidities such as dyslipidemia and obesity contribute to this risk[6]. It is known that presence of hypertension doubles the risk of coronary heart disease and stroke in patients with diabetes[7]. Moreover, diabetes is a major risk factor for left ventricular dysfunction and heart failure. In a Scottish study, incidence of left ventricular dysfunction in diabetic patients was four-fold that of nondiabetic individuals[8] and in the Framingham Study the relative risk of heart failure in diabetic women was 5.5 as compared to nondiabetic women[9]. These diabetic patients have a poor prognosis that can be explained by underlying diabetic cardiomyopathy that is exacerbated by hypertension[10].

BLOOD PRESSURE CONTROL IN DIABETES

As a proof of the contribution of hypertension to diabetic complications, robust clinical evidence indicates that adequate BP control in diabetic patients is highly beneficial[11]. These benefits have been clearly demonstrated in a number of large scale prospective studies[12-18]. However, diabetic patients require more intense treatment and only a minority of them meets the BP target[19]. Cumulative analyses of major clinical trials on hypertension treatment that have included patients with diabetes have shown that in these patients target diastolic BP values were met in approximately half of the studies whereas none of the studies met the target systolic BP[20]. The target BP to be achieved to provide effective protection from cardiovascular events to diabetic-hypertensive patients has been intensively debated and recommendation of recent guidelines on treatment of hypertension are somehow inconsistent[21-27] (Table 1) due to different relevance that has been given to some major randomized controlled trials (RCTs) showing the opportunity to reach lower BP levels in diabetic than nondiabetic hypertensive individuals[12,13].

Table 1 Summary of recommendations for treatment of hypertension in diabetic patients as provided in current guidelines of Scientific Societies

Guideline	Year	Blood pressure goals in diabetes
KDIGO[25]	2012	< 140/90 (< 130/80 with proteinuria)
ESH/ESC[21]	2013	< 140/85
CHEP[23]	2013	< 130/80
ADA[24]	2013	< 140/80
NICE[26]	2013	< 140/90
LAEG[27]	2013	< 140/85
JNC 8[22]	2014	< 140/90

KDIGO: Kidney Disease Improving Global Outcomes; ESH: European Society of Hypertension; ESC: European Society of Cardiology; CHEP: Canadian Hypertension Education Program; ADA: American Diabetes Association; NICE: National Institute for Health and Clinical Excellence; LAEG: Latin America Expert Group; JNC: Joint National Committee.

The United Kingdom Prospective Diabetes Study (UKPDS 38)[12] was the first important RCT to investigate whether tighter control of BP prevents macrovascular and microvascular complications of diabetes reporting a 24% reduction of diabetes related endpoints as compared to patients on a more conventional anti-hypertensive treatment. The Hypertension Optimal Treatment study[13] allocated 18790 hypertensive patients to three different diastolic BP goals (< 90, < 85, and < 80 mmHg, respectively) and reported a 51% reduction in major cardiovascular events in patients with diabetes in the target group < 80 mmHg as compared to the target group < 90 mmHg. Prompted by these and other observations a meta-analysis of 27 RCTs that included 33395 hypertensive-diabetic patients compared the effects of different BP lowering regimens on cardiovascular events and death[28]. In this meta-analysis, evidence that lower BP goals produce better outcomes in hypertensive individuals with *vs* without diabetes was limited to cardiovascular events, but was not reported for the combined endpoint of cardiovascular events and death. Thus, it was concluded that the cardiovascular effects of more less intensive BP lowering regimens were broadly comparable in patients with or without diabetes.

Traditional BP-treatment strategies set levels at which treatment is initiated and goals to which treatment should be titrated. Due to the uncertain cardiovascular benefit of more aggressive BP lowering regimens in diabetics, the Action in Diabetes and Vascular Disease trial[29] investigated the effects on cardiovascular events of the routine administration of a fixed-dose angiotensin

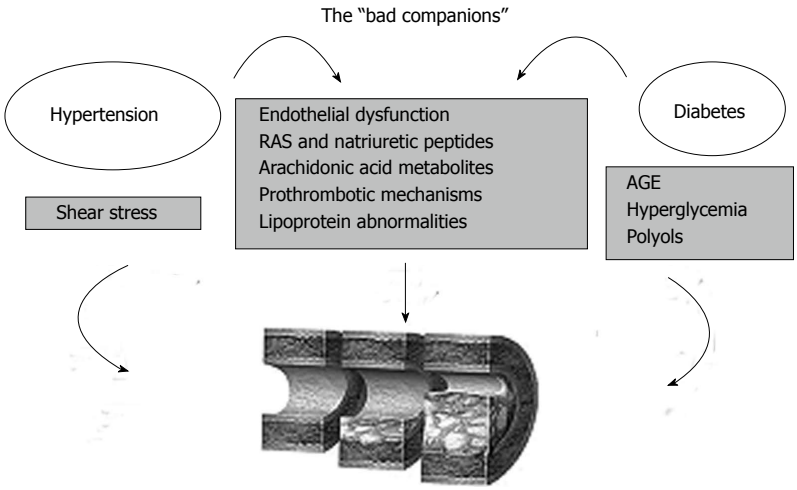

Figure 1 "The bad companions" - In addition to mechanisms of cardiac and vascular damage that are peculiar of hypertension or diabetes, these two conditions share many pathophysiologic mechanisms. RSA: Renin-angiotensin system; AGE: Advanced glycation end-product.

converting enzyme inhibitor-diuretic combination as an alternative to the more traditional BP goal-driven therapy. In this study the relative risk of combined macrovascular and microvascular events was reduced by 9% in diabetic patients treated with the fixed combination showing the possible validity of this alternative treatment approach. Later on, the Steno-2 Study[30] tested in 160 type-2 diabetic patients a multifactorial intervention with an intensive approach to correct blood pressure, glycated hemoglobin, and plasma cholesterol and triglyceride levels that was compared to conventional therapy. Blood pressure target was set at values below 130/80 mmHg in the intensively treated group and, in these patients, mortality and cardiovascular events were reduced by 50% by 29% respectively, as compared to conventional treatment in a follow-up of 13 years. Because of the weak evidence obtained in RCTs in support of a strategy of lowering systolic BP below 130 mmHg as recommended in some hypertension guidelines published in the late 2010s[31,32], the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[33] was specifically designed to test whether a systolic BP treatment target < 120 mmHg was more effective than a target < 140 mmHg in prevention of major cardiovascular events in high-risk patients with type-2 diabetes. A total of 4733 patients were randomly assigned to intensive or standard therapy and the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death was assessed after and average follow-up of 4.7 years. In this study, despite a sustained and significant difference in systolic BP, the annual rates of the composite primary outcome, myocardial infarction, stroke, and all cause death were not different from the intensive-treatment and standard-treatment group. Conversely, serious adverse events that could be attributed to anti-hypertensive treatment were significantly more frequent in the intensive-therapy group. Thus, despite the many limitations of the ACCORD trial (*e.g.*, open-label design, low-rate of cardiovascular events in treatment groups, exclusion of patients younger than 40 year, *etc.*) the current evidence, by no means, indicates the need to pursue in hypertensive individuals with diabetes lower BP goals than in the rest of people with high blood pressure.

The writing of guidelines is a difficult task and in the case of hypertension a myriad of factors can contribute to definition of blood pressure targets that should be reached with treatment. Frequency of disease and its complications is variable in different populations and, for instance, incidence of diabetes increases at different rates around the world. Also the impact of disease on organ complications and pattern of comorbidities are largely different explaining why the evidence obtained in randomized clinical trails often translates in different recommendations. Variability in drug responses among different populations, urbanization, availability of resources, and, last but not least, vested interests of governments or industry can have relevance[34]. Overall, the old tenet that one size does not fit all holds well when discussing blood pressure targets. And this is particularly true in diabetics in whom age, comorbidities, different types of organ complications have serious impact on treatment choices. For instance, elderly patients have no evidence of benefits when systolic blood pressure is reduced below 140 mmHg[21]. And in this view, specific consideration deserve diabetic patients with proteinuric nephropathy who notoriously are at very high risk of cardiovascular events and based upon the results of systematic reviews[35] guidelines still recommend a target blood pressure of less than 130 mmHg.

CONCLUSION

In conclusion, the BP target to be achieved in hypertensive patients with diabetes to guarantee effective protection from major cardiovascular events is still subject of intense debate. Although many hypertension guidelines had recommended a BP goal of less than 130/80 mmHg in these patients, a reappraisal of the available evidence[36] mainly based upon the results of the ACCORD trial does not support this recommendation and it appears that in hypertensive patients with diabetes the same BP targets of nondiabetic hypertensive individuals should be recommended. Based upon this evidence the most recent guidelines for treatment of hypertension have changed

their previous indications, but inconsistencies still exist making clear that further research will be needed to reach a shared opinion on this important topic.

REFERENCES

1 **Sowers JR**. Recommendations for special populations: diabetes mellitus and the metabolic syndrome. *Am J Hypertens* 2003; **16**: 41S-45S [PMID: 14625160 DOI: 10.1016/j.amjhyper.2003.07.009]

2 **Gress TW**, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000; **342**: 905-912 [PMID: 10738048 DOI: 10.1056/NEJM200003303421301]

3 **Crawford AG**, Cote C, Couto J, Daskiran M, Gunnarsson C, Haas K, Haas S, Nigam SC, Schuette R. Prevalence of obesity, type II diabetes mellitus, hyperlipidemia, and hypertension in the United States: findings from the GE Centricity Electronic Medical Record database. *Popul Health Manag* 2010; **13**: 151-161 [PMID: 20521902 DOI: 10.1089/pop.2009.0039]

4 **Sechi LA**. Mechanisms of insulin resistance in rat models of hypertension and their relationships with salt sensitivity. *J Hypertens* 1999; **17**: 1229-1237 [PMID: 10489099 DOI: 10.1097/00004872-199917090-00001]

5 **Sowers JR**. Insulin resistance and hypertension. *Am J Physiol Heart Circ Physiol* 2004; **286**: H1597-H1602 [PMID: 15072967 DOI: 10.1152/ajpheart.00026.2004]

6 **Bonow RO**, Mitch WE, Nesto RW, O'Gara PT, Becker RC, Clark LT, Hunt S, Jialal I, Lipshultz SE, Loh E. Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing Group V: management of cardiovascular-renal complications. *Circulation* 2002; **105**: e159-e164 [PMID: 11994267 DOI: 10.1161/01.cir.0000013956.95796.74]

7 **Stevens RJ**, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care* 2004; **27**: 201-207 [PMID: 14693990 DOI: 10.2337/diacare.27.1.201]

8 **McDonagh TA**, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997; **350**: 829-833 [PMID: 9310600 DOI: 10.1016/s0140-6736(97)03033-x]

9 **Iribarren C**, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001; **103**: 2668-2673 [PMID: 11390335 DOI: 10.1161/01.cir.103.22.2668]

10 **Bell DS**. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care* 2003; **26**: 2433-2441 [PMID: 12882875 DOI: 10.2337/diacare.26.8.2433]

11 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 854-865 [PMID: 9742977 DOI: 10.1016/s0140-6736(98)07037-8]

12 Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; **317**: 703-713 [PMID: 9732337 DOI: 10.1136/bmj.317.7160.703]

13 **Hansson L**, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351**: 1755-1762 [PMID: 9635947 DOI: 10.1016/s0140-6736(98)04311-6]

14 **Curb JD**, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996; **276**: 1886-1892 [PMID: 8968014 DOI: 10.1097/00132586-199712000-00060]

15 **Tuomilehto J**, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999; **340**: 677-684 [PMID: 10053176 DOI: 10.1056/nejm199903043400902]

16 **Estacio RO**, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; **23** Suppl 2: B54-B64 [PMID: 10860192 DOI: 10.1046/j.1525-1497.2000.15200-8.x]

17 Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; **355**: 253-259 [PMID: 10675071 DOI: 10.1016/s0140-6736(99)12323-7]

18 **Cooper-DeHoff RM**, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010; **304**: 61-68 [PMID: 20606150 DOI: 10.1001/jama.2010.884]

19 **Suh DC**, Kim CM, Choi IS, Plauschinat CA, Barone JA. Trends in blood pressure control and treatment among type 2 diabetes with comorbid hypertension in the United States: 1988-2004. *J Hypertens* 2009; **27**: 1908-1916 [PMID: 19491704 DOI: 10.1097/HJH.0b013e32832d4aee]

20 **Mancia G**, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002; **20**: 1461-1464 [PMID: 12172300 DOI: 10.1097/00004872-200208000-00001]

21 **Mancia G**, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281-1357 [PMID: 23817082 DOI: 10.1097/01.hjh.0000431740.32696.cc]

22 **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797 DOI: 10.1001/jama.2013.284427]

23 **Hackam DG**, Quinn RR, Ravani P, Rabi DM, Dasgupta K, Daskalopoulou SS, Khan NA, Herman RJ, Bacon SL, Cloutier L, Dawes M, Rabkin SW, Gilbert RE, Ruzicka M, McKay DW, Campbell TS, Grover S, Honos G, Schiffrin EL, Bolli P, Wilson TW, Feldman RD, Lindsay P, Hill MD, Gelfer M, Burns KD, Vallée M, Prasad GV, Lebel M, McLean D, Arnold JM, Moe GW, Howlett JG, Boulanger JM, Larochelle P, Leiter LA, Jones C, Ogilvie RI, Woo V, Kaczorowski J, Trudeau L, Petrella RJ, Milot A, Stone JA, Drouin D, Lavoie KL, Lamarre-Cliche M, Godwin M, Tremblay G, Hamet P, Fodor G, Carruthers SG, Pylypchuk GB, Burgess

E, Lewanczuk R, Dresser GK, Penner SB, Hegele RA, McFarlane PA, Sharma M, Reid DJ, Tobe SW, Poirier L, Padwal RS. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2013; **29**: 528-542 [PMID: 23541660 DOI: 10.1016/j.cjca.2013.01.005]

24 **American Diabetes Association**. Standards of medical care in diabetes--2013. *Diabetes Care* 2013; **36** Suppl 1: S11-S66 [PMID: 23264422 DOI: 10.2337/dc13-S011]

25 Chapter 4: Blood pressure management in CKD ND patients with diabetes mellitus. *Kidney Int Suppl* (2011) 2012; **2**: 363-369 [PMID: 25018963 DOI: 10.1038/kisup.2012.54]

26 **National Institute for Health and Clinical Excellence.** Hypertension: Clinical management of primary hypertension in adults (updated 2013 October). Available from: URL: http://www.nice.org.uk/guidance/cg127 [DOI: 10.1093/med/9780199609147.003.0121]

27 **López-Jaramillo P**, Sánchez RA, Diaz M, Cobos L, Bryce A, Parra Carrillo JZ, Lizcano F, Lanas F, Sinay I, Sierra ID, Peñaherrera E, Bendersky M, Schmid H, Botero R, Urina M, Lara J, Foss MC, Márquez G, Harrap S, Ramírez AJ, Zanchetti A. Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome. *J Hypertens* 2013; **31**: 223-238 [PMID: 23282894 DOI: 10.1097/HJH.0b013e32835c5444]

28 **Turnbull F**, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; **165**: 1410-1419 [PMID: 15983291 DOI: 10.1001/archinte.165.12.1410]

29 **Patel A**, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; **370**: 829-840 [PMID: 17765963 DOI: 10.1016/s0140-6736(07)61303-8]

30 **Gaede P**, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**: 580-591 [PMID: 18256393 DOI: 10.1056/NEJMoa0706245]

31 **Chobanian AV**, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560-2572 [PMID: 12748199 DOI: 10.1001/jama.289.19.2560]

32 **Mancia G**, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105-1187 [PMID: 17563527 DOI: 10.1097/01.hjh]

33 **Cushman WC**, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1575-1585 [PMID: 20228401 DOI: 10.1056/NEJMoa1001286]

34 **Jennings GL**, Touyz RM. Hypertension guidelines: more challenges highlighted by Europe. *Hypertension* 2013; **62**: 660-665 [PMID: 23959562 DOI: 10.1161/HYPERTENSIONAHA.113.02034]

35 **Upadhyay A**, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med* 2011; **154**: 541-548 [PMID: 21403055 DOI: 10.7326/0003-4819-154-8-201104190-00335]

36 **Arguedas JA**, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database Syst Rev* 2013; **10**: CD008277 [PMID: 24170669 DOI: 10.1002/14651858.CD008277.pub2]

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MINIREVIEWS

Contribution of miRNAs to ion-channel remodelling in atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia associated with pronounced mortality and morbidity, which are related to palpitations, fainting, congestive heart failure, and stroke. Prolonged episodes of AF promote AF persistence mainly due to electrical remodelling that alters ion-channel expression and/or function. MicroRNAs (miRNAs), a new class of non-coding mRNAs of around 22 nucleotides in length, have recently emerged as one of the key players in the gene-expression regulatory networks. The potential roles of miRNAs in controlling AF have recently been investigated. Several recent studies have provided promising results for a better understanding of the molecular mechanisms of AF. In this review, we summarize the mechanism of miRNAs as regulators of ion-channel gene expression and their role in causing AF through electrical remodelling.

Key words: Atrial fibrillation; MicroRNA; Ion channels; Electrical remodelling

Core tip: Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice associated with pronounced mortality and morbidity. MicroRNAs (miRNAs), which are approximately 22 nucleotide long RNA regulators of gene expression, have become a major focus of research in molecular biology miRNAs have emerged as key post-transcriptional regulators of gene expression therefore, it is important to comment on the roles of these small non-protein-coding mRNAs in the cardiovascular system and their involvement in AF. In this review, we summarize the mechanism of miRNAs as regulators of ion-channels genes and their role in electrical remodelling caused by AF.

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained

arrhythmia in clinical practice, with high prevalence in the geriatric population[1]. AF is a condition in which heart-rhythm control is displaced from the normal sinus node pacemaker by rapid activity in different areas of the atria, resulting in rapid and irregular atrial activity. This pathology is often underestimated because it is usually asymptomatic and rarely life-threatening. However, it can induce palpitations, fainting, congestive heart failure, and stroke due to electrical disturbance, as well as thromboembolism, all of which are associated with high morbidity and mortality[2]. Therefore, a better understanding of the mechanisms of and molecular basis for AF may uncover safer, more effective therapeutic targets and new treatment methods[3].

AF progresses as three different clinical forms, which have been previously well described. Initially, AF occurs in a paroxysmal form characterized by episodes of the arrhythmia that terminate spontaneously. Persistent AF is defined by episodes that are sustained longer than 7 d and require termination by pharmacological or direct-current electric cardioversion. In permanent AF the normal heart rhythm cannot be converted to sinus rhythm. It is believed that AF development from paroxysmal to persistent and permanent forms occurs through the influence of atrial remodelling caused by the arrhythmia itself and/or the progression of underlying heart disease[3]. Therefore, the molecular and electrical remodelling of ion channels determining the potential duration has been proposed as a major mechanism in chronic atrial fibrillation. Prolonged episodes of AF alter atrial properties ("atrial remodelling"), promoting AF persistence. Electrical remodelling alters ion-channel expression and/or function, increasing the likelihood of ectopic firing or re-entry, thereby promoting AF initiation and/or recurrence. Ion-channel remodelling shortens the atrial effective refractory period (ERP), favouring re-entrant arrhythmias, mainly due to the shortening of atrial action potential duration (APD)[4-6]. ERP reduction promotes the conduction block and wave break underlying fibrillatory conduction. APD shortening may lead to AF-related atrial contractile dysfunction[7-11]. The balance between inward currents that depolarize and outward currents that repolarize cardiac myocytes determines APD, and thus ERP. Thus, deregulation of ion expression as a molecular mechanism for AF has been considered quite interesting by many researchesIn addition to electrical remodelling it has been shown that structural alterations and fibrosis are implicated in AF generation and perpetuation[12,13].

Recently microRNA (miRNA) research has evolved rapidly, therefore it is important to comment on the roles of these non-coding short RNA molecules in the cardiovascular system and their involvement in AF. Primarily, miRNAs suppress protein synthesis by inhibiting the translation of protein from mRNA or by promoting the degradation of mRNA, thereby silencing gene expression on the post-transcriptional level. Notably, many recent reports have demonstrated that miRNAs regulate several properties of cardiac physiology and excitability, including automaticity, Ca^{2+} handling, conduction, and repolarization[14]. Several miRNAs have been shown to have a role in the triggering or prolonging AF, while other miRNAs target several genes considered to have the potential to regulate AF. Avaliable results show the potential role of miRNAs involved in AF.

In this review, we summarize the mechanism of miRNAs as regulators of ion-channels genes and their role in electrical remodelling caused by AF.

ROLE OF MIRNAS IN CARDIAC DISEASES, REMODELLING, AND HOMEOSTASIS

MiRNAs are endogenous, conserved, single-stranded, small (c. 22 nucleotides in length), noncoding RNAs that repress gene expression at the post-transcriptional level by targeting mRNAs[15,16]. A single miRNA can regulate multiple targets; therefore, modulating the expression of one miRNA often results in the modulation of an entire gene network. Genes coding for miRNAs, such as the protein-coding genes, are located in chromosomes as an integral part of the genome; however, these genes may appear more genomically diverse and dynamic. Based on the genomic organization of miRNA genes, miRNAs can be grouped into two classes: (1) intergenic miRNAs, when the miRNA-coding genes are located in genomic regions distinct from known transcription units and are found between protein-coding genes; and/or (2) intragenic miRNAs, if the miRNA-coding genes are located within annotated genes either of protein-coding genes or of long noncoding RNAs as their host genes and they are transcribed by using the host regulatory elements. Curiously, some miRNAs are transcribed from multiple copies of their genes whereas many other miRNAs appear in clusters on a single polycistronic transcript.

Two converging pathways have been demonstrated for the biogenesis of miRNAs: the canonical pathway and the noncanonical pathway[17]. The canonical pathway is Drosha-dependent and is usually used to generate intergenic miRNAs and intronic miRNAs. The first step of this pathway, transcription of miRNAs genes yields transcripts, termed primary miRNA transcripts (pri-miRNAs) with a characteristic hairpin morphology, comprising a loop and an imperfectly paired stem incorporating the mature miRNA sequence on on of the strands, operated mainly by RNA polymerase II. Subsequently, these pri-miRNAs are processed by the Class 2 Rnase enzyme Drosha together with Pasha protein to become precursor miRNAs (pre-miRNAs), which are then transported to the cytoplasm through the Ran-GTP-dependent nuclear pore exportin-5, where they are processed by Dicer (another RNase Ⅲ enzyme) to generate the final approximately 22 nucleotide product of mature miRNAs. The mature miRNAs are then loaded into the miRNA-associated multi-protein RNA-induced silencing complex (RISC) that includes the Argonaute

Proteins (mature miRNAs). A perfect base-pairing of the miRNA (within miRISC complex) motif(s), mainly in the 3'-untranslated region termed the "seed sequence", a critical site for miRNA actions[18,19], is required for effective repression of translation of the protein. Also, some miRNAs are involved in gene silencing through mRNA degradation. Alternatively, Drosha-independent and either Dicer-dependent or Dicer-independent noncanonical pathways are used to generate Mirtrons, small nucleolar miRNAs and short hairpin miRNAs transfer miRNAs. It is important to highlight that some properties of the miRNAs, such as their ability to influence whole cellular processes instead of single genes, the easy manipulation of miRNA activity *in vivo* using miRNA inhibitors, and the high intracellular stability of miRNAs, make them a promising therapeutic target[20].

To date, over a thousand miRNAs have been identified and they have been reported to participate in many fundamental biological processes, including cell proliferation, growth, differentiation, apoptosis, and tissue remodelling. The essential role of miRNA in early heart development was first revealed by a Dicer knockout. The early lethality of Dicer mutants, along with the complete depletion of mature miRNAs, indicated the crucial role of miRNAs in early heart development[21]. Additionally, Dicer activity is also required for normal functioning of the mature heart, as adult mice lacking Dicer in the myocardium suffer from high incidence of sudden death, cardiac hypertrophy, and reactivation of the foetal cardiac-gene programme[22]. These data demonstrate that miRNAs play an important role during normal heart development, cardiac remodelling, and homeostasis. Dysregulated miRNAs have been shown to be related to the pathology of many cardiovascular diseases, including arrhythmia, hypertrophy, and heart failure, gaining a critical position as potential therapeutical targets for cardiac diseases. For instance, multiple miRNAs, such as *miR-1*, *miR-133*, *miR-208*, *miR-195*, *miR-21*, and *miR-18b*, have been identified to participate in cardiac hypertrophy and can independently determine this pathological process. Importantly, *miR-1*, *miR-133*, *miR-21*, *miR-29*, *miR-199a*, and *miR-320* have also been reported to be involved in myocardial infarction[23]. Among them, *miR-1* and *miR-133* are considered muscle-specific miRNAs and they represent the most abundant miRNAs expressed in the heart[14].

Interestingly, recent studies have highlighted circulating micRNAs as biomarkers for the AF[24] Moreover, several miRNAs such as miR-24, miR-29b and miR133 have been shown to be involved in myocardial fibrosis[25,26] and open new perspectives to analyse the role of miRNAs in the structural alterations and fibrosis involved in AF generation and perpetuation.

Finally, a few miRNAs have been reported to regulate cardiac excitability through targeting genes encoding ion channels[27-30]. Here we focus on miRNAs which target different ion channels that play key roles in the electrical remodelling of AF.

ION-CHANNEL DYSFUNCTION IN ATRIAL FIBRILLATION

It has been previously shown that the factors responsible for onset of AF include triggers that induce arrhythmia. Triggers include not only sympathetic or parasympathetic stimulation, bradycardia, atrial premature beats or tachycardia, accessory AV pathways, and acute atrial stretch, but also ectopic foci occurring in "sleeves" of atrial tissue within the pulmonary veins or vena caval junctions as well[31].

After the onset of AF, prolonged episodes alter atrial properties ("atrial remodelling") promoting AF persistence. AF-associated remodelling events within the atria include electrical remodelling and, secondarily, structural remodelling and autonomic-nervous-system changes. AF-related electrical remodelling can result from altered expression and/or function of cardiac ion channels, leading to the development of functional re-entry substrates and finally contributing to persistent AF. Therefore, electrical remodelling shortens the atrial ERP and APD, and reduces its physiological rate of adaptation as a result of ion-channel remodelling and abnormal Ca^{2+} handling (Figure 1).

The inward sodium current (I_{Na}), which is encoded by the voltage-gated cardiac sodium channel *SCN5A*, initiates the cardiac action potential and this I_{Na} is involved in repolarization and refractoriness. It bears highlight that rapid cardiac rates can significantly reduce (I_{Na}) density and conduction velocity, triggering AF (Figure 1)[32]. In addition, mutations in *SCN5A* are related to diseases caused by abnormalities in cardiac conduction, including AF. In this context, Darbar *et al*[11] tested the hypothesis that vulnerability to AF is associated with variation in *SCN5A*, the gene encoding the cardiac sodium channel. They found novel as well as rare variants in nearly 6% of the population, including alleles that segregate with AF in other family members, supporting the hypothesis that *SCN5A* is an important AF-susceptibility gene.

It has been well documented that increased K^+ currents or decreased Ca^{2+} currents shorten APD, promoting re-entrant AF. Because Ca^{2+} enters atrial cells during AP depolarization, the high atrial rate in AF increase Ca^{2+} loading, which leads to activation of auto-protective mechanisms to reduce chronic Ca^{2+} overload. Therefore, in patients with chronic AF, mRNA transcription of the auxiliary L-type Ca^{2+}-channel subunits are significantly diminished reducing the inward Ca^{2+} currents, maintaining the AP plateau, shortening the AP duration, and finally contributing to re-entry[33]. Moreover, alterations in Ca^{2+} handling promote diastolic Ca^{2+} release by increasing open probability of the sarcoplasmic reticulum Ca^{2+} release channels (RyR2), this in turn promoting delayed after-depolarizations (DADs) and ectopic activity (Figure 1)[5,6,34].

Additionally, AF-related shortening of APD can also result from an increase in K^+ channel gene products and/or activity. The inward rectified K^+ current (I_{K1}) and $I_{K\text{-}ACh}$ are also altered in AF and both AF-related I_{K1} up-

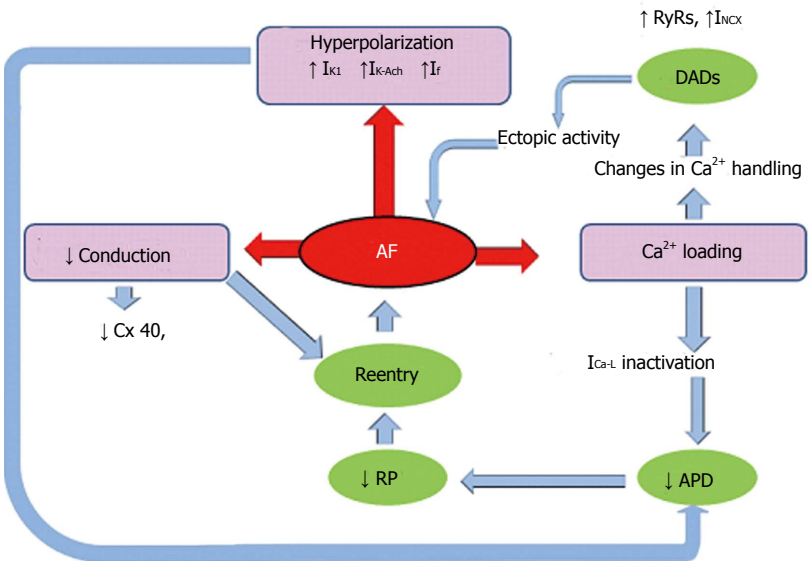

Figure 1 Mechanisms of atrial fibrillation. Cytotoxic overloading of Ca^{2+} occurs by a rapid atrial rate. As a result, this acts as a mechanism of cell protection *via* the inactivation of L-type Ca^{2+} current ($I_{Ca\text{-}L}$), which in turn reduces the action potential duration (APD) and this consequently shortens the refractory period (RP). This overloading of Ca^{2+} also contributes to an abnormal function of ryanodine receptor channels (RyRs) and intensifies the inward Na^{+}-Ca^{2+}-exchange current (I_{NCX}), leading to delayed afterpolarizations (DADs) and ectopic activity. In addition, AF produces hyperpolarization due to increased $I_{Ca\text{-}L}$, which increases the inward rectifier current (I_{K1}) and acetylcholine-regulated K^{+} current ($I_{K\text{-}Ach}$). This also reduces APD and promotes conduction by decreasing of connexin-40 (Cx40).

regulation and enhancement of the constitutive form of $I_{K\text{-}ACh}$ promote the persistence of AF by reducing APD (Figure 1)[35]. *KCNN3*, which encodes the small conductance calcium-activated potassium channel 3 (SK3), is a new locus strongly associated with AF[36]. The role of SK channels remains unclear, but it is believed that they contribute to the repolarization of cardiac action[37,38]. A recent study showed SK3 to be strongly down-regulated in permanent AF, which contributed to AF persistence and susceptibility by abbreviating APD[39].

Similarly, it has been well established that chronic AF in humans reduces the transient outward potassium currents (I_{to}) by transcriptional down-regulation of the Kv4.3 potassium channel[7,8]. The ultrarapid delayed rectifier K^{+} channel (I_{kur}) also plays a major part since it has been shown that the amplitude of I_{kur} is significantly reduced and the current density is lower in patients with AF[10]. More recently it has been demonstrated in human that chronic AF modifications in transcriptional and posttranscriptional mechanisms of HCN channels occur and are associated with a slight yet significant gain-of-function of the hyperpolarization activated "funny" current (I_f), which may contribute to enhanced atrial ectopy[40].

The slow delayed rectifier potassium channel (I_{Ks}), made up of a pore-forming subunit encoded by *KCNQ1*, has also been implicated in AF. Thus, several mutations in *KCNQ1* have been described in AF patients[41,42], some of which are associated with I_{Ks} block and AP[43]. The potassium channel voltage-gated subfamily member 2-(KCNH2) is an ion-channel gene that encodes an inwardly rectifying potassium channel (I_{Kr}), and a genetic variation in the *KCNH2* gene reportedly predisposes Chinese Han individuals to the risk of acquired AF[44]. In addition, lower expression levels of the ATP-sensitive potassium channel (Kir6.2); the acetylcholine-dependent potassium channel (Kir3.4) and the ultra-rapid delayed rectifier potassium channel (Kv1.5) in patients with AF have also been described[10,45]. However, the underlying mechanisms leading to these changes remain unclear.

Finally, although relatively little is known about gap-junction remodelling in the atria, changes in ion channels involved in cardiac conduction have also been reported in relation to AF. Atrial gap junctions are comprosed of two different subunit proteins, *i.e.*, Connexin40 (Cx40) and Connexin43 (Cx43). In the goat, Cx40 expression decreases and the protein becomes more heterogeneously distributed after long periods of fast pacing, contributing to the onset and self-perpetuation of re-entry pathways and AF[46]. Moreover, pacing can induce atrial tachyarrhythmias or fibrillation in Cx40-null mice[47]. These results are consistent with the extensive clinical evidence pointing to disturbances in connexin-40 as a basis for genetic AF predisposition. Importantly, a very recent report has shown a clear reduction in Cx40 but not Cx43 expression (both mRNA and protein) in atrial appendage tissues from patients with lone AF with no Cx40 coding-region mutations identified[47].

In summary, despite that many studies have pointed out the relevance of the AF-related electrical remodelling, our understanding of the underlying molecular mechanisms leading to and perpetuating ion-channel remodelling during AF is very limited. Better knowledge and deeper insights into the molecular mechanisms underlying AF may help to identify new and selective drug targets for improved AF treatment.

MICRORNAS AND ELECTRICAL REMODELLING IN AF

As mentioned above, electrical remodelling is a maladaptive process that can trigger and prolong AF. Recently, multiple research groups have uncovered an important role of several miRNAs in regulating cardiac excitability and arrhythmogenesis by targeting specific ion channels, which might have an important impact on AF onset and/or persistence[48,49].

Microarray analyses in a canine model of AF showed that *miR-223*, *miR-328*, and *miR-664* were significantly up-

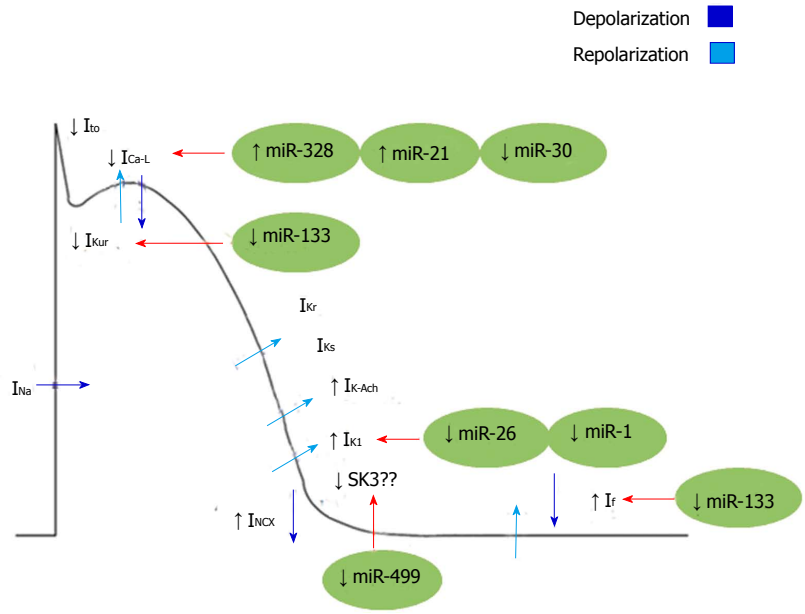

Figure 2 Mechanisms of electrical remodelling in atrial fibrillation regulated by microRNAs. I_{Na}: Inward sodium current; I_{K1}: Inward rectified K^+ current; I_{to}: Transient outward potassium currents; $I_{Ca\text{-}L}$: Inactivation of L-type Ca^{2+} current; I_{Kur}: Ultrarapid delayed rectifier K^+ channel; I_{Ks}: Slow delayed rectifier potassium channel; $I_{K\text{-}Ach}$: Acetylcholine-activated inward-rectifing potassium channel; I_{NCX}: Inward Na^+-Ca^{2+}-exchange current; SK3: Small conductance calcium-activated potassium channel 3; I_f: Funny current.

regulated, whereas *miR-101*, *miR-320*, and *miR-499* were down-regulated[14,50]. Among these, *miR-328* was the most significantly up-regulated and forced expression of *miR-328* through adenovirus infection in canine atrium as well as a transgenic approach in mice recapitulated the phenotypes of AF. Enhanced AF vulnerability by diminished L-type Ca^{2+} current, led to a shortened atrial action potential. Normalization of *miR-328* levels with antagomiR reversed the conditions, and genetic knockdown of endogenous *miR-328* dampened AF vulnerability, highlighting the importance of *miR-328* as a potential therapeutic target for AF[49].

Other miRNAs such as *miR-21* can also act as regulators of L-type Ca^{2+} channel. Barana *et al*[51] showed that *miR-21* was expressed in human myocytes with chronic AF. They demonstrated that this disease increases the expression of *miR-21*, which decreases $I_{Ca\text{-}L}$. Down-regulation of $I_{Ca\text{-}L}$ by *miR-21*, suggests that this miR could have an important function in AF through electrical remodelling (Figure 2).

On the other hand, *miR-26* has been demonstrated to target *KCNJ2,* the gene encoding the main component of the inward rectifier potassium-channel current I_{K1} (KIR 2.1). As stated above, the I_{K1} is an important regulator of reentrant-spiral dynamics and a major component of AF-related electrical remodelling. Recently, Luo *et al*[52] has found that *miR-26* was down-regulated in AF patients accompanied by I_{K1}/KIR2.1 protein up-regulation. Moreover, by gain and loss-of-function experiments in mice, these authors demonstrated that *miR-26* controls the expression of *KCNJ2* and thereby promotes AF.

In addition, it has also been shown that expression levels of *miR-1* (a muscle specific miRNA) are greatly reduced in the atrial tissue of AF patients. Yang *et al*[53] showed that the elimination of *miR-1* by an antisense inhibitor in infarcted rat hearts relieved arrhythmogenesis, whereas *miR-1* overexpression slowed conduction and depolarized the cytoplasmic membrane by post-transcriptionally repressing *KCNJ2* and *GJA1* (which encodes connexin 43). More recently it has been documented that increased I_{K1} currents in left atrial cardiomyocytes of AF patients are associated with greater Kir2.1 expression and lower levels of *miR-1*, reinforcing the notion of a role for *miR-1* in regulating atrial remodelling in AF[48]. However, no significant changes in Cx43 mRNA and protein expression nor in Cx43 localization were found in those cardiomyocytes, suggesting that *miR-1* may differentially regulate subunits such as Kir2.1 and Cx43 in different cell subtypes[48]. Moreover, a very recent miR array analysis in humans has revealed that *miR-1* is greater in the left atrium than in the right one, underscoring the notion that AF pathophysiology may affect the two atria differently[54] (Figure 2).

The possibility that another muscle-specific miRNA such as *miR-133* plays a role in AF has also been proposed, since down-regulation of *miR-133* favours atrial remodelling by derepression of KCNH2/I_{Kr} and KCNH1/I_{Ks}. However, there is no direct evidence on how *miR-133* affects I_{Ks} or I_{Kr} current[55,56]. In this way, Luo *et al*[52] found that *miR-1* and *miR-133* act to restrict overexpression of *HCN2* and *HCN4* (encoding for important components of I_f currents), and down-regulation of *miR-1*/*miR-133* acts partially causing the anomalistic re-expression of *HCN2* and *HCN4* in cardiac hypertrophy. Yet it remains unclear whether *miR-1* and *miR-133* affect *HCN* channels in the context of AF[57]. Notwithstanding, *mirR-133* together with *miR-30* were found to be down-regulated in a canine model of AF, reinforcing the potential role of *miR-133* in AF[58] (Figure 2).

Together with *miR-1* and *miR-133*, *miR-208a* is also a muscle-specific miRNA, which is encoded within an intron of the α-cardiac muscle myosin heavy-chain gene (*Myh6*). Although no direct evidence for the involvement of *miR-208a* in atrial electrical remodelling have been reported, *miR-208a* transgenic gain of function in mice lead to arrhythmias. In addition, Cx40 expression was increased in those transgenic mice, indicating that *miR-208a* could modulate electrical conduction in the heart[59] (Figure 2).

Finally, in a recently reported finding, a potential role of *miR-499* in AF-related electrical remodelling has been

proposed. Atrial *miRNA-499* is significantly upregulated in AF, (Figure 2), leading to down-regulation of the small-conductance SK3, possibly contributing to the electrical remodelling in AF[39].

MiRNA research has highlighted the roles of miRNAs in the cardiovascular system and their involvement in AF. Further studies on miRNA and AF will provide new insights into the mechanisms underlying that disorder and may offer new strategies for the treatment of AF.

CONCLUDING REMARKS AND CLINICAL PERSPECTIVES

Electrical remodelling secondary to the onset of atrial fibrillation dramatically contributes to the recurrence of AF, eventually leading to persistent AF. Many recent studies demonstrates that miRNAs are becoming one of the most fascinating regulatory molecules, due to their critical roles in fine-tuning of physiological processes and their deregulation in several disorders, including AF. The functional significance of miRs as direct or indirect post-transcriptional regulators of ion channels involved in electrical remodelling strongly suggests that these miRNAs may serve as potential biomarkers or promising drug targets in the treatment, and management of AF, though considerable work remains to be done. Further studies making use of existing AF models, miRNA expression signatures and miRNA target gene prediction should provide information finally applicable to clinical practice.

REFERENCES

1 **Kannel WB**, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; **82**: 2N-9N [PMID: 9809895 DOI: 10.1016/S0002-9149(98)00583-9]

2 **Nattel S**, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol* 2014; **63**: 2335-2345 [PMID: 24613319 DOI: 10.1016/j.jacc.2014.02.555]

3 **Fujiki A**. Progression of atrial fibrillation from paroxysmal to persistent. *Circ J* 2014; **78**: 1058-1060 [PMID: 24621659 DOI: 10.1253/circj.CJ-14-0264]

4 **Oh S**, Kim KB, Ahn H, Cho HJ, Choi YS. Remodeling of ion channel expression in patients with chronic atrial fibrillation and mitral valvular heart disease. *Korean J Intern Med* 2010; **25**: 377-385 [PMID: 21179275 DOI: 10.3904/kjim.2010.25.4.377]

5 **Kaumann AJ**, Lynham JA, Brown AM. Comparison of the densities of 5-HT4 receptors, beta 1- and beta 2-adrenoceptors in human atrium: functional implications. *Naunyn Schmiedebergs Arch Pharmacol* 1996; **353**: 592-595 [PMID: 8740155 DOI: 10.1007/BF00169181]

6 **Bosch RF**, Zeng X, Grammer JB, Popovic K, Mewis C, Kühlkamp V. Ionic mechanisms of electrical remodeling in human atrial fibrillation. *Cardiovasc Res* 1999; **44**: 121-131 [PMID: 10615396 DOI: 10.1016/S0008-6363(99)00178-9]

7 **Grammer JB**, Bosch RF, Kühlkamp V, Seipel L. Molecular remodeling of Kv4.3 potassium channels in human atrial fibrillation. *J Cardiovasc Electrophysiol* 2000; **11**: 626-633 [PMID: 10868735 DOI: 10.1111/j.1540-8167.2000.tb00024.x]

8 **Atienza F**, Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, Arenal A, Villacastín JP, Torrecilla EG, Sánchez A, Ploutz-Snyder R, Jalife J, Berenfeld O. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant mechanism. *Circulation* 2006; **114**: 2434-2442 [PMID: 17101853 DOI: 10.1161/CIRCULATIONAHA.106.633735]

9 **Dobrev D**, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, Knaut M, Ravens U. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation. *Circulation* 2005; **112**: 3697-3706 [PMID: 16330682 DOI: 10.1161/CIRCULATIONAHA.105.575332]

10 **Brandt MC**, Priebe L, Böhle T, Südkamp M, Beuckelmann DJ. The ultrarapid and the transient outward K(+) current in human atrial fibrillation. Their possible role in postoperative atrial fibrillation. *J Mol Cell Cardiol* 2000; **32**: 1885-1896 [PMID: 11013132 DOI: 10.1006/jmcc.2000.1221]

11 **Darbar D**, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL, Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation* 2008; **117**: 1927-1935 [PMID: 18378609 DOI: 10.1161/CIRCULATIONAHA.107.757955]

12 **Kallergis EM**, Manios EG, Kanoupakis EM, Mavrakis HE, Arfanakis DA, Maliaraki NE, Lathourakis CE, Chlouverakis GI, Vardas PE. Extracellular matrix alterations in patients with paroxysmal and persistent atrial fibrillation: biochemical assessment of collagen type-I turnover. *J Am Coll Cardiol* 2008; **52**: 211-215 [PMID: 18617070 DOI: 10.1016/j.jacc.2008.03.045]

13 **Fujita M**, Cheng XW, Inden Y, Shimano M, Yoshida N, Inoue A, Yamamoto T, Takeshita K, Kyo S, Taguchi N, Shi GP, Kuzuya M, Okumura K, Murohara T. Mechanisms with clinical implications for atrial fibrillation-associated remodeling: cathepsin K expression, regulation, and therapeutic target and biomarker. *J Am Heart Assoc* 2013; **2**: e000503 [PMID: 24342995 DOI: 10.1161/JAHA.113.000503]

14 **Luo X**, Zhang H, Xiao J, Wang Z. Regulation of human cardiac ion channel genes by microRNAs: theoretical perspective and pathophysiological implications. *Cell Physiol Biochem* 2010; **25**: 571-586 [PMID: 20511702 DOI: 10.1159/000315076]

15 **Xu J**, Zhao J, Evan G, Xiao C, Cheng Y, Xiao J. Circulating microRNAs: novel biomarkers for cardiovascular diseases. *J Mol Med* (Berl) 2012; **90**: 865-875 [PMID: 22159451 DOI: 10.1007/s00109-011-0840-5]

16 **Kumarswamy R**, Thum T. Non-coding RNAs in cardiac remodeling and heart failure. *Circ Res* 2013; **113**: 676-689 [PMID: 23989712 DOI: 10.1161/CIRCRESAHA.113.300226]

17 **Havens MA**, Reich AA, Duelli DM, Hastings ML. Biogenesis of mammalian microRNAs by a non-canonical processing pathway. *Nucleic Acids Res* 2012; **40**: 4626-4640 [PMID: 22270084 DOI: 10.1093/nar/gks026]

18 **Han J**, Lee Y, Yeom KH, Kim YK, Jin H, Kim VN. The Drosha-DGCR8 complex in primary microRNA processing. *Genes Dev* 2004; **18**: 3016-3027 [PMID: 15574589 DOI: 10.1101/gad.1262504]

19 **Han J**, Lee Y, Yeom KH, Nam JW, Heo I, Rhee JK, Sohn SY, Cho Y, Zhang BT, Kim VN. Molecular basis for the recognition of primary microRNAs by the Drosha-DGCR8 complex. *Cell* 2006; **125**: 887-901 [PMID: 16751099 DOI: 10.1016/j.cell.2006.03.043]

20 **Kwekkeboom RF**, Lei Z, Doevendans PA, Musters RJ, Sluijter JP. Targeted delivery of miRNA therapeutics for cardiovascular diseases: opportunities and challenges. *Clin Sci* (Lond) 2014; **127**: 351-365 [PMID: 24895056 DOI: 10.1042/CS20140005]

21 **Wilkins BJ**, Molkentin JD. Calcium-calcineurin signaling in the regulation of cardiac hypertrophy. *Biochem Biophys Res Commun* 2004; **322**: 1178-1191 [PMID: 15336966 DOI: 10.1016/j.bbrc.2004.07.121]

22 **da Costa Martins PA**, Bourajjaj M, Gladka M, Kortland M, van Oort RJ, Pinto YM, Molkentin JD, De Windt LJ. Conditional dicer gene deletion in the postnatal myocardium provokes spontaneous cardiac remodeling. *Circulation* 2008; **118**: 1567-1576 [PMID: 18809798 DOI: 10.1161/circulationaha.108.769984]

23 **Wang Z**. MicroRNAs and Cardiovascular Disease. Holland: Bentham Science Publishers, 2010

24 **Gomes da Silva AM**, Silbiger VN. miRNAs as biomarkers of atrial fibrillation. *Biomarkers* 2014; **19**: 631-636 [PMID: 25171770 DOI: 10.3109/1354750X.2014.954001]

25 **Wang J**, Huang W, Xu R, Nie Y, Cao X, Meng J, Xu X, Hu S, Zheng Z. MicroRNA-24 regulates cardiac fibrosis after myocardial infarction. *J Cell Mol Med* 2012; **16**: 2150-2160 [PMID: 22260784 DOI: 10.1111/j.1582-4934.2012.01523.x]

26 **Piccinini AM**, Midwood KS. Illustrating the interplay between the extracellular matrix and microRNAs. *Int J Exp Pathol* 2014; **95**: 158-180 [PMID: 24761792 DOI: 10.1111/iep.12079]

27 **Wang Z**, Yang B. MicroRNA Expression Detection Methods. Berlin, Heidelberg, Germany: Springer, 2010 [DOI: 10.1007/978-3-642-04928-6]

28 **Latronico MV**, Condorelli G. MicroRNAs and cardiac pathology. *Nat Rev Cardiol* 2009; 6: 419-429 [DOI: 10.1038/nrcardio.2009.56]

29 **Latronico MV**, Condorelli G. RNA silencing: small RNA-mediated posttranscriptional regulation of mRNA and the implications for heart electropathophysiology. *J Cardiovasc Electrophysiol* 2009; **20**: 230-237 [PMID: 19017333 DOI: 10.1111/j.1540-8167.2008.01357.x]

30 **Wang Z**. miRNA in the regulation of ion channel/transporter expression. *Compr Physiol* 2013; **3**: 599-653 [PMID: 23720324 DOI: 10.1002/cphy.c110002]

31 **Maass AH**, Van Gelder IC. Atrial resynchronization therapy: a new concept for treatment of heart failure with preserved ejection fraction and prevention of atrial fibrillation? *Eur J Heart Fail* 2012; **14**: 227-229 [PMID: 22357574 DOI: 10.1093/eurjhf/hfs014]

32 **Gaspo R**, Bosch RF, Bou-Abboud E, Nattel S. Tachycardia-induced changes in Na+ current in a chronic dog model of atrial fibrillation. *Circ Res* 1997; **81**: 1045-1052 [PMID: 9400386 DOI: 10.1161/01.RES.81.6.1045]

33 **Van Wagoner DR**, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca2+ currents and human atrial fibrillation. *Circ Res* 1999; **85**: 428-436 [PMID: 10473672 DOI: 10.1161/01.RES.85.5.428]

34 **Greiser M**, Halaszovich CR, Frechen D, Boknik P, Ravens U, Dobrev D, Lückhoff A, Schotten U. Pharmacological evidence for altered src kinase regulation of I (Ca,L) in patients with chronic atrial fibrillation. *Naunyn Schmiedebergs Arch Pharmacol* 2007; **375**: 383-392 [PMID: 17593353 DOI: 10.1007/s00210-007-0174-6]

35 **Voigt N**, Dobrev D. Ion Channel Remodelling in Atrial Fibrillation. *European Cardiology* 2011; **7**: 97-103 [DOI: 10.15420/ecr.2011.7.2.97]

36 **Ellinor PT**, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK, Sinner MF, de Bakker PI, Mueller M, Lubitz SA, Fox E, Darbar D, Smith NL, Smith JD, Schnabel RB, Soliman EZ, Rice KM, Van Wagoner DR, Beckmann BM, van Noord C, Wang K, Ehret GB, Rotter JI, Hazen SL, Steinbeck G, Smith AV, Launer LJ, Harris TB, Makino S, Nelis M, Milan DJ, Perz S, Esko T, Köttgen A, Moebus S, Newton-Cheh C, Li M, Möhlenkamp S, Wang TJ, Kao WH, Vasan RS, Nöthen MM, MacRae CA, Stricker BH, Hofman A, Uitterlinden AG, Levy D, Boerwinkle E, Metspalu A, Topol EJ, Chakravarti A, Gudnason V, Psaty BM, Roden DM, Meitinger T, Wichmann HE, Witteman JC, Barnard J, Arking DE, Benjamin EJ, Heckbert SR, Kääb S. Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet* 2010; **42**: 240-244 [PMID: 20173747 DOI: 10.1038/ng.537]

37 **Tuteja D**, Xu D, Timofeyev V, Lu L, Sharma D, Zhang Z, Xu Y, Nie L, Vázquez AE, Young JN, Glatter KA, Chiamvimonvat N. Differential expression of small-conductance Ca2+-activated K+ channels SK1, SK2, and SK3 in mouse atrial and ventricular myocytes. *Am J Physiol Heart Circ Physiol* 2005; **289**: H2714-H2723 [PMID: 16055520 DOI: 10.1152/ajpheart.00534.2005]

38 **Li N**, Timofeyev V, Tuteja D, Xu D, Lu L, Zhang Q, Zhang Z, Singapuri A, Albert TR, Rajagopal AV, Bond CT, Periasamy M, Adelman J, Chiamvimonvat N. Ablation of a Ca2+-activated K+ channel (SK2 channel) results in action potential prolongation in atrial myocytes and atrial fibrillation. *J Physiol* 2009; **587**: 1087-1100 [PMID: 19139040 DOI: 10.1113/jphysiol.2008.167718]

39 **Ling TY**, Wang XL, Chai Q, Lau TW, Koestler CM, Park SJ, Daly RC, Greason KL, Jen J, Wu LQ, Shen WF, Shen WK, Cha YM, Lee HC. Regulation of the SK3 channel by microRNA-499--potential role in atrial fibrillation. *Heart Rhythm* 2013; **10**: 1001-1009 [PMID: 23499625 DOI: 10.1016/j.hrthm.2013.03.005]

40 **Stillitano F**, Lonardo G, Giunti G, Del Lungo M, Coppini R, Spinelli V, Sartiani L, Poggesi C, Mugelli A, Cerbai E. Chronic atrial fibrillation alters the functional properties of If in the human atrium. *J Cardiovasc Electrophysiol* 2013; **24**: 1391-1400 [PMID: 23869794 DOI: 10.1111/jce.12212]

41 **Chu HM**, Feng MJ, Li YG, Zhang YX, Ma JF, He B, Yu YB, Liu J, Chen XM. Polymorphisms but not mutations of the KCNQ1 gene are associated with lone atrial fibrillation in the Chinese Han population. *ScientificWorldJournal* 2013; **2013**: 373454 [PMID: 23710137 DOI: 10.1155/2013/373454]

42 **Ki CS**, Jung CL, Kim HJ, Baek KH, Park SJ, On YK, Kim KS, Noh SJ, Youm JB, Kim JS, Cho H. A KCNQ1 mutation causes age-dependant bradycardia and persistent atrial fibrillation. *Pflugers Arch* 2014; **466**: 529-540 [PMID: 23989646 DOI: 10.1007/s00424-013-1337-6]

43 **Hancox JC**, Kharche S, El Harchi A, Stott J, Law P, Zhang H. In silico investigation of a KCNQ1 mutation associated with familial atrial fibrillation. *J Electrocardiol* 2014; **47**: 158-165 [PMID: 24411289 DOI: 10.1016/j.jelectrocard.2013.12.004]

44 **Wang QS**, Wang XF, Chen XD, Yu JF, Wang J, Sun J, Lu SB, Shen MY, Lu M, Li YG, Jin L. Genetic polymorphism of KCNH2 confers predisposition of acquired atrial fibrillation in Chinese. *J Cardiovasc Electrophysiol* 2009; **20**: 1158-1162 [PMID: 19490382 DOI: 10.1111/j.15408167.2009.01494.x]

45 **Kovoor P**, Wickman K, Maguire CT, Pu W, Gehrmann J, Berul CI, Clapham DE. Evaluation of the role of I(KACh) in atrial fibrillation using a mouse knockout model. *J Am Coll Cardiol* 2001; **37**: 2136-2143 [PMID: 11419900 DOI: 10.1016/S0735-1097(01)01304-3]

46 **van der Velden HM**, Ausma J, Rook MB, Hellemons AJ, van Veen TA, Allessie MA, Jongsma HJ. Gap junctional remodeling in relation to stabilization of atrial fibrillation in the goat. *Cardiovasc Res* 2000; **46**: 476-486 [PMID: 10912458 DOI: 10.1016/S0008-6363(00)00026-2]

47 **Bagwe S**, Berenfeld O, Vaidya D, Morley GE, Jalife J. Altered right atrial excitation and propagation in connexin40 knockout mice. *Circulation* 2005; **112**: 2245-2253 [PMID: 16203917 DOI: 10.1161/CIRCULATIONAHA.104.527325]

48 **Girmatsion Z**, Biliczki P, Bonauer A, Wimmer-Greinecker G, Scherer M, Moritz A, Bukowska A, Goette A, Nattel S, Hohnloser SH, Ehrlich JR. Changes in microRNA-1 expression and IK1 up-regulation in human atrial fibrillation. *Heart Rhythm* 2009; **6**: 1802-1809 [PMID: 19959133 DOI: 10.1016/j.hrthm.2009.08.035]

49 **Lu Y**, Zhang Y, Wang N, Pan Z, Gao X, Zhang F, Zhang Y, Shan H, Luo X, Bai Y, Sun L, Song W, Xu C, Wang Z, Yang B. MicroRNA-328 contributes to adverse electrical remodeling in atrial fibrillation. *Circulation* 2010; **122**: 2378-2387 [PMID: 21098446 DOI: 10.1161/circulationaha.110.958967]

50 **Olesen MS**, Refsgaard L, Holst AG, Larsen AP, Grubb S, Haunsø S, Svendsen JH, Olesen SP, Schmitt N, Calloe K. A novel KCND3 gain-of-function mutation associated with early-onset of persistent lone atrial fibrillation. *Cardiovasc Res* 2013; **98**: 488-495 [PMID: 23400760 DOI: 10.1093/cvr/cvt028]

51 **Barana A**, Matamoros M, Dolz-Gaitón P, Pérez-Hernández M, Amorós I, Núñez M, Sacristán S, Pedraz Á, Pinto Á, Fernández-Avilés F, Tamargo J, Delpón E, Caballero R. Chronic atrial fibrillation increases microRNA-21 in human atrial myocytes decreasing L-type calcium current. *Circ Arrhythm Electrophysiol* 2014; **7**: 861-868 [PMID: 25107449 DOI: 10.1161/CIRCEP.114.001709]

52 **Luo X**, Pan Z, Shan H, Xiao J, Sun X, Wang N, Lin H, Xiao

L, Maguy A, Qi XY, Li Y, Gao X, Dong D, Zhang Y, Bai Y, Ai J, Sun L, Lu H, Luo XY, Wang Z, Lu Y, Yang B, Nattel S. MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. *J Clin Invest* 2013; **123**: 1939-1951 [PMID: 23543060 DOI: 10.1172/JCI62185]

53 **Yang B**, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. *Nat Med* 2007; **13**: 486-491 [PMID: 17401374 DOI: 10.1038/nm1569]

54 **Slagsvold KH**, Johnsen AB, Rognmo O, Høydal M, Wisløff U, Wahba A. Comparison of left versus right atrial myocardium in patients with sinus rhythm or atrial fibrillation - an assessment of mitochondrial function and microRNA expression. *Physiol Rep* 2014; **pii:** e12124 [PMID: 25168873 DOI: 10.14814/phy2.12124]

55 **Wang Z**, Fermini B, Nattel S. Rapid and slow components of delayed rectifier outward current in human atrial myocytes. *Cardiovasc Res* 1994; **28**: 1540-1515 [DOI: 10.1093/cvr/28.10.1540]

56 **Luo X**, Xiao J, Lin H, Li B, Lu Y, Yang B, Wang Z. Transcriptional activation by stimulating protein 1 and post-transcriptional repression by muscle-specific microRNAs of IKs-encoding genes and potential implications in regional heterogeneity of their expressions. *J Cell Physiol* 2007; **212**: 358-367 [PMID: 17443681 DOI: 10.1002/jcp.21030]

57 **Luo X**, Lin H, Pan Z, Xiao J, Zhang Y, Lu Y, Yang B, Wang Z. Down-regulation of miR-1/miR-133 contributes to re-expression of pacemaker channel genes HCN2 and HCN4 in hypertrophic heart. *J Biol Chem* 2008; **283**: 20045-20052 [PMID: 18458081 DOI: 10.1074/jbc.M801035200]

58 **Li H**, Li S, Yu B, Liu S. Expression of miR-133 and miR-30 in chronic atrial fibrillation in canines. *Mol Med Rep* 2012; **5**: 1457-1460 [PMID: 22407060 DOI: 10.3892/mmr.2012.831]

59 **Callis TE**, Pandya K, Seok HY, Tang RH, Tatsuguchi M, Huang ZP, Chen JF, Deng Z, Gunn B, Shumate J, Willis MS, Selzman CH, Wang DZ. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in mice. *J Clin Invest* 2009; **119**: 2772-2786 [PMID: 19726871 DOI: 10.1172/JCI36154]

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REVIEW

Endocrine hypertension: An overview on the current etiopathogenesis and management options

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Abstract

Endocrine causes of secondary hypertension include primary aldosteronism, pheochromocytoma, cushing's syndrome, hyperparathyroidism and hypo- and hyperthyroidism. They comprise 5%-10% of the causes of secondary hypertension. Primary hyperaldosteronism, the most common of the endocrine cause of hypertension often presents with resistant or difficult to control hypertension associated with either normo-or hypokalemia. Pheochromocytoma, a great mimicker of many conditions, is associated with high morbidity and mortality if left untreated. A complete history including pertinent family history, physical examination along with a high index of suspicion with focused biochemical and radiological evaluation is important to diagnose and effectively treat these conditions. The cost effective targeted genetic screening for current known mutations associated with pheochromocytoma are important for early diagnosis and management in family members. The current review focuses on the most recent evidence regarding causes, clinical features, methods of diagnosis, and management of these conditions. A multidisciplinary approach involving internists, endocrinologists and surgeons is recommended in optimal management of these conditions.

Key words: Primary aldosteronism; Hyperaldosteronism; Adrenal; Adenoma; Pheochromocytoma

Core tip: This is an invited manuscript to present a summary of the most recent information on the etiology, diagnosis and management of endocrine diseases as a cause of secondary hypertension.

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INTRODUCTION

Secondary hypertension, a term used for the hypertension for which there is an identifiable cause, accounts for 10% of all patients with hypertension[1,2]. Endocrine conditions as a cause of secondary hypertension comprise 5%-10% of all patients with hypertension[2]. Although this form of hypertension is rare, identification and treatment of the underlying cause, might lead to the cure or significant improvement of the hypertension, thereby decreasing the cardiovascular risk and morbidities associated with hypertension.

The endocrine conditions causing secondary hypertension are primary aldosteronism, pheochromocytoma, Cushing's syndrome, acromegaly, hyperparathyroidism, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism and renin-secreting tumors. Current evidence shows no benefit of screening for endocrine causes of hypertension in all patients presenting with hypertension. However, it is important to maintain a high index of clinical suspicion based on the knowledge of the clinical features and presentation of these conditions.

In this review, we will focus on the etiopathogenesis, diagnosis and treatment of the most common endocrine causes of hypertension-primary hyperaldosteronsim (PAH) and pheochromocytoma.

PAH

Introduction

PAH is one of the most common causes of secondary hypertension[3]. As such, it is recommended that this condition be considered in the differential diagnosis of patients with uncontrolled hypertension. With the advent of more refined testing, it is widely quoted to account for 5%-13% of the population with age of onset between 30 and 60[3]. A recent prospective study of 1180 patients with newly diagnosed hypertension found a prevalence of primary hyperaldosteronism of 4.8%[4]. PAH is due to either idiopathic hyperaldosteronism (IHA) or due to aldosterone producing adenoma (APA). IHA involves bilateral adrenals and accounts for an estimated 60%-66% of diagnosis. APA, the classic case first discovered by Conn over 60 years ago, is a unilateral adrenal adenoma and makes up the majority of remaining cases of primary hyperaldosteronism (30%-35%)[3,5]. However, the prospective study described above found that the exact make up of what constitutes the majority of primary hyperaldosteronism diagnosis varies depending on access to confirmatory testing, notably adrenal vein sampling (AVS). More patients were diagnosed with bilateral than unilateral disease if there was no access to AVS and vice versa[4]. Thus, depending on access to an academic center with AVS expertise, the prevalence of bilateral *vs* unilateral disease will differ. Additionally, 2% of cases of primary hyperaldosteronism involve a unilateral hyperplasia also known as primary adrenal hyperplasia. This is thought to be a micro or macrondular area of hyperplasia in the zona glomerulosa of the adrenal gland that is limited to only one rather than both adrenals[3]. Further, 2% of patients have a familial hyperaldosteronism syndrome type 1 or 2[3]. Type 1 is glucocorticoid-remediable aldosteronism (GRA) and type 2 familial aldosterone-producing adenoma or IHA[6]. These are further discussed in the section on genetic disorders. The remaining rare categories of aldosterone producers (1%) are adrenocortical carcinoma, or ectopic production of aldosterone such as ovarian or renal source[5,7].

Clinical presentation: The classic patient with primary hyperaldosteronism presents with difficult to control hypertension and hypokalemia. If severe, hypokalemia may be accompanied by muscle weakness, cramping, headaches, palpitations, and polyuria. Hypokalemia may be unmasked with the addition of diuretics. The presentation of hyperaldosteronism varies and many patients may present with hypertension without hypokalemia. A higher index of suspicion is necessary in order to make the diagnosis.

Screening for PAH should be considered for hypertensive patients with the following presentation: hypokalemia, difficult to control hypertension on 3 or more anti-hypertensive drugs or hypertension of $\geqslant$ 160 mmHg systolic and $\geqslant$ 100 mmHg diastolic, or those with hypertension and an incidental adrenal mass, young onset of hypertension, or those being evaluated for other causes of secondary hypertension[3]. The Endocrine Society Guidelines published in 2008 echoed these recommendations adding that screening should also include those with hypertension and diuretic-induced hypokalemia, those with family history of early onset hypertension or stroke at age < 40, as well as all hypertensive patients with a first degree relatives with primary hyperaldosteronism[8].

APA: Patients with APA tend to be younger and present with severe symptoms in terms of degree and frequency of hypertension and hypokalemia, respectively. Biochemical analysis reveals higher plasma levels of aldosterone (> 25 ng/dL plasma aldosterone)[9,10].

Cardiovascular and renal effects: Recent evidence has called attention to the increase of cardiovascular events associated with hyperaldosteronism. Specifically, in a study with case matched patients with essential hypertension, those with hyperaldosteronism had more cardiovascular events and increased left ventricular hypertrophy independent of blood pressure levels[11]. These left ventricle changes appeared to be reversible post adrenalectomy[12].

A recent prospective Italian study > 1100 patients found that urine albumin was significantly increased as compared to patients with essential hypertension, presumably highlighting increased renal damage with

PAH[13].

Diagnosis

The biochemical hallmarks of primary hyperaldosteronism are low potassium, high aldosterone, and low renin. Hypokalemia itself, while helpful in recognizing the disease, is not required, with only 9%-37% of patients presenting with hypokalemia[14]. Normal potassium cannot rule out hyperaldosteronism as some patients with primary hyperaldosteronism will have normal potassium levels[15]. Additionally, most patients with hypertension who have hypokalemia do not have PAH[16]. Low renin and elevated aldosterone are hallmarks. However, low renin on its own can be found in patients taking beta-blockers, high sodium intake, steroids, licorice or with low renin essential hypertension[16]. Further, plasma and urine aldosterone levels are subject to confounders including incomplete urine assays, influence of hypokalemia and diurnal variation[16].

The diagnosis for primary hyperaldosteronism traditionally includes the following 3 steps: (1) screening; (2) confirmation; and (3) diagnosis of subtype[3,8]. Debate over exact cutoffs for screening, the need for confirmatory testing and the best way to distinguish APA from other subtypes is ongoing.

Screening: Initial screening of patients suspected to have hyperaldosteronism should be conducted with a morning (preferably 8-10 am) plasma aldosterone and renin values. For proper interpretation, aldosterone and renin testing should be performed in the morning on a seated ambulatory patient[8]. Though plasma aldosterone to renin ratio is considered a screening test, some physicians forgo additional lab testing once this screen is obtained[17]. It is important to note, however, that debate exists over the exact cutoffs for the ratio, with a recent study finding a ratio of 32 ng/mL per hour[18]. Some experts advocate for the use of both a ratio and an aldosterone level. For example, using a plasma aldosterone to plasma renin activity ratio of more than 30 ng/mL per hour and a plasma aldosterone of more than 20 ng/dL combination is 90% sensitive and 91% specific, with a positive predictive value of 69% and negative predictive value of 98%[16]. Physicians need to be aware that false positives and negatives do occur[19]. Testing in general is affected by medications (including many anti-hypertensive, oral contraceptives, and selective serotonin reuptake inhibitors), renal function, upright posture, age, sex and pregnancy[19,20]. Thus, tests should be interpreted with caution and in many cases repeated to confirm results. Additionally, biochemical results may be laboratory and assay dependent. There exists variability in assays and units used in reporting various cut offs[8,20]. Further, laboratories measuring renin must be able to detect renin at its lowest range; this has been found to be a limitation of some laboratories[8]. It is critical that providers become familiar with their own laboratories units and measurement assays while interpreting their results.

Impact of medications on screening: Ideally, hypertensive drugs interfering with renin and aldosterone measurements should be discontinued at least 2 wk prior to laboratory testing. However, for those patients with severe hypertension who are on multiple anti-hypertensives, this may not be safe and tolerable. Several studies suggest that anti-hypertensives need not be discontinued for screening[15,21], but the debate continues. Experts in the field suggest that if discontinuation of all antihypertensive medications is not feasible because of the concern of patient safety, providers should discontinue mineralocorticoid receptor antagonist such as spironolactone, eplerenone and amiloride for at least 4 wk prior to testing and use other medications to control hypertension[8]. The Endocrine Society practice guidelines suggest the following medications (verapamil, hydralazine, prazosin hydrochloride, doxazosin and terazosin) as alternatives during screening because of their minimal impact on screening assays[8].

Confirmatory testing: While an increased ratio of plasma aldosterone to plasma renin is highly suggestive of the diagnosis, some experts advocate for confirmatory testing. For patients with severe cardiac or renal disease, confirmatory testing may not be advised. Currently there are no gold standard confirmatory tests[8]. The Endocrine Society guidelines suggest the following as potential confirmatory test: oral sodium loading test, saline infusion test, fludrocortisone suppression test, and the captopril challenge test[8]. The selection of a confirmatory test should be based on cost, time, morbidity and conflicting data on sensitivity and specificity of the test[17].

A recent study in Japan of 120 cases examined the diagnostic relevance of captopril challenge and saline infusion testing to confirm positive screening test and concluded that most patients with positive screens also had positive confirmatory testing. The study challenges the point that not all cases may require confirmatory testing to establish the diagnosis[22].

Salt loading test is one of the most commonly used confirmatory tests. Once blood pressure is stable and potassium is replete, the patient is given oral salt tablets for 3 d. Subsequently, a 24 h urine aldosterone is measured. Careful monitoring of blood pressure and potassium is required. The test is considered positive when the 24 h urine aldosterone level is > 12 μg/24 h or 33 nmol/d with a concomitant 24 h urine sodium excretion of > 200 mmol/d (approximately 6 g/d). This test provides > 90% sensitivity and specificity[23].

Intravenous saline infusion test involves the infusion 2 L of normal saline over 4 h after an overnight fast and drawing plasma aldosterone level post infusion. Plasma aldosterone levels above 10 ng/dL or 277 pmol/L (as compared to less than 5 ng/dL or 139 pmol/L for controls) is considered confirmatory for a diagnosis of primary hyperaldosteronism[24].

The fludrocortisone suppression test and the captopril challenge test are not widely used in clinical practice due to cardiovascular concerns, the need to follow the patient closely during the test, challenges in interpreting the results, and risk for false negative and equivocal results[25].

Imaging modalities

Localization of the source of primary hyperaldosteronism is key to the treatment. Only unilateral adenomas or APA are treated with surgery. Imaging helps to distinguish between unilateral *vs* bilateral disease. Recent research has focused on how to best utilize computerized tomography (CT) scan *vs* AVS in order to correctly identify those patients who may potentially be cured with surgery[5,26,27].

CT imaging: Adrenal CT imaging alone cannot reliably distinguish a unilateral source of hyperaldosteronism, especially in older patients[5,9]. In a prospective study of 203 patients with primary hyperaldosteronism selected for AVS, CT scan could identify unilateral *vs* bilateral aldosterone source in about half (53%) of the cases[5]. CT can also creates confusion if it reveals normal adrenals, bilateral large nodules or bilateral small < 1 cm adrenal nodules[26]. Specifically, a small growth noted on adrenal gland with another on the other may be falsely categorized a patient as having bilateral hyperplasia whereas in reality the smaller growth is non-functioning and the patient has a unilateral adenoma that warrants referral for surgery[5].

Traditionally, unilateral adenomas appear as small nodules < 2 cm in diameter and are hypodense. In contrast, it should be noted that adrenal carcinomas are usually > 4 cm in diameter and are heterogenous on CT scan. IHA can appear as bilateral nodules on CT scan. However, sometimes, the CT scan can be read as normal. Given the caveats of adrenal CT scans, imaging must often be combined with other test modalities with most favoring AVS for biochemical confirmation of laterality prior to surgical intervention.

Scintigraphy: Scintigraphy iodomethyl-nor-cholesterol (NP-59) uptake also known as dexamethasone-suppression DS adrenal scintigraphy can be considered for adenomas > 1.5 cm in diameter. However, a definitive distinction of unilateral *vs* bilateral source of aldosterone cannot be made as tracer uptake for the most part correlates with tumor volume and less so with tumor secretion[28]. This imaging is not useful in cases with microadenomas. Imaging with scintigraphy does not reliably replace adrenal venous sampling in characterizing nodule function[28].

AVS: Selective AVS is the most reliable technique used to distinguish a true unilateral adenoma (APA) from bilateral disease notably IHA[29]. AVS is critical in categorizing certain patients correctly. In a prospective study of 203 patients selected for AVS to determine if the diagnosis could be made based solely on CT showed that 48 patients (24.7%) would have had inappropriate surgery and 42 patients (21.7%) would have been denied needed for surgery based on CT scan results alone[5]. AVS may be helpful for patients when adrenal CT is normal, shows micronodularity (unilateral or bilateral < 1 cm) or a combination of micro and macronodules[5,26]. In a recent radiological study, matching patients who underwent CT *vs* CT and AVS found that for tumors larger than 1 cm, CT can reliably predict unilateral disease and thus obviate the need for AVS. This study concluded that AVS is helpful when CT study is equivocal or shows bilateral disease[27]. An algorithm based partly on age of more or less than age 40, together with the nodule's appearance, size and uni-laterality as seen on CT scan may best guide next steps, including referral for AVS[26]. Based on this algorithm, it should be noted that patients younger than age 40 with a unilateral hypo-dense nodule > 1 cm on adrenal CT scan who have a very high probability of unilateral adenoma may proceed to surgery without AVS[26]. An expert consensus statement has defined the following exceptions to recommending AVS: age < 40 years with marked PA and a clear uni-lateral adrenal adenoma and a normal contralateral adrenal gland on CT, unacceptable high risks of adrenal surgery (*i.e.*, due to multiple comorbidities), those with suspected adrenocortical carcinoma and those with proven Familial Hyperaldosteronism-Ⅰ or with Familial Hyperaldosteronism-Ⅲ[30].

In AVS, adrenal veins are accessed *via* the femoral vein. Blood samples are taken from both adrenal veins and compared to that found in the inferior vena cava (IVC) at the level below the renal veins. The right adrenal vein may be particularly challenging to access. The left adrenal sample is accessed from the inferior phrenic vein next to the adrenal vein[5]. During the study, cosyntropin or ACTH is infused throughout the procedure to minimize fluctuations in aldosterone levels due to stress[26]. Using a radioimmunoassay, aldosterone and cortisol concentrations of the right and left adrenal glands as well as the IVC are measured. To account for dilution, the aldosterone concentration is then corrected using cortisol so that an aldosterone/cortisol ratio is obtained. The ratios of aldosterone to cortisol from each side are then compared[5]. Traditionally, the cut off for distinguishing a unilateral source of aldosterone is a lateralization ratio of > 5[31]. However, a recent study found a lateralization ratio of more than > 4 as indicative of APA[5]. Others suggest a cortisol-corrected aldosterone ratio from high side to low side more than 4:1 is indicative of unilateral aldosterone excess; a ratio less than 3:1 is suggestive of bilateral aldosterone hypersecretion[8].

There are several complications that may occur during AVS. These can be as high as 5%. These complications are: groin hematoma, adrenal hemorrhage, dissection

of adrenal vein and paroxysmal atrial fibrillation. Theoretically, Addisonian crisis could also occur[5]. There is a major limitation of AVS including the access to institutions that perform this specialized, highly skilled procedure. A recent international study of AVS, found that many referral centers worldwide, do not use AVS[32], mainly because of lack of skilled professionals with experience conducting the procedure. In a recent study, the failure rate of AVS was low at 4.4%. However, the study relied on one angiographer to perform the vast majority of procedures[5]. In general, the failure rate can be greater than 25%[33].

Management

Medical management: Medical management should be provided to all patients with demonstrated bilateral disease. Additionally, medical management is an option for patients with unilateral disease who do not undergo surgery. It has been noted that those with IHA are more likely to require multi drug treatment as compared to APA[34].

The main stay of treatment of PAH is spironolactone, a competitive aldosterone receptor antagonist[34]. Spironolactone should be started in patients without contraindications. The starting dose is 12.5-25 mg per day. It is recommended that the prescribing provider follow the patient's blood pressure and potassium levels closely. The follow up should be close for the first couple of weeks after starting this medication. Spironolactone should be titrated slowly until blood pressure is controlled to a maximum dose of 100 mg per day[8]. Spironolactone has multiple side effects that may affect quality of life particularly for male patients, the most notable side effect being gynecomastia. In general, side effects as noted by patients may include breast tenderness, breast engorgement, decreased libido, muscle cramps, erectile dysfunction, menstrual irregularities and loss of axillary hair[35].

Eplerenone, a selective aldosterone receptor antagonist, has fewer side effects as compared to spironolactone but is more costly. Due to minimal affinity for the androgen, estrogen and progesterone receptors, this drug does not result in significant androgen effects such as gynecomastia that is associated with spironolactone. In a small study comparing, blood pressure in patients with bilateral IHA, eplerenone dosed at 50-400 mg per day was shown to be just as effective as spironolactone. Furthermore, 2 patients had gynecomastia reversed by switching from spironolactone to eplerenone[34]. In a recent prospective study evaluating long term follow up of patients and renal function, they included: adrenalectomy (86 cases), eplerenone (18 cases) and spironolactone (65 cases), spironolactone was just a good at preserving Glomerular Filtration Rate (GFR) and urine albumin excretion as patients who had an adrenalectomy, however patients on eplerenone required on average more anti-hypertensive medications[36]. The starting dose for eplerenone is 25 mg per day or twice a day. Both, spironolactone and eplerenone, should be used with caution in patients with chronic kidney disease stage 3 because of the risk of hyperkalemia. They should be avoided in patients with end stage renal disease and chronic kidney disease stage 4. Amiloride, a sodium channel blocker can also correct hypokalemia and improve blood pressure without the side effects of spironolactone. Muscle cramps have been noted as side effect[35].

Calcium channel blockers can decrease aldosterone secretion and have variable success at lowering blood pressure. Angiotensin converting enzyme inhibitors may also improve blood pressure. It is postulated that IHA would be more responsive to treatment since APAs are autonomous and would therefore be less likely to respond to angiotensin Ⅱ. Angiotensin Ⅱ inhibitors have a role as additional agents in treatment[37]. In a small study looking at long term follow up of patients with APA who chose medical therapy, with a follow up time between 5-17 years, blood pressure was at goal for 75% of participants. The majority patients (n = 24) were receiving a potassium-sparing diuretic plus an additional blood pressure medication. All had resolution of hypokalemia. In the time of follow up, none had a malignant transformation and none experienced stroke, myocardial infarction or heart failure[35].

Surgery: Once potassium and blood pressure are controlled, laparoscopic adrenalectomy is indicated for unilateral source of aldosteronism. AVS should be considered prior to surgery as discussed in detail above. The laparoscopic approach is preferred because it offers faster recovery from surgery with associated shorter length of stay and lower morbidity[38].

A recent study, found that adrenalectomy (the majority of which was done laparoscopically) did have lower overall medical costs compared to medical treatment[39]. Further, surgery for APA has been shown to normalize hypokalemia and improve if not normalize blood pressure. In one third to half of patients it can offer a cure by normalizing blood pressure[40].

In contrast, for bilateral disease or IHA, unilateral or bilateral adrenalectomy is not indicated. Surgery for IHA in general does not correct the hypertension. In some select cases of bilateral disease, those with poorly controlled hypertension on more than three drugs, with incomplete lateralization on AVS, a unilateral adrenalectomy may be considered. In some cases, blood pressure may improve and the patient may be able to take fewer anti-hypertensive drugs post surgery[5,41].

Surgical outcome and post-operative follow up: Thirty to 60% of patients with a unilateral aldosterone tumor can be cured and achieve normal blood pressure after surgery. However, many may still require at least one blood pressure medication post surgery[42].

In general, mineralocorticoid receptor antagonist and potassium supplements are discontinued post

op. During the first month post surgery a generous salt diet is encouraged to stimulate the contralateral adrenal gland. Blood pressure normalizes within 6 mo but can take up to one year post surgery[42]. Patients that are more likely to have persistent hypertension despite adrenalectomy include: older age, chronic hypertension > 5 years, larger tumor size, significant family history of hypertension and those with additional secondary hypertension[40,43-47]. Also, one study found that higher creatinine levels also predicts persistent hypertension post surgery[48].

Recently, a score card of low, medium or high likelihood of hypertension resolution post surgery was recently developed using a predictive regression model that compiled data from 100 patients with primary hyperaldosteronism who underwent adrenalectomy. Based on 4 predictors: ⩽ 2 or fewer anti-hypertensive drugs (2 points), body mass index ⩽ 25 kg/m^2 (1 point), hypertension of ⩽ 6 years (1 point) and female sex (1 point), the likelihood of a cure was low (27% cured), medium or high (75% cured)[49]. Using data from 91 Japanese patients, this score card was validated in an Asian population[50].

PAH and associated genetic disorders: A minority of patients (1%-2%) with PAH have a familial syndrome type Ⅰ or Ⅱ. Type Ⅰ is GRA and type Ⅱ familial aldosterone-producing adenoma or IHA[6]. Recently, a new genetic form, familial hyperaldosteronism type Ⅲ has also been identified[51].

Type Ⅰ (GRA) is an autosomal dominant condition characterized by variable degree of aldosterone excess, increased steroids (18-hydroxycortisol and 18-oxocortisol), and suppression of disease with glucocorticoid treatment. It is due to a chimericic gene duplication between the CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase) genes. Genetic testing should be targeted to those with hypertension at age < 20 that is resistant, accompanied by hypokalemia, family history of hypertension, and cerebral hemorrhage at a young age[52]. The Endocrine Society guidelines recommend genetic testing to rule out GRA for those patients who have onset of hypertension at age < 20, and those with a family history primary hyperaldosteronism or stroke at age < 40[8].

Type Ⅱ familial hyperaldosteronism is an autosomal dominant condition that does not suppressed with exogenous glucocorticoids and has been linked to locus 7p22[6]. Type Ⅲ familial hyperaldosteronism involves a germline mutation in the gene coding for ion channel KCNJ5[51].

Conclusion

Primary hyperaldosteronism is found in 5%-13% of population[3] Prevalence has increased with the advent of more refined screening and confirmatory studies. However, specific screening cutoffs vary by institution. The majority of patients fall into one of two categories: APA, which is unilateral and should be surgically removed, and IHA which is bilateral and requires medical management.

The cost and morbidity of chronic medication, as well as new evidence that hyperaldosteronism itself aside from blood pressure may increase cardiac events and possibly renal dysfunction, needs to be considered. AVS is the most reliable technique used to distinguish a true unilateral adenoma (APA) from bilateral disease notably IHA. However, this procedure is highly specialized and is not available at every institution. With the advent of safe, less invasive, and shorter surgery, laparoscopic adrenalectomy for APA is preferred as it offers the best chance for a cure.

PHEOCHROMOCYTOMA

Introduction

Pheochromocytoma is a tumor of the adrenal medulla (chromaffin cells) that secretes excess catecholamines, epinephrine, norepinephrine, and dopamine. Paraganglioma is a tumor derived from extra-adrenal chromaffin cells of the sympathetic nervous system. Pheochromocytomas and catecholamine secreting paragangliomas account for 0.2%-0.6% of all causes of hypertension in the population[53-55]. Both of these tumors have similar clinical presentations and management. However, it is important to classify them separately because of the implications of genetic testing, risk of malignancy and associated neoplasms. In this review, we will focus mainly on pheochromocytomas arising from the adrenal gland.

Clinical presentation

Pheochromocytoma is often referred as the great mimicker of other conditions. The average age of presentation of pheochromocytoma is approximately 40-50 years with equally distribution between men and women[56]. Patients can present with different symptoms that can vary greatly between patients as well as within family members in familial syndromes associated with pheochromocytoma. The classic triad for pheochromocytoma: episodic headache, sweating and tachycardia are not always present in most patients[57,58]. The most common sign, found in about 80%-90% of patients with pheochromocytoma, is hypertension[59].

Types of hypertension in pheochromocytoma[54,60]: (1) Sustained hypertension - found in about 50% of the patients with pheochromocytoma; (2) Paroxysmal hypertension - found in 45% of the patients; and (3) Normotension in 5%-15% of the patients.

The type of hypertension is often dependent on the pattern of catecholamine secretion from the tumor - which is either continuous, episodic or both. There is an inversion of the circadian BP rhythm and increased blood pressure variability due to high circulating levels of catecholamines[61].

