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Contents

Monthly Volume 6 Number 2 February 26, 2014

- | | | |
|------------------------|----|---|
| TOPIC HIGHLIGHT | 26 | Hypertrophic cardiomyopathy in 2013: Current speculations and future perspectives
<i>Efthimiadis GK, Pagourelas ED, Gossios T, Zegkos T</i> |
| REVIEW | 38 | The role of nutrition and nutraceutical supplements in the treatment of hypertension
<i>Houston M</i> |
| MINIREVIEWS | 67 | Therapeutic interventions for heart failure with preserved ejection fraction: A summary of current evidence
<i>Asrar ul Haq M, Wong C, Mutha V, Anavekar N, Lim K, Barlis P, Hare DL</i> |
| CASE REPORT | 77 | Infiltrative cardiac lymphoma with tricuspid valve involvement in a young man
<i>Ngow HA, Wan Mohd Nowalid WK</i> |

Contents

World Journal of Cardiology
Volume 6 Number 2 February 26, 2014

APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Cardiology*, Zequan Yang, MD, PhD, Assistant Professor, Department of Surgery, Department of Biomedical Engineering, University of Virginia, Charlottesville, VA 22911, United States

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WJC 6th Anniversary Special Issues (3): Cardiomyopathy

Hypertrophic cardiomyopathy in 2013: Current speculations and future perspectives

Georgios K Efthimiadis, Efstathios D Pagourelas, Thomas Gossios, Thomas Zegkos

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Abstract

Hypertrophic cardiomyopathy (HCM), the most variable cardiac disease in terms of phenotypic presentation and clinical outcome, represents the most common inherited cardiomyopathic process with an autosomal dominant trait of inheritance. To date, more than 1400 mutations of myofilament proteins associated with the disease have been identified, most of them "private" ones. This striking allelic and locus heterogeneity of the disease certainly complicates the establishment of phenotype-genotype correlations. Additionally, topics pertaining to patients' everyday lives, such as sudden cardiac death (SCD) risk stratification and prevention, along with disease prognosis, are grossly related to the genetic variation of HCM. This review incorporates contemporary research findings and addresses major aspects of HCM, including preclinical diagnosis, genetic analysis, left ventricular outflow tract obstruction and SCD. More specifically, the spectrum of genetic analysis, the selection of the best method for obstruction alleviation and the need for a unique and accurate

factor for SCD risk stratification are only some of the controversial HCM issues discussed. Additionally, future perspectives concerning HCM and myocardial ischemia, as well as atrial fibrillation, are discussed. Rather than enumerating clinical studies and guidelines, challenging problems concerning the disease are critically appraised by this review, highlighting current speculations and recommending future directions.

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Key words: Hypertrophic cardiomyopathy; Preclinical diagnosis; Left ventricular outflow obstruction; Sudden cardiac death; Genetic analysis

Core tip: Hypertrophic cardiomyopathy (HCM) represents the most common inherited cardiomyopathic process with an autosomal dominant trait of inheritance. This review incorporates contemporary research findings and addresses major and controversial aspects of HCM, including preclinical diagnosis, genetic analysis, left ventricular outflow tract obstruction, sudden cardiac death, myocardial ischemia and atrial fibrillation. Rather than enumerating clinical studies and guidelines, challenging problems concerning the disease are critically appraised by this review, highlighting current speculations and recommending future directions.

Efthimiadis GK, Pagourelas ED, Gossios T, Zegkos T. Hypertrophic cardiomyopathy in 2013: Current speculations and future perspectives. *World J Cardiol* 2014; 6(2): 26-37 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i2/26.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i2.26>

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) represents the

most common inherited cardiac disease, affecting 1 in every 500 people in the general population^[1,2]. Classically, it is defined by the presence of a hypertrophied, non-dilated left ventricle (LV) in the absence of any cause capable of producing the magnitude of evident hypertrophy, such as pressure overload or storage/infiltrative diseases^[3,4]. The main features of the disease are: (1) clinical and genetic heterogeneity, altering phenotypic expression and complicating both clinical and preclinical diagnosis; (2) obstruction, either in the left ventricular outflow tract (LVOTO) or in the midventricular level (MVO), and their pathophysiological significance; and (3) sudden cardiac death (SCD) and risk factors predisposing to it. Evaluation of the mentioned characteristics is essential in the assessment of every patient with HCM.

In this context, the aim of this review is to critically present current knowledge concerning the most controversial fields of HCM, including preclinical diagnosis, obstruction and SCD, and to briefly discuss treatment modalities that might prove useful, especially when applied in the preclinical level. Rather than enumerating clinical studies and guidelines, the authors have tried to appraise challenging problems concerning the disease, highlight current speculations and recommend future directions.