Paroxysm or "spell" can be triggered by physical activity (exercise or postural changes) as well as from tumor manipulation[60]. In addition, the biochemical phenotype of the tumor, *i.e.*, type of catecholamine secreted influences the type of hypertension. Patient with high levels of norepinephrine and epinephrine more likely have sustained hypertension while patients with high levels of dopamine are often normotensive[62,63]. Orthostatic hypotension may occur more commonly in patients with sustained hypertension than in those with paroxysmal and normotensive hypertension. The mechanism for orthostatic hypotension is thought to be due to decreased blood volume caused by persistent vasoconstriction and diminished sympathetic reflex[64].

Characteristic symptoms include headache (90% of symptomatic patients), pallor and anxiety, feeling of doom, generalized sweating, fever, nausea or vomiting. Rarely secondary erythrocytosis, new onset diabetes mellitus and isolated dilated cardiomyopathy are associated with pheochromocytoma[57,65-68].

Pheochromocytomas represent one of the main causes of hypertensive crisis in the hospital. These crises are precipitated by postural changes, physical stress, surgery and invasive procedures in undiagnosed patients. Further, it can be precipitated by the use of medications such as corticosteroids, histamine, metoclopramide, phenothiazines, tricyclic antidepressants or anesthetic agents[69]. The clinical presentation during a crisis will depend on the effect of the catecholamine release on the target organs[65].

Diagnosis

Clinicians should keep a high index of clinical suspicion in young adults (< 25 years) with new-onset hypertension, people with clinical features typical of pheochromocytoma, a history of resistant hypertension, an incidental adrenal adenoma, severe hypertension during general anesthesia or during sedation, idiopathic cardiomyopathy and in patients with a family history of pheochromocytoma.

The cornerstone for diagnosis of pheochromoctyoma is the measurement of urine and plasma fractionated metanephrines. Most pheochromocytomas have fluctuating levels of catecholamines, but the metabolism of catecholamines into metanephrines is constant[57,70,71].

There is no consensus regarding the "best test" for diagnosis. However, most endocrinologists favor choosing the best test based on the degree of clinical suspicion. If clinical suspicion is high (family history, genetic syndrome, past history of pheochromocytoma, positive adrenal gland imaging characteristics) then plasma fractionated metanephrines are measured (sensitivity is 96%-100% and specificity 85%-89%)[71-73]. If clinical suspicion is low (resistant hypertension, hyperadrenergic spells, no classical imaging characteristics of adrenal gland), then 24-h urinary fractionated catecholamines and metanephrines (sensitivity 98% and specificity 98%) should be measured[72,74,75]. Twenty-four hour urinary creatinine should be measured simultaneously with urinary metanephrines to confirm that urine collection is completed[76]. For plasma metanephrines measurement, blood sample collection in the supine position is recommended after 30 min in recumbent position before sampling[76]. If the blood sample collection is obtained in a seated position, the clinician should be aware of the potential for false positive result from sympathoadrenal activation of the upright position[77,78]. In patients with positive test results from seated sampling, repeat testing with samples obtained in supine position might be necessary[76]. The reference interval of plasma metanephrines should be used as established in the same position of blood draw to avoid the inaccurate interpretation. Caffeine intake and medications that interfere with the catecholamine or metanephrine levels should be avoided at least 24 h before the diagnostic work up for pheochromocytoma[79,80].

Imaging modalities

CT imaging: Adrenal pheochromocytomas with a size larger than 0.5 cm as well as metastatic pheochromocytomas can be detected by CT scan with high sensitivity of 85%-94% (Figure 1)[81]. Ninety-five percent of tumors are within the abdomen and pelvis and 10% of tumors are extra-adrenal[68]. Pheochromocytomas have a varied appearance on a non-contrast CT ranging from low density to soft-tissue attenuation. An attenuation threshold of 10 Hounsfield units (HU) on a non-contrast CT has a sensitivity of 71% and a specificity of 98% to differentiate a benign from malignant tumor[82]. Approximately two thirds of pheochromocytomas are solid and the rest are complex or cystic[83]. Hemorrhage and calcifications in a pheochromocytoma can be found in approximately 10% of all pheochromocytomas and it may increase the density of the pheochromocytoma[83]. CT with low-osmolar contrast is safe in patients with pheochromocytoma not on alpha-or beta-blockers[84]. Pheochromoctyomas can show either homogenous or variable enhancement (depending on the solid and cystic components) on contrast enhanced CT scan. The characteristic appearance seen on contrast CT scan of a pheochromocytoma include increased contrast uptake (40-50 HU) with delayed washout with necrosis and calcifications[81,85].

Magnetic resonance imaging: Magnetic resonance imaging (MRI) are more expensive and lacks the spatial resolution offered by CT scan. The classical imaging description for pheochromocytoma is a "light bulb" bright lesion on T2-weighted imaging comparable to signal intensity of CSF in 11%-65% of pheochromocytomas[86,87]. This variability in the appearance on T2-weighted imaging is due to the water content present in cystic or necrotic components of the tumor. T1-weighted imaging of pheochromocytomas are typically isointense to muscle and hypointense to liver[81]. MRI gadolinium enhancement on MRI is variable

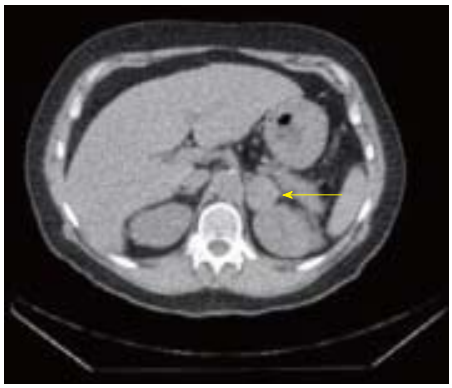

Figure 1 Computerized tomography scan of the abdomen demonstrating left adrenal nodule 3.5 cm.

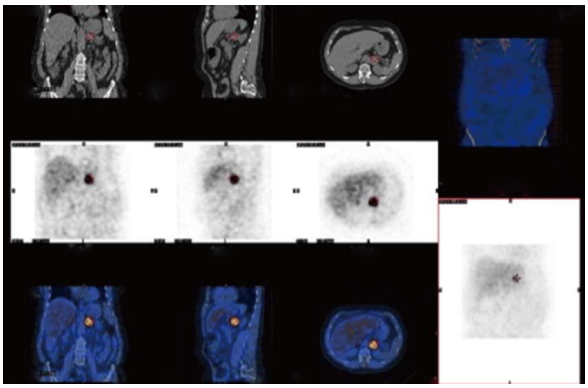

Figure 2 I-123-metaiodobenzylguanidine-SPECT images demonstrated focal increased tracer activity in the left adrenal nodule compatible with metaiodobenzylguanidine avid tumor.

depending on the presence of cystic-necrotic areas, which do not enhance[88].

Functional imaging is indicated in-patient with large (> 10 cm) adrenal pheochromocytomas, extra-adrenal pheochromocytomas, metastatic disease and tumor recurrence assessment. Functional imaging examinations are performed using ^{131}I- and ^{123}I-metaiodobenzylguanidine (MIBG) (Figure 2), ^{111}In-pentetreotide (Octreoscan, Covidien), and several PET ligands including ^{18}F-fluorodopamine, ^{18}F-dihydroxyphenylalanine (DOPA), and ^{18}F-FDG (FDG)[81,89]. FDG-PET is more sensitive than ^{123}I-MIBG and CT/MRI for detection of metastatic disease[90,91].

Management

Pre-operative management: A detailed history, physical examination and cardiac evaluation of patients is necessary as part of the preparation for surgery.

Medical management: Appropriate and optimal pharmacological therapy to block the effects of released catecholamines, is of critical importance in the pre-operative phase of the surgical management of pheochromocytoma[92]. The main goals for therapy includes: normalization of blood pressure, heart rate, restores volume depletion and prevention of intraoperative hypertensive crisis.

Phenoxybenzamine (Dibenzyline), a long lasting, non-selective, irreversible, and noncompetitive alpha-receptor blocker. This medication reduces blood pressure fluctuations, eases vasoconstriction and prevents intra-operative hypertensive crisis[93]. Phenoxybenzamine is usually started at a dose of 10 mg twice a day with increments of 10-20 mg every 2-3 d until clinical symptoms from pheochromocytoma are controlled or side effects of the medication appears, which usually takes 7-14 d. Maximum dose is 1 mg/kg per day[76]. The side effects of this medication are postural hypotension with reflex tachycardia, dizziness, syncope and nasal congestion. Selective, competitive, short-acting alpha-blockers like doxazosin (Cardura), prazosin (Minipress) and terazosin (Hytrin) are preferred in some institutions as they are associated with less reflex tachycardia and a lower incidence of postoperative hypotension as compared to phenoxybenzamine. However, because of the short half life of these selective alpha-1 blockers, these medications should be given on the morning of the surgery. In a study, comparing the use of these different classes of alpha blockers in the preoperative management of laparoscopic resection of pheochromocytoma, phenoxybenzamine use was associated with better decrease in intra-operative hypertension at the expense of prolonged post-operative hypotension requiring the use of vasopressors. In contrast, patients treated with doxazocin had no clinically significant differences in post surgical outcomes[94].

Once optimal α-blockade is achieved, β-blockers are used for the management of catecholamine-induced tachyarrhythmias. These medications should not be used in the absence of α-blockers as they will exacerbate epinephrine-induced vasoconstriction by blocking the vasodilator component (β2). The most commonly used β-blockers are the non-selective β-receptor blocker propranolol (Inderal LA) (20-40 mg - 3 times a day) and the cardio selective β-1 blockers atenolol (Tenormin) (25-50 mg per a day)[76].

Calcium channel blockers are the second line anti-hypertensive medications use to supplement α-blockers[95]. They block norepinephrine mediated calcium influx into vascular smooth muscle and help in controlling hypertension and tachyarrhythmia. In addition, they might prevent catecholamine induced coronary vasospasm[96,97]. The calcium channel blockers used are amlodipine (Norvasc) in a dose of 10-20 mg, nicardipine (Cardene) in a dose from 60-90 mg per day, nifedipine SR (Adalat) in a dose of 30-90 mg and verapamil ER (Isoptin SR, Calan SR) in a dose from 180-540 mg per day[98].

Metyrosine (alpha-methyl-para-tyrosine, Demser) is an analog of tyrosine that is a competitive inhibitor of tyrosine hydroxylase, the rate limiting enzyme in catecholamine biosynthesis. Metyrosine is added to α- and β-blockers in patients with extensive metastatic

disease or large tumor burden[99]. This medication incompletely depletes the catecholamine stores after 3 d of treatment. The recommended dose in all surgical candidates is 250 mg orally every 8-12 h with increments of dose by 250 to 500 mg every 2-3 d up to a total of 1.5 to 2 g per day. The medication is usually initiated 1-3 wk prior to surgery[98]. Metyrosine helps to control blood pressure during induction of anesthesia and surgical manipulation of the tumor[100,101]. The side effects of this medication include depression, anxiety, sedation, extra-pyramidal signs, crystalluria and galactorrhea[102].

Optimizing cardiovascular function prior to surgery with normalization of blood pressure 10-14 d prior to surgery, initiating a normal or high-salt diet (usually 3 d after alpha-blockers are initiated) and expansion of blood volume by initiating pre-operative isotonic intravenous fluids minimizes protracted post-operative hypotension or shock from sudden diffuse vasodilatation at time of tumor removal[98]. In patients with resistant hypertension or hypertensive crisis, sodium nitroprusside or phentolamine infusion, can be used preoperatively.

Intra-operative management: The intra-operative management of hypertension or hypertensive crisis along with prevention of postoperative hypotension is important for successful and safe surgical resection of pheochromocytoma. Nitroprusside (Nitropress), an intravenous vasodilator is the preferred medication for intraoperative control of hypertension due to its rapid onset and short duration of action. Nicardipine (Cardene) is a calcium channel blocker that may be used as an alternative. Intravenous magnesium sulfate is used in some centers, in a dose of 40-60 mg/kg before intubation followed by an infusion of 2 g/h. Magnesium sulfate inhibits catecholamine release, enhances vasodilatation, blocks catecholamine receptors and stabilizes the myocardium from arrhythmias[103].

Surgery: Surgical resection is the only curative treatment of pheochromocytomas. Laparoscopic adrenalectomy is a well-established approach in intra-adrenal pheochromocytomas 6 cm or less in diameter, with no malignant features. This approach has been shown to improve surgical outcomes, reduced hospital stay and is better for patient comfort and recovery time compared to open adrenalectomy[104,105]. Laparoscopic adrenalectomy is also often used in tumors above 6 cm in diameter but often these procedures are converted to open procedure intraoperative[106,107]. More recently, experienced surgeons have preferred retroperitoneal endoscopic approach for adrenalectomy, as this provides direct access to the adrenal glands without requiring mobilization of adjacent organs (liver or pancreas), better in bilateral tumors and avoid repositioning as compared to the transabdominal approach[108,109].

Postoperative management: Potential postoperative complications after pheochromocytoma resection include tachyarrhythmias, splenic injury (left sided lesions), renal impairment, hypoglycemia and persistent hypotension. These complications have been shown to correlate with preoperative systolic blood pressure, urinary metanephrines and tumor size[110,111]. Postoperative hypoglycemia is related to catecholamine-induced depletion of glycogen stores, overstimulation of insulin production by pre-operative α-blockade and hyperinsulinemia after loss of catecholamine inhibitory effect on the β2-receptors of the pancreatic islet cell[112,113].

Hemodynamic and blood glucose monitoring with optimal blood pressure, tachyarrhythmia's and intravenous fluids (including glucose) are critical for a smooth postoperative course.

Surgical outcome and post-operative follow up: Surgical removal of pheochromocytoma does not always lead to a long-term cure of hypertension. Some studies report 80% of patients may become normotensive. However, postoperative hypertension may persist due to residual tumor, metastatic disease or intra operative injury to the renal artery or most commonly due to acquired renovascular changes due to pre-operative hypertension.

Plasma fractionated catecholamines or urinary metanephrines should be measured two weeks after surgery, and thereafter every three months for the first year and then annually. Regular blood pressure monitoring and optimal management of hypertension should be done.

Pheochromocytoma and associated genetic disorders: Most of the pheochromocytomas are sporadic although 15%-20% of patients with pheochromocytoma have an associated familial disease. These patients tend to have bilateral adrenal pheochromocytomas or have paragangliomas. The frequency of pheochromocytomas in some of the autosomal dominant familial disorders are 10% to 20% in Von Hippel-Lindau syndrome, 50% in Multiple endocrine neoplasia type 2, and 0.1% to 5.7% in neurofibromatosis type 1. Genetic testing should be considered if a patient has bilateral pheochromocytomas, onset less than 45 years, paragangliomas, family history of pheochromocytomas or clinical findings with strong evidence for hereditary syndrome[114,115]. A sequential genetic testing algorithm, based on these findings, tailored for cost efficacy has been proposed[116].

Pheochromocytoma and pregnancy: Pheochromocytoma is a rare cause of hypertension in pregnancy with a frequency of 0.002% of all pregnancies and untreated it carries a high maternal and fetal mortality of around 50%[117]. Early detection and proper treatment during pregnancy decrease the maternal and fetal mortality to < 5% and 15% respectively. The clinical features of pheochromocytoma in pregnancy are similar to non-pregnant patients. The characteristics of

Table 1 Key clinical features, screening and confirmatory tests, radiological and management modalities for primary aldosteronism and pheochromocytoma

	Primary aldosteronism	Pheochromocytoma
Clinical features	Difficult to control HTN	
Common Symptoms	on 3 or more hypertensive agents	Episodes or paroxysmal hypertension
		Headache
	Young age of onset of HTN	Sweating
		Palpitations
Signs	With or without hypokalemia	
	Asymptomatic *vs* Symptomatic	Hypertension
	Muscle weakness, cramping, headaches, palpitations, and polyuria	Tachycardia
		Orthostatic hypotension
		Heart failure
Screening tests	AM plasma aldosterone to renin ratio > 30	24-h urine fractionated metanephrines
	+/- Aldosterone > 20 ng/dL	Plasma fractionated metanephrines (high suspicion)
Confirmatory tests	Oral sodium loading test with 24 h aldosterone level > 12 μg/24 h	Same as above
	Saline infusion test	
	Fludrocortisone suppression test	
	Captopril challenge test	
Radiology	Adrenal protocol CT	Adrenal protocol CT/MRI
	+/- Scintigraphy	^{123}I-MIBG scan/^{111}In-pentetreotide/FDG-PET
	Adrenal vein sampling	
Treatment	For bilateral disease (or for those with unilateral disease who are unable to undergo surgery)	Pre-op preparation (10-14 d prior to surgery)
Medical		Phenoxybenzamine
	Spirinolactone (best choice)	Alpha-blockers blockers-Doxazocin, Prazocin or Terazocin
	Eplerenone	Calcium channel blockers
	Amiloride	Beta-blockers
		Metyrosine
Surgical	For unilateral source of aldosteronism: Laparoscopic adrenalectomy	Laparoscopic/retro-peritoneal adrenalectomy of adrenal pheochromocytoma

CT: Computed tomography; MRI: Magnetic resonance imaging; FDG-PET: Fluorodeoxyglueose-positron emission tomography.

hypertension that should lead to a clinical consideration of pheochromocytoma are severe hypertension diagnosed in the first and second trimesters, uncontrolled hypertension in the third trimester, unexplained postural hypotension or cardiogenic shock in the antepartum period. Plasma free metanephrines and urinary fractionated metanephrines assessment are the first recommended tests in the diagnostic workup. MRI without gadolinium as well as ultrasonography is imaging modalities of choice. Pre-operative management is similar to non-pregnant adults. Laparoscopic adrenalectomy is the surgery of choice in the first 24 wk of gestation. If the tumor is diagnosed in the third trimester, the patient should be managed until the fetus is viable with medication management and caesarean section with tumor removal in the same session or at a later stage is then preferred since vaginal delivery is possibly associated with higher mortality[117].

Conclusion

In summary, both primary hyperaldosteronism and pheochromocytoma are important causes of endocrine hypertension that carry significant mortality and morbidity, if left untreated. A high index of clinical suspicion, a systematic approach to diagnosis, localization and management of both these conditions is important. Personalized approach with multidisciplinary team of internists, endocrinologists and surgeons is recommended in optimal management of these conditions.

Key clinical features, investigations and management modalities of primary hyperaldosteronism and pheochromocytoma are summarized in Table 1.

REFERENCES

1 **Vega J**, Bisognano JD. The prevalence, incidence, prognosis, and associated conditions of resistant hypertension. *Semin Nephrol* 2014; **34**: 247-256 [PMID: 25016397 DOI: 10.1016/j.semnephrol.2014.04.002]

2 **Velasco A**, Vongpatanasin W. The evaluation and treatment of endocrine forms of hypertension. *Curr Cardiol Rep* 2014; **16**: 528 [PMID: 25119722 DOI: 10.1007/s11886-014-0528-x]

3 **Young WF**. Primary aldosteronism: renaissance of a syndrome. *Clin Endocrinol* (Oxf) 2007; **66**: 607-618 [PMID: 17492946 DOI: 10.1111/j.1365-2265.2007.02775.x]

4 **Rossi GP**, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006; **48**: 2293-2300 [PMID: 17161262 DOI: 10.1016/j.jacc.2006.07.059]

5 **Young WF**, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004; **136**: 1227-1235 [PMID: 15657580 DOI: 10.1016/j.surg.2004.06.051]

6 **So A**, Duffy DL, Gordon RD, Jeske YW, Lin-Su K, New MI, Stowasser M. Familial hyperaldosteronism type II is linked to the chromosome 7p22 region but also shows predicted heterogeneity. *J Hypertens* 2005; **23**: 1477-1484 [PMID: 16003173]

7 **Abdelhamid S**, Müller-Lobeck H, Pahl S, Remberger K, Bönhof JA, Walb D, Röckel A. Prevalence of adrenal and extra-adrenal Conn syndrome in hypertensive patients. *Arch Intern Med* 1996; **156**: 1190-1195 [PMID: 8639013]

8 **Funder JW**, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF, Montori VM. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2008; **93**: 3266-3281 [PMID: 18552288 DOI: 10.1210/jc.2008-0104]

9 **Phillips JL**, Walther MM, Pezzullo JC, Rayford W, Choyke PL, Berman AA, Linehan WM, Doppman JL, Gill Jr JR. Predictive value of preoperative tests in discriminating bilateral adrenal hyperplasia from an aldosterone-producing adrenal adenoma. *J Clin Endocrinol Metab* 2000; **85**: 4526-4533 [PMID: 11134103 DOI: 10.1210/jcem.85.12.7086]

10 **Espiner EA**, Ross DG, Yandle TG, Richards AM, Hunt PJ. Predicting surgically remedial primary aldosteronism: role of adrenal scanning, posture testing, and adrenal vein sampling. *J Clin Endocrinol Metab* 2003; **88**: 3637-3644 [PMID: 12915648 DOI: 10.1210/jc.2002-022051]

11 **Milliez P**, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005; **45**: 1243-1248 [PMID: 15837256 DOI: 10.1016/j.jacc.2005.01.015]

12 **Rossi GP**, Sacchetto A, Visentin P, Canali C, Graniero GR, Palatini P, Pessina AC. Changes in left ventricular anatomy and function in hypertension and primary aldosteronism. *Hypertension* 1996; **27**: 1039-1045 [PMID: 8621194]

13 **Rossi GP**, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, Letizia C, Maccario M, Mannelli M, Matterello MJ, Montemurro D, Palumbo G, Rizzoni D, Rossi E, Pessina AC, Mantero F. Renal damage in primary aldosteronism: results of the PAPY Study. *Hypertension* 2006; **48**: 232-238 [PMID: 16801482 DOI: 10.1161/01.HYP.0000230444.01215.6a]

14 **Mulatero P**, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, Gomez-Sanchez CE, Veglio F, Young WF. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab* 2004; **89**: 1045-1050 [PMID: 15001583 DOI: 10.1210/jc.2003-031337]

15 **Hiramatsu K**, Yamada T, Yukimura Y, Komiya I, Ichikawa K, Ishihara M, Nagata H, Izumiyama T. A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity. Results in hypertensive patients. *Arch Intern Med* 1981; **141**: 1589-1593 [PMID: 7030245]

16 **Weinberger MH**, Fineberg NS. The diagnosis of primary aldosteronism and separation of two major subtypes. *Arch Intern Med* 1993; **153**: 2125-2129 [PMID: 8379804]

17 **Aronova A**, Iii TJ, Zarnegar R. Management of hypertension in primary aldosteronism. *World J Cardiol* 2014; **6**: 227-233 [PMID: 24944753 DOI: 10.4330/wjc.v6.i5.227]

18 **Ducher M**, Mounier-Véhier C, Baguet JP, Tartière JM, Sosner P, Régnier-Le Coz S, Perez L, Fourcade J, Jabourek O, Lejeune S, Stolz A, Fauvel JP. Aldosterone-to-renin ratio for diagnosing aldosterone-producing adenoma: a multicentre study. *Arch Cardiovasc Dis* 2012; **105**: 623-630 [PMID: 23199617 DOI: 10.1016/j.acvd.2012.07.006]

19 **Stowasser M**, Ahmed AH, Pimenta E, Taylor PJ, Gordon RD. Factors affecting the aldosterone/renin ratio. *Horm Metab Res* 2012; **44**: 170-176 [PMID: 22147655 DOI: 10.1055/s-0031-1295460]

20 **Tomaschitz A**, Pilz S. Aldosterone to renin ratio--a reliable screening tool for primary aldosteronism? *Horm Metab Res* 2010; **42**: 382-391 [PMID: 20225167 DOI: 10.1055/s-0030-1248326]

21 **Gallay BJ**, Ahmad S, Xu L, Toivola B, Davidson RC. Screening for primary aldosteronism without discontinuing hypertensive medications: plasma aldosterone-renin ratio. *Am J Kidney Dis* 2001; **37**: 699-705 [PMID: 11273868]

22 **Nanba K**, Tamanaha T, Nakao K, Kawashima ST, Usui T, Tagami T, Okuno H, Shimatsu A, Suzuki T, Naruse M. Confirmatory testing in primary aldosteronism. *J Clin Endocrinol Metab* 2012; **97**: 1688-1694 [PMID: 22419718 DOI: 10.1210/jc.2011-2504]

23 **Bravo EL**, Tarazi RC, Dustan HP, Fouad FM, Textor SC, Gifford RW, Vidt DG. The changing clinical spectrum of primary aldosteronism. *Am J Med* 1983; **74**: 641-651 [PMID: 6340491]

24 **Mulatero P**, Milan A, Fallo F, Regolisti G, Pizzolo F, Fardella C, Mosso L, Marafetti L, Veglio F, Maccario M. Comparison of confirmatory tests for the diagnosis of primary aldosteronism. *J Clin Endocrinol Metab* 2006; **91**: 2618-2623 [PMID: 16670162 DOI: 10.1210/jc.2006-0078]

25 **Lim PO**, Farquharson CA, Shiels P, Jung RT, Struthers AD, MacDonald TM. Adverse cardiac effects of salt with fludrocortisone in hypertension. *Hypertension* 2001; **37**: 856-861 [PMID: 11244008]

26 **Young WF**, Stanson AW, Grant CS, Thompson GB, van Heerden JA. Primary aldosteronism: adrenal venous sampling. *Surgery* 1996; **120**: 913-919; discussion 913-919 [PMID: 8957473]

27 **Zarnegar R**, Bloom AI, Lee J, Kerlan RK, Wilson MW, Laberge JM, Gordon RL, Kebebew E, Clark OH, Duh QY. Is adrenal venous sampling necessary in all patients with hyperaldosteronism before adrenalectomy? *J Vasc Interv Radiol* 2008; **19**: 66-71 [PMID: 18192469 DOI: 10.1016/j.jvir.2007.08.022]

28 **Nomura K**, Kusakabe K, Maki M, Ito Y, Aiba M, Demura H. Iodomethylnorcholesterol uptake in an aldosteronoma shown by dexamethasone-suppression scintigraphy: relationship to adenoma size and functional activity. *J Clin Endocrinol Metab* 1990; **71**: 825-830 [PMID: 2401712 DOI: 10.1210/jcem-71-4-825]

29 **Stowasser M**, Gordon RD. Primary aldosteronism--careful investigation is essential and rewarding. *Mol Cell Endocrinol* 2004; **217**: 33-39 [PMID: 15134798 DOI: 10.1016/j.mce.2003.10.006]

30 **Rossi GP**, Auchus RJ, Brown M, Lenders JW, Naruse M, Plouin PF, Satoh F, Young WF. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. *Hypertension* 2014; **63**: 151-160 [PMID: 24218436 DOI: 10.1161/hypertensionaha.113.02097]

31 **Doppman JL**, Gill JR, Miller DL, Chang R, Gupta R, Friedman TC, Choyke PL, Feuerstein IM, Dwyer AJ, Jicha DL. Distinction between hyperaldosteronism due to bilateral hyperplasia and unilateral aldosteronoma: reliability of CT. *Radiology* 1992; **184**: 677-682 [PMID: 1509049 DOI: 10.1148/radiology.184.3.1509049]

32 **Rossi GP**, Barisa M, Allolio B, Auchus RJ, Amar L, Cohen D, Degenhart C, Deinum J, Fischer E, Gordon R, Kickuth R, Kline G, Lacroix A, Magill S, Miotto D, Naruse M, Nishikawa T, Omura M, Pimenta E, Plouin PF, Quinkler M, Reincke M, Rossi E, Rump LC, Satoh F, Schultze Kool L, Seccia TM, Stowasser M, Tanabe A, Trerotola S, Vonend O, Widimsky J, Wu KD, Wu VC, Pessina AC. The Adrenal Vein Sampling International Study (AVIS) for identifying the major subtypes of primary aldosteronism. *J Clin Endocrinol Metab* 2012; **97**: 1606-1614 [PMID: 22399502 DOI: 10.1210/jc.2011-2830]

33 **Young WF**, Klee GG. Primary aldosteronism. Diagnostic evaluation. *Endocrinol Metab Clin North Am* 1988; **17**: 367-395 [PMID: 3042391]

34 **Karagiannis A**, Tziomalos K, Kakafika AI, Athyros VG, Harsoulis F, Mikhailidis DP. Medical treatment as an alternative to adrenalectomy in patients with aldosterone-producing adenomas. *Endocr Relat Cancer* 2008; **15**: 693-700 [PMID: 18586836 DOI: 10.1677/erc-08-0094]

35 **Ghose RP**, Hall PM, Bravo EL. Medical management of aldosterone-producing adenomas. *Ann Intern Med* 1999; **131**: 105-108 [PMID: 10419425]

36 **Fourkiotis V**, Vonend O, Diederich S, Fischer E, Lang K, Endres S, Beuschlein F, Willenberg HS, Rump LC, Allolio B, Reincke M, Quinkler M. Effectiveness of eplerenone or spironolactone treatment in preserving renal function in primary aldosteronism. *Eur J Endocrinol* 2013; **168**: 75-81 [PMID: 23033260 DOI: 10.1530/eje-12-0631]

37 **Stokes GS**, Monaghan JC, Ryan M, Woodward M. Efficacy of an angiotensin II receptor antagonist in managing hyperaldosteronism.

J Hypertens 2001; **19**: 1161-1165 [PMID: 11403366]
38 **Assalia A**, Gagner M. Laparoscopic adrenalectomy. *Br J Surg* 2004; **91**: 1259-1274 [PMID: 15376201 DOI: 10.1002/bjs.4738]
39 **Sywak M**, Pasieka JL. Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism. *Br J Surg* 2002; **89**: 1587-1593 [PMID: 12445071 DOI: 10.1046/j.1365-2168.2002.02261.x]
40 **Sawka AM**, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA. Primary aldosteronism: factors associated with normalization of blood pressure after surgery. *Ann Intern Med* 2001; **135**: 258-261 [PMID: 11511140]
41 **Blumenfeld JD**, Sealey JE, Schlussel Y, Vaughan ED, Sos TA, Atlas SA, Müller FB, Acevedo R, Ulick S, Laragh JH. Diagnosis and treatment of primary hyperaldosteronism. *Ann Intern Med* 1994; **121**: 877-885 [PMID: 7978702]
42 **Carey RM**. Primary aldosteronism. *J Surg Oncol* 2012; **106**: 575-579 [PMID: 22806599 DOI: 10.1002/jso.23206]
43 **Lumachi F**, Ermani M, Basso SM, Armanini D, Iacobone M, Favia G. Long-term results of adrenalectomy in patients with aldosterone-producing adenomas: multivariate analysis of factors affecting unresolved hypertension and review of the literature. *Am Surg* 2005; **71**: 864-869 [PMID: 16468537]
44 **Meyer A**, Brabant G, Behrend M. Long-term follow-up after adrenalectomy for primary aldosteronism. *World J Surg* 2005; **29**: 155-159 [PMID: 15650803 DOI: 10.1007/s00268-004-7496-z]
45 **Harris DA**, Au-Yong I, Basnyat PS, Sadler GP, Wheeler MH. Review of surgical management of aldosterone secreting tumours of the adrenal cortex. *Eur J Surg Oncol* 2003; **29**: 467-474 [PMID: 12798753]
46 **Pang TC**, Bambach C, Monaghan JC, Sidhu SB, Bune A, Delbridge LW, Sywak MS. Outcomes of laparoscopic adrenalectomy for hyperaldosteronism. *ANZ J Surg* 2007; **77**: 768-773 [PMID: 17685956 DOI: 10.1111/j.1445-2197.2007.04225.x]
47 **Gockel I**, Heintz A, Polta M, Junginger T. Long-term results of endoscopic adrenalectomy for Conn's syndrome. *Am Surg* 2007; **73**: 174-180 [PMID: 17305298]
48 **Fukudome Y**, Fujii K, Arima H, Ohya Y, Tsuchihashi T, Abe I, Fujishima M. Discriminating factors for recurrent hypertension in patients with primary aldosteronism after adrenalectomy. *Hypertens Res* 2002; **25**: 11-18 [PMID: 11924716]
49 **Zarnegar R**, Young WF, Lee J, Sweet MP, Kebebew E, Farley DR, Thompson GB, Grant CS, Clark OH, Duh QY. The aldosteronoma resolution score: predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. *Ann Surg* 2008; **247**: 511-518 [PMID: 18376197 DOI: 10.1097/SLA.0b013e318165c075]
50 **Utsumi T**, Kawamura K, Imamoto T, Kamiya N, Komiya A, Suzuki S, Nagano H, Tanaka T, Nihei N, Naya Y, Suzuki H, Tatsuno I, Ichikawa T. High predictive accuracy of Aldosteronoma Resolution Score in Japanese patients with aldosterone-producing adenoma. *Surgery* 2012; **151**: 437-443 [PMID: 22000827 DOI: 10.1016/j.surg.2011.08.001]
51 **Zennaro MC,** Boulkroun S, Fernandes-Rosa FL. An update on novel mechanisms of primary aldosteronism. *J Endocrinol* 2015; **224**: R63-R77 [PMID: 25424518 DOI: 10.1530/joe-14-0597]
52 **Gates LJ**, Benjamin N, Haites NE, MacConnachie AA, McLay JS. Is random screening of value in detecting glucocorticoid-remediable aldosteronism within a hypertensive population? *J Hum Hypertens* 2001; **15**: 173-176 [PMID: 11317201 DOI: 10.1038/sj.jhh.1001152]
53 **Ariton M**, Juan CS, AvRuskin TW. Pheochromocytoma: clinical observations from a Brooklyn tertiary hospital. *Endocr Pract* 2000; **6**: 249-252 [PMID: 11421540 DOI: 10.4158/EP.6.3.249]
54 **Manger WM**. The protean manifestations of pheochromocytoma. *Horm Metab Res* 2009; **41**: 658-663 [PMID: 19242899 DOI: 10.1055/s-0028-1128139]
55 **Omura M**, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res* 2004; **27**: 193-202 [PMID: 15080378]
56 **Guerrero MA**, Schreinemakers JM, Vriens MR, Suh I, Hwang J, Shen WT, Gosnell J, Clark OH, Duh QY. Clinical spectrum of pheochromocytoma. *J Am Coll Surg* 2009; **209**: 727-732 [PMID: 19959041 DOI: 10.1016/j.jamcollsurg.2009.09.022]
57 **Lenders JW**, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *Lancet* 2005; **366**: 665-675 [PMID: 16112304 DOI: 10.1016/s0140-6736(05)67139-5]
58 **Baguet JP**, Hammer L, Mazzuco TL, Chabre O, Mallion JM, Sturm N, Chaffanjon P. Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients. *Eur J Endocrinol* 2004; **150**: 681-686 [PMID: 15132724]
59 **Calhoun DA**, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; **51**: 1403-1419 [PMID: 18391085 DOI: 10.1161/hypertensionaha.108.189141]
60 **Zelinka T**, Eisenhofer G, Pacak K. Pheochromocytoma as a catecholamine producing tumor: implications for clinical practice. *Stress* 2007; **10**: 195-203 [PMID: 17514588 DOI: 10.1080/10253890701395896]
61 **Zelinka T,** Strauch B, Petrák O, Holaj R, Vranková A, Weisserová H, Pacák K, Widimský J. Increased blood pressure variability in pheochromocytoma compared to essential hypertension patients. *J Hypertens* 2005; **23**: 2033-2039 [PMID: 16208146]
62 **Ito Y**, Fujimoto Y, Obara T. The role of epinephrine, norepinephrine, and dopamine in blood pressure disturbances in patients with pheochromocytoma. *World J Surg* 1992; **16**: 759-763; discussion 763-764 [PMID: 1413846]
63 **Proye C**, Fossati P, Fontaine P, Lefebvre J, Decoulx M, Wemeau JL, Dewailly D, Rwamasirabo E, Cecat P. Dopamine-secreting pheochromocytoma: an unrecognized entity? Classification of pheochromocytomas according to their type of secretion. *Surgery* 1986; **100**: 1154-1162 [PMID: 3787474]
64 **Streeten DH**, Anderson GH. Mechanisms of orthostatic hypotension and tachycardia in patients with pheochromocytoma. *Am J Hypertens* 1996; **9**: 760-769 [PMID: 8862222]
65 **Mazza A**, Armigliato M, Marzola MC, Schiavon L, Montemurro D, Vescovo G, Zuin M, Chondrogiannis S, Ravenni R, Opocher G, Colletti PM, Rubello D. Anti-hypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features. *Endocrine* 2014; **45**: 469-478 [PMID: 23817839 DOI: 10.1007/s12020-013-0007-y]
66 **Drénou B**, Le Tulzo Y, Caulet-Maugendre S, Le Guerrier A, Leclercq C, Guilhem I, Lecoq N, Fauchet R, Thomas R. Pheochromocytoma and secondary erythrocytosis: role of tumour erythropoietin secretion. *Nouv Rev Fr Hematol* 1995; **37**: 197-199 [PMID: 7567437]
67 **La Batide-Alanore A**, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. *J Hypertens* 2003; **21**: 1703-1707 [PMID: 12923403 DOI: 10.1097/01.hjh.0000084729.53355.ce]
68 **Bravo EL**. Pheochromocytoma: new concepts and future trends. *Kidney Int* 1991; **40**: 544-556 [PMID: 1787652]
69 **Yu R**, Nissen NN, Chopra P, Dhall D, Phillips E, Wei M. Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007. *Am J Med* 2009; **122**: 85-95 [PMID: 19114176 DOI: 10.1016/j.amjmed.2008.08.021]
70 **Chen H**, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas* 2010; **39**: 775-783 [PMID: 20664475 DOI: 10.1097/MPA.0b013e3181ebb4f0]
71 **Lenders JW**, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, Keiser HR, Goldstein DS, Eisenhofer G. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002; **287**: 1427-1434 [PMID: 11903030]
72 **Sawka AM**, Jaeschke R, Singh RJ, Young WF. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin*

Endocrinol Metab 2003; **88**: 553-558 [PMID: 12574179 DOI: 10.1210/jc.2002-021251]
73 **Sawka AM**, Prebtani AP, Thabane L, Gafni A, Levine M, Young WF. A systematic review of the literature examining the diagnostic efficacy of measurement of fractionated plasma free metanephrines in the biochemical diagnosis of pheochromocytoma. *BMC Endocr Disord* 2004; **4**: 2 [PMID: 15225350 DOI: 10.1186/1472-6823-4-2]
74 **Kudva YC**, Sawka AM, Young WF. Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab* 2003; **88**: 4533-4539 [PMID: 14557417 DOI: 10.1210/jc.2003-030720]
75 **Perry CG**, Sawka AM, Singh R, Thabane L, Bajnarek J, Young WF. The diagnostic efficacy of urinary fractionated metanephrines measured by tandem mass spectrometry in detection of pheochromocytoma. *Clin Endocrinol* (Oxf) 2007; **66**: 703-708 [PMID: 17388796 DOI: 10.1111/j.1365-2265.2007.02805.x]
76 **Lenders JW,** Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr; Endocrine Society.. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014; **99**: 1915-1942 [PMID: 24893135 DOI: 10.1210/jc.2014-1498]
77 **Lenders JW**, Willemsen JJ, Eisenhofer G, Ross HA, Pacak K, Timmers HJ, Sweep CG. Is supine rest necessary before blood sampling for plasma metanephrines? *Clin Chem* 2007; **53**: 352-354 [PMID: 17200132 DOI: 10.1373/clinchem.2006.076489]
78 **Deutschbein T**, Unger N, Jaeger A, Broecker-Preuss M, Mann K, Petersenn S. Influence of various confounding variables and storage conditions on metanephrine and normetanephrine levels in plasma. *Clin Endocrinol* (Oxf) 2010; **73**: 153-160 [PMID: 20039892 DOI: 10.1111/j.1365-2265.2009.03761.x]
79 **Eisenhofer G**, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, Pacak K. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* 2003; **88**: 2656-2666 [PMID: 12788870 DOI: 10.1210/jc.2002-030005]
80 **Grassi G**, Seravalle G, Calhoun DA, Bolla G, Mancia G. Cigarette smoking and the adrenergic nervous system. *Clin Exp Hypertens A* 1992; **14**: 251-260 [PMID: 1541039]
81 **Ilias I**, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab* 2004; **89**: 479-491 [PMID: 14764749 DOI: 10.1210/jc.2003-031091]
82 **Boland GW**, Lee MJ, Gazelle GS, Halpern EF, McNicholas MM, Mueller PR. Characterization of adrenal masses using unenhanced CT: an analysis of the CT literature. *AJR Am J Roentgenol* 1998; **171**: 201-204 [PMID: 9648789 DOI: 10.2214/ajr.171.1.9648789]
83 **Park BK**, Kim CK, Kwon GY, Kim JH. Re-evaluation of pheochromocytomas on delayed contrast-enhanced CT: washout enhancement and other imaging features. *Eur Radiol* 2007; **17**: 2804-2809 [PMID: 17549484 DOI: 10.1007/s00330-007-0695-x]
84 **Baid SK**, Lai EW, Wesley RA, Ling A, Timmers HJ, Adams KT, Kozupa A, Pacak K. Brief communication: radiographic contrast infusion and catecholamine release in patients with pheochromocytoma. *Ann Intern Med* 2009; **150**: 27-32 [PMID: 19124817]
85 **Leung K**, Stamm M, Raja A, Low G. Pheochromocytoma: the range of appearances on ultrasound, CT, MRI, and functional imaging. *AJR Am J Roentgenol* 2013; **200**: 370-378 [PMID: 23345359 DOI: 10.2214/ajr.12.9126]
86 **Jacques AE**, Sahdev A, Sandrasagara M, Goldstein R, Berney D, Rockall AG, Chew S, Reznek RH. Adrenal phaeochromocytoma: correlation of MRI appearances with histology and function. *Eur Radiol* 2008; **18**: 2885-2892 [PMID: 18641999 DOI: 10.1007/s00330-008-1073-z]
87 **Varghese JC**, Hahn PF, Papanicolaou N, Mayo-Smith WW, Gaa JA, Lee MJ. MR differentiation of phaeochromocytoma from other adrenal lesions based on qualitative analysis of T2 relaxation times. *Clin Radiol* 1997; **52**: 603-606 [PMID: 9285420]
88 **Krestin GP**, Steinbrich W, Friedmann G. Adrenal masses: evaluation with fast gradient-echo MR imaging and Gd-DTPA-enhanced dynamic studies. *Radiology* 1989; **171**: 675-680 [PMID: 2717737 DOI: 10.1148/radiology.171.3.2717737]
89 **Havekes B**, Lai EW, Corssmit EP, Romijn JA, Timmers HJ, Pacak K. Detection and treatment of pheochromocytomas and paragangliomas: current standing of MIBG scintigraphy and future role of PET imaging. *Q J Nucl Med Mol Imaging* 2008; **52**: 419-429 [PMID: 19088695]
90 **Timmers HJ**, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, Adams KT, Solis D, Lenders JW, Pacak K. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *J Clin Oncol* 2007; **25**: 2262-2269 [PMID: 17538171 DOI: 10.1200/jco.2006.09.6297]
91 **Timmers HJ**, Chen CC, Carrasquillo JA, Whatley M, Ling A, Eisenhofer G, King KS, Rao JU, Wesley RA, Adams KT, Pacak K. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. *J Natl Cancer Inst* 2012; **104**: 700-708 [PMID: 22517990 DOI: 10.1093/jnci/djs188]
92 **Pacak K**, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, Kimura N, Mannelli M, McNicol AM, Tischler AS. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. October 2005. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 92-102 [PMID: 17237836 DOI: 10.1038/ncpendmet0396]
93 **Bravo EL**, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. *Endocr Rev* 2003; **24**: 539-553 [PMID: 12920154 DOI: 10.1210/er.2002-0013]
94 **Weingarten TN**, Cata JP, O'Hara JF, Prybilla DJ, Pike TL, Thompson GB, Grant CS, Warner DO, Bravo E, Sprung J. Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. *Urology* 2010; **76**: 508.e6-508.11 [PMID: 20546874 DOI: 10.1016/j.urology.2010.03.032]
95 **Lebuffe G**, Dosseh ED, Tek G, Tytgat H, Moreno S, Tavernier B, Vallet B, Proye CA. The effect of calcium channel blockers on outcome following the surgical treatment of phaeochromocytomas and paragangliomas. *Anaesthesia* 2005; **60**: 439-444 [PMID: 15819762 DOI: 10.1111/j.1365-2044.2005.04156.x]
96 **Proye C**, Thevenin D, Cecat P, Petillot P, Carnaille B, Verin P, Sautier M, Racadot N. Exclusive use of calcium channel blockers in preoperative and intraoperative control of pheochromocytomas: hemodynamics and free catecholamine assays in ten consecutive patients. *Surgery* 1989; **106**: 1149-1154 [PMID: 2588118]
97 **Takahashi S**, Nakai T, Fujiwara R, Kutsumi Y, Tamai T, Miyabo S. Effectiveness of long-acting nifedipine in pheochromocytoma. *Jpn Heart J* 1989; **30**: 751-757 [PMID: 2614935]
98 **Pacak K**. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab* 2007; **92**: 4069-4079 [PMID: 17989126 DOI: 10.1210/jc.2007-1720]
99 **Sjoerdsma A**, Engelman K, Spector S, Udenfriend S. Inhibition of catecholamine synthesis in man with alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. *Lancet* 1965; **2**: 1092-1094 [PMID: 4158803]
100 **Steinsapir J**, Carr AA, Prisant LM, Bransome ED. Metyrosine and pheochromocytoma. *Arch Intern Med* 1997; **157**: 901-906 [PMID: 9129550]
101 **Perry RR**, Keiser HR, Norton JA, Wall RT, Robertson CN, Travis W, Pass HI, Walther MM, Linehan WM. Surgical management of pheochromocytoma with the use of metyrosine. *Ann Surg* 1990; **212**: 621-628 [PMID: 1978640]
102 **Young WF**. Pheochromocytoma: issues in diagnosis & amp; treatment. *Compr Ther* 1997; **23**: 319-326 [PMID: 9195121]
103 **James MF**. The use of magnesium sulfate in the anesthetic management of pheochromocytoma. *Anesthesiology* 1985; **62**: 188-190 [PMID: 3970373]
104 **Hansen P**, Bax T, Swanstrom L. Laparoscopic adrenalectomy: history, indications, and current techniques for a minimally invasive approach to adrenal pathology. *Endoscopy* 1997; **29**: 309-314 [PMID: 9255537 DOI: 10.1055/s-2007-1004195]

105 **Bulus H**, Uslu HY, Karakoyun R, Koçak S. Comparison of laparoscopic and open adrenalectomy. *Acta Chir Belg* 2013; **113**: 203-207 [PMID: 24941717]

106 **Conzo G**, Musella M, Corcione F, De Palma M, Ferraro F, Palazzo A, Napolitano S, Milone M, Pasquali D, Sinisi AA, Colantuoni V, Santini L. Laparoscopic adrenalectomy, a safe procedure for pheochromocytoma. A retrospective review of clinical series. *Int J Surg* 2013; **11**: 152-156 [PMID: 23267853 DOI: 10.1016/j.ijsu.2012.12.007]

107 **Cheah WK**, Clark OH, Horn JK, Siperstein AE, Duh QY. Laparoscopic adrenalectomy for pheochromocytoma. *World J Surg* 2002; **26**: 1048-1051 [PMID: 12045856 DOI: 10.1007/s00268-002-6669-x]

108 **Huyghe E**, Crenn G, Duly-Bouhanick B, Vezzosi D, Bennet A, Atallah F, Mazerolles M, Salloum A, Thoulouzan M, Delaunay B, Grunenwald S, Amar J, Plante P, Chamontin B, Caron P, Soulié M. Retroperitoneoscopic adrenalectomy: comparison of retrograde and antegrade approach among a series of 279 cases. *Urology* 2013; **81**: 85-91 [PMID: 23273074 DOI: 10.1016/j.urology.2012.08.059]

109 **Dickson PV**, Alex GC, Grubbs EG, Ayala-Ramirez M, Jimenez C, Evans DB, Lee JE, Perrier ND. Posterior retroperitoneoscopic adrenalectomy is a safe and effective alternative to transabdominal laparoscopic adrenalectomy for pheochromocytoma. *Surgery* 2011; **150**: 452-458 [PMID: 21878230 DOI: 10.1016/j.surg.2011.07.004]

110 **Plouin PF**, Duclos JM, Soppelsa F, Boublil G, Chatellier G. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. *J Clin Endocrinol Metab* 2001; **86**: 1480-1486 [PMID: 11297571 DOI: 10.1210/jcem.86.4.7392]

111 **Kinney MA**, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothorac Vasc Anesth* 2002; **16**: 359-369 [PMID: 12073213 DOI: 10.1053/jcan.2002.124150]

112 **Reynolds C**, Wilkins GE, Schmidt N, Doll WA, Blix PM. Hyperinsulinism after removal of a pheochromocytoma. *Can Med Assoc J* 1983; **129**: 349-353 [PMID: 6871802]

113 **Meeke RI**, O'Keeffe JD, Gaffney JD. Phaeochromocytoma removal and postoperative hypoglycaemia. *Anaesthesia* 1985; **40**: 1093-1096 [PMID: 4073425]

114 **Neumann HP**, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Altehoefer C, Zerres K, Januszewicz A, Eng C, Smith WM, Munk R, Manz T, Glaesker S, Apel TW, Treier M, Reineke M, Walz MK, Hoang-Vu C, Brauckhoff M, Klein-Franke A, Klose P, Schmidt H, Maier-Woelfle M, Peçzkowska M, Szmigielski C, Eng C. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002; **346**: 1459-1466 [PMID: 12000816 DOI: 10.1056/NEJMoa020152]

115 **Erlic Z**, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, Müssig K, Muresan M, Schäffler A, Reisch N, Schott M, Fassnacht M, Opocher G, Klose S, Fottner C, Forrer F, Plöckinger U, Petersenn S, Zabolotny D, Kollukch O, Yaremchuk S, Januszewicz A, Walz MK, Eng C, Neumann HP. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. *Clin Cancer Res* 2009; **15**: 6378-6385 [PMID: 19825962 DOI: 10.1158/1078-0432.CCR-09-1237]

116 **Welander J**, Söderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. *Endocr Relat Cancer* 2011; **18**: R253-R276 [PMID: 22041710 DOI: 10.1530/ERC-11-0170]

117 **Lenders JW**. Pheochromocytoma and pregnancy: a deceptive connection. *Eur J Endocrinol* 2012; **166**: 143-150 [PMID: 21890650 DOI: 10.1530/eje-11-0528]

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REVIEW

Novel contributions of multimodality imaging in hypertension: A narrative review

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Abstract

Hypertension is currently one of the most prevalent illnesses worldwide, and is the second most common cause of heart failure, only behind ischemic cardiomyopathy. The development of novel multimodality imaging techniques in recent years has broadened the diagnostic methods, risk stratification and monitoring of treatment of cardiovascular diseases available for clinicians. Cardiovascular magnetic resonance (CMR) has a great capacity to evaluate cardiac dimensions and ventricular function, is extremely useful in ruling-out ischemic cardiomyopathy, the evaluation of the vascular system, in making the differential diagnosis for resistant hypertension and risk stratification for hypertensive cardiomyopathy and constitutes today, the method of choice to evaluate left ventricular systolic function. Computed tomography (CT) is the method of choice for the evaluation of vascular anatomy, including coronary arteries, and is also able to provide both functional and structural information. Finally, nuclear cardiology studies have been traditionally used to evaluate myocardial ischemia, along with offering the capacity to evaluate ventricular, endothelial and cardiac innervation function; information that is key in directing the treatment of the patient. In this narrative review, the most recent contributions of multimodality imaging to the patient with hypertension (CMR, CT and nuclear cardiology) will be reviewed.

Key words: Cardiac imaging techniques; Multimodality imaging; Magnetic resonance imaging; Multidetector computed tomography; Cardiac-gated single photon

emission computed tomography; Positron emission tomography; Hypertension

Core tip: Diverse imaging modalities are playing a larger role every day in the diagnosis, treatment decisions and follow-up of patients. This is especially true in patients with hypertension. The merger of diverse imaging techniques has led to the rise of Multimodality Imaging, using tools such as cardiovascular magnetic resonance, computed tomography and nuclear cardiology that aid clinicians make the best therapeutic decisions. In this article, we will make a comprehensive review of the most novel contributions of multimodality imaging to patients with hypertension.

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INTRODUCTION

Hypertension is one of the most prevalent illnesses worldwide. Data from the NHANES 2007-2010 found that approximately 6% of adults in the United States have undiagnosed hypertension and that in the adult general population; up to one-third might present this illness. It is considered that a 65% of patients presenting with heart failure have a history of Hypertension, and is currently its second most common etiology, only behind ischemic cardiomyopathy[1]. Furthermore, besides its impact on the heart, Hypertension also produces serious damage in blood vessels (including the aorta), kidneys, eyes and brain.

During the last few years, the development of multimodality imaging has contributed to a better understanding of the pathophysiology of cardiovascular diseases, also aiding in its early diagnosis and also monitoring the response to treatment. Traditionally, echocardiogram has been used as the standard imaging method for patient evaluation. However, multimodality imaging has made available a wide array of other imaging techniques [cardiovascular magnetic resonance (CMR), computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT)] for the patient with Hypertension, which might help improve treatment and monitoring of the patients, thus contributing to control this worldwide pandemic. In this review we will touch on the most novel contributions on this subject.

CMR

CMR is an imaging method that does not use ionizing radiation, and can evaluate both cardiovascular anatomy and function with high spatial resolution and diagnostic certainty. Furthermore, with the use of gadolinium-based contrasts, it is possible to evaluate vascular anatomy. The 1.5 tesla (T) machines are the most widely used models around the world, although there have been reports of the usefulness of new 3.0 T machines. Traditionally, the most used sequences in patients with hypertensive cardiomyopathy are: tracers, Steady-state Free Precision (SSFP) cine imaging, weighted T2 STIR (short-tau inversion recovery), fast spin-echo weighted T1 and T2, first step myocardial perfusion with gadolinium, phase contrast sequences, inversion recovery sequences for late enhancement and 3D angiographies. All imaging sequences must be acquired with electrocardiographic (ECG) gating, meaning that patients presenting rhythms other than sinus might generate imaging artifacts or suboptimal images. The complete protocol has a duration of approximately 45-60 min, during which the patient must be able to withstand performing 10-20 s apneas, and must also deal with being enclosed in a tight space. Therefore, the success of the study depends greatly on the appropriate selection of the patients. In case that the patient cannot tolerate the study, the best course of action is to perform the study with the patient under general anesthesia with invasive mechanical ventilation.

The following are the most relevant contributions of CMR to patients with Hypertension.

Measurements of volumes and ventricular mass

Hypertension has a direct impact on the heart, which is most pronounced in patients with poor control. The most common repercussions in cardiac anatomy are left ventricular hypertrophy and left atrial dilation (Figure 1).

The Framingham study demonstrated that left ventricular hypertrophy is associated with higher cardiovascular mortality, independently of the presence of coronary artery disease[2]. CMR is currently considered the gold standard for the quantification of cardiac dimensions, including ventricular mass, since CMR is a highly exact and reproducible method, when compared with 2D echocardiography. In a study that compared these 2 tools in a sample composed of patients with dilated cardiomyopathy, hypertrophic cardiomyopathy and healthy controls, the coefficients of intra-study variability for left ventricular mass were -1.0 ± 7.7 g for CMR and 8.7 ± 25 g for 2D echocardiography ($P < 0.001$)[3]. 3D echocardiography has demonstrated accuracy and reproducibility similar to CMR, however, it is still hindered by the same limitations as 2D echo: the need of a good acoustic window and experienced personnel in the usage of the device[4].

Besides the diagnosis of ventricular hypertrophy,

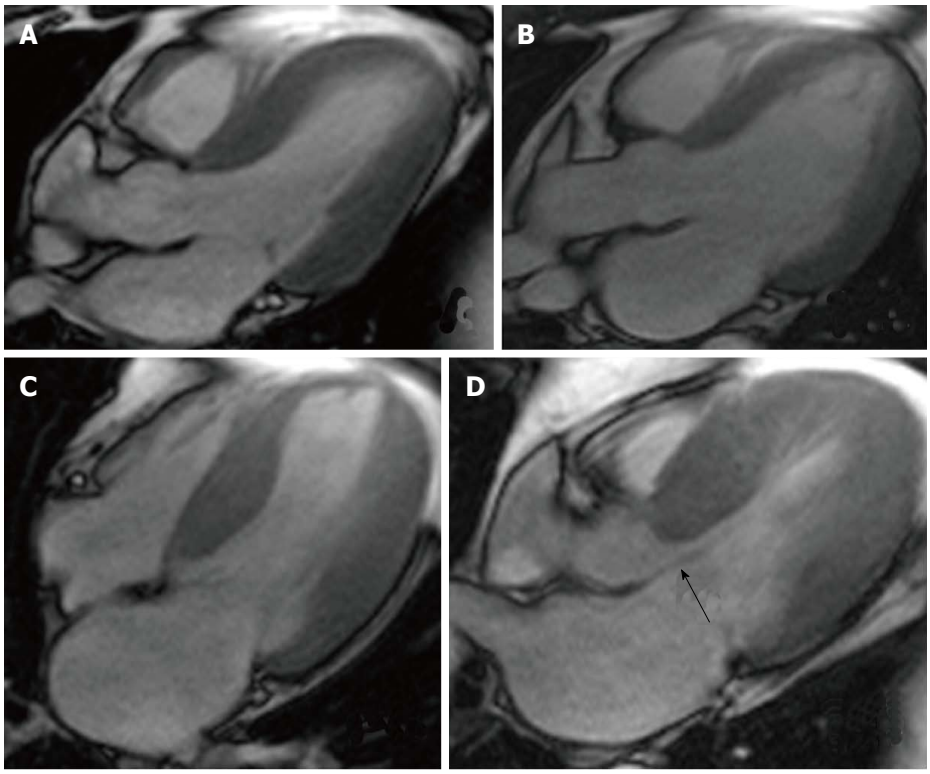

Figure 1 Cardiovascular magnetic resonance showing Steady-state Free Precision Sequences. A: Patient with hypertension presenting slight ventricular hypertrophy (septal wall of 13 mm); B: Patient with hypertensive cardiomyopathy in dilated phase with a LVDD = 70 mm, LVEF = 40%, left atrium = 65 mm; C: 51-year-old male patient with asymmetrical septal hypertrophy, with a maximum thickness of 27 mm; D: Same patient as in C, the arrow shows the anterior systolic movement of the mitral valve, generating outflow tract obstruction.

CMR can also contribute to the monitoring of these patients. Adequate antihypertensive treatment has demonstrated to revert ventricular hypertrophy, which is associated to a better prognosis, since it prevents the progression to heart failure. These studies have used CMR as the method of choice for serial measurement of ventricular mass[5-7].

However, ventricular hypertrophy is not exclusive of hypertensive cardiomyopathy and can be observed in other illnesses, such as infiltrative diseases (Fabry's disease, cardiac sarcoidosis, and cardiac amyloidosis), hypertrophic cardiomyopathy, aortic stenosis, exercise-induced hypertrophy, *etc.* CMR can readily differentiate between these different diseases and help in making the differential diagnosis in favor of hypertensive cardiomyopathy.

Left atrial dilation correlates with the severity and duration of hypertension. Traditionally, this has been measured by echocardiogram; however, CMR has proven to be a more reliable technique for measuring auricular volumes. The presence of left atrial dilation has been linked to the development of atrial fibrillation and increased mortality[8]. Furthermore, the morphology of the left atrial appendage can differentiate between patients with low and high risk of thrombus formation and subsequent embolic events[9]. Finally, left atrial dilation is related to the chronicity of ventricular diastolic dysfunction, as long as mitral valvular disease has been ruled out. Unlike echocardiography, an area of more than 20 cm^2 indicates an enlarged left atrium, with the enlargement being classified as severe if the area surpasses 40 cm^2[10].

Diastolic function evaluation

The gold standard for the evaluation of diastolic dysfunction has traditionally been the echocardiogram, which evaluates the pattern of the flow across the mitral valve with Doppler technique. CMR is able to obtain very similar information, by realizing ECG-gated sequences of contrast-phase in the around the mitral valve and the pulmonary veins. This way, it is possible to obtain a time/speed curve very similar to that shown by the echo, with similar diastolic dysfunction patterns[10-12]. Also, novel indexes, such as the Normalized average sweep rate, early diastole normalized sweep peak rate and the relationship between the normalized peak sweep rate in early diastole and the normalized peak sweep rate in atrial systole with an area under the curve of 0.93, 0.88 and 0.88 respectively[13].

Ruling out ischemic cardiomyopathy

Coronary artery disease is extremely prevalent in the hypertensive population. The presence of chest pain in patients with hypertensive cardiomyopathy is complex, since most of the times it can be due to the hemodynamic changes that arise as consequence of poor blood pressure control. This is complicated even further since traditional tests, such as the cardiac stress

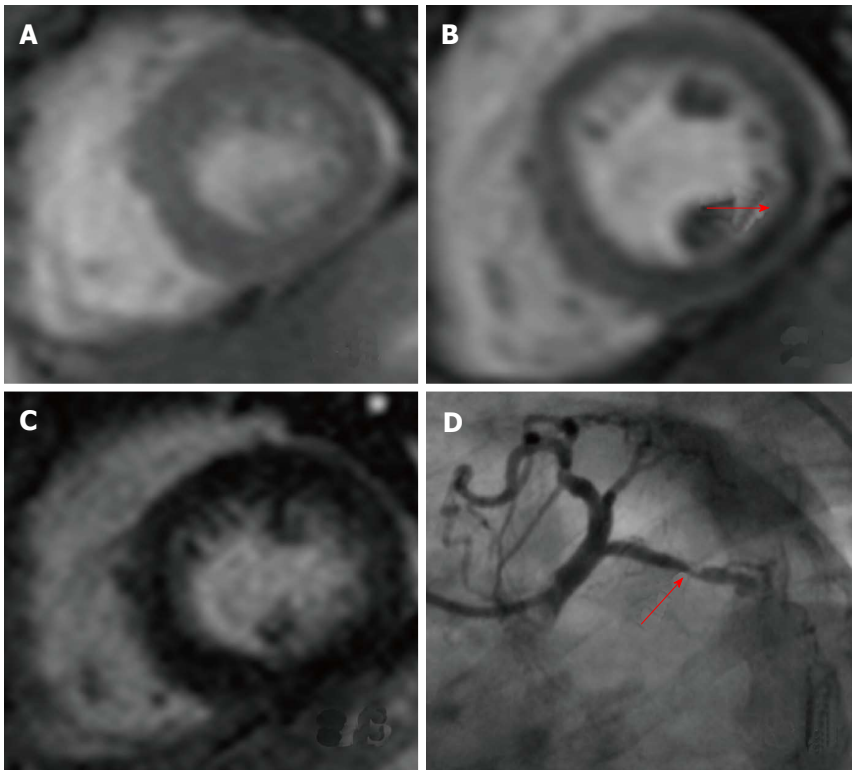

Figure 2 Evaluation of ischemia using cardiovascular magnetic resonance. A: Rest perfusion image using cardiovascular magnetic resonance that doesn't show any defects; B: Same patient post adenosine-induced stress test, the arrow shows a perfusion defect in the inferolateral wall (territory of the circumflex artery); C: Inversion recovery sequence that doesn't show the presence of late enhancement, which demonstrates the absence of infarction in the ischemic area; D: Invasive coronariography of the same patient, which shows a significant plaque in the circumflex artery.

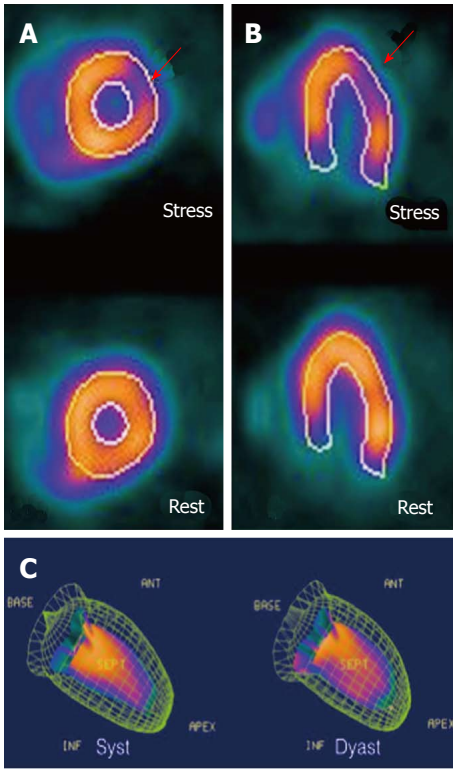

Figure 3 Evaluation of ischemia using single-photon emission computed tomography. A: Short axis view of the left ventricle with a perfusion defect visible after pharmacologic stress test in the anterior lateral wall (territory of the circumflex artery); B: Confirmation of the perfusion defect in the long axis view; C: Gated-single-photon emission computed tomography used to evaluate left ventricular function.

test yields suboptimal results due to the non-ischemic electrocardiographical changes seen in hypertensive patients. CMR has proven itself as a very useful diagnostic aid to rule-out the presence of ischemic cardiomyopathy. Through the use of myocardial perfusion imaging at rest, and after pharmacological stress (Figures 2 and 3), myocardial ischemia can be diagnosed with a sensitivity of 89% and a specificity of 76%[14]. Also, in patients with hypertensive cardiomyopathy and severe systolic dysfunction, the absence of ischemic patterns (transmural or subendocardic) excludes the coexistence of coronary artery disease as the cause of heart failure.

Evaluation of vascular disease

Hypertension exerts direct damage to the great blood vessels, especially the aorta. Magnetic Resonance Angiography is a very exact method to diagnose aortic dilation, and can also be used in the presence of acute aortic syndromes. There are studies that have shown that patients with cardiovascular risk factors (including hypertension) have an increased aortic wall thickness, which directly correlates to the presence of atherosclerosis and a poor prognosis[15]. CMR is able to quantify the atherosclerotic burden and plaque composition.

Furthermore, CMR can detect the presence of vulnerable plaques, mainly by the detection of necrotic lipid cores, calcification and hemorrhage in T1 and T2 sequences, with a sensitivity ranging from 84%-100%, both in autopsy studies and in live patients[16,17]. Recent studies have demonstrated that it is possible to quantify the necrotic lipid core, which does not differ from the pathology findings (23.7% *vs* 20.3%, P = 0.1)[18]. Other findings that can readily be detected by CMR are: plaque fissure, endothelial denudation with

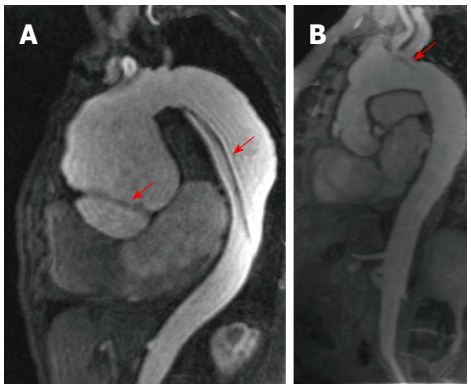

Figure 4 Evaluation of vascular anatomy using cardiovascular magnetic resonance. A: Patient with Marfan's syndrome that presents a Stanford A type dissected aortic aneurysm; the arrows point to the two sites of dissection; B shows post-surgical changes after a Bentall and Bono procedure; the arrow points to a dissection flap in the aortic arch.

platelet adhesion and fibrin deposit, late enhancement in plaques with active inflammatory activity and the severity of vascular stenosis[19].

The study of plaque composition with CMR has been used to demonstrate the beneficial effects of some therapeutic approaches. Lipid apheresis has proven to be statistically significant in diminishing the prevalence of necrotic lipid core in carotid plaques (28.1% *vs* 56.3%, $P < 0.05$)[20]. It also showed it reduced its lipid content (5.0% *vs* 11.6%, $P < 0.05$). Lipid lowering therapy has been shown to reduce the area of the lipid core of the plaques (0.7 mm^2 *vs* 10.2 mm^2, $P = 0.01$), along with the progression of vascular stenosis[21].

As for functional evaluation, there are studies that have demonstrated an increased vascular rigidity in patients with hypertension and diabetes mellitus, measured by the speed of the aortic pulse wave and vascular compliance[22,23]. The severity of the rigidity has also been associated with an increased degree of endothelial injury. The significance of these findings is still being clarified.

Aortic angioresonance has proven to have excellent diagnostic accuracy for the diagnosis of aortic dissection, with a sensitivity and specificity of 98% and an excellent performance compared to transesophageal echocardiography and CT (Diagnostic OR of 6.8, 6.5 and 6.1, respectively)[24]. It also offers a very high spatial resolution that allows an easy differentiation between the false and true aortic lumen and its branches. In dissections involving the aortic root, SSFP cine imaging allows the evaluation of aortic valve function, to assess the presence of regurgitation and at the same time, to measure both ventricular dimensions and function (Figure 4); all of which are vital parameters which directly affect therapeutic decisions in patients with acute aortic syndromes. The presence of liquid with an increased signal output in the pleura or pericardium are highly suggestive of aortic rupture with subsequent presence of free blood.

The fact that CMR does not emit ionizing radiation and its non-invasive nature make it a very attractive alternative to serially evaluate the diameter of aortic aneurysms. CMR has the potential to establish itself as the diagnostic tool of choice in the follow-up of patients with aortic pathology, due to the high reproducibility of its measurements.

In the case of intramural hematomas, the high spatial resolution allows to identify small hematomas that might have been overlooked even by CT. These blood collections are seen as hyperintense thickening in the aortic wall in weighted T1 sequence.

One of the drawbacks of CMR is that it is a study that requires a lot of time, and can be very uncomfortable for a patient in an acute setting.

Detection of intramyocardial fibrosis

The administration of gadolinium allows the evaluation of late enhancement, which correlates with the presence of interstitial fibrosis in hypertensive cardiomyopathy. The characteristic pattern is diffuse, and found mainly in the interventricular septum[25] (Figure 5). The presence of interstitial fibrosis correlates directly with the prognosis, since it is directly associated with an increased ventricular remodeling, systolic dysfunction and malignant arrhythmias[25]. Several small studies have demonstrated that around 45% of the patients with hypertension present late enhancement after gadolinium administration, which is associated with interstitial fibrosis and coronary microangiopathy[26]. However, it is necessary to assess the direct impact these findings have regarding mortality, progression to heart failure and the development of arrhythmias. Hopefully, quantitative evaluation will shed some light on this issue, as it did with hypertrophic cardiomyopathy. At this moment, there is no available evidence that clarifies the usefulness of diagnosing interstitial fibrosis in patients with hypertensive cardiomyopathy using CMR.

Diagnosis of secondary causes of hypertension

Patients who present with resistant hypertension (patients without blood pressure control that are already taking 3 different drugs, one of them being a diuretic) must undergo differential diagnosis in order to rule out a secondary cause of hypertension, which are present in approximately 5% of the population[27]. The majority of secondary causes are due to endocrine dysfunction, for which the first diagnostic step are biochemical panels and hormone level tests, only after those, are imaging methods solicited. However, CMR is a very useful tool used to speed up the diagnosis of these patients. The most common causes of secondary hypertension are: primary hyperaldosteronism, renovascular disease, chronic renal insufficiency and obstructive sleep apnea. Here we will make a very brief summary of the secondary causes that can be evaluated using CMR.

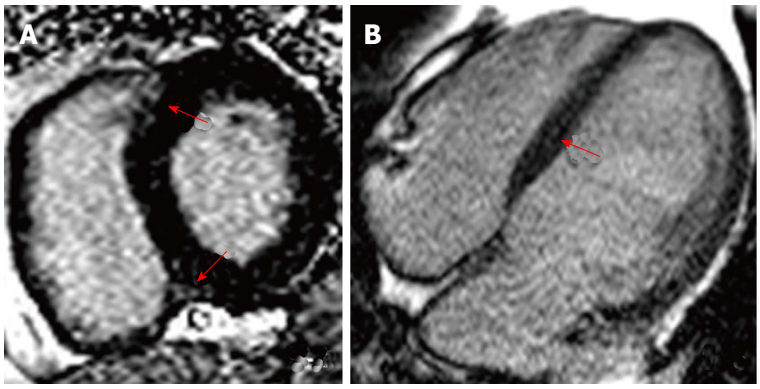

Figure 5 Cardiovascular magnetic resonance using inversion-recovery sequences. A: Patient with chronic hypertension that presents late enhancement in the areas connecting with the right ventricle (shown by red arrows); B: Patient with hypertensive cardiomyopathy in dilated phase, showing linear late enhancement in the septal wall.

PRIMARY HYPERALDOSTERONISM

The prevalence of this disease is still a matter of debate. Some studies report that it might be responsible for up to 6.1% of the cases of hypertension, and this number goes up to 18% when taking into account patients with BP of over 180/110 mmHg. It makes up 20% of the cases of secondary hypertension[28]. Clinical and laboratory findings typical of this disease include hypokalemia and hypertension; however, hypokalemia is only present in around half of the cases, and it's only found in latter stages of the disease[28,29]. A high degree of clinical suspicion is necessary to diagnose this illness, followed by biochemical confirmation (aldosterone/renin relationship in blood serum, confirmed with oral or parenteral sodium overload). The two principal causes of primary hyperaldosteronism are: adrenal adenoma (35%) and bilateral adrenal hyperplasia (65%). In these patients, it is mandatory to realize an imaging study to rule out the presence of neoplasm, since in these cases, surgical removal of the aldosterone producing tumor can cure the patient. Adenomas are usually hypo or isointense in T1 (when compared to the liver) and slightly hyperintense in T2. CMR has demonstrated a sensitivity of 70% and a specificity of 100% for the diagnosis of these tumors[30]; these values are very similar to those offered by CT[31].

RENOVASCULAR DISEASE

Up to 20% of patients who undergo cardiac catheterization present significant unilateral or bilateral renal artery stenosis[32] as an incidental finding; mainly in patients with extrarenal atherosclerosis[33], but it is still unclear how many of these patients have a direct repercussion on their BP. Renovascular disease is responsible for 35% of the cases of resistant hypertension[28]. CMR sequences used to study renal arteries are the same ones used during aortic angio-resonance. CMR with gadolinium has shown a sensitivity of 97% and a specificity of 93% for the diagnosis of renal artery stenosis[34], with the limitation of being contraindicated in patients with a creatinine clearance of less than 30 mL/min per 1.73 m^2. It must be noted that treatment using either balloon angioplasty or stenting has not shown to improve BP control or renal function[35,36] (Figure 6).

Other less frequent causes of secondary hypertension include Cushing's syndrome and pheocromocytoma. Both these entities have very characteristic clinical presentations, so once that there is enough clinical suspicion, a biochemical confirmation must be made. Once both these criteria have been met, CMR might be used; offering a very similar diagnostic capacity to that of CT.

CT

Over the last few decades, impressive technological advances have been made in the field of CT. The rise of machines with a very high spatial and temporal resolution coupled with ECG gating have allowed to obtain high precision coronary artery images, which is currently CT's main use in cardiology. Among the most relevant contributions to patients with hypertension we can find the following:

Coronary artery evaluation

The use of CT for the evaluation of coronary artery disease (CAD) constitutes one of the most important breakthroughs in non-invasive cardiology in the last few decades. The CT machines best suited for the acquisition of these studies are those with 16 detectors or more; nowadays the most used CT scanners have 64 detectors. The acquisition must always be ECG-gated and coordinated with contrast administration. Today, thanks to the various acquisition techniques (prospective protocols, diminished voltage, high pitch, *etc.*) the radiation dose per study has been reduced to around 1-2 mSv.

Coronary CT has shown a great diagnostic certainty when it comes to ruling out CAD with a sensitivity of 85% (95%CI: 79%-90%) and a specificity of 90% (95%CI: 83%-94%), with an area under the curve of 0.93[37]. Furthermore, the result of the Coronary CT has a direct relationship with prognosis, having a 3-year survival of over 95%[38].

The presence of coronary artery tortuosity has been related to female gender and the presence of chronic hypertension[39]. It is believed that these changes are

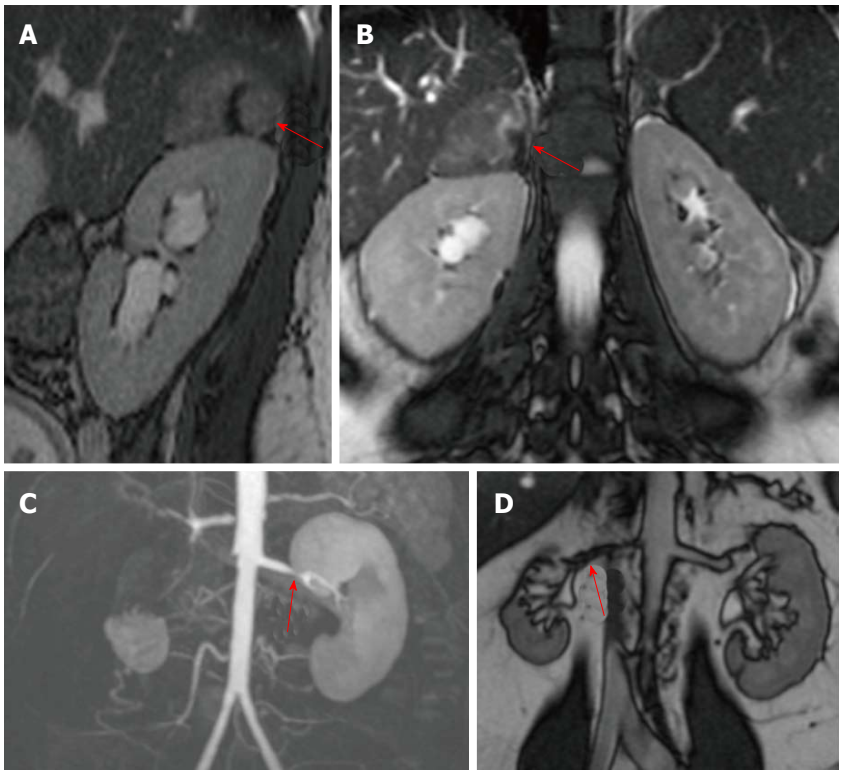

Figure 6 Evaluation of secondary hypertension. Cardiovascular magnetic resonance T2- sequences. Above is show a study taken in a 27-year-old female patient that presented with hypertension and a 5 cm × 4 cm adrenal mass, hyperintense when compared to the liver (marked by red arrows). On the bottom panels we see the contrast angiography study and T2 sequence, which show significant bilateral renal artery stenosis.

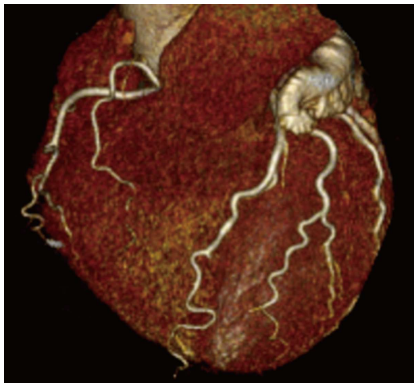

Figure 7 Coronary computed tomography of an 81-year-old hypertensive patient that demonstrates the presence of coronary tortuosity without atherosclerotic plaques.

due to an increase in the pressure and volume load in coronary vessels, therefore these changes can be seen as a consequence of hypertension[40]. There are studies that have related coronary tortuosity with diastolic dysfunction[41]; however, this finding has not been linked with worsening in the prognosis. The relevance of the presence of coronary artery tortuosity in coronary CT studies is still being debated (Figure 7).

Coronary calcium

Coronary calcium quantification currently is made with CT machines with prospective ECG-gating capacity, which translates to reduced radiation dosage per study (1-2 mSv). CT has a sensitivity of 96% and a positive predictive value of 80% for coronary calcium, with the drawback being that it only has a specificity of 46%[42]. Patients with an Agatston score of under 100 have a very good prognosis, with a very low probability of having a positive SPECT scan[43]. The risk for coronary disease increases linearly as the Agatson score rises[44-48]; the same is seen with mortality[49].

It is known that hypertension is an important risk factor for the development of atherosclerosis. Recently, a study included 8238 asymptomatic subjects and then divided them by category of BP (according to JNC-7), demonstrating that the risk of subclinical atherosclerosis, non-calcified coronary plaques and coronary calcium score of over 100 AU increase linearly as BP levels rise[50]. Previous studies have demonstrated that the progression of coronary calcification was significantly slower in patients with adequate BP control[51]. Erbel *et al*[52] have shown that as BP levels rise, so does coronary calcium scores (mainly in men) as does the rate of major adverse cardiovascular events. This suggests that in patients with a stage 2 hypertension (BP > 160/100) might be candidates for a CT study to rule out subclinical atherosclerotic. However, the impact of this strategy must be evaluated in future studies.

Ventricular volume and mass quantification

Retrospective protocols with radiation modulation have allowed the evaluation of volumes, dimensions and mass of cardiac structures. CT offers the advantage of being able to evaluate cardiac cavities with a great temporal and spatial resolution, along with the possibility of 3D volumetric visualization. A meta-analysis comprising 27 comparative studies between CT and CMR demonstrated excellent correlations in the measurement of telesystolic, telediastolic, ejection

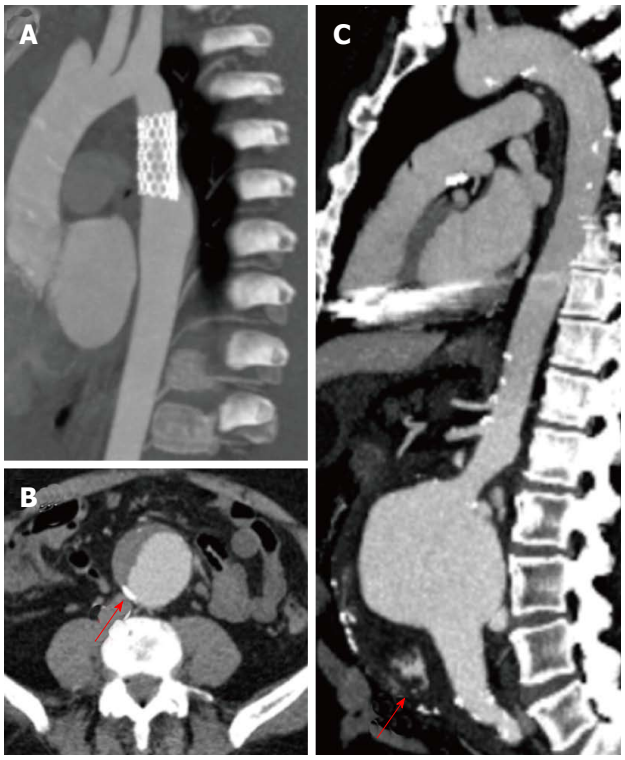

Figure 8 Aortic computed tomography. A: Patient with vascular endoprothesis, without vascular leaks; B: Dissected abdominal aortic aneurysm, arrow points to calcified atherosclerotic plaques; C: Ruptured infrarenal aortic aneurysm, seen as hyperdense material in the abdominal cavity (arrow).

fraction and left ventricular mass volumes (r = 0.93, 0.95, 0.93, 0.86 respectively)[53]. In hypertensive patients, the acquisition of this data has a direct impact on prognosis.

Right ventricular function has also been compared to CMR in several studies, showing good correlation between the 2 imaging modalities (r = 0.88), with an even higher reproducibility in CT[54,55]. However, the exactitude of the measurement of the right ventricle depends on the quality of the attenuation of right cavities, being necessary at least 175 HU to achieve a good measurement[56].

Vascular disease evaluation

CT is currently the method of choice to evaluate vascular anatomy, playing a key role in the diagnosis, risk stratification and treatment of aortic disease[57]. ECG-gated studies allow the acquisition of precise aortic root images free of movement artifacts. Also, CT is a diagnostic tool that is present in most hospital centers and unlike CMR, the acquisition times are very short.

The traditional CT protocol must include non-contrast images, mainly when an acute coronary syndrome is suspected, since this sequence allows the detection of intramural hematomas. Afterwards, ECG-gated angiography is performed using contrast, allowing the evaluation of vascular anatomy. Finally, in patients with vascular implants, late images can identify vascular leaks (Figure 8). In general, CT has a great performance in the diagnosis of aortic disease (up to 92%), including its main branches[58].

In Korean hypertensive patients of over 65 years, CT studies have shown a prevalence of thoracic aortic aneurysms in 36.5% and abdominal aortic aneurysms in 6%[59]. In another study, high coronary calcium scores correlated with an increased abdominal aortic diameter and a higher incidence of aneurysms (14%) when the score was > 400 AU, especially when this coincided with other cardiovascular risk factors[60]. However, due to the scarce evidence regarding this issue, there is currently no recommendation about screening studies in these patients.

Diagnosis of causes of secondary hypertension

The advantages of CT for the diagnosis of renovascular disease or adrenal adenomas have been mentioned previously: good spatial resolution, short acquisition times and widely available in many hospital centers. CT has demonstrated a sensitivity of 85%-87% and a specificity of 82%-93% for the diagnosis of adrenal adenomas[31]. In the evaluation of resistant hypertension, the usage of either CT or CMR can be used interchangeably, since their diagnostic accuracy is very similar.

NUCLEAR CARDIOLOGY

Nuclear cardiology is the most studied non-invasive cardiovascular imaging modality, only behind echocardiogram. Since the 1970's, SPECT established itself as the most widely diffused imaging technique to evaluate the presence of myocardial ischemia all around the world; today, PET and hybrid imaging offer valuable information used in everyday cardiologic practice.

Myocardial perfusion evaluation

Both SPECT and PET have developed protocols for the evaluation for myocardial ischemia, which is extremely useful in hypertensive patients with angina and multiple cardiovascular risk factors. Both techniques use protocols that involve image acquisition in rest and stress, either physical or pharmacological. In a meta-analysis, the validity for SPECT to detect myocardial ischemia has shown a sensitivity of 88% (95%CI: 88%-89%) with specificity of 61% (95%CI: 59%-62%) and an area under the curve of 0.86[14]. Regarding PET, it showed a better diagnostic capability, with a sensitivity of 84% (95%CI: 81%-87%) with a specificity of 81% (95%CI: 74%-87%) and an area under the curve of 0.92[14]. When merging different techniques, a modality called hybrid imaging, SPECT/CT has shown a sensitivity of 94%-96%, specificity of 92%-95% and a negative predictive value of 97%-99%. Finally, PET/CT has shown a slightly better performance over other imaging techniques, with a sensitivity of 93% and a specificity of 99% when using ^{15}O-H_2O radioisotope[61] (Figure 9).

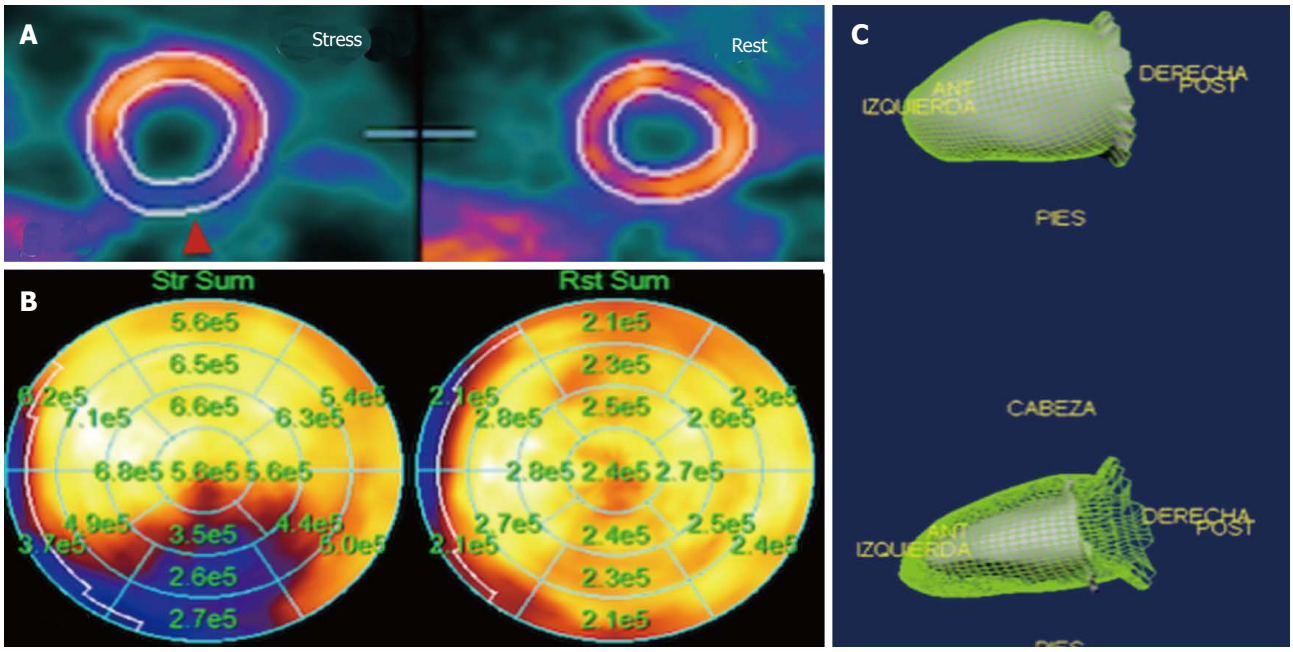

Figure 9 Myocardial perfusion positron emission tomography. A shows a perfusion defect in the posterior wall during stress; B shows flow quantification; the regional flows during stress are significantly increased in all areas, except in the inferior wall (territory of the right coronary artery), where the increase is significantly diminished; C shows a Gated-positron emission tomography to evaluate left ventricular function.

Patients with several risk factors can present with silent ischemia. A study of hypertensive patients without angina demonstrated that, when evaluated with pharmacologic stress-SPECT, the prevalence of reversible perfusion defects was of 27.7% and increased to 41.4% in patients with diabetes (P = 0.001), many of these being moderate to severe defects. In a sub-analysis of the same study, dyspnea and proteinuria were found to be independent predictors of silent ischemia[62].

Evaluation of ventricular function

The incorporation of cardiac-gating allowed evaluating left ventricular function at the same time as myocardial perfusion without the need of performing an additional radioisotope ventriculography, which implied a longer study time and radiation exposure. The calculation of the left ventricular ejection fraction (LVEF) is done automatically by software, without human intervention, which makes it a highly reproducible method.

Furthermore, it has shown to have a very good correlation with CMR (r = 0.82), without being statistically significant in the Bland-Altman analysis and high reproducibility[63-65]. LVEF calculation with Gated-PET has shown to have a good correlation with CMR (r = 0.76)[66], however, it has been observed that it underestimates both telesystolic and telediastolic volumes. Today, the clinical implications of this method are limited to complementing the myocardial perfusion study, with isolated LVEF measurement being reserved for investigation protocols exclusively.

Evaluation of endothelial lesion

Nuclear cardiology studies have been able to demonstrate the presence of endothelial lesions in patients with hypertension. A study made by our group evaluated the endothelial function using a triphasic protocol of 13N-Amonia PET (rest, cold pressor test and adenosine induced-hyperemia) in patients with recent diagnosis of hypertension, compared with a healthy control group. We found that 84% of the hypertensive patients had endothelial dysfunction measured by an ENDEVI score < 1.5 (Endothelial-dependent Vasodilation Index) and 58% presented vasomotor abnormalities measured by a CFR (coronary flow reserve) of < 2.5. These findings might be early findings of coronary artery disease[67]. Another similar study also found more significant endothelial dysfunction in patients with dyslipidemia, when compared with a healthy control group. Notably, the study group showed improvement after 8 wk of treatment with ezetimibe-simvastatin[68]. The findings of this study are very promising, especially regarding its implications in vascular risk screening, therapeutic decision-making and patient follow-up. However, more information is needed before this method demonstrates its usefulness in daily practice.

Sympathetic innervation

The autonomic sympathetic nervous system plays a fundamental role in the maintenance of hormonal and hemodynamic harmony in the cardiovascular system. In hypertensive patients, the increase in this system's activity leads to the development of hypertensive cardiomyopathy. The synaptic vesicles contain adrenaline, noradrenaline and the false neurotransmitter, an analogue of noradrenaline, guanetidine. This last one can be radioactively marked, transforming itself into meta-iodinebenylguanidine (^{123}I-*m*IBG) which,

when found in a great enough concentration can be measured by conventional gamma-cameras[69]. There are studies that have shown altered myocardial retention of ^{123}I-*m*IBG in hypertensive patients that also present left ventricular hypertrophy, mainly in the lateral and inferior left ventricular wall[70-72]. This translates to an abnormal neuroadrenergic cardiac function, which might be related to hypertension-induced myocardial damage.

This neurohormonal unbalance, diagnosed with ^{123}I-*m*IBG SPECT has shown to be related with the prognosis of patients in other diseases. In patients with heart failure, a heart/mediastinum ratio (H/M) < 1.6 is related with a higher mortality, progression of disease and arrhythmias[69]. These findings have been used to evaluate the appropriateness of the therapeutic choice, mainly concerning beta-blocker therapy, although there are studies that involve ACE/ARB inhibitors and spironolactone[69]. However, the role of sympathetic innervation evaluation in hypertensive patients hasn't been clearly defined.

Evaluation of causes of secondary hypertension

In patients with hypertension of renovascualr origin, the abnormalities in sympathetic innervation diagnosed with ^{123}I-*m*IBG SPECT are independent of the development of ventricular hypertrophy, which is a key aspect in which it differs from patients with essential hypertension. This might be due to the fact that myocardial injury due to hypertension of renal origin occurs earlier in the history of the disease compared with essential hypertension[73].

The use of FDG-PET in hyperaldosteronism is focused in the evaluation of adrenal masses, which show no retention of the tracer in the setting of a benign mass, unlike malignant tumors. A meta-analysis reported that FDG-PET showed an excellent diagnostic capacity to differentiate between benign and malignant adrenal masses, with a sensitivity of 97% (95%CI: 93%-98%) specificity of 91% (95%CI: 87%-94%) and an area under the curve of 0.96%[74]. When studying adrenal hyperplasia, it was seen that it did not demonstrated FDG activity.

Regarding pheochromocytoma, the vast majority showed activity when using both FDG and ^{123}I-*m*IBG, though the latter was found to be unable to diagnose pheochromocytomas associated with Von-Hippel-Lindau syndrome.

CONCLUSION

Multimodality imaging studies have helped to improve the understanding of a vast number of cardiovascular illnesses, including hypertension. Among the most recent contributions we can find the evaluation of dimensions and ventricular function using CMR, CT and Gated SPECT/PET studies, the ability to exclude the presence of coronary artery disease using non-invasive methods with a high diagnostic certainty; risk stratification in hypertensive cardiomyopathy using late enhancement techniques with the aid of gadolinium contrast in CMR or the evaluation of sympathetic innervation and the evaluation of different causes of resistant hypertension. The use of these techniques is still not commonplace in everyday clinical practice, and further studies are needed before they become a standard of common clinical practice; however, the future is certainly very promising.

REFERENCES

1 **Go AS**, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; **127**: 143-152 [PMID: 23283859 DOI: 10.1161/CIR.0b013e318282ab8f]

2 **Levy D**, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561-1566 [PMID: 2139921]

3 **Grothues F**, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002; **90**: 29-34 [PMID: 12088775 DOI: 10.1016/S0002-9149(02)02381-0]

4 **Kühl HP**, Bücker A, Franke A, Maul S, Nolte-Ernsting C, Reineke T, Hoffmann R, Günther RW, Hanrath P. Transesophageal 3-dimensional echocardiography: in vivo determination of left ventricular mass in comparison with magnetic resonance imaging. *J Am Soc Echocardiogr* 2000; **13**: 205-215 [PMID: 10708469 DOI: 10.1067/mje.2000.104474]

5 **Pitt B**, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, Kleiman J, Krause S, Burns D, Williams GH. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation* 2003; **108**: 1831-1838 [PMID: 14517164 DOI: 10.1161/01.CIR.0000091405.00772.6E]

6 **Friedrich MG**, Dahlöf B, Sechtem U, Unger T, Knecht M, Dietz R; TELMAR Investigators. Reduction (TELMAR) as assessed by magnetic resonance imaging in patients with mild-to-moderate hypertension--a prospective, randomised, double-blind comparison of telmisartan with metoprolol over a period of six months rationale and study design. *J Renin Angiotensin Aldosterone Syst* 2003; **4**: 234-243 [PMID: 14689371 DOI: 10.3317/jraas.2003.038]

7 **Solomon SD**, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, Cherif Papst C, Smith BA, Dahlöf B; Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators. Effect of the direct Renin inhibitor aliskiren, the Angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009; **119**: 530-537 [PMID: 19153265 DOI: 10.1161/CIRCULATIONAHA.108.826214]

8 **Milan A**, Caserta MA, Dematteis A, Naso D, Pertusio A, Magnino C, Puglisi E, Rabbia F, Pandian NG, Mulatero P, Veglio F. Blood pressure levels, left ventricular mass and function are correlated with left atrial volume in mild to moderate hypertensive patients. *J Hum Hypertens* 2009; **23**: 743-750 [PMID: 19262581 DOI: 10.1038/jhh.2009.15]

9 **Yamamoto M**, Seo Y, Kawamatsu N, Sato K, Sugano A, Machino-Ohtsuka T, Kawamura R, Nakajima H, Igarashi M, Sekiguchi Y, Ishizu T, Aonuma K. Complex left atrial appendage morphology

and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circ Cardiovasc Imaging* 2014; **7**: 337-343 [PMID: 24523417 DOI: 10.1161/CIRCIMAGING.113.001317]

10 **Fernández-Pérez GC**, Duarte R, Corral de la Calle M, Calatayud J, Sánchez González J. [Analysis of left ventricular diastolic function using magnetic resonance imaging]. *Radiologia* 2012; **54**: 295-305 [PMID: 22226377 DOI: 10.1016/j.rxeng.2011.09.003]

11 **Kawaji K**, Codella NC, Prince MR, Chu CW, Shakoor A, LaBounty TM, Min JK, Swaminathan RV, Devereux RB, Wang Y, Weinsaft JW. Automated segmentation of routine clinical cardiac magnetic resonance imaging for assessment of left ventricular diastolic dysfunction. *Circ Cardiovasc Imaging* 2009; **2**: 476-484 [PMID: 19920046 DOI: 10.1161/CIRCIMAGING.109.879304]

12 **Mendoza DD**, Codella NC, Wang Y, Prince MR, Sethi S, Manoushagian SJ, Kawaji K, Min JK, LaBounty TM, Devereux RB, Weinsaft JW. Impact of diastolic dysfunction severity on global left ventricular volumetric filling - assessment by automated segmentation of routine cine cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010; **12**: 46 [PMID: 20673372 DOI: 10.1186/1532-429X-12-46]

13 **Wu V,** Chyou JY, Chung S, Bhagavatula S, Axel L. Evaluation of diastolic function by three-dimensional volume tracking of the mitral annulus with cardiovascular magnetic resonance: comparison with tissue Doppler imaging. *J Cardiovasc Magn Reson* 2014; **16**: 71 [PMID: 25242199]

14 **Jaarsma C**, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, Nelemans PJ, Schalla S. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2012; **59**: 1719-1728 [PMID: 22554604 DOI: 10.1016/j.jacc.2011.12.040]

15 **Gupta S**, Berry JD, Ayers CR, Peshock RM, Khera A, de Lemos JA, Patel PC, Markham DW, Drazner MH. Left ventricular hypertrophy, aortic wall thickness, and lifetime predicted risk of cardiovascular disease: the Dallas Heart Study. *JACC Cardiovasc Imaging* 2010; **3**: 605-613 [PMID: 20541716 DOI: 10.1016/j.jcmg.2010.03.005]

16 **Shinnar M**, Fallon JT, Wehrli S, Levin M, Dalmacy D, Fayad ZA, Badimon JJ, Harrington M, Harrington E, Fuster V. The diagnostic accuracy of ex vivo MRI for human atherosclerotic plaque characterization. *Arterioscler Thromb Vasc Biol* 1999; **19**: 2756-2761 [PMID: 10559022 DOI: 10.1161/01.ATV.19.11.2756]

17 **Yuan C**, Mitsumori LM, Ferguson MS, Polissar NL, Echelard D, Ortiz G, Small R, Davies JW, Kerwin WS, Hatsukami TS. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation* 2001; **104**: 2051-2056 [PMID: 11673345 DOI: 10.1161/hc4201.097839]

18 **Saam T**, Ferguson MS, Yarnykh VL, Takaya N, Xu D, Polissar NL, Hatsukami TS, Yuan C. Quantitative evaluation of carotid plaque composition by in vivo MRI. *Arterioscler Thromb Vasc Biol* 2005; **25**: 234-239 [PMID: 15528475 DOI: 10.1161/01.ATV.0000149867.61851.31]

19 **Saam T**, Hatsukami TS, Takaya N, Chu B, Underhill H, Kerwin WS, Cai J, Ferguson MS, Yuan C. The vulnerable, or high-risk, atherosclerotic plaque: noninvasive MR imaging for characterization and assessment. *Radiology* 2007; **244**: 64-77 [PMID: 17581895 DOI: 10.1148/radiol.2441051769]

20 **Grimm JM,** Nikolaou K, Schindler A, Hettich R, Heigl F, Cyran CC, Schwarz F, Klingel R, Karpinska A, Yuan C, Dichgans M, Reiser MF, Saam T. Characteristics of carotid atherosclerotic plaques of chronic lipid apheresis patients as assessed by in vivo high-resolution CMR--a comparative analysis. *J Cardiovasc Magn Reson* 2012; **14**: 80 [PMID: 23194143 DOI: 10.1186/1532-429X-14-80]

21 **Zhao XQ**, Yuan C, Hatsukami TS, Frechette EH, Kang XJ, Maravilla KR, Brown BG. Effects of prolonged intensive lipid-lowering therapy on the characteristics of carotid atherosclerotic plaques in vivo by MRI: a case-control study. *Arterioscler Thromb Vasc Biol* 2001; **21**: 1623-1629 [PMID: 11597936 DOI: 10.1161/hq1001.098463]

22 **Verwoert GC**, Franco OH, Hoeks AP, Reneman RS, Hofman A, V Duijn CM, Sijbrands EJ, Witteman JC, Mattace-Raso FU. Arterial stiffness and hypertension in a large population of untreated individuals: the Rotterdam Study. *J Hypertens* 2014; **32**: 1606-1612; discussion 1612 [PMID: 24886821 DOI: 10.1097/HJH.0000000000000237]

23 **Shan Y**, Lin J, Xu P, Zeng M, Lin H, Yan H. The combined effect of hypertension and type 2 diabetes mellitus on aortic stiffness and endothelial dysfunction: an integrated study with high-resolution MRI. *Magn Reson Imaging* 2014; **32**: 211-216 [PMID: 24462301 DOI: 10.1016/j.mri.2013.12.011]

24 **Shiga T**, Wajima Z, Apfel CC, Inoue T, Ohe Y. Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: systematic review and meta-analysis. *Arch Intern Med* 2006; **166**: 1350-1356 [PMID: 16831999 DOI: 10.1001/archinte.166.13.1350]

25 **Maceira AM**, Mohiaddin RH. Cardiovascular magnetic resonance in systemic hypertension. *J Cardiovasc Magn Reson* 2012; **14**: 28 [PMID: 22559053 DOI: 10.1186/1532-429X-14-28]

26 **Andersen K**, Hennersdorf M, Cohnen M, Blondin D, Mödder U, Poll LW. Myocardial delayed contrast enhancement in patients with arterial hypertension: initial results of cardiac MRI. *Eur J Radiol* 2009; **71**: 75-81 [PMID: 18434065 DOI: 10.1016/j.ejrad.2008.03.009]

27 **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group.** Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981-2997 [PMID: 12479763 DOI: 10.1001/jama.288.23.2981]

28 **Calhoun DA**, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; **51**: 1403-1419 [PMID: 18391085 DOI: 10.1161/HYPERTENSIONAHA.108.189141]

29 **Mosso L**, Carvajal C, González A, Barraza A, Avila F, Montero J, Huete A, Gederlini A, Fardella CE. Primary aldosteronism and hypertensive disease. *Hypertension* 2003; **42**: 161-165 [PMID: 12796282 DOI: 10.1161/01.hyp.0000079505.25750.11]

30 **Sohaib SA**, Peppercorn PD, Allan C, Monson JP, Grossman AB, Besser GM, Reznek RH. Primary hyperaldosteronism (Conn syndrome): MR imaging findings. *Radiology* 2000; **214**: 527-531 [PMID: 10671606 DOI: 10.1148/radiology.214.2.r00fe09527]

31 **Lingam RK**, Sohaib SA, Rockall AG, Isidori AM, Chew S, Monson JP, Grossman A, Besser GM, Reznek RH. Diagnostic performance of CT versus MR in detecting aldosterone-producing adenoma in primary hyperaldosteronism (Conn's syndrome). *Eur Radiol* 2004; **14**: 1787-1792 [PMID: 15241622 DOI: 10.1007/s00330-004-2308-2]

32 **Aqel RA**, Zoghbi GJ, Baldwin SA, Auda WS, Calhoun DA, Coffey CS, Perry GJ, Iskandrian AE. Prevalence of renal artery stenosis in high-risk veterans referred to cardiac catheterization. *J Hypertens* 2003; **21**: 1157-1162 [PMID: 12777953 DOI: 10.1097/00004872-200306000-00016]

33 **de Mast Q**, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens* 2009; **27**: 1333-1340 [PMID: 19365285 DOI: 10.1097/HJH.0b013e328329bbf4]

34 **Tan KT**, van Beek EJ, Brown PW, van Delden OM, Tijssen J, Ramsay LE. Magnetic resonance angiography for the diagnosis of renal artery stenosis: a meta-analysis. *Clin Radiol* 2002; **57**: 617-624 [PMID: 12096862 DOI: 10.1053/crad.2002.0941]

35 **van Jaarsveld BC**, Krijnen P, Pieterman H, Derkx FH, Deinum J, Postma CT, Dees A, Woittiez AJ, Bartelink AK, Man in't Veld AJ, Schalekamp MA. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal

Artery Stenosis Intervention Cooperative Study Group. *N Engl J Med* 2000; **342**: 1007-1014 [PMID: 10749962 DOI: 10.1056/NEJM200004063421403]

36 **Shetty R**, Biondi-Zoccai GG, Abbate A, Amin MS, Jovin IS. Percutaneous renal artery intervention versus medical therapy in patients with renal artery stenosis: a meta-analysis. *EuroIntervention* 2011; **7**: 844-851 [PMID: 22082580 DOI: 10.4244/EIJV7I7A132]

37 **Miller JM**, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; **359**: 2324-2336 [PMID: 19038879 DOI: 10.1056/NEJMoa0806576]

38 **Min JK**, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011; **58**: 849-860 [PMID: 21835321 DOI: 10.1016/j.jacc.2011.02.074]

39 **Li Y**, Shen C, Ji Y, Feng Y, Ma G, Liu N. Clinical implication of coronary tortuosity in patients with coronary artery disease. *PLoS One* 2011; **6**: e24232 [PMID: 21904618 DOI: 10.1371/journal.pone.0024232]

40 **Xie X**, Wang Y, Zhou H. Impact of coronary tortuosity on the coronary blood flow: a 3D computational study. *J Biomech* 2013; **46**: 1833-1841 [PMID: 23777815 DOI: 10.1016/j.jbiomech.2013.05.005]

41 **Turgut O**, Yilmaz A, Yalta K, Yilmaz BM, Ozyol A, Kendirlioglu O, Karadas F, Tandogan I. Tortuosity of coronary arteries: an indicator for impaired left ventricular relaxation? *Int J Cardiovasc Imaging* 2007; **23**: 671-677 [PMID: 17216126 DOI: 10.1007/s10554-006-9186-4]

42 **He ZX**, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, Mahmarian JJ. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 2000; **101**: 244-251 [PMID: 10645919 DOI: 10.1161/01.CIR.101.3.244]

43 **Lamont DH**, Budoff MJ, Shavelle DM, Shavelle R, Brundage BH, Hagar JM. Coronary calcium scanning adds incremental value to patients with positive stress tests. *Am Heart J* 2002; **143**: 861-867 [PMID: 12040349 DOI: 10.1067/mhj.2002.120972]

44 **Taylor AJ**, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol* 2005; **46**: 807-814 [PMID: 16139129 DOI: 10.1016/j.jacc.2005.05.049]

45 **Arad Y**, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol* 2005; **46**: 158-165 [PMID: 15992651 DOI: 10.1016/j.jacc.2005.02.088]

46 **Raggi P**, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J* 2001; **141**: 375-382 [PMID: 11231434 DOI: 10.1067/mhj.2001.113220]

47 **Raggi P**, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004; **43**: 1663-1669 [PMID: 15120828 DOI: 10.1016/j.jacc.2003.09.068]

48 **Wayhs R**, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002; **39**: 225-230 [PMID: 11788211 DOI: 10.1016/S0735-1097(01)01737-5]

49 **Budoff MJ**, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 2007; **49**: 1860-1870 [PMID: 17481445 DOI: 10.1016/j.jacc.2006.10.079,]

50 **Im TS**, Chun EJ, Lee MS, Adla T, Kim JA, Choi SI. Grade-response relationship between blood pressure and severity of coronary atherosclerosis in asymptomatic adults: assessment with coronary CT angiography. *Int J Cardiovasc Imaging* 2014; **30** Suppl 2: 105-112 [PMID: 25178841 DOI: 10.1007/s10554-014-0522-9]

51 **Sipahi I**, Tuzcu EM, Schoenhagen P, Wolski KE, Nicholls SJ, Balog C, Crowe TD, Nissen SE. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. *J Am Coll Cardiol* 2006; **48**: 833-838 [PMID: 16904557 DOI: 10.1016/j.jacc.2006.05.045]

52 **Erbel R**, Lehmann N, Möhlenkamp S, Churzidse S, Bauer M, Kälsch H, Schmermund A, Moebus S, Stang A, Roggenbuck U, Bröcker-Preuss M, Dragano N, Weimar C, Siegrist J, Jöckel KH. Subclinical coronary atherosclerosis predicts cardiovascular risk in different stages of hypertension: result of the Heinz Nixdorf Recall Study. *Hypertension* 2012; **59**: 44-53 [PMID: 22124435 DOI: 10.1161/HYPERTENSIONAHA.111.180489]

53 **Sharma A**, Einstein AJ, Vallakati A, Arbab-Zadeh A, Mukherjee D, Lichstein E. Meta-analysis of global left ventricular function comparing multidetector computed tomography with cardiac magnetic resonance imaging. *Am J Cardiol* 2014; **113**: 731-738 [PMID: 24355312 DOI: 10.1016/j.amjcard.2013.11.016]

54 **Raman SV**, Shah M, McCarthy B, Garcia A, Ferketich AK. Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *Am Heart J* 2006; **151**: 736-744 [PMID: 16504643 DOI: 10.1016/j.ahj.2005.04.029]

55 **Guo YK**, Gao HL, Zhang XC, Wang QL, Yang ZG, Ma ES. Accuracy and reproducibility of assessing right ventricular function with 64-section multi-detector row CT: comparison with magnetic resonance imaging. *Int J Cardiol* 2010; **139**: 254-262 [PMID: 19028401 DOI: 10.1016/j.ijcard.2008.10.031]

56 **Aho MR**, Gebregziabher M, Schoepf UJ, Suranyi P, Lee H, Gregg D, Costello P, Zwerner PL. Impact of right ventricular contrast attenuation on the accuracy of right ventricular function analysis at cardiac multi-detector-row CT. *Eur J Radiol* 2010; **73**: 560-565 [PMID: 19167178 DOI: 10.1016/j.ejrad.2008.12.011]

57 **Erbel R,** Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B,Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**: 2873-2926 [PMID: 25173340 DOI: 10.1093/eurheartj/ehu281]

58 **Agarwal PP**, Chughtai A, Matzinger FR, Kazerooni EA. Multidetector CT of thoracic aortic aneurysms. *Radiographics* 2009; **29**: 537-552 [PMID: 19325064 DOI: 10.1148/rg.292075080]

59 **Cho IJ**, Jang SY, Chang HJ, Shin S, Shim CY, Hong GR, Chung N. Aortic aneurysm screening in a high-risk population: a non-contrast computed tomography study in korean males with hypertension. *Korean Circ J* 2014; **44**: 162-169 [PMID: 24876857 DOI: 10.4070/kcj.2014.44.3.162]

60 **Cho IJ**, Heo R, Chang HJ, Shin S, Shim CY, Hong GR, Min JK, Chung N. Correlation between coronary artery calcium score and aortic diameter in a high-risk population of elderly male hypertensive patients. *Coron Artery Dis* 2014; **25**: 698-704 [PMID: 25051100 DOI: 10.1097/MCA.0000000000000150]

61 **Gaemperli O**, Bengel FM, Kaufmann PA. Cardiac hybrid imaging. *Eur Heart J* 2011; **32**: 2100-2108 [PMID: 21406437 DOI: 10.1093/eurheartj/ehr057]

62 **Lacourcière Y**, Côté C, Lefebvre J, Dumont M. Noninvasive detection of silent coronary artery disease in patients with essential hypertension, alone or associated with type 2 diabetes mellitus, using dipyridamole stress 99mtechnetium-sestamibi myocardial

perfusion imaging. *Can J Cardiol* 2006; **22** Suppl A: 16A-21A [PMID: 16485055]

63 **Abidov A**, Germano G, Hachamovitch R, Slomka P, Berman DS. Gated SPECT in assessment of regional and global left ventricular function: an update. *J Nucl Cardiol* 2013; **20**: 1118-1143; quiz 1118-1143 [PMID: 24234974 DOI: 10.1007/s12350-013-9792-1]

64 **Thorley PJ**, Plein S, Bloomer TN, Ridgway JP, Sivananthan UM. Comparison of 99mTc tetrofosmin gated SPECT measurements of left ventricular volumes and ejection fraction with MRI over a wide range of values. *Nucl Med Commun* 2003; **24**: 763-769 [PMID: 12813194]

65 **Thorley PJ**, Smith JM. Repeatability of left ventricular ejection fraction and volume measurement for 99mTc-tetrofosmin gated single photon emission computed tomography (SPECT). *Nucl Med Commun* 2005; **26**: 345-349 [PMID: 15753794]

66 **Li Y**, Wang L, Zhao SH, He ZX, Wang DY, Guo F, Fang W, Yang MF. Gated F-18 FDG PET for assessment of left ventricular volumes and ejection fraction using QGS and 4D-MSPECT in patients with heart failure: a comparison with cardiac MRI. *PLoS One* 2014; **9**: e80227 [PMID: 24404123 DOI: 10.1371/journal.pone.0080227]

67 **Alexánderson E**, Jácome R, Jiménez-Santos M, Ochoa JM, Romero E, Cabral MA, Ricalde A, Iñarra F, Meave A, Alexánderson G. Evaluation of the endothelial function in hypertensive patients with 13N-ammonia PET. *J Nucl Cardiol* 2012; **19**: 979-986 [PMID: 22689073 DOI: 10.1007/s12350-012-9584-z]

68 **Alexanderson E**, García-Rojas L, Jiménez M, Jácome R, Calleja R, Martínez A, Ochoa JM, Meave A, Alexanderson G. Effect of ezetimibe-simvastatine over endothelial dysfunction in dyslipidemic patients: assessment by 13N-ammonia positron emission tomography. *J Nucl Cardiol* 2010; **17**: 1015-1022 [PMID: 20737263 DOI: 10.1007/s12350-010-9273-8]

69 **Chirumamilla A**, Travin MI. Cardiac applications of 123I-mIBG imaging. *Semin Nucl Med* 2011; **41**: 374-387 [PMID: 21803188 DOI: 10.1053/j.semnuclmed.2011.04.001]

70 **Mitani I,** Sumita S, Takahashi N, Ochiai H, Ishii M. 123I-MIBG myocardial imaging in hypertensive patients: abnormality progresses with left ventricular hypertrophy. *Ann Nucl Med* 1996; **10**: 315-21 [PMID: 8883707]

71 **Kuwahara T**, Hamada M, Hiwada K. Direct evidence of impaired cardiac sympathetic innervation in essential hypertensive patients with left ventricular hypertrophy. *J Nucl Med* 1998; **39**: 1486-1491 [PMID: 9744329]

72 **Shimizu M**, Ino H, Okeie K, Emoto Y, Yamaguchi M, Yasuda T, Fujino N, Fujii H, Fujita S, Nakajima K, Taki J, Mabuchi H. Cardiac sympathetic activity in the asymmetrically hypertrophied septum in patients with hypertension or hypertrophic cardiomyopathy. *Clin Cardiol* 2000; **23**: 365-370 [PMID: 10803446 DOI: 10.1002/clc.4960230512]

73 **Ohya Y**, Sasaki M, Fujishima S, Kagiyama S, Onaka U, Kaseda S, Ohmori S, Kuwabara Y, Abe I, Fujishima M. Myocardial imaging with 123I-metaiodobenzylguanidine in essential hypertension and renovascular hypertension. *Clin Exp Hypertens* 2001; **23**: 293-304 [PMID: 11349821]

74 **Boland GW**, Dwamena BA, Jagtiani Sangwaiya M, Goehler AG, Blake MA, Hahn PF, Scott JA, Kalra MK. Characterization of adrenal masses by using FDG PET: a systematic review and meta-analysis of diagnostic test performance. *Radiology* 2011; **259**: 117-126 [PMID: 21330566 DOI: 10.1148/radiol.11100569]

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REVIEW

Hypertensive cardiomyopathy: A clinical approach and literature review

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Abstract

Hypertensive cardiomyopathy (HTN-CM) is a structural cardiac disorder generally accompanied by concentric left ventricular hypertrophy (LVH) associated with diastolic or systolic dysfunction in patients with persistent systemic hypertension. It occurs in the absence of other cardiac diseases capable of causing myocardial hypertrophy or cardiac dysfunction. Persistent systemic hypertension leads to structural and functional myocardial abnormalities resulting in myocardial ischemia, fibrosis, and hypertrophy. HTN-CM is predominantly a disease of impaired relaxation rather than impaired contractility, so patients are usually asymptomatic during resting conditions. However, their stiff left ventricles become incapable of handling increased blood volume and cannot produce appropriate cardiac output with the slight change of circulating volume that may occur during exercise. Importantly, the accompanying LVH is itself a risk factor for mortality and morbidity. Therefore, early detection of LVH development in patients with hypertension (referred to as HTN-CM) is critical for optimal treatment. In addition to pathological findings, echocardiography and cardiac magnetic resonance imaging are ideal tools for the diagnosis of HTN-CM. Timely diagnosis of this condition and utilization of appropriate treatment are required to improve morbidity and mortality in hypertensive patients. This review article presents an overview of the multidimensional impact of myocardial disorder in patients with hypertension. Relevant literature is highlighted and the effects of hypertension on cardiac hypertrophy and heart failure development are discussed, including possible therapeutic options.

Key words: Hypertension; Diagnosis; Cardiomyopathy; Hypertrophy; Risk assessment

Core tip: Hypertensive cardiomyopathy is a structural cardiac disorder generally accompanied by left ventricular hypertrophy associated with diastolic and/or systolic dysfunction in patients with persistent systemic hypertension, in the absence of other cardiac diseases. Because regression of myocardial hypertrophy is associated with a reduction in cardiovascular risk along with the improvement of cardiac function, timely diagnosis of the disease-specific pathophysiology and appropriate treatment strategy including maintaining optimal blood pressure control is very important in the care of patients with hypertension. In the present review manuscript, we have described the outline of hypertensive cardiomyopathy,

pathophysiological feature of the disease, diagnosis and the treatment.

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INTRODUCTION

Hypertensive cardiomyopathy (HTN-CM) is a structural cardiac disorder generally accompanied by concentric left ventricular hypertrophy (LVH) associated with diastolic or systolic dysfunction in patients with persistent systemic hypertension. HTN-CM is difficult to distinguish from other cardiac diseases that cause myocardial hypertrophy, such as hypertrophic cardiomyopathy, Fabry disease, or cardiac amyloidosis. However, when other causes are ruled out, leaving hypertension the only possible cause for LVH development, this is considered to be HTN-CM.

Hypertension (HTN) is a major global health issue, accounting for approximately 50% cases of both stroke and ischemic heart disease, and approximately 13% of the total deaths worldwide[1]. Persistent hypertension can cause structural and functional myocardial abnormalities. LVH and remodeling, frequently seen in patients with hypertension[2], is initially an adaptive response of a normal heart to an increased afterload. Hypertension leads to interstitial myocardial fibrosis[3], which has been linked to LVH development and diastolic dysfunction[4].

The renin-angiotensin-aldosterone system (RAAS) is also an important determinant of the hypertrophic response[5-7]. A relationship between angiotensin Ⅱ and development of myocardial fibrosis has been described as well[8]. Importantly, the Framingham Heart Study revealed that LVH is a risk factor for cardiovascular morbidity and mortality, independent of other cardiovascular risk factors, including elevated blood pressure itself[4,9,10]. In addition, patients with persistent hypertension and LVH are susceptible to sudden death[11]. These observations emphasize the importance of early diagnosis and effective treatment of hypertension to prevent cardiac complications[12].

In this review article, we summarize the pathophysiology, mechanism, diagnostic evaluation, and management options of HTN-CM. We have focused on human studies in order to emphasize the importance of early identification and optimization of treatment in patients with hypertension.

EPIDEMIOLOGY

The prevalence of LVH varies with the severity of hypertension, ranging from 20% in mild to almost 100% in severe or complicated hypertension[13]. Cuspidi *et al*[14], who performed a review of the echocardiographic data of 37700 individuals, reported that the prevalence rate of LVH was 19%-48% in untreated hypertensive cohorts and 58%-77% in high-risk hypertensive patients.

The development of LVH is a relatively early response to hypertension, particularly in children and adolescents[15]. Transient hypertension induced by mental stress as well as extensive elevation of blood pressure during exercise can also induce LVH[16,17]. The Framingham Heart Study showed that the left ventricular (LV) mass can be increased prior to the development of overt hypertension[18]. LVH in patients with hypertension predominantly results not only from a chronic increase in LV afterload but also a genetic component such as the DD genotype of the angiotensin-converting-enzyme (*ACE*) gene and B2 bradykinin receptor polymorphism[19-22].

Devereux *et al*[23] reported that the prevalence of LVH among hypertensive patients is influenced by gender, obesity, and possibly age. Sex-specific criteria for LV mass index identify LVH in more women than men with systemic hypertension[24].

MYOCARDIAL REMODELING AND PATTERNS OF LVH IN HTN-CM

Conventional echocardiography provides useful morphological information of LVH patterns. For example, patients with hypertrophic cardiomyopathy (HCM) frequently show asymmetrical septal hypertrophy of the LV; this is the most characteristic finding[25]. In contrast, LVH associated with hypertension or HTN-CM is characterized by symmetrical (concentric) LV hypertrophy. However, 13%-31% of patients with HCM show symmetrical hypertrophy[26,27], whereas 4%-47% of hypertensive patients manifest asymmetrical septal hypertrophy[27,28].

LV remodeling/hypertrophy in HTN-CM may represent an adaptive response to hemodynamic overload imposed by systemic hypertension[2]. This compensatory response can be explained by the Laplace law (Figure 1, reproduced from[2,29]). Sustained elevated blood pressure leads to an increase in LV wall stress, which is a major determinant of myocardial oxygen demand. In response to increased LV wall stress, the LV wall thickens and the LV mass increases, thereby resulting in the normalization of wall stress and development of a structural pattern known as concentric hypertrophy. Alternatively, an increase in blood volume could lead to an increase in the chamber radius, resulting in eccentric hypertrophy[2].

Ganau *et al*[24] investigated patterns of LVH and geometric remodeling in patients with essential hypertension. They reported that LV mass index and relative wall thickness were normal in 52% of the patients,

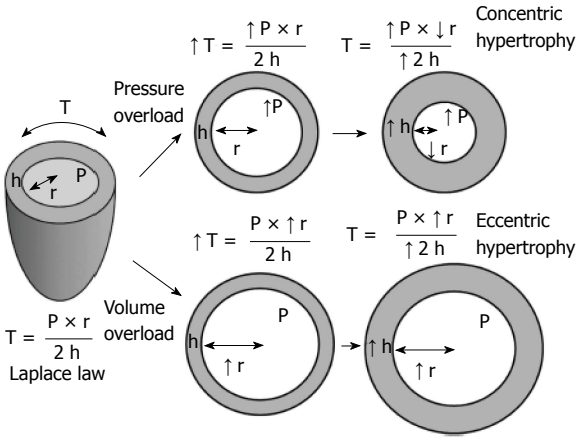

Figure 1 The Laplace law and how it may explain the development of concentric and eccentric left ventricular hypertrophy in response to pressure and volume overload, respectively. Reproduced from Nadruz and Hum[2], 2015; Frolich and Susic[29], 2012. T: Tension or stress in the LV wall; P: LV pressure; r: Radius of the chamber; h: LV wall thickness.

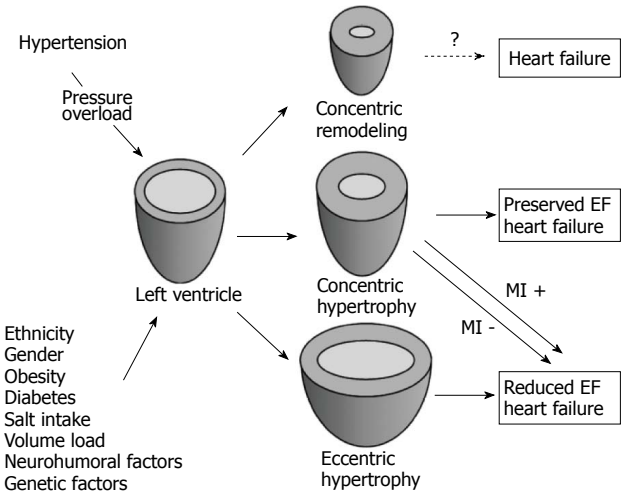

Figure 2 Pathways of left ventricular remodeling progression secondary to systemic hypertension. Reproduced from Nadruz and Hum[2], 2015. EF: Ejection fraction; MI: Myocardial infarction.

whereas 13% had increased relative wall thickness with normal ventricular mass (concentric remodeling), 27% had increased mass with normal relative wall thickness (eccentric hypertrophy), and only 8% had "typical" hypertensive concentric hypertrophy (increase in both variables). Cuspidi *et al*[14] also reported that concentric LV hypertrophy is not the most frequent geometric pattern and is less commonly seen than is eccentric hypertrophy in the hypertensive subjects. Indeed, the geometric pattern of LVH affects the prognosis[30]. Patients without an increase in absolute mass, but with an increase in relative wall thickness or in the wall thickness-to-cavity diameter ratio (concentric remodeling) have the same adverse risk as those with an increase in both mass and relative wall thickness (concentric hypertrophy)[24]. Velagaleti recently reported that the data from the Framingham Heart Study revealed that heart failure risk varied by LV geometric pattern, with eccentric and concentric hypertrophy predisposing to heart failure with reduced and preserved ejection fraction, respectively, after a mean follow-up of 21 years[31].

Recent reports[32,33] have described that a transition from LV concentric hypertrophy to dilation and systolic dysfunction is not a common finding, especially in the absence of coronary heart disease[2]. Observation of over one thousand patients with concentric LV hypertrophy and normal ejection fraction by Milani *et al*[32] revealed only 13% who progressed to systolic dysfunction by three years follow-up and this transition occurred after myocardial infarction in 42.5% of the patients. The various pathways of LV remodeling progression among hypertensive subjects are well described by Nadruz (Figure 2, reproduced from[2])

Interestingly, Khouri *et al*[34] recently suggested that concentric or eccentric LVH can each be subclassified into two subgroups using cardiac magnetic resonance imaging. This yields four distinct geometric patterns: eccentric non-dilated, eccentric dilated, concentric non-dilated, and concentric dilated[34]. They found that dilated type LVH was more frequently associated with low ejection fraction and elevated troponin levels. Their findings were also supported by the investigation using echocardiography performed by Bang *et al*[35]. This newly suggested re-classification of hypertensive patients with LVH into four groups according to the LV dilatation and increased concentricity may provide new insights into the hemodynamic and LV functional alteration in this population.

CLINICAL MANIFESTATION IN PATIENTS WITH HTN-CM

Persistent systemic hypertension induces LVH, fibrosis, diastolic dysfunction, and an increase in the activation of the RAAS, which leads to congestive heart failure[36,37]. One of the mechanisms of heart failure in patients with hypertension is LV diastolic dysfunction. LV diastolic dysfunction associated with hypertension is morphologically characterized by LV wall thickening and increased left atrial (LA) volume. In particular, LA volume is related to LV filling pressure or LA pressure, and is a prognostic marker of various cardiac diseases[38,39]. In advanced stages, hypertension induces eccentric LVH and LV systolic dysfunction[40]. Data from the Framingham Heart Study revealed that LVH is consistently identified as an independent risk factor for cardiovascular morbidity and mortality[4,9,10]. Further, hypertensive LVH or HTN-CM is associated with atrial fibrillation: the incidence increases by 40%-50% in the presence of hypertension[41]. Messerli *et al*[42] documented a strong correlation between hypertensive LVH or HTN-CM and an increased frequency of ventricular arrhythmias. This emphasizes the importance of understanding of the clinical manifestations of HTN-CM.

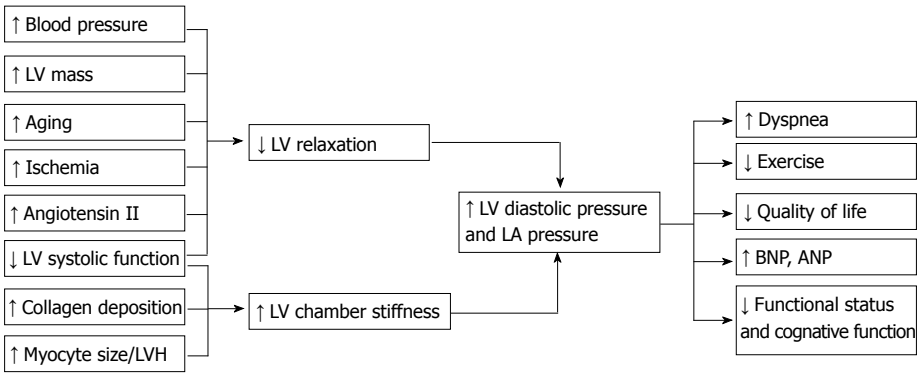

Figure 3 Causes of left ventricular diastolic dysfunction and its clinical consequences. Reproduced from Phillips and Diamond[48], 2001. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; LA: Left atrial; LVH: Left ventricular hypertrophy.

LVH

The pathophysiological mechanism by which LVH develops in patients with persistent systemic hypertension has been described in the previous sections. Both hypertension and LVH are affected by the same factors, such as angiotensin II, norepinephrine and epinephrine, and an increased peripheral and cardiac sympathetic drive[43,44]. LVH is a significant predictor for heart failure development and is associated with increased mortality[4,9,10]. Notably, patients with persistent hypertension causing HTN-CM often concomitantly have other atherosclerotic risk factors, such as obesity and diabetes. Although hypertension is the leading risk factor for LVH development, substantial evidence indicates that diabetes can also trigger this pathological remodeling response[45]. Obesity is associated with an increased risk of concentric LVH independent of elevated blood pressures[23]. Hypertensive LVH can lead to ventricular diastolic dysfunction; it is also a risk factor for myocardial infarction, which is a principal cause of LV systolic dysfunction[46,47].

Diastolic dysfunction

In addition to LVH, diastolic dysfunction is a major factor contributing to hypertensive heart disease and the progression to "symptomatic" congestive heart failure[48]. Approximately 40% of patients with hypertensive heart disease have normal systolic function but abnormal diastolic function[48,49]. In fact, LV diastolic dysfunction is the main cause of symptomatic heart failure development in patients with hypertension[50]. LV diastolic dysfunction in HTN-CM is morphologically characterized by LV wall thickening and a persistent elevation of LV end-diastolic pressure, causing increased LA volume. The increased LA volume is the result of elevated LV filling pressure or LA pressure, which presents as exercise intolerance in patients with HTN-CM.

Ischemia is also an important factor leading to diastolic impairment in HTN-CM. Hypertension itself accelerates arteriosclerosis in both systemic and coronary arteries[11,51]. Furthermore, a long-standing increase in LV wall stress and workload causes LVH, and is associated with an increase in the diameter of myocardial cells without a proportional proliferation of the capillary vasculature[11]. Therefore, myocardial tissues in patients with persistent hypertension suffer from ischemia, the so-called mismatch between coronary circulation and oxygen requirement of the myocardium. This underlying myocardial ischemia and hypertrophy leads to the association of HTN-CM rather predominantly with relaxation abnormalities. The impairment of LV pressure/volume reserve means that patients with HTN-CM who have impaired relaxation are usually asymptomatic during resting conditions, but a slight change in circulating volume or an elevation of systemic vascular resistance, such as occurs during exercise, renders their stiff LV incapable of handling the increased blood volume and it cannot produce appropriate cardiac output. This can lead to a progressive decline in ventricular function and ultimately congestive heart failure. Phillips *et al*[48] described the mechanisms underlying LV diastolic dysfunction and the clinical consequences of this dysfunction in patients with hypertensive LVH or HTN-CM (Figure 3, reproduced from[50]).

Systolic dysfunction

The Framingham Heart Study reported that severe LV systolic dysfunction occurs in 3%-6% of hypertensive patients[40]. An eccentric pattern of hypertrophy is a particularly strong risk factor for LV systolic dysfunction, as shown by the Cardiovascular Health Study[52]. Severe LV systolic dysfunction [ejection fraction (EF) < 30%] occurred in 6% in the Framingham Heart Study[52]; however, hypertensive LV remodeling/hypertrophy is certainly followed by chamber dilation and heart failure if not treated appropriately. Although LV function may be initially compensatory, it is followed by progressive worsening of symptoms that ends with cardiac death[2,53]. This phenomenon was consistently reproduced in animal models of pressure overload due to aortic banding, as well as in humans with aortic stenosis and hypertrophic cardiomyopathy[53].

DIAGNOSIS OF HTN-CM

Pathological findings of HTN-CM

Pathological evaluation is important in the differential

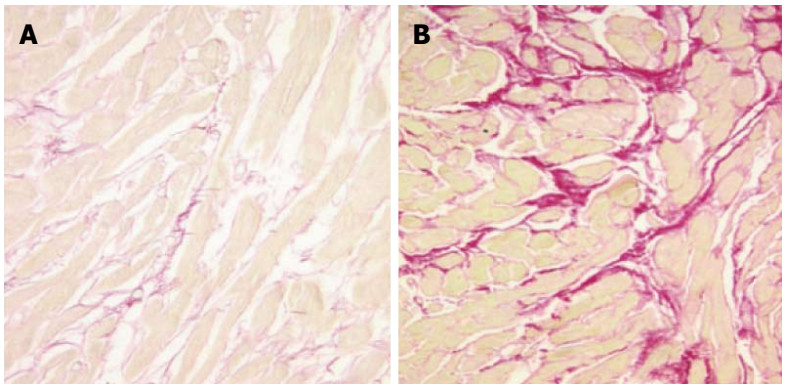

Figure 4 Comparison of collagen fibers in endomyocardial tissue. A: Specimen from a normotensive person; B: Specimen from a patient with hypertensive heart disease. The sections were stained with picrosirius red. Collagen fibers are stained red. Reproduced from Deiz *et al*[54], 2005.

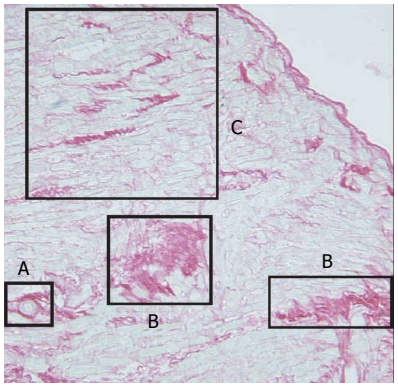

Figure 5 Endomyocardial tissue from a hypertensive patient with left ventricular hypertrophy. A: Perivascular fibrosis; B: Microscopic scarring; C: Interstitial fibrosis. Sections were stained with picrosirius red. Collagen tissue is stained red. Reproduced from Diez[56] 2007.

diagnosis of HTN-CM. Invasive endomyocardial biopsy (EMB) remains a powerful tool for obtaining a specific diagnosis in HTN-CM patients. A histopathological study revealed myocyte hypertrophy and moderate interstitial fibrosis, which was consistent with HTN-CM[54,55]. Cardiomyocyte hypertrophy in HTN-CM occurs as a result of structural remodeling of the myocardium. It is a consequence of a number of pathologic processes that are mediated by mechanical, neurohormonal, and cytokine routes and take place in the cardiomyocyte and noncardiomyocyte compartments of the heart[54]. An exaggerated accumulation of fibers within the myocardial interstitium and surrounding intramural coronary arteries and arterioles has been consistently found in postmortem human hearts and biopsy samples from patients with HTN-CM[55-57].

The collagen volume fraction is significantly increased in the hearts of patients with HTN-CM when compared with normotensive patients (Figures 4 and 5, reproduced from[54,56]). Several clinical observations support the possibility that fibrosis occurs by mechanical stress. Tanaka *et al*[58] reported that the collagen volume fraction of the LV free wall probably reflects transmural gradients of wall stress. Rossi found that the extent and severity of ventricular fibrosis paralleled the enlargement of cardiomyocytes[59]. Querejeta *et al*[60] reported that the collagen volume fraction correlated with systolic blood pressure and pulse pressure in the myocardium of patients with hypertension.

The RAAS and ACE activity may be an important determinant of the hypertrophic response[5-7]. The effect of angiotensin Ⅱ may be a factor in the promotion of myocardial fibrosis[61]. Myocardial disarray (defined as bundles of myocytes oriented perpendicularly or obliquely to each other or interspersed in different directions), which is generally seen in patients with HCM, may also appear in patients in HTN-CM, although the distribution of myocardial disarray is relatively smaller in HTN-CM than in HCM. A previous study by Kato et *al*[62] classified patients as HCM if they showed > 33% myocyte disarray in at least one of the cross sections examined. Patients with no or < 5% myocyte disarray in all cross sections examined were classified as HTN-CM (Figure 6, reproduced from[62]).

HTN-CM arises as the result of an increase in the quantity of myocardium but it also emerges due to alterations in myocardial quality (*i.e.*, fibrosis)[54]. Mechanical stress and hormones such as RAAS lead to fibrosis, which in turn leads to chronic heart failure.

Echocardiography

Echocardiography is a powerful tool that provides morphological information about the LVH pattern in patients with hypertension. LVH can be detected with both electrocardiography and echocardiography[63]. The sensitivity of electrocardiography for LVH diagnosis is relatively low; therefore, echocardiography should be performed to evaluate LV morphology in patients with persistent hypertension. Levy *et al*[64] reviewed electrocardiographic criteria for LVH in 4684 subjects of the Framingham Heart Study and detected echocardiographic LVH in 290 men (14.2%) and 465 women (17.6%), although they found electrocardiographic features of LVH in only 2.9% of men and 1.5% of women[64]. Indeed, a prevalence of echocardiographic LVH was reported in 40% of patients with hypertension[4,65].

LV mass (LVM), LV mass index, and relative wall thickness (RWT) are the most common measurements employed in evaluation of LVH in hypertensive patients[66]. LV geometry is classified into 4 groups based on LVM and RWT: concentric LVH (increased mass and increased RWT), eccentric LVH (increased mass and normal RWT),

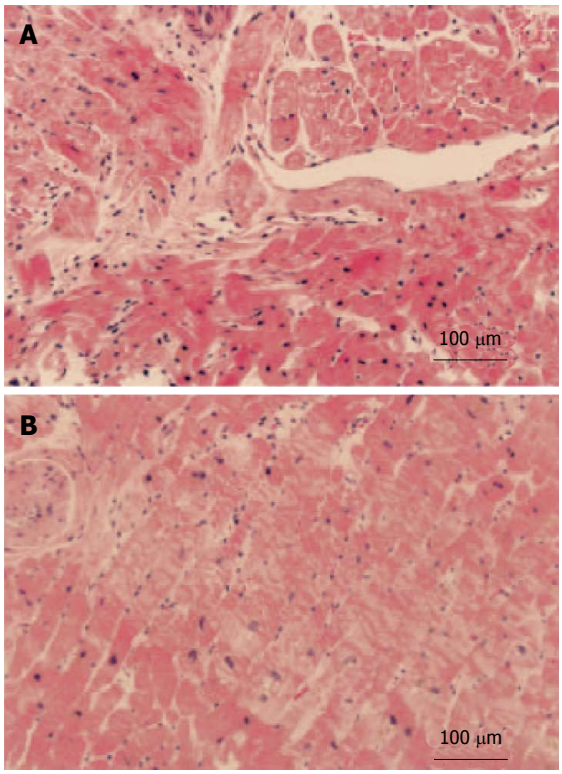

Figure 6 Representative cross sections of myocardial biopsy specimens. A: Hypertrophic cardiomyopathy showing disorganized arrangement of hypertrophic myocytes; B: Hypertensive cardiomyopathy patients showing parallel alignment of hypertrophic myocytes. Sections were stained with hematoxylin-eosin. (Reproduced from Kato *et al*[62], 2004).

concentric remodeling (normal mass and increased RWT), and normal geometry (normal mass and normal RWT)[4,65,66].

Several formulas are used to estimate LV mass. The original calculations from Troy were the first to be recommended as a standard for estimating LVM from M-mode measurements (Formula 1)[67].

Formula 1: LV mass = 1.05 [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3] g.

Where: LVIDD = LV Internal Diameter in Diastole

PWTD = Posterior Wall Thickness in Diastole

IVSTD = Interventricular Septum Thickness in Diastole

Devereux added a slight modification by using the Penn convention as the border definition criteria (Formula 2)[68].

Formula 2: LV mass = 1.04 [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3] - 13.6 g.

Subsequently, Devereux proposed a new, adjusted equation (validated on necropsy findings of 52 individuals)[69] that used the ASE convention and accounted for this discrepancy (Formula 3).

Formula 3: LV mass = 0.8 {1.04 [(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3]} + 0.6 g.

Relative wall thickness (RWT) is measured in clinical studies as:

RWT = (IVST + PWTD)/LVIDD

The usual reference cutoff value for increased RWT, derived from upper limits of normal samples, is 0.45[4]. The RWT provides information regarding LV geometry independent of other calculations[70], thereby precluding a requirement for most corrections. Nevertheless, significant LVH can occur without major changes in RWT, particularly when simultaneous pressure and volume overload are present; these conditions can be seen in patients with hypertension.

The American Society of Echocardiography with the European Association of Echocardiography has issued the following criteria for LVH using the modified Simpson's rule[71]: Estimated LVM of 201-227 g (103-116 g/m^2) for men and 151-171 g (89-100 g/m^2) for women is mildly abnormal; Estimated LVM of 228-254 g (117-130 g/m^2) for men and 172-182 g (101-112 g/m^2) for women is moderately abnormal; Estimated LV mass of > 255 g (> 131 g/m^2) for men and > 193 g (> 113 g/m^2) for women is severely abnormal.

Assessment of diastolic dysfunction by echocardiography is also important in the management of patients with HTN-CM. Diastolic dysfunction is seen in approximately 50% of patients with hypertension[72]. The changes in conventional Doppler echocardiographic parameters, such as peak early filling velocity (E), late diastolic filling velocity (A) and its ratio, as well as deceleration time, should be monitored. Patients with long-standing hypertension and advanced stage of HTN-CM may show a pseudonormalization of E/A ratio, known as restrictive physiology.

Tissue Doppler imaging (TDI) allows quantitative assessment of ventricular function and early diastolic mitral annular velocity (E'); the ratio of E/E', which is a parameter with correction of preload. This is a useful tool to assess the severity of diastolic dysfunction in patients with HTN-CM[73]. Kasner *et al*[73] performed both invasive and noninvasive assessment of diastolic dysfunction and identified the LV filling index of E/E' (lateral) as the best index for detection of diastolic dysfunction in patients with heart failure with normal ejection fraction.

Strain and strain rate parameters derived from TDI, as well as speckle tracking echocardiography have also been reported as useful tools for detection of diastolic dysfunction, and these can aid in discriminating patients with HTN-CM from those with other causes of LVH[62,74]. The abnormalities in strain parameters may occur in a stage of subclinical diastolic dysfunction in hypertensive patients[75,76] making this a useful strategy for disease prevention[4].

Cardiac magnetic resonance

Cardiac magnetic resonance imaging (CMR) offers a unique opportunity for noninvasive quantitation of both LVH with high reproducibility and myocardial fibrosis with high spatial and contrast resolution[77]. Takeda *et al*[78] described the power of CMR for distinguishing among cardiac amyloidosis, hypertrophic cardiomyopathy, and hypertensive heart disease, all of which present with LVH and heart failure.

Advances in CMR provide the potential to address all

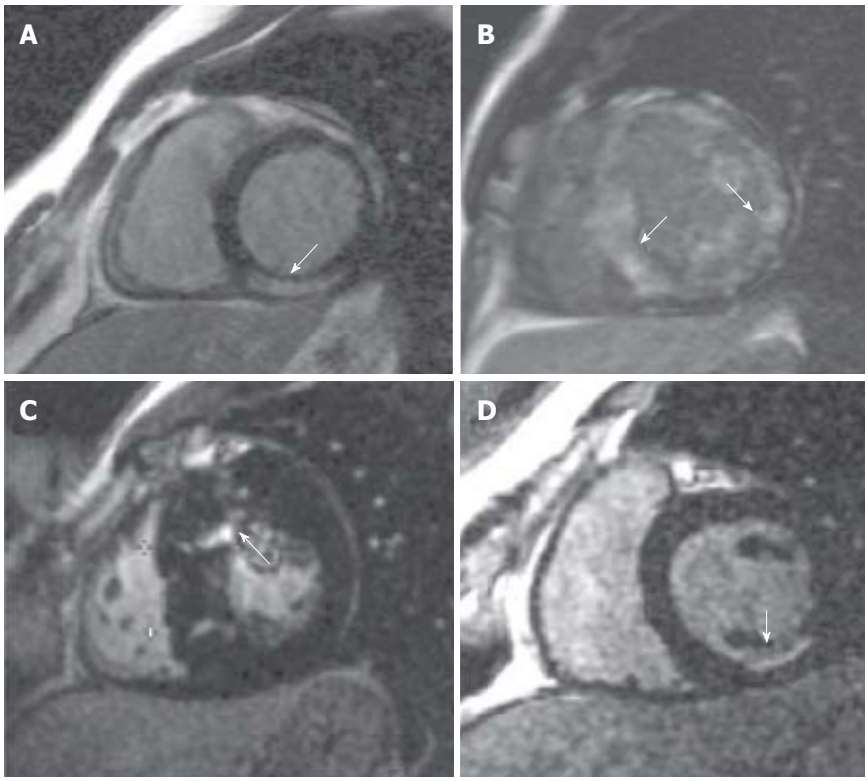

Figure 7 Diagnostic patterns of late gadolinium enhancement distribution pattern and location of late gadolinium enhancement. These features contribute to the differential diagnosis of hypertensive cardiomyopathy (HCM) and non-ischemic cardiomyopathy. (A) sub-epicardial fibrosis following myocarditis, (B) circumferential diffuse enhancement in amyloidosis, (C) patchy fibrosis in affected hypertrophied segments in HCM and a typical ischemic sub-endocardial enhancement (D). (Reproduced from Parsai *et al*[80], 2012).

these important issues in a single scan setting, thereby complementing other noninvasive tools and genetic testing[79]. CMR can provide three-dimensional data on cardiac anatomy, function, tissue characterization, coronary and microvascular perfusion and valvular disease without the use of ionizing radiation. Myocardial fibrosis or infiltration can be assessed following administration of gadolinium, an extracellular agent that accumulates in areas of interstitial expansion (*i.e.*, due to myocardial fibrosis, edema, or infiltration). Late gadolinium enhancement (LGE) imaging detects accumulation of contrast in areas of infarction or fibrosis due to the slower contrast kinetics and greater volume of distribution in the extracellular matrix. The extent and pattern of LGE establish the correct diagnosis between HCM and HTN-CM (Figure 7, reproduced from[80]).

The use of CMR in HTN-CM diagnosis allows reproducible assessment of wall thickness and LV mass with greater accuracy when compared to echocardiography. This is particularly important for assessing small LV mass changes over time as a consequence of treatment. In addition, this capability is also of prognostic value as it represents an independent predictor of cardiac mortality[81,82]. Up to 50% of hypertensive patients display LGE[77,83]. Although no typical pattern of LGE has been described, focal nonsubendocardial distribution predominates. No correlation was found between presence of LGE and LVEF or LV end-diastolic dimensions; however, patients displaying LGE had, in general, a greater LV mass[81]. The LGE patterns in HTN-CM offer new insights into risk stratification. This modality can identify patients with HTN-CM who are at risk of diastolic heart failure as a known relationship exists between myocardial fibrosis and diastolic heart failure. This clearly can be of use in therapeutic decision making[84].

TREATMENT OF HTN-CM

Hypertensive cardiomyopathy (HTN-CM) is a result of a complex interaction of genetic and hemodynamic factors inducing structural and functional adaptations[85]. LVH in HTN-CM is a recognized risk factor for congestive heart failure, dysrhythmia, and sudden death[4,9,10]. Better elucidation of the mechanisms producing cardiovascular end-organ damage should lead to treatment targeted at reducing the effects of hypertension on the heart and vascular system. Most antihypertensive treatments promote regression of LVH and reversal of diastolic dysfunction, which may decrease symptoms of congestive heart failure and improve survival rates[85]. LV mass regression improves survival rates in hypertensive patients[86] and is associated with reduced rate of complications of essential hypertension[87].

The RAAS is implicated in the development of cardiac hypertrophy associated with pressure overload[5-7,32,35,88]. Brilla *et al*[57] indicated ACE inhibition with lisinopril can regress myocardial fibrosis, regardless of LVH regression, and is accompanied by improved LV diastolic function. The Losartan Intervention for Endpoint Reduction (LIFE) study showed that the angiotensin Ⅱ type 1 (AT1) receptor antagonist, Losartan, reduced LV mass and improved systolic performance, despite only a small drop in blood pressure[89]. Furthermore, in their animal study, Nagata *et al*[90] revealed the beneficial cardiac effects of eplerenone, which attenuates myocardial oxidative stress and coronary vascular inflammation induced by

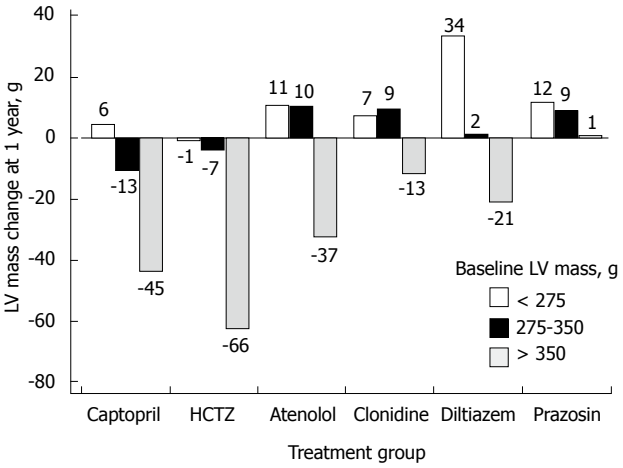

Figure 8 Effect of randomized treatments with single-drug therapy on left ventricular mass. In this group of 493 hypertensive patients, the 1-year change in left ventricular (LV) mass from baseline is shown for each of three baseline mass tertiles. The highest baseline tertile shows significant reductions with hydrochlorothiazide (HCTZ), captopril, and atenolol ($P < 0.05$). (Reproduced from Diamond *et al*[85], 2003; Gottdiener *et al*[91], 2007).

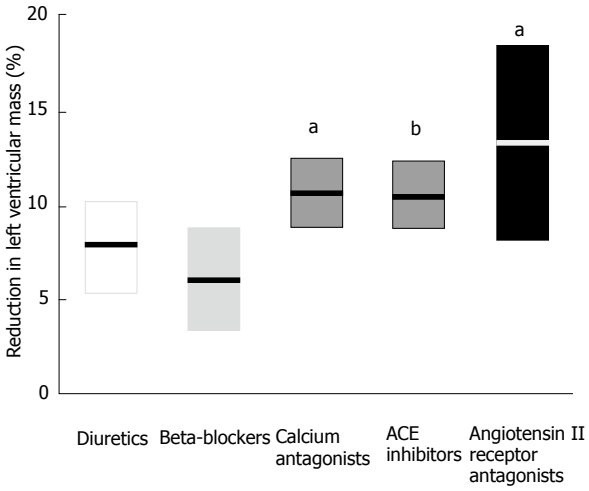

Figure 9 Change in left ventricular mass index (as percentage from baseline) with antihypertensive treatment by drug class. Data represent the mean values and 95% confidence intervals, adjusted for change in diastolic blood pressure and treatment duration. The $^{a}P < 0.05$ *vs* beta-blockers, and $^{b}P < 0.01$ *vs* beta-blocker (after Bonferroni correction). ACE: Angiotensin-converting-enzyme. (Reproduced from Klingbeil *et al*[97], 2003).

glucocorticoid-activated mineralocorticoid receptors. Gottdiener *et al*[91] showed that hydrochlorothiazide administration was associated with greater overall reduction of LA size when compared with other drugs used for the treatment of hypertension. In this study, an ACE inhibitor was nearly as beneficial as hydrochlorothiazide therapy (Figure 8, reproduced from[85,91]). Past studies indicated treatment with statins also reduces ACE activity in the cardiac tissue of rats.

The 3-hydroxy-3-methylgutaryl-CoA (HMG-CoA) reductase inhibitors, commonly referred to as statins, are well-known and potent lipid-lowering agents that reduce the incidence of myocardial infarction and ischemic stroke. In addition to their primary effects, the statins have pleiotropic effects on the cardiovascular system[92], including anti-inflammatory, anti-oxidative, and endothelial protective effects, and thus have been tested as therapeutic agents in heart failure[93]. Chang *et al*[93] showed that Rosuvastatin therapy attenuated myocardial fibrosis and LV stiffness. Saka *et al*[94] suggested that the effects of pitavastatin on load-induced cardiac hypertrophy and fibrosis are independent of its cholesterol lowering action and may be mediated, at least in part, through inhibition of RhoA-ERK-SRF signaling, which activates stretch-induced hypertrophy.

Considering these drug therapies, the most important issues in the treatment of HTN-CM are appropriate blood pressure control, weight loss, and dietary sodium restriction[12,13,95]. Regression of LVH and, more importantly, the prognosis of patients with HTN-CM, are both highly related to the antihypertensive response as well as the therapy used[13]. Regression of LVH continues gradually over time and may be associated with complete reversal of LVH and other abnormalities induced by hypertension, such as LA enlargement and diastolic dysfunction[96].

A meta-analysis published in 2003 evaluated the relative efficacy of different antihypertensive drugs for their ability to reverse LVH in patients with hypertension (Figure 9, reproduced from[97]). Notably, after statistical adjustments for duration of therapy and degree of blood pressure lowering, angiotensin Ⅱ receptor blockers, calcium channel blockers, and ACE inhibitors showed more significant regression of LVH than did beta-blockers. Note that regression of LVH is associated with improvement in both systolic and diastolic function[85], as well as with a reduction in cardiovascular risk[95].

CONCLUSION

To summarize, HTN-CM is characterized by LVH and LVH-induced diastolic dysfunction rather than systolic dysfunction. This is associated with increased risk of heart failure, arrhythmias, and death. LVH itself is a risk factor for mortality and morbidity, independent of other cardiovascular risk factors, including high blood pressure. Therefore, early detection of LVH development in patients with hypertension is important in order to start effective treatment when the myocardial damage is still reversible. Echocardiography, rather than electrocardiography alone, would be an ideal tool for detection of LVH in its early stage, along with advanced measurements such as tissue Doppler and strain parameters. CMR represents another powerful tool for detection and discrimination of patients with HTN-CM from those with other LVH diseases. Because the regression of LVH is associated with a reduction in cardiovascular risk and improved cardiac function, achieving good blood pressure control is very important in the treatment of patients with HTN-CM. This can be achieved with the use of antihypertensive agents (ACE inhibitors, angiotensin receptor blockers, and

aldosterone receptor antagonists), which can be effective for reverse remodeling of the myocardium, weight loss, and sodium restriction.

REFERENCES

1 **Lawes CM**, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008; **371**: 1513-1518 [PMID: 18456100 DOI: 10.1016/S0140-6736(08)60655-8]

2 **Nadruz W**. Myocardial remodeling in hypertension. *J Hum Hypertens* 2015; **29**: 1-6 [PMID: 24804791 DOI: 10.1038/jhh.2014.36]

3 **van Hoeven KH**, Factor SM. A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive-diabetic heart disease. *Circulation* 1990; **82**: 848-855 [PMID: 2394006 DOI: 10.1161/01.CIR.82.3.848]

4 **Janardhanan R**, Kramer CM. Imaging in hypertensive heart disease. *Expert Rev Cardiovasc Ther* 2011; **9**: 199-209 [PMID: 21453216 DOI: 10.1586/erc.10.190]

5 **Re RN**. Intracellular renin and the nature of intracrine enzymes. *Hypertension* 2003; **42**: 117-122 [PMID: 12860832 DOI: 10.1161/01.HYP.0000082495.93495.5B]

6 **Dzau VJ**. Tissue renin-angiotensin system in myocardial hypertrophy and failure. *Arch Intern Med* 1993; **153**: 937-942 [PMID: 8386920 DOI: 10.1001/archinte.1993.00410080011002]

7 **Sadoshima J**, Xu Y, Slayter HS, Izumo S. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. *Cell* 1993; **75**: 977-984 [PMID: 8252633 DOI: 1016/0092-8674(93)90541-W]

8 **Cuspidi C**, Ciulla M, Zanchetti A. Hypertensive myocardial fibrosis. *Nephrol Dial Transplant* 2006; **21**: 20-23 [PMID: 16263734 DOI: 10.1093/ndt/gfi237]

9 **Levy D**, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561-1566 [PMID: 2139921 DOI: 10.1056/NEJM199005313222203]

10 **Verdecchia P**, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, Santucci A, Santucci C, Reboldi G, Porcellati C. Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. *Am J Cardiol* 1996; **78**: 197-202 [PMID: 8712142 DOI: 10.1016/S0002-9149(96)90395-1]

11 **Grossman E**, Messerli FH. Diabetic and hypertensive heart disease. *Ann Intern Med* 1996; **125**: 304-310 [PMID: 8678395 DOI: 10.7326/0003-4819-125-4-199608150-00009]

12 **Vasan RS**, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Arch Intern Med* 1996; **156**: 1789-1796 [PMID: 8790072 DOI: 10.1001/archinte.1996.00440150033003]

13 **Ruilope LM**, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. *Am J Hypertens* 2008; **21**: 500-508 [PMID: 18437140 DOI: 10.1038/ajh.2008.16]

14 **Cuspidi C**, Sala C, Negri F, Mancia G, Morganti A. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. *J Hum Hypertens* 2012; **26**: 343-349 [PMID: 22113443 DOI: 10.1038/jhh.2011.104]

15 **Daniels SD**, Meyer RA, Loggie JM. Determinants of cardiac involvement in children and adolescents with essential hypertension. *Circulation* 1990; **82**: 1243-1248 [PMID: 2401062 DOI: 10.1161/01.CIR.82.4.1243]

16 **Schnall PL**, Pieper C, Schwartz JE, Karasek RA, Schlussel Y, Devereux RB, Ganau A, Alderman M, Warren K, Pickering TG. The relationship between 'job strain,' workplace diastolic blood pressure, and left ventricular mass index. Results of a case-control study. *JAMA* 1990; **263**: 1929-1935 [PMID: 2138234 DOI: 10.1001/jama.1990.03440140055031]

17 **Devereux RB**, Pickering TG, Harshfield GA, Kleinert HD, Denby L, Clark L, Pregibon D, Jason M, Kleiner B, Borer JS, Laragh JH. Left ventricular hypertrophy in patients with hypertension: importance of blood pressure response to regularly recurring stress. *Circulation* 1983; **68**: 470-476 [PMID: 6223721 DOI: 10.1161/01.CIR.68.3.470]

18 **Post WS**, Larson MG, Levy D. Impact of left ventricular structure on the incidence of hypertension. The Framingham Heart Study. *Circulation* 1994; **90**: 179-185 [PMID: 8025994 DOI: 10.1161/01.CIR.90.1.179]

19 **Akhter SA**, Luttrell LM, Rockman HA, Iaccarino G, Lefkowitz RJ, Koch WJ. Targeting the receptor-Gq interface to inhibit in vivo pressure overload myocardial hypertrophy. *Science* 1998; **280**: 574-577 [PMID: 9554846 DOI: 10.1126/science.280.5363.574]

20 **Ohishi M**, Rakugi H, Ogihara T. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. *N Engl J Med* 1994; **331**: 1097-1098 [PMID: 7993479 DOI: 10.1056/NEJM199410203311616]

21 **Brull D**, Dhamrait S, Myerson S, Erdmann J, Woods D, World M, Pennell D, Humphries S, Regitz-Zagrosek V, Montgomery H. Bradykinin B2BKR receptor polymorphism and left-ventricular growth response. *Lancet* 2001; **358**: 1155-1156 [PMID: 11597672 DOI: 10.1016/S0140-6736(01)06273-0]

22 **Kizer JR**, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux RB. Differences in left ventricular structure between black and white hypertensive adults: the Hypertension Genetic Epidemiology Network study. *Hypertension* 2004; **43**: 1182-1188 [PMID: 15123573 DOI: 10.1161/01.HYP]

23 **Devereux RB**, Roman MJ. Left ventricular hypertrophy in hypertension: stimuli, patterns, and consequences. *Hypertens Res* 1999; **22**: 1-9 [PMID: 10221344 DOI: 10.1291/hypres.22.1]

24 **Ganau A**, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992; **19**: 1550-1558 [PMID: 1534335 DOI: 10.1016/0735-1097(92)90617-V]

25 **Wigle ED**, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. *Circulation* 1995; **92**: 1680-1692 [PMID: 7671349 DOI: 10.1161/01.CIR.92.7.1680]

26 **Shapiro LM**, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. *J Am Coll Cardiol* 1983; **2**: 437-444 [PMID: 6683731 DOI: 10.1016/S0735-1097(83)80269-1]

27 **Nakamura T**, Sugihara H, Kinoshita N, Yoneyama S, Azuma A, Nakagawa M. Can serum carnitine levels distinguish hypertrophic cardiomyopathy from hypertensive hearts? *Hypertension* 2000; **36**: 215-219 [PMID: 10948080 DOI: 10.1161/01.HYP.36.2.215]

28 **Dunn FG**, Chandraratna P, deCarvalho JG, Basta LL, Frohlich ED. Pathophysiologic assessment of hypertensive heart disease with echocardiography. *Am J Cardiol* 1977; **39**: 789-795 [PMID: 140601 DOI: 10.1016/S0002-9149(77)80028-3]

29 **Frohlich ED**, Susic D. Pressure overload. *Heart Fail Clin* 2012; **8**: 21-32 [PMID: 22108724 DOI: 10.1016/j.hfc.2011.08.005]

30 **Krumholz HM**, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. *J Am Coll Cardiol* 1995; **25**: 879-884 [PMID: 7884091 DOI: 10.1016/0735-1097(94)00473-4]

31 **Velagaleti RS**, Gona P, Pencina MJ, Aragam J, Wang TJ, Levy D, D'Agostino RB, Lee DS, Kannel WB, Benjamin EJ, Vasan RS. Left ventricular hypertrophy patterns and incidence of heart failure with preserved versus reduced ejection fraction. *Am J Cardiol* 2014; **113**: 117-122 [PMID: 24210333 DOI: 10.1016/j.amjcard.2013.09.028]

32 **Milani RV**, Drazner MH, Lavie CJ, Morin DP, Ventura HO. Progression from concentric left ventricular hypertrophy and normal ejection fraction to left ventricular dysfunction. *Am J Cardiol* 2011; **108**: 992-996 [PMID: 21784383 DOI: 10.1016/j.amjcard.2011.05.038]

33 **Krishnamoorthy A**, Brown T, Ayers CR, Gupta S, Rame JE, Patel PC, Markham DW, Drazner MH. Progression from normal to reduced left ventricular ejection fraction in patients with concentric left ventricular hypertrophy after long-term follow-up. *Am J Cardiol* 2011; **108**: 997-1001 [PMID: 21798496 DOI: 10.1016/

j.amjcard.2011.05.037]
34 **Khouri MG**, Peshock RM, Ayers CR, de Lemos JA, Drazner MH. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: the Dallas heart study. *Circ Cardiovasc Imaging* 2010; **3**: 164-171 [PMID: 20061518 DOI: 10.1161/CIRCIMAGING.109.883652]
35 **Bang CN**, Gerdts E, Aurigemma GP, Boman K, Dahlöf B, Roman MJ, Køber L, Wachtell K, Devereux RB. Systolic left ventricular function according to left ventricular concentricity and dilatation in hypertensive patients: the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens* 2013; **31**: 2060-2068 [PMID: 23838656 DOI: 10.1097/HJH.0b013e328362bbd6]
36 **González A**, López B, Díez J. Fibrosis in hypertensive heart disease: role of the renin-angiotensin-aldosterone system. *Med Clin North Am* 2004; **88**: 83-97 [PMID: 14871052 DOI: 10.1016/S0025-7125(03)00125-1]
37 **Gardin JM**, Lauer MS. Left ventricular hypertrophy: the next treatable, silent killer? *JAMA* 2004; **292**: 2396-2398 [PMID: 15547168 DOI: 10.1001/jama.292.19.2396]
38 **Kizer JR**, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET, Roman MJ, Devereux RB. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). *Am Heart J* 2006; **151**: 412-418 [PMID: 16442908 DOI: 10.1016/j.ahj.2005.04.031]
39 **Rossi A**, Temporelli PL, Quintana M, Dini FL, Ghio S, Hillis GS, Klein AL, Marsan NA, Prior DL, Yu CM, Poppe KK, Doughty RN, Whalley GA. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE Heart Failure). *Eur J Heart Fail* 2009; **11**: 929-936 [PMID: 19789395 DOI: 10.1093/eurjhf/hfp112]
40 **Devereux RB**, Bella JN, Palmieri V, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Morgan D, Paranicas M, Fishman D, Arnett DK. Left ventricular systolic dysfunction in a biracial sample of hypertensive adults: The Hypertension Genetic Epidemiology Network (HyperGEN) Study. *Hypertension* 2001; **38**: 417-423 [PMID: 11566915 DOI: 10.1161/01.HYP.38.3.417]
41 **Kannel WB**, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; **82**: 2N-9N [PMID: 9809895 DOI: 10.1016/S0002-9149(98)00583-9]
42 **Messerli FH**, Ventura HO, Elizardi DJ, Dunn FG, Frohlich ED. Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. *Am J Med* 1984; **77**: 18-22 [PMID: 6234799 DOI: 10.1016/0002-9343(84)90430-3]
43 **Greenwood JP**, Scott EM, Stoker JB, Mary DA. Hypertensive left ventricular hypertrophy: relation to peripheral sympathetic drive. *J Am Coll Cardiol* 2001; **38**: 1711-1717 [PMID: 11704385 DOI: 10.1016/S0735-1097(01)01600-X]
44 **Schlaich MP**, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 2003; **108**: 560-565 [PMID: 12847071 DOI: 10.1161/01.CIR.0000081775.72651.B6]
45 **Musilli C**, Paccosi S, Pala L, Gerlini G, Ledda F, Mugelli A, Rotella CM, Parenti A. Characterization of circulating and monocyte-derived dendritic cells in obese and diabetic patients. *Mol Immunol* 2011; **49**: 234-238 [PMID: 21940050 DOI: 10.1016/j.molimm.2011.08.01]
46 **Kjeldsen SE**, Devereux RB, Hille DA, Lyle PA, Dahlöf B, Julius S, Edelman JM, Snapinn SM, de Faire U, Fyhrquist F, Ibsen H, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Predictors of cardiovascular events in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention for Endpoint reduction in hypertension study. *Blood Press* 2009; **18**: 348-361 [PMID: 20001655 DOI: 10.3109/08037050903460590]
47 **Diamond JA**, Phillips RA. Hypertensive heart disease. *Hypertens Res* 2005; **28**: 191-202 [PMID: 16097361 DOI: 10.1291/hypres.28.191]
48 **Phillips RA**, Diamond JA. Diastolic function in hypertension. *Curr Cardiol Rep* 2001; **3**: 485-497 [PMID: 11602080 DOI: 10.1007/s11886-001-0071-4]
49 **Aurigemma GP**, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. *J Am Coll Cardiol* 2001; **37**: 1042-1048 [PMID: 11263606 DOI: 10.1016/S0735-1097(01)01110-X]
50 **Gandhi SK**, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, Little WC. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001; **344**: 17-22 [PMID: 11136955 DOI: 10.1056/NEJM200101043440103]
51 **Chobanian AV**, Brecher PI, Haudenschild CC. Effects of hypertension and antihypertensive therapy on atherosclerosis: state of the heart lecture. *Hypertension* 1986; **8** (Suppl l): 15-21
52 **Wang TJ**, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003; **108**: 977-982 [PMID: 12912813 DOI: 10.1161/01.CIR.0000085166.44904.79]
53 **Drazner MH**. The progression of hypertensive heart disease. *Circulation* 2011; **123**: 327-334 [PMID: 21263005 DOI: 10.1161/CIRCULATIONAHA.108.845792]
54 **Díez J**, González A, López B, Querejeta R. Mechanisms of disease: pathologic structural remodeling is more than adaptive hypertrophy in hypertensive heart disease. *Nat Clin Pract Cardiovasc Med* 2005; **2**: 209-216 [PMID: 16265485 DOI: 10.1038/ncpcardio0158]
55 **Díez J**. Diagnosis and treatment of myocardial fibrosis in hypertensive heart disease. *Circ J* 2008; **72** Suppl A: A8-12 [PMID: 18772529 DOI: 10.1253/circj.CJ-07-1067]
56 **Díez J**. Mechanisms of cardiac fibrosis in hypertension. *J Clin Hypertens* (Greenwich) 2007; **9**: 546-550 [PMID: 17617765 DOI: 10.1111/j.1524-6175.2007.06626.x]
57 **Brilla CG**, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000; **102**: 1388-1393 [PMID: 10993857 DOI: 10.1161/01.CIR.102.12.1388]
58 **Tanaka M**, Fujiwara H, Onodera T, Wu DJ, Hamashima Y, Kawai C. Quantitative analysis of myocardial fibrosis in normals, hypertensive hearts, and hypertrophic cardiomyopathy. *Br Heart J* 1986; **55**: 575-581 [PMID: 3718796 DOI: 10.1136/hrt.55.6.575]
59 **Rossi MA**. Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. *J Hypertens* 1998; **16**: 1031-1041 [PMID: 9794745]
60 **Querejeta R**, Varo N, López B, Larman M, Artiñano E, Etayo JC, Martínez Ubago JL, Gutierrez-Stampa M, Emparanza JI, Gil MJ, Monreal I, Mindán JP, Díez J. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation* 2000; **101**: 1729-1735 [PMID: 10758057 DOI: 10.1161/01.CIR.101.14.1729]
61 **Mazzolai L**, Nussberger J, Aubert JF, Brunner DB, Gabbiani G, Brunner HR, Pedrazzini T. Blood pressure-independent cardiac hypertrophy induced by locally activated renin-angiotensin system. *Hypertension* 1998; **31**: 1324-1330 [PMID: 9622149 DOI: 10.1161/01.HYP.31.6.1324]
62 **Kato TS**, Noda A, Izawa H, Yamada A, Obata K, Nagata K, Iwase M, Murohara T, Yokota M. Discrimination of nonobstructive hypertrophic cardiomyopathy from hypertensive left ventricular hypertrophy on the basis of strain rate imaging by tissue Doppler ultrasonography. *Circulation* 2004; **110**: 3808-3814 [PMID: 15583080 DOI: 10.1161/01.CIR.0000150334.69355.00]
63 **Lorell BH**, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation* 2000; **102**: 470-479 [PMID: 10908222 DOI: 10.1161/01.CIR.102.4.470]
64 **Levy D**, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation* 1990; **81**: 815-820 [PMID: 2137733 DOI: 10.1161/01.CIR.81.3.815]
65 **Savage DD**, Drayer JI, Henry WL, Mathews EC, Ware JH, Gardin JM, Cohen ER, Epstein SE, Laragh JH. Echocardiographic assessment of cardiac anatomy and function in hypertensive

subjects. *Circulation* 1979; **59**: 623-632 [PMID: 421302 DOI: 10.1161/01.CIR.59.4.623]
66 **Foppa M**, Duncan BB, Rohde LE. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? *Cardiovasc Ultrasound* 2005; **3**: 17 [PMID: 15963236 DOI: 10.1186/1476-7120-3-17]
67 **Troy BL**, Pombo J, Rackley CE. Measurement of left ventricular wall thickness and mass by echocardiography. *Circulation* 1972; **45**: 602-611 [PMID: 4258936 DOI: 10.1161/01.CIR.45.3.602]
68 **Devereux RB**, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977; **55**: 613-618 [PMID: 138494 DOI: 10.1161/01.CIR.55.4.613]
69 **Devereux RB**, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450-458 [PMID: 2936235 DOI: 10.1016/0002-9149(86)90771-X]
70 **Li L**, Shigematsu Y, Hamada M, Hiwada K. Relative wall thickness is an independent predictor of left ventricular systolic and diastolic dysfunctions in essential hypertension. *Hypertens Res* 2001; **24**: 493-499 [PMID: 11675942 DOI: 10.1291/hypres.24.493]
71 **Lang RM**, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440-1463 [PMID: 16376782 DOI: 10.1016/j.echo.2005.10.005]
72 **Redfield MM**, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289**: 194-202 [PMID: 12517230 DOI: 10.1001/jama.289.2.194]
73 **Kasner M**, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschöpe C. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 2007; **116**: 637-647 [PMID: 17646587 DOI: 10.1161/CIRCULATIONAHA.106.661983]
74 **Kato TS**, Izawa H, Komamura K, Noda A, Asano H, Nagata K, Hashimoto S, Oda N, Kamiya C, Kanzaki H, Hashimura K, Ueda HI, Murohara T, Kitakaze M, Yokota M. Heterogeneity of regional systolic function detected by tissue Doppler imaging is linked to impaired global left ventricular relaxation in hypertrophic cardiomyopathy. *Heart* 2008; **94**: 1302-1306 [PMID: 18198205 DOI: 10.1136/hrt.2007.124453]
75 **Narayanan A**, Aurigemma GP, Chinali M, Hill JC, Meyer TE, Tighe DA. Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. *Circ Cardiovasc Imaging* 2009; **2**: 382-390 [PMID: 19808626 DOI: 10.1161/CIRCIMAGING.108.811620]
76 **Solomon SD**, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourcière Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007; **369**: 2079-2087 [PMID: 17586303 DOI: 10.1016/S0140-6736(07)60980-5]
77 **Rudolph A**, Abdel-Aty H, Bohl S, Boyé P, Zagrosek A, Dietz R, Schulz-Menger J. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. *J Am Coll Cardiol* 2009; **53**: 284-291 [PMID: 19147047 DOI: 10.1016/j.jacc.2008.08.064]
78 **Takeda M**, Amano Y, Tachi M, Tani H, Mizuno K, Kumita S. MRI differentiation of cardiomyopathy showing left ventricular hypertrophy and heart failure: differentiation between cardiac amyloidosis, hypertrophic cardiomyopathy, and hypertensive heart disease. *Jpn J Radiol* 2013; **31**: 693-700 [PMID: 23996116 DOI: 10.1007/s11604-013-0238-0]
79 **Assomull RG**, Shakespeare C, Kalra PR, Lloyd G, Gulati A, Strange J, Bradlow WM, Lyne J, Keegan J, Poole-Wilson P, Cowie MR, Pennell DJ, Prasad SK. Role of cardiovascular magnetic resonance as a gatekeeper to invasive coronary angiography in patients presenting with heart failure of unknown etiology. *Circulation* 2011; **124**: 1351-1360 [PMID: 21900085 DOI: 10.1161/CIRCULATIONAHA.110.011346]
80 **Parsai C**, O'Hanlon R, Prasad SK, Mohiaddin RH. Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. *J Cardiovasc Magn Reson* 2012; **14**: 54 [PMID: 22857649 DOI: 10.1186/1532-429X-14-54]
81 **Myerson SG**, Bellenger NG, Pennell DJ. Assessment of left ventricular mass by cardiovascular magnetic resonance. *Hypertension* 2002; **39**: 750-755 [PMID: 11897757 DOI: 10.1161/hy0302.104674]
82 **Yusuf S**, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**: 1547-1559 [PMID: 18378520 DOI: 10.1056/NEJMoa0801317]
83 **Andersen K**, Hennersdorf M, Cohnen M, Blondin D, Mödder U, Poll LW. Myocardial delayed contrast enhancement in patients with arterial hypertension: initial results of cardiac MRI. *Eur J Radiol* 2009; **71**: 75-81 [PMID: 18434065 DOI: 10.1016/j.ejrad.2008.03.00]
84 **Martos R**, Baugh J, Ledwidge M, O'Loughlin C, Conlon C, Patle A, Donnelly SC, McDonald K. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation* 2007; **115**: 888-895 [PMID: 17283265 DOI: 10.1161/CIRCULATIONAHA.106.638569]
85 **Diamond JA**, Phillips RA. Regression of left ventricular hypertrophy: are there preferred drugs? *Curr Hypertens Rep* 2003; **5**: 368-371 [PMID: 12948428 DOI: 10.1007/s11906-003-0081-2]
86 **Muiesan ML**, Salvetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E. Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 1995; **13**: 1091-1095 [PMID: 8586800]
87 **Koren MJ**, Ulin RJ, Koren AT, Laragh JH, Devereux RB. Left ventricular mass change during treatment and outcome in patients with essential hypertension. *Am J Hypertens* 2002; **15**: 1021-1028 [PMID: 12460696 DOI: 10.1016/S0895-7061(02)03061-3]
88 **Yamazaki T**, Yazaki Y. Is there major involvement of the renin-angiotensin system in cardiac hypertrophy? *Circ Res* 1997; **81**: 639-642 [PMID: 9351435]
89 **Wachtell K**, Palmieri V, Olsen MH, Gerdts E, Papademetriou V, Nieminen MS, Smith G, Dahlöf B, Aurigemma GP, Devereux RB. Change in systolic left ventricular performance after 3 years of antihypertensive treatment: the Losartan Intervention for Endpoint (LIFE) Study. *Circulation* 2002; **106**: 227-232 [PMID: 12105163 DOI: 10.1161/01.CIR.0000021601.49664.2A]
90 **Nagata K**, Obata K, Xu J, Ichihara S, Noda A, Kimata H, Kato T, Izawa H, Murohara T, Yokota M. Mineralocorticoid receptor antagonism attenuates cardiac hypertrophy and failure in low-aldosterone hypertensive rats. *Hypertension* 2006; **47**: 656-664 [PMID: 16505208 DOI: 10.1161/01.HYP.0000203772.78696.67]
91 **Gottdiener JS**, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Circulation* 1997; **95**: 2007-2014 [PMID: 9133508 DOI: 10.1161/01.CIR.95.8.2007]
92 **Ray KK**, Cannon CP. Early time to benefit with intensive statin treatment: could it be the pleiotropic effects? *Am J Cardiol* 2005; **96**: 54F-60F [PMID: 16126024 DOI: 10.1016/j.amjcard.2005.06.027]
93 **Chang SA**, Kim YJ, Lee HW, Kim DH, Kim HK, Chang HJ, Sohn DW, Oh BH, Park YB. Effect of rosuvastatin on cardiac remodeling, function, and progression to heart failure in hypertensive heart with established left ventricular hypertrophy.