PRECLINICAL DIAGNOSIS

According to current guidelines, HCM diagnosis is mainly based on the detection [either by echocardiography or magnetic resonance imaging (MRI)] of a maximal wall thickness ≥ 15 mm or on the presence of a mild hypertrophy (13-14 mm) coexisting with a positive family history of HCM and/or an HCM compatible ECG^[3-5]. Although diagnosis in cases of overt hypertrophy seems simplified, with the clinical distinction and differentiation of phenocopies being rather challenging, the real challenge in terms of HCM diagnostic evaluation today is preclinical diagnosis.

Preclinical diagnosis refers to the detection of subjects that carry any HCM-causing gene mutation, before or even without the development of LV hypertrophy [genotype (+)/phenotype (-) subjects]. The concept that HCM pathology may exist in the absence of LV hypertrophy is quite old^[6], but the ability to recognize the presence of early myocardial changes is quite new. Although genetic testing may become the ultimate tool for assessing the risk of disease development, several issues complicate its use as a screening tool.

In 60% of cases, HCM is a familial disease with an autosomal dominant trait of inheritance. To date, more than 1400 HCM-related mutations in genes encoding different sarcomere or non-sarcomere proteins have been identified^[4]. Among them, definitive HCM causative mutations are those implicating 8 sarcomere genes with approximately 80% of identified mutations concerning cardiac β -myosin heavy chain and cardiac myosin binding protein C^[7-18]. Apart from the great number of mutations recognized up to now, some genetic defects, especially

those concerning the cardiac myosin binding protein C gene, are founding mutations and referred to as homogeneous and closed concentrated populations. To further complicate things, the latest studies have documented that 5% of HCM families carry 2^[19-21] or even 3 distinct causative mutations^[22], including homozygous and double or compound heterozygous mutations. The “privacy” of many mutations (unique genetic defects inside specific families), the variable penetrance of recorded mutations allowing various phenotypic severity, the complexity of distinction between a genetic polymorphism and a causative mutation, and the involvement of multiple potential disease modifying variants^[23] have led to a decrease of initial enthusiasm about the utility of genetic analysis in preclinical diagnosis. While still in search of the “Holy Grail” which is the phenotype-genotype correlation, the utility of genetic analysis is confined mostly to identify the proband’s relatives sharing the mutation and to diagnose HCM phenocopies, such as Anderson-Fabry’s disease and other glycogen or lysosomal storage diseases.

The complexity of genetic analysis has led to the adoption of other diagnostic approaches to unveil HCM in the preclinical stage, mainly by discovering disease features that precede the development of overt hypertrophy. In the excellent paper by Geisterfer-Lowrance *et al.*^[7], based on a mouse model of familial HCM, cardiac dysfunction preceded histopathological changes, myocyte disarray came next, while hypertrophy and fibrosis tended to increase with age (Figure 1). Reflecting on this experiment in clinical settings, cardiac dysfunction (detected by tissue Doppler imaging), myocyte disarray (encoded by new ECG abnormalities), hypertrophy (visualised by echocardiography or cardiac MRI) and fibrosis [detected by cardiac MRI Late Gadolinium Enhancement (LGE)] are early signs of HCM that should be properly searched for (Figure 2)^[24-26]. Overall, several clinical reports have demonstrated that the majority of HCM genotype (+)/phenotype (-) subjects display “early” myocardial functional or histopathological changes, such as reduced tissue Doppler imaging-derived systolic and diastolic velocities, abnormal ECG, cardiac magnetic resonance (CMR)-visualized myocardial crypts, mitral leaflet elongation and evidence of a fibrotic state, such as increased type I procollagen synthesis, CMR-increased myocardial extracellular volume, and late gadolinium myocardial enhancement^[24-27].

Preclinical diagnosis of HCM has many medical and social implications. At present, there is no evidence that early detection will change the course of the disease; however, early application of therapy may improve the lifelong management of these subjects. Experimental therapies in HCM-models using conventional medications have shown promising results on reversal or prevention of hypertrophy and fibrosis. Larger studies in clinical settings during the preclinical stage of HCM are necessary to demonstrate the potential benefit in prevention of HCM phenotypic changes or complications, including SD.