Hypertension 2009; **54**: 591-597 [PMID: 19564547 DOI: 10.1161/HYPERTENSIONAHA.109.131243]

94 **Saka M**, Obata K, Ichihara S, Cheng XW, Kimata H, Noda A, Izawa H, Nagata K, Yokota M. Attenuation of ventricular hypertrophy and fibrosis in rats by pitavastatin: potential role of the RhoA-extracellular signal-regulated kinase-serum response factor signalling pathway. *Clin Exp Pharmacol Physiol* 2006; **33**: 1164-1171 [PMID: 17184496 DOI: 10.1111/j.1440-1681.2006.04508.x]

95 **Levy D**, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; **90**: 1786-1793 [PMID: 7923663 DOI: 10.1111/j.1440-1681.2006.04508.x]

96 **Franz IW**, Tönnesmann U, Müller JF. Time course of complete normalization of left ventricular hypertrophy during long-term antihypertensive therapy with angiotensin converting enzyme inhibitors. *Am J Hypertens* 1998; **11**: 631-639 [PMID: 9657621 DOI: 10.1016/S0985-7061(98)00024-7]

97 **Klingbeil AU**, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003; **115**: 41-46 [PMID: 12867233 DOI: 10.1016/S0002-9343(03)00158-X]

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REVIEW

Antihypertensive effects of foods

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Abstract

Hypertension is one of the major risk factors for arteriosclerosis, which leads to cardiovascular disease and stroke. Several clinical trials revealed that control of the blood pressure is useful to reduce the morbidity and mortality associated with these diseases. However, the protective efficacy against these complications still remains at less than 50% even if the high blood pressure is treated by current medical drugs. Healthy diets are expected to not only prevent but also treat lifestyle-related diseases. Improvement of the dietary life, including low-salt diets, appropriate alcohol consumption, and calorie restriction, is important for the prevention of hypertension. In addition, green tea, which has been drunk on a daily basis in Japan and China since ancient times, possesses an antihypertensive effect, and it was revealed that its components with this effect are catechins. Many studies have been performed on the antihypertensive effects of foods. Therefore, functional foods and their ingredients, reported to possess antihypertensive effects in animal experiments and human clinical trials, are summarized in this review. Blood pressure might be controlled by improvement of the daily eating habits based on evidence regarding these functional foods, and a healthy longevity can be expected.

Key words: Foods; Hypertension; Antihypertensive effect; Cardiovascular disease; Renin

Core tip: Management of the blood pressure leads to decreases in morbidity and mortality associated with arteriosclerosis-related diseases. It is well known that the improvement of eating habits, including a low-salt diet, appropriate alcohol drinking, and calorie restriction, has marked effects for the prevention of hypertension. In this review, we have summarized functional foods and their components whose antihypertensive effects have already been reported in animal experiments and human clinical trials. The evidence indicates that hypertension could be effectively controlled by daily functional food intake and healthy longevity could be achieved.

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INTRODUCTION

Hypertension is one of the major risk factors of cardiovascular disease (CVD), stroke, and renal failure. Therefore, management of the blood pressure decreases the risk of morbidity and mortality. In 2008, approximately 40% of adults aged 25 or older had been diagnosed with hypertension globally; the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008[1]. Of the 57 million global deaths in 2008, 36 million (63%) were primarily due to noncommunicable diseases and 17.3 million (30%) were due to CVDs. Death from cardiovascular disease is primarily due to stroke and heart disease, and it has been reported this number will increase to 23.3 million in 2030[2,3]. Therefore, it has become a serious global problem. This assessment of the situation shows that CVD has a high rank regarding disease-related mortality in the world. Hypertension is one of the major risk factors for CVD. The heart is one of the target organs of hypertension. Increasing pressure overload leads to coronary artery endothelial dysfunction, cardiac hypertrophy, and myocardial remodeling. They increase the risk of coronary sclerosis and myocardial ischemia. Several large-scale trials targeting cardiovascular high-risk patients revealed that when their systolic blood pressure (SBP) dropped to 160 mmHg and diastolic blood pressure (DBP) to 90 mmHg, the morbidity and mortality due to CVD decreased[4]. Hypertension is defined as 140/90 mmHg or above. The Hypertension Optimal Treatment study revealed that cardiovascular benefit is maximized when the blood pressure drops to 139/83 mmHg. Survey data of clinics targeting the general population have suggested that the lower the blood pressure, the lower cardiovascular event onset rate. Also, it has been estimated that a 5 mmHg reduction in the population average reduces mortality from stroke by 14%, coronary artery disease by 9%, and total mortality by 7%[5]. In this way, hypertension is one of the highest risk factors for CVD and stroke. Control of the blood pressure is indispensable to improve the prognosis. In hypertension guidelines, diet and exercise therapy are important along with drug therapy. In the future, hypertension will be further improvement by consuming functional foods and lifestyle reconsideration. We expect them to make a contribution to the development of preventive medicine.

Japan has the longest lifespan in the world. One of the reasons is that the balanced diet in Japan is markedly reduces stroke and tuberculosis. Furthermore, Mechnikov, who was awarded the Nobel Prize, reported that large numbers of healthy and long-lived people in the vicinity of Bulgaria may be due to the habit that they have of consuming a large quantity of yogurt. It has also been reported that few Inuk living mainly on a diet of fish contract heart disease or show hardening of the arteries. For these reasons, the diet and healthy longevity are considered to be closely related. Research on the relationship between food and health has been conducted throughout the world. As a result, it has been indicated that the ingredients in some foods have effects on biological regulation, such as on the immune, endocrine, and nervous systems, and also on digestion, absorption, and circulatory systems. That is, in certain foods, there are substances which have significant effects on the regulatory function of the body. It has been clarified that these ingredients have the ability to prevent various diseases developing because of an abnormal biological regulatory system. Foods with effects like this are called functional foods, and they have attracted global attention[6]. Diseases such as hypertension, hypercholesterolemia, and hypertriglyceridemia are lifestyle-related diseases. They are caused by inadequate lifestyle, such as an unbalanced diet, lack of exercise, drinking, and insufficient sleep. In developed countries with increasing lifestyle-related diseases and aging of the population, people have an increased awareness of self-medication, the act of taking care of yourself. Attention has been focused on functional foods. Functional foods having particularly beneficial effects on hypertension in animal experiments (Table 1) and human clinical trials (Table 2) are summarized in this paper. This manuscript is focusing on clinical findings than experimental ones. Moreover, we emphasize interventional studies yielded results with statistical significance. Functional foods reduce the blood pressure by different mechanisms, such as rennin-angiotensin-aldosterone system (RAAS) inhibition, antioxidant effect, diuretic effect, NOS production-promoting effect. And there are also some foods with multiple mechanisms (Figure 1).

CATECHINS

Green tea is a beverage that has been found to be useful for maintaining and recovering health. People have continued to drink it on a daily basis from ancient times in East Asia such as Japan and China. Using stroke-prone spontaneously hypertensive rats (SHRSP), treatment of black tea polyphenols or green tea polyphenols showed significant reductions of SBP and DBP. Moreover, several experiments indicated that the regular consumption of black and green tea may also provide some protection against hypertension in humans[7]. The major active constituents of tea are polyphenols such as catechins and tannins. In recent years, many studies have reported that catechins have a variety of actions, such as antihypertensive effects[8-10]. The action mechanism of catechins for their antihypertensive effect is considered to be through an antioxidant action. That is, reduction of oxidative stress in the vascular endothelium increases the bioavailability of NO, which enhances the vasodilatory action. Also, it is related to the diuretic action of caffeine contained

Table 1 Antihypertensive effects of functional foods in animal experiments

Functional foods	Active ingredients	Animal experiments	Results	Ref.
Tea	Catechin Flavonoid	Taking the green tea polyphenol water containing 3.5 g/L catechins, 0.5 g/L flavonols and 1 g/L polymetric flavonoids to SHRSP	Decreases in SBP and DBP	[7]
GABA	GABA	Single oral administration of GABA (0.5 mg/kg) to SHR and normotensive Wistar-Kyoto rats	Decrease in SBP in SHR rats, but not in normotensive rats	[16]
Stevia	Stevioside	Intraperitoneally administration of stevioside (50, 100 and 200 mg/kg) to normotensive Wistar-Kyoto rats (NTR), SHR, DOCA-NaCl, DHR and RHR	Hypotensive effect was noted in different strains of rats at the dose of 50 mg/kg. The dose of 100 and 200 mg/kg caused slow and persistent lowering of blood pressure in SHR and NTR Blood pressure decreased in a dose-dependent manner in SHR	[22]
Black vinegar	Acetic acid Black vinegar-derived peptides	Single (3 g/kg body weight) and continuous administration (8 wk; 10% (w/w) of diet) of black malt vinegar to SHR	Decrease in SBP in the administration of either	[32]
Goma	Sesamin	Taking a sesamin-containing diets (0.1, 1 w/w%) to DOCA-salt hypertensive rats for 5 wk	Decrease in SBP	[34]
Fish oil	EPA DHA	Daily oral administration of 30 to 300 mg/kg EPA to SHR and normotensive rats for eight weeks	Treatment of 30, 100, and 300 mg/kg EPA decreased mean SBP in SHR	[40]
Garlic	S-allyl cysteine (SAC), Allicin	Daily oral administration of 50 mg of aqueous extract of garlic totwo-kidney-one-clip hypertensive rat for 4 wk	SBP and ACE activity in serum and different tissues such as aorta, heart, kidney and lung decreased	[46]
		5/6 nephrectomized rats were treated with SAC (200 mg/kg ip) or aged garlic extract (1.2 mL/kg ip) every other day for 30 d	SBP and renal failure decreased, SOD activity increased	[47]
Onion	Quercetin	Taking a 5% dried onion diet to L-NAME induced-hypertensive rats and SHRSP for 4 wk	SBP decreased from 1 wk in both rats, and TBARS decreased at 4 wk Urinary nitrite, NOS activity was increased in SHRSP rats	[58]
Pea	PPH	Oral administration of the PPH to spontaneously hypertensive rats (SHR) at doses of 100 and 200 mg/kg	Decrease in SBP	[64]

A list of animal experiments. Hypotensive actions have been confirmed in multiple types of rat, mainly SHR. GABA: G-aminobutyric acid; PPH: Pea protein hydrolysate; DOCA-NaCl: Deoxycorticosterone acetate-salt; DHR: Sensitive hypertensive rats; RHR: Renal hypertensive rats.

in green tea. Studies on the hypotensive action of green tea have been conducted throughout the world. Clinical trials in humans reported that hypertensive patients with obese who consumed green tea extract for 3 mo showed significant decreases in their SBP and DBP compared with a placebo group[11]. In addition to this, it was reported that subjects who were classified as being healthy but had a slightly high blood pressure or mild hypertension consumed Benifuuki tea from a tea bag containing 2 g of Benifuuki leaves [containing 25 mg of epigallocatechin-3-O-(3-O-methyl) gallate, EGCG] for 8 wk, leading to significant decreases in SBP and DBP[12]. Overweight or obese male subjects with a BMI of 28-38 who took 400 mg of EGCG twice daily for 8 wk showed a DBP reduction below 2.8 mmHg[10]. Mildly hypertensive patients with type 2 diabetes mellitus showed a decreased SBP after drinking green tea three times a day 2 h after each meal for 4 wk[13]. No adverse effects were observed either study. From the above, it has been suggested that polyphenols such as catechins contained in green tea have not only a hypotensive action but also improve lifestyle-related diseases. Although the causal relationship is unknown, the elderly in Shizuoka Prefecture, considered the home of green tea in Japan, consume large amounts of green tea and show a healthy longevity that is a longer compared with other prefectures. Green tea may therefore play a role for health and longevity.

GABA

GABA is γ-aminobutyric acid, a kind of amino acid, and one of a large number of inhibitory neurotransmitters in the central nervous system such as the brain, cerebellum, and spinal cord. In recent years, GABA has been found to improve blood flow and metabolism in the brain. In addition to being produced by the brain during sleep, GABA can be obtained from food. GABA is included in trace amounts in rice, vegetables, tea, and fermented food. Especially, sprouted brown rice contains about 10 times more GABA than rice. GABA is produced from glutamic acid decarboxylase (GAD) synthesized by lactic acid bacteria. Therefore, it is also abundant in pickles which is a lactic acid fermentation product made from plants[14,15]. Antihypertensive mechanisms of GABA have been considered as follow: an inhibitory effect on the sympathetic nervous system and peripheral sympathetic ganglia, a diuretic effect by the inhibition of anti-diuretic hormone secretion, and angiotensin converting enzyme (ACE) activity inhibition[16,17]. Some

Table 2 Antihypertensive effects of functional foods in human clinical trials

Functional foods	Human clinical trials		Ref.
	Targets	Study designs	
Tea	Obese (BMI ⩾ 30), hypertensive subjects	Taking 379 mg of Green Tea extract (including 208 mg of EGCG) for 3 mo. (randomized double-blind, placebo-controlled trial)	[11]
	Overweight or obese subjects (BMI > 28)	Taking 400 mg of EGCG twice daily for 8 wk. (randomized double-blind, placebo-controlled trial)	[10]
GABA	Subjects with high normal blood pressure	Drinking 100 mL of fermented milk containing 12.3 mg of GABA for 12 wk. (randomized double-blind, placebo-controlled trial)	[17]
	Mildly hypertensive subjects	Drinking 100 mL of fermented milk product containing 10-12 mg of GABA for 12 wk. (randomized single-blind, placebo-controlled trial	[18]
	Subjects with high-normal blood pressure	Taking less-sodium soy sauce containing 120 mg of GABA once daily for 12 wk. (double-blind, placebo-controlled trial	[19]
Stevia	Subjects with mild to moderate essential hypertension	Taking 250 mg of stevioside 3 times daily for 1 yr. (randomized double-blind, placebo-controlled trial)	[25]
	Subjects with mild essential hypertension	Taking 500 mg of stevioside 3 times daily for 2 yr. (randomized double-blind, placebo-controlled trial)	[26]
Black vinegar	Subjects with high normal, mild hypertension	Taking a drink containing 15% black vinegar or 15% apple vinegar for 10 wk (double-blind, placebo-controlled trial)	[29]
	Subjects with high normal, mild hypertension	taking a drink containing tomato vinega (750 mg/100 g per day) for 12 wk (double-blind placebo-controlled trial)	[30]
	Subjects with mild to moderate hypertension	Taking a drink containing apple vinegar (acetic acid 0.75 g/100 mL) or acetic acid (acetic acid 1.5 g/100 mL) for 8 wk (three groups parallel, placebo-controlled trial)	[31]
Goma	Subjects with mild hypertension	Taking 60 mg of sesamin for 4 wk (double-blind, cross-over, placebo-controlled trial)	[37]
Fish oil	Subjects with essential hypertension	Taking 2.7 g of EPA for 8 wk (randomized double-blind, cross-over, placebo-controlled trial)	[41]
	Subjects with hypertension and/or hypercholesterolemia	Taking a 2 g of DHA for 5 wk (randomized double-blind, placebo-controlled trial)	[45]
Garlic	Subjects with uncontrolled systolic hypertension (SBP ⩾ 140 mmHg)	Taking aged garlic extract (240/480/960 mg containing 0.6/1.2/2.4 mg of S-allylcysteine) for 12 wk (randomized double-blind, placebo-controlled trial)	[51]
	Subjects with uncontrolled hypertension	Taking 960 mg of aged garlic extract containing 2.4 mg S-allylcysteine daily for 12 wk (randomized double-blind, placebo-controlled trial)	[55]
Onion	Subjects with prehypertension and stage 1 hypertension	Taking 730 mg quercetin for 4 wk (randomized double-blind, cross-over, placebo-controlled trial)	[63]
Pea	subjects with SBP ranging from 125 to 170 mmHg	Taking 1.5 and 3 g of PPH for 3 wk (randomized double-blind, cross-over, placebo-controlled trial)	[64]

A list of human clinical trials. We reviewed mainly clinical trials involving hypertensive patients. BMI: Body mass index; GABA: G-aminobutyric acid; EGCG: Epigallocatechin-3-O-(3-O-methyl) gallate.

subjects with a high-normal blood pressure were given 100 mL of fermented milk containing 12.3 mg of GABA. They showed significant decreases of SBP after 8 wk and DBP after 12 wk. A reincrease in the blood pressure was observed after 4 wk following the discontinuation of ingestion[17]. The same hypotensive effect was observed in a trial of hypertensive patients, and no adverse reactions were observed[18,19]. From these results, the benefits and safety for hypertensive patients of GABA-containing fermentation foods are expected.

STEVIOSIDE

Stevioside, contained in Stevia which is a perennial plant of the Asteraceae, is a natural sweetener used widely in Japan and South America. It has been traditionally used as a herbal medicine in South America. A variety of physiological activities have been reported, such as improving insulin resistance in type 2 diabetes, an antihypertensive action, a diuretic action, and an antioxidant action[20,21]. Antihypertensive action has been indicated by several experiments using different hypertensive rat models[22]. The hypotensive effect of stevioside may be mediated by inhibiting Ca^{2+} influx into blood vessels and vasodilation[23,24]. In a human clinical trial, patients with mild to moderate essential hypertension given 250 mg of stevioside showed significantly decreased both SBP and DBP after 3 mo, and the effect persisted for one year[25]. Patients with mild essential hypertension taking 500 mg of stevioside 3 times daily for 2 years showed significantly decreased SBP and DBP. These hypotensive effects were noted to begin about 1 wk after the start of treatment and persisted throughout the study and no significant adverse effects were noted[26]. In a involving the administration of crude stevioside at 15.0 mg/kg per day for 6 wk to patients with essential hypertension, SBP and DBP decreased during the treatment, but a similar effect was observed in a placebo group. Therefore, crude stevioside did not show a significant antihypertensive effect compared to the placebo group[27]. These results indicate that stevioside contained in food

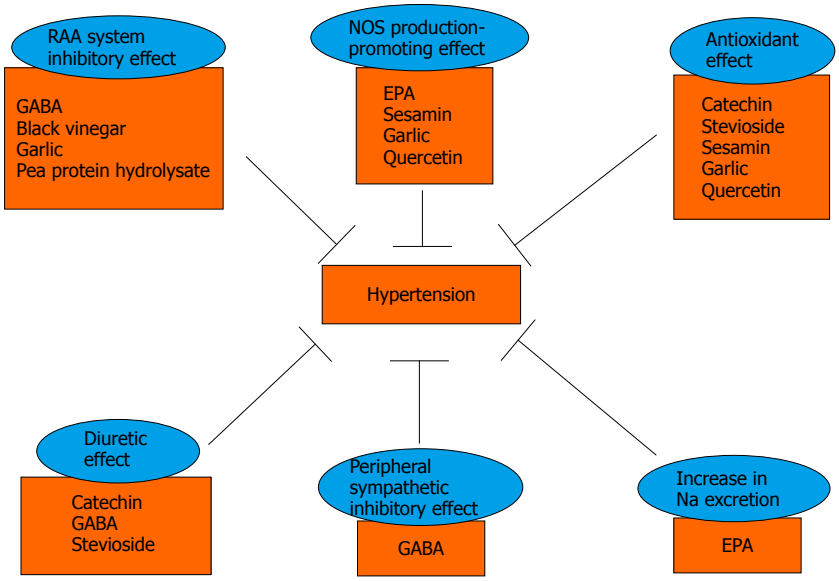

Figure 1 Antihypertensive mechanism of functional foods. Anti-hypertensive mechanism of functional foods in this paper. There are also some foods with multiple mechanisms. These suggest that they synergistically promote the hypotensive action. GABA: G-aminobutyric acid; RAA: Rennin-angiotensin-aldosterone.

has an insufficient antihypertensive effect, and so there is a need to take it as a supplement.

BLACK VINEGAR

Black vinegar is made from rice and produced by fermentation and aging. Since it contains an abundance of amino acids, various physiological activities, including antioxidant activity, have been reported. It has been reported that the activities are due to amino acids, acetic acid, and low-molecular-weight peptides[28]. When subjects were given a drink containing 15% black vinegar or 15% apple vinegar (each contains acetic acid at 750 mg/100 mL) for 8 wk, SBP was significantly reduced both at 2 and 10 wk after the intake, and no side effects were observed[29]. In another trial involving subjects given a drink containing tomato vinegar (750 mg/100 g per day) for 12 wk, SBP was significantly reduced at 10 and 12 wk after intake compared to a placebo group, and DBP was also reduced at 10 and 12 wk compared to the value before ingestion[30]. Moreover, subject given a drink containing apple vinegar (acetic acid 0.75 g/100 mL) or acetic acid (acetic acid 1.5 g/100 mL) for 8 wk, SBP was decreased from 6 wk after intake of apple vinegar drink, SBP and DBP were decreased from 4 wk after intake of acetic acid drink[31]. By experiment using spontaneously hypertensive rats (SHR) rats, the mechanism of this hypotensive action has been suggested to be the inhibitory effect of the renin-angiotensin system, such as the inhibitions of renin activity and ACE activity by peptides present in black vinegar[28,32]. Also, it has been reported that acetate has effects on lipid metabolism[33], and that drinking vinegar routinely improves lifestyle-related diseases as well as decreases blood pressures.

SESAMIN

Sesamin is a kind of lignan compound contained in a small amount of sesame. In recent years, a variety of bioactivities has been reported, such as antioxidant, cholesterol-lowering, lipid metabolism-enhancing, and liver-protective effects. Sesamin is also known for a hypotensive effect. However, there are many unclear points regarding the mechanism of action. Several animal experiments suggest that the hypotensive action of sesamin is involved in the vasodilating effect caused by NOS production enhancement and oxidative stress reduction in blood vessels due to the antioxidant effect[34-36]. In human clinical trials, mildly hypertensive subjects taking 60 mg/d of sesamin for 4 wk, showed significantly decreased SBP and DBP. No significant side effects were observed[37]. Since sesamin is often used in small amounts in cooking and its calorie content is high, the ingestion of a large amount at one time is difficult. Therefore, it is desirable for the active ingredient of sesamin to be taken as a supplement.

EPA, DHA

The results of epidemiological studies in the 1970s showed that people who lived on mainly a diet of fish in Greenland and Canada suffered less from coronary artery disease than Danes eating mainly meat. Human trials have indicated that diet supplementation with fish oil, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension[38,39]. Components exhibiting this anti-hypertensive effect of fish oil have been reported to be EPA and DHA, n = 3 fatty acids abundant in fish, and researches on them is progressing. Many animal experiments indicate that daily administration of EPA significantly decreased the development of hypertension in SHR dose dependently, although it did not affect to BP in normotensive rats[40]. Patients with uncomplicated mild to moderate essential hypertension treated with EPA (2.7 g/d) for 4 wk showed decreases in SBP and the

intraerythrocyte sodium content (R-Na), accompanied by an increase in the erythrocyte membrane EPA content. The decrease in R-Na was correlated positively with the decrease in SBP, and correlated negatively with the change in Na^+-K^+ ATPase activity. EPA may lower the blood pressure by altering the activities of the membrane sodium transport systems[41]. Antihypertensive mechanisms of fish oil, such as EPA and DHA, are considered to explain the decrease in the intercellular sodium concentration[41], increase in eNOS expression, decrease in oxidative stress[42], and altered biosynthesis of eicosanoids[43]. In human trials, patients with hyperlipidemia were assigned to receive 1800 mg/d of EPA or 10 mg/d of pravastatin for 3 mo. In the EPA group, the radial augmentation index (AI, a parameter for vascular aging), SBP, DBP, and C-SBP (the systolic pressure at the ascending aortic root, representing the vascular load of the left ventricle afterload), were decreased, respectively. In the pravastatin group, there were no significant changes in brachial BP, AI, or C-SBP. These results suggest that EPA but not pravastatin reduces cardiac afterload by reducing vascular reflected waves and lowering C-SBP[44]. On the other hand, subjects with hypertension and/or hypercholesterolemia supplemented with 2 g of DHA for 5 wk showed significantly decreased SBP, DBP, and heart rate[45].

GARLIC

Garlic preparations contain a wide variety of organosulfur compounds, of which allicin is the most notable, and it is responsible for the characteristic garlic odor[46]. Antihypertensive effects of garlic were reported in many studies using hypertensive rat models. The antihypertensive mechanism of garlic is assumed to involve ACE inhibitory effect[46], antioxidant effect[47], activation of NO formation[48], and reduction in the synthesis of vasoconstrictor prostanoids[49]. Although SHR fed diets containing either aged garlic extract (AGE) or raw garlic (RG) powder for 10 wk showed a reduction of SBP from 4 wk, Harmful effects were observed in the RG group, including a decrease in erythrocytes, an increase in reticulocytes, and the generation of a papilloma in the forestomach. These findings suggest that the long-term intake of raw garlic can be harmful to health[50]. Patients with uncontrolled systolic hypertension were allocated aged garlic extract (240, 480, and 960 mg containing 0.6, 1.2, and 2.4 mg of S-allylcysteine, respectively). SBP was significantly reduced in the 480 mg/d group over 12 wk, and reached borderline significant reduction in the 960 mg/d group at 8 wk, although blood pressure in the 240 mg/d group was not significantly different compared to the placebo group[51]. The efficacy of some clinical trials have been reported in addition to these[52-54]. Some trials suggested that garlic is associated with blood pressure reductions in patients with elevated SBP, but not in those without SBP elevation[55,56]. These reports suggest that the risk of excessive decreases in blood pressure is low when a healthy person ingests garlic.

QUERCETIN

Onion is a vegetable which is used in a variety of dishes in the world and has excellent storage stability. Onion is rich in phenolic compounds such as quercetin, which have an antioxidant effect[57]. It is expected to provide considerable health benefits. There are several reports that quercetin shows an antihypertensive effect through the antioxidant activity[58], inhibition of ACE activity[59] and Ca^{2+} influx[60]. It has been considered that these results show synergistic antihypertensive effect. Animal experiment using abdominal aortic constriction rat indicated that quercetin is also useful for preventing cardiovascular disease[61]. In human studies, apparently healthy subjects showed decreased arterial blood pressure 5 h after the administration of an onion-olive-oil maceration capsule formulation. In addition to this, a significant reduction in the plasma viscosity and hematocrit were observed[62]. Subjects with prehypertension and stage 1 hypertension ingested 730 mg quercetin per day for 28 d, and the blood pressure was not altered in prehypertensive patients after quercetin supplementation. In contrast, reductions in SBP, DBP, and mean arterial pressures were observed in the stage 1 hypertensive patients after quercetin treatment. However, indices of oxidant stress measured in the plasma and urine were not affected by quercetin[63], and so it is considered that components other than quercetin are also involved in the hypotensive effect of onion.

PEA PROTEIN HYDROLYSATE

Pea protein has been a focus of attention as an important and cheap vegetable protein with high nutritional and functional values and marked potency as an ingredient for the production of bioactive peptides[64]. Pea protein hydrolysate (PPH) showed high-level inhibition of ACE and renin activities[65]. PPH shows antihypertensive effects by influencing the renin-angiotensin system in rat model[64]. In clinical trials, subjects with SBP ranging from 125 to 170 mmHg took 3 g/d of PPH showed significant reductions in SBP of 5 and 6 mmHg in 2 and 3 wk, respectively. None of the participants reported any adverse side effects[64]. Beans such as peas, rich in vegetable protein with low lipids and low calories, are very important in health promotion. However, a complex process of protein purification, as described above, is necessary to obtain PPH with a hypotensive action. So, an abundant consumption of peas is not recommended. We expect that it will become possible to control the blood pressure based on these results and further research on bean proteins and the development of PPH supplements.

MANAGEMENT OF HYPERTENSION BY FUNCTIONAL FOODS

Besides the foods introduced in this paper, grains,

vegetables, fruits, milk, cheese, meat, chicken, wine, mushrooms, lactic acid bacteria, nicotianamine and egg are various food sources with potential antihypertensive effects. Their main bioactive constituents include ACE inhibitory peptides, vitamins C and E, flavonoids, flavanols, catechins, anthocyanins, phenolic acids, polyphenols, tannins, resveratrol, polysaccharides, fiber, saponin, sterols, as well as K, Ca, and P. These functional foods may provide new therapeutic applications for hypertension prevention and treatment, and contribute to a cardiovascularly healthy population[66]. In recent years, the DASH (Dietary Approaches to Stop Hypertension) diet has caught attention as a dietary therapy for blood pressure control. The DASH diet is a composite diet that cuts down fat, based on fruits and vegetables, beans, fish, low-fat dairy products, and cereals. It has been frequently reported as useful for lowering the blood pressure[5,67-72]. The mechanism of the the hypotensive action of the DASH diet has been considered mainly through the Na diuretic effect. In addition to this, as it is rich in K, its hypotensive action is particularly effective for blood pressure elevation due to salt overdose. Since Na is added and K is lost during food processing, actively taking K should be recommended in developed countries where processed foods are commonly consumed. It has also been reported that the intake of Mg reduces the onset risk of metabolic syndrome[73]. A DASH diet rich in Mg may reduce the risk of obesity.

We have reviewed the functions of foods, but such foods should be taken with care to complement human physiology. For example, there is a risk of causing high K hyperlipidemia in some patients with marked renal failure or who are taking anti-aldosterone drugs, ACE inhibitors, or angiotensin Ⅱ receptor blocker (ARB). For this reason, such people are not recommended to abundantly consume vegetables and fruits rich in K. Patients with obesity and diabetes who have restricted energy intake should not abundantly consume nuts and fruits containing much sugar. It is necessary for them to avoid excess calorie intake[74]. On the other hand, the intake of food with a diuretic effect is suitable for patients with renal failure because it has the action of body fluid volume control and lowering the blood pressure. However, overconsuming certain functional foods with a hypotensive effect may lead to unbalanced nutrition and adverse interaction with antihypertensive agents. Therefore, recommendations of a balanced diet based on functional foods and dietary advice tailored to an individual's physiology are recommended.

We summarize the functional foods with antihypertensive effects from the evidences in clinical studies. In contradiction to these studies, there are several reports indicating opposite results and many interventional studies with no statistical significance. For example, Green tea consumption was inversely associated with mortality due to all causes and cardiovascular disease[75], and there are a few reports described no effect of EPA on the blood pressure[76,77]. So, the potential of clinical applications of functional foods remains undetermined. Randomized controlled trials are needed to establish the clinical applications of functional foods.

CONCLUSION

In addition to drug therapy, the management of high blood pressure is essential for the improvement of lifestyle habits. Simply taking medicine for health is not enough. It is necessary to adopt a balanced diet and regular life with drug therapy. The first dietary step is to take a low-salt diet (optimal value: less than 6 g/d) in order to reduce the load on the kidneys and blood vessels. We hope that you will enjoy a richer dietary life by positively taking functional foods when presented. Also, we expect people to utilize them effectively as a means to practice "self-medication".

We are confident that in the future, further studies will expand the field of functional foods, and identify more useful functions of other foods, not only functional fruits and vegetables, for preventing hypertension-related and other diseases.

REFERENCES

1 **WHO**. A global brief on hypertension. Available from: URL: http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/

2 **WHO;** World Heart Federation; World Stroke Organization. Global atlas on cardiovascular disease prevention and control. Available from: URL: http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/

3 **Mathers CD**, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**: e442 [PMID: 17132052 DOI: 10.1371/journal.pmed.0030442]

4 **WHO**. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. Available from: URL: http://www.who.int/cardiovascular_diseases/publications/Prevention_of_Cardiovascular_Disease/en/

5 **Whelton PK**, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002; **288**: 1882-1888 [PMID: 12377087 DOI: 10.1001/jama.288.15.1882]

6 **Kaminogawa S**. Functional foods. In: Kaminogawa S, Shimizu T, Shimizu M, Suzuki H, Takeda E, editors. The Encyclopedia about safety and effect of functional foods. Toukyou: Maruzen Publishing, 2012: 3-8

7 **Negishi H**, Xu JW, Ikeda K, Njelekela M, Nara Y, Yamori Y. Black and green tea polyphenols attenuate blood pressure increases in stroke-prone spontaneously hypertensive rats. *J Nutr* 2004; **134**: 38-42 [PMID: 14704290]

8 **Khan N**, Mukhtar H. Tea and health: studies in humans. *Curr Pharm Des* 2013; **19**: 6141-6147 [PMID: 23448443 DOI: 10.2174/1381612811319340008]

9 **Frei B**, Higdon JV. Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. *J Nutr* 2003; **133**: 3275S-3284S [PMID: 14519826]

10 **Brown AL**, Lane J, Coverly J, Stocks J, Jackson S, Stephen A, Bluck L, Coward A, Hendrickx H. Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated metabolic risk factors: randomized controlled trial. *Br J Nutr* 2009; **101**: 886-894 [PMID: 18710606 DOI: 10.1017/S0007114508047727]

11 **Bogdanski P**, Suliburska J, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure,

inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. *Nutr Res* 2012; **32**: 421-427 [PMID: 22749178 DOI: 10.1016/j.nutres.2012.05.007]

12 **Kurita I**, Maeda-Yamamoto M, Tachibana H, Kamei M. Antihypertensive effect of Benifuuki tea containing O-methylated EGCG. *J Agric Food Chem* 2010; **58**: 1903-1908 [PMID: 20078079 DOI: 10.1021/jf904335g]

13 **Mozaffari-Khosravi H**, Ahadi Z, Barzegar K. The effect of green tea and sour tea on blood pressure of patients with type 2 diabetes: a randomized clinical trial. *J Diet Suppl* 2013; **10**: 105-115 [PMID: 23725524 DOI: 10.3109/19390211.2013.790333]

14 **Yokoyama S**, Hiramatsu J, Hayakawa K. Production of gamma-aminobutyric acid from alcohol distillery lees by Lactobacillus brevis IFO-12005. *J Biosci Bioeng* 2002; **93**: 95-97 [PMID: 16233172 DOI: 10.1263/jbb.93.95]

15 **Higuchi T**, Hayashi H, Abe K. Exchange of glutamate and gamma-aminobutyrate in a Lactobacillus strain. *J Bacteriol* 1997; **179**: 3362-3364 [PMID: 9150237]

16 **Hayakawa K**, Kimura M, Kamata K. Mechanism underlying gamma-aminobutyric acid-induced antihypertensive effect in spontaneously hypertensive rats. *Eur J Pharmacol* 2002; **438**: 107-113 [PMID: 11906718 DOI: 10.1016/S0014-2999(02)01294-3]

17 **Kajimoto O**, Hirata H, Nakagawa S, Kajimoto Y, Hayakawa K, Kimura M. Hypotensive Effect of Fermented Milk Containing γ-Aminobutyric Acid (GABA) in Subjects with High Normal Blood Pressure. *Nippon Shokuhin Kagaku Kogaku kaishi* 2004; **51**: 79-86

18 **Inoue K**, Shirai T, Ochiai H, Kasao M, Hayakawa K, Kimura M, Sansawa H. Blood-pressure-lowering effect of a novel fermented milk containing gamma-aminobutyric acid (GABA) in mild hypertensives. *Eur J Clin Nutr* 2003; **57**: 490-495 [PMID: 12627188 DOI: 10.1038/sj.ejcn.1601555]

19 **Yamakoshi J**, Shimojo R, Nakagawa S, Izui N, Ogihara T. Hypotensive effects and safety of less-sodium soy sauce containing γ- aminobutyric acid (GABA) on high-normal blood pressure and mild hypertensive subjects. *Jpn Pharmacol Ther* 2006; **34**: 691-709

20 **Chatsudthipong V**, Muanprasat C. Stevioside and related compounds: therapeutic benefits beyond sweetness. *Pharmacol Ther* 2009; **121**: 41-54 [PMID: 19000919 DOI: 10.1016/j.pharmthera.2008.09.007]

21 **Mohd-Radzman NH**, Ismail WI, Adam Z, Jaapar SS, Adam A. Potential Roles of Stevia rebaudiana Bertoni in Abrogating Insulin Resistance and Diabetes: A Review. *Evid Based Complement Alternat Med* 2013; **2013**: 718049 [PMID: 24324517 DOI: 10.1155/2013/718049]

22 **Hsu YH**, Liu JC, Kao PF, Lee CN, Chen YJ, Hsieh MH, Chan P. Antihypertensive effect of stevioside in different strains of hypertensive rats. *Zhonghua Yixue Zazhi* (Taipei) 2002; **65**: 1-6 [PMID: 11939668]

23 **Lee CN**, Wong KL, Liu JC, Chen YJ, Cheng JT, Chan P. Inhibitory effect of stevioside on calcium influx to produce antihypertension. *Planta Med* 2001; **67**: 796-799 [PMID: 11745013 DOI: 10.1055/s-2001-18841]

24 **Wong KL**, Yang HY, Chan P, Cheng TH, Liu JC, Hsu FL, Liu IM, Cheng YW, Cheng JT. Isosteviol as a potassium channel opener to lower intracellular calcium concentrations in cultured aortic smooth muscle cells. *Planta Med* 2004; **70**: 108-112 [PMID: 14994186 DOI: 10.1055/s-2004-815485]

25 **Chan P**, Tomlinson B, Chen YJ, Liu JC, Hsieh MH, Cheng JT. A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. *Br J Clin Pharmacol* 2000; **50**: 215-220 [PMID: 10971305 DOI: 10.1002/ptr.1944]

26 **Hsieh MH**, Chan P, Sue YM, Liu JC, Liang TH, Huang TY, Tomlinson B, Chow MS, Kao PF, Chen YJ. Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. *Clin Ther* 2003; **25**: 2797-2808 [PMID: 14693305 DOI: 10.1016/S0149-2918(03)80334-X]

27 **Ferri LA**, Alves-Do-Prado W, Yamada SS, Gazola S, Batista MR, Bazotte RB. Investigation of the antihypertensive effect of oral crude stevioside in patients with mild essential hypertension. *Phytother Res* 2006; **20**: 732-736 [PMID: 16775813]

28 **Kondo S**, Tayama K, Tsukamoto Y, Ikeda K, Yamori Y. Antihypertensive effects of acetic acid and vinegar on spontaneously hypertensive rats. *Biosci Biotechnol Biochem* 2001; **65**: 2690-2694 [PMID: 11826965 DOI: 10.1271/bbb.65.2690]

29 **Kajimoto O**，Oshima Y，Tayama K, Hirata H, Nishimura A, Tsukamoto Y. Hypotensive effects of drinks containing vinegar on high normal blood pressure and mild hypertensive subjects. *J Nutr Food* 2003; **6**: 51-68

30 **Sado T**, Arita J, Miyamoto S, Iwasaki H, Nishimura A, Kajimoto Y, Kajimoto O. Antihypertensive Effect and Safety of a Drink Containing Tomato Vinegar in Case of Long-term Intake for Subjects with High-normal Blood Pressure or Mild Hypertension. *Jpn Pharmacol Ther* 2006; **34**: 723-35

31 **Kajimoto O**, Tayama K, Hirata H, Takahashi T, Tsukamoto Y. Effect of a drink containing vinegar on blood pressure in mildly and moderately hypertensive subjects. *J Nutr Food* 2001; **4**: 47-60

32 **Odahara M**, Ogino y, Takizawa K, Kimura M, Nakamura N, Kimoto K. Hypotensive Effect of Black Malt Vinegar on Spontaneously Hypertensive Rats. *J Jpn Soc Food Sci Tech* 2008; **55**: 81-86

33 **Yamashita H**, Maruta H, Jozuka M, Kimura R, Iwabuchi H, Yamato M, Saito T, Fujisawa K, Takahashi Y, Kimoto M, Hiemori M, Tsuji H. Effects of acetate on lipid metabolism in muscles and adipose tissues of type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Biosci Biotechnol Biochem* 2009; **73**: 570-576 [PMID: 19270372 DOI: 10.1271/bbb.80634]

34 **Nakano D**, Itoh C, Ishii F, Kawanishi H, Takaoka M, Kiso Y, Tsuruoka N, Tanaka T, Matsumura Y. Effects of sesamin on aortic oxidative stress and endothelial dysfunction in deoxycorticosterone acetate-salt hypertensive rats. *Biol Pharm Bull* 2003; **26**: 1701-1705 [PMID: 14646174 DOI: 10.1248/bpb.26.1701]

35 **Nakano D**, Kurumazuka D, Nagai Y, Nishiyama A, Kiso Y, Matsumura Y. Dietary sesamin suppresses aortic NADPH oxidase in DOCA salt hypertensive rats. *Clin Exp Pharmacol Physiol* 2008; **35**: 324-326 [PMID: 17941888 DOI: 10.1111/j.1440-1681.2007.04817.x]

36 **Nakano D**, Kwak CJ, Fujii K, Ikemura K, Satake A, Ohkita M, Takaoka M, Ono Y, Nakai M, Tomimori N, Kiso Y, Matsumura Y. Sesamin metabolites induce an endothelial nitric oxide-dependent vasorelaxation through their antioxidative property-independent mechanisms: possible involvement of the metabolites in the antihypertensive effect of sesamin. *J Pharmacol Exp Ther* 2006; **318**: 328-335 [PMID: 16597711 DOI: 10.1124/jpet.105.100149]

37 **Miyawaki T**, Aono H, Toyoda-Ono Y, Maeda H, Kiso Y, Moriyama K. Antihypertensive effects of sesamin in humans. *J Nutr Sci Vitaminol* (Tokyo) 2009; **55**: 87-91 [PMID: 19352068 DOI: 10.3177/jnsv.55.87]

38 **Russo C**, Olivieri O, Girelli D, Azzini M, Stanzial AM, Guarini P, Friso S, De Franceschi L, Corrocher R. Omega-3 polyunsaturated fatty acid supplements and ambulatory blood pressure monitoring parameters in patients with mild essential hypertension. *J Hypertens* 1995; **13**: 1823-1826 [PMID: 8903660]

39 **Appel LJ**, Miller ER, Seidler AJ, Whelton PK. Does supplementation of diet with ‚fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. *Arch Intern Med* 1993; **153**: 1429-1438 [PMID: 8141868 DOI: 10.1001/archinte.1993.00410120017003]

40 **Kasuya Y**, Utsunomiya N, Matsuki N. Attenuation of the development of hypertension in spontaneously hypertensive rats by chronic oral administration of eicosapentaenoic acid. *J Pharmacobiodyn* 1986; **9**: 239-243 [PMID: 3014107]

41 **Miyajima T**, Tsujino T, Saito K, Yokoyama M. Effects of eicosapentaenoic acid on blood pressure, cell membrane fatty acids, and intracellular sodium concentration in essential hypertension. *Hypertens Res* 2001; **24**: 537-542 [PMID: 11675948 DOI: 10.1291/hypres.24.537]

42 **Nyby MD**, Matsumoto K, Yamamoto K, Abedi K, Eslami P, Hernandez G, Smutko V, Berger ME, Tuck ML. Dietary

fish oil prevents vascular dysfunction and oxidative stress in hyperinsulinemic rats. *Am J Hypertens* 2005; **18**: 213-219 [PMID: 15752949 DOI: 10.1016/j.amjhyper.2004.08.030]
43 **Knapp HR**, FitzGerald GA. The antihypertensive effects of fish oil. A controlled study of polyunsaturated fatty acid supplements in essential hypertension. *N Engl J Med* 1989; **320**: 1037-1043 [PMID: 2648152 DOI: 10.1056/NEJM198904203201603]
44 **Iketani T**, Takazawa K, Yamashina A. Effect of eicosapentaenoic acid on central systolic blood pressure. *Prostaglandins Leukot Essent Fatty Acids* 2013; **88**: 191-195 [PMID: 23246023 DOI: 10.1016/j.plefa.2012.11.008]
45 **Sagara M**, Njelekela M, Teramoto T, Taguchi T, Mori M, Armitage L, Birt N, Birt C, Yamori Y. Effects of docosahexaenoic Acid supplementation on blood pressure, heart rate, and serum lipids in Scottish men with hypertension and hypercholesterolemia. *Int J Hypertens* 2011; **2011**: 809198 [PMID: 21423683 DOI: 10.4061/2011/809198]
46 **Sharifi AM**, Darabi R, Akbarloo N. Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rat. *J Ethnopharmacol* 2003; **86**: 219-224 [PMID: 12738090 DOI: 10.1016/S0378-8741(03)00080-1]
47 **Cruz C**, Correa-Rotter R, Sánchez-González DJ, Hernández-Pando R, Maldonado PD, Martínez-Martínez CM, Medina-Campos ON, Tapia E, Aguilar D, Chirino YI, Pedraza-Chaverri J. Renoprotective and antihypertensive effects of S-allylcysteine in 5/6 nephrectomized rats. *Am J Physiol Renal Physiol* 2007; **293**: F1691-F1698 [PMID: 17686953 DOI: 10.1152/ajprenal.00235.2007]
48 **Ku DD**, Abdel-Razek TT, Dai J, Kim-Park S, Fallon MB, Abrams GA. Garlic and its active metabolite allicin produce endothelium- and nitric oxide-dependent relaxation in rat pulmonary arteries. *Clin Exp Pharmacol Physiol* 2002; **29**: 84-91 [PMID: 11906464 DOI: 10.1046/j.1440-1681.2002.03596.x]
49 **Al-Qattan KK**, Khan I, Alnaqeeb MA, Ali M. Thromboxane-B2, prostaglandin-E2 and hypertension in the rat 2-kidney 1-clip model: a possible mechanism of the garlic induced hypotension. *Prostaglandins Leukot Essent Fatty Acids* 2001; **64**: 5-10 [PMID: 11161580 DOI: 10.1054/plef.2000.0232]
50 **Harauma A**, Moriguchi T. Aged garlic extract improves blood pressure in spontaneously hypertensive rats more safely than raw garlic. *J Nutr* 2006; **136**: 769S-773S [PMID: 16484560]
51 **Ried K**, Frank OR, Stocks NP. Aged garlic extract reduces blood pressure in hypertensives: a dose-response trial. *Eur J Clin Nutr* 2013; **67**: 64-70 [PMID: 23169470 DOI: 10.1038/ejcn.2012.178]
52 **Ashraf R**, Khan RA, Ashraf I, Qureshi AA. Effects of Allium sativum (garlic) on systolic and diastolic blood pressure in patients with essential hypertension. *Pak J Pharm Sci* 2013; **26**: 859-863 [PMID: 24035939]
53 **Andrianova IV**, Fomchenkov IV, Orekhov AN. [Hypotensive effect of long-acting garlic tablets allicor (a double-blind placebo-controlled trial)]. *Ter Arkh* 2002; **74**: 76-78 [PMID: 11980131]
54 **Stabler SN**, Tejani AM, Huynh F, Fowkes C. Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients. *Cochrane Database Syst Rev* 2012; **8**: CD007653 [PMID: 22895963 DOI: 10.1002/14651858.CD007653.pub2]
55 **Ried K**, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. *Maturitas* 2010; **67**: 144-150 [PMID: 20594781 DOI: 10.1016/j.maturitas.2010.06.001]
56 **Reinhart KM**, Coleman CI, Teevan C, Vachhani P, White CM. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Ann Pharmacother* 2008; **42**: 1766-1771 [PMID: 19017826 DOI: 10.1345/aph.1L319]
57 **Boots AW**, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. *Eur J Pharmacol* 2008; **585**: 325-337 [PMID: 18417116 DOI: 10.1016/j.ejphar.2008.03.008]
58 **Sakai Y**, Murakami T, Yamamoto Y. Antihypertensive effects of onion on NO synthase inhibitor-induced hypertensive rats and spontaneously hypertensive rats. *Biosci Biotechnol Biochem* 2003; **67**: 1305-1311 [PMID: 12843658 DOI: 10.1271/bbb.67.1305]
59 **Häckl LP**, Cuttle G, Dovichi SS, Lima-Landman MT, Nicolau M. Inhibition of angiotesin-converting enzyme by quercetin alters the vascular response to brandykinin and angiotensin I. *Pharmacology* 2002; **65**: 182-186 [PMID: 12174832 DOI: 10.1159/000064341]
60 **Naseri MK**, Arabian M, Badavi M, Ahangarpour A. Vasorelaxant and hypotensive effects of Allium cepa peel hydroalcoholic extract in rat. *Pak J Biol Sci* 2008; **11**: 1569-1575 [PMID: 18819643 DOI: 10.3923/pjbs.2008.1569.1575]
61 **Jalili T**, Carlstrom J, Kim S, Freeman D, Jin H, Wu TC, Litwin SE, David Symons J. Quercetin-supplemented diets lower blood pressure and attenuate cardiac hypertrophy in rats with aortic constriction. *J Cardiovasc Pharmacol* 2006; **47**: 531-541 [PMID: 16680066 DOI: 10.1097/01.fjc.0000211746.78454.50]
62 **Kalus U**, Pindur G, Jung F, Mayer B, Radtke H, Bachmann K, Mrowietz C, Koscielny J, Kiesewetter H. Influence of the onion as an essential ingredient of the Mediterranean diet on arterial blood pressure and blood fluidity. *Arzneimittelforschung* 2000; **50**: 795-801 [PMID: 11050695 DOI: 10.1055/s-0031-1300291]
63 **Edwards RL**, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T. Quercetin reduces blood pressure in hypertensive subjects. *J Nutr* 2007; **137**: 2405-2411 [PMID: 17951477]
64 **Li H**, Prairie N, Udenigwe CC, Adebiyi AP, Tappia PS, Aukema HM, Jones PJ, Aluko RE. Blood pressure lowering effect of a pea protein hydrolysate in hypertensive rats and humans. *J Agric Food Chem* 2011; **59**: 9854-9860 [PMID: 21854068 DOI: 10.1021/jf201911p]
65 **Li H**, Aluko RE. Identification and inhibitory properties of multifunctional peptides from pea protein hydrolysate. *J Agric Food Chem* 2010; **58**: 11471-11476 [PMID: 20929253 DOI: 10.1021/jf102538g]
66 **Huang WY**, Davidge ST, Wu J. Bioactive natural constituents from food sources-potential use in hypertension prevention and treatment. *Crit Rev Food Sci Nutr* 2013; **53**: 615-630 [PMID: 23627503 DOI: 10.1080/10408398.2010.550071]
67 **Sacks FM**, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, Simons-Morton DG, Karanja N, Lin PH. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**: 3-10 [PMID: 11136953 DOI: 10.1056/NEJM200101043440101]
68 **Padwal R**, Campbell N, Touyz RM. Applying the 2005 Canadian Hypertension Education Program recommendations: 3. Lifestyle modifications to prevent and treat hypertension. *CMAJ* 2005; **173**: 749-751 [PMID: 16186578 DOI: 10.1503/cmaj.050186]
69 **Blumenthal JA**, Babyak MA, Hinderliter A, Watkins LL, Craighead L, Lin PH, Caccia C, Johnson J, Waugh R, Sherwood A. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med* 2010; **170**: 126-135 [PMID: 20101007 DOI: 10.1001/archinternmed.2009.470]
70 **Chen ST**, Maruthur NM, Appel LJ. The effect of dietary patterns on estimated coronary heart disease risk: results from the Dietary Approaches to Stop Hypertension (DASH) trial. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 484-489 [PMID: 20807884 DOI: 10.1161/CIRCOUTCOMES.109.930685]
71 **de Paula TP**, Steemburgo T, de Almeida JC, Dall'Alba V, Gross JL, de Azevedo MJ. The role of Dietary Approaches to Stop Hypertension (DASH) diet food groups in blood pressure in type 2 diabetes. *Br J Nutr* 2012; **108**: 155-162 [PMID: 22142820 DOI: 10.1017/S0007114511005381]
72 **Akita S**, Sacks FM, Svetkey LP, Conlin PR, Kimura G. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on the pressure-natriuresis relationship. *Hypertension* 2003; **42**: 8-13 [PMID: 12756219 DOI: 10.1161/01.HYP.0000074668.08704.6E]
73 **He K**, Liu K, Daviglus ML, Morris SJ, Loria CM, Van Horn L, Jacobs DR, Savage PJ. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; **113**: 1675-1682 [PMID: 16567569 DOI: 10.1161/CIRCULATIONAHA.105.588327]
74 **Lindholm LH**, Carlberg B. The new Japanese Society of Hypertension guidelines for the management of hypertension (JSH

2014): a giant undertaking. *Hypertens Res* 2014; **37**: 391-392 [PMID: 24705437]

75 **Kuriyama S**, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *JAMA* 2006; **296**: 1255-1265 [PMID: 16968850 DOI: 10.1001/jama.296.10.1255]

76 **Erkkilä AT**, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr* 2008; **47**: 319-328 [PMID: 18665413 DOI: 10.1007/s00394-008-0728-5]

77 **Szabo de Edelenyi F**, Vergnaud AC, Ahluwalia N, Julia C, Hercberg S, Blacher J, Galan P. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD. *Br J Nutr* 2012; **107**: 921-927 [PMID: 21801476 DOI: 10.1017/S0007114511003692]

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REVIEW

Progress in neuregulin/ErbB signaling and chronic heart failure

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Abstract

Heart failure is one of the leading causes of death today. It is a complex clinical syndrome in which the heart has a reduced contraction ability and decreased viable myocytes. Novel approaches to the clinical management of heart failure have been achieved through an understanding of the molecular pathways necessary for normal heart development. Neuregulin-1 (NRG-1) has emerged as a potential therapeutic target based on the fact that mice null for NRG-1 or receptors mediating its activity, ErbB2 and ErbB4, are embryonic lethal and exhibit severe cardiac defects. Preclinical studies performed with animal models of heart failure demonstrate that treatment with NRG-1 significantly improves heart function and survival. Clinical data further support NRG-1 as a promising drug candidate for the treatment of cardiac dysfunction in patients. Recent studies have revealed the mechanism underlying the therapeutic effects of NRG-1/ErbB signaling in the treatment of heart failure. Through activation of upstream signaling molecules such as phosphoinositide 3-kinase, mitogen-activated protein kinase, and focal adhesion kinase, NRG-1/ErbB pathway activation results in increased cMLCK expression and enhanced intracellular calcium cycling. The former is a regulator of the contractile machinery, and the latter triggers cell contraction and relaxation. In addition, NRG-1/ErbB signaling also influences energy metabolism and induces epigenetic modification in cardiac myocytes in a way that more closely resembles healthy heart. These observations reveal potentially new treatment options for heart failure.

Key words: ErbB; Epigenetic modification; Heart failure; Metabolism; Neuregulin-1

Core tip: Neuregulin (NRG)-1/ErbB signaling plays a critical role in the development of the heart and the maintenance of cardiac function. In both pre-clinical and clinical studies, NRG-1 has demonstrated efficacy as a therapeutic agent for the treatment of heart failure. In model animals and clinical trials, short-term treatment with recombinant NRG-1 protein results in a long-term beneficial effect. Here, the mechanisms underlying the therapeutic effects of NRG-1 during heart failure are reviewed. The results indicate that NRG-1 induces a cardiac reverse remodeling process through the initiation of changes in both cell metabolism and epigenetic modification.

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INTRODUCTION

The neuregulins (NRGs) are a group of growth factors that regulate multiple cellular processes, including proliferation, apoptosis, adhesion, differentiation, metabolism, and epigenetic modification, through the activation of ErbB receptors and downstream signaling pathways. Increasing evidence demonstrates that NRG-1/ErbB signaling plays a critical role in the development of the heart and the maintenance of cardiac function. In both pre-clinical and clinical studies, NRG-1 has demonstrated efficacy as a therapeutic agent for the treatment of heart failure. This review will focus on the underlying mechanisms and recent achievements in the treatment of heart failure with NRG therapy.

NRG FAMILY AND THEIR RECEPTORS

NRGs are ligands for receptor tyrosine kinases of the ErbB family. In mammals, NRGs are a family of homologous proteins encoded by four genes, *NRG1*, *NRG2*, *NRG3*, and *NRG4*. NRG-1 is the most abundant family member expressed in the cardiovascular system and the only NRG currently known to play a role in the development and function of the heart[1-4].

Six NRG-1 isoforms generated by alternative splicing have been identified. All NRG-1 isoforms contain an epidermal growth factor (EGF)-like domain, which is critical for function. Proteolytic cleavage at the C-terminal end of the domain results in the release of a secreted, bioactive form of NRG-1[5,6]. Due to alternative splicing, the EGF-like domain of NRG-1 differs at the C-terminal end. An α- or β-variant is generated, and *in vitro* studies have demonstrated that NRG-1β isoforms are 10-100-fold more biologically active than NRG-1α isoforms[3,7-9].

NRG-1 is a growth factor that elicits function through interaction with the ErbB family of tyrosine kinase receptors and is regulated by stress[10,11]. The ErbB family contains four members: ErbB1, ErbB2, ErbB3, and ErbB4. ErbB1, also known as EGF receptor, does not bind NRG-1[2]. ErbB2 does not directly bind any ligands, but functions as the heterodimeric partner of the other three ErbB family members[12]. NRG-1 binds to ErbB3 and ErbB4, which results in the formation of ErbB2/ErbB3 and ErbB2/ErbB4 heterodimers and leads to the phosphorylation of cytoplasmic receptor tyrosine residues. Multiple intracellular signal transduction cascades, such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) 1/2, and focal adhesion kinase (FAK), are induced and stimulate cell proliferation, differentiation, and survival in many tissues including the heart[13-15].

NRG-1/ERBB SIGNALING IN CARDIAC DEVELOPMENT AND HEART FAILURE

The importance of NRG-1 in heart development was demonstrated in *Nrg1*-knockout mice. The *Nrg1* knockout was embryonic lethal, with the animals exhibiting cardiac developmental defects, such as the absence of ventricular trabeculation and insufficient myocyte differentiation[16,17]. Such results indicate that NRG-1 activity during cardiac development is not functionally redundant among family members[18-20]. The fact that NRG-2 and NRG-3 are expressed in the central nervous system and NRG-4 is expressed in pancreas and skeletal muscle further underscores the essential role for NRG-1 in cardiac development. Proteolytic cleavage is critical for the function of NRG-1, *Adam17*-knockout mice died at birth[21]. Interestingly, a deletion mutation in the cytoplasmic tail of NRG-1 is resistant to proteolysis and cannot activate ErbB receptors, suggesting that the intracellular domain is essential for the proteolytic processing of NRG-1 proteins[22]. Mice with disrupted *ErbB2* or *ErbB4* were also embryonic lethal before day 11, mirroring the phenotype of the *Nrg1*-knockout mice[23,24]. These findings implicate an essential role in cardiac development for NRG-1/ErbB2/ErbB4 signaling. *ErbB3*, however, is only expressed in mesenchymal cells of the endocardial cushion of the fetal heart. *ErbB3*-knockout mice were embryonic lethal at day 13.5 with defects in the endocardial cushion; however, the trabeculae had developed normally[24-26].

A function for NRG-1/ErbB2/ErbB4 signaling has also been confirmed in the adult heart[27]. Expression of *NRG-1* is found in the microvascular endothelial cells in the adult heart, but not in the large coronary arteries or in the aorta[10]. *ErbB2* and *ErbB4* are expressed in adult cardiomyocytes, while *ErbB3* is only expressed in fetal myocytes[27]. However, in one recent study, ErbB3 expression was detected in the adult myocardium, although its function in adult heart still remains to be determined[28]. Mice with a cardiac-specific knockout of *ErbB2* were phenotypically normal at birth, but spontaneously developed dilated cardiomyopathy at eight weeks of life. These animals were furthermore unable to survive pressure overload induced by aortic binding, and cardiac hypertrophy markers, skeletal α-actin and atrial natriuretic peptide, also significantly increased during the progression of heart failure[29]. The same result was observed in transgenic mice with a cardiomyocyte-specific null mutation in *ErbB2*[30]. In addition, the *ErbB4* conditional-knockout mice developed dilated cardiomyopathy with delayed conduction and impaired contractility by the third month after birth[31]. Based on these results, ErbB2/ErbB4 appears to be critical also for the maintenance of normal

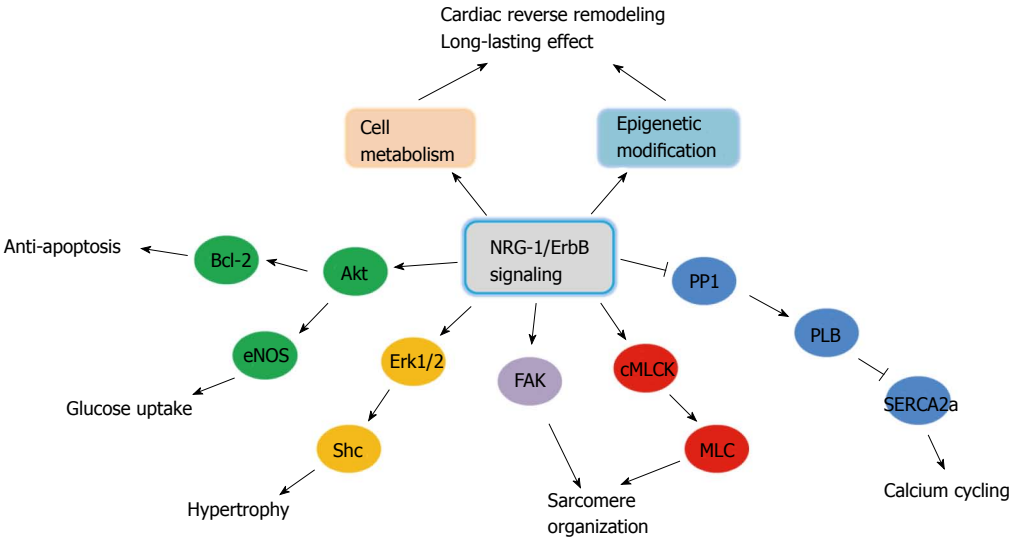

Figure 1 Role of neuregulin-1/ErbB signaling in heart. Neuregulin (NRG)-1 treatment affects various signaling pathways as well as leads to changes in cell metabolism and epigenetic modification that more closely resemble normal heart function. Akt: Protein kinase B; cMLK: Cardiac myosin light-chain kinase; eNOS: Endothelial nitric oxide synthase; Erk: Extracellular signal-regulated kinase; FAK: Focal adhesion kinase; MLC: Myosin light chain; PLB: Phospholamban; PP1: Protein phosphatase 1; SERCA2a: Sarcoplasmic reticulum Ca^{2+}-ATPase 2a.

function of the adult heart.

In clinical trials, breast cancer patients treated with trastuzumab (a humanized monoclonal ErbB2-targeted antibody) were found to have an increased risk for symptomatic heart failure and cardiac dysfunction[32,33]. This finding provided strong evidence for the critical role of ErbB2 in the adult human heart. In adult rat ventricular myocytes, treatment with NRG-1β resulted in activation of Erk1/2 and Akt, and significantly inhibited anthracycline-induced myofilament disarray. In contrast, simultaneous treatment of myocytes with anti-ErbB2 and doxorubicin led to more severe myofibrillar disarray than doxorubicin alone[34]. In the stress-induced rat model, administration of NRG-1β also led to significant improvement in the prevention of cardiac dilatation[35]. These results implicate a role for NRG-1/ErbB signaling in the maintenance of adult cardiac myocyte function and structure. Interestingly, *NRG1* mRNA levels were found to be increased in chronic heart failure patients, while the expression of *ERBB2* and *ERBB4* was reduced in a potential feedback mechanism[6,36], indicating a possible role for NRG-1/ErbB signaling during heart failure.

POSSIBLE MECHANISMS MEDIATING NRG-1/ERBB SIGNALING IN ADULT HEART

Based on *in vitro* and *in vivo* studies of cardiac myocytes, NRG-1/ErbB signaling regulates a number of cellular processes by activating signaling pathways such as PI3K/Akt, MAPK-Erk1/2, and FAK[15,27,34,37]. These canonical signaling cascades have been extensively reviewed elsewhere and will be addressed very briefly in this review[1,38,39]. In addition, recent studies indicate that NRG-1 functions as an effector molecule regulating energy metabolism[7] and epigenetic modification in cardiomyocytes[40]. A working model for NRG-1/ErbB signaling in heart is summarized in Figure 1.

CANONICAL SIGNALING PATHWAYS MEDIATING NRG-1/ERBB ACTIVITY

The PI3K/Akt pathway has been well studied in cell proliferation, growth, and apoptosis. In cardiac myocytes, activated Akt signaling inhibits apoptosis[41,42] and protects cardiomyocytes from apoptosis induced by serum starvation[27], cardiotoxic anthracycline[43], as well as β-adrenergic receptor activation[44,45]. This protective effect is dependent on the downstream activation of members of the Bcl-2 family, which typically block apoptosis[45,46]. Interestingly, NRG-1 shows a biphasic dose effect on p70S6K (a downstream protein kinase in the Akt/mTOR pathway) phosphorylation, as higher NRG-1 concentration leads to a decreased response[13]. In addition, Akt also promotes glucose uptake as well as activates endothelial nitric oxide synthase, which may contribute to cell survival under metabolic stress[7,47].

In adult cardiac myocytes, NRG-1 stimulates the Erk1/2 pathway, which leads to expression of genes associated with cardiac hypertrophy[13] as well as myofilament organization[34,37]. Erk1/2 activation is mediated by Grb2, Grb7, and Shc, which are downstream targets of ErbB2 and thus, also play a role in cardiac hypertrophy[48-51].

FAK signaling is involved in the formation of focal adhesion complexes as well as the restoration of sarcomeres in cardiac myocytes[52,53], and contributes to the growth and survival of myocytes[54,55]. In addition, cardiomyocyte FAK conditional knockout in mice was embryonic lethal,

and embryos exhibited a phenotype similar to the ErbB2 or ErbB4 cardiac-specific knockout mice[56,57]. These results provide evidence for a role of FAK in cardiac development.

Recent studies have identified cardiac myosin light chain kinase (cMLCK) as a downstream target of NRG-1/ErbB signaling in cardiomyocytes[58]. As a cardiac specific kinase[59], cMLCK is capable of activating myosin light chain[60], resulting in sarcomere organization[61]. Ventricular myocyte hypertrophy was found in cMLCK-deficient mice with histologic evidence of necrosis and fibrosis[62]. In our previous study, adenovirus-mediated gene delivery of cMLCK significantly improved cardiac function of post-myocardial infarction (MI) rats, and RNA interference of cMLCK reduced the beneficial effect of recombinant human NRG-1, rhNRG-1β (Ser177-Glu237 of the EGF-like domain of human NRG-1β2a developed by scientists at Zensun Company; Shanghai, China), on sarcomere organization[58]. Interestingly, although the cMLCK-knockout mice had attenuated MLC phosphorylation and decreased fraction shortening, NRG-1 infusion still improved cardiac performance, indicating that the beneficial effect of NRG-1 on heart function is not completely mediated by cMLCK[63].

Disruption of calcium homeostasis also occurs during the development of heart failure[64,65]. Sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) is a Ca^{2+}-ATPase that regulates calcium uptake and contributes to cardiomyocyte relaxation[66,67]. SERCA2a activity is negatively regulated by phospholamban, a target of protein phosphatase 1[68,69]. It has been reported that rhNRG-1β enhances the intracellular calcium cycle in post-MI rats through the suppression of protein phosphatase 1 expression, which results in the improved SERCA2a activity[58]. The first clinical trial of gene therapy using adeno-associated virus (AAV) in the treatment of heart failure was performed in the United States. Both the safety and efficacy of SERCA2a delivery by gene transfer through a recombinant AAV1/SERCA2a were evaluated in patients with advanced heart failure[70,71]. A further 250 patients are currently being enrolled in a phase 2b trial for intracoronary administration of AAV1/SERCA2a[72].

EPIGENETIC MODIFICATION

Chronic heart failure is considered to be a remodeling process affected by multiple environmental factors, and too complex to be addressed by single pathway interventions[73]. NRG-1 treatment results in long-lasting benefits in animal models and human studies, indicating that NRG-1 at least partially stimulates cardiac reverse remodeling, as evidenced by a switch to fetal gene expression, rather than merely preventing cardiac dysfunction[35]. DNA methylation is one epigenetic mechanism known to directly regulate the expression of genes by altering the binding of transcription factors to DNA recognition elements[74], and dynamic DNA methylation/demethylation has been observed *in vivo*[75].

Epigenetic modification has been linked to cardiac hypertrophy and heart failure[76]. For example, class Ⅱ histone deacetylases (HDACs) suppress cardiac hypertrophy, partially through inhibition of the activity of myocyte enhancer factor 2[77]. In contrast, inhibition of HDAC activity results in increased cell size[78] and sarcomere disorganization in cultured cardiac myocytes[79]. Furthermore, the activity of histone acetyltransferase cofactors, such as cyclic AMP response element-binding protein (CREB)-binding protein and p300, is required in phenylephrine-induced cardiomyocyte hypertrophy[80]. In a model for congestive heart failure, the Dahl salt-sensitive rat[81], H3K4 and H3K9 were identified as two primary histone modification sites that were markedly altered in cardiac myocytes during the development of the disease. High-throughput analysis performed by chromatin immunoprecipitation of H3K4 or H3K9 on DNA prepared from human heart also revealed global epigenetic changes in cardiac myocytes, and changes occurred in multiple signaling pathways previously associated with the progression of heart failure[82].

In cultured rat Schwann cells, NRG-1β dose-dependently activated the transcription factor CREB, a protein with endogenous histone acetyltransferase activity[83]. In cultured muscle cells, NRG-1 activated mitogen and stress-activated kinase 1 and 2 and phosphorylated histone H3 in an Erk-dependent manner, resulting in chromatin remodeling[40]. Such results implicate a role for NRG-1 in epigenetic modification as well as provide a possible molecular mechanism.

Expression profiles of mRNA from NRG-1 treated and untreated cardiomyocytes have also been compared[58,84,85]. In our previous study, post-MI rats were infused with rhNRG-1β, and the total RNA extracted from the non-infarcted area of the left ventricle was analyzed on GeneChip arrays (Affymetrix, Santa Clara, CA, United States). The results demonstrated that improvement in cardiac function was accompanied by an increase in expression of several epigenetic-related genes[58] (Table 1).

The global epigenetic changes observed in our study reveal epigenetic modification as an important molecular mechanism underlying changes in cardiac myocytes induced by rhNRG-1β treatment. How these epigenetic changes are triggered by rhNRG-1β requires further investigation. Epigenetic modification also plays an important role in the development of cardiac dysfunction as well as hypertrophy, so that characterization of the epigenetic changes that occur will also help to improve our understanding of the molecular basis of heart failure.

CELL METABOLISM

Normal cardiac function relies on the maintenance of energetic homeostasis to a large degree. The cardiac myocyte is a highly oxidative cell type that utilizes mitochondrial respiration to generate most of its energy. In newborn heart, about half of the ATP production is derived from glycolysis[86]. After birth, fatty acid oxidation is significantly increased and accompanied

Table 1 Changes in mRNA levels of chromosome remodeling and histone modification genes in rat cardiomyocytes treated with rhneuregulin-1β

Gene	Fold increase (rhNRG-1β/vehicle)	Biologic process	Ref.
Embryonic ectoderm development (*Eed*)	1.56	Genetic imprinting, histone methylation	[114]
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (*Smarca4*)	1.48	Nucleosome disassembly, methylation-dependent chromatin silencing, ATP-dependent chromatin remodeling	[115]
Jumonji domain containing 6 (*Jmjd6*)	1.61	Histone H3-R2 demethylation, histone H4-R3 demethylation, histone lysyl 5-hydroxylation	[116,117]
Histone cluster 1, H4b (*Hist1h4b*)	1.49	Nucleosome assembly	[118]
CSRP2 binding protein (*Csrp2bp*)	2	Histone acetylation	[119]
H2A histone family, member Z (*H2afz*)	1.63	Nucleosome assembly	[120]
MYST histone acetyltransferase (monocytic leukemia) 3 (*Myst3*)	1.48	Chromatin modification, histone acetylation	[121]
Nuclear receptor coactivator 3 (*Ncoa3*)	2.33	Chromatin modification, histone acetylation	[122]
Nucleophosmin (nucleolar phosphoprotein B23, numatrin) (*Nmp1*)	1.8	Nucleosome assembly	[123]

NRG: Neuregulin.

by a parallel decrease in glycolytic rates[87]. The energy generated by mitochondrial oxidation is primarily derived from the fatty acid β-oxidation pathway, and in healthy heart, β-oxidation of fatty acids provides more than two thirds of cardiac energy[88].

Metabolic abnormalities are clearly involved in the development of heart failure; however, controversy remains concerning the specific alterations in cardiac metabolism and the underlying mechanisms. In late-stage heart failure induced in dogs through pacing-overdrive, fatty acid oxidation-related enzymes were found to be downregulated, while the rate of glucose oxidation dramatically increased[89,90]. Analysis of ^{13}C nuclear magnetic resonance demonstrated that fatty acid oxidation was suppressed in hypertrophic, compensated heart, whereas lactate and glucose oxidation were unaffected[91]. In contrast, pressure overload-induced hypertrophy in a rat model exhibited a significant increase only in glucose oxidation[92]. This phenomenon was confirmed in a second rat model, in which supra-renal aortic constriction was used to induce hypertrophy; glycolytic capacity was modestly elevated but no significant decline in fatty acid oxidation occurred in the hypertrophic heart[93]. These conflicting observations highlight the complexity of energy metabolism in the failing heart.

Emerging evidence indicates that the shift in substrate preference from fatty acids towards glucose in cardiac myocytes can improve heart function and slow the progression of heart failure[94], possibly due to the fact that fatty acids waste more ATPs in cardiac metabolism[95,96]. Furthermore, in advanced or end-stage heart failure, the levels of long- and medium-chain acyl-CoA dehydrogenases were dramatically downregulated, resulting in the suppression of fatty acid oxidation[88]. Thus, a switch to carbohydrate metabolism appears to improve heart function in the short term, whereas fatty acid oxidation benefits long-term cardiac reverse remodeling.

In a different NRG-1 study, freshly isolated adult rat cardiomyocytes were treated with recombinant human NRG-1β (Neomarkers; P.H. Stehelin and Cie; Basel, Switzerland), and expression profiles were generated with cDNA arrays[84]. Expression reprogramming of several cellular processes was revealed, such as improved redox regulation, enhanced utilization of carbohydrates, and increased fatty acid β-oxidation[84]. In our experiments, rats with sustained MI were intravenously infused with rhNRG-1β, and microarray analysis was performed. Expression profiling revealed alterations in a number of genes, including carnitine palmitoyltransferase-1, a key enzyme responsible for the mitochondrial entry of fatty acids[97]. A series of fatty acid metabolism enzymes were also upregulated in myocardium[58] (Table 2). Our microarray data therefore support a model where cardiac fatty acid β-oxidation is increased during rhNRG-1β treatment, and this model is consistent with the observation that rhNRG-1β plays a role in reverse remodeling. However, the causality between energy metabolism and NRG-1-induced reverse remodeling is still an unanswered question, and thus whether a shift in metabolism is the cause or consequence of remodeling requires further investigation.

PRECLINICAL STUDIES WITH NRG-1 FOR THE TREATMENT OF HEART FAILURE

Multiple isoforms of NRG-1 in humans are generated as a result of alternative splicing. Preclinical *in vivo* studies have demonstrated that several of the isoforms are capable of improving heart function by reducing hypertension[47], improving cardiomyocyte proliferation[27], inhibiting apoptosis[43], and enhancing angiogenesis[98] and Ca^{2+} handling[99]. rhNRG-1β was used in a series of animal models to evaluate its effect on heart function[35]. Intravenous administration of rhNRG-1β significantly improved cardiac function and survival in

Table 2 Changes in mRNA levels of fatty acid metabolism enzyme genes in rat cardiomyocytes treated with rhneuregulin-1β

Gene	Fold increase (rhNRG-1β/vehicle)	Function	Ref.
Carnitine palmitoyltransferase Ib, muscle (*Cpt1b*)	1.83	Rate-limiting enzyme which imports fatty acid for mitochondrial oxidation	[124]
Acyl-CoA synthetase, long-chain family 4 (*Acsl4*)	2.31	Promotes fatty acid uptake	[125]
2,4-dienoyl CoA reductase, mitochondrial (*Decr1*)	2.04	Catalyzes the rate-limiting step that prepares polyunsaturated fatty acids to be utilized as substrates for β-oxidation	[126]
Hydroxyacyl-CoA dehydrogenase (*Hadhb*)	1.59	β-subunit of the mitochondrial trifunctional protein, catalyzes the last three steps of mitochondrial β-oxidation of long-chain fatty acids	[127,128]
Transketolase (*Tkt*)	1.97	Necessary for the production of NADPH, especially in tissues actively engaged in biosyntheses, such as fatty acid synthesis	[129]
Acetyl-CoA acetyltransferase 1 (*Acat1*)	1.89	Enzyme participates in ten metabolic pathways including fatty acid metabolism	[130]
Hydroxysteroid (17-beta) dehydrogenase 4 (*Hsd17b4*)	1.64	Enzyme involved in peroxisomal fatty acid β-oxidation	[131]
Dodecenoyl-coenzyme A delta isomerase (*Dci*)	1.66	Mitochondrial fatty acid oxidation enzyme	[132]
Protein kinase, AMP-activated, β1 non-catalytic subunit (*Prkab1*)	1.98	Regulatory subunit of the AMP-activated protein kinase, involved in regulating de novo biosynthesis of fatty acid and cholesterol	[133]

NRG: Neuregulin.

a rat model of heart failure induced by the ligation of left anterior descending coronary artery. In the heart failure model induced by chronic pacing, rhNRG-1β treatment improved the left ventricular end diastolic and systolic pressures, as well as cardiac contractility and relaxation. In addition, a second recombinant form of NRG-1 (recombinant human glial growth factor 2, rhGGF2) also prevented cardiac dysfunction and improved survival in doxorubicin-induced heart failure in the mouse[100].

An engineered bivalent human NRG-1β (generated through the synthetic linkage of two NRG-1β moieties) protected against acute doxorubicin-induced cardiomyopathy without proneoplastic effects[101]. In another study, administration of recombinant human NRG-1 (Novartis Pharmaceuticals, Basel, Switzerland) significantly improved heart function and reversed cardiac remodeling of diabetic cardiomyopathy in rats with chronic heart failure[102]. In addition, rhGGF2 treatment improved residual left ventricular function and normalized a number of myocardial genes altered by MI in rats[85].

CLINICAL STUDIES OF NRG-1/ERBB IN HEART FAILURE

During the past 30 years, many drugs have been developed for the treatment of heart failure, including β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and brain natriuretic peptide. Despite the fact that these therapies have improved clinical outcomes significantly, heart failure has become the major cause of cardiovascular death[103]. Therefore, the development of new treatments for heart failure continues to be necessary.

Multiple *in vitro* and *in vivo* studies have confirmed the beneficial effects of NRG-1 on cardiac function[27,98,99], thus rendering NRG-1 a promising drug candidate for the treatment of heart failure. To date, two different isoforms of NRG-1 have been tested in human clinical trials. Since 2004, phase 1 and phase 2 trials in China, Australia, and the United States have confirmed that rhNRG-1β is safe and well tolerated in both chronic heart failure patients and healthy controls. In a phase 2, randomized, double-blind, multicenter, placebo-controlled study, 44 patients with New York Heart Association functional class II or III stable chronic heart failure were randomly assigned to four groups and treated with placebo or rhNRG-1β (0.3 μg/kg per day, 0.6 μg/kg per day, or 1.2 μg/kg per day) through a ten-hour intravenous infusion per day for ten consecutive days. At day 30, patients treated with rhNRG-1β exhibited significantly increased left ventricular ejection fraction (LVEF%), as well as reduced end-diastolic and end-systolic volumes, which continued to decrease at day 90 and were accompanied by a sustained increase in LVEF%, indicating a long-term effect for rhNRG-1β in cardiac reverse remodeling[104]. In another clinical trial, 15 patients with stable chronic heart failure received a daily infusion of rhNRG-1β for 11 d. Improved hemodynamic effects were observed, and the increase in LVEF% was sustained for 12 wk[105]. A phase 3 trial designed to measure the safety and efficacy of rhNRG-1β in a larger cohort of chronic heart failure patients is currently ongoing in China.

Another NRG-1 isoform utilized in clinical trials is GGF2 (also known as NRG-1β3). In a phase 1, single-infusion, dose-escalation study, a single dose of rhGGF2 was well tolerated up to 0.75 mg/kg, whereas higher doses were associated with serious adverse events[106]. Patients with symptomatic heart failure receiving a single dose of rhGGF2 exhibited increased left

ventricular function over 28 d compared to placebo[107]. A phase 1b study designed to evaluate the effect of rhGGF2 single intravenous infusion on midazolam pharmacokinetics is ongoing (registration at www.clinicaltials.gov, NCT01944683).

A complicating issue is the fact that *ERBB2* has a well-described role as an oncogene, particularly in the development of breast cancers[108,109]. Although recent publications support the idea that *NRG1* functions instead as a tumor-suppressor gene[110], NRG-1 treatment for cardiac therapy raises a concern for a potential increased risk of cancer. However, ErbB2-associated cancer is often NRG-independent, and furthermore *NRG1* is often silenced by methylation in breast cancers[111]. In addition, chromosome translocation breakpoints targeting *NRG1* on 8p12 have been found in breast and pancreas cancer cell lines[112,113]. Finally, our previous clinical experience demonstrated that the incidence of cancer of any type in > 1000 subjects treated with rhNRG-1β was no different than in patients treated with placebo. Together, these findings indicate that there is a low risk for the development of cancer during NRG-1 treatment.

CONCLUSION

A number of experimental results from both clinical studies and animal models have demonstrated the importance of NRG-1/ErbB signaling in adult heart function. Expression profiling has firmly established that in addition to canonical ErbB2 downstream pathways, energy metabolism and epigenetic modification also play roles in NRG-1-mediated reverse remodeling of heart failure. Additional studies, however, are still necessary to elucidate the precise molecular mechanisms utilized. Finally, a recombinant human NRG-1 peptide has demonstrated significant potential as a novel drug candidate for chronic heart failure in preclinical and clinical studies. Further studies illuminating mechanisms mediating NRG-1/ErbB signaling will therefore help to facilitate the development of novel strategies for the treatment of chronic heart failure and to better understand the function of NRG-1 in cardiac physiology.

REFERENCES

1 **Pentassuglia L**, Sawyer DB. The role of Neuregulin-1beta/ErbB signaling in the heart. *Exp Cell Res* 2009; **315**: 627-637 [PMID: 18801360 DOI: 10.1016/j.yexcr.2008.08.015]

2 **Britsch S**. The neuregulin-I/ErbB signaling system in development and disease. *Adv Anat Embryol Cell Biol* 2007; **190**: 1-65 [PMID: 17432114]

3 **Falls DL**. Neuregulins: functions, forms, and signaling strategies. *Exp Cell Res* 2003; **284**: 14-30 [PMID: 12648463 DOI: 10.1016/S0014-4827(02)00102-7]

4 **Fuller SJ**, Sivarajah K, Sugden PH. ErbB receptors, their ligands, and the consequences of their activation and inhibition in the myocardium. *J Mol Cell Cardiol* 2008; **44**: 831-854 [PMID: 18430438 DOI: 10.1016/j.yjmcc.2008.02.278]

5 **Parodi EM**, Kuhn B. Signalling between microvascular endothelium and cardiomyocytes through neuregulin. *Cardiovasc Res* 2014; **102**: 194-204 [PMID: 24477642 DOI: 10.1093/cvr/cvu021]

6 **Lemmens K**, Doggen K, De Keulenaer GW. Role of neuregulin-1/ErbB signaling in cardiovascular physiology and disease: implications for therapy of heart failure. *Circulation* 2007; **116**: 954-960 [PMID: 17709650 DOI: 10.1161/circulationaha.107.690487]

7 **Cote GM**, Miller TA, Lebrasseur NK, Kuramochi Y, Sawyer DB. Neuregulin-1alpha and beta isoform expression in cardiac microvascular endothelial cells and function in cardiac myocytes in vitro. *Exp Cell Res* 2005; **311**: 135-146 [PMID: 16185687 DOI: 10.1016/j.yexcr.2005.08.017]

8 **Lu HS**, Chang D, Philo JS, Zhang K, Narhi LO, Liu N, Zhang M, Sun J, Wen J, Yanagihara D. Studies on the structure and function of glycosylated and nonglycosylated neu differentiation factors. Similarities and differences of the alpha and beta isoforms. *J Biol Chem* 1995; **270**: 4784-4791 [PMID: 7876251 DOI: 10.1074/jbc.270.9.4784]

9 **Hobbs SS**, Coffing SL, Le AT, Cameron EM, Williams EE, Andrew M, Blommel EN, Hammer RP, Chang H, Riese DJ. Neuregulin isoforms exhibit distinct patterns of ErbB family receptor activation. *Oncogene* 2002; **21**: 8442-8452 [PMID: 12466964 DOI: 10.1038/sj.onc.1205960]

10 **Lemmens K**, Segers VF, Demolder M, De Keulenaer GW. Role of neuregulin-1/ErbB2 signaling in endothelium-cardiomyocyte cross-talk. *J Biol Chem* 2006; **281**: 19469-19477 [PMID: 16698793 DOI: 10.1074/jbc.M600399200]

11 **Yarden Y**, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol* 2001; **2**: 127-137 [PMID: 11252954 DOI: 10.1038/35052073]

12 **Bublil EM**, Yarden Y. The EGF receptor family: spearheading a merger of signaling and therapeutics. *Curr Opin Cell Biol* 2007; **19**: 124-134 [PMID: 17314037 DOI: 10.1016/j.ceb.2007.02.008]

13 **Baliga RR**, Pimental DR, Zhao YY, Simmons WW, Marchionni MA, Sawyer DB, Kelly RA. NRG-1-induced cardiomyocyte hypertrophy. Role of PI-3-kinase, p70(S6K), and MEK-MAPK-RSK. *Am J Physiol* 1999; **277**: H2026-H2037 [PMID: 10564160]

14 **Muthuswamy SK**, Gilman M, Brugge JS. Controlled dimerization of ErbB receptors provides evidence for differential signaling by homo- and heterodimers. *Mol Cell Biol* 1999; **19**: 6845-6857 [PMID: 10490623]

15 **Kuramochi Y**, Guo X, Sawyer DB. Neuregulin activates erbB2-dependent src/FAK signaling and cytoskeletal remodeling in isolated adult rat cardiac myocytes. *J Mol Cell Cardiol* 2006; **41**: 228-235 [PMID: 16769082 DOI: 10.1016/j.yjmcc.2006.04.007]

16 **Kramer R**, Bucay N, Kane DJ, Martin LE, Tarpley JE, Theill LE. Neuregulins with an Ig-like domain are essential for mouse myocardial and neuronal development. *Proc Natl Acad Sci USA* 1996; **93**: 4833-4838 [PMID: 8643489]

17 **Meyer D**, Birchmeier C. Multiple essential functions of neuregulin in development. *Nature* 1995; **378**: 386-390 [PMID: 7477375 DOI: 10.1038/378386a0]

18 **Ring HZ**, Chang H, Guilbot A, Brice A, LeGuern E, Francke U. The human neuregulin-2 (NRG2) gene: cloning, mapping and evaluation as a candidate for the autosomal recessive form of Charcot-Marie-Tooth disease linked to 5q. *Hum Genet* 1999; **104**: 326-332 [PMID: 10369162 DOI: 10.1007/s004390050961]

19 **Hayes NV**, Newsam RJ, Baines AJ, Gullick WJ. Characterization of the cell membrane-associated products of the Neuregulin 4 gene. *Oncogene* 2008; **27**: 715-720 [PMID: 17684490 DOI: 10.1038/sj.onc.1210689]

20 **Harari D**, Tzahar E, Romano J, Shelly M, Pierce JH, Andrews GC, Yarden Y. Neuregulin-4: a novel growth factor that acts through the ErbB-4 receptor tyrosine kinase. *Oncogene* 1999; **18**: 2681-2689 [PMID: 10348342 DOI: 10.1038/sj.onc.1202631]

21 **Shi W**, Chen H, Sun J, Buckley S, Zhao J, Anderson KD, Williams RG, Warburton D. TACE is required for fetal murine cardiac development and modeling. *Dev Biol* 2003; **261**: 371-380 [PMID: 14499647 DOI: 10.1016/S0012-1606(03)00315-4]

22 **Liu X**, Hwang H, Cao L, Buckland M, Cunningham A, Chen J, Chien KR, Graham RM, Zhou M. Domain-specific gene disruption reveals critical regulation of neuregulin signaling by its cytoplasmic tail. *Proc Natl Acad Sci USA* 1998; **95**: 13024-13029 [PMID:

9789034 DOI: 10.1073/pnas.95.22.13024]
23 **Lee KF**, Simon H, Chen H, Bates B, Hung MC, Hauser C. Requirement for neuregulin receptor erbB2 in neural and cardiac development. *Nature* 1995; **378**: 394-398 [PMID: 7477377 DOI: 10.1038/378394a0]
24 **Gassmann M**, Casagranda F, Orioli D, Simon H, Lai C, Klein R, Lemke G. Aberrant neural and cardiac development in mice lacking the ErbB4 neuregulin receptor. *Nature* 1995; **378**: 390-394 [PMID: 7477376 DOI: 10.1038/378390a0]
25 **Erickson SL**, O'Shea KS, Ghaboosi N, Loverro L, Frantz G, Bauer M, Lu LH, Moore MW. ErbB3 is required for normal cerebellar and cardiac development: a comparison with ErbB2-and heregulin-deficient mice. *Development* 1997; **124**: 4999-5011 [PMID: 9362461]
26 **Camenisch TD**, Schroeder JA, Bradley J, Klewer SE, McDonald JA. Heart-valve mesenchyme formation is dependent on hyaluronan-augmented activation of ErbB2-ErbB3 receptors. *Nat Med* 2002; **8**: 850-855 [PMID: 12134143 DOI: 10.1038/nm742]
27 **Zhao YY**, Sawyer DR, Baliga RR, Opel DJ, Han X, Marchionni MA, Kelly RA. Neuregulins promote survival and growth of cardiac myocytes. Persistence of ErbB2 and ErbB4 expression in neonatal and adult ventricular myocytes. *J Biol Chem* 1998; **273**: 10261-10269 [PMID: 9553078]
28 **Campreciós G**, Lorita J, Pardina E, Peinado-Onsurbe J, Soley M, Ramírez I. Expression, localization, and regulation of the neuregulin receptor ErbB3 in mouse heart. *J Cell Physiol* 2011; **226**: 450-455 [PMID: 20672328 DOI: 10.1002/jcp.22354]
29 **Crone SA**, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, Peterson KL, Chen J, Kahn R, Condorelli G, Ross J, Chien KR, Lee KF. ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med* 2002; **8**: 459-465 [PMID: 11984589 DOI: 10.1038/nm0502-459]
30 **Ozcelik C**, Erdmann B, Pilz B, Wettschureck N, Britsch S, Hübner N, Chien KR, Birchmeier C, Garratt AN. Conditional mutation of the ErbB2 (HER2) receptor in cardiomyocytes leads to dilated cardiomyopathy. *Proc Natl Acad Sci USA* 2002; **99**: 8880-8885 [PMID: 12072561 DOI: 10.1073/pnas.122249299]
31 **García-Rivello H**, Taranda J, Said M, Cabeza-Meckert P, Vila-Petroff M, Scaglione J, Ghio S, Chen J, Lai C, Laguens RP, Lloyd KC, Hertig CM. Dilated cardiomyopathy in Erb-b4-deficient ventricular muscle. *Am J Physiol Heart Circ Physiol* 2005; **289**: H1153-H1160 [PMID: 15863464 DOI: 10.1152/ajpheart.00048.2005]
32 **Slamon DJ**, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**: 783-792 [PMID: 11248153 DOI: 10.1056/nejm200103153441101]
33 **Jones LW**, Haykowsky M, Peddle CJ, Joy AA, Pituskin EN, Tkachuk LM, Courneya KS, Slamon DJ, Mackey JR. Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 1026-1031 [PMID: 17507633 DOI: 10.1158/1055-9965.epi-06-0870]
34 **Sawyer DB**, Zuppinger C, Miller TA, Eppenberger HM, Suter TM. Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity. *Circulation* 2002; **105**: 1551-1554 [PMID: 11927521]
35 **Liu X**, Gu X, Li Z, Li X, Li H, Chang J, Chen P, Jin J, Xi B, Chen D, Lai D, Graham RM, Zhou M. Neuregulin-1/erbB-activation improves cardiac function and survival in models of ischemic, dilated, and viral cardiomyopathy. *J Am Coll Cardiol* 2006; **48**: 1438-1447 [PMID: 17010808 DOI: 10.1016/j.jacc.2006.05.057]
36 **Rohrbach S**, Niemann B, Silber RE, Holtz J. Neuregulin receptors erbB2 and erbB4 in failing human myocardium -- depressed expression and attenuated activation. *Basic Res Cardiol* 2005; **100**: 240-249 [PMID: 15685397 DOI: 10.1007/s00395-005-0514-4]
37 **Pentassuglia L**, Timolati F, Seifriz F, Abudukadier K, Suter TM, Zuppinger C. Inhibition of ErbB2/neuregulin signaling augments paclitaxel-induced cardiotoxicity in adult ventricular myocytes. *Exp Cell Res* 2007; **313**: 1588-1601 [PMID: 17400210 DOI: 10.1016/j.yexcr.2007.02.007]
38 **Odiete O**, Hill MF, Sawyer DB. Neuregulin in cardiovascular development and disease. *Circ Res* 2012; **111**: 1376-1385 [PMID: 23104879 DOI: 10.1161/circresaha.112.267286]
39 **Jiang Z**, Zhou M. Neuregulin signaling and heart failure. *Curr Heart Fail Rep* 2010; **7**: 42-47 [PMID: 20425496 DOI: 10.1007/s11897-010-0003-y]
40 **Basu U**, Gyrd-Hansen M, Baby SM, Lozynska O, Krag TO, Jensen CJ, Frödin M, Khurana TS. Heregulin-induced epigenetic regulation of the utrophin-A promoter. *FEBS Lett* 2007; **581**: 4153-4158 [PMID: 17692845 DOI: 10.1016/j.febslet.2007.07.021]
41 **Matsui T**, Li L, del MonteF Y, Franke TF, Hajjar RJ, Rosenzweig A. Adenoviral gene transfer of activated phosphatidylinositol 3'-kinase and Akt inhibits apoptosis of hypoxic cardiomyocytes in vitro. *Circulation* 1999; **100**: 2373-2379 [PMID: 10587343]
42 **Fujio Y**, Nguyen T, Wencker D, Kitsis RN, Walsh K. Akt promotes survival of cardiomyocytes in vitro and protects against ischemia-reperfusion injury in mouse heart. *Circulation* 2000; **101**: 660-667 [PMID: 10673259]
43 **Fukazawa R**, Miller TA, Kuramochi Y, Frantz S, Kim YD, Marchionni MA, Kelly RA, Sawyer DB. Neuregulin-1 protects ventricular myocytes from anthracycline-induced apoptosis via erbB4-dependent activation of PI3-kinase/Akt. *J Mol Cell Cardiol* 2003; **35**: 1473-1479 [PMID: 14654373]
44 **Okoshi K**, Nakayama M, Yan X, Okoshi MP, Schuldt AJ, Marchionni MA, Lorell BH. Neuregulins regulate cardiac parasympathetic activity: muscarinic modulation of beta-adrenergic activity in myocytes from mice with neuregulin-1 gene deletion. *Circulation* 2004; **110**: 713-717 [PMID: 15289373 DOI: 10.1161/01.cir.0000138109.32748.80]
45 **Jamnicki-Abegg M**, Weihrauch D, Pagel PS, Kersten JR, Bosnjak ZJ, Warltier DC, Bienengraeber MW. Isoflurane inhibits cardiac myocyte apoptosis during oxidative and inflammatory stress by activating Akt and enhancing Bcl-2 expression. *Anesthesiology* 2005; **103**: 1006-1014 [PMID: 16249675]
46 **Das S**, Cordis GA, Maulik N, Das DK. Pharmacological preconditioning with resveratrol: role of CREB-dependent Bcl-2 signaling via adenosine A3 receptor activation. *Am J Physiol Heart Circ Physiol* 2005; **288**: H328-H335 [PMID: 15345477 DOI: 10.1152/ajpheart.00453.2004]
47 **Lemmens K**, Fransen P, Sys SU, Brutsaert DL, De Keulenaer GW. Neuregulin-1 induces a negative inotropic effect in cardiac muscle: role of nitric oxide synthase. *Circulation* 2004; **109**: 324-326 [PMID: 14732742 DOI: 10.1161/01.cir.0000114521.88547.5e]
48 **Zhang S**, Weinheimer C, Courtois M, Kovacs A, Zhang CE, Cheng AM, Wang Y, Muslin AJ. The role of the Grb2-p38 MAPK signaling pathway in cardiac hypertrophy and fibrosis. *J Clin Invest* 2003; **111**: 833-841 [PMID: 12639989 DOI: 10.1172/jci16290]
49 **Pero SC**, Shukla GS, Cookson MM, Flemer S, Krag DN. Combination treatment with Grb7 peptide and Doxorubicin or Trastuzumab (Herceptin) results in cooperative cell growth inhibition in breast cancer cells. *Br J Cancer* 2007; **96**: 1520-1525 [PMID: 17426702 DOI: 10.1038/sj.bjc.6603732]
50 **Obreztchikova M**, Elouardighi H, Ho M, Wilson BA, Gertsberg Z, Steinberg SF. Distinct signaling functions for Shc isoforms in the heart. *J Biol Chem* 2006; **281**: 20197-20204 [PMID: 16699171 DOI: 10.1074/jbc.M601859200]
51 **Yoshizumi M**, Tsuchiya K, Kirima K, Kyaw M, Suzaki Y, Tamaki T. Quercetin inhibits Shc- and phosphatidylinositol 3-kinase-mediated c-Jun N-terminal kinase activation by angiotensin II in cultured rat aortic smooth muscle cells. *Mol Pharmacol* 2001; **60**: 656-665 [PMID: 11562426]
52 **Ilić D**, Furuta Y, Kanazawa S, Takeda N, Sobue K, Nakatsuji N, Nomura S, Fujimoto J, Okada M, Yamamoto T. Reduced cell motility and enhanced focal adhesion contact formation in cells from FAK-deficient mice. *Nature* 1995; **377**: 539-544 [PMID:

7566154 DOI: 10.1038/377539a0]
53 **Mansour H**, de Tombe PP, Samarel AM, Russell B. Restoration of resting sarcomere length after uniaxial static strain is regulated by protein kinase Cepsilon and focal adhesion kinase. *Circ Res* 2004; **94**: 642-649 [PMID: 14963000 DOI: 10.1161/01.res.0000121101.32286.c8]
54 **Kuppuswamy D**. Importance of integrin signaling in myocyte growth and survival. *Circ Res* 2002; **90**: 1240-1242 [PMID: 12089060]
55 **Pfister R**, Acksteiner C, Baumgarth J, Burst V, Geissler HJ, Margulies KB, Houser S, Bloch W, Flesch M. Loss of beta1D-integrin function in human ischemic cardiomyopathy. *Basic Res Cardiol* 2007; **102**: 257-264 [PMID: 17186162 DOI: 10.1007/s00395-006-0640-1]
56 **Peng X**, Wu X, Druso JE, Wei H, Park AY, Kraus MS, Alcaraz A, Chen J, Chien S, Cerione RA, Guan JL. Cardiac developmental defects and eccentric right ventricular hypertrophy in cardiomyocyte focal adhesion kinase (FAK) conditional knockout mice. *Proc Natl Acad Sci USA* 2008; **105**: 6638-6643 [PMID: 18448675 DOI: 10.1073/pnas.0802319105]
57 **Peng X**, Kraus MS, Wei H, Shen TL, Pariaut R, Alcaraz A, Ji G, Cheng L, Yang Q, Kotlikoff MI, Chen J, Chien K, Gu H, Guan JL. Inactivation of focal adhesion kinase in cardiomyocytes promotes eccentric cardiac hypertrophy and fibrosis in mice. *J Clin Invest* 2006; **116**: 217-227 [PMID: 16374517 DOI: 10.1172/jci24497]
58 **Gu X**, Liu X, Xu D, Li X, Yan M, Qi Y, Yan W, Wang W, Pan J, Xu Y, Xi B, Cheng L, Jia J, Wang K, Ge J, Zhou M. Cardiac functional improvement in rats with myocardial infarction by up-regulating cardiac myosin light chain kinase with neuregulin. *Cardiovasc Res* 2010; **88**: 334-343 [PMID: 20615916 DOI: 10.1093/cvr/cvq223]
59 **Seguchi O**, Takashima S, Yamazaki S, Asakura M, Asano Y, Shintani Y, Wakeno M, Minamino T, Kondo H, Furukawa H, Nakamaru K, Naito A, Takahashi T, Ohtsuka T, Kawakami K, Isomura T, Kitamura S, Tomoike H, Mochizuki N, Kitakaze M. A cardiac myosin light chain kinase regulates sarcomere assembly in the vertebrate heart. *J Clin Invest* 2007; **117**: 2812-2824 [PMID: 17885681 DOI: 10.1172/jci30804]
60 **Warren SA**, Briggs LE, Zeng H, Chuang J, Chang EI, Terada R, Li M, Swanson MS, Lecker SH, Willis MS, Spinale FG, Maupin-Furlowe J, McMullen JR, Moss RL, Kasahara H. Myosin light chain phosphorylation is critical for adaptation to cardiac stress. *Circulation* 2012; **126**: 2575-2588 [PMID: 23095280 DOI: 10.1161/circulationaha.112.116202]
61 **Aoki H**, Sadoshima J, Izumo S. Myosin light chain kinase mediates sarcomere organization during cardiac hypertrophy in vitro. *Nat Med* 2000; **6**: 183-188 [PMID: 10655107 DOI: 10.1038/72287]
62 **Ding P**, Huang J, Battiprolu PK, Hill JA, Kamm KE, Stull JT. Cardiac myosin light chain kinase is necessary for myosin regulatory light chain phosphorylation and cardiac performance in vivo. *J Biol Chem* 2010; **285**: 40819-40829 [PMID: 20943660 DOI: 10.1074/jbc.M110.160499]
63 **Chang AN**, Huang J, Battiprolu PK, Hill JA, Kamm KE, Stull JT. The effects of neuregulin on cardiac Myosin light chain kinase gene-ablated hearts. *PLoS One* 2013; **8**: e66720 [PMID: 23776695 DOI: 10.1371/journal.pone.0066720]
64 **Kubalova Z**, Terentyev D, Viatchenko-Karpinski S, Nishijima Y, Györke I, Terentyeva R, da Cuñha DN, Sridhar A, Feldman DS, Hamlin RL, Carnes CA, Györke S. Abnormal intrastore calcium signaling in chronic heart failure. *Proc Natl Acad Sci USA* 2005; **102**: 14104-14109 [PMID: 16172392 DOI: 10.1073/pnas.0504298102]
65 **Jiang MT**, Lokuta AJ, Farrell EF, Wolff MR, Haworth RA, Valdivia HH. Abnormal Ca2+ release, but normal ryanodine receptors, in canine and human heart failure. *Circ Res* 2002; **91**: 1015-1022 [PMID: 12456487]
66 **Bassani JW**, Yuan W, Bers DM. Fractional SR Ca release is regulated by trigger Ca and SR Ca content in cardiac myocytes. *Am J Physiol* 1995; **268**: C1313-C1319 [PMID: 7762626]
67 **Go LO**, Moschella MC, Watras J, Handa KK, Fyfe BS, Marks AR. Differential regulation of two types of intracellular calcium release channels during end-stage heart failure. *J Clin Invest* 1995; **95**: 888-894 [PMID: 7860772 DOI: 10.1172/jci117739]
68 **MacDougall LK**, Jones LR, Cohen P. Identification of the major protein phosphatases in mammalian cardiac muscle which dephosphorylate phospholamban. *Eur J Biochem* 1991; **196**: 725-734 [PMID: 1849481]
69 **Gupta RC**, Mishra S, Rastogi S, Imai M, Habib O, Sabbah HN. Cardiac SR-coupled PP1 activity and expression are increased and inhibitor 1 protein expression is decreased in failing hearts. *Am J Physiol Heart Circ Physiol* 2003; **285**: H2373-H2381 [PMID: 14613911 DOI: 10.1152/ajpheart.00442.2003]
70 **Hajjar RJ**, Zsebo K, Deckelbaum L, Thompson C, Rudy J, Yaroshinsky A, Ly H, Kawase Y, Wagner K, Borow K, Jaski B, London B, Greenberg B, Pauly DF, Patten R, Starling R, Mancini D, Jessup M. Design of a phase 1/2 trial of intracoronary administration of AAV1/SERCA2a in patients with heart failure. *J Card Fail* 2008; **14**: 355-367 [PMID: 18514926 DOI: 10.1016/j.cardfail.2008.02.005]
71 **Jaski BE**, Jessup ML, Mancini DM, Cappola TP, Pauly DF, Greenberg B, Borow K, Dittrich H, Zsebo KM, Hajjar RJ. Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID Trial), a first-in-human phase 1/2 clinical trial. *J Card Fail* 2009; **15**: 171-181 [PMID: 19327618 DOI: 10.1016/j.cardfail.2009.01.013]
72 **Greenberg B**, Yaroshinsky A, Zsebo KM, Butler J, Felker GM, Voors AA, Rudy JJ, Wagner K, Hajjar RJ. Design of a phase 2b trial of intracoronary administration of AAV1/SERCA2a in patients with advanced heart failure: the CUPID 2 trial (calcium up-regulation by percutaneous administration of gene therapy in cardiac disease phase 2b). *JACC Heart Fail* 2014; **2**: 84-92 [PMID: 24622121 DOI: 10.1016/j.jchf.2013.09.008]
73 **Cohn JN**. Critical review of heart failure: the role of left ventricular remodeling in the therapeutic response. *Clin Cardiol* 1995; **18**: IV4-I12 [PMID: 7489620]
74 **Hendrich B**, Tweedie S. The methyl-CpG binding domain and the evolving role of DNA methylation in animals. *Trends Genet* 2003; **19**: 269-277 [PMID: 12711219 DOI: 10.1016/s0168-9525(03)00080-5]
75 **Métivier R**, Gallais R, Tiffoche C, Le Péron C, Jurkowska RZ, Carmouche RP, Ibberson D, Barath P, Demay F, Reid G, Benes V, Jeltsch A, Gannon F, Salbert G. Cyclical DNA methylation of a transcriptionally active promoter. *Nature* 2008; **452**: 45-50 [PMID: 18322525 DOI: 10.1038/nature06544]
76 **Movassagh M**, Choy MK, Knowles DA, Cordeddu L, Haider S, Down T, Siggens L, Vujic A, Simeoni I, Penkett C, Goddard M, Lio P, Bennett MR, Foo RS. Distinct epigenomic features in end-stage failing human hearts. *Circulation* 2011; **124**: 2411-2422 [PMID: 22025602 DOI: 10.1161/circulationaha.111.040071]
77 **Zhang CL**, McKinsey TA, Chang S, Antos CL, Hill JA, Olson EN. Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. *Cell* 2002; **110**: 479-488 [PMID: 12202037]
78 **Iezzi S**, Di Padova M, Serra C, Caretti G, Simone C, Maklan E, Minetti G, Zhao P, Hoffman EP, Puri PL, Sartorelli V. Deacetylase inhibitors increase muscle cell size by promoting myoblast recruitment and fusion through induction of follistatin. *Dev Cell* 2004; **6**: 673-684 [PMID: 15130492]
79 **Antos CL**, McKinsey TA, Dreitz M, Hollingsworth LM, Zhang CL, Schreiber K, Rindt H, Gorczynski RJ, Olson EN. Dose-dependent blockade to cardiomyocyte hypertrophy by histone deacetylase inhibitors. *J Biol Chem* 2003; **278**: 28930-28937 [PMID: 12761226 DOI: 10.1074/jbc.M303113200]
80 **Gusterson RJ**, Jazrawi E, Adcock IM, Latchman DS. The transcriptional co-activators CREB-binding protein (CBP) and p300 play a critical role in cardiac hypertrophy that is dependent on their histone acetyltransferase activity. *J Biol Chem* 2003; **278**: 6838-6847 [PMID: 12477714 DOI: 10.1074/jbc.M211762200]
81 **Rapp JP**, Wang SM, Dene H. A genetic polymorphism in the renin gene of Dahl rats cosegregates with blood pressure. *Science* 1989; **243**: 542-544 [PMID: 2563177 DOI: 10.1126/science.2563177]
82 **Kaneda R**, Takada S, Yamashita Y, Choi YL, Nonaka-Sarukawa M, Soda M, Misawa Y, Isomura T, Shimada K, Mano H. Genome-wide

histone methylation profile for heart failure. *Genes Cells* 2009; **14**: 69-77 [PMID: 19077033 DOI: 10.1111/j.1365-2443.2008.01252.x]

83 **Tabernero A,** Stewart HJS, Jessen KR, Mirsky R.The Neuron-Glia Signal beta Neuregulin Induces Sustained CREB Phosphorylation on Ser-133 in Cultured Rat Schwann Cells. *Mol Cell Neurosci* 1998; **10**: 309-322 [PMID: 9618221 DOI: 10.1006/mcne.1998.0662]

84 **Giraud MN**, Flück M, Zuppinger C, Suter TM. Expressional reprogramming of survival pathways in rat cardiocytes by neuregulin-1beta. *J Appl Physiol* (1985) 2005; **99**: 313-322 [PMID: 16036905 DOI: 10.1152/japplphysiol.00609.2004]

85 **Hill MF**, Patel AV, Murphy A, Smith HM, Galindo CL, Pentassuglia L, Peng X, Lenneman CG, Odiete O, Friedman DB, Kronenberg MW, Zheng S, Zhao Z, Song Y, Harrell FE, Srinivas M, Ganguly A, Iaci J, Parry TJ, Caggiano AO, Sawyer DB. Intravenous glial growth factor 2 (GGF2) isoform of neuregulin-1β improves left ventricular function, gene and protein expression in rats after myocardial infarction. *PLoS One* 2013; **8**: e55741 [PMID: 23437060 DOI: 10.1371/journal.pone.0055741]

86 **Lopaschuk GD**, Spafford MA, Marsh DR. Glycolysis is predominant source of myocardial ATP production immediately after birth. *Am J Physiol* 1991; **261**: H1698-H1705 [PMID: 1750528]

87 **Itoi T**, Lopaschuk GD. The contribution of glycolysis, glucose oxidation, lactate oxidation, and fatty acid oxidation to ATP production in isolated biventricular working hearts from 2-week-old rabbits. *Pediatr Res* 1993; **34**: 735-741 [PMID: 8108185 DOI: 10.1203/00006450-199312000-00008]

88 **Stanley WC**, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005; **85**: 1093-1129 [PMID: 15987803 DOI: 10.1152/physrev.00006.2004]

89 **Lei B**, Lionetti V, Young ME, Chandler MP, d'Agostino C, Kang E, Altarejos M, Matsuo K, Hintze TH, Stanley WC, Recchia FA. Paradoxical downregulation of the glucose oxidation pathway despite enhanced flux in severe heart failure. *J Mol Cell Cardiol* 2004; **36**: 567-576 [PMID: 15081316 DOI: 10.1016/j.yjmcc.2004.02.004]

90 **Osorio JC**, Stanley WC, Linke A, Castellari M, Diep QN, Panchal AR, Hintze TH, Lopaschuk GD, Recchia FA. Impaired myocardial fatty acid oxidation and reduced protein expression of retinoid X receptor-alpha in pacing-induced heart failure. *Circulation* 2002; **106**: 606-612 [PMID: 12147544 DOI: 10.1161/01.CIR.0000023531.22727.C1]

91 **Recchia FA**, McConnell PI, Bernstein RD, Vogel TR, Xu X, Hintze TH. Reduced nitric oxide production and altered myocardial metabolism during the decompensation of pacing-induced heart failure in the conscious dog. *Circ Res* 1998; **83**: 969-979 [PMID: 9815144 DOI: 10.1161/01.RES.83.10.969]

92 **Young ME**, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. *J Biol Chem* 2001; **276**: 44390-44395 [PMID: 11574533 DOI: 10.1074/jbc.M103826200]

93 **Degens H**, de Brouwer KF, Gilde AJ, Lindhout M, Willemsen PH, Janssen BJ, van der Vusse GJ, van Bilsen M. Cardiac fatty acid metabolism is preserved in the compensated hypertrophic rat heart. *Basic Res Cardiol* 2006; **101**: 17-26 [PMID: 16136293 DOI: 10.1007/s00395-005-0549-0]

94 **Stanley WC**, Chandler MP. Energy metabolism in the normal and failing heart: potential for therapeutic interventions. *Heart Fail Rev* 2002; **7**: 115-130 [PMID: 11988636 DOI: 10.1023/A:1015320423577]

95 **Himms-Hagen J**, Harper ME. Physiological role of UCP3 may be export of fatty acids from mitochondria when fatty acid oxidation predominates: an hypothesis. *Exp Biol Med* (Maywood) 2001; **226**: 78-84 [PMID: 11446442]

96 **Schrauwen P**, Saris WH, Hesselink MK. An alternative function for human uncoupling protein 3: protection of mitochondria against accumulation of nonesterified fatty acids inside the mitochondrial matrix. *FASEB J* 2001; **15**: 2497-2502 [PMID: 11689475 DOI: 10.1096/fj.01-0400hyp]

97 **Jogl G**, Tong L. Crystal structure of carnitine acetyltransferase and implications for the catalytic mechanism and fatty acid transport. *Cell* 2003; **112**: 113-122 [PMID: 12526798 DOI: 10.1016/S0092-8674(02)01228-X]

98 **Russell KS**, Stern DF, Polverini PJ, Bender JR. Neuregulin activation of ErbB receptors in vascular endothelium leads to angiogenesis. *Am J Physiol* 1999; **277**: H2205-H2211 [PMID: 10600838]

99 **Brero A**, Ramella R, Fitou A, Dati C, Alloatti G, Gallo MP, Levi R. Neuregulin-1beta1 rapidly modulates nitric oxide synthesis and calcium handling in rat cardiomyocytes. *Cardiovasc Res* 2010; **88**: 443-452 [PMID: 20634213 DOI: 10.1093/cvr/cvq238]

100 **Bian Y**, Sun M, Silver M, Ho KK, Marchionni MA, Caggiano AO, Stone JR, Amende I, Hampton TG, Morgan JP, Yan X. Neuregulin-1 attenuated doxorubicin-induced decrease in cardiac troponins. *Am J Physiol Heart Circ Physiol* 2009; **297**: H1974-H1983 [PMID: 19801490 DOI: 10.1152/ajpheart.01010.2008]

101 **Jay SM**, Murthy AC, Hawkins JF, Wortzel JR, Steinhauser ML, Alvarez LM, Gannon J, Macrae CA, Griffith LG, Lee RT. An engineered bivalent neuregulin protects against doxorubicin-induced cardiotoxicity with reduced proneoplastic potential. *Circulation* 2013; **128**: 152-161 [PMID: 23757312 DOI: 10.1161/circulationaha.113.002203]

102 **Li B**, Zheng Z, Wei Y, Wang M, Peng J, Kang T, Huang X, Xiao J, Li Y, Li Z. Therapeutic effects of neuregulin-1 in diabetic cardiomyopathy rats. *Cardiovasc Diabetol* 2011; **10**: 69 [PMID: 21798071 DOI: 10.1186/1475-2840-10-69]

103 **Rosamond W**, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008; **117**: e25-146 [PMID: 18086926 DOI: 10.1161/circulationaha.107.187998]

104 **Gao R**, Zhang J, Cheng L, Wu X, Dong W, Yang X, Li T, Liu X, Xu Y, Li X, Zhou M. A Phase II, randomized, double-blind, multicenter, based on standard therapy, placebo-controlled study of the efficacy and safety of recombinant human neuregulin-1 in patients with chronic heart failure. *J Am Coll Cardiol* 2010; **55**: 1907-1914 [PMID: 20430261 DOI: 10.1016/j.jacc.2009.12.044]

105 **Jabbour A**, Hayward CS, Keogh AM, Kotlyar E, McCrohon JA, England JF, Amor R, Liu X, Li XY, Zhou MD, Graham RM, Macdonald PS. Parenteral administration of recombinant human neuregulin-1 to patients with stable chronic heart failure produces favourable acute and chronic haemodynamic responses. *Eur J Heart Fail* 2011; **13**: 83-92 [PMID: 20810473 DOI: 10.1093/eurjhf/hfq152]

106 **Lenihan DJ,** Anderson S, Geisberg C, Caggiano A, Eisen A, Brittain E, Muldowney Iii JAS, Mendes L, Sawyer D. Safety and tolerability of glial growth factor 2 in patients with chronic heart failure: a phase I single dose escalation study. *J Am College Cardiol* 2013; **61** (Suppl 10): E707 [DOI: 10.1016/S0735-1097(13)60707-X]

107 **Brittain E,** Muldowney J, Geisberg C, Caggiano A, Eisen A, Anderson S, Sawyer D, Mendes L, Lenihan D. Evaluation of cardiac function in symptomatic heart failure patients in a single infusion, phase 1, dose escalation study of glial growth factor 2. *J Am College Cardiol* 2013; **61** (Suppl 10): E715 [DOI: 10.1016/S0735-1097(13)60715-9]

108 **Yu D**, Hung MC. Overexpression of ErbB2 in cancer and ErbB2-targeting strategies. *Oncogene* 2000; **19**: 6115-6121 [PMID: 11156524 DOI: 10.1038/sj.onc.1203972]

109 **Atlas E**, Cardillo M, Mehmi I, Zahedkargaran H, Tang C, Lupu R. Heregulin is sufficient for the promotion of tumorigenicity and metastasis of breast cancer cells in vivo. *Mol Cancer Res* 2003; **1**: 165-175 [PMID: 12556556]

110 **Alajati A**, Sausgruber N, Aceto N, Duss S, Sarret S, Voshol H, Bonenfant D, Bentires-Alj M. Mammary tumor formation and metastasis evoked by a HER2 splice variant. *Cancer Res* 2013; **73**: 5320-5327 [PMID: 23867476 DOI: 10.1158/0008-5472.can-12-3186]

111 **Chua YL**, Ito Y, Pole JC, Newman S, Chin SF, Stein RC, Ellis IO,

Caldas C, O'Hare MJ, Murrell A, Edwards PA. The NRG1 gene is frequently silenced by methylation in breast cancers and is a strong candidate for the 8p tumour suppressor gene. *Oncogene* 2009; **28**: 4041-4052 [PMID: 19802002 DOI: 10.1038/onc.2009.259]

112 **Adélaïde J**, Huang HE, Murati A, Alsop AE, Orsetti B, Mozziconacci MJ, Popovici C, Ginestier C, Letessier A, Basset C, Courtay-Cahen C, Jacquemier J, Theillet C, Birnbaum D, Edwards PA, Chaffanet M. A recurrent chromosome translocation breakpoint in breast and pancreatic cancer cell lines targets the neuregulin/NRG1 gene. *Genes Chromosomes Cancer* 2003; **37**: 333-345 [PMID: 12800145 DOI: 10.1002/gcc.10218]

113 **Huang HE**, Chin SF, Ginestier C, Bardou VJ, Adélaïde J, Iyer NG, Garcia MJ, Pole JC, Callagy GM, Hewitt SM, Gullick WJ, Jacquemier J, Caldas C, Chaffanet M, Birnbaum D, Edwards PA. A recurrent chromosome breakpoint in breast cancer at the NRG1/neuregulin 1/heregulin gene. *Cancer Res* 2004; **64**: 6840-6844 [PMID: 15466169 DOI: 10.1158/0008-5472.can-04-1762]

114 **Ura H**, Murakami K, Akagi T, Kinoshita K, Yamaguchi S, Masui S, Niwa H, Koide H, Yokota T. Eed/Sox2 regulatory loop controls ES cell self-renewal through histone methylation and acetylation. *EMBO J* 2011; **30**: 2190-2204 [PMID: 21540835 DOI: 10.1038/emboj.2011.126]

115 **Orvis T**, Hepperla A, Walter V, Song S, Simon J, Parker J, Wilkerson MD, Desai N, Major MB, Hayes DN, Davis IJ, Weissman B. BRG1/SMARCA4 inactivation promotes non-small cell lung cancer aggressiveness by altering chromatin organization. *Cancer Res* 2014; **74**: 6486-6498 [PMID: 25115300 DOI: 10.1158/0008-5472.can-14-0061]

116 **Chang B**, Chen Y, Zhao Y, Bruick RK. JMJD6 is a histone arginine demethylase. *Science* 2007; **318**: 444-447 [PMID: 17947579 DOI: 10.1126/science.1145801]

117 **Unoki M**, Masuda A, Dohmae N, Arita K, Yoshimatsu M, Iwai Y, Fukui Y, Ueda K, Hamamoto R, Shirakawa M, Sasaki H, Nakamura Y. Lysyl 5-hydroxylation, a novel histone modification, by Jumonji domain containing 6 (JMJD6). *J Biol Chem* 2013; **288**: 6053-6062 [PMID: 23303181 DOI: 10.1074/jbc.M112.433284]

118 **Albig W**, Kioschis P, Poustka A, Meergans K, Doenecke D. Human histone gene organization: nonregular arrangement within a large cluster. *Genomics* 1997; **40**: 314-322 [PMID: 9119399 DOI: 10.1006/geno.1996.4592]

119 **Weiskirchen R**, Gressner AM. The cysteine- and glycine-rich LIM domain protein CRP2 specifically interacts with a novel human protein (CRP2BP). *Biochem Biophys Res Commun* 2000; **274**: 655-663 [PMID: 10924333 DOI: 10.1006/bbrc.2000.3187]

120 **Hatch CL**, Bonner WM. The human histone H2A.Z gene. Sequence and regulation. *J Biol Chem* 1990; **265**: 15211-15218 [PMID: 1697587]

121 **Dreveny I**, Deeves SE, Fulton J, Yue B, Messmer M, Bhattacharya A, Collins HM, Heery DM. The double PHD finger domain of MOZ/MYST3 induces α-helical structure of the histone H3 tail to facilitate acetylation and methylation sampling and modification. *Nucleic Acids Res* 2014; **42**: 822-835 [PMID: 24150941 DOI: 10.1093/nar/gkt931]

122 **Esteyries S**, Perot C, Adelaide J, Imbert M, Lagarde A, Pautas C, Olschwang S, Birnbaum D, Chaffanet M, Mozziconacci MJ. NCOA3, a new fusion partner for MOZ/MYST3 in M5 acute myeloid leukemia. *Leukemia* 2008; **22**: 663-665 [PMID: 17805331 DOI: 10.1038/sj.leu.2404930]

123 **Lindström MS**. NPM1/B23: A Multifunctional Chaperone in Ribosome Biogenesis and Chromatin Remodeling. *Biochem Res Int* 2011; **2011**: 195209 [PMID: 21152184 DOI: 10.1155/2011/195209]

124 **Yamazaki N**, Yamanaka Y, Hashimoto Y, Shinohara Y, Shima A, Terada H. Structural features of the gene encoding human muscle type carnitine palmitoyltransferase I. *FEBS Lett* 1997; **409**: 401-406 [PMID: 9224698 DOI: 10.1016/S0014-5793(97)00561-9]

125 **Kang MJ**, Fujino T, Sasano H, Minekura H, Yabuki N, Nagura H, Iijima H, Yamamoto TT. A novel arachidonate-preferring acyl-CoA synthetase is present in steroidogenic cells of the rat adrenal, ovary, and testis. *Proc Natl Acad Sci USA* 1997; **94**: 2880-2884 [PMID: 9096315 DOI: 10.1073/pnas.94.7.2880]

126 **Fillgrove KL**, Anderson VE. The mechanism of dienoyl-CoA reduction by 2,4-dienoyl-CoA reductase is stepwise: observation of a dienolate intermediate. *Biochemistry* 2001; **40**: 12412-12421 [PMID: 11591162 DOI: 10.1021/bi0111606]

127 **Eaton S**, Bursby T, Middleton B, Pourfarzam M, Mills K, Johnson AW, Bartlett K. The mitochondrial trifunctional protein: centre of a beta-oxidation metabolon? *Biochem Soc Trans* 2000; **28**: 177-182 [PMID: 10816122]

128 **Mannaerts GP**, Van Veldhoven PP, Casteels M. Peroxisomal lipid degradation via beta- and alpha-oxidation in mammals. *Cell Biochem Biophys* 2000; **32** Spring: 73-87 [PMID: 11330072 DOI: 10.1385/CBB:32:1-3:73]

129 **Nilsson U**, Meshalkina L, Lindqvist Y, Schneider G. Examination of substrate binding in thiamin diphosphate-dependent transketolase by protein crystallography and site-directed mutagenesis. *J Biol Chem* 1997; **272**: 1864-1869 [PMID: 8999873 DOI: 10.1074/jbc.272.3.1864]

130 **Reza JZ**, Doosti M, Salehipour M, Packnejad M, Mojarrad M, Heidari M. Modulation peroxisome proliferators activated receptor alpha (PPAR alpha) and acyl coenzyme A: cholesterol acyltransferase1 (ACAT1) gene expression by fatty acids in foam cell. *Lipids Health Dis* 2009; **8**: 38 [PMID: 19725980 DOI: 10.1186/1476-511x-8-38]

131 **Möller G**, Leenders F, van Grunsven EG, Dolez V, Qualmann B, Kessels MM, Markus M, Krazeisen A, Husen B, Wanders RJ, de Launoit Y, Adamski J. Characterization of the HSD17B4 gene: D-specific multifunctional protein 2/17beta-hydroxysteroid dehydrogenase IV. *J Steroid Biochem Mol Biol* 1999; **69**: 441-446 [PMID: 10419023 DOI: 10.1016/S0960-0760(99)00066-7]

132 **Rasmussen AL**, Diamond DL, McDermott JE, Gao X, Metz TO, Matzke MM, Carter VS, Belisle SE, Korth MJ, Waters KM, Smith RD, Katze MG. Systems virology identifies a mitochondrial fatty acid oxidation enzyme, dodecenoyl coenzyme A delta isomerase, required for hepatitis C virus replication and likely pathogenesis. *J Virol* 2011; **85**: 11646-11654 [PMID: 21917952 DOI: 10.1128/jvi.05605-11]

133 **Stapleton D**, Mitchelhill KI, Gao G, Widmer J, Michell BJ, Teh T, House CM, Fernandez CS, Cox T, Witters LA, Kemp BE. Mammalian AMP-activated protein kinase subfamily. *J Biol Chem* 1996; **271**: 611-614 [PMID: 8557660 DOI: 10.1074/jbc.271.2.611]

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Symplicity-3 hypertension trial: Basic and clinical insights

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Abstract

Symplicity-3 hypertension (HTN) was a recently completed clinical trial that was assumed to be the basis for the approved use of renal artery denervation for the treatment of resistant hypertension in the United States. Dramatic reductions in blood pressure had been reported in two clinical trials (Symplicity-1HTN, -2HTN) carried out in Europe, however Symplicity-3HTN did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 mo after renal artery denervation as compared with a sham control. (Denervation group, blood pressure reduction: -14 ± 24, Sham control: -12 ± 26 mmHg). In this review we discuss several potential explanations for the failure of efficacy of Symplicity-3HTN taking into account basic and clinical factors which could have played a role in the discrepancy between the European and American experience.

Key words: Hypertension; Renal artery denervation; Aorticorenal ganglia; Atrial fibrillation

Core tip: The failure of the Symplicity-3 trial which subjected patients to renal artery denervation to significantly reduce resistant hypertension has been ascribed to many factors. In this review, we focus on the lack of a "biomarker" as a major deficiency in achieving the expected efficacy. We also present experimental and clinical evidence to support the importance of a biomarker to acutely predict long term success of renal artery denervation for effective treatment for drug resistant hypertension.

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INTRODUCTION

Renal artery denervation as a procedure for patients with resistant forms of hypertension burst onto the clinical scene in 2009[1] and quickly was followed by clinical trials, Symplicity-1 hypertension (HTN)[2] and Symplicity-2HTN[3]. What was predicted to be a reduction of 5 to 10 mmHg turned out to be a mean reduction of systolic pressure by as much as 32 mmHg even for follow-up periods of 2-3 years. When Medtronic sponsored Symplicity-3HTN as a multi-center trial, enrolling 530 patients, in the United States, it was expected that the European extensive experience would be confirmed. One important difference in Symplicity-3HTN was the inclusion of a sham controlled

group, which is common in pharmacological trials but unusual for a procedural study due to potential ethical reservations. In any event, the recently published report[4] concluded that the results did not show a significant reduction of systolic blood pressure 6 mo after renal artery denervation (-14 ± 24 mmHg) compared to the sham controls (-12 ± 26 mmHg). However, there was no issue with the safety of the procedure using the Symplicity renal-denervation catheter. In this review we consider the potential factors and their relative importance to explain the striking differences in the outcomes of these Symplicity trials.

HISTORICAL BACKGROUND

Experimental animal studies have shown that sympathetic nerve hyperactivity is a critical component in the initiation and maintenance of systemic hypertension. For example it has been shown that chronic HTN can be induced by chronic electrical stimulation of the left stellate ganglion[5]. In this regard, Smithwick and Thompson[6] reported on 1266 cases of surgical splanchnicetomies performed to treat malignant HTN. There was a successful lowering of blood pressure, however, these methods were associated with high perioperative morbidity and mortality and long-term complications, including bowel, bladder, and erectile dysfunction, in addition to severe postural hypotension. Although this clinical approach was generally abandoned, experimental studies progressed on the neurogenic basis for essential hypertension[7,8]. These ongoing studies were eclipsed by the general acceptance of the concept that hypertension was based on an abnormality of the rennin-angiotensin-aldosterone system[9].

The seminal study which brought the neurogenic basis of hypertension to the forefront was published in 2009 in which sympathetic nerves in the adventitia of the renal arteries were ablated by transvascular application of radiofrequency energy (8-10 watts) caused a marked reduction of blood pressure in patient with drug resistant hypertension. Specifically, Krum *et al*[1] using a monopolar electrode catheter (Symplicity) performed renal denervation in 45 patients, 5 untreated patients served as controls. Entry blood pressure (BP) averaged 177/101 ± 20/15 mmHg. At 6 mo, the treated patients showed an office-based BP reduction of -22/-11 ± 10/5 mmHg while the 5 controls had BP increases of +14/+9 mmHg. These startling results, that even surprised the initial investigators quickly morphed into 2 prospective randomized controlled trials, simplicity-HTN 1, HTN2 with as similar or greater dramatic results over follow-up periods as long as 3 years.

The mechanism proposed to explain these findings was suggested to be ablation of sympathetic afferents which after months modulate the vasomotor centers to decrease general sympathetic efferent outflow[10]. This hypothesis was supported by radiotracer dilution studies which showed a 47% spillover of nor-epinephrine within 1 mo of bilateral renal denervation.

POTENTIAL FACTORS TO EXPLAIN THE FAILURE OF SYMPLICITY-HTN3

The unexpected efficacy failure of Symplicity-3 as reported by Bhatt *et al*[4] has engendered a flurry of letters to the editor of the New England Journal of Medicine[11] raising multiple concerns regarding the findings reported in the Symplicity-3 trial. It is interesting to note that Dr Bhatt, the lead investigator in the Symplicity-3 trial, in reply to these letters stated: "We agree that various selection criteria and characteristics of our patient population-such as the exclusion of patients with white-coat hypertension, the inclusion of obese patients and a variety of baseline characteristics or medications could account for the null results of this trial, as compared with the findings of previous trials[11]". Thus, the lead investigator concedes that trial differences could have been the basis of the negative results for Symplicity-3. Many of the same caveats were detailed in a joint consensus statement[12] by respected investigators in the field indicating potential flaws in the Symplicity-3 trial. In a recent report Messerli and Bangalore[13] addressed the possible causes of the failure of the Symplicity-3 trial in light of the dramatic successes of Symplicity-1 and -2. "At first blush, the most likely explanation for the findings of the SYMPLICITY HTN-3 study is the inclusion of a sham-control group. In clinical trials testing interventional procedures and medical devices, sham procedures are seminal, analogous to the use of a placebo in pharmaceutical trials. However, for ethical reasons sham procedures are frowned upon; neither the SYMPLICITY HTN-1 study nor the HTN-2 study had a sham-control cohort. For this reason, placebo effects may well explain all or most of the blood-pressure differences noted in the first two trials. Lack of efficacy could also be caused by incomplete or ineffective denervation. No reliable markers of renal denervation are available, and questions remain as to what exactly the procedure accomplishes. Nevertheless, the ablation catheter used in the SYMPLICITY HTN-3 study was no different from that used in the SYMPLICITY HTN-1 and HTN-2 studies." In this regard, we suggest that the focus of each of the Simplicity trials on ablating the variable structure of the post-ganglionic axons on the renal artery adventitia provides an important impediment for achieving sympathetic denervation. Indeed, the percent of non-responders in a number of previously reported studies, using the Symplicity approach, ranges from 10%-43%[10,14].

In regard to the lack of biomarkers there is a striking analogy between catheter ablation for atrial fibrillation and catheter ablation for refractory hypertension. Besides the fact that both groups of patients who are candidates for these procedures have failed drug therapy: (1) Both

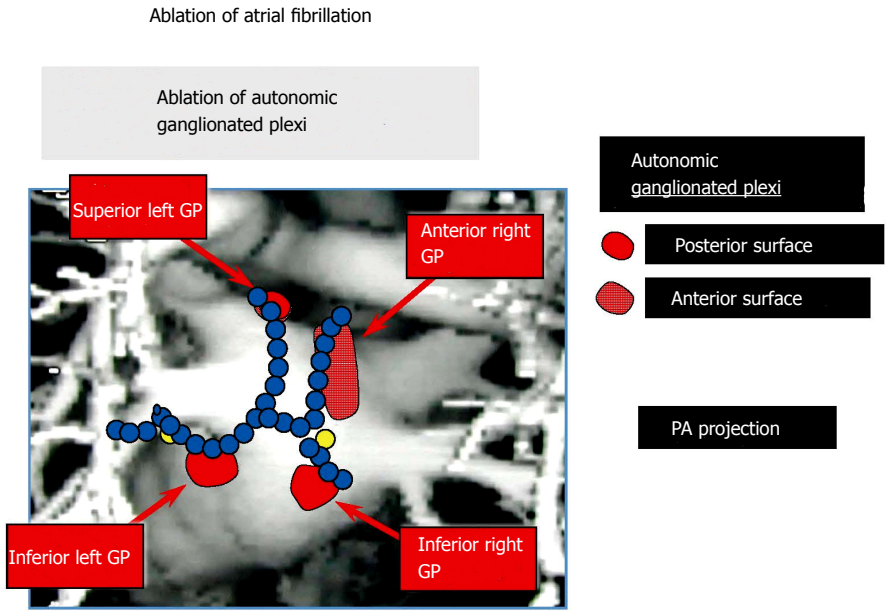

Figure 1 An anatomic figure of the left atrium depicting the lines of radiofrequency applications used to isolate the pulmonary veins in patients undergoing catheter ablation for atrial fibrillation. Note that the lesion lines may, in part, also ablate the ganglionated plexi (GP), albeit incompletely. These nerve clusters are situated at the pulmonary vein - atrial junctions and contribute to the neural basis of atrial fibrillation[12].

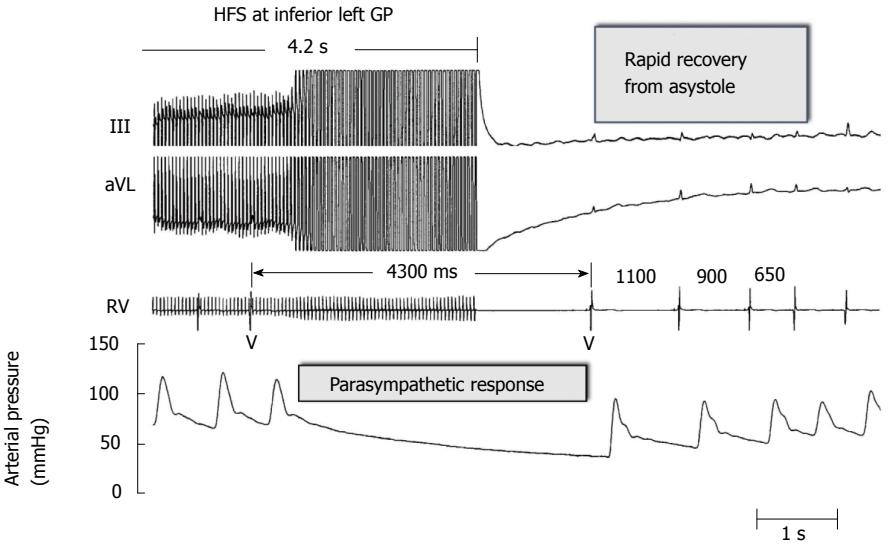

Figure 2 The use of high frequency electrical stimulation applied to the left ganglionated plexi in a patient with atrial fibrillation induced a marked slowing of the ventricular rate by a parasympathetic response at the A-V node. The ensuing heart block manifested an asystolic pause of 4300 milliseconds (ms) which showed a rapid recovery with the cessation of electrical stimulation. The traces from above are: Leads III and aVL of the electrocardiogram; an electrogram recorded from the right ventricle (RV); and arterial blood pressure. GP: Ganglionated plexi; HFS: High-frequency stimulation.

invasive procedures use radiofrequency applications to achieve pulmonary vein isolation (PVI) or renal artery denervation (RAD); (2) It is common that after the procedure AF or high BP is not any different than prior to the procedure. A "blanking" period of various durations ensues before a salutary effect is determined; (3) There is no "biomarker" at the time of the procedure to gauge the success or failure of the intervention; and (4) In both cases neural factors appear to play a critical role in the outcomes.

INFLUENCE OF A BIOMARKER IN ATRIAL FIBRILLATION AND RENAL NERVE DENERVATION

Since 2004[15], in our clinical electrophysiological procedures for AF catheter ablation, we have used additional ablation of clusters of nerves called ganglionated plexi (GP) located at the pulmonary vein-atrial junctions as adjunctive to pulmonary vein isolation (PVI) (Figure 1). High frequency electrical stimulation of these GP invariably leads to marked A-V block induced bradycardia *via* a parasympathetic effect on the AV node (Figure 2). Destructive radiofrequency current application to the GP causes inability of the same high frequency stimulation to slow the heart rate (Figure 3). A recent study by Katritsis *et al*[16] consisting of 242 patients who were candidates for catheter ablation were randomized to PVI alone, GP ablation alone or a combination of PVI + GP and followed for 2 years after a single procedure. The success rates were: 44 (56%), 39 (48%), and 61 (74%), respectively.

Could an analogous scenario be in play with renal sympathetic denervation? The articorenal ganglion was studied by Doelzel[17] in the dog and Norvell in the human[18]. In the latter study, a detailed dissection of the renal plexus and the aorticorenal area was carried out in 57 adult cadavers of both sexes. Figure 4 shows that the aorticorenal ganglia was found localized in

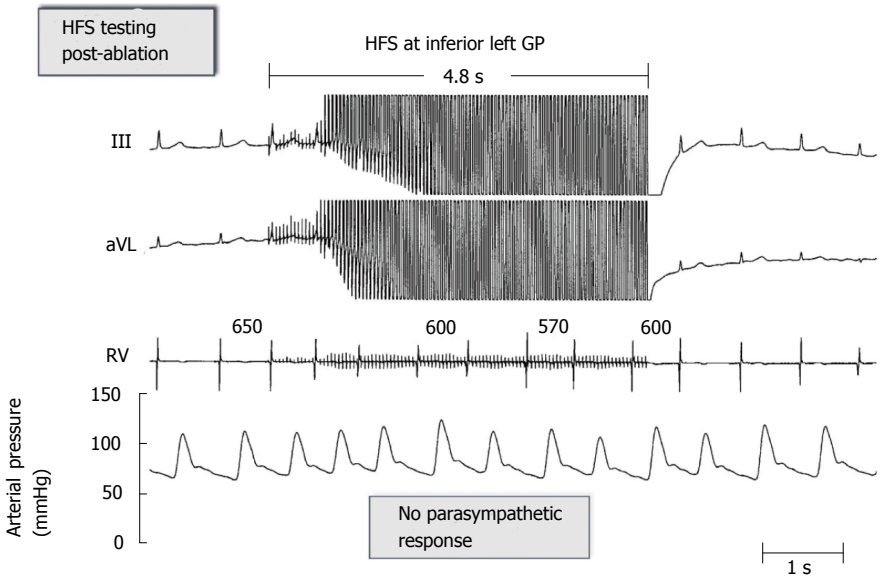

Figure 3 After ablation of the ganglionated plexi at the pulmonary vein-atrial junctions the same level of high frequency stimulation failed to elicit any parasympathetic response and no slowing of the ventricular rate. Traces are the same as in figure 2. See text for further discussion. GP: Ganglionated plexi; HFS: High-frequency stimulation.

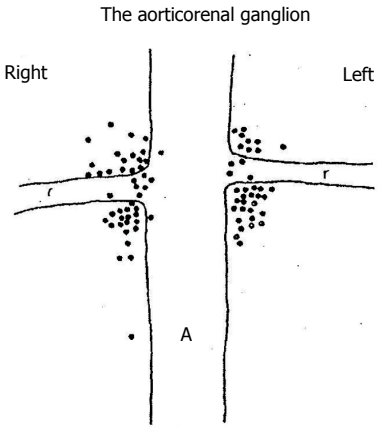

Figure 4 Diagrammatic representation of the junction of the aorta (A) and the renal arteries (R). The dots indicate the localization of the aorticorenal ganglia determined by detailed dissection in 57 cadavers[15].

the area of the real artery at the ostium and junction of the aorta. To test the hypothesis that this bilateral ganglion could have a similar biomarker role in renal denervation as the GP contribute to catheter ablation of AF, in the anesthetized dog, we compared the effects of electrical stimulation of sympathetic nerves on the adventitial surface of the renal arteries to similar frequency and intensity applied to the aorticorenal ganglia on heart rate and blood pressure.

Electrical stimulation applied to the renal artery adventitia did not affect the heart rate but significantly increased systolic and diastolic blood pressure (Baseline: 134 ± 24/96 ± 18 mmHg, RAs stimulation: 157 ± 26/114 ± 18 mmHg. Electrical stimulation applied to the aorticorenal ganglia did not affect heart rate but significantly increased systolic and diastolic blood pressure: 207 ± 44/147 ± 26 mmHg, $P < 0.05$ compared to baseline. In summary, there was a significantly greater effect on both systolic and diastolic BP caused by the same level of electrical stimulation applied to the aorticorenal ganglia than to the adventitial nerves of the renal arteries[18].

Could a similar biomarker be shown in the clinical setting of hypertension? A recent report by Pokushalov *et al*[19] involved 27 patients (14 randomized to PVI only, and 13 randomized to PVI and renal artery denervation), all of whom were followed for 12 mo after ablation. All had a history of paroxysmal atrial fibrillation and hypertension. "To confirm renal denervation, we used high-frequency stimulation (HFS) before the initial and after each RF delivery within the renal artery. Rectangular electrical stimuli were delivered at the ostium of the targeted renal artery at a frequency of 20 Hz, with an amplitude of 15 V and pulse duration of 10 ms… for 10 s…Renal sympathetic denervation was considered to have been achieved when the sudden increase of blood pressure …was eliminated in the presence of HFS."

Nine of the 13 patients (69%) treated with PVI with renal denervation were AF-free at the 12-mo post-ablation follow-up examination *vs* 4 (29%) of the 14 patients in the PVI-only group ($P = 0.033$). At the end of the follow-up, significant reductions in systolic (from 181 ± 7 to 156 ± 5, $P < 0.001$) and diastolic blood pressure (from 97 ± 6 to 87 ± 4, $P < 0.001$) were observed in patients treated with PVI with renal denervation without significant change in the PVI only group.

CONCLUSION

Although many explanations have been put forward to try to explain the lack of efficacy of the Symplicity-3 trial for renal artery denervation to treat resistant forms of hypertension, it appears that one major reservation has been the lack of a biomarker for the induction of an increase in blood pressure and then after ablation the inability to show the same hypertensive response. A clinical trial to test this acute effect as a predictor of success would negate the reliance on a blanking period (weeks) for central

autonomic remodeling to occur in order to determine whether the reduction of blood pressure has been achieved.

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REFERENCES

1 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]

2 Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; **57**: 911-917 [PMID: 21403086 DOI: 10.1161/HYPERTENSIONAHA.110.163014]

3 **Esler MD**, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903-1909 [PMID: 21093036 DOI: 10.1016/S0140-6736(10)62039-9]

4 **Bhatt DL**, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; **370**: 1393-1401 [PMID: 24678939 DOI: 10.1056/NEJMoa1402670]

5 **Liard JF**, Tarazi RC, Ferrario CM, Manger WM. Hemodynamic and humoral characteristics of hypertension induced by prolonged stellate ganglion stimulation in conscious dogs. *Circ Res* 1975; **36**: 455-464 [PMID: 1112001]

6 **Smithwick RH**, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. *J Am Med Assoc* 1953; **152**: 1501-1504 [PMID: 13061307]

7 **DiBona GF**, Kopp UC. Neural control of renal function. *Physiol Rev* 1997; **77**: 75-197 [PMID: 9016301 DOI: 10.1002/cphy.c100043]

8 **Esler M**, Jennings G, Lambert G. Noradrenaline release and the pathophysiology of primary human hypertension. *Am J Hypertens* 1989; **2**: 140S-146S [PMID: 2647104]

9 **Laragh JH**. Renin, angiotensin, aldosterone and hormonal regulation of arterial pressure and salt balance. Introductory remarks. *Fed Proc* 1967; **26**: 39-41 [PMID: 4289566]

10 **Schlaich MP**, Hering D, Sobotka PA, Krum H, Esler MD. Renal denervation in human hypertension: mechanisms, current findings, and future prospects. *Curr Hypertens Rep* 2012; **14**: 247-253 [PMID: 22457244 DOI: 10.1007/s11906-012-0264-9]

11 **Bhatt DL**, Bakris GL. Renal denervation for resistant hypertension. *N Engl J Med* 2014; **371**: 184 [PMID: 25006731 DOI: 10.1056NEJMc1405677]

12 **Lobo MD**, de Belder MA, Cleveland T, Collier D, Dasgupta I, Deanfield J, Kapil V, Knight C, Matson M, Moss J, Paton JF, Poulter N, Simpson I, Williams B, Caulfield MJ. Joint UK societies' 2014 consensus statement on renal denervation for resistant hypertension. *Heart* 2015; **101**: 10-16 [PMID: 25431461 DOI: 10.1136/heartjnl-2014-307029]

13 **Messerli FH**, Bangalore S. Renal denervation for resistant hypertension? *N Engl J Med* 2014; **370**: 1454-1457 [PMID: 24678938 DOI: 10.1056/NEJMe1402388]

14 **Persu A**, Jin Y, Azizi M, Baelen M, Völz S, Elvan A, Severino F, Rosa J, Adiyaman A, Fadl Elmula FE, Taylor A, Pechère-Bertschi A, Wuerzner G, Jokhaji F, Kahan T, Renkin J, Monge M, Widimský P, Jacobs L, Burnier M, Mark PB, Kjeldsen SE, Andersson B, Sapoval M, Staessen JA. Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens* 2014; **28**: 150-156 [PMID: 24067345 DOI: 10.1038/jhh.2013.88]

15 **Scherlag BJ**, Nakagawa H, Jackman WM, Yamanashi WS, Patterson E, Po S, Lazzara R. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. *J Interv Card Electrophysiol* 2005; **13** Suppl 1: 37-42 [PMID: 16133854]

16 **Katritsis DG**, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J Am Coll Cardiol* 2013; **62**: 2318-2325 [PMID: 23973694 DOI: 10.1016/j.jacc.2013.06.053]

17 **Dolezel S**. Monoaminergic innervation of the kidney. Aorticorenal ganglion--A sympathetic, monoaminergic ganglion supplying the renal vessels. *Experientia* 1967; **23**: 109-111 [PMID: 6032095]

18 **Norvell JE**. The aorticorenal ganglion and its role in renal innervation. *J Comp Neurol* 1968; **133**: 101-111 [PMID: 5721480]

19 **Pokushalov E**, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012; **60**: 1163-1170 [PMID: 22958958 DOI: 10.1016/j.jacc.2012.05.036]

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MINIREVIEWS

Diagnosis and management of thoracic aortic dissection: An update

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Abstract

Acute thoracic aortic dissection is part of the acute aortic syndrome triad. Caused by an intimal tear in the lumen of the aorta, it leads to the creation and propagation of a false lumen. In the acute setting this can lead to malignant hypertension, pain and end organ malperfusion. In the chronic setting it can lead to aneurysm formation and rupture. It remains the most common aortic emergency, affecting up to 4 per 100000 people per year in the United Kingdom and United States. Despite advances in treatment and centralisation of vascular services, it continues to be associated with a high pre-admission and in-hospital mortality. Dissection is classified in several ways according to anatomical extent, timing and underlying pathology, all of which guides clinical management. Traditionally, medical management has been the mainstay of treatment in patients with uncomplicated disease. Surgery has been used in symptomatic patients. With published information now available from several prospective international registries, we are beginning to see the advantages of newer surgical treatment options such as endovascular repair, in the acute setting. This review provides an update on diagnosis and management of aortic dissection, including new information that has become available in recent years.

Key words: Aortic dissection; Endovascular; Acute aortic syndrome; Aneurysm; Dissecting; Endovascular procedures; Hypertension, Malignant; Registries

Core tip: Aortic dissection remains the most common aortic emergency, affecting up to 4 per 100000 people per year in the United Kingdom and United States. Surgical management is indicated in dissection complicated by uncontrolled pain and hypertension, end-organ malperfusion and aneurysmal dilatation with risk of rupture. This update discusses results of thoracic stenting from more recently published prospective international registries, including risks and benefits to treated patients affected by this incredibly high risk condition.

Benson RA, Patterson BO, Loftus IM. Diagnosis and management of thoracic aortic dissection: An update. *World J Hypertens* 2015; 5(2): 79-84 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i2/79.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i2.79

INTRODUCTION

Aortic dissection is one of the conditions included in the term "acute aortic syndrome". This collection includes true dissection, intramural haematoma and penetrating aortic ulcer[1]. Of these acute dissection is the most common, affecting up to 4 people in 100000 annually[2]. Despite advances in therapies, pre-hospital mortality remains high at 20%. Thirty percent of all dissections surviving to a vascular centre will die before discharge[2]. Mortality depends on dissection type, cause and treatment options. New information on the management of type B acute dissection has been published in recent years. This review will discuss all forms of thoracic aortic dissection, with a focus on the recent shifts towards use of surgical management of acute type B dissection using thoracic endovascular repair (TEVAR) rather than best medical therapy alone.

DEFINITION

Dissection refers to the separation of the intima/inner media and outer media/adventitia of any artery, due to the tracking of blood into this potential space *via* a tear in the intima. The false passage can track both antegrade and retrograde[3]. Traditionally they are considered acute if within 14 d of onset and chronic after 14 d. However, publication of survival curves in patient presenting with dissection has shown that survival drops sharply around 30 d post-presentation[4,5]. Therefore the terms acute (< 2 wk), subacute (2-6 wk) and chronic (> 6 wk) have been suggested by a recent European panel[6].

CLASSIFICATION

Three classification systems are in common use. The Stanford and DeBakey classification systems use anatomical markers to differentiate dissection type (Figure 1). Stanford type A dissections involve the ascending aorta, while type B originate anywhere distal to the origin of the left subclavian artery[7]. The DeBakey system has three groups. Type 1 involves ascending and descending aorta, type 2 ascending aorta only and type 3 descending aorta only[8]. The European Society of Cardiologists categorise dissection by aetiology using 5 classifications based on pathogenesis of the intimal injury. The advantage of this system, is that it can be used to guide clinical management toward medical or surgical therapy[1]. During this review, the authors will use the Stanford classification due to its wide use within the literature.

RISK FACTORS

As with other aortic pathologies such as aneurysmal disease, those at greatest risk overall are white, male and over 60[8,9]. Type B dissection accounts for 25%-40% of all dissections[10] although recent literature suggests type B dissection is more common than type A amongst African American patients[11]. A study by the international Registry of Acute Aortic Dissection (IRAD) using data from 12 international centres showed that men accounted for 68% of acute presentation[9]. Hypertension, increasing age and pre-existing arterial disease were also common factors.

Systemic hypertension is present in up to 75% of patients at presentation. Physical exertion or a period of emotional stress may be identified as a trigger, likely due to it leading to an acute episode of hypertension[12]. Familial aneurysmal syndromes and connective tissue disease is an important factor in younger patients, more specifically Marfan's syndrome with fibrillin-1 deficiency, Ehler-Dahnlos type Ⅳ (abnormal type Ⅲ procollagen) and any other cause of cystic medial necrosis[13-15]. Other congenital defects related to younger presentation are a bicuspid aortic valve (likely due to associated aortic root abnormalities) and coarctation of the aorta (and its associated hypertension)[16]. Other causes of disease in the younger patient include pre-existing vasculitic disease, pregnancy and cocaine abuse[9,17]. Vascular interventions may also act as a trigger, for example following percutaneous cardiac catheterisation, coronary artery bypass grafting, or thoracic stenting procedures for aneurysmal disease.

CLINICAL PRESENTATION

Ninety percent of patients present with sudden onset pain in the chest. In type A dissection it may radiate to the neck, and in type B to the interscapular area[18]. Diabetes is thought to account for the remaining, asymptomatic dissections[19]. New aortic regurgitation is picked up in 31% of patients, and a radio-radio/radio-femoral delay in 15%[8]. Type A presents with hypotension in up to 25% of patients, whereas type B dissections tend to present with hypertension[8]. If both true and false lumens are perfused the aortic branches, and therefore end organs, will remain perfused. If this is not the case, dissection can present with neurological symptoms such as stroke, renal failure, bowel ischaemia or limb ischaemia[20]. These are considered high-risk features, and their effect on management is discussed below. On occasion, an asymptomatic dissection can lead to aortic dilatation and rupture, either acutely, or up to three years after the initial event[10].

DIAGNOSIS AND INVESTIGATION

Differential diagnoses include myocardial infarction, pulmonary embolus, perforated viscus, stroke or other neurological insult and embolic disease[21]. ECG and X-ray are not sensitive enough to diagnose dissection, but will identify concomitant acute coronary syndromes or act as indicators of alternative diagnoses[22]. CT angiography remains the recommended first line investigation in those suspected of having dissection[1]. It is also useful for planning surgical intervention. Other first

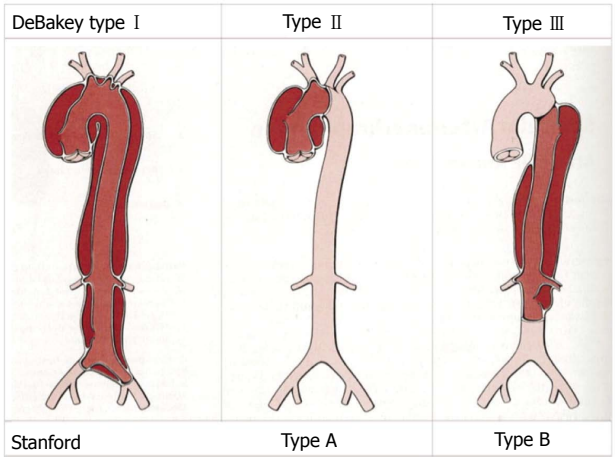

Figure 1 Illustration of the DeBakey and Stanford classifications for aortic dissection. The DeBakey system takes into account tear entry site and propagation within ascending or descending aorta. The Stanford system is more blunt. Type A is one with any involvement of the ascending aorta, type B any involvement of the descending aorta[43].

line modalities include transoesophageal ECHO, which has the advantage of identifying new aortic regurgitation or pericardial effusion. However it cannot image the entire aorta, and is heavily operator dependent[1]. Magnetic resonance angiography lacks radiation exposure, and uses less nephrotoxic agent, which benefits patients with evidence of renal hypoperfusion. However availability is more limited and imaging takes longer, making it more suitable in the chronic setting or for patient follow-up. All three of these modalities have sensitivity and specificity of over 95% for diagnosis[23].

INITIAL MANAGEMENT

The mainstay of initial management is resuscitation and stabilisation, to allow transfer for diagnostic imaging and subsequent treatment. Large bore venous access and invasive monitoring including arterial line, cardiac monitoring and urinary catheterisation should be instigated. Close monitoring of end organ function will help identify any deterioration quickly. This includes cardiac monitoring as a proxy for coronary perfusion, cerebral perfusion, limb perfusion and urine output. Wherever possible, this should be in a high dependency setting.

In those patients presenting with hypertension, a target systolic blood pressure of between 100-120 mmHg and heart rate of 60-80 beats per minute should be sought[1,24]. The aim of this is to decrease shear force on the aortic wall and prevent further propagation of the dissection flap[25]. Systolic pressure control in the emergency setting is commonly in the form of a short acting intravenous beta-blocker such as Labetalol. This should be balanced against any deterioration of end organ perfusion. Once haemodynamically stable, the patient should be imaged without delay.

MANAGEMENT OF CONFIRMED DISSECTION

Acute type A dissection

The mainstay of treatment for type A dissection is surgical. Left untreated, it carries a 50%-91% mortality at 7 d, due to rupture, stroke, visceral malperfusion, cardiac tamponade and heart failure[8]. Surgery involves open replacement of the aortic root and affected arch with a prosthetic graft. In extensive dissection involving the ascending and descending aorta, a portion of the graft can be sutured in a way that leaves a free section within native aorta. This provides a landing zone for the stent graft required to treat the rest of the diseased aorta and is known as a hybrid repair. The time lag between first and second stages of repair remains controversial[26]. In hospital mortality following a procedure such as this remains 24%[27]. Further surgical intervention in the form of aortic valve replacement or coronary artery bypass may also be indicated. Three and five year survival rates are 75% and 73% respectively[28].

Acute type B dissection

Uncomplicated: Despite earlier trends towards stenting all acute type B dissection, international consensus is yet to publish recommendations for its use over medical management in uncomplicated disease. The VIRTUE registry's intermediate findings indicate support for use of stenting in this setting, following favourable results for all-cause mortality (18%), dissection related mortality (12%) aortic rupture (2%), retrograde type A dissection (5%), and aortic reintervention rates (20%) at a follow up of three years[29]. One year results from the ADSORB trial have shown similar results to this. However the main advantage of stenting over medical management appears to be improved rates of false lumen thrombosis alone[10].

Medical management involves careful blood pressure control, to prevent further tearing or aortic dilatation. Beta blockers remain first line therapy, with follow-up shared between cardiology and the vascular surgeon[1,20]. Alternatives such as calcium channel blockers can be used in patients unable to tolerate first line therapy for any reason, *e.g.*, chronic obstructive pulmonary disease. Survival rates of up to 78% at three years are reported[30] (Table 1).

Complicated

This group includes patients presenting with evidence of end-organ ischaemia, aortic rupture, pain or refractory hypertension, as well as those patients initially described as uncomplicated in whom disease has progressed despite optimal medical treatment[22,24]. These patients have a much poorer prognosis, with mortality approaching 50% in the untreated group[31]. Endovascular repair is the mainstay of treatment, with a 30 d mortality of

Table 1 Trials looking at outcomes of type B dissection according to management strategy

Registry	Authors	Design	Indication	Duration	Conclusion
Instead trial	Nienaber *et al*[37]	Prospective randomised trial	Comparison of TEVAR *vs* medical therapy in chronic type B dissection	2 yr	TEVAR failed to improve survival or adverse events despite favourable aortic remodeling
Instead-XL	Nienaber *et al*[39]	Prospective randomised trial	Long-term outcomes of cohorts recruited to INSTEAD trial	5 yr	TEVAR plus best medical therapy improved 5-yr aorta-specific survival
Mother registry	Patterson *et al*[36]	Collation of data from 5 clinical trials including VIRTUE and INSTEAD	Mid-term outcomes following endovascular repair using TEVAR for acute type B dissection	5 yr	TEVAR provides good midterm protection from aortic-specific pathology High rates of re-intervention
Virtue registry	The Virtue registry investigators[29]	Prospective Multicentre Clinical trial	Safety, performance and health economic data in patients receiving the Valiant endograft	3 yr (2006-2012)	TEVAR provides protection from aortic related death in midterm High rates of re-intervention
Adsorb trial	Hughes[10]	Multicentre randomised clinical trial	Comparison of best medical therapy *vs* medical therapy and TEVAR for acute type B dissection	1 yr	TEVAR leads to improved aortic remodeling compared to medical therapy alone

TEVAR: Thoracic endovascular repair.

9.8%[32]. Even following surgery, 56% of cases will have ongoing false lumen perfusion, which can progress towards aortic expansion and rupture in 20%[33]. False lumen re-perfusion occurs in up to 16%, and this may require further surgery[34]. Over a 34 mo follow-up period data indicated 26% of patients required re-intervention for endoleak, distal fenestrations and concomitant pathology[35]. Retrograde type A dissection following TEVAR is a rare complication. Pooled data including the MOTHER registry found an incidence of 1.7% after TEVAR for all causes, with a mortality rate of 33.6%. Treatment for dissection was a significant risk factor, with an odds ratio of 10.0 (CI: 4.7-21.9) in acute disease and 3.4 (CI: 1.3-8.8) in chronic disease[36].

CHRONIC TYPE B DISSECTION

Medical management in chronic dissection has remained the mainstay of treatment. This follows results from randomised trials comparing optimal medical management alone to that in combination with thoracic stenting, the most significant being the INSTEAD trial[37]. This trial recruited patients with uncomplicated type B dissection in the sub-acute phase, and randomised 140 into one of the two groups described above. Follow up was 2 years, during which time endovascular repair failed to demonstrate a survival advantage for all cause mortality (88.9% ± 3.7% *vs* 95.6% ± 2.5% with optimal medical therapy) or aortic related mortality[38]. As with acute dissection, it did lead to higher rates of false lumen thrombosis (91.3% *vs* 19.4%).

A recently published analysis of the data from the same cohort, analysing outcomes from years 2 to 5 post randomisation (INSTEAD-XL) found a reduction in aorta-specific mortality in patients who underwent surgery (0% *vs* 3.6%, $P = 0.001$)[39]. By 5 years, there were significant differences in maximum aortic diameter (56.4 ± 6.8 mm *vs* 44.5 ± 11.5 mm medical management *vs* stenting respectively), false lumen diameter (37.1 ± 9.1 mm *vs* 10.4 ± 13.2 mm) and complete false lumen thrombosis (22% *vs* 90.6%). This appears to indicate that although there is little difference in survival between the two management strategies before two years, the advantages of stenting become apparent between 2 and five years post presentation. Despite this, two patients suffered from spinal cord ischaemia post TEVAR, and three patients required conversion to an open procedure following TEVAR within two years of randomisation.

Up to 15% of chronic dissection will be complicated by aneurysm formation; a survival analysis from the IRAD registry identified aortic growth and aneurysm formation to be the most common complication during follow-up[5]. Despite this, accurate prediction of the timing and course of progression remain elusive[6]. Once progression occurs, intervention should be planned. As with most surgery, TEVAR has an appreciable reduction in short-term morbidity and mortality in these patients, compared to an open operation (93% *vs* 79% respectively)[24,31]. At 10 years, survival following open surgery has been reported at 35%, while equivalent data for endovascular management is still unknown[31].

FOLLOW-UP

It is clear that dissection carries significant risk of disease progression despite optimal treatment and irrespective of aetiology. In those with hereditary aortic wall structure defects, mortality from rupture in an aorta measuring greater than 6 cm is 12%, with women at higher risk than men[40]. Therefore lifelong surveillance is mandatory, with axial imaging in the very least being used for routine imaging. MRA reduces the contrast and radiation exposure over a patient's lifetime compared to CTA[41]. Imaging at 1, 3, 6 and 12 mo followed by annual review is recommended by the European Society of Cardiology[1]. Intervals should be altered depending on aortic size. All patients should receive

life-long blood pressure management, and treatment should involve cardiology and vascular surgical input at all stages[42].

CONCLUSION

Optimal management of all type A dissections and uncomplicated or chronic type B dissections has changed little in recent years. However with the publication of results from multi-centre randomised controlled trials now becoming available, we are seeing the potential advantages in early use of endovascular repair on both short and longer-term mortality, progressive aortic dilatation and aortic remodeling. Throughout all of this, the message persists; aortic dissection remains a disease with a high mortality and need for life-long follow-up.

REFERENCES

1 **Erbel R**, Alfonso F, Boileau C, Dirsch O, Eber B, Haverich A, Rakowski H, Struyven J, Radegran K, Sechtem U, Taylor J, Zollikofer C, Klein WW, Mulder B, Providencia LA. Diagnosis and management of aortic dissection. *Eur Heart J* 2001; **22**: 1642-1681 [PMID: 11511117 DOI: 10.1053/euhj.2001.2782]

2 **Olsson C**, Thelin S, Ståhle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation* 2006; **114**: 2611-2618 [PMID: 17145990 DOI: 10.1161/CIRCULATIONAHA.106.630400]

3 **Srichai MB**, Lieber ML, Lytle BW, Kasper JM, White RD. Acute dissection of the descending aorta: noncommunicating versus communicating forms. *Ann Thorac Surg* 2004; **77**: 2012-220; discussion 2020 [PMID: 15172256 DOI: 10.1016/j.athoracsur.2003.08.030]

4 **Booher AM**, Isselbacher EM, Nienaber CA, Trimarchi S, Evangelista A, Montgomery DG, Froehlich JB, Ehrlich MP, Oh JK, Januzzi JL, O'Gara P, Sundt TM, Harris KM, Bossone E, Pyeritz RE, Eagle KA. The IRAD classification system for characterizing survival after aortic dissection. *Am J Med* 2013; **126**: 730.e19-730.e24 [PMID: 23885677 DOI: 10.1016/j.amjmed.2013.01.020]

5 **Fattori R**, Montgomery D, Lovato L, Kische S, Di Eusanio M, Ince H, Eagle KA, Isselbacher EM, Nienaber CA. Survival after endovascular therapy in patients with type B aortic dissection: a report from the International Registry of Acute Aortic Dissection (IRAD). *JACC Cardiovasc Interv* 2013; **6**: 876-882 [PMID: 23968705 DOI: 10.1016/j.jcin.2013.05.003]

6 **Fattori R**, Bacchi-Reggiani L, Bertaccini P, Napoli G, Fusco F, Longo M, Pierangeli A, Gavelli G. Evolution of aortic dissection after surgical repair. *Am J Cardiol* 2000; **86**: 868-872 [PMID: 11024403 DOI: 10.1016/S0002-9149(00)01108-5]

7 **Crawford ES**, Svensson LG, Coselli JS, Safi HJ, Hess KR. Surgical treatment of aneurysm and/or dissection of the ascending aorta, transverse aortic arch, and ascending aorta and transverse aortic arch. Factors influencing survival in 717 patients. *J Thorac Cardiovasc Surg* 1989; **98**: 659-673; discussion 673-674 [PMID: 2811404]

8 **DeBakey ME**, McCollum CH, Crawford ES, Morris GC, Howell J, Noon GP, Lawrie G. Dissection and dissecting aneurysms of the aorta: twenty-year follow-up of five hundred twenty-seven patients treated surgically. *Surgery* 1982; **92**: 1118-1134 [PMID: 7147190]

9 **Suzuki T**, Mehta RH, Ince H, Nagai R, Sakomura Y, Weber F, Sumiyoshi T, Bossone E, Trimarchi S, Cooper JV, Smith DE, Isselbacher EM, Eagle KA, Nienaber CA. Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD). *Circulation* 2003; **108** Suppl 1: II312-II317 [PMID: 12970252 DOI: 10.1161/01.cir.0000087386.07204.09]

10 **Hughes GC.** Management of acute type B aortic dissection; ADSORB trial. *J Thorac Cardiovasc Surg* 2015; **149** (2 Suppl): S158-S162 [PMID: 25306065 DOI: 10.1016/j.jtcvs.2014.08.083.]

11 **Bossone E**, Pyeritz RE, O'Gara P, Harris KM, Braverman AC, Pape L, Russo MJ, Hughes GC, Tsai TT, Montgomery DG, Nienaber CA, Isselbacher EM, Eagle KA. Acute aortic dissection in blacks: insights from the International Registry of Acute Aortic Dissection. *Am J Med* 2013; **126**: 909-915 [PMID: 23953874 DOI: 10.1016/j.amjmed.2013.04.020]

12 **Hinchliffe RJ**, Halawa M, Holt PJ, Morgan R, Loftus I, Thompson MM. Aortic dissection and its endovascular management. *J Cardiovasc Surg* (Torino) 2008; **49**: 449-460 [PMID: 18665107]

13 **Judge DP**, Dietz HC. Marfan's syndrome. *Lancet* 2005; **366**: 1965-1976 [PMID: 16325700 DOI: 10.1016/S0140-6736(05)67789-6]

14 **Pepin M**, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; **342**: 673-680 [PMID: 10706896 DOI: 10.1056/NEJM200003093421001]

15 **He R**, Guo DC, Estrera AL, Safi HJ, Huynh TT, Yin Z, Cao SN, Lin J, Kurian T, Buja LM, Geng YJ, Milewicz DM. Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. *J Thorac Cardiovasc Surg* 2006; **131**: 671-678 [PMID: 16515922 DOI: 10.1016/j.jtcvs.2005.09.018]

16 **Januzzi JL**, Isselbacher EM, Fattori R, Cooper JV, Smith DE, Fang J, Eagle KA, Mehta RH, Nienaber CA, Pape LA. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). *J Am Coll Cardiol* 2004; **43**: 665-669 [PMID: 14975480 DOI: 10.1016/j.jacc.2003.08.054]

17 **Eagle KA**, Isselbacher EM, DeSanctis RW. Cocaine-related aortic dissection in perspective. *Circulation* 2002; **105**: 1529-1530 [PMID: 11927514 DOI: 10.1161/01.CIR.105.13.1529]

18 **Karthikesalingam A**, Holt PJ, Hinchliffe RJ, Thompson MM, Loftus IM. The diagnosis and management of aortic dissection. *Vasc Endovascular Surg* 2010; **44**: 165-169 [PMID: 20308170 DOI: 10.1177/1538574410362118]

19 **von Kodolitsch Y**, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med* 2000; **160**: 2977-2982 [PMID: 11041906 DOI: 10.1001/archinte.160.19.2977]

20 **Hiratzka LF**, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010; **121**: e266-e369 [PMID: 20233780 DOI: 10.1161/CIR.0b013e3181d4739e]

21 **Thrumurthy SG**, Karthikesalingam A, Patterson BO, Holt PJ, Hinchliffe RJ, Loftus IM, Thompson MM. A systematic review of mid-term outcomes of thoracic endovascular repair (TEVAR) of chronic type B aortic dissection. *Eur J Vasc Endovasc Surg* 2011; **42**: 632-647 [PMID: 21880515 DOI: 10.1016/j.ejvs.2011.08.009]

22 **Golledge J**, Eagle KA. Acute aortic dissection. *Lancet* 2008; **372**: 55-66 [PMID: 18603160 DOI: 10.1016/S0140-6736(08)60994-0]

23 **Shiga T**, Wajima Z, Apfel CC, Inoue T, Ohe Y. Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: systematic review and meta-analysis. *Arch Intern Med* 2006; **166**: 1350-1356 [PMID: 16831999 DOI: 10.1001/archinte.166.13.1350]

24 **Svensson LG**, Crawford ES, Hess KR, Coselli JS, Safi HJ. Variables predictive of outcome in 832 patients undergoing repairs of the descending thoracic aorta. *Chest* 1993; **104**: 1248-1253 [PMID: 8404201 DOI: 10.1378/chest.104.4.1248]

25 **Thrumurthy SG**, Karthikesalingam A, Patterson BO, Holt PJ, Thompson MM. The diagnosis and management of aortic

dissection. *BMJ* 2012; **344**: d8290 [PMID: 22236596 DOI: 10.1136/bmj.d8290]
26 **Chavan A**, Karck M, Hagl C, Winterhalter M, Baus S, Galanski M, Haverich A. Hybrid endograft for one-step treatment of multisegment disease of the thoracic aorta. *J Vasc Interv Radiol* 2005; **16**: 823-829 [PMID: 15947046 DOI: 10.1097/01.RVI.0000159205.00299.97]
27 **Rampoldi V**, Trimarchi S, Eagle KA, Nienaber CA, Oh JK, Bossone E, Myrmel T, Sangiorgi GM, De Vincentiis C, Cooper JV, Fang J, Smith D, Tsai T, Raghupathy A, Fattori R, Sechtem U, Deeb MG, Sundt TM, Isselbacher EM. Simple risk models to predict surgical mortality in acute type A aortic dissection: the International Registry of Acute Aortic Dissection score. *Ann Thorac Surg* 2007; **83**: 55-61 [PMID: 17184630 DOI: 10.1016/j.athoracsur.2006.08.007]
28 **Ince H**, Nienaber CA. Diagnosis and management of patients with aortic dissection. *Heart* 2007; **93**: 266-270 [PMID: 17228080]
29 VIRTUE Registry Investigators. Mid-term outcomes and aortic remodelling after thoracic endovascular repair for acute, subacute, and chronic aortic dissection: the VIRTUE Registry. *Eur J Vasc Endovasc Surg* 2014; **48**: 363-371 [PMID: 24952999 DOI: 10.1016/j.ejvs.2014.05.007]
30 **Tsai TT**, Trimarchi S, Nienaber CA. Acute aortic dissection: perspectives from the International Registry of Acute Aortic Dissection (IRAD). *Eur J Vasc Endovasc Surg* 2009; **37**: 149-159 [PMID: 19097813 DOI: 10.1016/j.ejvs.2008.11.032]
31 **Estrera AL**, Miller CC, Goodrick J, Porat EE, Achouh PE, Dhareshwar J, Meada R, Azizzadeh A, Safi HJ. Update on outcomes of acute type B aortic dissection. *Ann Thorac Surg* 2007; **83**: S842-S845; discussion S842-S845 [PMID: 17257938 DOI: 10.1016/j.athoracsur.2006.10.081]
32 **Eggebrecht H**, Nienaber CA, Neuhäuser M, Baumgart D, Kische S, Schmermund A, Herold U, Rehders TC, Jakob HG, Erbel R. Endovascular stent-graft placement in aortic dissection: a meta-analysis. *Eur Heart J* 2006; **27**: 489-498 [PMID: 16227309 DOI: 10.1093/eurheartj/ehi493]
33 **Böckler D**, Schumacher H, Ganten M, von Tengg-Kobligk H, Schwarzbach M, Fink C, Kauczor HU, Bardenheuer H, Allenberg JR. Complications after endovascular repair of acute symptomatic and chronic expanding Stanford type B aortic dissections. *J Thorac Cardiovasc Surg* 2006; **132**: 361-368 [PMID: 16872963 DOI: 10.1016/j.jtcvs.2006.02.056]
34 **Moon MC**, Pablo Morales J, Greenberg RK. Complicated acute type B dissection and endovascular repair: indications and pitfalls. *Perspect Vasc Surg Endovasc Ther* 2007; **19**: 146-159 [PMID: 17704484 DOI: 10.1177/1531003507304166]
35 **Hanna JM**, Andersen ND, Ganapathi AM, McCann RL, Hughes GC. Five-year results for endovascular repair of acute complicated type B aortic dissection. *J Vasc Surg* 2014; **59**: 96-106 [PMID: 24094903 DOI: 10.1016/j.jvs.2013.07.001]
36 **Patterson B**, De Bruin JL, Brownrigg JR, Holt PJ, Loftus IM, Thompson MM, Hinchliffe RJ. Current endovascular management of acute type B aortic dissection - whom should we treat and when? *J Cardiovasc Surg* (Torino) 2014; **55**: 491-496 [PMID: 24941236]
37 **Nienaber CA**, Rousseau H, Eggebrecht H, Kische S, Fattori R, Rehders TC, Kundt G, Scheinert D, Czerny M, Kleinfeldt T, Zipfel B, Labrousse L, Ince H. Randomized comparison of strategies for type B aortic dissection: the INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) trial. *Circulation* 2009; **120**: 2519-2528 [PMID: 19996018 DOI: 10.1161/CIRCULATIONAHA.109.886408]
38 **Kwolek CJ**, Watkins MT. The INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) trial: the need for ongoing analysis. *Circulation* 2009; **120**: 2513-2514 [PMID: 19996013 DOI: 10.1161/CIRCULATIONAHA.109.911883]
39 **Nienaber CA**, Kische S, Rousseau H, Eggebrecht H, Rehders TC, Kundt G, Glass A, Scheinert D, Czerny M, Kleinfeldt T, Zipfel B, Labrousse L, Fattori R, Ince H. Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv* 2013; **6**: 407-416 [PMID: 23922146 DOI: 10.1161/CIRCINTERVENTIONS.113.000463]
40 **Davies RR**, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg* 2002; **73**: 17-27; discussion 27-28 [PMID: 11834007 DOI: 10.1016/S0003-4975(01)03236-2]
41 **Mastracci TM**, Greenberg RK. Follow-up paradigms for stable aortic dissection. *Semin Vasc Surg* 2009; **22**: 69-73 [PMID: 19573744 DOI: 10.1053/j.semvascsurg.2009.04.007]
42 **Shores J**, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994; **330**: 1335-1341 [PMID: 8152445 DOI: 10.1056/NEJM199405123301902]
43 **Nienaber CA**, Eagle KA. Aortic dissection: new frontiers in diagnosis and management: Part I: from etiology to diagnostic strategies. *Circulation* 2003; **108**: 628-635 [PMID: 12900496 DOI: 10.1161/01.CIR.0000087009.16755.E4]

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MINIREVIEWS

From hypertension to heart failure

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Abstract

Hypertension is an increasing health problem worldwide especially among the elderly. Its therapeutical importance is indicated by the caused organ damages like hypertensive heart disease (HHD) and heart failure with the subsequent higher morbidity and mortality in the population. In HHD ventricular hypertrophy develops as a compensatory mechanism for pressure overload but as the left ventricular compliance decreases, the process can transform into heart failure with firstly preserved and then into reduced ejection fraction (HFpEF, HFrEF). The main characteristics of underlying mechanisms involve cardiomyocyte growth, vessel changes, increased collagen production in all of which several mechanical stress induced neurohumoral agents, signal transduction pathways are involved. According to the new ESC and AHA guidelines five main groups of antihypertensive agents can be applied for decreasing blood pressure and for the prevention of organ damages. Occasionally, patients are not able to tolerate antihypertensive medication because of side effects, drug intolerance or interactions thus it is more difficult to reach the target blood pressure values. Therefore there are several efforts to complete the existing therapeutical possibilities against the development of organ damages like inhibition of Rho/ROCK pathway (*e.g.*, statins), regulation of ROS formation, influence on mitochondrial biogenesis and enhancing recombinant adenovirus hepatocyte growth factor gene. Hypertension induced oxidative stress causes DNA breaks producing the activation of nuclear poly(ADP-ribose) polymerase-1 (PARP) enzyme that leads to energy depletion and unfavorable modulation of different kinase cascades. PARP activation promotes the development of HHD, and its transition to heart failure. Therefore inhibition of PARP-enzyme offers another new therapeutical approach among hypertensive patients. The purpose of this review is to give a comprehensive summary about the most significant mechanisms in HHD and an insight into new potential therapies.

Key words: Hypertension; Hypertensive heart disease; HfpEF; Organ damage; PARP-inhibition

Core tip: There is numerous literature dealing with hypertensive heart disease and its therapeutical opportunities. In our work we have tried to combine clinical aspects with experimental data, which represent the future scope of the therapeutical opportunities in the prevention of organ damages not only *via* antihypertensive effect.

Magyar K, Gal R, Riba A, Habon T, Halmosi R, Toth K. From hypertension to heart failure. *World J Hypertens* 2015; 5(2): 85-92 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i2/85.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i2.85

INTRODUCTION

Hypertension is a major public health problem associated with high cardiovascular morbidity and mortality. Generally the prevalence of high blood pressure appears to be around 30%-45% in the whole population, which shows a higher prevalence with ageing. In case of adults, hypertension is defined as a systolic blood pressure of at least 140 mmHg and a diastolic of 90 mmHg according to the various guidelines (*e.g.*, the new ESH/ESC guideline). However, there are some subgroups of patients in whom the goal blood pressure is different. For instance, the elderly can benefit from lowering systolic blood pressure only to between 140 and 150 mmHg. In diabetic patients, however, the target blood pressure is lower than in the general population. In these patients the diastolic blood pressure should be less than 85 mmHg. According to the concept of J-curve hypothesis, it can be harmful to reduce both systolic and diastolic blood pressure to markedly low values.

Hypertension is an important risk factor of cardiovascular diseases, stroke, renal disease and peripherial artery disease[1]. According to epidemiological data, hypertensive heart disease (HHD) is one of the most important hypertensive organ damage. The most common consequences of HHD are heart failure, ischemic heart disease and arrhythmias. The Framingham Heart Study showed that 20 mmHg elevation of systolic blood pressure is associated with 50% increased risk of heart failure[2]. Hypertension is of course not the sole factor contributing to the development of heart failure but multi-variate analysis using time-dependent modelling revealed that myocardial infarction conferred the greatest risk of developing heart failure. As a consequence of its high prevalence, hypertension carried the greatest population-attributable risk[3]. Thus blood pressure lowering (antihypertensive therapy) markedly reduces the incidence of major cardiovascular (CV) events like HHD and heart failure[4].

Registries proved that nearly half of the patients with heart failure have a preserved ejection fraction (HfpEF). HFpEF is most common among the elderly, women and patients with left ventricular hypertrophy[5].

DEVELOPMENT OF HHD

Hypertensive heart disease encompasses a wide spectrum including asymptomatic cardiac hypertrophy and clinical heart failure (with either preserved or reduced ejection fraction). Elevated blood pressure changes the structure and function of blood vessels and left ventricle. These alterations are also known as remodeling, which is an adaptive mechanism in response to long-term changes in hemodynamic conditions, but it may also subsequently contribute to the pathophysiology of circulatory disorders[6,7].

Alterations in left ventricle, for instance hypertrophy and ischemia, predispose to heart failure in hypertensive patients. Cardiac hypertrophy is an adaptive response, a compensatory mechanism to pressure or volume overload directing to the attenuation of wall tension and the maintenance of cardiac output. The left ventricle mass can increase either as a result of wall thickening or ventricular dilation. The relative wall thickness (the ratio of the left ventricular wall thickness to diastolic diameter) determines the type of hypertrophy (eccentric or concentric). It is influenced by the type of overload (pressure or volume), by the neurohormonal activation (plasma renin level), extracellular matrix changes, concomitant diseases (coronary artery disease, diabetes mellitus, obesity), demographic and genetic factors (*e.g.*, ACE gene polymorphism)[7,8].

Sustained hypertrophy is often the initial step towards the progression of congestive heart failure[7].

It is now well known that symptomatic heart failure can occur either in the setting of reduced (HFrEF) or preserved ejection fraction (HFpEF)[9]. The classic course of HHD progression is a so-called "burned-out" of left ventricle in which hypertension leads to concentric hypertrophy followed by diastolic and finally systolic insufficiency[10].

In an other group of hypertensive patients the development of myocardial infarction causes directly systolic heart failure (HFrEF) independently from hypertrophy[8] (Figure 1).

HISTOLOGY

High blood pressure caused alterations in cardiac structure and function, eventually resulting in impaired myocardial performance, coronary haemodynamics and apoptosis.

It has been well established that pathogenesis of HHD involves all components of the heart, including myocytes and non-myocytic cells, such as fibroblasts and endothelial cells, extracellular matrix proteins, fibrillar collagen, and coronary vessels[11].

Structural remodeling of HHD is characterized by enlarged cardiac myocytes with altered energy metabolism, fibroblast proliferation and activation, fibroblast-myofibroblast transformation and excessive collagen deposition, which all lead to a more rigid myocardium[12,13]. Coronary resistance vessels are also affected, perivascular fibrosis of intramyocardial coronary arteries and arterioles produce intimal-medial thickening[14].

NEUROHUMORAL MECHANISMS

The remodeling and growth regulation of the heart involve several mechanisms including neurogenic, humoral, autocrine and paracrine factors.

The activation of renin-angiotensin-aldosterone

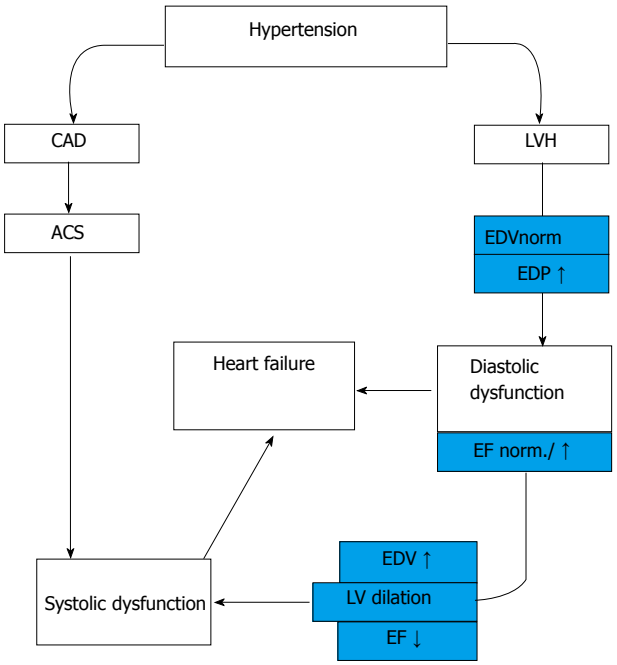

Figure 1 Development of hypertensive heart disease. HT: Hypertension; LVH: Left ventricle hypertrophy; EDV: End-diastolic volume; EDP: End-diastolic pressure; EF: Ejection fraction; CAD: Coronary artery disease; ACS: Acut coronary syndrome.

system (RAAS) is one of the most important processes, which contribute to the development of hypertension including vasoconstriction, generation of reactive oxygen species (ROS), vascular inflammation, vascular and cardiac remodeling (hypertrophy and fibrosis). Therefore the RAAS system plays a prominent part in accelerating hypertensive organ damages[15,16]. Moreover angiotensin converting enzyme (ACE) is responsible for the production of angiotensin Ⅱ (Ang Ⅱ), which correlates to left ventricle hypertrophy. Individuals have different plasma ACE concentrations due to the insertion/deletion polymorphism of ACE gene, which also shows a close relationship to ventricular hypertrophy[12].

Mineralocorticoids have a physiological role in volume regulation, but they also activate the sympathetic nervous system (SNS), which results in baroreceptor dysfunction, impaired arterial compliance and marked myocardial and vascular fibrosis[17].

The sympathetic hyperactivity rises blood pressure directly (even without RAAS activation), possesses metabolic effects (*e.g.*, insulin resistance) and facilitates the development of LVH.

It has been well established that pathogenesis of cardiac remodeling is also associated with insulin resistance, increased activity of insulin-like growth factor-1 and myocardial pro-fibrotic matricellular protein osteopontin, thyroid hormons and the elevated level of brain and atrial natriuretic peptides[12].

STRESS-INDUCED SIGNALING PATHWAYS

It is well known that hypertension induced oxidative stress plays an important role in the development of cardiac injury. Potential sources of ROS are the NADPH oxidases, nitric oxide synthase, lipoxygenases, cyclo-oxygenases, xanthine oxidase, cytochrome P450 enzymes, and the mitochondrial respiratory chain[18]. ROS mediated damages are implicated in endothelial dysfunction, inflammation, hypertrophy, apoptosis, cell migration, fibrosis and angiogenesis[19]. ROS impair the function of ion-channels and decrease the amount of high energy phosphates. These changes can result in alterations of myocyte and smooth muscle cell calcium homeostasis leading to increased cell proliferation[20]. Oxidative stress can lead to single stranded DNA breaks and changes in signaling pathways evolving alterations in LV structural and mechanical properties[21].

The single stranded DNA breaks provoke the activation of nuclear poly(ADP-ribose) polymerase-1 (PARP) enzyme, which can decrease the cellular NAD^+ and ATP pools leading to energy depletion with inadequate glycolysis and mitochondrial respiration, promoting apoptotic or necrotic cell death[21-25].

The activation of PARP-enzyme has a central role in the pathophysiology of several cardiovascular diseases including the development of HHD, transition of HHD to HF by influencing collagen production *via* modulation of different kinase cascades[21,22]. Cellular adaptations of the heart are typically initiated by stress responsive signaling pathways, which serve as central transducers of cardiac hypertrophic growth and/or ventricular dilation.

These signaling pathways include extracellular signal-regulated protein kinases (ERK), p38 mitogen-activated protein kinases (p38-MAPK), c-Jun NH2-terminal kinases (JNK), several protein kinase C (*e.g.*, PKC delta and epsilon) isoforms and Akt-1/glycogen synthase kinase-3b (GSK-3β) signaling cascade. These cascades have also been implicated in affecting the decision of myocytes to either survive (Akt-1/GSK-3β, ERK, PKCepsilon, JAK) or undergo programmed cell death (p38 MAPK, PKC delta, JNK)[20-22] (Figure 2).

It has been observed that RhoA/ROCK pathway is also involved in hypertension and in the development of consequent cardiac hypertrophy. It has a close relationship to Ang Ⅱ, which can increase ROCK activity and contributes to the maintenance of hypertension, to the increased medial thickness and perivascular fibrosis in coronary arteries[26]. This mechanism also affects stretch-induced ERK activation and vascular smooth muscle cell growth[27].

TREATMENT STRATEGIES IN HYPERTENSION

The main goal of antihypertensive therapy is the prevention of organ damages thus the prevention of life-threatening consequences such as stroke, myocardial infarction HHD or heart failure[1]. Although previous clinical trials focused mainly on improving mortality in HF, nowadays it is recognized that preventing heart failure is better for the patients and financially it is cost-

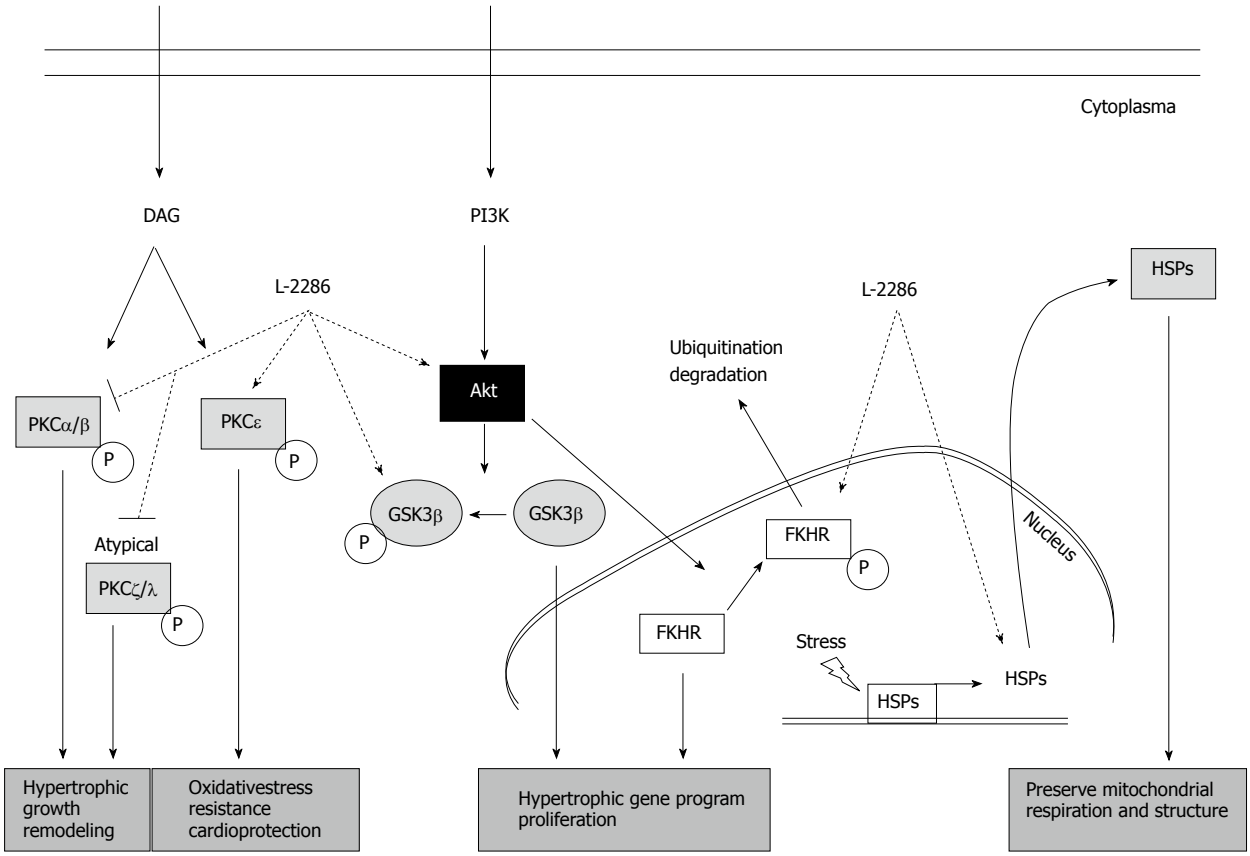

Figure 2 Summary of protein kinase C and Akt-1/GSK-3β signal pathway and the alterations due to poly(ADP-ribose) polymerase-1 inhibition (22 with permission of Deres L and the authors). DAG: Diacylglycerol; FKHR: Forkhead transcription factor; GSK-3β: Glycogen synthase kinase-3 β; HSP: Heat shock protein; PARP: Poly(ADP-ribose) polymerase-1; PI3K: Phosphatidylinositide 3-kinase; PKC: Protein kinase C.

effective for the health care system. It is well-known that effective antihypertensive therapy reduces the incidence of heart failure by more than fifty percent[28].

Based on current guidelines, the cornerstones of antihypertensive pharmacological therapy are diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and calcium antagonists (CA)[29].

Blocking sympathetic hyperactivity is thought to be an essential tool in the treatment of CV diseases. Besides the blood pressure lowering effect of beta-blockers, they are able to reduce sympathetic overactivation. Moreover, they reverse left ventricular remodeling and can decrease the incidence of heart failure. Among diuretics, the thiazides mean the first line of choice because of efficacy and price. They are recommended in left ventricular hypertrophy, and can reduce cardiovascular morbidity and mortality.

ARBs and especially ACE-inhibitors significantly decrease all cause mortality in patients with hypertension. ACE-I can both prevent developing HF and decrease LV and vascular wall remodeling. A large body of evidence suggests that all of these are induced by the downregulation of enzymatic pathways involved in the interstitial collagen formation. CA effectively reduce blood pressure by dilating arteries with decreasing Ca(2+) influx into smooth muscle cells of the arterial wall. They can be used in combination therapy with most of the antihypertensive drugs. According to the statement of ESC and ESH, all above mentioned drugs are suitable for the initiation and maintenance of antihypertensive treatment because the main benefits of these drugs are due to the lowering of BP *per se* and are largely independent of the drugs employed[28].

NEW THERAPEUTIC POSSIBILITIES IN HYPERTENSION

Although there is an increasing number of effective antihypertensive drugs that can be used in the clinical practice, there are many patients who can not reach the goal blood pressure. In the United States, there are approximately 70 million hypertensive patients and about 40 million of them do not have their blood pressure under proper control. The main factors in the background of this phenomenon are side effects, drug intolerance or interactions and therefore poor adherence of patients to the prescribed medication[29]. Therefore in the last several years experimental researches tried to focus on treatments that alleviate end-organ damage itself without lowering blood pressure.

This approach is supported firstly by large trials with statin therapy. The main role of statins was the prevention

of coronary artery disease, myocardial infarction and other adverse cardiovascular events. Statins possess both lipid-dependent and lipid independent effects. They are able to lessen inflammation, improve endothelial function and decrease thrombogenicity[30].

In the background of the favorable pleiotropic effects of statins, we need to mention the modulation of intracellular pathways, involved in cell growth regulation/apoptosis and gene expression (Ras, Rac, Rab and Rho)[30,31]. It has already been demonstrated primarily in experimental but also in human studies that high dose atorvastatin inhibits the synthesis of isoprenoids, which are functionally important in the Rho/Rho-associated coiled-coil containing kinase (ROCK) pathway[30]. Moreover, the inhibition of Rho/ROCK pathway by statins may cause improvement in endothelial function and decrease vascular inflammation and atherosclerosis. The localization of these proteins has been shown in vascular smooth muscle cells but their role needs to be determined in the context of atherosclerosis. These findings open an option for specific ROCK1 or ROCK2 inhibitors, which could have greater therapeutic effect with less toxicity[30]. Furthermore, statins decrease the number of angiotensin-1 receptors through RhoA, Ras, Rac1 and the Rho/kinase system, which regulates the ROS formation through NADPH oxidase[32].

The ASCOT-LLA study revealed the role of statins in the prevention of CV events among hypertensive patients[33,34]. Large clinical trials demonstrated that statin therapy may provide clinical benefits to patients with heart failure. Analysis of the Daunia Heart Failure Registry in 2013 elucidated that treatments with atorvastatin are associated with fewer cardiac deaths and better left ventricular performance[35,36].

Mitochondrial dysfunction also seems to be an important factor in the development of HHD[29,37,38]. Another therapeutic strategy can be the stimulation of mitochondrial biogenesis through the AMPK or the eNOS/Nitric Oxide/Cyclic Guanosine Monophosphate pathway[37-43]. Resveratrol, which has a well-known positive effect in the prevention of cardiovascular diseases, is a potent stimulator of the mitochondrial biogenesis[44-49]. An other way is to augment the mitochondrium against oxidative stress. ACE-I and ATII receptor blockers, which are originally antihypertensive drugs, bear antioxidant properties beside blood pressure lowering effect. However, it is not clear whether they target mitochondrial reactive oxygen species (ROS) formation directly or indirectly[50,51]. Thirdly, regulating mitochondrial iron homeostasis and reducing mitochondrial iron content may also yield to cardioprotection because of inhibition of hydroxyl radical formation and mitigation of oxidative stress[36].

There is an expanding number of evidence that the previously mentioned resveratrol significantly attenuates the development of cardiac dysfunction[52]. This ability is already proved in spontaneously hypertensive rats (SHR), transverse aortic constricted rats (TAC), models of hypertension and pressure overload-induced heart failure. Although resveratrol alone does not have any systolic or diastolic blood pressure lowering effect, in TAC rats resveratrol markedly increased glutathione, sodium oxide dismutase 2 levels and decreased 4-hydroxy-2-nonenal - a marker of lipid peroxidation - and LV macrophage and mast cell infiltration. Furthermore, a combination of resveratrol with hydralazine treatment significantly reduced blood pressure, improved systolic and diastolic function, decreased fibrosis and improved vascular geometry. The low-dose resveratrol itself was unable to reach these favourable actions. However, resveratrol alone alleviated cardiac fibrosis and some of the functional abnormalities in SHRs[53].

The cardiomyocyte function enhancer ranolazine reduces myoplasmic free Ca(2+) during diastole at high-stimulus rates. Therefore ranolazine showed to be effective in reducing diastolic dysfunction with inhibition of the increased late sodium current in the SHR leading to reduced Ca(2+) overload[54].

Hu *et al*[55] found that HGF expression is attenuated in hypertrophic and fibrotic myocardium of spontaneolusly hypertensive rats (SHR) and injected recombinant adenovirus hepatocyte growth factor gene (Ad-HGF gene) in the left ventricular free wall. The upregulation of myocardial HGF expression in SHR animals significantly suppressed myocardial fibrosis, collagen I content, LVMI, LVEDP, and increased -dP/dt_{max} value[55].

In the last decade PARP inhibitors received growing attention. Although they do not have any antihypertensive effect, our workgroup demonstrated that an isoquinoline derivative PARP-inhibitor, *i.e.*, L-2286 has beneficial effects against oxidative cell damage, ischemia-reperfusion injury and the development of postinfarction, or long-term high blood pressure-induced heart failure in hypertensive animals (SHR)[21,22,25,56,57]. The PARP-inhibitor treatment significantly decreased the collagen deposition in the myocardium thus with echocardiography less prominent septal and posterior wall thickness could be measured. Moreover, in old SHR animals the transition of already developed HHD into manifest heart failure was also blocked by pharmacological PARP-inhibition. In an other long-term experiment, PARP-inhibitors decreased also the hypertensive remodeling of the great vessels in spontaneously hypertensive rats. Our experimental data also proved that the influence on the Akt-1/GSK-3β, MAPKs, MKP-1 and PKC pathways could be the underlying mechanism behind the PARP-inhibition[21,22,25,56,57].

The concept that it is possible to prevent organ damages without blood pressure lowering effect in hypertension is very promising since the goal blood pressure can not be reached in a high number of patients. This is why PARP-inhibitor co-administration could give us a potential new therapeutical approach beside the antihypertensive therapy to prevent hypertension induced

organ damages.

CONCLUSION

Although several effective novel and modern anti-hypertensive therapies were introduced in the last decade, hypertension caused organ damages, especially HHD and heart failure, remain a leading cause of morbidity and mortality in hypertensive patients. That is the reason for the growing number of researches trying to focus on treatments that alleviate end-organ damage itself even without lowering blood pressure. Several drugs, like statins or PARP-inhibitors exert beneficial effect on intracellular signaling, and could be an important part of the treatment of hypertensive patients in the future.

REFERENCES

1 **Mancia G**, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; **34**: 2159-2219 [PMID: 23771844 DOI: 10.1093/eurheartj/eht151]

2 **Haider AW**, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2003; **138**: 10-16 [PMID: 12513039]

3 **Levy D**, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996; **275**: 1557-1562 [PMID: 8622246]

4 **ALLHAT Collaborative Research Group**. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000; **283**: 1967-1975 [PMID: 10789664]

5 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

6 **Gibbons GH**, Dzau VJ. The emerging concept of vascular remodeling. *N Engl J Med* 1994; **330**: 1431-1438 [PMID: 8159199]

7 **Kokubo M**, Uemura A, Matsubara T, Murohara T. Noninvasive evaluation of the time course of change in cardiac function in spontaneously hypertensive rats by echocardiography. *Hypertens Res* 2005; **28**: 601-609 [PMID: 16335889]

8 **Drazner MH**. The progression of hypertensive heart disease. *Circulation* 2011; **123**: 327-334 [PMID: 21263005 DOI: 10.1161/CIRCULATIONAHA.108.845792]

9 **Bursi F**, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. *JAMA* 2006; **296**: 2209-2216 [PMID: 17090767]

10 **Meerson FZ**. Compensatory hyperfunction of the heart and cardiac insufficiency. *Circ Res* 1962; **10**: 250-258 [PMID: 14472098]

11 **Susic D**, Varagic J, Ahn J, Matavelli L, Frohlich ED. Long-term mineralocorticoid receptor blockade reduces fibrosis and improves cardiac performance and coronary hemodynamics in elderly SHR. *Am J Physiol Heart Circ Physiol* 2007; **292**: H175-H179 [PMID: 16905598]

12 **Lip GY**, Felmeden DC, Li-Saw-Hee FL, Beevers DG. Hypertensive heart disease. A complex syndrome or a hypertensive 'cardiomyopathy'? *Eur Heart J* 2000; **21**: 1653-1665 [PMID: 11032692]

13 **Levick S**, Loch D, Rolfe B, Reid RC, Fairlie DP, Taylor SM, Brown L. Antifibrotic activity of an inhibitor of group IIA secretory phospholipase A2 in young spontaneously hypertensive rats. *J Immunol* 2006; **176**: 7000-7007 [PMID: 16709861]

14 **Schwartzkopff B**, Frenzel H, Dieckerhoff J, Betz P, Flasshove M, Schulte HD, Mundhenke M, Motz W, Strauer BE. Morphometric investigation of human myocardium in arterial hypertension and valvular aortic stenosis. *Eur Heart J* 1992; **13** Suppl D: 17-23 [PMID: 1396854]

15 **Sun Y**, Weber KT. Angiotensin II and aldosterone receptor binding in rat heart and kidney: response to chronic angiotensin II or aldosterone administration. *J Lab Clin Med* 1993; **122**: 404-411 [PMID: 8228554]

16 **Ronald GV.** Systemic hypertension: Mechanisms and diagnosis. Braunwald's heart disease. Textbook of cardiovascular medicine. Eds Bonow OR. Philadelphia: Elservier Saunders, 2012: 935-954

17 **MacFadyen RJ**, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. *Cardiovasc Res* 1997; **35**: 30-34 [PMID: 9302344]

18 **Puddu P**, Puddu GM, Cravero E, Rosati M, Muscari A. The molecular sources of reactive oxygen species in hypertension. *Blood Press* 2008; **17**: 70-77 [PMID: 18568695 DOI: 10.1080/08037050802029954]

19 **Csiszar A**, Pacher P, Kaley G, Ungvari Z. Role of oxidative and nitrosative stress, longevity genes and poly(ADP-ribose) polymerase in cardiovascular dysfunction associated with aging. *Curr Vasc Pharmacol* 2005; **3**: 285-291 [PMID: 16026324]

20 **Bendhack LM**, Sharma RV, Bhalla RC. Altered signal transduction in vascular smooth muscle cells of spontaneously hypertensive rats. *Hypertension* 1992; **19**: II142-II148 [PMID: 1310480]

21 **Bartha E**, Solti I, Kereskai L, Lantos J, Plozer E, Magyar K, Szabados E, Kálai T, Hideg K, Halmosi R, Sumegi B, Toth K. PARP inhibition delays transition of hypertensive cardiopathy to heart failure in spontaneously hypertensive rats. *Cardiovasc Res* 2009; **83**: 501-510 [PMID: 19443425 DOI: 10.1093/cvr/cvp144]

22 **Deres L**, Bartha E, Palfi A, Eros K, Riba A, Lantos J, Kalai T, Hideg K, Sumegi B, Gallyas F, Toth K, Halmosi R. PARP-inhibitor treatment prevents hypertension induced cardiac remodeling by favorable modulation of heat shock proteins, Akt-1/GSK-3β and several PKC isoforms. *PLoS One* 2014; **9**: e102148 [PMID: 25014216 DOI: 10.1371/journal.pone.0102148]

23 **Pacher P**, Szabó C. Role of poly(ADP-ribose) polymerase 1 (PARP-1) in cardiovascular diseases: the therapeutic potential of PARP inhibitors. *Cardiovasc Drug Rev* 2007; **25**: 235-260 [PMID: 17919258]

24 **Baines CP**, Molkentin JD. STRESS signaling pathways that modulate cardiac myocyte apoptosis. *J Mol Cell Cardiol* 2005; **38**: 47-62 [PMID: 15623421]

25 **Palfi A**, Toth A, Hanto K, Deres P, Szabados E, Szereday Z, Kulcsar G, Kalai T, Hideg K, Gallyas F, Sumegi B, Toth K, Halmosi R. PARP inhibition prevents postinfarction myocardial remodeling and heart failure via the protein kinase C/glycogen synthase kinase-3beta pathway. *J Mol Cell Cardiol* 2006; **41**: 149-159 [PMID: 16716347]

26 **Kataoka C**, Egashira K, Inoue S, Takemoto M, Ni W, Koyanagi M, Kitamoto S, Usui M, Kaibuchi K, Shimokawa H, Takeshita A. Important role of Rho-kinase in the pathogenesis of cardiovascular inflammation and remodeling induced by long-term blockade of nitric oxide synthesis in rats. *Hypertension* 2002; **39**: 245-250 [PMID: 11847192]

27 **Zeidan A**, Nordström I, Albinsson S, Malmqvist U, Swärd K, Hellstrand P. Stretch-induced contractile differentiation of vascular smooth muscle: sensitivity to actin polymerization inhibitors. *Am J Physiol Cell Physiol* 2003; **284**: C1387-C1396 [PMID: 12734104]

28 **McMurray JJ**, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787-1847 [PMID: 22611136 DOI: 10.1093/eurheartj/ehs104]

29 **Ong KL**, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007; **49**: 69-75 [PMID: 17159087]

30 **Sawada N**, Liao JK. Rho/Rho-associated coiled-coil forming kinase pathway as therapeutic targets for statins in atherosclerosis. *Antioxid Redox Signal* 2014; **20**: 1251-1267 [PMID: 23919640 DOI: 10.1089/ars.2013.5524]

31 **Nohria A**, Prsic A, Liu PY, Okamoto R, Creager MA, Selwyn A, Liao JK, Ganz P. Statins inhibit Rho kinase activity in patients with atherosclerosis. *Atherosclerosis* 2009; **205**: 517-521 [PMID: 19167712 DOI: 10.1016/j.atherosclerosis.2008.12.023]

32 **Nickenig G**. Should angiotensin II receptor blockers and statins be combined? *Circulation* 2004; **110**: 1013-1020 [PMID: 15326080]

33 **Osende JI**, Ruiz-Ortega M, Blanco-Colio LM, Egido J. Statins to prevent cardiovascular events in hypertensive patients. The ASCOT-LLA study. *Nephrol Dial Transplant* 2004; **19**: 528-531 [PMID: 14767002]

34 **O'Driscoll G**, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997; **95**: 1126-1131 [PMID: 9054840]

35 **Correale M**, Totaro A, Passero T, Abruzzese S, Musaico F, Ferraretti A, Ieva R, Di Biase M, Brunetti ND. Treatment with atorvastatin is associated with a better prognosis in chronic heart failure with systolic dysfunction: results from The Daunia Heart Failure Registry. *Neth Heart J* 2013; **21**: 408-416 [PMID: 23712465 DOI: 10.1007/s12471-013-0430-y]

36 **Bayeva M**, Gheorghiade M, Ardehali H. Mitochondria as a therapeutic target in heart failure. *J Am Coll Cardiol* 2013; **61**: 599-610 [PMID: 23219298 DOI: 10.1016/j.jacc.2012.08.1021]

37 **Balligand JL**, Feron O, Dessy C. eNOS activation by physical forces: from short-term regulation of contraction to chronic remodeling of cardiovascular tissues. *Physiol Rev* 2009; **89**: 481-534 [PMID: 19342613 DOI: 10.1152/physrev.00042.2007]

38 **Manoury B**, Montiel V, Balligand JL. Nitric oxide synthase in post-ischaemic remodelling: new pathways and mechanisms. *Cardiovasc Res* 2012; **94**: 304-315 [PMID: 22227153 DOI: 10.1093/cvr/cvr360]

39 **Clementi E**, Nisoli E. Nitric oxide and mitochondrial biogenesis: a key to long-term regulation of cellular metabolism. *Comp Biochem Physiol A Mol Integr Physiol* 2005; **142**: 102-110 [PMID: 16091305]

40 **Miyashita K**, Itoh H, Tsujimoto H, Tamura N, Fukunaga Y, Sone M, Yamahara K, Taura D, Inuzuka M, Sonoyama T, Nakao K. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. *Diabetes* 2009; **58**: 2880-2892 [PMID: 19690065 DOI: 10.2337/db09-0393]

41 **Nisoli E**, Clementi E, Tonello C, Sciorati C, Briscini L, Carruba MO. Effects of nitric oxide on proliferation and differentiation of rat brown adipocytes in primary cultures. *Br J Pharmacol* 1998; **125**: 888-894 [PMID: 9831929]

42 **Nisoli E**, Clementi E, Paolucci C, Cozzi V, Tonello C, Sciorati C, Bracale R, Valerio A, Francolini M, Moncada S, Carruba MO. Mitochondrial biogenesis in mammals: the role of endogenous nitric oxide. *Science* 2003; **299**: 896-899 [PMID: 12574632]

43 **De Toni L**, Strapazzon G, Gianesello L, Caretta N, Pilon C, Bruttocao A, Foresta C. Effects of type 5-phosphodiesterase inhibition on energy metabolism and mitochondrial biogenesis in human adipose tissue ex vivo. *J Endocrinol Invest* 2011; **34**: 738-741 [PMID: 22234177]

44 **Lagouge M**, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell* 2006; **127**: 1109-1122 [PMID: 17112576]

45 **Takahashi S**, Nakashima Y. Repeated and long-term treatment with physiological concentrations of resveratrol promotes NO production in vascular endothelial cells. *Br J Nutr* 2012; **107**: 774-780 [PMID: 21791144 DOI: 10.1017/S0007114511003588]

46 **Zang M**, Xu S, Maitland-Toolan KA, Zuccollo A, Hou X, Jiang B, Wierzbicki M, Verbeuren TJ, Cohen RA. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor-deficient mice. *Diabetes* 2006; **55**: 2180-2191 [PMID: 16873680]

47 **Thandapilly SJ**, Wojciechowski P, Behbahani J, Louis XL, Yu L, Juric D, Kopilas MA, Anderson HD, Netticadan T. Resveratrol prevents the development of pathological cardiac hypertrophy and contractile dysfunction in the SHR without lowering blood pressure. *Am J Hypertens* 2010; **23**: 192-196 [PMID: 19942861 DOI: 10.1038/ajh.2009.228]

48 **Biala A**, Tauriainen E, Siltanen A, Shi J, Merasto S, Louhelainen M, Martonen E, Finckenberg P, Muller DN, Mervaala E. Resveratrol induces mitochondrial biogenesis and ameliorates Ang II-induced cardiac remodeling in transgenic rats harboring human renin and angiotensinogen genes. *Blood Press* 2010; **19**: 196-205 [PMID: 20429690]

49 **Rimbaud S**, Ruiz M, Piquereau J, Mateo P, Fortin D, Veksler V, Garnier A, Ventura-Clapier R. Resveratrol improves survival, hemodynamics and energetics in a rat model of hypertension leading to heart failure. *PLoS One* 2011; **6**: e26391 [PMID: 22028869 DOI: 10.1371/journal.pone.0026391]

50 **Yamazaki T**, Tanimoto M, Gohda T, Ohara I, Hagiwara S, Murakoshi M, Matsumoto M, Kaneko S, Aoki T, Toyoda H, Ishikawa Y, Funabiki K, Horikoshi S, Tomino Y. Combination effects of enalapril and losartan on lipid peroxidation in the kidneys of KK-Ay/Ta mice. *Nephron Exp Nephrol* 2009; **113**: e66-e76 [PMID: 19609084 DOI: 10.1159/000228714]

51 **Goyal BR**, Mehta AA. Beneficial role of spironolactone, telmisartan and their combination on isoproterenol-induced cardiac hypertrophy. *Acta Cardiol* 2012; **67**: 203-211 [PMID: 22641978]

52 **Tang PC**, Ng YF, Ho S, Gyda M, Chan SW. Resveratrol and cardiovascular health - Promising therapeutic or hopeless illusion? *Pharmacol Res* 2014; **90C**: 88-115 [PMID: 25151891 DOI: 10.1016/j.phrs.2014.08.001]

53 **Thandapilly SJ**, Louis XL, Behbahani J, Movahed A, Yu L, Fandrich R, Zhang S, Kardami E, Anderson HD, Netticadan T. Reduced hemodynamic load aids low-dose resveratrol in reversing cardiovascular defects in hypertensive rats. *Hypertens Res* 2013; **36**: 866-872 [PMID: 23784505 DOI: 10.1038/hr.2013.55]

54 **Williams S**, Pourrier M, McAfee D, Lin S, Fedida D. Ranolazine improves diastolic function in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 2014; **306**: H867-H881 [PMID:

24464752 DOI: 10.1152/ajpheart.00704.2013]
55 **Hu ZP**, Bao Y, Chen DN, Cheng Y, Song B, Liu M, Li D, Wang BN. Effects of recombinant adenovirus hepatocyte growth factor gene on myocardial remodeling in spontaneously hypertensive rats. *J Cardiovasc Pharmacol Ther* 2013; **18**: 476-480 [PMID: 23739651 DOI: 10.1177/1074248413490832]
56 **Magyar K**, Deres L, Eros K, Bruszt K, Seress L, Hamar J, Hideg K, Balogh A, Gallyas F, Sumegi B, Toth K, Halmosi R. A quinazoline-derivative compound with PARP inhibitory effect suppresses hypertension-induced vascular alterations in spontaneously hypertensive rats. *Biochim Biophys Acta* 2014; **1842**: 935-944 [PMID: 24657811 DOI: 10.1016/j.bbadis.2014.03.008]
57 **Bartha E**, Solti I, Szabo A, Olah G, Magyar K, Szabados E, Kalai T, Hideg K, Toth K, Gero D, Szabo C, Sumegi B, Halmosi R. Regulation of kinase cascade activation and heat shock protein expression by poly(ADP-ribose) polymerase inhibition in doxorubicin-induced heart failure. *J Cardiovasc Pharmacol* 2011; **58**: 380-391 [PMID: 21697725 DOI: 10.1097/FJC.0b013e318225c]

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MINIREVIEWS

Clinical implication of hematological indices in the essential hypertension

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Abstract

Prognostic value of haematological indices, especially red cell distribution width, neutrophil lymphocyte ratio and mean platelet volume, was reported with numerous investigations in miscellaneous cardiovascular settings. Their major prognostic value was linked to oxidative stress and inflammation since their level was correlated with major inflammatory markers such as high sensitive C-reactive protein and interleukins. Oxidative stress and chronic inflammation are also postulated as the main pathophysiologic mechanism of essential hypertension (HT) and its vascular complication. Recently, correlation between HT and haematological parameters was searched in numerous studies, which has made the topic more popular. Herein, we reveal the correlation between haematological indices and HT and we also demonstrate the clinical implication of this correlation. Impaired haematological parameters may strongly indicate hypertensive end-organ damage.

Key words: Hypertension; Inflammation; End-organ damage; Haematological indice; Platelet activation

Core tip: We demonstrated the correlation between haematological indices, particularly red cell distribution width, neutrophil lymphocyte ratio and mean platelet volume, and hypertension and we also clarified the clinical implication of the haematological markers in hypertensive end-organ failure. Impaired haematological parameters may strongly indicate the hypertensive end-organ damage.

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INTRODUCTİON

Systemic arterial hypertension (HT) is a common health disorder with uncertain aetiology and pathophysiology.

It affects 20%-30% of the adult population and it can lead to severe end-organ damage and clinical manifestation, including coronary heart disease and stroke, which constitute the leading cause of mortality in the general population[1]. Beside genetic predisposition, several mechanisms were proposed to clarify the pathophysiology of essential HT[1-3]. Vascular reactivity and endothelial dysfunction, which result in increased peripheral vascular resistance, is one of the major hypotheses in the pathogenesis. Recently, it has become evident that the immune system and chronic inflammatory status may play a role in the pathogenesis of HT[2-5]. Many inflammatory markers, such as high sensitive c-reactive protein (hsCRP), cytokines, and adhesion molecules have been found elevated in HT, supporting the role of inflammation[2-6].

Haematological indices, particularly red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR) and mean platelet volume (MPV), were established as markers of systemic inflammation and vascular pathology[7-15]. Their prognostic value was clearly demonstrated in coronary artery disease, stroke and several other vascular diseases. Correlation of such haematological indices and HT was also investigated and it was proposed that haematological indices may predict the severity of HT and end-organ damage[16-22]. With this review, we aimed to show the place of haematological indices in the essential HT and demonstrate its clinical implication.

MECHANISM OF ESSENTIAL HT

The aetiology of essential HT is not clear, however, it has been accepted as a multifactorial disease arising from the combined action of many genetic, environmental and behavioural factors. Renal sodium retention, vascular hypertrophy, endothelial cell dysfunction, sympathetic nervous system hyperactivity, upregulation of the renin-angiotensin-aldosterone system, altered T-cell function, insulin resistance and dietary and habitual factors were postulated as common mechanisms of HT[1-5]. However, oxidative stress and inflammation seem to play a major role in the pathophysiology of HT and also concomitant end-organ damage[4-6]. Excessive reactive oxygen species generation decreases nitric oxide level, which predisposes to endothelial cell dysfunction. Enhanced oxidative stress reduces antioxidant capacity in the cardiovascular, renal and nervous systems. In the cardiovascular system, reactive oxygen radicals play a pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis, angiogenesis and rarefaction, which are important processes contributing to endothelial dysfunction and cardiovascular remodelling in HT[4-6]. Recently, the synergy of haematological indices and HT was searched in many HT-associated clinical conditions after clear demonstration of the correlation between haematological indices and endothelial cell dysfunction[16-22]. Non-dipper HT had carried about three times the risk of atherosclerotic cardiovascular events compared to the dipper group. The majority of the investigations focused on this specific non-dipping group, since atherotrombosis and inflammation was more prominent in this group[23-29].

RED BLOOD CELL INDICES

Red cell distribution width

Red cell distribution width is a measure of the variability in the circulating erythrocytes' size, which is usually used for haematological disorders. It can be obtained easily from a routine complete blood count in a short period. Although the initial application of RDW was the differential diagnosis of anaemia, recent investigation revealed that RDW is also an important prognostic factor in cardiovascular diseases[7-8]. It was proposed that there is a linkage between RDW and inflammatory and neurohormonal activation and also accelerated atherosclerotic process which may enhance the impact of RDW in the was cardiovascular diseases. Several mechanisms were proposed to explain the exact role of RDW in the clinical setting[7-8]. Inflammatory and neurohormonal activation could be one of the mechanistic links between elevated RDW and increased mortality. The correlation between elevated RDW and inflammatory markers such as B-type natriuretic peptide, sedimentation and white blood cells was established. Higher RDW may result from ineffective erythropoiesis due to chronic inflammation. Inflammatory cytokines have been found to suppress the maturation of erythrocytes, which enable juvenile red cells to enter into the circulation and increases the heterogeneity in size[30-31]. Moreover, elevated RDW may reflect enhanced erythropoiesis resulting from the circulating levels of neurohormonal mediators, which lead to an increment in the heterogeneity of circulating red cells. Elevated RDW levels were also associated with carotis intima-media thickness, which reflects atherosclerotic process[32]. Finally, all these mechanisms, including chronic inflammatory state, neurohormonal activation and accelerated atherosclerotic process, may contribute to adverse clinical outcomes and bad prognosis in the variety of cardiovascular diseases. Oxidative stress was proposed as another mechanism of the prognostic value of RDW. Red blood cells have powerful antioxidant capacity and serve as a primary oxidative sink. They are prone to oxidative damage, which reduces cell survival, and enhance the release of juvenile erythrocytes into the circulation. Elevated RDW levels were associated with poorer pulmonary function and progression of pulmonary HT, which reflect oxidative stress conditions[7].

The correlation between RDW and HT was also well established. Higher RDW values are strongly correlated with higher systolic and diastolic blood pressure[19-21]. Elevated levels of RDW were also documented in non-dipping HT, which are closely related to adverse

cardiovascular outcomes and higher inflammatory status[21,23]. Elevated levels of RDW were linked to hypertensive end-organ damage. Kilicaslan *et al*[16] showed that an elevated RDW level was associated with concentric left ventricular hypertrophy. It was speculated that the development of target organ damage in HT is accompanied by the increasing impairment of erytropoiesis by the mechanism of inflammation[23]. In patients with HT, RDW levels showed a significant relationship with inflammatory markers such as hsCRP, interleukin-6 and fibrinogen[16,18,33]. Elevated RDW was also correlated with pulse wave velocity and carotid intima media thickness[32]. In the HT group, RDW levels and glomerular filtration rate seemed to be linked[30]. Erythrocyte deformability may serve as a marker of endothelial dysfunction in the kidney, which may trigger nephropathy.

Hematocrit

Haematocrit is a determinant of whole blood viscosity. Viscosity affects peripheral resistance to blood flow, and peripheral resistance affects blood pressure[34]. Most hypertensive patients exhibit increased blood viscosity compared with healthy controls[35]. Although, the details of this association is unclear, reduction of the red cell deformability and an increase in the size, numbers and aggregability of red blood cells may worsen the microcirculation and enhance the end-organ damage. Therefore, the diameter of a red cell is about 8.5 micron, and that of the smallest capillaries about 3 micron, the deformability of the red cells plays an important role in capillary flow[36]. Decreased red cell deformability could cause an increased microvascular flow resistance, which may result in target organ damage. Haematocrit in upper quartiles may indicate end-organ damage in HT.

Mean corpuscular volume

Epidemiological studies show no relation with higher mean corpuscular volume (MCV) in hypertensive, whereas, some studies suggest that hypertensive patients have lower MCV. Decreased MCV levels may reflect higher blood viscosity, since a high red cell level may lead to down-regulation of MCV as an adaptive mechanism[34].

WHITE BLOOD CELL INDICES

White blood cells play a major role in both the initiation and progression of atherosclerosis and have been implicated in acute rupture of atherosclerotic plaques[37]. In addition, neutrophils aggregate with platelets to exacerbate vascular plugging in the microcirculation. Neutrophils also prompt the secretion of inflammatory mediators[38].

Neutrophil-lymphocyte ratio

The neutrophil-lymphocyte ratio is associated with a worse outcome in various diseases and is defined as an emerging potent marker of inflammation[38]. It was reported that NLR is an independent factor of mortality and major adverse cardiac events in acute and chronic ischaemic heart diseases[13]. The NLR was also found to be significantly higher in non-dipping HT[27,28]. Increased NRL may indicate hypertensive end-organ damage. The neutrophil-lymphocyte ratio is not static, and varies with the of critical illness. Thus, NLR may give prognostic clues about the activity of disease and response to therapy. In addition, the protective effect of some anti-hypertensive drugs correlated with NLR decrement, which suggests the role of NLR in the severity of HT[39,40].

White blood cell count

White blood cell (WBC) count constitutes an inflammatory marker and it tends to increase in HT. The WBC count was higher in non-dipping HT and WBC counts in the highest quartile may reflect enhanced inflammatory response and end-organ damage[41]. Hypertensive men with a high Framingham 10-year cardiovascular risk score showed higher levels of WBC[42].

PLATELET INDICES

Mean platelet volume

Mean platelet volume has known to be an indicator of platelet activation and, its correlation with cardiovascular disease is well established[9,11-12]. Platelets play a pivotal role in the development of atherosclerotic lesions, plaque destabilization, and atherothrombosis. It has been clearly demonstrated that MPV is an unfavourable prognostic factor in ischaemic coronary heart disease[11,12]. A few studies have also proposed that MPV may predict microvascular injury in coronary vessels and diabetic microvascular complications, including nephropathy and hypertensive microvascular end-organ damage[17,43-45]. Gunebakmaz *et al*[17] reported that higher MPV quartile values were more common in left ventricular concentric hypertrophy compared to normal cases. High MPV levels were also linked to non-dipping HT[24-26]. Platelet activation and inflammatory response is the probable mechanism of MPV prognostic value. Hence, an increased MPV value usually accompanies high hsCRP value. Mean platelet volume levels were associated with severity of end end-organ damage, including carotid atherosclerosis, left ventricular hypertrophy and renal damage[43-45]. There is a stepwise increase between MPV and the severity of hypertensive disease. Mean platelet volume was also found higher in ophthalmologic complications[46]. Moreover, its level was increased in masked HT[47].

Platelet distribution width

Platelet distribution width reflects the platelets' reactivity. The platelet distribution width (PDW) is a more specific marker of platelet activation, since it does not increase during simple platelet swelling[10]. Spencer *et al*[48] reported that there is a strong correlation between PDW and the severity of hypertensive disease.

P-selectin (CD62P)

P-selectin also shows platelet activation. It is a direct mediator of vascular inflammation and injury[49]. Preston *et al*[49] showed that platelet activation and p-selectin may participate in the accelerated target organ injury in high-risk hypertensive patients[50].

Anti-hypertensive therapy results in a reversal of platelet morphology abnormalities and indices of platelet activation. This may contribute to a reduction in thrombosis-related complications seen in those whose blood pressure lowering is effective[51].

CONCLUSION

Haematological indices, predominantly RDW, NLR and MPV, reflect oxidative stress and inflammatory state, which also postulate as major mechanisms of HT and its vascular complication. There is a stepwise relation between the severity of HT, hypertensive end-organ damage and haematological indices. However, it is still not clear whether these parameters are responsible in the pathogenesis of HT or they increase as a result of the progression of hypertensive disease. There is a need of further investigations to clarify definitive pathophysiologic mechanism of HT regarding the role of hematological indices. Nevertheless, there is a clear consensus that these haematological parameters have a prognostic value in the essential HT and their abnormality may strongly suggest hypertensive end-organ damage.

REFERENCES

1 **Kaplan NM**. Systemic hyertension: mechanism and diagnosis. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease. Philadelphia: Elsevier Saunders, 2005: 959-987

2 **Bolívar JJ**. Essential hypertension: an approach to its etiology and neurogenic pathophysiology. *Int J Hypertens* 2013; **2013**: 547809 [PMID: 24386559 DOI: 10.1155/2013/547809]

3 **Harrison DG**. The mosaic theory revisited: common molecular mechanisms coordinating diverse organ and cellular events in hypertension. *J Am Soc Hypertens* 2013; **7**: 68-74 [PMID: 23321405 DOI: 10.1016/j.jash.2012.11.007]

4 **González J**, Valls N, Brito R, Rodrigo R. Essential hypertension and oxidative stress: New insights. *World J Cardiol* 2014; **6**: 353-366 [PMID: 24976907 DOI: 10.4330/wjc.v6.i6.353]

5 **Montezano AC**, Touyz RM. Molecular mechanisms of hypertension--reactive oxygen species and antioxidants: a basic science update for the clinician. *Can J Cardiol* 2012; **28**: 288-295 [PMID: 22445098 DOI: 10.1016/j.cjca.2012.01.017]

6 **Tsounis D**, Bouras G, Giannopoulos G, Papadimitriou C, Alexopoulos D, Deftereos S. Inflammation markers in essential hypertension. *Med Chem* 2014; **10**: 672-681 [PMID: 25102200 DOI: 10.2174/1573406410666140318111328]

7 **Karabulut A**, Uzunlar B. Correlation between red cell distribution width and coronary ectasia in the acute myocardial infarction. *Clin Appl Thromb Hemost* 2012; **18**: 551-552 [PMID: 22962309 DOI: 10.1177/1076029611436198]

8 **Karabulut A**, Uzunlar B, Çakmak M. Impact of mean platelet volume on postinterventional TIMI flow in the acute myocardial infarction treated with primary coronary intervention. *Clin Appl Thromb Hemost* 2013; **19**: 103-104 [PMID: 22387579 DOI: 10.1177/1076029612438708]

9 **Karabulut A**, Uyarel H, Uzunlar B, Çakmak M. Elevated red cell distribution width level predicts worse postinterventional thrombolysis in myocardial infarction flow reflecting abnormal reperfusion in acute myocardial infarction treated with a primary coronary intervention. *Coron Artery Dis* 2012; **23**: 68-72 [PMID: 22167053 DOI: 10.1097/MCA.0b013e32834f1188]

10 **Sahan E**, Polat S. [Neutrophil to lymphocyte ratio is associated with more extensive, severe and complex coronary artery disease and impaired myocardial perfusion]. *Turk Kardiyol Dern Ars* 2014; **42**: 415 [PMID: 24899494 DOI: 10.5543/tkda.2014.87036]

11 **Sahin I**, Karabulut A, Avci II, Okuyan E, Biter HI, Yildiz SS, Can MM, Gungor B, Dinckal M, Serebruany V. Contribution of platelets indices in the development of contrast-induced nephropathy. *Blood Coagul Fibrinolysis* 2015; **26**: 246-249 [PMID: 24695089 DOI: 10.1097/MBC.0000000000000107]

12 **Yaghoubi A**, Golmohamadi Z, Alizadehasl A, Azarfarin R. Role of platelet parameters and haematological indices in myocardial infarction and unstable angina. *J Pak Med Assoc* 2013; **63**: 1133-1137 [PMID: 24601192]

13 **Balta S**, Demirkol S, Aparcı M, Celik T, Ozturk C. The neutrophil lymphocyte ratio in coronary heart disease. *Int J Cardiol* 2014; **176**: 267 [PMID: 25074555 DOI: 10.1016/j.ijcard.2014.06.098]

14 **Chu SG**, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, Mohler ER, Reilly MP, Berger JS. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost* 2010; **8**: 148-156 [PMID: 19691485 DOI: 10.1111/j.1538-7836.2009.03584]

15 **He J**, Li J, Wang Y, Hao P, Hua Q. Neutrophil-to-lymphocyte ratio (NLR) predicts mortality and adverse-outcomes after ST-segment elevation myocardial infarction in Chinese people. *Int J Clin Exp Pathol* 2014; **7**: 4045-4056 [PMID: 25120783]

16 **Fornal M**, Wizner B, Cwynar M, Królczyk J, Kwater A, Korbut RA, Grodzicki T. Association of red blood cell distribution width, inflammation markers and morphological as well as rheological erythrocyte parameters with target organ damage in hypertension. *Clin Hemorheol Microcirc* 2014; **56**: 325-335 [PMID: 23719424 DOI: 10.3233/CH-131745]

17 **Gunebakmaz O**, Kaya MG, Duran M, Akpek M, Elcik D, Eryol NK. Red blood cell distribution width in 'non-dippers' versus 'dippers'. *Cardiology* 2012; **123**: 154-159 [PMID: 23128599 DOI: 10.1159/000342667]

18 **Isik T**. Is red cell distribution width a marker for hypertension? *Cardiology* 2012; **123**: 195-196 [PMID: 23147470 DOI: 10.1159/000343679]

19 **Kaya MG**, Yarlioglues M, Gunebakmaz O, Gunturk E, Inanc T, Dogan A, Kalay N, Topsakal R. Platelet activation and inflammatory response in patients with non-dipper hypertension. *Atherosclerosis* 2010; **209**: 278-282 [PMID: 19782364 DOI: 10.1016/j.atherosclerosis.2009.09.010]

20 **Kilicaslan B**, Dursun H, Aydin M, Ekmekci C, Ozdogan O. The relationship between red-cell distribution width and abnormal left ventricle geometric patterns in patients with untreated essential hypertension. *Hypertens Res* 2014; **37**: 560-564 [PMID: 24599016 DOI: 10.1038/hr.2014.39]

21 **Tanindi A**, Topal FE, Topal F, Celik B. Red cell distribution width in patients with prehypertension and hypertension. *Blood Press* 2012; **21**: 177-181 [PMID: 22243409 DOI: 10.3109/08037051.2012.645335]

22 **Elbasan Z**, Gür M, Sahin DY, Tanboğa IH, Cayli M. Mean platelet volume and abnormal left ventricle geometric patterns in patients with untreated essential hypertension. *Platelets* 2013; **24**: 521-527 [PMID: 23216609 DOI: 10.3109/09537104.2012.738839]

23 **Inanc T**, Kaya MG, Yarlioglues M, Ardic I, Ozdogru I, Dogan A, Kalay N, Gunturk E, Gunebakmaz O, Gul I, Topsakal R. The mean platelet volume in patients with non-dipper hypertension compared to dippers and normotensives. *Blood Press* 2010; **19**: 81-85 [PMID: 20367545 DOI: 10.3109/08037050903516284]

24 **Ozcan F**, Turak O, Durak A, Işleyen A, Uçar F, Giniş Z, Uçar F, Başar FN, Aydoğdu S. Red cell distribution width and inflammation in patients with non-dipper hypertension. *Blood Press* 2013; **22**: 80-85 [PMID: 22835009 DOI: 10.3109/08037051.2012.707336]

25 **Ordu S**, Ozhan H, Caglar O, Alemdar R, Basar C, Yazici M, Erden I. Mean platelet volume in patients with dipper and non-dipper

hypertension. *Blood Press* 2010; **19**: 26-30 [PMID: 19929284 DOI: 10.3109/08037050903416402]

26 **Demir M**. The relationship between neutrophil lymphocyte ratio and non-dipper hypertension. *Clin Exp Hypertens* 2013; **35**: 570-573 [PMID: 23387864 DOI: 10.3109/10641963.2013.764893]

27 **Sunbul M**, Gerin F, Durmus E, Kivrak T, Sari I, Tigen K, Cincin A. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. *Clin Exp Hypertens* 2014; **36**: 217-221 [PMID: 23786430 DOI: 10.3109/10641963.2013.804547]

28 **Surgit O**, Erturk M, Akgul O, Pusuroglu H, Korkmaz AF, Isiksacan N, Gul M, Uzun F, Ozal E, Eksik A. Assessment of mean platelet volume and soluble CD40 ligand levels in patients with non-dipper hypertension, dippers and normotensives. *Clin Exp Hypertens* 2015; **37**: 70-74 [PMID: 24866755 DOI: 10.3109/10641963.2014.897725]

29 **Fornal M**, Korbut RA, Grodzicki T. Relevance of erythrocyte deformability to the concentration of soluble cell adhesion molecules and glomerular filtration rate in patients with untreated essential hypertension. *Clin Hemorheol Microcirc* 2011; **49**: 323-329 [PMID: 22214704 DOI: 10.3233/CH-2011-1483]

30 **Turchetti V**, Bellini MA, Guerrini M, Forconi S. Evaluation of hemorheological parameters and red cell morphology in hypertension. *Clin Hemorheol Microcirc* 1999; **21**: 285-289 [PMID: 10711756]

31 **Wen Y**. High red blood cell distribution width is closely associated with risk of carotid artery atherosclerosis in patients with hypertension. *Exp Clin Cardiol* 2010; **15**: 37-40 [PMID: 20959889]

32 **Tosu AR**, Demir S, Selcuk M, Kaya Y, Akyol A, Ozdemir M, Tenekecioglu E. Comparison of inflammatory markers in non-dipper hypertension vs. dipper hypertension and in normotensive individuals: uric acid, C-reactive protein and red blood cell distribution width readings. *Postepy Kardiol Interwencyjnej* 2014; **10**: 98-103 [PMID: 25061455 DOI: 10.5114/pwki.2014.43514]

33 **Sharp DS**, Curb JD, Schatz IJ, Meiselman HJ, Fisher TC, Burchfiel CM, Rodriguez BL, Yano K. Mean red cell volume as a correlate of blood pressure. *Circulation* 1996; **93**: 1677-1684 [PMID: 8653873 DOI: 10.1161/01.CIR.93.9.1677]

34 **Rampling MW**. Haemorheological disturbances in hypertension: the influence of diabetes and smoking. *Clin Hemorheol Microcirc* 1999; **21**: 183-187 [PMID: 10711741]

35 **Sandhagen B**. Red cell fluidity in hypertension. *Clin Hemorheol Microcirc* 1999; **21**: 179-181 [PMID: 10711740]

36 **Julius S**, Egan BM, Kaciroti NA, Nesbitt SD, Chen AK. In prehypertension leukocytosis is associated with body mass index but not with blood pressure or incident hypertension. *J Hypertens* 2014; **32**: 251-259 [PMID: 24275841 DOI: 10.1097/HJH.0000000000000032]

37 **Imtiaz F**, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 2012; **5**: 2 [PMID: 22281066 DOI: 10.1186/1755-7682-5-2]

38 **Karaman M**, Balta S, Seyit Ahmet AY, Cakar M, Naharci I, Demirkol S, Celik T, Arslan Z, Kurt O, Kocak N, Sarlak H, Demirbas S, Bulucu F, Bozoglu E. The comparative effects of valsartan and amlodipine on vWf levels and N/L ratio in patients with newly diagnosed hypertension. *Clin Exp Hypertens* 2013; **35**: 516-522 [PMID: 23289969 DOI: 10.3109/10641963.2012.758734]

39 **Fici F**, Celik T, Balta S, Iyisoy A, Unlu M, Demitkol S, Yaman H, Brambilla G, Kardesoglu E, Kilic S, Yokusoglu M, Grassi G. Comparative effects of nebivolol and metoprolol on red cell distribution width and neutrophil/lymphocyte ratio in patients with newly diagnosed essential hypertension. *J Cardiovasc Pharmacol* 2013; **62**: 388-393 [PMID: 23921307 DOI: 10.1097/FJC.0b013e31829f716a]

40 **Kim DJ**, Noh JH, Lee BW, Choi YH, Chung JH, Min YK, Lee MS, Lee MK, Kim KW. The associations of total and differential white blood cell counts with obesity, hypertension, dyslipidemia and glucose intolerance in a Korean population. *J Korean Med Sci* 2008; **23**: 193-198 [PMID: 18436999 DOI: 10.3346/jkms.2008.23.2.193]

41 **Spencer CG**, Martin SC, Felmeden DC, Blann AD, Beevers GD, Lip GY. Relationship of homocysteine to markers of platelet and endothelial activation in "high risk" hypertensives: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. *Int J Cardiol* 2004; **94**: 293-300 [PMID: 15093996 DOI: 10.1016/j.ijcard.2003.06.002]

42 **Gasparyan AY**, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des* 2011; **17**: 47-58 [PMID: 21247392 DOI: 10.2174/138161211795049804]

43 **Erdogan D**, Icli A, Aksoy F, Akcay S, Ozaydin M, Ersoy I, Varol E, Dogan A. Relationships of different blood pressure categories to indices of inflammation and platelet activity in sustained hypertensive patients with uncontrolled office blood pressure. *Chronobiol Int* 2013; **30**: 973-980 [PMID: 23834704 DOI: 10.3109/07420528.2013.790045]

44 **Yarlioglues M**, Kaya MG, Ardic I, Dogdu O, Kasapkara HA, Gunturk E, Akpek M, Kalay N, Dogan A, Ozdogru I, Oguzhan A. Relationship between mean platelet volume levels and subclinical target organ damage in newly diagnosed hypertensive patients. *Blood Press* 2011; **20**: 92-97 [PMID: 21105760 DOI: 10.3109/08037051.2010.532317]

45 **Onder HI**, Kilic AC, Kaya M, Bulur S, Onder E, Tunc M. Relation between platelet indices and branch retinal vein occlusion in hypertensive patients. *Indian J Ophthalmol* 2013; **61**: 160-162 [PMID: 23619481 DOI: 10.4103/0301-4738.111063]

46 **Guven A**, Caliskan M, Ciftci O, Barutcu I. Increased platelet activation and inflammatory response in patients with masked hypertension. *Blood Coagul Fibrinolysis* 2013; **24**: 170-174 [PMID: 23358199 DOI: 10.1097/MBC.0b013e32835aba36]

47 **Boos CJ,** Beevers GD, Lip GYH. Assessment of platelet activation indices using the ADVIATM 120 amongst "high-risk" patients with hypertension. *Ann Med* 2007; **39**: 72-78 [PMID: 17364453 DOI: 10.1080/07853890601040063]

48 **Spencer CG**, Felmeden DC, Blann AD, Lip GY. Haemorheological, platelet and endothelial indices in relation to global measures of cardiovascular risk in hypertensive patients: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. *J Intern Med* 2007; **261**: 82-90 [PMID: 17222171 DOI: 10.1111/j.1365-2796.2006.01735.x]

49 **Preston RA**, Coffey JO, Materson BJ, Ledford M, Alonso AB. Elevated platelet P-selectin expression and platelet activation in high risk patients with uncontrolled severe hypertension. *Atherosclerosis* 2007; **192**: 148-154 [PMID: 16764881 DOI: 10.1016/j.atherosclerosis.2006.04.028]

50 **Nadar S**, Blann AD, Lip GY. Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipine-based antihypertensive therapy. *Ann Med* 2004; **36**: 552-557 [PMID: 15513305 DOI: 10.1080/07853890410017386]

51 **Meiselman HJ**. Hemorheologic alterations in hypertension: chicken or egg? *Clin Hemorheol Microcirc* 1999; **21**: 195-200 [PMID: 10711743]

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ORIGINAL ARTICLE

Retrospective Study

Catheter ablation for atrial fibrillation in a subset of patients with concomitant hypertension

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Ethics approval: This is a retrospective study which does not require IRB evaluation. See informed consent below.
Informed consent: All patient provided informed consent prior to the catheter ablation procedure for the treatment of atrial fibrillation. Included in that consent was the collection and publication of follow-up data.
Conflict-of-interest: Tushar Sharma, Benjamin J Scherlag, Ralph Lazzara and Sunny S Po have no conflicts to disclose; Hiroshi Nakagawa: Research Grant by Biosense Webster, Inc., St. Jude Medical AF Division, EndoSense SA and Boston Scientific; Warren M Jackman is Consultant of Biosense Webster, EndoSense SA, Rhythmia Medical, ACT, VyTronUS, CyberHeart and Cardiofocus.
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Abstract

AIM: To study patients with atrial fibrillation and hypertension who had successful catheter ablation for changes in blood pressure 1 year later.

METHODS: A retrospective study was performed on patients who had catheter ablation for atrial fibrillation (AF) and hypertension (HTN) which included local autonomic ganglionated plexi denervation and pulmonary veins isolation. Of the records of 119 patients, follow-up data was found in order to determine the presence of sinus rhythm and data on systolic (SBP) and diastolic blood pressure at 2 wk, 3 mo, 6 mo and 1 year after the ablation procedure. Transthoracic echocardiograms were taken at the time of the catheter procedure to determine left atrial dimensions (LADs) and left ventricular size.

RESULTS: There was no significant difference in the pre-ablation mean blood pressures between the two groups (P = 0.08). After 1 year 33 of the 60 with AF and HTN were in sinus rhythm, of whom 12 had normal LADs, $\leqslant$ 4 cm Group 1, and 21 had enlarged left atria (LADs > 4 cm, Group 2). For Group 1, at 1 year of follow up, there was a significant difference in the SBP (119.2 ± 13 mmHg) compared to pre-ablation (142.6 ± 13.7 mmHg, P = 0.001). For Group 2, there was no significant difference in the SBP, pre-ablation (130.3 ± 17.5 mmHg) and at 1 year of follow up (130.4 ± 13.4 mmHg, P = 0.75). All patients were on similar anti-hypertensive medications. There was a trend for a greater left ventricular size in Group 2 compared to Group 1.

CONCLUSION: We suggest that Group 1 had HTN due to sympathetic hyperactivity, neurogenic HTN; whereas HTN in Group 2 was based on arterial vasoconstriction.

Key words: Atrial fibrillation; Hypertension; Autonomic nervous system; Catheter ablation

Core tip: A retrospective study of 119 patient with atrial fibrillation (AF) and hypertension (HTN) underwent catheter ablation consisting of pulmonary vein isolation and local cardiac autonomic denervation. After 1 year 33 were in sinus rhythm and fell into 2 categories based on significant differences in left atrial dimensions (LADs). Although similarly medicated, Group I (LADs $\leqslant$ 4 cm) had a significant decrease in blood pressure compared to Group 2, LAD > 4 cm. We conclude that HTN in Group 1 was neurogenic and ameliorated by neural ablation; whereas HTN in Group 2, manifested arterial vasoconstriction as the mechanism for HTN.

Sharma T, Scherlag BJ, Nakagawa H, Jackman WM, Lazzara R, Po SS. Catheter ablation for atrial fibrillation in a subset of patients with concomitant hypertension. *World J Hypertens* 2015; 5(2): 98-103 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i2/98.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i2.98

INTRODUCTION

Early studies seeking the mechanism for clinical hypertension (HTN) focused on the sympathetic nervous system as the underlying cause. It was well known that sympathetic stimulation of the heart led to increased contractility leading to high blood pressure. Indeed, a concept was put forth by several investigators suggesting that HTN was neurogenic in origin[1-5]. The seminal studies of Goldblatt *et al*[6], induced chronic HTN in animals who had a clip (stenosis) on the renal arteries which provided the basis for the discovery of the role of the renin/angiotensin/aldosterone syndrome as a cause of HTN[7]. This concept became the prevalent view and has become the mainstay of therapeutic strategies to control HTN, *i.e.*, use of angiotensin blocking agents and diuretics. The acceptance of a sympathetic contribution is evidenced by the addition of beta-blockers to the antihypertensive regimen. The Framingham study has provided evidence linking HTN and atrial fibrillation (AF). In a multivariate analysis it was found that HTN was an independent predictor for developing AF, with an odds ratio of 1.5 for men and 1.4 for women[1]. The sequence of pathological events in this association might start with increased vascular resistance followed by ventricular hypertrophy and atrial dilatation, the last providing the substrate for AF[8].

The recent dramatic effects of renal sympathetic denervation[9] has revived the neurogenic concept[10] particularly in regard to the treatment for resistant forms of hypertension. In this regard, Schlaich *et al*[11] cited experimental[12] and clinical[13] evidence that afferent nerve denervation may play a more significant role in "the sustained blood pressure-lowering (by) renal denervation … *via* the removal of renal afferent activity and the subsequent effects on central sympathetic outflow". It is interesting to note that renal sympathetic denervation has also been applied to patients with concomitant hypertension and atrial fibrillation. Scherlag *et al*[14] reported that renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with pulmonary vein isolation (PVI).

Since 2004 the procedure for catheter ablation in patients with AF in our clinical electrophysiological practice has consisted of PVI plus ablation of hyperactive autonomic nerve clusters called ganglionated plexi (GP) at the PV-atrial junctions. This combined procedure has been shown to increase the success rates for maintaining sinus rhythm compared to PVI alone[15,16]. It was in this context that we hypothesized that a subset of our patients presenting with HTN and AF would manifest the neurogenic form of HTN based on hyperactivity of the intrinsic cardiac autonomic nervous system. Furthermore, based on the previous report[15] we surmised that the patients with the neurogenic and drug resistant form of HTN would respond with a significant blood pressure reduction due to the decrease of autonomic hyperactivity caused by PVI plus GP ablation.

MATERIALS AND METHODS

We performed a retrospective study of 119 patients who had undergone catheter ablation using an irrigated tip ablation catheter (Biosense/Webster, Navi-Star, Thermocool catheter, Diamond Bar, CA, United States) for mapping and ablation.

The procedure for catheter ablation has been previously described in detail[15]. Briefly, General anesthesia was administered in all patients. Localization of GP was obtained by application of high-frequency stimulation to each GP (HFS; 20 Hz, 10-150 V and pulse width 1-10 ms; S-88 stimulator, Grass Instruments Division, Astro Med Inc., Warwick, RI, United States). Within 5 s of HFS, a marked parasympathetic response is elicited, which is arbitrarily defined as a $\geqslant$ 50% increase in mean R-R interval during AF. Each parasympathetic response is verified by both hypotension and high grade AV block. For GP ablation, radiofrequency (RF) current is delivered at 25-35 W for 40-60 s during saline irrigation at each site of positive parasympathetic response to HFS. RF applications are repeated until the parasympathetic response to HFS is eliminated.

After the 4 left atrial GP are ablated, pulmonary vein antrum isolation is performed. The endpoint of PV antrum isolation is elimination of potentials within the isolated antral area. As antrum isolation typically transects the ARGP and SLGP areas, we use the ARGP and SLGP ablation sites as the starting points for right and left antrum isolation, respectively. Echocardiographic studies were accomplished transthoracically which provided an anterior-posterior measurement of the left atrial dimensions.

Inclusion criteria were: (1) Successful catheter ablation for AF involving both GP ablation and PV isolation

Table 1 Anti-hypertensive drugs taken by patients before and after catheter ablation procedures

No. of patients	Anti-hypertensive agents
7	ACE inhibitor
7	Calcium channel blockers
2	Beta blockers
1	Angiotensin 2 receptor blocker
6	ACE inhibitor, beta blocker
3	Calcium channel blocker, angiotensin 2 receptor blocker
2	ACE inhibitor blocker. Calcium channel blocker
2	ACE inhibitor, diuretic
1	Calcium channel blocker, beta blocker, diuretic
1	Calcium channel blocker, beta blocker
1	ACE inhibitor, calcium channel blocker, diuretic

(patient should have been in sinus rhythm after one year); (2) Co-existence of AF and HTN; (3) Knowledge of left atrial dimension (LAD) by echocardiographic measurement; and (4) All patients were on anti-hypertensive drug regimens.

The exclusion criteria included: (1) Recurrence of AF at the end of one year; (2) No GP ablation; and (3) No follow up blood pressure data.

Of the 119 patients reviewed, there were 60 patients with co-existing AF and HTN. Of these 60 patients, only 33 patients who had been contacted were in sinus rhythm at the end of one year of follow up. The purpose of the study was to determine the differences in the blood pressure levels before ablation and at different periods of follow-up. The pre-ablation systolic (SBP) and diastolic (DBP) blood pressures of the patients in the two groups were compared with the post-ablation SBP and DBP at two weeks, three months, six months and one year of follow-up.

Statistical analysis

Statistical analyses were done using the SAS software (V 9.1). All statistical tests were carried out at an alpha of 0.05. Data is expressed as mean ± SD. Repeated measures analysis of variance (ANOVA) was used to determine if the mean SBP and DBP changed over the follow up periods for the two groups. Post-hoc analysis was done to compare the mean blood pressures across the individual follow up periods.

RESULTS

Patient medications

All of the 33 patients included in the chart review were on single or multiple antihypertensive medications prior to the ablation procedure (Table 1). Although 8 patients were on a single medication all the others were taking multiple anti-hypertensive agents and all continued these same regimens during the follow-up period.

Echocardiographic analysis

There were 12 patients with normal sized left atria (LAD ⩽ 4.0 cm) and 21 patients with enlarged left atria (LAD > 4.0 cm). On the basis of the blood pressure responses during progressive periods of follow-up, the 33 patients could be divided into two groups based on their LAD, *viz*., < 4.0 or > 4.0. Table 2 compares the descriptive statistics for all 33 patients that met the inclusion criteria divided into the 2 groups. Although there was a greater absolute mean value in group 1 (142/83 mmHg) *vs* group 2 (130/80 mmHg) the difference was not statistically significant prior to ablation (P = 0.08) For patients with LA dimensions ⩽ 4.0 cm (Group 1), there was a significant difference in the mean SBP levels, at 2 wk after the ablation procedure (126.8 ± 19.4 mmHg) compared to SBP, pre-ablation (142 ± 13.7 mmHg, P = 0.008). This change persisted at three and six months of follow up. The mean SBP levels at one year of follow up (119.2 ± 13 mmHg) were significantly lower than the pre-ablation mean SBP levels (142 ± 13.7 mmHg), for patients with LADs ⩽ 4.0 cm, P = 0.001.

Table 2 Comparison of descriptive statistics between Study Groups

Variable	Group 1 (LAD ⩽ 4 cm), mean ± SD	Group 2 (LAD > 4 cm), mean ± SD
AGE (yr)	58.3 ± 9.2	60.4 ± 6.8
LAD (cm)	3.63 ± 0.34	4.54 ± 0.4
Pre-ablation SBP (mmHg)	142.6 ± 13.7	130.3 ± 17.5
Pre-ablation DBP (mmHg)	83.8 ± 11.6	80.6 ± 15.6
SBP - 2 wk (mmHg)	126.8 ± 19.4[a]	129.6 ± 16.9
DBP - 2 wk (mmHg)	76.2 ± 13.5	78.9 ± 11.5
SBP - 3 mo (mmHg)	129.1 ± 15.4[a]	132.1 ± 13.6
DBP - 3 mo (mmHg)	77.6 ± 12.8	79.1 ± 12.2
SBP - 6 mo (mmHg)	123.7 ± 16.8[a,b]	134.3 ± 14.4
DBP - 6 mo (mmHg)	76 ± 10.1	77.7 ± 9.5
SBP - 1 yr (mmHg)	119.2 ± 13[a,b]	130.4 ± 13.4
DBP - 1 yr (mmHg)	70.4 ± 12.2	78.7 ± 9.1

Group 1: LAD ⩽ 4.0 cm; Group 2: LAD > 4.0 cm; [a]P ⩽ 0.05 compared to SBP pre-ablation; [b]P = 0.008, P = 0.001, Group 1 SBP compared to Group 2 SBP at 6 mo and 1 year, respectively, after the GP and PVI ablation procedure. LAD: Left atrial dimension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

For patients with LADs > 4.0 cm (Group 2), there was no significant difference in the mean SBP levels, pre-ablation (130 ± 17.5 mmHg) and at 2 wk of follow-up (129 ± 16.9 mmHg) (P = 0.92). For patients with LADs > 4.0 cm, there was no significant difference in the mean SBP levels, pre-ablation and at 1 year of follow up (130 ± 13.4 mmHg, P = 0.75). There was no significant difference in the mean DBP throughout the follow up periods for both groups.

Figure 1 compares the proportion of patients with left ventricular hypertrophy (LVH) in both groups. Although the number of patients with or without LVH were not significantly different, the trend showed a lower incidence of LVH in Group 1 (33%) *vs* Group 2 (56%) and a corresponding higher number lacking LVH in Group 1 (67%) *vs* Group 2 (44%). The small sample size and wide range of standard deviation may have precluded obtaining statistical significance (P =

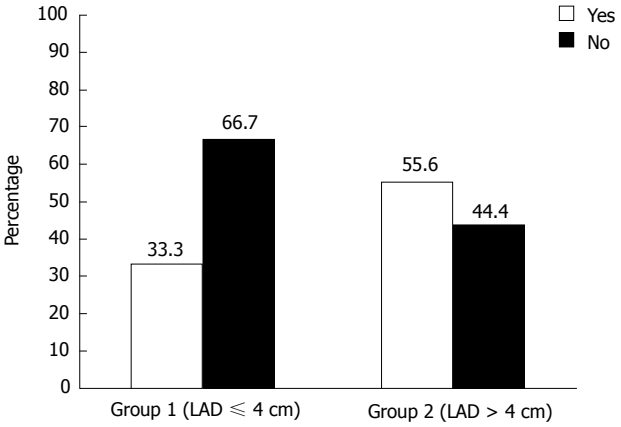

Figure 1 Distribution of the percent incidence of left ventricular hypertrophy in the two study groups. Although the number of patients with or without left ventricular hypertrophy (LVH) were not significantly different, the trend showed a lower incidence of LVH in Group 1 (33%) *vs* Group 2 (56%) and a corresponding higher number lacking LVH in Group 1 (67%) *vs* Group 2 (44%).

0.08).

DISCUSSION

Major findings

Although there was no significant difference between the initial blood pressures of the two groups, the response to GP ablation and PVI were dramatically different during the follow-up periods. Specifically, in Group 1 patients, there was a marked decrease in the mean SBP over the short term (from 142 ± 13.7 mmHg to 126.8 ± 19.4 mmHg within 2 wk) which was maintained after 3 and 6 mo. At 1 year the mean SBP was even more significantly decreased compared to the initial values (119 ± 13 mmHg, P = 0.001). In contrast, in Group 2, there was no change in SBP over the same time periods, even though the response to AF ablation was exactly the same as in Group 1. Since the anti-hypertensive drug history was heterogeneously distributed for both groups, these findings suggest that Group 1 patients with the putative "neurogenic" form of HTN, *i.e.*, due to increased ventricular contractility, represented a sub-population of HTN resistant to drugs prior to catheter ablation. It is of interest that recent studies of another group of patients with a resistant form of HTN have been shown to respond to renal artery denervation with an endovascular method for applying radiofrequency ablation to adventitial sympathetic nerves[10,11]. Experimental evidence has shown that the neurogenic form of HTN derives from an increase of sympathetic activity which increases the BP through enhanced ventricular contractility, so-called "cardiogenic hypertension". Sustained HTN has been shown to occur experimentally by chronic electrical stimulation of the left stellate ganglion[17].

In a recent study from our laboratory, we developed an acute model simulating inappropriate sinus tachycardia[18]. In 14 anesthetized dogs; 0.3 mg of 10^{-3} solution of epinephrine was injected into the anterior right ganglionated plexi (ARGP). In eight of the dogs there was a significant increase in the average heart rate of 57 beats/min but no change in systolic blood pressure. In six dogs both heart rate and systolic blood pressure were equally and significantly accentuated and remained elevated for at least 30 min. In addition ventricular arrhythmias were also observed which overwhelmed sinus rhythm. Other studies provided functional evidence of neural connections between ganglionated plexi in the atria which, when stimulated chemically, caused marked sympathetic effects on the ventricles, including ventricular arrhythmias[19].

It should be mentioned that sympathetic afferents may also play a critical role in the marked reduction of SBP in the Group 1 patients after GP ablation and PVI. Ardell[20] in a review of the cardiac neurons that inhabit the GP and the atrial neural network emphasized the afferent connections from these intrinsic cardiac elements to the brainstem. How does this scenario for reduction of BP by renal denervation translate to the present study? We hypothesize that the findings of the present studies suggest that multiple visceral sites, *e.g.*, the heart and renal arteries, which are autonomically innervated can be a source of abnormal sympathetic afferent conduction to central vasomotor centers leading to excessive efferent return to neuro-effector junctions to the same structures. Hyperactivity of GP has been shown to contribute to the propensity for AF by excessive release of cholinergic and adrenergic neurotransmitters *via* postganglionic axons innervating the PVs and atria[21-23]. Hyperactive GP may also send excessive afferent signals to central sympathetic centers which in turn would increase sympathetic outflow returning to the heart and vasculature. The results would be enhanced propensity for AF and increased ventricular contractility and vasoconstriction, *i.e.*, the neurogenic form of AF and HTN. Ablation of the GP would therefore, have a dual salutary effect by reducing both efferent and afferent activity leading to amelioration of HTN and suppression of AF. This scenario is what was found in the sub-population of patients in the present study with the appropriate biomarkers, *i.e.*, normal LAD dimensions and drug resistant HTN. In this regard a recent case report, described the application of renal artery denervation without PVI in a patient with drug resistant HTN and symptomatic, persistent AF. After a short follow-up of 5 mo the patient is in sinus rhythm with a reduction of blood pressure prior to renal sympathetic denervation (148/80 mmHg) to 111/60 mmHg. Of interest, echocardiography showed a left atrial diameter of 45 mm prior to ablation which was slightly reduced after ablation[24].

Study limitations

We do not know if eliminating anti-hypertensive drugs from those patients with the "neurogenic" form of HTN manifesting normal left atrial dimensions would have resulted in a reduction in SBP than we found. However, in those patients with the "arterial vasoconstrictor"

form of HTN manifesting LADs greater than 4 cm, there was no significant change in mean SBP over the same follow-up period, even though they had the same AF ablation procedure and the same salutary outcome, *i.e.*, restoration of sinus rhythm while still on antihypertensive agents. It has been noted by the authors of the Symplicity trials that the extension of renal artery denervation to patients who respond favorably to drugs is problematic. Indeed, Frohlich[25] in a recent editorial indicated that, "Only a small fraction of patients with hypertension have "drug resistant hypertension"…Consequently, the mass extrapolation to all patients with hypertension for…this specialized procedure does not seem appropriate at this time. Therefore, we do not know if patients in Group 2, off drugs, would have also responded with significant reductions of SBP after catheter ablation. A distinct limitation of this study is the small numbers of patients in groups 1 and 2 which requires that the findings be interpreted with caution. Further studies of the co-morbidity (AF and HTN) in a larger cohort of patients will help to corroborate the present findings, particularly if one group contains those having PVI alone or PVI plus GP ablation[14].

Significant differences were found in the mean SBP before ablation and at follow up intervals, with the SBP being lower post GP ablation in patients with AF and HTN with normal LADs. Based on previous experimental and clinical studies we conclude that HTN in Group 1 was sympathetically based, *i.e.,* neurogenic HTN, and drug resistant whereas HTN in Group 2, mainly drug responders, manifested arterial vasoconstriction as the mechanism for HTN. We hypothesize that GP ablation in Group 1 served to reduce afferent and efferent sympathetic enhanced ventricular contractility leading to HTN amelioration. Further studies in patients with hypertension and AF undergoing PVI and GP ablation, using a prospective protocol and a larger sample size, may be required to achieve more definitive results.

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COMMENTS

Background

Hypertension commonly occurs with atrial fibrillation. The authors studied patients who were successfully treated for atrial fibrillation over a period of 1 year. A sub-group of these patients also had a dramatic reduction of blood pressure into the normal range. The authors determined the mechanisms for the concomitant suppression of these two morbidities on the basis of the singular ablation procedure performed by our cardiologists.

Innovations and breakthroughs

Since 2004 the authors' clinical laboratories have used a singular hybrid procedure which combines the isolation of the muscle tissue of the pulmonary veins, the atrial fibrillation origin, from the rest of the atrium with ablation of the nerve clusters at the pulmonary vein-atrial junctions which induce the abnormal activity arising in the pulmonary veins. A retrospective study was performed in patients who underwent this procedure and collected follow-up data at 2 wk to 1 year after the procedure. Of the 33 patients who were in normal heart rhythm throughout the authors found that 21 had no change in blood pressure whereas in 12 their blood pressures were normal. All patients were on similar multiple anti-hypertensive drugs. The authors found that the non-responders had enlarged atria while the responders had normal sized atria before and after the procedure and follow-up. These finding suggested that there was a sub-population of patients whose hypertension was neurally based in the heart while the others had hypertension due to factors outside the heart, *i.e.*, abnormality of the renin-angiotensin-aldosterone system, which caused the arteries to constrict leading to enlargement of the heart chambers.

Applications

Only recently has it been shown that patients with forms of hypertension resistant to multiple drug regimens had a neurogenic basis for their condition which could be dramatically reduced by neural ablation procedures. Just as in small population the resistant forms of hypertension represent a small proportion of the general population with high blood pressure which does not respond to multiple drug therapy. The authors suggest that non-invasive methods for determining heart size by ultrasound, particularly the atrial dimensions can be used to categorize patients with drug resistant and drug responsive hypertension thereby foregoing weeks or months of drug trial for the former group.

Terminology

Hypertension: Abnormally high blood pressure; Atrial Fibrillation: A very rapid and irregular heart rate which can become persistent and can lead to heart failure and strokes; Ablation: A procedure in which an electrode catheter is introduced into the heart which allows the application of radiofrequency energy to create lesion to destroy abnormal heart or nerve tissues.

Peer-review

The authors performed a retrospective study to discuss the significant differences in the mean systolic blood pressure before ablation and at follow up intervals, with the systolic blood pressure being lower post ganglionated plexi ablation in patients with atrial fibrillation and hypertension with normal left atrial dimensions. These observations are interesting, and could be helpful in further clinical studies.

REFERENCES

1 **Benjamin EJ**, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; **271**: 840-844 [PMID: 8114238]
2 **Campese VM**. Neurogenic factors and hypertension in renal disease. *Kidney Int Suppl* 2000; **75**: S2-S6 [PMID: 10828754]
3 **Dustan HP**, Tarazi RC. Cardiogenic hypertension. *Annu Rev Med* 1978; **29**: 485-493 [PMID: 348044 DOI: 10.1146/annurev.me.29.020178.002413]
4 **DiBona GF**. Neural control of the kidney: functionally specific renal sympathetic nerve fibers. *Am J Physiol Regul Integr Comp Physiol* 2000; **279**: R1517-R1524 [PMID: 11049831]
5 **Esler M**. Sympathetic nervous system moves toward center stage in cardiovascular medicine: from Thomas Willis to resistant hypertension. *Hypertension* 2014; **63**: e25-e32 [PMID: 24420544 DOI: 10.1161/HYPERTENSIONAHA.113.02439]
6 **Goldblatt H**, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension: I. the production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934; **59**: 347-379 [PMID: 19870251 DOI: 10.1084/jem.59.3.347]
7 **Laragh JH**. Renal and adrenal factors in hypertension: diagnostic approaches. *Bull N Y Acad Med* 1969; **45**: 859-876 [PMID: 4308842]
8 **Gregory YH**, Lip D, Beavers G, Singh SP, Watson RDS. ABC of atrial fibrillation: Aetiology, pathophysiology and clinical features. *BMJ* 1995; **311**: 1425-1428 [DOI: 10.1136/bmj.311.7017.1425]
9 **Esler M**. Sympathetic nervous system: contribution to human hypertension and related cardiovascular diseases. *J Cardiovasc Pharmacol* 1995; **26** Suppl 2: S24-S28 [PMID: 8642801 DOI: 10.1097/00005344-199512020-00004]

10 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]

11 **Schlaich MP**, Hering D, Sobotka PA, Krum H, Esler MD. Renal denervation in human hypertension: mechanisms, current findings, and future prospects. *Curr Hypertens Rep* 2012; **14**: 247-253 [PMID: 22457244 DOI: 10.1007/s11906-012-0264-9]

12 **Kline RL**, Mercer PF. Functional reinnervation and development of supersensitivity to NE after renal denervation in rats. *Am J Physiol* 1980; **238**: R353-R358 [PMID: 7377374]

13 **Symplicity HTN-1 Investigators.** Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; **57**: 911-917 [PMID: 21403086 DOI: 10.1161/HYPERTENSIONAHA.110.163014]

14 **Pokushalov E,** Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012; **60**: 1163-1170 [DOI: 10.1016/j.jacc.2012.05.036]

15 **Scherlag BJ**, Nakagawa H, Jackman WM, Yamanashi WS, Patterson E, Po S, Lazzara R. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. *J Interv Card Electrophysiol* 2005; **13** Suppl 1: 37-42 [PMID: 16133854 DOI: 10.1007/s10840-005-2492-2]

16 **Katritsis DG**, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J Am Coll Cardiol* 2013; **62**: 2318-2325 [PMID: 23973694 DOI: 10.1016/j.jacc.2013.06.053]

17 **Tarazi RC**, Fouad FM, Ferrario CM. Can the heart initiate some forms of hypertension? *Fed Proc* 1983; **42**: 2691-2697 [PMID: 6602718]

18 **Scherlag BJ**, Yamanashi WS, Amin R, Lazzara R, Jackman WM. Experimental model of inappropriate sinus tachycardia: initiation and ablation. *J Interv Card Electrophysiol* 2005; **13**: 21-29 [PMID: 15976974 DOI: 10.1007/s10840-005-1045-z]

19 **Huang MH**, Wolf SG, Armour JA. Ventricular arrhythmias induced by chemically modified intrinsic cardiac neurones. *Cardiovasc Res* 1994; **28**: 636-642 [PMID: 7517790 DOI: 10.1093/cvr/28.5.636]

20 **Ardell JL**. Structure and Function of the Mammalian Intrinsic Cardiac Neurons. In: Neurocardiology. Eds: Armour JA, Ardell JL. Oxford University Press, New York, NY, 1994: Chap 5

21 **Sharifov OF**, Fedorov VV, Beloshapko GG, Glukhov AV, Yushmanova AV, Rosenshtraukh LV. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. *J Am Coll Cardiol* 2004; **43**: 483-490 [PMID: 15013134 DOI: 10.1016/j.jacc.2003.09.030]

22 **Patterson E**, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. *Heart Rhythm* 2005; **2**: 624-631 [PMID: 15922271 DOI: 10.1016/j.hrthm.2005.02.012]

23 **Shen MJ**, Choi EK, Tan AY, Han S, Shinohara T, Maruyama M, Chen LS, Shen C, Hwang C, Lin SF, Chen PS. Patterns of baseline autonomic nerve activity and the development of pacing-induced sustained atrial fibrillation. *Heart Rhythm* 2011; **8**: 583-589 [PMID: 21118728 DOI: 10.1016/j.hrthm.2010.11.040]

24 **Vollmann D**, Sossalla S, Schroeter MR, Zabel M. Renal artery ablation instead of pulmonary vein ablation in a hypertensive patient with symptomatic, drug-resistant, persistent atrial fibrillation. *Clin Res Cardiol* 2013; **102**: 315-318 [PMID: 23239408 DOI: 10.1007/s00392-012-0529-y]

25 **Frohlich ED**. Renal denervation using an irrigated radiofrequency ablation catheter for management of drug-resistant hypertension: a demonstrated value? *JACC Cardiovasc Interv* 2012; **5**: 766-768 [PMID: 22814782 DOI: 10.1016/j.jcin.2012.02.019]

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World Journal of Hypertension (*World J Hypertens*, *WJH*, online ISSN 2220-3168, DOI: 10.5494) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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EDITORIAL

Dairy: A lower percent investment in the volatile hypertensive environment

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Abstract

In cross-sectional and intervention studies, low-fat dairy has proven to be effective in lowering blood pressure in a hypertensive population. Contributing mechanisms include the angiotensin-converting enzyme-inhibiting effects of peptides and possible interplay between calcium and vitamin D. Easily added to the diet, low-fat dairy is an attractive addition to nutritional, lifestyle, and pharmacological interventions to treat hypertension.

Key words: Dairy; Blood pressure; Hypertension; Milk; Cardiovascular

Core tip: Low-fat dairy has shown to be effective in lowering blood pressure in a hypertensive population. Contributing mechanisms include the angiotensin-converting enzyme-inhibiting effects of peptides and possible interplay between calcium and vitamin D. Easily added to the diet, low-fat dairy is an attractive addition to nutritional, lifestyle, and pharmacological interventions to treat hypertension.

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BRIEF REVIEW: LOW-FAT DAIRY AND HYPERTENSION

Hypertension affects nearly 1/3 of Americans over the age of 20 and 3/4 of those over 65 years of age[1]. Hypertension can be treated with pharmacological interventions, but the drug therapies are often accompanied by unwanted side effects including reduced functional capacity and orthostatic hypotension[2]. Accordingly, non-pharmacological lifestyle modifications that can help resolve hypertension without the associated side effects of medication are increasingly emphasized. Indeed, recommendations by the Joint National Committee on Prevention,

Detection, Evaluation, and Treatment of High Blood Pressure indicate that lifestyle-based interventions can elicit hypotensive effects and should be incorporated into any treatment plan for high blood pressure[3]. Some interventions require a lot of effort (*e.g.*, regular exercise) or drastic changes (*e.g.,* hypocaloric diet) that compliance and adherence rates may be substantially low. In this context, an idea of simply adding milk into the routine diet is attractive as it is easy and simple to implement. Does that help lower blood pressure?

Cross-sectional studies have found higher intakes of low-fat dairy are associated with lower risk of hypertension[4]. Consuming 2 or more servings a day of low fat dairy products decreased the relative risk of incident hypertension by 11%[5]. The results of the dietary intervention studies are consistent with the cross-sectional or observational findings. The Dietary Approaches to Stop Hypertension (DASH) diet is low in total fat, saturated fat, and sodium, but high in fruit and vegetables. In a hypertensive population, consuming the DASH diet combined with low-fat dairy products decreased blood pressure more than a diet high in fruits and vegetables alone[6]. The hypotensive effects seen from the inclusion of low-fat dairy in the DASH diet are preserved by adding 4 servings/d of low-fat dairy without further adjustments to a typical diet[7]. Yet this effect is not seen with the addition of a single serving of low-fat dairy[8] suggesting that there is minimum dose required for the hypotensive effects of low fat dairy. Further, beneficial effects of dairy on retinal vascular structures offer promise for improved microcirculation and end-organ vascular health potentially achieved with chronic dairy consumption[9,10].

Physiological mechanisms underlying the hypotensive effects of dairy are unknown but multiple mechanisms are likely involved. Increasing serum calcium through dietary intake would decrease serum 1,25-OH_2-vitamin D concentrations and decrease the calcium ion flux into cells thereby preventing the intracellular calcium-mediated vasoconstriction of smooth muscle cells in the muscularis externa of the arterial wall[11]. In fact, the DASH diet with low-fat dairy included lowered 1,25-OH_2-vitamin D and intracellular calcium more than the DASH diet alone; the decreased intracellular calcium correlated with a fall in blood pressure[12]. Additionally, an independent association between the isoform of vitamin D and increased blood pressure has been established further reinforcing the link between calcium, vitamin D, and blood pressure[13].

Bovine milk is comprised of 31%-33% protein of which 80% is casein and 20% is whey. Both forms of proteins have been implicated in eliciting the hypotensive effects of dairy[14-17]. These effects are likely due to the ACE-inhibiting properties of peptides, specifically casein and whey derived lactotripeptides, casokinins and lactokinins, respectively[11,18]. Both require enzymatic hydrolysis to release the functional peptides, which is accomplished through the fermentation process of digestion by lactic acid-producing bacteria. Proline-proline dipeptides, including Ile-Pro-Pro and Val-Pro-Pro, have shown to resist degradation during digestion and may be more effective at lowering blood pressure than other peptides[11,18]. Twelve weeks of casein and whey supplementation in overweight men and women decreased blood pressure with no difference between the two forms of proteins[19]. These hypotensive effects may require regular consumption of proteins as acute ingestion of whey and casein do not exert an effect on blood pressure[15]. Certain milk peptides may inhibit endothelin-1 release by endothelium cells, reduce chronic vasoconstrictor tone, and exert the hypotensive effects[20]. Interestingly, fermented strains of Lactobacillus helveticus (naturally high in ACE inhibitory tripeptides) have also been shown to reduce blood pressure, suggesting the bacteria responsible for fermentation may also play a role[17,21].

Is there any benefit of consuming whole milk and full-fat dairy products? In the 1970s, the link between saturated fat intake and cardiovascular disease (CVD) was identified, but it wasn't until the early 1990s when recommendations to reduce saturated fat intake led to the emergence and popularity of low fat diets. As a result, the notion that whole milk/dairy would exert unfavorable effects on blood cholesterol and thus cardiovascular health became wide spread among the public. Recent reviews and meta-analyses on dairy and blood pressure have found no such link between full-fat dairy and CVD[14,22]. In regards to blood pressure, while low fat dairy has consistently demonstrated hypotensive effects, full-fat dairy showed no such association[4,23]. Interestingly, if peptides and calcium are the primary contributors to the hypotensive effects of dairy, it seems reasonable that full-fat dairy products would also elicit the hypotensive effects seen from low-fat dairy as these components are still present at similar quantities. Future dietary interventions using whole milk and full-fat dairy are needed to answer this important and relevant question.

Clearly, simply adding milk and dairy to the routine diet does not elicit unwanted side effects and is an easy lifestyle modification to make. It is much easier than performing strenuous exercise or undergoing hypocaloric diet. Obviously, this dietary intervention is not suitable for those with lactose intolerance but is highly generalizable to most individuals with high blood pressure. However, there are a lot of unanswered questions regarding the relation between dairy products and hypertension. Is whole milk and full-fat dairy effective in lowering blood pressure? What is the dominant physiological mechanisms underlying the hypotensive effects of dairy? What dairy products (*e.g.,* milk, yogurt, cheese) are most effective in reducing blood pressure? Is there any additive hypotensive effects of dairy when they were combined with other lifestyle modifications[24]? Regardless, for those diagnosed with hypertension, adding low-fat dairy to a treatment plan of nutritional, lifestyle, and pharmacological interventions could be a small

investment that yields a lifetime of returns.

REFERENCES

1 **National Center for Health Statistics**. Health United States: With Special Feature on Socioeconomic Status and Health. [Accessed 2013 Feb 21]. Available from: URL: http://www.cdc.gov/nchs/data/hus/hus11.pdf

2 **Curb JD**, Borhani NO, Blaszkowski TP, Zimbaldi N, Fotiu S, Williams W. Long-term surveillance for adverse effects of antihypertensive drugs. *JAMA* 1985; **253**: 3263-3268 [PMID: 3999311 DOI: 10.1001/jama.1985.03350460063022]

3 **Chobanian AV**, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560-2572 [PMID: 12748199 DOI: 10.1001/jama.289.19.2560]

4 **Wang L**, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension* 2008; **51**: 1073-1079 [PMID: 18259007 DOI: 10.1161/HYPERTENSIONAHA.107.107821]

5 **Alonso A**, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr* 2005; **82**: 972-979 [PMID: 16280427]

6 **Appel LJ**, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; **336**: 1117-1124 [PMID: 9099655 DOI: 10.1056/NEJM199704173361601]

7 **Machin DR**, Park W, Alkatan M, Mouton M, Tanaka H. Hypotensive effects of solitary addition of conventional nonfat dairy products to the routine diet: a randomized controlled trial. *Am J Clin Nutr* 2014; **100**: 80-87 [PMID: 24808486 DOI: 10.3945/ajcn.114.085761]

8 **Maki KC**, Rains TM, Schild AL, Dicklin MR, Park KM, Lawless AL, Kelley KM. Effects of low-fat dairy intake on blood pressure, endothelial function, and lipoprotein lipids in subjects with prehypertension or stage 1 hypertension. *Vasc Health Risk Manag* 2013; **9**: 369-379 [PMID: 23901280 DOI: 10.2147/VHRM.S45684]

9 **Gopinath B**, Flood VM, Burlutsky G, Louie JC, Baur LA, Mitchell P. Dairy food consumption, blood pressure and retinal microcirculation in adolescents. *Nutr Metab Cardiovasc Dis* 2014; **24**: 1221-1227 [PMID: 24996501 DOI: 10.1016/j.numecd.2014.05.014]

10 **Gopinath B**, Flood VM, Louie JC, Wang JJ, Burlutsky G, Rochtchina E, Mitchell P. Consumption of dairy products and the 15-year incidence of age-related macular degeneration. *Br J Nutr* 2014; **111**: 1673-1679 [PMID: 24502821 DOI: 10.1017/S000711451300408X]

11 **Dugan CE**, Fernandez ML. Effects of dairy on metabolic syndrome parameters: a review. *Yale J Biol Med* 2014; **87**: 135-147 [PMID: 24910559]

12 **Hilpert KF**, West SG, Bagshaw DM, Fishell V, Barnhart L, Lefevre M, Most MM, Zemel MB, Chow M, Hinderliter AL, Kris-Etherton PM. Effects of dairy products on intracellular calcium and blood pressure in adults with essential hypertension. *J Am Coll Nutr* 2009; **28**: 142-149 [PMID: 19828899 DOI: 10.1080/07315724.10719765]

13 **Kris-Etherton PM**, Grieger JA, Hilpert KF, West SG. Milk products, dietary patterns and blood pressure management. *J Am Coll Nutr* 2009; **28** Suppl 1: 103S-119S [PMID: 19571168 DOI: 10.1080/07315724.2009.107019804]

14 **German JB**, Gibson RA, Krauss RM, Nestel P, Lamarche B, van Staveren WA, Steijns JM, de Groot LC, Lock AL, Destaillats F. A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. *Eur J Nutr* 2009; **48**: 191-203 [PMID: 19259609 DOI: 10.1007/s00394-009-0002-5]

15 **Pal S**, Ellis V. Acute effects of whey protein isolate on blood pressure, vascular function and inflammatory markers in overweight postmenopausal women. *Br J Nutr* 2011; **105**: 1512-1519 [PMID: 21272399 DOI: 10.1017/S0007114510005313]

16 **Pal S**, Radavelli-Bagatini S. The effects of whey protein on cardiometabolic risk factors. *Obes Rev* 2013; **14**: 324-343 [PMID: 23167434 DOI: 10.1111/obr.12005]

17 **Tholstrup T**. Dairy products and cardiovascular disease. *Curr Opin Lipidol* 2006; **17**: 1-10 [PMID: 16407709 DOI: 10.1097/01.mol.0000199813.08602.58]

18 **Fekete ÁA**, Givens DI, Lovegrove JA. The impact of milk proteins and peptides on blood pressure and vascular function: a review of evidence from human intervention studies. *Nutr Res Rev* 2013; **26**: 177-190 [PMID: 24135454 DOI: 10.1017/S0954422413000139]

19 **Pal S**, Ellis V. The chronic effects of whey proteins on blood pressure, vascular function, and inflammatory markers in overweight individuals. *Obesity* (Silver Spring) 2010; **18**: 1354-1359 [PMID: 19893505 DOI: 10.1038/oby.2009.397]

20 **Maes W**, Van Camp J, Vermeirssen V, Hemeryck M, Ketelslegers JM, Schrezenmeir J, Van Oostveldt P, Huyghebaert A. Influence of the lactokinin Ala-Leu-Pro-Met-His-Ile-Arg (ALPMHIR) on the release of endothelin-1 by endothelial cells. *Regul Pept* 2004; **118**: 105-109 [PMID: 14759563 DOI: 10.1016/j.regpep.2003.11.005]

21 **Seppo L**, Jauhiainen T, Poussa T, Korpela R. A fermented milk high in bioactive peptides has a blood pressure-lowering effect in hypertensive subjects. *Am J Clin Nutr* 2003; **77**: 326-330 [PMID: 12540390]

22 **Elwood PC**, Pickering JE, Givens DI, Gallacher JE. The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. *Lipids* 2010; **45**: 925-939 [PMID: 20397059 DOI: 10.1007/s11745-010-3412-5]

23 **Ralston RA**, Lee JH, Truby H, Palermo CE, Walker KZ. A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. *J Hum Hypertens* 2012; **26**: 3-13 [PMID: 21307883 DOI: 10.1038/jhh.2011.3]

24 **Yoshizawa M**, Maeda S, Miyaki A, Misono M, Choi Y, Shimojo N, Ajisaka R, Tanaka H. Additive beneficial effects of lactotripeptides intake with regular exercise on endothelium-dependent dilatation in postmenopausal women. *Am J Hypertens* 2010; **23**: 368-372 [PMID: 20075849 DOI: 10.1038/ajh.2009.270]

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Multi-slice computerized tomography critical role in transcatheter aortic valve implantation plan: Review of current literature

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Abstract

Transcatheter aortic valve implantation (TAVI) has been shown in improve outcome of severe aortic stenosis (AS) patients, deemed surgical high-risk or inoperable, and has grown popular in the past decade. The procedure requires accurate prior planning, and demands an integration of a "Heart Team" consisted from cardiac surgeons, interventional cardiologists, and imaging experts. The role of cardiac imaging and especially multi-slice computerized tomography (MSCT) has been a mainstay of pre-evaluation of severe AS patients that allows to accurately depict and size the cardiac and vascular structures, and has become the primary tool for procedural planning. This article is aimed to evaluate current uses of MSCT in severe AS patients undergoing TAVI, delineate the various measurements derived from this modality and review current literature regarding it's advantages over other techniques.

Key words: Transcatheter aortic valve implantation; Multi-slice computerized tomography; Aortic annular sizing; Vascular access

Core tip: Transcatheter aortic valve implantation (TAVI) has been shown in improve outcome of severe aortic stenosis patients, deemed surgical high-risk or inoperable, and has grown popular in the past decade. The procedure requires accurate prior planning, and demands an integration of a "Heart Team" approach consisted from cardiac surgeons, interventional cardiologists, and imaging experts. The role of cardiac imaging and especially multi-slice computerized tomography (MSCT) has been a mainstay of TAVI evaluation, and allows accurate depiction and sizing of the cardiac and vascular structures. This article is aimed to review current use of MSCT in TAVI patients.

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been shown to improve outcome of severe aortic stenosis patients deemed inoperable[1] or high risk[2], with mortality rates lower than surgical aortic valve replacement[3]. However, this procedure incurs complications such as paravalvular leak, vascular access complications, stroke, conduction defects requiring pacemaker implantation, and less commonly, annular rupture[4,5].

A "heart team" approach is recommended in any patient considered for TAVI[6,7]. This team is comprised of a multidisciplinary team including general cardiologists, cardiac surgeons, interventional cardiologists, anesthesiologists and imaging cardiologists. The assessment of each patient requires evaluation of symptoms, cardiac and valvular function[8] to determine the severity of aortic stenosis and appropriateness of intervention. Once a patient is considered for intervention, the risk of surgery should be determined according to comorbidities, patient function and frailty and technical aspects such as porcelain aorta and prior cardiac surgery[9,10]. In case of inoperability or high surgical risk, additional imaging should be performed for the evaluation of suitability for TAVI in order to determine annular size, distance between annulus and coronary artery ostium, implantation angle, and vascular access. This can be done by various methods, most commonly by multi-slice computerized tomography (MSCT). This review aim is to describe MSCT for evaluation of patients referred for TAVI.

MSCT DATA

Unlike surgery, where direct visualization and sizing of the valve is done, TAVI is performed with a 2-dimentional fluoroscopy guidance, where it is difficult to asses proper valvular size and access routes. MSCT enables extracting a large amount of data from a 3-dimentional image which include access options by measuring the diameters of the arteries and aorta in the perpendicular plane, establishing the presence of protruding atherosclerotic plaques, assessing the calcification of the arteries and aortic annulus and evaluating annular dimensions and its proximity to important anatomical landmarks such as the coronary arteries ostium (Table 1). These measurements require an accurate alignment of images in the appropriate plane done by an imaging expert and reviewed by the interventional cardiologist.

MSCT DATA ACQUISITION

The acquisition of the CT data should be performed during an inspiratory breathhold while the electrocardiogram (ECG) should be recorded simultaneously to allow retrospective or prospective gating of the data. Imaging of the annulus in systole, when the aortic annulus size increases[11], may be preferable over the diastole; however, analysis of the aorta and peripheral arteries can be performed without ECG synchrony.

Table 1 Data derived from multi-slice computerized tomography imaging

Assessment of the aortic annulus
Annular shape
Calcification
Annular diameters, area and perimeter coronary artery ostia and additional
Aortic root dimensions
Coronary ostium height
Sinus of valsava diameter and height
Sinutubular junction diameter
Ascending aorta diameter
Aortic annulus plane for fluoroscopy
Degree of aortic angulation in relation to the annulus
Optimal projection angle
Access route evaluation
Pelvic and aortic minimal diameters
Vascular calcification
Vascular tortuosity
Presence of protruding atherosclerotic plaques and thrombi

ASSESSMENT OF THE AORTIC ANNULUS

The aortic root is a complex anatomic structure comprised from a tri-leaflet valve inserted in a semi-lunar mode into the left ventricle and aortic root, which creates the sinuses of valsava that accommodate the coronaries origin. It lies in a close proximity to the atrioventricular node and the left bundle of the cardiac conduction system[12].

Accurate measurement of the aortic annulus is a critical step in the planning of TAVI, since it enables proper valve sizing, grades calcification of aortic annulus and measure the distance to the coronaries origin. These parameters point to possible complications including paravalvular leaks[13,14], annular rupture[15,16] and coronary arteries obstruction[17,18], all of which have adverse impact on patients outcome[19,20].

The aortic annulus has an oval shape, thus measuring its diameter in a single plane is inaccurate and misleads the operators when sizing the valve[21]. Therefore measuring annular diameter by 2D echocardiography usually provides the shorter diameter and consequently undersizes annular dimensions[22]. Precise measurement of annular dimensions requires alignment of the image in a perpendicular plane to the basal part of leaflets insertion (Figure 1). The parameters derived from annular measurements include short and long diameters, mean diameter, perimeter and area. The aortic annulus, generally elliptic, assumes a more round shape in systole, thus increasing cross sectional area without substantial change in perimeter. Perimeter changes are negligible in patients with calcified valves, because tissue properties allow very little expansion. Aortic annulus perimeter appears therefore ideally

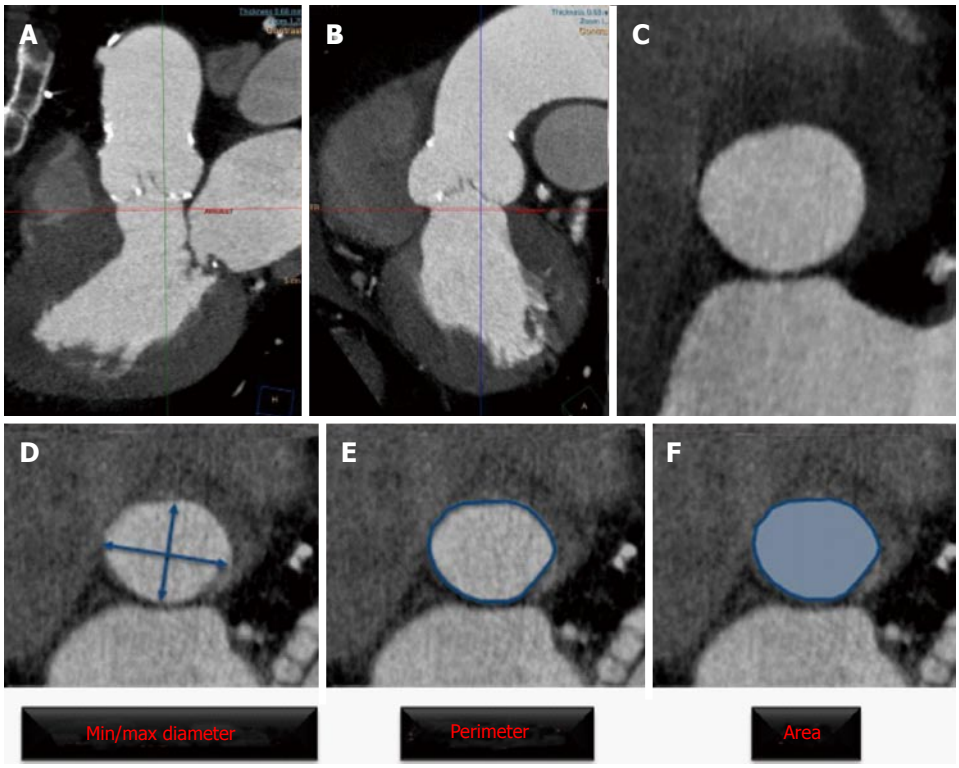

Figure 1 Aortic annulus dimensions.

suited for accurate sizing in TAVI[11]. Inter- and Intra-observer variability of these measurement by MSCT is small and highly reproducible as shown in a recent study[23] and studies comparing different modalities for prosthesis sizing have shown reduction in paravalvular leak with MSCT measurement compared with 2D echocardiography[24,25] and therefore MSCT is currently regarded as an essential tool for accurate prosthesis sizing.

CORONARY ARTERY OSTIA AND ADDITIONAL AORTIC ROOT DIMENSIONS

Besides aortic annular dimension, other considerations should be taken into account upon deciding valve type and size. Coronary ostia height and sinus of valsalva diameter should be measured (Figures 2 and 3), and coronary obstruction risk must be assessed since the native valve leaflets are displaced and could potentially obstruct the coronary flow. In a multicenter registry, coronary obstruction was reported in less than 1% of TAVI patients[17]. Predictors of coronary obstruction were low coronary ostia height and small sinus of valsalva diameter along with female gender, valve-in-valve procedure and balloon expandable valve[17]. The outcome of this complication is catastrophic with a 30-d mortality rate of more than 40%. Therefore, it is crucial to measure coronary ostia height, ensure adequate sinus of valsalva diameter and height according to the device requirements, as published by the manufacturer.

Sinotubular junction diameter (Figure 4) should also be considered since a smaller diameter than the valve implanted could pose a risk of aortic injury upon balloon inflation in balloon expandable valves. In self-expandable valves the ascending aorta (Figure 5) acts as an anchorage point, hence, large diameters as in aortic aneurysm are a contraindication for the use of this type of valve.

AORTIC ANNULUS PLANE FOR FLUOROSCOPY

Positioning of the valve is a critical step in TAVI procedure, which is usually performed under angiography guidance. Since, angiography is a 2D image, precise planar projection is required for accurate centered implantation of the valve in a perpendicular angle to the native valve plane. Assessment of the proper implantation plane can be located by angiography, however, this methods has some caveats such as, additional contrast injection and radiation exposure along with the inherent requirement for interpreting a 2D image in a 3 dimensional manner. Moreover, certain anatomic features can complicate this task, like severe calcification of the aortic valve and root, which can obscure the leaflet insertion, and chest deformation, which can require extreme angles for implantation. MSCT allows a 3D image reconstruction without the need for additional contrast or radiation, and has been shown to accurately predict the valve deployment

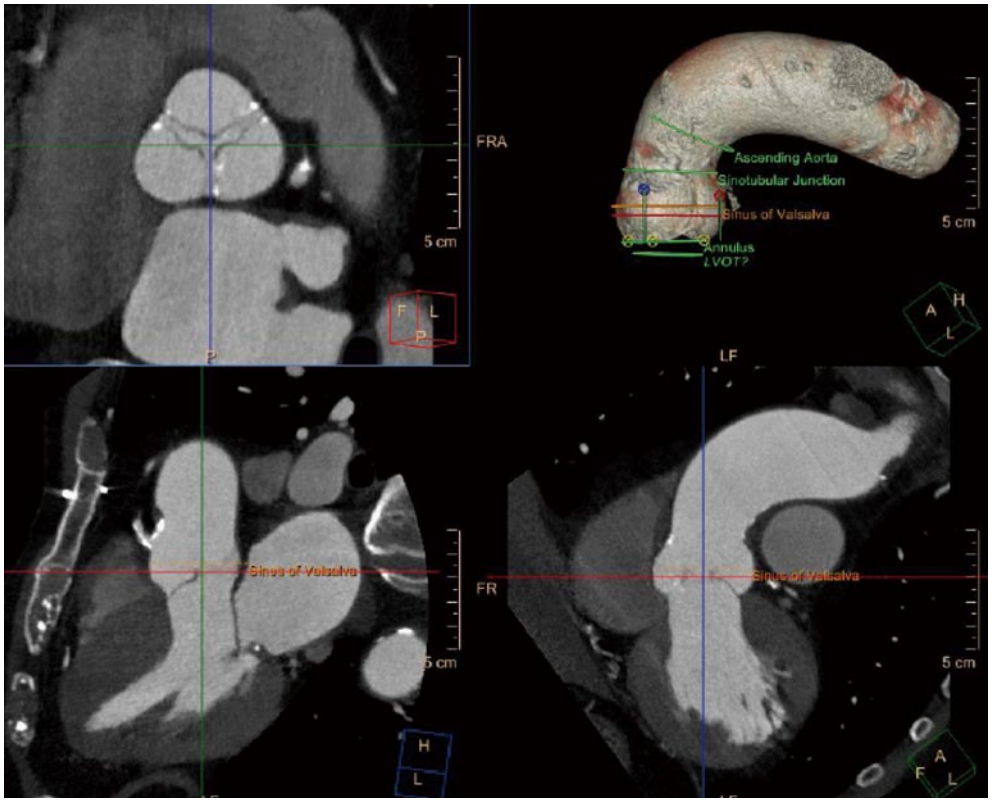

Figure 2 Sinus of valsalva dimensions.

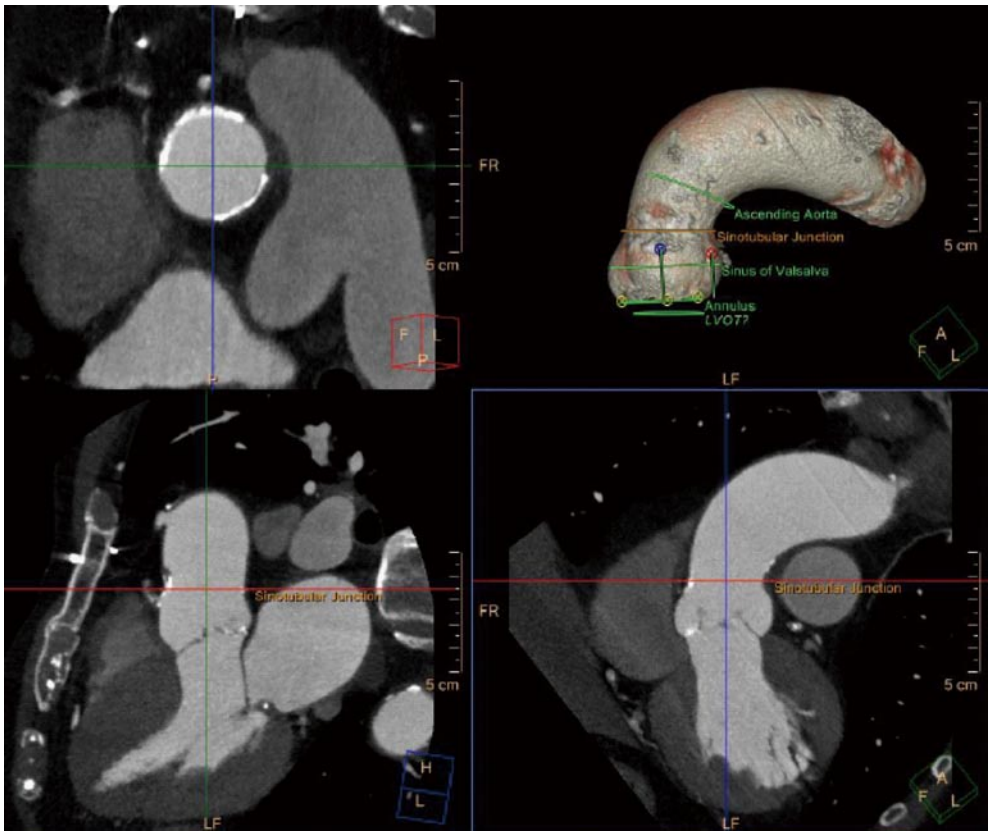

Figure 3 Sinotubular junction dimensions

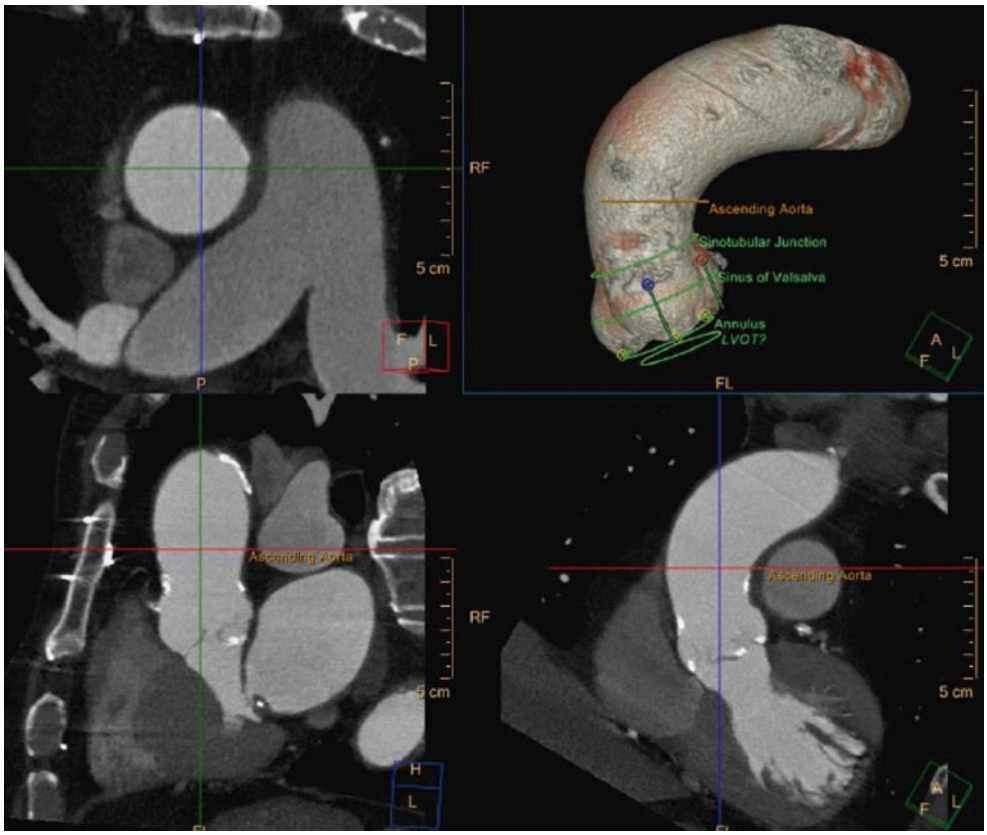

Figure 4 Sinotubular junction dimensions.

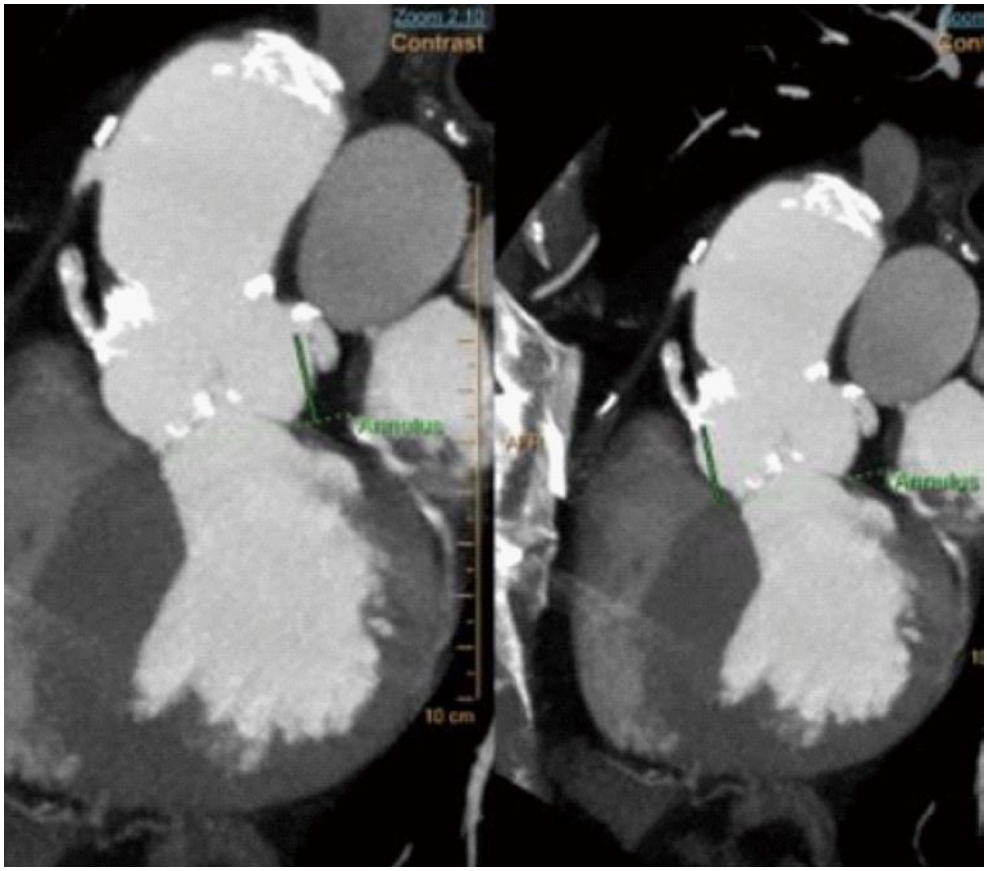

Figure 5 Coronary height for the left main (right image) and right coronary artery (left image).

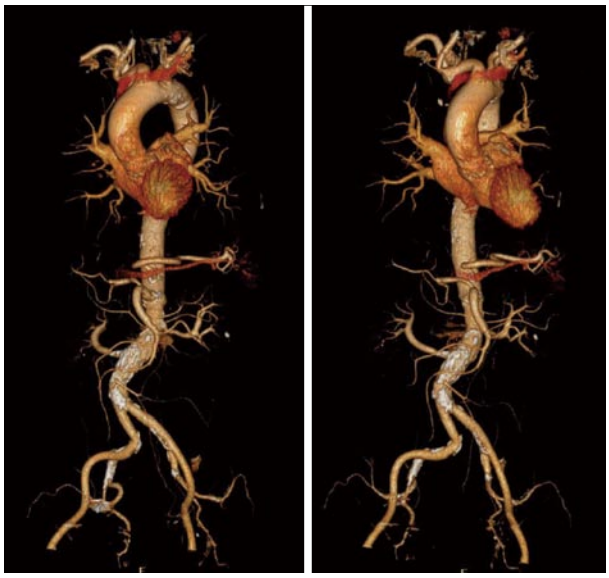

Figure 6 Aorta and iliac arteries 3D reconstruction.

projection[26], by creating a "line of perpendicularity" which denotes the projections that can be used in order to implant the valve in an orthogonal plane to the native valve[26].

ACCESS ROUTE EVALUATION

The transfemoral route is currently the default approach for TAVI procedure. The femoral arteries can accommodate a sheath with slightly higher diameter if it is not calcified; however, circumferential calcification and tortuosity especially with involvement of bifurcations are predictors of vascular complication. Thus, utilization of transfemoral approach requires precise evaluation of vascular diameters, calcification and tortuosity (Figure 6). This can be achieved by MSCT, which accurately depicts the vascular anatomy in a 3D imaging. Vascular complications have been shown to impact outcome of TAVI patients, and its incidence was above 30% in the PARTNER trial[1], where route assessment was performed by angiography. The utilization of MSCT have reduced major vascular complications rate from 8% to 1% and minor vascular complications from 24% to 8% over the 2-year study period. The vessel minimal luminal diameter being smaller than the sheath external diameter (23% *vs* 5%) and the presence of calcified vessels (29% *vs* 9%) were strong predictors for vascular complications[27].

Measurements of minimal vessel diameters should be performed after a multi-planar reconstruction along the entire course of the vessels in order to attain a perpendicular image. Vessel calcifications should be assessed according to circumferential involvement due to its limitations in accommodating the sheath, and prohibiting the safe passage of the delivery system. Vessel calcification can falsely cause underestimation of its diameter due to the "blooming" effect, in which the calcified segment appears larger than it true dimension thus reducing the size of the true lumen. Tortuosity can be evaluated after 3D reconstruction the aorta and iliofemoral vessels[28], and although severe tortuosity can be straightened. Assessment of alternative routes can be performed by reconstructing images depicting the subclavian artery diameter, calcification and course for this route, and aortic calcification for a transaortic route.

CONCLUSION

TAVI frequency is growing worldwide, and accordingly the experience with regard to planning the procedure, avoiding complications, and treating them when they occur. The utilization of advanced imaging techniques such as MSCT, with sophisticated data acquisition protocols have significantly improved our ability to assess the access site, accurately size the aortic root dimension and select the appropriate device size, and importantly estimate and avoid fatal complications. Accordingly, most of TAVI programs include an imaging specialist in the heart team. We expect that the use and experience of MSCT will grow and enhanced techniques and algorithms will allow us to further improve the outcome of patients undergoing TAVI in light of the large number of new devices that are currently available or on trial.

REFERENCES

1 **Leon MB**, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; **363**: 1597-1607 [PMID: 20961243 DOI: 10.1056/NEJMoa1008232]

2 **Smith CR**, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364**: 2187-2198 [PMID: 21639811 DOI: 10.1056/NEJMoa1103510]

3 **Adams DH**, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014; **370**: 1790-1798 [PMID: 24678937 DOI: 10.1056/NEJMoa1400590]

4 **Eltchaninoff H**, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavie A, Gueret P. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J* 2011; **32**: 191-197 [PMID: 20843959 DOI: 10.1093/eurheartj/ehq261]

5 **Zahn R**, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, Hambrecht R, Sack S, Hauptmann KE, Richardt G, Figulla HR, Senges J. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J* 2011; **32**: 198-204 [PMID: 20864486 DOI: 10.1093/eurheartj/ehq339]

6 **Nishimura RA**, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 2014 AHA/ACC guideline for the management

of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: e57-185 [PMID: 24603191 DOI: 10.1016/j.jacc.2014.02.537]

7 **Vahanian A**, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33**: 2451-2496 [PMID: 22922415 DOI: 10.1093/eurheartj/ehs109]

8 **Zoghbi WA**, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; **16**: 777-802 [PMID: 12835667 DOI: 10.1016/S0894-7317(03)00335-3]

9 **Hattler BG**, Madia C, Johnson C, Armitage JM, Hardesty RL, Kormos RL, Pham SM, Payne DN, Griffith BP. Risk stratification using the Society of Thoracic Surgeons Program. *Ann Thorac Surg* 1994; **58**: 1348-1352 [PMID: 7979657 DOI: 10.1016/0003-4975(94)91911-9]

10 **Roques F**, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999; **15**: 816-822; discussion 822-823 [PMID: 10431864 DOI: 10.1016/S1010-7940(99)00106-2]

11 **Hamdan A**, Guetta V, Konen E, Goitein O, Segev A, Raanani E, Spiegelstein D, Hay I, Di Segni E, Eldar M, Schwammenthal E. Deformation dynamics and mechanical properties of the aortic annulus by 4-dimensional computed tomography: insights into the functional anatomy of the aortic valve complex and implications for transcatheter aortic valve therapy. *J Am Coll Cardiol* 2012; **59**: 119-127 [PMID: 22222074 DOI: 10.1016/j.jacc.2011.09.045]

12 **Piazza N**, de Jaegere P, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Interv* 2008; **1**: 74-81 [PMID: 20031657 DOI: 10.1161/CIRCINTERVENTIONS.108.780858]

13 **Hayashida K**, Lefèvre T, Chevalier B, Hovasse T, Romano M, Garot P, Bouvier E, Farge A, Donzeau-Gouge P, Cormier B, Morice MC. Impact of post-procedural aortic regurgitation on mortality after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012; **5**: 1247-1256 [PMID: 23257373 DOI: 10.1016/j.jcin.2012.09.003]

14 **Sinning JM**, Hammerstingl C, Vasa-Nicotera M, Adenauer V, Lema Cachiguango SJ, Scheer AC, Hausen S, Sedaghat A, Ghanem A, Müller C, Grube E, Nickenig G, Werner N. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012; **59**: 1134-1141 [PMID: 22440213 DOI: 10.1016/j.jacc.2011.11.048]

15 **Rezq A**, Basavarajaiah S, Latib A, Takagi K, Hasegawa T, Figini F, Cioni M, Franco A, Montorfano M, Chieffo A, Maisano F, Corvaja N, Alfieri O, Colombo A. Incidence, management, and outcomes of cardiac tamponade during transcatheter aortic valve implantation: a single-center study. *JACC Cardiovasc Interv* 2012; **5**: 1264-1272 [PMID: 23257375 DOI: 10.1016/j.jcin.2012.08.012]

16 **Hayashida K**, Bouvier E, Lefèvre T, Hovasse T, Morice MC, Chevalier B, Romano M, Garot P, Farge A, Donzeau-Gouge P, Cormier B. Potential mechanism of annulus rupture during transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2013; **82**: E742-E746 [PMID: 22718400 DOI: 10.1002/ccd.24524]

17 **Ribeiro HB**, Webb JG, Makkar RR, Cohen MG, Kapadia SR, Kodali S, Tamburino C, Barbanti M, Chakravarty T, Jilaihawi H, Paradis JM, de Brito FS, Cánovas SJ, Cheema AN, de Jaegere PP, del Valle R, Chiam PT, Moreno R, Pradas G, Ruel M, Salgado-Fernández J, Sarmento-Leite R, Toeg HD, Velianou JL, Zajarias A, Babaliaros V, Cura F, Dager AE, Manoharan G, Lerakis S, Pichard AD, Radhakrishnan S, Perin MA, Dumont E, Larose E, Pasian SG, Nombela-Franco L, Urena M, Tuzcu EM, Leon MB, Amat-Santos IJ, Leipsic J, Rodés-Cabau J. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. *J Am Coll Cardiol* 2013; **62**: 1552-1562 [PMID: 23954337 DOI: 10.1016/j.jacc.2013.07.040]

18 **Ribeiro HB**, Nombela-Franco L, Urena M, Mok M, Pasian S, Doyle D, DeLarochellière R, Côté M, Laflamme L, DeLarochellière H, Allende R, Dumont E, Rodés-Cabau J. Coronary obstruction following transcatheter aortic valve implantation: a systematic review. *JACC Cardiovasc Interv* 2013; **6**: 452-461 [PMID: 23602458 DOI: 10.1016/j.jcin.2012.11.014]

19 **Tamburino C**, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napodano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011; **123**: 299-308 [PMID: 21220731 DOI: 10.1161/CIRCULATIONAHA.110.946533]

20 **Seiffert M**, Conradi L, Baldus S, Schirmer J, Blankenberg S, Reichenspurner H, Diemert P, Treede H. Severe intraprocedural complications after transcatheter aortic valve implantation: calling for a heart team approach. *Eur J Cardiothorac Surg* 2013; **44**: 478-484; discussion 484 [PMID: 23389474 DOI: 10.1093/ejcts/ezt032]

21 **Tops LF**, Wood DA, Delgado V, Schuijf JD, Mayo JR, Pasupati S, Lamers FP, van der Wall EE, Schalij MJ, Webb JG, Bax JJ. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovasc Imaging* 2008; **1**: 321-330 [PMID: 19356444 DOI: 10.1016/j.jcmg.2007.12.006]

22 **Ng AC**, Delgado V, van der Kley F, Shanks M, van de Veire NR, Bertini M, Nucifora G, van Bommel RJ, Tops LF, de Weger A, Tavilla G, de Roos A, Kroft LJ, Leung DY, Schuijf J, Schalij MJ, Bax JJ. Comparison of aortic root dimensions and geometries before and after transcatheter aortic valve implantation by 2- and 3-dimensional transesophageal echocardiography and multislice computed tomography. *Circ Cardiovasc Imaging* 2010; **3**: 94-102 [PMID: 19920027 DOI: 10.1161/CIRCIMAGING.109.885152]

23 **Schuhbaeck A**, Achenbach S, Pflederer T, Marwan M, Schmid J, Nef H, Rixe J, Hecker F, Schneider C, Lell M, Uder M, Arnold M. Reproducibility of aortic annulus measurements by computed tomography. *Eur Radiol* 2014; **24**: 1878-1888 [PMID: 24845112 DOI: 10.1007/s00330-014-3199-5]

24 **Jilaihawi H**, Kashif M, Fontana G, Furugen A, Shiota T, Friede G, Makhija R, Doctor N, Leon MB, Makkar RR. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol* 2012; **59**: 1275-1286 [PMID: 22365424 DOI: 10.1016/j.jacc.2011.11.045]

25 **Hayashida K**, Bouvier E, Lefèvre T, Hovasse T, Morice MC, Chevalier B, Romano M, Garot P, Mylotte D, Farge A, Donzeau-Gouge P, Cormier B. Impact of CT-guided valve sizing on post-procedural aortic regurgitation in transcatheter aortic valve implantation. *EuroIntervention* 2012; **8**: 546-555 [PMID: 22995080 DOI: 10.4244/EIJV8I5A85]

26 **Kurra V**, Kapadia SR, Tuzcu EM, Halliburton SS, Svensson L, Roselli EE, Schoenhagen P. Pre-procedural imaging of aortic root orientation and dimensions: comparison between X-ray angiographic planar imaging and 3-dimensional multidetector row computed tomography. *JACC Cardiovasc Interv* 2010; **3**: 105-113 [PMID: 20129578 DOI: 10.1016/j.jcin.2009.10.014]

27 **Toggweiler S**, Gurvitch R, Leipsic J, Wood DA, Willson AB, Binder RK, Cheung A, Ye J, Webb JG. Percutaneous aortic valve replacement: vascular outcomes with a fully percutaneous

procedure. *J Am Coll Cardiol* 2012; **59**: 113-118 [PMID: 22222073 DOI: 10.1016/j.jacc.2011.08.069]

28 **Achenbach S**, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). *J Cardiovasc Comput Tomogr* 2012; **6**: 366-380 [PMID: 23217460 DOI: 10.1016/j.jcct.2012.11.002]

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EDITORIAL

Kidney and cardiovascular risk in primary hypertension

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Abstract

In patients with primary hypertension, therapeutic strategies should be based on global cardiovascular risk profile rather than on the severity of blood pressure alone. Accurate assessment of concomitant risk factors and especially of the presence and extent of subclinical organ damage is of paramount importance in defining individual risk. Given the high prevalence of hypertension in the population at large, however, extensive diagnostic evaluation is often impractical or unfeasible in clinical practice. Low cost, easy to use markers of risk are needed to improve the clinical management of patients with hypertension. Early renal abnormalities such as a slight reduction in glomerular filtration rate and/or the presence of microalbuminuria are well known and powerful predictors of cardio-renal morbidity and mortality and provide a useful, low cost tools to optimize cardiovascular risk assessment. A greater use of these tests should therefore be implemented in clinical practice in order to optimize the management of hypertensive patients.

Key words: Hypertension; Albuminuria; Cardiovascular risk; Glomerular filtration rate; Risk assessment; Kidney

Core tip: Accurate assessment of global cardiovascular risk, including the search for subclinical organ damage is key for devising effective therapeutic strategies in patients with primary hypertension but is often unfeasible for economic and logistic reasons given the very high prevalence of this condition. Early renal abnormalities such as slight reduction in glomerular filtration rate and/or the presence of microalbuminuria are well known and powerful predictors of cardio-renal morbidity and mortality and provide the useful, low cost tools to optimize cardiovascular risk assessment. A greater use of these tests should therefore be implemented in clinical practice in order to optimize the management of hypertensive patients.

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INTRODUCTION

The worldwide prevalence of arterial hypertension, currently the most important modifiable risk factor for cardiac and cerebrovascular diseases, is going to increase dramatically over the next decades[1]. Recent surveys indicate that 30%-45% of adult population has high blood pressure (BP) in Western countries, with greater figures in at risk subgroups such as the elderlies, diabetics and patients with chronic kidney disease (CKD)[2]. Prevention and treatment of high BP therefore represent a big public health issue worldwide and a priority for many National Health Systems in developed countries.

Most International Guidelines recommend that therapeutic targets and strategies should be based not only on the severity of BP increase but rather on global cardiovascular (CV) risk profile in any given patient[2]. Accurate assessment of concomitant risk factors and especially of the presence and extent of subclinical target organ damage (OD) is of paramount importance in defining individual risk profile and therefore often becomes a key factor to improve cost effectiveness in the therapeutic algorithm[3].

Given the high prevalence of hypertension in the population however, extensive evaluation of risk factors including in-depth search for asymptomatic OD is often impractical or unfeasible both from a logistic and an economic point of view[4]. Low cost, easy to use, integrated markers of risk are therefore needed to improve the clinical management of patients with hypertension[5].

MILD RENAL ABNORMALITIES: USEFUL CLINICAL TOOLS FOR CARDIOVASCULAR RISK STRATIFICATION

Even modest abnormalities of renal function, such as the presence of microalbuminuria or a slight reduction in glomerular filtration rate (GFR), have been shown to predict future cardiovascular events and death[6]. While these two features of CKD do not always coexist in the same patient, they are thought to reflect, at least in part, different pathogenic mechanisms and to carry independent predictive power in patients with high BP[7].

Microalbuminuria is currently regarded as an early sign of widespread vascular damage[8]. It has been shown to cluster with a variety of unfavourable risk factors such as metabolic syndrome, lipid abnormalities, hyperuricemia as well as with a greater haemodynamic load and blood pressure profile[9]. Furthermore, it has been shown to be an integrated marker of OD, as its presence often entails the concomitant occurrence of left ventricular hypertrophy (LVH) and systemic atherosclerosis (Figure 1)[10,11]. Increased urine albumin excretion (UAE) is a strong independent predictor of CV events, renal complications and death[12]. The relationship between UAE and risk is linear and holds also for albuminuria values well within the normal range[6]. These data, together with the relatively low cost and wide availability of this test, make searching for albuminuria an ideal screening and diagnostic tool to be used in clinical practice[5].

Even a mild reduction in GFR entails a cluster of unfavourable haemodynamic and metabolic modifications that negatively impact global and cardiovascular prognosis in hypertensive patients[13]. In fact, CKD, albeit often asymptomatic and therefore largely undetected in clinical practice, is known to bring about a number of atherogenic mechanisms such as insulin resistance, secondary hyperparathyroidism, vitamin D deficit, anaemia, subclinical inflammation, increased oxidative stress, lipids abnormalities, mild hyperuricemia and endothelial dysfunction[14].

Needless to say that the coexistence of GFR reduction and increase in UAE, a condition thought to occur in 20%-30% of CKD patients, entails an even higher risk as the two components of CKD retain independent prognostic power. Hence, GFR and UAE should be measured together to improve the assessment of risk[13].

SHOULD WE LOOK AT CHANGES IN ALBUMINURIA TO DETECT CHANGES IN CARDIOVASCULAR RISK?

The presence of subclinical OD at the cardiac, vascular and renal level has traditionally been regarded as an intermediate step between long-term exposure to risk factors and the incidence of major events[15]. As the development of OD signals a condition of greater risk, so prevention or regression of OD as a result of an effective treatment has been demonstrated to entail a parallel reduction of risk. Thus, regression of LVH has been shown to be associated with a better prognosis and has been proposed as an independent therapeutic target[16].

More recently, it has been suggested that albuminuria changes under treatment may provide additional information on the effectiveness of treatment[2,17]. Several clinical trials however, have yielded contrasting data on this issue. Thus, results of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study indicated that on-treatment modifications of UAE go in parallel to the incidence of fatal events[17,18]. On the contrary, in the ACCOMPLISH trial, antihypertensive treatment with angiotensin converting enzyme-inhibitors (ACE-I)/Calcium Channel Blockers combination was associated with better CV outcome as compared to ACE-I/diuretic combination, although the latter entailed a significantly greater reduction in urine albumin excretion[19]. In this context, results of the ONTARGET trial may give rise to conflicting interpretations. In fact, while a larger reduction in UAE was recorded in the arm treated with ACE-I/angiotensin Ⅱ receptors blockers (ARB) combination, this treatment provided no clear benefit in

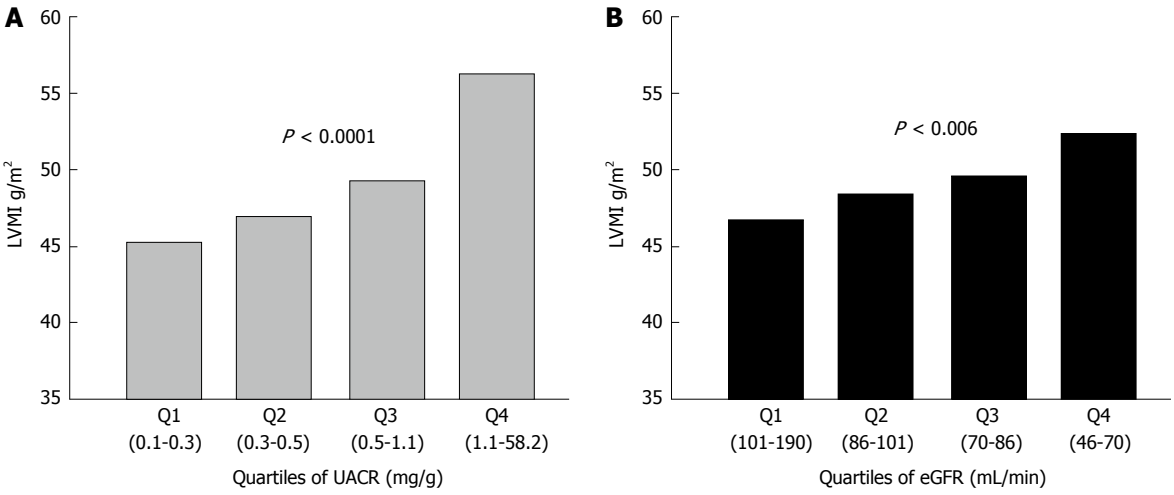

Figure 1 Cardiac organ damage is associated with subclinical renal abnormalities. Left ventricular mass increases along with changes in albuminuria (A) and reduction of eGFR (B) in patients with primary hypertension (n = 400). Modified from Leoncini *et al*[11]. LVMI: Left ventricular mass index; eGFR: Estimated glomerular filtration rate; UACR: Urine albumin to creatinine ratio.

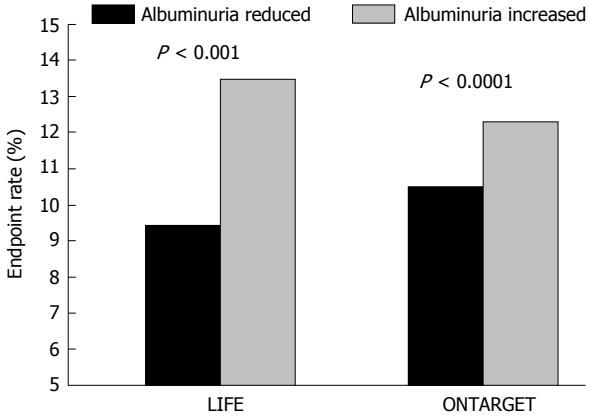

Figure 2 Changes in albuminuria translate into parallel changes in cardiovascular risk. In the LIFE study (left) and in the ONTARGET study the incidence of cardiovascular events was significantly greater in patients showing increases in urine albumin excretion over time as compared to those who showed reduction or no change. Modified from Ibsen *et al*[17] and Schmieder *et al*[21]. LIFE: The Losartan Intervention For Endpoint reduction in hypertensionstudy.

the incidence of major endpoints as compared to ACE-I or ARB monotherapy[20]. However, when changes in UAE were analysed independently of randomization to specific treatment, those patients experiencing a greater reduction of albuminuria under treatment also showed better CV outcome as compared to patients with an increase or no change in albuminuria[21] (Figure 2). This issue has recently been the object of a large meta-regression analysis, involving thirty-two randomized studies and a total of 80812 hypertensive and/or diabetic patients[22]. In fact, Savarese *et al*[22] reported that reduction in UAE was associated with reduced risk of myocardial infarction and stroke, suggesting that UAE changes may represent a valuable intermediate end-point for CV risk evaluation in clinical practice. However, the conclusions of the above mentioned study were weakened by a number of biases, such as the heterogeneity of therapeutic interventions and length of follow-up that may limit the value of reported findings.

CONCLUSION

Accurate risk stratification is of paramount importance to devise cost-effective diagnostic and therapeutic strategies in patients with primary hypertension. An extensive search for subclinical OD is essential to assess global risk profile in most patients, but is often unfeasible for economic and logistic reasons due to the very high prevalence of hypertension. Early renal abnormalities such as slight reduction in GFR and/or the presence of microalbuminuria are well known and powerful predictors of cardio-renal morbidity and mortality and provide useful, low cost tools to optimize CV risk assessment. Furthermore, monitoring treatment-induced changes of UAE may be helpful in the management of high-risk patients.

REFERENCES

1 **Ezzati M**, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; **360**: 1347-1360 [PMID: 12423980 DOI: 10.1016/S0140-6736(02)11403-6]

2 **Mancia G**, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press* 2014; **23**: 3-16 [PMID: 24359485 DOI: 10.3109/08037051.2014.868629]

3 **Viazzi F**, Leoncini G, Parodi D, Ratto E, Vettoretti S, Vaccaro V, Parodi A, Falqui V, Tomolillo C, Deferrari G, Pontremoli R. Impact of target organ damage assessment in the evaluation of global risk in patients with essential hypertension. *J Am Soc Nephrol* 2005; **16** Suppl 1: S89-S91 [PMID: 15938043 DOI: 10.1681/ASN.2004110956]

4 **Leoncini G**, Ratto E, Viazzi F, Conti N, Falqui V, Parodi A, Tomolillo C, Deferrari G, Pontremoli R. Global risk stratification in primary hypertension: the role of the kidney. *J Hypertens* 2008;

26: 427-432 [PMID: 18300851]
5 **Leoncini G**, Viazzi F, Pontremoli R. Overall health assessment: a renal perspective. *Lancet* 2010; **375**: 2053-2054 [PMID: 20483450 DOI: 10.1016/S0140-6736(10)60748-9]
6 **Matsushita K**, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073-2081 [PMID: 20483451 DOI: 10.1016/S0140-6736(10)60674-5]
7 **Viazzi F**, Leoncini G, Conti N, Tomolillo C, Giachero G, Vercelli M, Deferrari G, Pontremoli R. Combined effect of albuminuria and estimated glomerular filtration rate on cardiovascular events and all-cause mortality in uncomplicated hypertensive patients. *J Hypertens* 2010; **28**: 848-855 [PMID: 20087212 DOI: 10.1097/HJH.0b013e328336ed09]
8 **Leoncini G**, Sacchi G, Viazzi F, Ravera M, Parodi D, Ratto E, Vettoretti S, Tomolillo C, Deferrari G, Pontremoli R. Microalbuminuria identifies overall cardiovascular risk in essential hypertension: an artificial neural network-based approach. *J Hypertens* 2002; **20**: 1315-1321 [PMID: 12131528 DOI: 10.1097/00004872-200207000-00018]
9 **Pontremoli R**. Microalbuminuria in essential hypertension--its relation to cardiovascular risk factors. *Nephrol Dial Transplant* 1996; **11**: 2113-2115 [PMID: 8941561 DOI: 10.1093/oxfordjournals.ndt.a027119]
10 **Pedrinelli R**, Dell'Omo G, Di Bello V, Pontremoli R, Mariani M. Microalbuminuria, an integrated marker of cardiovascular risk in essential hypertension. *J Hum Hypertens* 2002; **16**: 79-89 [PMID: 11850764 DOI: 10.1038/sj.jhh.1001316]
11 **Leoncini G**, Viazzi F, Conti N, Baratto E, Tomolillo C, Bezante GP, Deferrari G, Pontremoli R. Renal and cardiac abnormalities in primary hypertension. *J Hypertens* 2009; **27**: 1064-1073 [PMID: 19357534 DOI: 10.1097/HJH.0b013e3283281213]
12 **Wachtell K**, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med* 2003; **139**: 901-906 [PMID: 14644892 DOI: 10.7326/0003-4819-139-11-200312020-00008]
13 **Viazzi F**, Leoncini G, Pontremoli R. Global cardiovascular risk assessment in the management of primary hypertension: the role of the kidney. *Int J Hypertens* 2013; **2013**: 542646 [PMID: 23984048 DOI: 10.1155/2013/542646]
14 **Levey AS**, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137-147 [PMID: 12859163 DOI: 10.7326/0003-4819-139-2-200307150-00013]
15 **Devereux RB**, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation* 1993; **88**: 1444-1455 [PMID: 8403291 DOI: 10.1161/01.CIR.88.4.1444]
16 **Schmieder RE**, Schlaich MP, Klingbeil AU, Martus P. Update on reversal of left ventricular hypertrophy in essential hypertension (a meta-analysis of all randomized double-blind studies until December 1996). *Nephrol Dial Transplant* 1998; **13**: 564-569 [PMID: 9550628 DOI: 10.1093/ndt/13.3.564]
17 **Ibsen H**, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005; **45**: 198-202 [PMID: 15655123 DOI: 10.1161/01.HYP.0000154082.72286.2a]
18 **Ibsen H**, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Snapinn SM, Wan Y, Lyle PA. Does albuminuria predict cardiovascular outcomes on treatment with losartan versus atenolol in patients with diabetes, hypertension, and left ventricular hypertrophy? The LIFE study. *Diabetes Care* 2006; **29**: 595-600 [PMID: 16505512 DOI: 10.2337/diacare.29.03.06.dc05-1724]
19 **Bakris GL**, Sarafidis PA, Weir MR, Dahlöf B, Pitt B, Jamerson K, Velazquez EJ, Staikos-Byrne L, Kelly RY, Shi V, Chiang YT, Weber MA; ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010; **375**: 1173-1181 [PMID: 20170948 DOI: 10.1016/S0140-6736(09)62100-0]
20 **Yusuf S**, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**: 1547-1559 [PMID: 18378520 DOI: 10.1056/NEJMoa0801317]
21 **Schmieder RE**, Mann JF, Schumacher H, Gao P, Mancia G, Weber MA, McQueen M, Koon T, Yusuf S; ONTARGET Investigators. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J Am Soc Nephrol* 2011; **22**: 1353-1364 [PMID: 21719791 DOI: 10.1681/ASN.2010091001]
22 **Savarese G**, Dei Cas A, Rosano G, D'Amore C, Musella F, Mosca S, Reiner MF, Marchioli R, Trimarco B, Perrone-Filardi P. Reduction of albumin urinary excretion is associated with reduced cardiovascular events in hypertensive and/or diabetic patients. A meta-regression analysis of 32 randomized trials. *Int J Cardiol* 2014; **172**: 403-410 [PMID: 24502877 DOI: 10.1016/j.ijcard.2014.01.065]

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REVIEW

Dashing away hypertension: Evaluating the efficacy of the dietary approaches to stop hypertension diet in controlling high blood pressure

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Abstract

The dietary approaches to stop hypertension (DASH) diet has been developed and popularized as a non-pharmaceutical intervention for high blood pressure reduction since 1995. However, to date, a comprehensive description of the biochemical rationale behind the diet's principal guidelines has yet to be compiled. With rising interest for healthy and reliable life-style modifications to combat cardiovascular disease, this review aims to compile the most recent and relevant studies on this topic and make an informed assessment as to the efficacy of and underlying mechanisms operant in the DASH diet. Specifically, the merits of lowering dietary intake of sodium and saturated fat, as well as increasing the intake of fruits, vegetables, fiber, and dairy, have been shown to attenuate hypertension individually. Upon review of this evidence, we conclude that the combination of dietary patterns proposed in the DASH diet is effective in attenuating high blood pressure. We also suggest that efforts to more widely implement adoption of the DASH diet would be beneficial to public health.

Key words: Dietary approaches to stop hypertension diet; Hypertension; Salt restriction; Oxidative stress; Biochemistry

Core tip: As a non-pharmaceutical intervention for hypertension, the dietary approaches to stop hypertension (DASH) diet have emerged as the most prevalent choice. Based on the principles of salt restrictions, lowering fat and sugar intake, increasing fruit, vegetable, and fiber intake, this program serves great promise for patients diagnosed with high blood pressure. This

review aimed to assess the biochemical rational behind the diet's principle guidelines to evaluate the efficacy of the DASH diet in the treatment of hypertension. We conclude that the combined tenets of the DASH diet are effective in lowering blood pressure.

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INTRODUCTION

Currently suspected as an underlying cause of approximately 7.1 million (13% of) deaths worldwide, hypertension remains a prevalent affliction[1]. To complicate the matter, the etiology of primary (essential) hypertension which accounts for 90%-95% of adult cases is still unclear[2]. Uncontrolled hypertension serves to be a major risk factor for the development of a multitude of neural[3], cardiac[4], and renal[5] disorders. Similar to the "All roads lead to Rome" adage, several factors have been implicated in the pathogenesis of hypertension including, but not limited to: Oxidative stress, genetic factors, renal injury, inadequate nutrient intake, overproduction of sodium retaining hormones, disruption of the renin-angiotensin or kallikrein-kinin systems, deficiencies in vasodilators[6]. This review utilized studies dating back to the early 1900's in order to establish a background for the research being conducted today, however, the majority of data compiled for review in this paper was conducted from the INTERSALT study[7] in 1988 through present day.

Until recently, hypertension has been classified into three stages that increase in severity: Pre-hypertension, [systolic blood pressure (BP) of 120-139 mmHg and diastolic BP of 80-89 mmHg], stage 1 (systolic BP of 140-159 mmHg and diastolic BP of 90-99 mmHg), and stage 2 (systolic BP of 160-179 mmHg and diastolic BP of 90-99 mmHg). These classifications arose in 2003 with the 7th JNC report on hypertension[8]. More recently in 2014, the 8th JNC report was released to the public. The 8th edition of the report modified the above specifications, and took an alternate approach regarding the BP threshold of intervention, which treatment should be administered, and also the target BP to be achieved. JNC 8 proposes to begin treatment for those over the age of 60 at an increased BP threshold of > 150/90 mmHg, while the goal BP for those below the age of 60 is still < 140/90[9]. The change originated from multidisciplinary analysis of many randomly controlled trial studies. The idea behind this decision was based on the reevaluation of the risks of side effects *vs* the benefits of treatment of hypertension[9]. A great deal of controversy has arisen surrounding the 8th JNC report, some dissent arising from the JNC panel itself. In a paper published shortly after the JNC 8, Wright *et al*[10] cited insufficient evidence for increasing the benchmark of treatment in patients over 60, proposing that the goal BP eligible for treatment should be lowered. Wright *et al*[10] argued that increasing the benchmark BP of this age group would also increase the group's risk of cardiovascular disease (CVD), especially in high risk populations, and would undo the progress of steadily decreasing levels of cardiovascular mortality. The team proposed that it would be more appropriate to raise the BP threshold for treatment in individuals aged 80 and above, as the benefits of therapy would be far more likely to exceed the risks[10]. For the purpose of this review, we refer to JNC 7 stages of hypertension, due to the vast majority of research published before the presentation of the new guidelines.

To help manage and attenuate disease pathogenesis, intervention by way of lifestyle modification and/or pharmaceutical therapies are strongly recommended. However, due to the economic burden and potential adverse side effects associated with pharmaceutical therapies, a growing demand for alternate means of treatment quickly arose. Consequently, before the turn of the century, a dietary plan known as dietary approaches to stop hypertension (DASH) was publicized after successful results following two multicenter, randomized outpatient feeding studies[11-13]. The principal guidelines of the DASH diet[14] (depicted in Table 1) focus on increased consumption of fruits, vegetables, whole grains, fish, poultry, beans, and seeds; in addition to consuming low- and non-fat dairy products, the diet calls for limited intake of: Sodium, saturated and trans fats, sugar, and red meat. This diet further encourages consumption of mineral-rich foods containing potassium, calcium, and magnesium, and foods rich in fiber.

This review aims to breakdown and examine the biochemical rationales behind specific tenets of the DASH diet in an effort to evaluate its efficacy.

DIETARY SODIUM RESTRICTION

Sodium plays an integral role in the biomechanical function of muscle and nerve fibers, and is largely responsible for the auto regulation of fluid balance at the cellular level. Yet, similar to other essential nutrients, excessive sodium levels can yield damaging effects physiologically. Research has delved into the relationship between sodium intake and hypertension for the past 50 years, and it is widely regarded as a major component to the development of high BP[15]. Investigators Ambard *et al*[16] first evidenced this relationship in 1904, in which six hypertensive patients were placed on three separate diets with modified salt and protein content. Outcomes of the study revealed that sodium content, irrespective of protein content, was inversely related to BP within and across each diet. Specifically, when sodium intake was reduced, corresponding decreases in BP were observed.

Similar beneficial effects of dietary sodium restriction were reported in 1948, when Walter Kempner's Rice

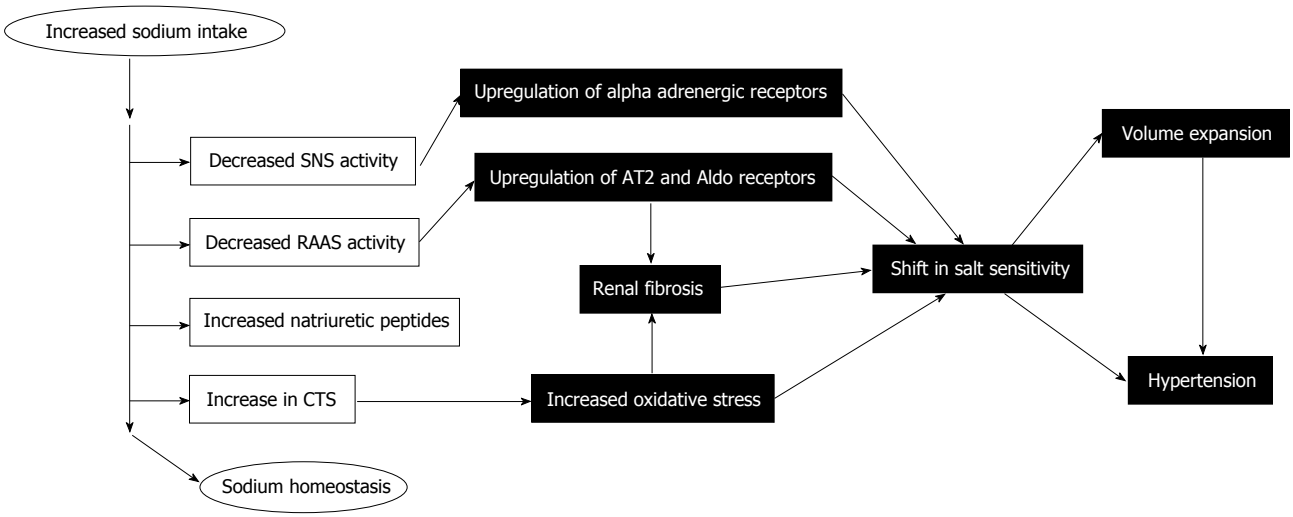

Figure 1 Schematic summarizes tradeoff by which physiological mechanisms that lead to sodium homeostasis in face of increased sodium intake might, over time, lead to a shift in salt sensitivity and sustained hypertension. SNS: Sympathetic nervous system; RAAS: Renin, angiotensin, aldosterone, system; CTS: Cardiotonic steroids; AT2: Angiotensin Ⅱ; Aldo: Aldosterone.

Table 1 Breaking down the dietary approaches to stop hypertension diet

Food group	Daily servings	Nutritional value
Grains/dietary fiber	7-8	Rich in dietary fiber
Vegetables	4-5	Rich in nitrate, fiber, potassium, and magnesium
Fruits	4-5	Rich in nitrate, fiber, potassium, and magnesium
Protein (poultry, fish, *etc.*)	2-5	High in bioactive proteins and magnesium
Low and non-fat dairy	2-3	High in calcium, vitamin D, and bioactive proteins
Nuts, seeds, and dry beans	4-5	High in potassium, magnesium, proteins, and fiber
Fats and oil	2-3	Accounts for 27% of caloric intake and essential fats and oils
Sugar	5 per week	Sweets should be low in fat

A breakdown of the dietary approaches to stop hypertension (DASH) diet by food group, serving size per diem, and the nutritional goal of each of the DASH guidelines. These specific guidelines have been endorsed and published by the National Institutes of Health[14].

Diet became publicized. The initial study involved 500 hypertensive patients placed on a diet predominantly consisting of rice, supplemented with fruits. Dietary salt content was maintained below 500 mg, and the subsequent effects of the diet were tremendous; along with attenuation of high BP, the patients' demonstrated reduced cardiac hypertrophy and amelioration of hypertensive retinopathy[17]. Although the practicality of maintaining this fairly tasteless diet proved bleak, the implications of the study were inescapable.

More recently, in 1980 Srinivasan *et al*[18] tested the effects of a high salt *vs* high salt/sucrose diets on spider monkeys. Findings from the study indicated that both high salt and high salt/sucrose diets resulted in elevated BP, and most importantly, in a dose-dependent manner[18]. In 1988, the monumental Intersalt study was compiled. Examining approximately 10000 patients from 52 examination centers worldwide, Intersalt remains the largest study of its kind to date. The major findings extended over international population and individual levels, and supported the direct correlation between sodium intake and hypertension. Regional differences in salt intake were also found to correlate with regional levels of hypertension. Perhaps of even greater relevance, the increases in systolic BP noted with age appeared to correlate on a population level even better with sodium intake than absolute levels of BP[7].

Although the relationship between salt and BP is readily accepted, the exact biochemical mechanism behind salt's role in the development of hypertension remains unclear. The renal renin-angiotensin-aldosterone system (RAAS) appears to be largely implicated in the development of salt driven hypertension and is the site of many pharmacological treatments for stage 2 hypertension, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin Ⅱ (Ang Ⅱ) receptor blockers[19].

Under physiological conditions, high salt diets typically suppress Ang Ⅱ levels through BP control mechanisms[20]. Despite this, 40%-50% of patients with essential hypertension do not engage this expected renal response to Ang Ⅱ and thus, do not react appropriately to changes in dietary sodium intake (depicted in Figure 1)[20,21]. This is one avenue of salt sensitivity, and while it has been documented clinically, its mechanisms have yet to be resolved[22,23]. Salt sensitivity has also been attributed to genetic mutations of the renin and *ACE* genes[24]. These individuals appear to exhibit high BP and low plasma renin levels in response to salt intake[25].

Additionally, RAAS, nitric oxide (NO), and superoxide anion (O_2^-) in the kidney, work together in a regulatory fashion. Activation of RAAS leads to the production of

O_2^-, a vasoconstrictor, and NO, a vasodilator, and both molecules readily react with one another. Dysfunction within the RAAS can lead to an imbalance of NO and O_2^-, which has been linked to salt sensitivity and hypertension[26,27]. In short, high levels of dietary sodium appear to induce inappropriate RAAS activity, leading to vascular maladaptation[28]. While certainly not the only avenue of hypertension, these studies highlight the importance of the RAAS in management of hypertension.

Sustained levels of high dietary sodium intake have been implicated not only in the pathogenesis of hypertension, but also albuminuria, altered gene expression, and even renal structural damage[29]. Further experiments have been crafted to test the efficacy of lowering sodium intake on hypertensive patients. He *et al*[30] demonstrated that a diet modified to lower only sodium content, with no other dietary restrictions, caused a significant reduction in BP in both normotensive and hypertensive patients. Moreover, as recently as 2015, a study conducted by Barros *et al*[31] highlighted the use of "light salt", a salt developed with lower sodium content and higher potassium levels as a significantly effective agent in reducing BP.

The first major tenet of the DASH diet is a substantial reduction in sodium intake[11]. It is estimated that the average adult American consumes roughly 3700 mg of sodium per day; by contrast, the DASH diet recommends that dietary sodium should be limited to < 2300 mg/d (< 1500 mg/d for high-risk individuals)[32]. In a comprehensive analysis of the effect of sodium consumption on BP, Bray *et al*[33] evaluated variations of sodium intake within the context of the standard American diet *vs* the DASH diet. In total, the study consisted of six groups: A control diet similar to the standard American diet and a DASH diet group were each divided into low, moderate, and average (high) sodium groups[33]. The researchers demonstrated a dose-dependent relationship between sodium consumption and BP; the findings corresponded with the results of previous experiments (discussed above): The lower the sodium intake, the greater the drop in BP. Furthermore, while both control and DASH groups experienced a drop in BP, limiting dietary sodium had an additive relationship when coupled with the DASH diet; these results demonstrate that patients consuming lower dietary sodium, in accompaniment with the rest of the DASH dietary patterns, experience an even greater drop in BP[30,33]. Biochemical analysis of the DASH diet yield similar optimistic results. Using the same six-group approach as Bray *et al*[33], analysis was performed by examining their corresponding pressure-natriuresis curves. The DASH diet appeared to decrease tubular sodium reabsorption without increasing glomerular filtration rate[34]; thus, the DASH diet is natriuretic in a sustainable way. Compiling the evidence-based research together, as a whole, we find overwhelming support of sodium restriction aiding the efficacy of the DASH diet in controlling hypertension.

EFFECTS OF INCREASING FRUIT AND VEGETABLE INTAKE

As discussed above, the origin and development of hypertension is complex, yet substantial literature also suggests that a sustained increase in peripheral vascular resistance due to arterial structural remodeling plays a prominent role in the pathogenesis of this disease[6,35,36]. Research suggests that the high inorganic nitrate (NO_3^-) content present in many vegetables may play vasoprotective[37-39] and cardioprotective[40] roles, *via* endogenous conversion to NO - a potent vasodilator. Consequently, endothelial dysfunction often characterized by a reduction in NO bioavailability has been largely implicated in patients with essential hypertension[41-43]. Discussion considering the physiological biosynthesis and function of NO can be found in several references[40,44-48].

It is estimated that the largest source of dietary nitrates (roughly 80%) comes directly from vegetable consumption; alternate dietary sources of nitrate and nitrite (a reduced form of nitrate) can also be found in fruits, vegetables, and processed meats[38]. In 2008, Webb *et al*[37] provided the first clinical evidence supporting the vasoprotective role of dietary nitrate harbored by a vegetable-rich diet in normotensive volunteers. The team of researchers utilized beetroot juice to display that consumption of an acute nitrate load corresponds with a significant reduction of both systolic and diastolic BP, as well as a reduction of platelet activation; these effects appear to be associated with the simultaneous rise in circulating nitrite levels[37] *via* entero-salivary conversion of the original dietary nitrate load, and further reduction of nitrite to NO[37,49,50].

The DASH diet calls for 4-5 servings of fruits and 4-5 servings of vegetables per day (based on a 2000 calorie diet); the range of daily servings per food group may fluctuate depending on an individual's daily caloric needs, which take one's age and activity level into account[14]. In response to the substantial literature present supporting the physiological benefits of dietary nitrate and nitrite, Hord *et al*[38] extended these findings to assess the high fruit and vegetable recommendations emphasized by the DASH diet. The researchers utilized High-performance liquid chromatography (HPLC) on a convenience sample of foods in order to quantify and compare various nitrate and nitrite concentrations. Results from HPLC indicated a wide range of nitrate and nitrite content amongst various fruits and vegetables. From this data, the researchers generated two hypothetical high- and low-nitrate vegetable and fruit DASH diet patterns (*i.e.*, 1222 mg nitrate *vs* 174 mg); the analysis revealed that the general dietary pattern of fruits and vegetables outlined in the DASH guidelines have the potential to vary drastically in terms of nitrate intake, based on specific vegetable and fruit selection[38]. The results further suggest that simply increasing fruit and vegetable intake does not directly translate to

higher dietary nitrate and nitrite consumption, this may alter the extent of vasoprotective and cardioprotective implications mediated by these molecules (as discussed above).

In the pathologic state, increasing evidence implicates oxidative stress to largely influence the induction and progression of hypertension[51]. The unregulated production of reactive oxygen species (ROS) can largely disrupt function of essential cellular lipids and proteins[52,53]. Accordingly, several natural antioxidant components of fruits and vegetables (*i.e.,* vitamins, minerals, polyphenols) are shown to assist the bodies' ROS scavenging system *via* multiple mechanisms, and are greatly implicated in controlling high BP and endothelial dysfunction[54-56]. The rich vitamin and mineral content found within fruits and vegetables contribute to both the enzymatic and non-enzymatic (direct ROS scavengers) antioxidant defense systems[57]. In regards to enzymatic ROS quenching, many of these enzymes exist as metalloenzymes. Three isoforms of superoxide dismutase help confer vascular protection as potent defenders of superoxide *via* dismutation[58], and utilize metals such as zinc, copper, and manganese. Additionally, glutathione peroxidases readily quench reactive hydrogen peroxide (by product of previous reaction), and are selenium-dependent enzymes[57]. Fruits and vegetables are often great sources of these essential minerals, and thus can contribute to enzymatic ROS defense.

In a similar vein, other micronutrients abundant in fruits and vegetables further bolster antioxidant defense by non-enzymatic means *via* direct scavenging of ROS. Lipid-soluble vitamin E and water-soluble vitamin C are both capable of reacting with peroxyl radicals[59]. It was later reported that vitamin E might synergistically interact with vitamin C in order to enhance its role as a peroxyl radical scavenger[60]. Additionally, Pierdomenico *et al*[61] observed drastically reduced plasma levels of vitamin C in hypertensive patients compared to their normotensive counterparts. Subsequently, Block *et al*[62] supported this observation by demonstrating that vitamin C depletion in normotensive subjects resulted in increased diastolic and systolic BP[62]. However, it should be noted that the relative antioxidant capacity[63] and content[64] of various constituents in fruits and vegetables is variable. This disparity is seen with plant-derived polyphenolic flavonoids, which are found to possess nearly four times the antioxidant activity than vitamin E analogue[63].

As of recent, fructose and its relation to BP has been a popular topic of contention. In the United States, this monosaccharide - naturally available in fruits - is most abundantly obtained from added fructose-glucose sweeteners such as, table sugar (sucrose) and high-fructose corn syrup[65]. Although, high fructose consumption is evidenced to be associated with insulin resistance[66], obesity[67,68], and renal[69] complications, epidemiological studies are controversial[70-72]; moreover, the source of dietary fructose may be of importance. The rich antioxidant properties associated with fruits (discussed above) may counter the potential harmful effects suggested by fructose. While this relationship or mechanism has yet to be established, Forman *et al*[70] found no association with fructose consumption and hypertension, in which individuals consumed a high intake of fruits. Excluding fructose content from natural fruit, a 2010 cross sectional analysis of United States adults with no prior history of hypertension reported an independent association between high fructose intake (from added sugar) and elevated BP[71]. Cumulatively, the multitude of micronutrients found in fruits and vegetables (as evidenced above) make them a beneficial and necessary inclusion in the major tenets of the DASH diet program.

BENEFITS OF FAT-FREE AND LOW-FAT DAIRY PRODUCTS

Dairy products and fatty acids are closely intertwined biochemically, and comprise one of the major tenets of the DASH diet program. The effect of saturated fats on BP has been a popular research topic during the last twenty years. It has been observed that populations consuming diets low in both total and saturated fats, are often the ones exhibiting low to moderate BPs[73]. Analysis of three vegetarian diets: the first consisting of high carbohydrates and low fat, the second high in polyunsaturated fat, and the third low in saturated fat content, revealed that all conditions were shown to reduce BP in their respective populations[73-75]. Further support for the relationship between dietary saturated fat content and BP was demonstrated by a study compiled in Finland; the experimental group that consumed high levels of saturated fats subsequently had higher BP than their control counterparts[76,77].

Unlike saturated fatty acids, diets high in polyunsaturated fats[78] and monounsaturated fats[79] have been shown to have an inverse relationship with BP. Fish oil, high in polyunsaturated fat, has been shown to have protective effects against the risk factors for CVD, including hypertension[80]. The fatty acids found in fish oil are precursors for 3-series prostaglandins, known for their antiaggregatory and vasodilator properties[81]; furthermore, polyunsaturated fats (such as linoleic acid and those found in fish oil) have been shown to lower low-density lipoprotein (LDL) cholesterol levels. This is vitally important in protection against CVD because the oxidized form of LDLs are absorbed by macrophages, creating foam cells that latch onto the walls of arteries, leading to atherosclerosis[82]. Frenoux *et al*[81] study went on to show that polyunsaturated fatty acids had antihypertensive effects, and also boosted resistance to free radical aggregation and lipid peroxidation.

Dairy, in contrast, consists of a more complex makeup of constituents: 89% water, 3.5% protein, 4.6% carbohydrates, and 3.3% lipid[83]. The protein constituents in dairy products are made up of bioactive peptides, known as lactotripeptides[84], and are similar to those found in lean red meat; both varieties of bioactive peptides have

been shown to block ACE[85]. The lipid components of dairy products generally consist of about 60% saturated fatty acids (FA) and about 30% unsaturated FA[86]. The other about 10% consist of short to medium length FA chains that are readily absorbed into the bloodstream, where they preferentially become oxidized rather than stored as triglycerides; and, in short, is associated with weight loss[86,87]. An inverse relationship was found to exist between dairy intake and BP; and, this relationship was strengthened if saturated fat intake was below about 11%[88].

Additionally, dairy intake, while not associated with overall mortality, appears to be inversely related to the multitude of risk factors for CVD including hypertension[89]. More recently, Drouin-Chartier *et al*[84] reported dairy intake to improve endothelial function and attenuate mild to moderate hypertension. Subsequent studies have shown that vitamin D alone also displays a curative effect on hypertension and other CVD risk factors[90]. The body of evidence here supports the DASH diet's recommendations in emphasizing the consumption of fat-free and low-fat dairy products, as well as reducing the intake of saturated and trans fats.

RICH ENERGY SOURCES: WHOLE GRAINS AND DIETARY FIBER

Dietary fiber is the indigestible cell wall component found in plants[91]. It is divided into two categories, soluble fiber and insoluble fiber. Soluble fibers include pectins, gums, mucilages, and some hemicelluloses; alternatively, insoluble fibers include lignins, cellulose, and the remainder of the hemicelluloses[92]. Early studies, conducted by Burkitt[93] in 1975, demonstrated that low dietary fiber intake is linked to many diseases, such as cardiovascular disease. This lent credence to the idea that dietary fiber may also be related to hypertension, a major risk factor in CVD. The recommended daily intake value of dietary fiber is between 20-35 g/d[94]. This is twice the amount of fiber that the average American typically consumes[95]. Initially, studies sought to analyze high-fiber vegetarian diets, which were previously shown to attenuate hypertension[91]. Subsequently, there was a rise in controversy; critics suggested that the decrease in BP seen in these studies could have easily arisen from other factors present in a vegetarian diet. Another setback arose with the discovery that increases in dietary fiber alone had little to no effect on normotensive patients[96].

Despite these setbacks, new research emerged showing the benefits of dietary fiber in regards to cardiac distress. In 1997, Stamler *et al*[97] demonstrated an inverse relationship between increased dietary fiber intake and BP. Additionally, whole grains were shown to be associated with lowering BP[98]. Whole grains themselves offer much nutritional value, providing complex carbohydrates, resistant starch, dietary fiber, minerals, vitamins, phytochemicals (which serve as antioxidants) and other nutrients[99,100]. A 4-fold decrease was seen in the cardiovascular death rate between men who ingested a high fiber diet (> 37 g/d) *vs* those who ingested a low fiber diet (< 20 g/d)[101]. Similar results were demonstrated, during a 6-year prospective study, in which an inverse relationship was found between dietary fiber intake and CVD rates[102]. Additionally, cereal fiber was revealed to be strongly associated with a reduction in CVD death rates; this result was further supported by the documented protective nature of whole grains[103,104].

Adding support to the inverse relationship between dietary fiber and cardiovascular risk factors, Lairon *et al*[105] further demonstrated that this correlation existed for all forms of fiber (Soluble, insoluble, fruits, grains, vegetables, cereal, *etc*.), specifically in regards to the prevalence of hypertension. While mechanistic data is yet to be confirmed, it is thought to be associated with a reduction of abdominal obesity and increased vascular reactivity[105]. Fiber has also been shown to attenuate endothelial dysfunction associated with hypercholesterolemia[106]; this finding suggests that fiber may indirectly play a protective role against hypertension, as the endothelium serves as an important regulator of vascular tone in response to altering needs for blood amongst different organs and tissues[107,108]. Taken together, a substantial body of evidence suggests that increasing dietary fiber plays a beneficial role in the battle against hypertension.

CONCLUSION

The DASH diet has provided the general public with a non-pharmaceutical option to combat hypertension. The last twenty years have been filled with studies breaking down each aspect of the DASH program. Many of these studies showed great success in highlighting the benefits of lowering sodium and saturated fat intake, while increasing intake of fruits, vegetables, dairy, and dietary fiber. However, the biochemical mechanisms behind these dietary guidelines have only been vaguely illuminated. Dietary biochemistry itself is a very complex story to tell, consisting of a diverse array of mechanistic pathways and byproducts. Although a complete understanding of each of these mechanisms and their implications has not yet been established, substantial effort has been made to fill in the gaps. This review attempted to compile the most recent available research in order to paint as vivid a picture as possible of how individual aspects of the DASH diet effect BP, and ultimately draw a conclusion as to the efficacy of such a diet for the treatment of hypertension. Despite the limitations of the total scope of our analysis, the abundant evidence in support of these dietary modifications is compelling, and we recommend the DASH diet to be an effective non-pharmaceutical treatment of hypertension. Further publicity and implementation could dramatically reduce the number of hypertensives both nationally and internationally. In American culture, focus should be placed on the maintainability of the diet. Stigmata has been placed

on healthy diets for being overly expensive, and out of reach for the average family. According to Sacks *et al*[109], the DASH program should cost approximately $130.00 per week for a family of 4. Adjusting for inflation, this translates to less than $200.00 per week today, still a very low total for a family of 4. Internationally, focus should be shifted to modification of diets depending on the cultural tendencies of the various groups of people who are regionally predisposed to high salt diets. These actions taken together could have a great impact on the health of individuals worldwide. Future research will need to elucidate the biochemical mechanisms inherent in the DASH diet. This could lead to further, more tailored and effective, dietary modifications for the masses; we predict that as further comprehensive understanding of this anti-hypertensive diet grows, we will see an overall attenuation of this disease.

REFERENCES

1 **Guilbert JJ**. The world health report 2002 - reducing risks, promoting healthy life. *Educ Health* (Abingdon) 2003; **16**: 230 [PMID: 14741909 DOI: 10.1080/1357628031000116808]

2 **Bolívar JJ**. Essential hypertension: an approach to its etiology and neurogenic pathophysiology. *Int J Hypertens* 2013; **2013**: 547809 [PMID: 24386559 DOI: 10.1155/2013/547809]

3 **Ariesen MJ**, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* 2003; **34**: 2060-2065 [PMID: 12843354 DOI: 10.1161/01.STR.0000080678.09344.8D]

4 **Sowers JR**, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 2001; **37**: 1053-1059 [PMID: 11304502 DOI: 10.1161/01.HYP.37.4.1053]

5 **Tylicki L**, Rutkowski B. [Hypertensive nephropathy: pathogenesis, diagnosis and treatment]. *Pol Merkur Lekarski* 2003; **14**: 168-173 [PMID: 12728683]

6 **Oparil S**, Zaman MA, Calhoun DA. Pathogenesis of hypertension. *Ann Intern Med* 2003; **139**: 761-776 [PMID: 14597461 DOI: 10.7326/0003-4819-139-9-200311040-00011]

7 Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ* 1988; **297**: 319-328 [PMID: 3416162 DOI: 10.1136/bmj.297.6644.319]

8 **Chobanian AV**, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560-2572 [PMID: 12748199 DOI: 10.1001/jama.289.19.2560]

9 **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797 DOI: 10.1001/jama.2013.284427]

10 **Wright JT**, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. *Ann Intern Med* 2014; **160**: 499-503 [PMID: 24424788 DOI: 10.7326/M13-2981]

11 **Appel LJ**, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; **336**: 1117-1124 [PMID: 9099655 DOI: 10.1056/NEJM199704173361601]

12 **Svetkey LP**, Simons-Morton D, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, Ard J, Kennedy BM. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med* 1999; **159**: 285-293 [PMID: 9989541 DOI: 10.1001/archinte.159.3.285]

13 **Svetkey LP**, Sacks FM, Obarzanek E, Vollmer WM, Appel LJ, Lin PH, Karanja NM, Harsha DW, Bray GA, Aickin M, Proschan MA, Windhauser MM, Swain JF, McCarron PB, Rhodes DG, Laws RL. The DASH Diet, Sodium Intake and Blood Pressure Trial (DASH-sodium): rationale and design. DASH-Sodium Collaborative Research Group. *J Am Diet Assoc* 1999; **99**: S96-S104 [PMID: 10450301 DOI: 10.1016/s0002-8223(99)00423-x]

14 **NIH National Heart, Lung, and Blood Institutes**. Your Guide to Lowering Your Blood Pressure With DASH. [Accessed 2006]. Available from: URL: https://www.nhlbi.nih.gov/health/resources/heart/hbp-dash-index

15 **Obarzanek E**, Proschan MA, Vollmer WM, Moore TJ, Sacks FM, Appel LJ, Svetkey LP, Most-Windhauser MM, Cutler JA. Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. *Hypertension* 2003; **42**: 459-467 [PMID: 12953018 DOI: 10.1161/01.HYP.0000091267.39066.72]

16 **Ambard L**, Beaujard E. Causes of arterial hypertension. *Arch Gen Med* 1904; **1**: 520-533

17 **Kempner W**. Treatment of hypertensive vascular disease with rice diet. *Am J Med* 1948; **4**: 545-577 [PMID: 18909456 DOI: 10.1001/archinte.1974.00320170040005]

18 **Srinivasan SR**, Berenson GS, Radhakrishnamurthy B, Dalferes ER, Underwood D, Foster TA. Effects of dietary sodium and sucrose on the induction of hypertension in spider monkeys. *Am J Clin Nutr* 1980; **33**: 561-569 [PMID: 6766658]

19 **Pichler RH**, de Boer IH. Dual renin-angiotensin-aldosterone system blockade for diabetic kidney disease. *Curr Diab Rep* 2010; **10**: 297-305 [PMID: 20532701 DOI: 10.1007/s11892-010-0126-2]

20 **Williams GH**, Hollenberg NK. Sodium-sensitive essential hypertension: emerging insights into an old entity. *J Am Coll Nutr* 1989; **8**: 490-494 [PMID: 2695548 DOI: 10.1080/07315724.1989.10720318]

21 **Franco V**, Oparil S. Salt sensitivity, a determinant of blood pressure, cardiovascular disease and survival. *J Am Coll Nutr* 2006; **25**: 247S-255S [PMID: 16772636 DOI: 10.1080/07315724.2006.10719574]

22 **Campese VM**. Salt sensitivity in hypertension. Renal and cardiovascular implications. *Hypertension* 1994; **23**: 531-550 [PMID: 8144222 DOI: 10.1161/01.HYP.23.4.531]

23 **Weinberger MH**. Salt sensitivity of blood pressure in humans. *Hypertension* 1996; **27**: 481-490 [PMID: 8613190 DOI: 10.1161/01.HYP.27.3.481]

24 **Hasimu B**, Nakayama T, Mizutani Y, Izumi Y, Asai S, Soma M, Kokubun S, Ozawa Y. Haplotype analysis of the human renin gene and essential hypertension. *Hypertension* 2003; **41**: 308-312 [PMID: 12574100 DOI: 10.1161/01.HYP.0000049762.77830.89]

25 **Poch E**, González D, Giner V, Bragulat E, Coca A, de La Sierra A. Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. *Hypertension* 2001; **38**: 1204-1209 [PMID: 11711524 DOI: 10.1161/hy1101.099479]

26 **Kopkan L**, Husková Z, Vanourková Z, Thumová M, Skaroupková P, Cervenka L, Majid DS. Superoxide and its interaction with nitric oxide modulates renal function in prehypertensive Ren-2 transgenic rats. *J Hypertens* 2007; **25**: 2257-2265 [PMID: 17921820 DOI: 10.1097/HJH.0b013e3282efb195]

27 **Kopkan L**, Husková Z, Vanourková Z, Thumová M, Skaroupková P, Malý J, Kramer HJ, Dvorák P, Cervenka L. Reduction of oxidative stress does not attenuate the development of angiotensin II-dependent hypertension in Ren-2 transgenic rats. *Vascul Pharmacol* 2009; **51**: 175-181 [PMID: 19539780 DOI: 10.1016/j.vph.2009.06.001]

28 **Bayorh MA**, Ganafa AA, Emmett N, Socci RR, Eatman D, Fridie

IL. Alterations in aldosterone and angiotensin II levels in salt-induced hypertension. *Clin Exp Hypertens* 2005; **27**: 355-367 [PMID: 15921072 DOI: 10.1081/CEH-57423]
29 **Gu JW**, Young E, Pan ZJ, Tucker KB, Shparago M, Huang M, Bailey AP. Long-term high salt diet causes hypertension and alters renal cytokine gene expression profiles in Sprague-Dawley rats. *Beijing Daxue Xuebao* 2009; **41**: 505-515 [PMID: 19829664 DOI: 10.1016/j.jash.2008.03.001]
30 **He FJ**, MacGregor GA. How far should salt intake be reduced? *Hypertension* 2003; **42**: 1093-1099 [PMID: 14610100 DOI: 10.1161/01.HYP.0000102864.05174.E8]
31 **Barros CL**, Sousa AL, Chinem BM, Rodrigues RB, Jardim TS, Carneiro SB, Souza WK, Jardim PC. Impact of light salt substitution for regular salt on blood pressure of hypertensive patients. *Arq Bras Cardiol* 2015; **104**: 128-135 [PMID: 25409877 DOI: 10.5935/abc.20140174]
32 **Cogswell ME**, Zhang Z, Carriquiry AL, Gunn JP, Kuklina EV, Saydah SH, Yang Q, Moshfegh AJ. Sodium and potassium intakes among US adults: NHANES 2003-2008. *Am J Clin Nutr* 2012; **96**: 647-657 [PMID: 22854410 DOI: 10.3945/ajcn.112.034413]
33 **Bray GA**, Vollmer WM, Sacks FM, Obarzanek E, Svetkey LP, Appel LJ. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. *Am J Cardiol* 2004; **94**: 222-227 [PMID: 15246908 DOI: 10.1016/j.amjcard.2004.03.070]
34 **Akita S**, Sacks FM, Svetkey LP, Conlin PR, Kimura G. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on the pressure-natriuresis relationship. *Hypertension* 2003; **42**: 8-13 [PMID: 12756219 DOI: 10.1161/01.HYP.0000074668.08704.6E]
35 **Folkow B**, Grimby G, Thulesius O. Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance. *Acta Physiol Scand* 1958; **44**: 255-272 [PMID: 13617022 DOI: 10.1111/j.1748-1716.1958.tb01626.x]
36 **Folkow B**. Physiological aspects of primary hypertension. *Physiol Rev* 1982; **62**: 347-504 [PMID: 6461865]
37 **Webb AJ**, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, Rashid R, Miall P, Deanfield J, Benjamin N, MacAllister R, Hobbs AJ, Ahluwalia A. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. *Hypertension* 2008; **51**: 784-790 [PMID: 18250365 DOI: 10.1161/HYPERTENSIONAHA.107.103523]
38 **Hord NG**, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. *Am J Clin Nutr* 2009; **90**: 1-10 [PMID: 19439460 DOI: 10.3945/ajcn.2008.27131]
39 **Lundberg JO**, Carlström M, Larsen FJ, Weitzberg E. Roles of dietary inorganic nitrate in cardiovascular health and disease. *Cardiovasc Res* 2011; **89**: 525-532 [PMID: 20937740 DOI: 10.1093/cvr/cvq325]
40 **Moore C**, Tymvios C, Emerson M. Functional regulation of vascular and platelet activity during thrombosis by nitric oxide and endothelial nitric oxide synthase. *Thromb Haemost* 2010; **104**: 342-349 [PMID: 20508906 DOI: 10.1160/TH09-11-0764]
41 **Panza JA**, Quyyumi AA, Brush JE, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990; **323**: 22-27 [PMID: 2355955 DOI: 10.1056/NEJM199007053230105]
42 **Panza JA**, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. *Circulation* 1993; **87**: 1468-1474 [PMID: 8491001 DOI: 10.1161/01.CIR.87.5.1468]
43 **Taddei S**, Virdis A, Mattei P, Ghiadoni L, Sudano I, Salvetti A. Defective L-arginine-nitric oxide pathway in offspring of essential hypertensive patients. *Circulation* 1996; **94**: 1298-1303 [PMID: 8822983 DOI: 10.1161/01.CIR.94.6.1298]
44 **Radomski MW**, Palmer RM, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. *Lancet* 1987; **2**: 1057-1058 [PMID: 2889967 DOI: 10.1016/S0140-6736(87)91481-4]
45 **Palmer RM**, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature* 1988; **333**: 664-666 [PMID: 3131684 DOI: 10.1038/333664a0]
46 **Förstermann U**, Closs EI, Pollock JS, Nakane M, Schwarz P, Gath I, Kleinert H. Nitric oxide synthase isozymes. Characterization, purification, molecular cloning, and functions. *Hypertension* 1994; **23**: 1121-1131 [PMID: 7515853 DOI: 10.1161/01.HYP.23.6.1121]
47 **Hermann M**, Flammer A, Lüscher TF. Nitric oxide in hypertension. *J Clin Hypertens* (Greenwich) 2006; **8**: 17-29 [PMID: 17170603 DOI: 10.1111/j.1524-6175.2006.06032.x]
48 **Hirst DG**, Robson T. Nitric oxide physiology and pathology. *Methods Mol Biol* 2011; **704**: 1-13 [PMID: 21161625 DOI: 10.1007/978-1-61737-964-2_1]
49 **Duncan C**, Dougall H, Johnston P, Green S, Brogan R, Leifert C, Smith L, Golden M, Benjamin N. Chemical generation of nitric oxide in the mouth from the enterosalivary circulation of dietary nitrate. *Nat Med* 1995; **1**: 546-551 [PMID: 7585121 DOI: 10.1038/nm0695-546]
50 **McKnight GM**, Smith LM, Drummond RS, Duncan CW, Golden M, Benjamin N. Chemical synthesis of nitric oxide in the stomach from dietary nitrate in humans. *Gut* 1997; **40**: 211-214 [PMID: 9071933 DOI: 10.1136/gut.40.2.211]
51 **Kizhakekuttu TJ**, Widlansky ME. Natural antioxidants and hypertension: promise and challenges. *Cardiovasc Ther* 2010; **28**: e20-e32 [PMID: 20370791 DOI: 10.1111/j.1755-5922.2010.00137.x]
52 **Davies KJ**. Protein damage and degradation by oxygen radicals. I. general aspects. *J Biol Chem* 1987; **262**: 9895-9901 [PMID: 3036875]
53 **Rochette L**, Zeller M, Cottin Y, Vergely C. Diabetes, oxidative stress and therapeutic strategies. *Biochim Biophys Acta* 2014; **1840**: 2709-2729 [PMID: 24905298 DOI: 10.1016/j.bbagen.2014.05.017]
54 **Moore TJ**, Vollmer WM, Appel LJ, Sacks FM, Svetkey LP, Vogt TM, Conlin PR, Simons-Morton DG, Carter-Edwards L, Harsha DW. Effect of dietary patterns on ambulatory blood pressure : results from the Dietary Approaches to Stop Hypertension (DASH) Trial. DASH Collaborative Research Group. *Hypertension* 1999; **34**: 472-477 [PMID: 10489396 DOI: 10.1161/01.HYP.34.3.472]
55 **John JH**, Ziebland S, Yudkin P, Roe LS, Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* 2002; **359**: 1969-1974 [PMID: 12076551 DOI: 10.1016/S0140-6736(02)98858-6]
56 **Ulker S**, McKeown PP, Bayraktutan U. Vitamins reverse endothelial dysfunction through regulation of eNOS and NAD(P)H oxidase activities. *Hypertension* 2003; **41**: 534-539 [PMID: 12623955 DOI: 10.1161/01.HYP.0000057421.28533.37]
57 **Lampe JW**. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. *Am J Clin Nutr* 1999; **70**: 475S-490S [PMID: 10479220]
58 **Faraci FM**, Didion SP. Vascular protection: superoxide dismutase isoforms in the vessel wall. *Arterioscler Thromb Vasc Biol* 2004; **24**: 1367-1373 [PMID: 15166009 DOI: 10.1161/01.ATV.0000133604.20182.cf]
59 **Sies H**, Stahl W, Sundquist AR. Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. *Ann N Y Acad Sci* 1992; **669**: 7-20 [PMID: 1444060 DOI: 10.1111/j.1749-6632.1992.tb17085.x]
60 **Niki E**. Role of vitamin E as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence. *Free Radic Biol Med* 2014; **66**: 3-12 [PMID: 23557727 DOI: 10.1016/j.freeradbiomed.2013.03.022]
61 **Pierdomenico SD**, Costantini F, Bucci A, De Cesare D, Cuccurullo F, Mezzetti A. Low-density lipoprotein oxidation and vitamins E and C in sustained and white-coat hypertension. *Hypertension* 1998; **31**: 621-626 [PMID: 9461231 DOI: 10.1161/01.HYP.31.2.621]
62 **Block G**, Mangels AR, Norkus EP, Patterson BH, Levander OA, Taylor PR. Ascorbic acid status and subsequent diastolic and systolic blood pressure. *Hypertension* 2001; **37**: 261-267 [PMID: 11230282 DOI: 10.1161/01.HYP.37.2.261]
63 **Rice-Evans CA**, Miller NJ, Bolwell PG, Bramley PM, Pridham JB. The relative antioxidant activities of plant-derived polyphenolic

flavonoids. *Free Radic Res* 1995; **22**: 375-383 [PMID: 7633567 DOI: 10.3109/10715769509145649]
64 **Carlsen MH**, Halvorsen BL, Holte K, Bøhn SK, Dragland S, Sampson L, Willey C, Senoo H, Umezono Y, Sanada C, Barikmo I, Berhe N, Willett WC, Phillips KM, Jacobs DR, Blomhoff R. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J* 2010; **9**: 3 [PMID: 20096093 DOI: 10.1186/1475-2891-9-3]
65 **White JS**. Straight talk about high-fructose corn syrup: what it is and what it ain't. *Am J Clin Nutr* 2008; **88**: 1716S-1721S [PMID: 19064536 DOI: 10.3945/ajcn.2008.25825B]
66 **Stanhope KL**, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest* 2009; **119**: 1322-1334 [PMID: 19381015 DOI: 10.1172/JCI37385]
67 **Bray GA**, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 2004; **79**: 537-543 [PMID: 15051594]
68 **Malik VS**, Popkin BM, Bray GA, Després JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* 2010; **121**: 1356-1364 [PMID: 20308626 DOI: 10.1161/CIRCULATIONAHA.109.876185]
69 **Shoham DA**, Durazo-Arvizu R, Kramer H, Luke A, Vupputuri S, Kshirsagar A, Cooper RS. Sugary soda consumption and albuminuria: results from the National Health and Nutrition Examination Survey, 1999-2004. *PLoS One* 2008; **3**: e3431 [PMID: 18927611 DOI: 10.1371/journal.pone.0003431]
70 **Forman JP**, Choi H, Curhan GC. Fructose and vitamin C intake do not influence risk for developing hypertension. *J Am Soc Nephrol* 2009; **20**: 863-871 [PMID: 19144761 DOI: 10.1681/ASN.2008050473]
71 **Jalal DI**, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol* 2010; **21**: 1543-1549 [PMID: 20595676 DOI: 10.1681/ASN.2009111111]
72 **Nguyen S**, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. *J Pediatr* 2009; **154**: 807-813 [PMID: 19375714 DOI: 10.1016/j.jpeds.2009.01.015]
73 **Sacks FM**, Rosner B, Kass EH. Blood pressure in vegetarians. *Am J Epidemiol* 1974; **100**: 390-398 [PMID: 4418801]
74 **Sacks FM**, Kass EH. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am J Clin Nutr* 1988; **48**: 795-800 [PMID: 3414588]
75 **Rouse IL**, Beilin LJ, Mahoney DP, Margetts BM, Armstrong BK, Vandongen R. Vegetarian diet and blood pressure. *Lancet* 1983; **2**: 742-743 [PMID: 6136871 DOI: 10.1016/s0140-6736(83)92281-x]
76 **Salonen JT**, Tuomilehto J, Tanskanen A. Relation of blood pressure to reported intake of salt, saturated fats, and alcohol in healthy middle-aged population. *J Epidemiol Community Health* 1983; **37**: 32-37 [PMID: 6875442 DOI: 10.1136/jech.37.1.32]
77 **Salonen JT**, Salonen R, Ihanainen M, Parviainen M, Seppänen R, Kantola M, Seppänen K, Rauramaa R. Blood pressure, dietary fats, and antioxidants. *Am J Clin Nutr* 1988; **48**: 1226-1232 [PMID: 3189209 DOI: 10.3109/07853899109148063]
78 **Berry EM**, Hirsch J. Does dietary linolenic acid influence blood pressure? *Am J Clin Nutr* 1986; **44**: 336-340 [PMID: 2875645]
79 **Rasmussen BM**, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G, Rivellese AA, Tapsell L, Hermansen K. Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. *Am J Clin Nutr* 2006; **83**: 221-226 [PMID: 16469978]
80 **Chen HW**, Lii CK, Chen WT, Wang ML, Ou CC. Blood pressure-lowering effect of fish oil is independent of thromboxane A2 level in spontaneously hypertensive rats. *Prostaglandins Leukot Essent Fatty Acids* 1996; **54**: 147-154 [PMID: 8848434 DOI: 10.1016/s0952-3278(96)90072-1]
81 **Frenoux JM**, Prost ED, Belleville JL, Prost JL. A polyunsaturated fatty acid diet lowers blood pressure and improves antioxidant status in spontaneously hypertensive rats. *J Nutr* 2001; **131**: 39-45 [PMID: 11208936]
82 **Suzukawa M**, Abbey M, Howe PR, Nestel PJ. Effects of fish oil fatty acids on low density lipoprotein size, oxidizability, and uptake by macrophages. *J Lipid Res* 1995; **36**: 473-484 [PMID: 7775859 DOI: 10.1016/0021-9150(94)93308-1]
83 **German JB**, Dillard CJ. Composition, structure and absorption of milk lipids: a source of energy, fat-soluble nutrients and bioactive molecules. *Crit Rev Food Sci Nutr* 2006; **46**: 57-92 [PMID: 16403683 DOI: 10.1080/10408690590957098]
84 **Drouin-Chartier JP**, Gigleux I, Tremblay AJ, Poirier L, Lamarche B, Couture P. Impact of dairy consumption on essential hypertension: a clinical study. *Nutr J* 2014; **13**: 83 [PMID: 25123170 DOI: 10.1186/1475-2891-13-83]
85 **McGregor RA**, Poppitt SD. Milk protein for improved metabolic health: a review of the evidence. *Nutr Metab* (Lond) 2013; **10**: 46 [PMID: 23822206 DOI: 10.1186/1743-7075-10-46]
86 **Molkentin J**. Occurrence and biochemical characteristics of natural bioactive substances in bovine milk lipids. *Br J Nutr* 2000; **84** Suppl 1: S47-S53 [PMID: 11242446 DOI: 10.1017/s0007114500002245]
87 **Dougkas A**, Reynolds CK, Givens ID, Elwood PC, Minihane AM. Associations between dairy consumption and body weight: a review of the evidence and underlying mechanisms. *Nutr Res Rev* 2011; **24**: 72-95 [PMID: 21320381 DOI: 10.1017/S095442241000034X]
88 **Djoussé L**, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension* 2006; **48**: 335-341 [PMID: 16801477 DOI: 10.1161/01.HYP.0000229668.73501.e8]
89 **Soedamah-Muthu SS**, Ding EL, Al-Delaimy WK, Hu FB, Engberink MF, Willett WC, Geleijnse JM. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2011; **93**: 158-171 [PMID: 21068345 DOI: 10.3945/ajcn.2010.29866]
90 **Zhang Y**, Hao X, Sun W, Ma H, Yang Y, Zhu Y, Zhu H. The Study Advance on The Role of Vitamin D in Hypertension and Cardiovascular Disease (CVD). *J Am SCI* 2015; **11**: 120-125
91 **Anderson JW**, Smith BM, Gustafson NJ. Health benefits and practical aspects of high-fiber diets. *Am J Clin Nutr* 1994; **59**: 1242S-1247S [PMID: 8172129]
92 **Brown L**, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999; **69**: 30-42 [PMID: 9925120]
93 **Burkitt D**. Food fiber and disease prevention. *Compr Ther* 1975; **1**: 19-22 [PMID: 1220921]
94 **Pilch SM**. Physiological Effects and Health Consequences of Dietary Fiber. Bethesda, MD: Life Sciences Research Office, 1987: 55-67
95 **Anderson JW**, Bridges SR, Tietyen J, Gustafson NJ. Dietary fiber content of a simulated American diet and selected research diets. *Am J Clin Nutr* 1989; **49**: 352-357 [PMID: 2537004]
96 **Swain JF**, Rouse IL, Curley CB, Sacks FM. Comparison of the effects of oat bran and low-fiber wheat on serum lipoprotein levels and blood pressure. *N Engl J Med* 1990; **322**: 147-152 [PMID: 2152973 DOI: 10.1056/NEJM199001183220302]
97 **Stamler J**, Caggiula AW, Grandits GA. Relation of body mass and alcohol, nutrient, fiber, and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 1997; **65**: 338S-365S [PMID: 8988947]
98 **Anderson JW**, Hanna TJ. Whole grains and protection against coronary heart disease: what are the active components and mechanisms? *Am J Clin Nutr* 1999; **70**: 307-308 [PMID: 10479191]
99 **Anderson JW**, Bridges SR. Dietary fiber content of selected foods. *Am J Clin Nutr* 1988; **47**: 440-447 [PMID: 2831703]

100 **Anderson JW**, Deakins DA, Floore TL, Smith BM, Whitis SE. Dietary fiber and coronary heart disease. *Crit Rev Food Sci Nutr* 1990; **29**: 95-147 [PMID: 2165783 DOI: 10.1080/10408399009527518]
101 **Kromhout D**, Bosschieter EB, de Lezenne Coulander C. Dietary fibre and 10-year mortality from coronary heart disease, cancer, and all causes. The Zutphen study. *Lancet* 1982; **2**: 518-522 [PMID: 6125679 DOI: 10.1016/s0140-6736(82)90600-6]
102 **Rimm EB**, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996; **275**: 447-451 [PMID: 8627965 DOI: 10.1001/jama.275.6.447]
103 **Jacobs DR**, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr* 1998; **68**: 248-257 [PMID: 9701180 DOI: 10.2105/ajph.89.3.322]
104 **Liu S**, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr* 1999; **70**: 412-419 [PMID: 10479204]
105 **Lairon D**, Arnault N, Bertrais S, Planells R, Clero E, Hercberg S, Boutron-Ruault MC. Dietary fiber intake and risk factors for cardiovascular disease in French adults. *Am J Clin Nutr* 2005; **82**: 1185-1194 [PMID: 16332650]
106 **Momenizadeh A**, Heidari R, Sadeghi M, Tabesh F, Ekramzadeh M, Haghighatian Z, Golshahi J, Baseri M. Effects of oat and wheat bread consumption on lipid profile, blood sugar, and endothelial function in hypercholesterolemic patients: A randomized controlled clinical trial. *ARYA Atheroscler* 2014; **10**: 259-265 [PMID: 25477983]
107 **Bonetti PO**, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003; **23**: 168-175 [PMID: 12588755 DOI: 10.1161/01.atv.0000051384.43104.fc]
108 **Weissberg P**. Mechanisms modifying atherosclerotic disease - from lipids to vascular biology. *Atherosclerosis* 1999; **147** Suppl 1: S3-S10 [PMID: 10575056 DOI: 10.1016/s0021-9150(99)00249-x]
109 **Sacks FM**, Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) Study. *Clin Cardiol* 1999; **22**: III6-II10 [PMID: 10410299 DOI: 10.1002/clc.4960221503]

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ORIGINAL ARTICLE

Prospective Study

Estimated net endogenous acid production and risk of prevalent and incident hypertension in community-dwelling older people

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Author contributions: Chan R conceptualized the study, performed data analysis and drafted the manuscript; Leung J assisted in data analysis and results interpretation and provided comments on the manuscript; Woo J provided administrative support for the study and commented on the manuscript; all authors read and approved the final manuscript.

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Abstract

AIM: To investigate the associations of dietary acid-base load with prevalent and incident hypertension in community-living Chinese older adults in Hong Kong.

METHODS: Participants aged ⩾ 65 years participating in a cohort study examining the risk factors for osteoporosis completed a validated food frequency questionnaire (FFQ) at baseline between 2001 and 2003. Estimated net endogenous acid production (NEAP) was calculated using Frassetto's method based on the diet's protein to potassium ratio derived from the FFQ. Prevalent and 4-year incident hypertension was defined as systolic blood pressure ⩾ 140 mmHg and/or diastolic blood pressure ⩾ 90 mmHg and/or self-reported use of anti-hypertensive medications. Multivariable logistic regression was used for cross-sectional analysis (*n* =

3956) to assess the association between estimated NEAP and prevalent hypertension, and for longitudinal analysis (n = 795) on its association with 4-year incident hypertension, with adjustment for various potential socio-demographic and lifestyle factors.

RESULTS: Median estimated NEAP of the participants was 47.7 (interquartile range: 36.2, 60.9) g/mEq. Participants in the highest quartile of energy-adjusted estimated NEAP was associated with increased likelihood of prevalent hypertension than those in the lowest quartile of energy-adjusted estimated NEAP [multivariable OR = 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002)]. No significant association was observed between energy-adjusted estimated NEAP and risk of incident hypertension.

CONCLUSION: A high dietary acid load was independently associated with an increased likelihood of prevalent hypertension in ambulant older Chinese people in Hong Kong. The longitudinal analyses failed to show any causal relationship between dietary acid load and hypertension in this population.

Key words: Acid-base balance; Cohort; Hypertension; Nutrition; Chinese

Core tip: This prospective study investigated the associations between baseline dietary acid-base load and prevalent and 4-year incident hypertension in community-dwelling Chinese older adults in Hong Kong. Baseline dietary data were collected using a validated food frequency questionnaire (FFQ). Estimated dietary net endogenous acid production (NEAP) was calculated based on the diet's protein to potassium ratio from the FFQ. Higher quartile of energy-adjusted estimated NEAP was associated with increased likelihood of prevalent hypertension [multivariable OR = 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002)]. No significant association was observed between energy-adjusted estimated NEAP and risk of incident hypertension.

Chan R, Leung J, Woo J. Estimated net endogenous acid production and risk of prevalent and incident hypertension in community-dwelling older people. *World J Hypertens* 2015; 5(4): 129-136 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i4/129.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i4.129

INTRODUCTION

Hypertension is a global health challenge in view of its prevalence and burden on morbidity and mortality. Diet is one of the modifiable factors affecting blood pressure and hypertension[1]. A diet high in sodium content and low in potassium, calcium and magnesium intake is associated with an elevated blood pressure[1,2]. Other dietary approaches, like The Dietary Approaches to Stop Hypertension diet also play a prominent role in the etiology of hypertension[3].

A possible link between acid-base balance and cardiometabolic risk has been recently proposed[4]. Long-term excessive intake of acid-generating foods, like meat together with an inadequate consumption of the alkaline-producing foods, like fruits and vegetables may cause acidosis and have negative effects on blood pressure and hypertension[4]. However, there have been few studies investigating how dietary acidity was related to hypertension. Dietary acidity was positively linked with blood pressure in healthy young women[5], middle-aged women[6] as well as healthy children and adolescents[7,8]. In contrast, no association of baseline dietary acidity with incident hypertension was observed among Western older adults[9,10].

With ageing, the body's ability to excrete acid drops to a great extent because of a decline in kidney function[11]. Therefore, consuming diets that induce minimal or no net acid load may be particularly vital when people are getting old. More importantly, the prevalence of hypertension rises with age, and recent data from China show a high prevalence of hypertension (58.2%) for the older adults as compared to the younger adults (17.5%)[12]. Therefore, identifying modifiable lifestyle factors that are associated with hypertension is important to determine the effective way for hypertension prevention and control. Considering the scanty evidences on this area and the differences in the dietary habits between Chinese and Caucasians, we explored how dietary acid-base load was linked with prevalent and incident hypertension in Chinese ambulatory older people. We expected that higher dietary acidity was linked with an elevated risk of hypertension.

MATERIALS AND METHODS

Study population

The sample population was subjects from a longitudinal study investigating the risk factors for osteoporosis in Hong Kong and the study details have been reported elsewhere[13]. Briefly, 4000 Chinese (50% men) aged ⩾ 65 years were recruited in a community health survey between 2001 and 2003. They attended the 4-year follow-up between 2005 and 2007. The 4-year follow-up was carried out through a mailed reminder and phone reminders for a follow-up health check appointment. The average follow-up year was 4 years. This study was carried out according to the Declaration of Helsinki. This study was granted an approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All subjects provided written informed consent.

Forty-four participants were excluded because of baseline missing/invalid data on diet or demographics. A final sample of 3956 participants was included for the cross-sectional analysis. The 4-year longitudinal analysis further excluded participants with hypertension

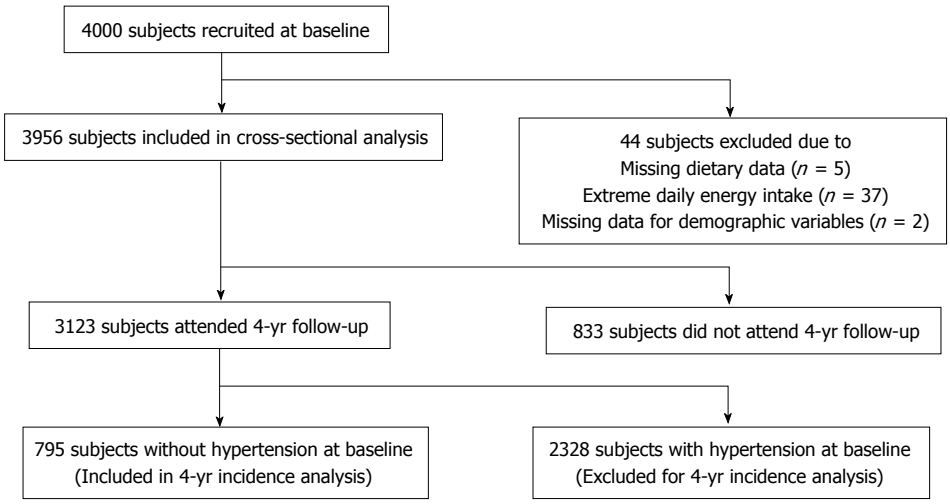

Figure 1 Number of subjects included and excluded for baseline and 4-year follow-up analyses.

at baseline, thus 795 participants were finally included (Figure 1).

Demographic and general lifestyle data

A structured interview was done to capture data on age, gender, education achievement, smoking habit, alcohol use and self-reported health conditions. Smoking status was categorized into three categories, namely former (100 or over cigarettes smoked in a lifetime), current or never. Alcohol use was categorized as never, past or current. Subjects self-reported their health conditions and the research staff validated the data by checking the relevant physician's reports and the medications used.

Physical activity assessment

The Physical Activity Scale of the Elderly (PASE) was used to assess the physical activity level[14]. The scale consists of twelve items and measures the average time (in hours) each day on leisure, household and occupational physical activities by participants in the past week. Higher summary scores indicates higher daily level of physical activity.

Dietary assessment

Baseline dietary intake was evaluated with a validated semi-quantitative food frequency questionnaire (FFQ)[15]. The FFQ consisted of 280 food items. Participants reported the frequency and the amount of consumption of each food over the previous year. Nine frequency categories were presented and ranged from never or seldom to more than once a day. A food photo album with pictures of standardized food portion size was presented to assist quantifying the amount of food consumption. Daily intake of various food groups covering cereals, egg and egg products, marine foods, fresh or dried fruits, legumes/nuts/seeds, meat and poultry, dairy and dairy products, and vegetables was derived. Average daily nutrient intake was generated with food composition tables of various sources[16,17]. Residual method was applied to generate energy-adjusted intakes[18].

Estimation of net endogenous acid production

Estimated net endogenous acid production (NEAP) of diet can be derived using different algorithms[19]. While Frassetto *et al*[20] derived the dietary estimated NEAP with reference to the dietary protein to potassium ratio, Remer *et al*[21] calculated the estimated NEAP based on the average intestinal absorption rates of the dietary intake of protein and other minerals and the anthropometry-based estimate for organic acid excretion. Each algorithm has its rationale and pitfalls[22]. Frassetto's method was applied in the present study to make it consistent with our previous study[23]. The estimated NEAP by this method was expressed using g/mEq and could explain approximate 70% variation in renal net acid excretion[20]. Residual method was also applied to generate the energy-adjusted estimated NEAP[18].

Anthropometry

Body weight and height were measured with the Physician Balance Beam Scale (Healthometer, Illinois, United States) and the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, United Kingdom) respectively. Body mass index (BMI) was calculated.

Assessment of hypertension

Trained staff measured participant's blood pressure using a standard mercury sphygmomanometer (WA Baum Co. Inc., Copiague, NY, United States). The first and fifth Korotkoff phases were measured twice after 5 min rest in the sitting position and the average of the two readings was taken as systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively. Hypertension was defined as SBP $\geqslant$ 140 mmHg and/or DBP $\geqslant$ 90 mmHg and/or use of anti-hypertensive medication[24]. Participants were asked to bring and show all the drugs he/she was currently using and the interviewer recorded the names, types and doses

accordingly.

Statistical analysis

SPSS version 21.0 (SPSS Inc., Illinois, United States) was used for the statistical analyses. Normality was checked using histograms and logarithmic transformation was performed where necessary. Independent *t* test and χ^2 test were applied to check for differences in baseline characteristics between participants included and participants excluded for data analysis.

Since the distribution of the energy-adjusted estimated NEAP (continuous) was skewed, it was categorized using quartile values according to the distribution of the final sample. Differences across energy-adjusted estimated NEAP quartiles were checked using χ^2 test for categorical variables and analysis of variance for continuous variables unless otherwise specified. Spearman's correlation was applied for assessing the correlation of energy-adjusted nutrient intakes or food group intakes with the estimated NEAP.

Multivariable logistic regression was performed to calculate the odds ratio (OR) and 95%CIs for prevalent hypertension as well as 4-year incident hypertension according to the energy-adjusted estimated NEAP quartiles. The first model was controlled for age (years) and sex at baseline. The second model was further controlled for baseline BMI, PASE, education attainment, tobacco use, alcohol use, and baseline energy-adjusted intakes of fiber, sodium, magnesium, calcium and potassium. P_{trend} was assessed by inputting quartiles of energy-adjusted estimated NEAP into all models. Since participants might have made dietary changes due to chronic diseases, several sensitivity analyses were further done by ruling out participants with a history of stroke, diabetes mellitus, or heart diseases, such as myocardial infarction. We also examined if the association between estimated NEAP and hypertension varied according to sex, age ($\leqslant$ 69 years *vs* > 69 years), and BMI (underweight < 18.5 kg/m^2 *vs* normal 18.5 kg/m^2 to < 23 kg/m^2 *vs* overweight/obese $\geqslant$ 23 kg/m^2). Stratified multivariable analyses were also done and appropriate interaction terms were generated to test for the presence of signification interactions. An α level of 5%, 2-sided was considered as statistically significant.

RESULTS

There were no significant differences in the baseline characteristics between participants who were included and those who were excluded for baseline analysis. Those who did not attend 4-year follow-up were older, physically less active, had lower education level and lower BMI, and suffered from more chronic diseases (P < 0.05) than those who attended the follow-up (details not listed).

Mean (SD) baseline age of the studied sample (1979 men, 1977 women) was 72.5 (5.2) years. Mean (SD) baseline BMI was 23.7 (3.3) kg/m^2. Mean (SD) baseline SBP and DBP was 142.6 (19.4) mmHg and 77.8 (9.2) mmHg respectively. Majority (75.2%) of the participants had hypertension at baseline. Among 795 participants included in the incidence analysis, 310 incident cases were identified and the cumulative incidence was 0.39. Median baseline estimated NEAP was 47.7 (interquartile range: 36.2, 60.9) g/mEq. Participants' baseline characteristics according to the quartiles of energy-adjusted estimated NEAP are listed in Table 1. Those with higher energy-adjusted estimated NEAP were of lower BMI, physically more sedentary, higher education attainment, and were prone to be non-smokers, and had lower dietary intakes of fiber, magnesium, potassium and sodium.

Estimated NEAP was positively correlated with total protein, calcium and phosphorus intake, and inversely linked with vitamin C, fiber, magnesium, vitamin K and potassium intake (P < 0.05, Table 2). Increasing estimated NEAP was linked with greater intake of protein rich animal foods, and lower fruits and vegetables consumption (P < 0.05, Table 2).

Participants in the highest quartile of energy-adjusted estimated NEAP had significantly increased likelihood of having prevalent hypertension than those in the lowest quartile in unadjusted and adjusted models (Table 3). The multivariable OR comparing those in the highest quartile with those in the lowest quartile was 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002). Although increasing trend was detected between energy-adjusted estimated NEAP and risk of incident hypertension, the trend did not reach statistical significance (Table 4).

Sensitivity analyses ruling out participants with some major chronic diseases showed similar results (details not listed). Risk estimates for the relationship of estimated NEAP with prevalent hypertension tended to be higher in male, in those aged $\geqslant$ 69 years, and in those with BMI below 18.5 kg/m^2, but the differences did not reach statistical significance (all with P-interaction > 0.05) (details not listed).

DISCUSSION

Our study indicated that higher estimated NEAP was associated with greater likelihood of prevalent hypertension but was not with the risk of incident hypertension in older Chinese adults. To our knowledge, such association in Chinese population has not been previously reported.

Few studies examined the link between dietary acid-base load and hypertension risk in older adults. Our cross-sectional findings were consistent with those reported in healthy children and adolescents[7] and young women[5], but different from those reported among community-based older Swedish men[10]. A cross-sectional analysis in 267 healthy children and adolescents showed that various markers of a higher dietary acidity were associated with higher blood pressure independent of BMI and other potential factors[7]. Similar findings were reported from a cross-sectional study investigating the relationship of dietary acid-base load with cardiometabolic risk factors in apparently healthy

Table 1 Baseline characteristics and prevalent hypertension by quartiles of energy adjusted estimated net endogenous acid production (*n* = 3956)

Variable	Quartile of energy adjusted estimated NEAP (g/mEq)								P_{trend}[1]
	Q1 (*n* = 987)		Q2 (*n* = 991)		Q3 (*n* = 989)		Q4 (*n* = 989)		
	Mean	SD, %	Mean	SD, %	Mean	SD, %	Mean	SD, %	
[2]Estimated NEAP (g/mEq)									
Original	26.9	21.3, 32.7	41.2	37.0, 45.7	53.4	48.7, 58.2	71.2	64.5, 79.7	< 0.001
Energy adjusted	28.7	23.8, 32.7	41.8	39.0, 44.7	54.0	50.7, 57.3	71.2	65.7, 79.8	< 0.001
Age (yr)	72.3	4.9	72.4	5.3	72.5	5.2	72.7	5.4	0.055
BMI (kg/m^2)	23.8	3.3	23.7	3.3	23.6	3.3	23.5	3.3	0.027
Male (%)		50.1		49.9		50.1		50.1	0.989
Education level (%)									
Primary or below		77.7		72.4		67.2		68.8	< 0.001
Secondary/matriculation		16.8		19.0		19.8		19.4	
University or above		5.5		8.7		12.9		11.8	
Smoking habit (%)									
Never smoke		58.5		62.6		65.4		66.5	< 0.001
Former smoker		33.0		31.1		29.3		26.1	
Current smoker		8.5		6.4		5.3		7.4	
Alcohol use (%)									
Never		84.1		84.8		84.6		86.6	0.155
Former drinker		2.4		1.4		1.6		2.1	
Current drinker		13.5		13.8		13.8		11.3	
[3]Prevalent hypertension (%)		72.8		74.9		75.2		77.8	0.014
Energy intake (kcal/d)	1832.5	587.3	1847.5	555.1	1848.6	568.7	1821.6	561.2	0.696
[2]Energy adjusted fiber (g/d)	9.1	7.0, 11.7	8.9	6.8, 11.2	8.5	6.6, 10.5	7.5	5.7, 8.9	< 0.001
[2]Energy adjusted calcium (mg/d)	535.6	418.9, 692.4	573.6	452.3, 725.8	590.7	460.1, 763.1	547.5	418.8, 726.2	0.098
[2]Energy adjusted magnesium (mg/d)	358.5	297.9, 487.8	356.6	292.7, 471.5	344.4	291.2, 434.8	312.0	262.1, 373.2	< 0.001
[2]Energy adjusted potassium (mg/d)	3782.3	3180.4, 4507.6	2977.9	2536.0, 3437.3	2462.8	2092.3, 2935.4	2021.0	1677.8, 2440.5	< 0.001
[2]Energy adjusted sodium (mg/d)	1453.4	1036.9, 1963.4	1379.7	1040.7, 1886.0	1345.6	1030.3, 1793.3	1254.3	930.1, 1651.4	< 0.001
PASE score	93.2	43.6	92.5	42.4	91.2	43.0	88.4	42.9	0.011

[1]P_{trend} was assessed by linear-by-linear association χ^2 test linear and ANOVA test for trend, or non-parametric Jonckheere-Terpstra test; [2]Data are presented as median (interquartile range); [3]Defined as average systolic or diastolic blood pressure ⩾ 140 or 90 mmHg respectively, or use of anti-hypertensive medications. NEAP: Net endogenous acid production; PASE: The Physical Activity Scale of the Elderly; BMI: Body mass index; ANOVA: Analysis of variance.

Table 2 Spearman's correlation between estimated net endogenous acid production and selected nutrients and main food groups (*n* = 3956)

Energy adjusted nutrients/ main food groups	Energy adjusted estimated NEAP (g/mEq)	
	r_s	*P*
Total protein (g)	0.27	< 0.001
Vitamin C (mg)	-0.27	< 0.001
Calcium (mg)	0.04	0.015
Phosphorus (mg)	0.16	< 0.001
Fiber (g)	-0.23	< 0.001
Magnesium (mg)	-0.20	< 0.001
Vitamin K (mcg)	-0.17	< 0.001
Potassium (mg)	-0.68	< 0.001
Sodium (mg)	-0.10	< 0.001
Cereals (g)	-0.03	0.063
Egg and egg products (g)	0.03	0.034
Fish and shellfish (g)	0.07	< 0.001
Fruits and dried fruits (g)	-0.31	< 0.001
Legumes, seeds and nuts (g)	0.01	0.678
Meat and poultry (g)	0.13	< 0.001
Milk and milk products (g)	0.03	0.041
Vegetables (g)	-0.18	< 0.001

NEAP: Net endogenous acid production.

young female adults[5]. Several possible mechanisms by which acid-base balance affects blood pressure have been suggested. Diet-induced mild metabolic acidosis may influence blood pressure possibly through increased cortisol production[25], increased calcium excretion[26,27] or reduced citrate excretion[28,29].

The absence of association in our prospective analysis was in line with the results by Engberink *et al*[9] and Luis *et al*[10] but was different from the findings by Zhang *et al*[6]. Several reasons may explain these inconclusive findings. Different study design and participants' characteristics may lead to these mixed findings. First, both Engberink's and Luis as well as our studies included older men and women whereas Zhang *et al*[6] recruited middle-aged women in their study. However, this age difference seems to be unlikely to explain the null findings as older people are expected to be more vulnerable to dietary acid base load in view of their declining renal function. In contrast, we are uncertain whether there is age-dependent difference regarding the influence of dietary acidity on hypertension through other mechanisms. Second, multiple measures of dietary intakes were available in Zhang's study whereas dietary data were only collected at a single time at baseline in Engberink's study, Luis's study and our study. Although sensitivity analyses not including participants with chronic diseases that might lead to dietary alterations did not change the null findings between estimated NEAP and incident hypertension in Engberink's and our studies, we cannot

Table 3 Logistic regression linking to quartiles of energy adjusted estimated net endogenous acid production to prevalent hypertension (*n* = 3956)

	Quartiles of energy adjusted estimated NEAP (g/mEq)				P_{trend}[1]
	Q1 (*n* = 987)	Q2 (*n* = 991)	Q3 (*n* = 989)	Q4 (*n* = 989)	
No. of case and control	719/268	742/249	744/245	769/220	
Unadjusted OR (95%CI)	1 (reference)	1.11 (0.91-1.36)	1.13 (0.93-1.38)	1.30 (1.06-1.60)	0.014
Age and sex adjusted OR (95%CI)	1 (reference)	1.11 (0.91-1.36)	1.13 (0.92-1.38)	1.29 (1.05-1.58)	0.020
[2]Multivariable adjusted OR (95%CI)	1 (reference)	1.22 (0.97-1.52)	1.35 (1.03-1.76)	1.66 (1.22-2.26)	0.002

[1]P_{trend} by entering quartiles of energy adjusted NEAP as a fixed factor and testing the contrast by using the polynomial option in all models; [2]Model adjusted for age, sex, BMI, PASE, education level, smoking status, alcohol use, and quartiles of energy adjusted intakes of fiber, calcium, magnesium, potassium and sodium. NEAP: Net endogenous acid production; BMI: Body mass index; PASE: The Physical Activity Scale of the Elderly.

Table 4 Logistic regression linking to quartiles of energy adjusted estimated net endogenous acid production to incident hypertension (*n* = 795)

	Quartiles of energy adjusted estimated NEAP (g/mEq)				P_{trend}[1]
	Q1 (*n* = 198)	Q2 (*n* = 201)	Q3 (*n* = 198)	Q4 (*n* = 198)	
No. of case and control	78/120	80/121	75/123	77/121	
Unadjusted OR (95%CI)	1 (reference)	1.02 (0.68-1.52)	0.94 (0.63-1.41)	0.98 (0.65-1.47)	0.842
Age and sex adjusted OR (95%CI)	1 (reference)	1.03 (0.69-1.54)	0.95 (0.63-1.43)	0.99 (0.66-1.49)	0.873
[2]Multivariable adjusted OR (95%CI)	1 (reference)	1.15 (0.74-1.80)	1.11 (0.66-1.86)	1.32 (0.72-2.43)	0.436

[1]P_{trend} by entering quartiles of energy adjusted NEAP as a fixed factor and testing the contrast by using the polynomial option in all models; [2]Model adjusted for age, sex, BMI, PASE, education level, smoking status, alcohol use, and quartiles of energy adjusted intakes of fiber, calcium, magnesium, potassium and sodium. NEAP: Net endogenous acid production; BMI: Body mass index; PASE: The Physical Activity Scale of the Elderly.

rule out the possibility that some participants might have changed their diets for other reasons during the follow-up. Third, different dietary habits of the study participants of various studies might explain these different findings. The median estimated NEAP in our study (approximately 47 mEq/d), Engberink's study (39 mEq/d) and Luis's study (40.7 mEq/d) might be too low to have an effect on blood pressure. Zhang *et al*[6] showed an elevated risk of incident hypertension starting at an estimated NEAP of 44 mEq/d or above.

Several methods have been derived to estimate dietary NEAP, thus we compared the Frassetto's model with the Remer's model. Estimated NEAP derived from both methods were strongly correlated (r_s = 0.95, P < 0.001). By including both protein and potassium as independent variables in a multivariate regression model, estimated NEAP derived using the latter varied proportionally with the protein intake (P < 0.001) and inversely with the potassium intake (P < 0.001). The multiple correlation coefficient was 0.95. Therefore, the Remer's model's ability in predicting estimated NEAP was mainly from the dietary protein and potassium contents. Furthermore, the results were consistent when all analyses were repeated using estimated NEAP by the Remer's model.

Our study had some limitations. Unlike previous similar studies among older adults, our study did not have data on kidney function but kidney function was unlikely to modify the associations between dietary acid load and blood pressure[10]. Moreover, recall bias may arise from dietary data captured using FFQ. The assessment of salt intake using FFQ but not using 24-h urine method was a limitation. Dietary assessment of the salt intake, in particular the discretionary salt intake often results in an underestimation and this may partially account for the unexpected inverse association between estimated NEAP and sodium intake in our study. Another possibility may be due to the differences in the way of serving vegetables in Chinese diets as compared to Western diets. While vegetables are commonly served raw or boiled in Western diets, stir fried vegetables with salt added during cooking is a common way of serving vegetables in Chinese diets[30]. Furthermore, we did not have dietary data at 4 years whereas participants might have altered their diet over the 4 years period. We performed sensitivity analyses ruling out participants with major chronic diseases and the results were similar. Moreover, we did not include markers, like serum anion gap or bicarbonate in the study, which are more reflective of acid base load. Although we controlled for different factors in the analysis, residual potential confounding from other factors related to hypertension, like family history and sleep patterns might still be present. The differences in demographic and lifestyle characteristics between those included and those excluded for the analysis, and between those who attended and those who did not attend the follow-up may also limit the study generalizability. Finally, our study may be underpowered in view of the small sample size for the prospective analysis.

In summary, our results suggest an increased likelihood of prevalent hypertension in older adults with

an elevated dietary acid load. However, as limited by the small number of the participants and the study methodology, our prospective analyses were unable to demonstrate a causal relationship between dietary acid load and hypertension in this population. Further longitudinal studies in populations of different dietary habits are required to confirm the influence of dietary acid load on hypertension. Moreover, the underlying mechanisms linking dietary acid-base load and blood pressure require further investigations.

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COMMENTS

Background

Long-term excessive intake of acid-generating foods in combination with a low intake of the alkalizing fruits and vegetables may lead to acidosis and have negative effects on blood pressure and hypertension. The authors studied the association of dietary acid-base load with risk of prevalent and incident hypertension in Chinese community-dwelling older adults in Hong Kong. The authors speculated that higher dietary acid-base load was associated with an elevated risk of hypertension.

Research frontiers

Diet is one of the modifiable factors for blood pressure and hypertension. The ability to excrete acid drops significantly with age because of a decline in kidney function. Therefore, consuming diets that induce minimal or no net acid load may be vital at the older age, and identifying modifiable lifestyle factors that are associated with hypertension is important to determine the effective way for hypertension prevention and control.

Innovations and breakthroughs

There have been few studies investigating the association between dietary acid-base load and hypertension. Positive associations have been reported in healthy young women, middle-aged women as well as healthy children and adolescents. Negative findings were observed among Western older adults. However, no such study has been conducted in Chinese population. In this study, data from participants aged 65 years or above participating in a cohort study examining the risk factors for osteoporosis at baseline and 4-year follow-up were examined. Baseline estimated net endogenous acid production (NEAP) was calculated based on the diet's protein to potassium ratio derived from the Food Frequency Questionnaire and was related to the hypertension status at baseline (n = 3956) and 4-year follow-up (n = 795). The authors' findings show that participants in the highest quartile of energy-adjusted estimated NEAP was associated with increased likelihood of prevalent hypertension than those in the lowest quartile of energy-adjusted estimated NEAP [multivariable OR = 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002)]. No significant association was observed between energy-adjusted estimated NEAP and risk of incident hypertension.

Applications

This study serves as an additional evidence supporting the potential link between dietary acid-base load and hypertension. The authors' findings show that a diet lower in dietary acid-base load might be beneficial for lowering risk of hypertension. However, further prospective studies in populations with different dietary habits are warranted to confirm the role of dietary acid-base balance in hypertension as well as the underlying mechanisms linking dietary acid-base load to blood pressure.

Terminology

Estimated NEAP: A diet's net acid load that is estimated from the composition of the diet based on collected dietary data; Hypertension: Abnormally high blood pressure.

Peer-review

The authors had declared some of the limitation in which may affects the generalizability of this study, such as the differences in demographic and lifestyle characteristics between those included and those exclude for the analysis; and vegetables intake of those participants in their study groups. It is also an interesting prospective cohort study which may accept for publication.

REFERENCES

1 **Woo J**. Relationships among diet, physical activity and other lifestyle factors and debilitating diseases in the elderly. *Eur J Clin Nutr* 2000; **54** Suppl 3: S143-S147 [PMID: 11041086]
2 **Miura K**, Okuda N, Turin TC, Takashima N, Nakagawa H, Nakamura K, Yoshita K, Okayama A, Ueshima H. Dietary salt intake and blood pressure in a representative Japanese population: baseline analyses of NIPPON DATA80. *J Epidemiol* 2010; **20** Suppl 3: S524-S530 [PMID: 20351473]
3 **Bazzano LA**, Green T, Harrison TN, Reynolds K. Dietary approaches to prevent hypertension. *Curr Hypertens Rep* 2013; **15**: 694-702 [PMID: 24091874 DOI: 10.1007/s11906-013-0390-z]
4 **Adeva MM**, Souto G. Diet-induced metabolic acidosis. *Clin Nutr* 2011; **30**: 416-421 [PMID: 21481501 DOI: 10.1016/j.clnu.2011.03.008]
5 **Murakami K**, Sasaki S, Takahashi Y, Uenishi K. Association between dietary acid-base load and cardiometabolic risk factors in young Japanese women. *Br J Nutr* 2008; **100**: 642-651 [PMID: 18279559 DOI: 10.1017/S0007114508901288]
6 **Zhang L**, Curhan GC, Forman JP. Diet-dependent net acid load and risk of incident hypertension in United States women. *Hypertension* 2009; **54**: 751-755 [PMID: 19667248 DOI: 10.1161/HYPERTENSIONAHA.109.135582]
7 **Krupp D**, Shi L, Maser-Gluth C, Pietzarka M, Remer T. 11β Hydroxysteroid dehydrogenase type 2 and dietary acid load are independently associated with blood pressure in healthy children and adolescents. *Am J Clin Nutr* 2013; **97**: 612-620 [PMID: 23364022 DOI: 10.3945/ajcn.112.047829]
8 **Krupp D**, Shi L, Remer T. Longitudinal relationships between diet-dependent renal acid load and blood pressure development in healthy children. *Kidney Int* 2014; **85**: 204-210 [PMID: 24025638 DOI: 10.1038/ki.2013.331]
9 **Engberink MF**, Bakker SJ, Brink EJ, van Baak MA, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Dietary acid load and risk of hypertension: the Rotterdam Study. *Am J Clin Nutr* 2012; **95**: 1438-1444 [PMID: 22552032 DOI: 10.3945/ajcn.111.022343]
10 **Luis D**, Huang X, Riserus U, Sjögren P, Lindholm B, Arnlöv J, Cederholm T, Carrero JJ. Estimated dietary acid load is not associated with blood pressure or hypertension incidence in men who are approximately 70 years old. *J Nutr* 2015; **145**: 315-321 [PMID: 25644353 DOI: 10.3945/jn.114.197020]
11 **Frassetto LA**, Morris RC, Sebastian A. Effect of age on blood acid-base composition in adult humans: role of age-related renal functional decline. *Am J Physiol* 1996; **271**: F1114-F1122 [PMID: 8997384]
12 **Wang J**, Zhang L, Wang F, Liu L, Wang H. Prevalence, awareness, treatment, and control of hypertension in China: results from a national survey. *Am J Hypertens* 2014; **27**: 1355-1361 [PMID: 24698853 DOI: 10.1093/ajh/hpu053]
13 **Wong SY**, Kwok T, Woo J, Lynn H, Griffith JF, Leung J, Tang YY, Leung PC. Bone mineral density and the risk of peripheral arterial disease in men and women: results from Mr. and Ms Os, Hong Kong. *Osteoporos Int* 2005; **16**: 1933-1938 [PMID: 16079958]
14 **Washburn RA**, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993; **46**: 153-162 [PMID: 8437031]
15 **Woo J**, Leung SSF, Ho SC, Lam TH, Janus ED. A food frequency questionnaire for use in the Chinese population in Hong Kong: Description and examination of validity. *Nutr Res* 1997; **17**: 1633-1641 [DOI: 10.1016/S0271-5317(97)00170-X]

16 **Paul AA**, Southgate DAT. McCance & Widdowson's: The Composition of Foods. 4th ed. London: HMSO, 1978
17 **Yang Y**, Wang G, Pan X. China Food Composition 2002. 2002 ed. Peking: University Medical Press, 2002
18 **Willett WC**, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 1997; **65**: 1220S-1228S; discussion 1229S-1231S [PMID: 9094926]
19 **Frassetto LA**, Lanham-New SA, Macdonald HM, Remer T, Sebastian A, Tucker KL, Tylavsky FA. Standardizing terminology for estimating the diet-dependent net acid load to the metabolic system. *J Nutr* 2007; **137**: 1491-1492 [PMID: 17513412]
20 **Frassetto LA**, Todd KM, Morris RC, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr* 1998; **68**: 576-583 [PMID: 9734733]
21 **Remer T**, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. *Am J Clin Nutr* 2003; **77**: 1255-1260 [PMID: 12716680]
22 **Frassetto LA**, Morris RC, Sebastian A. A practical approach to the balance between acid production and renal acid excretion in humans. *J Nephrol* 2006; **19** Suppl 9: S33-S40 [PMID: 16736439]
23 **Chan RS**, Woo J, Chan DC, Cheung CS, Lo DH. Estimated net endogenous acid production and intake of bone health-related nutrients in Hong Kong Chinese adolescents. *Eur J Clin Nutr* 2009; **63**: 505-512 [PMID: 18231119 DOI: 10.1038/ejcn.2008.3]
24 **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797]
25 **Maurer M**, Riesen W, Muser J, Hulter HN, Krapf R. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. *Am J Physiol Renal Physiol* 2003; **284**: F32-F40 [PMID: 12388390]
26 **Cappuccio FP**, Kalaitzidis R, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. *J Nephrol* 2000; **13**: 169-177 [PMID: 10928292]
27 **Oshima T**, Young EW. Systemic and cellular calcium metabolism and hypertension. *Semin Nephrol* 1995; **15**: 496-503 [PMID: 8588109]
28 **Taylor EN**, Mount DB, Forman JP, Curhan GC. Association of prevalent hypertension with 24-hour urinary excretion of calcium, citrate, and other factors. *Am J Kidney Dis* 2006; **47**: 780-789 [PMID: 16632016]
29 **Mandel EI**, Taylor EN, Curhan GC. Dietary and lifestyle factors and medical conditions associated with urinary citrate excretion. *Clin J Am Soc Nephrol* 2013; **8**: 901-908 [PMID: 23449767 DOI: 10.2215/CJN.07190712]
30 **Albala K**. Food cultures of the world encyclopedia. In: Albala K, editor. Santa Barbara, California: Greenwood, 2011

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