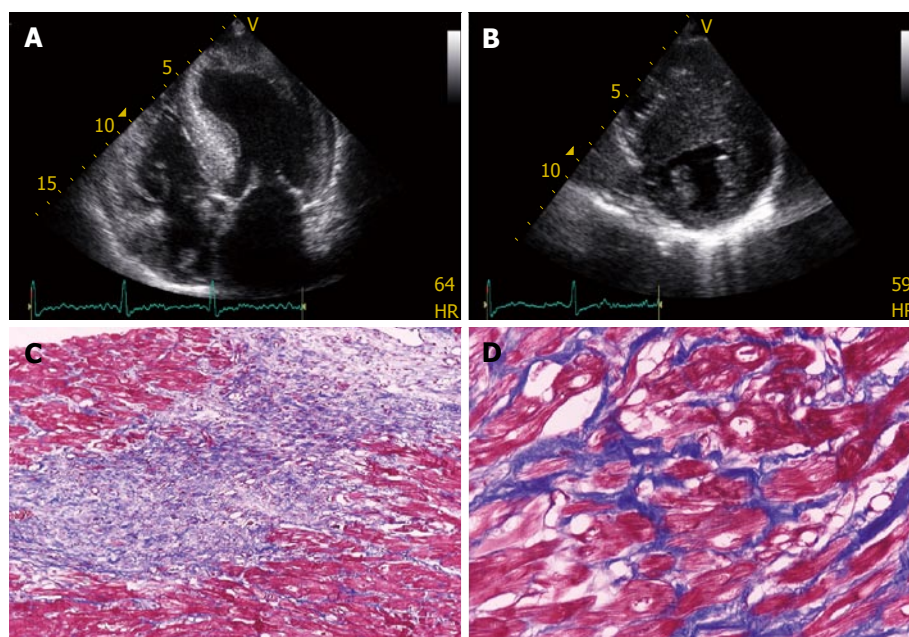


Figure 1 Echocardiographical and pathological features of hypertrophic cardiomyopathy. A: An apical 4-chamber view of a patient with hypertrophic cardiomyopathy showing a hypertrophied, non-dilated left ventricle; B: Excessive thickness of interventricular septum (eccentric hypertrophy) is also optimally visualized from parasternal short axis views; C: Myocardial disarray and extensive fibrosis ($\times 10$ Trichrome Masson); D: Myocardial disarray and interstitial fibrosis ($\times 40$ Trichrome Masson).

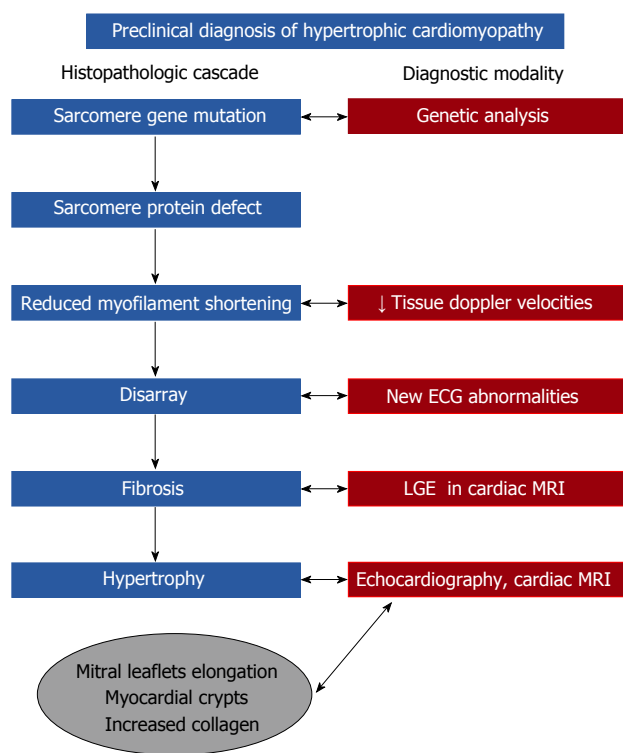


Figure 2 Preclinical diagnosis in hypertrophic cardiomyopathy. The figure shows histopathological cascade of the disease and diagnostic modalities used to detect abnormalities in each stage. LGE: Late gadolinium enhancement; MRI: Magnetic resonance imaging.

SIGNIFICANCE AND TREATMENT OF OBSTRUCTION

After a lasting controversy concerning its role in HCM, obstruction is evidenced to be related to severity of symptoms, especially by augmentation of gradient during exercise, in the context of diastolic dysfunction and myocardial ischemia^[28]. Maron *et al.*^[29] in 2003 docu-

mented that obstruction at rest is a strong, independent predictor of progression to severe heart failure and death, while according to another study, 70% of patients are echocardiographically found to have obstruction at rest or during exercise^[30]. Despite establishing a connection between LVOTO and progression to heart failure in HCM, a controversy concerning the potential impact of LVOTO on SCD survival is still ongoing. Two major studies have demonstrated that a resting gradient > 30 mmHg was associated with a 2.4-fold increase in the risk of SCD^[29,31], presenting, however, a very low positive predictive value ($< 10\%$) and a very low SCD annual rate (0.37%-1.5%)^[29,31,32]. In our cohort of HCM patients, obstruction did not show a significant correlation with SCD incidence^[33]. At present, obstruction at rest does not serve as a sole risk factor for SCD^[34]. Probably, severe gradients (> 100 mmHg) may serve as SCD arbitrator in the context of other risk factors^[4].

A minority of HCM patients present with a mid-LV level obstruction due to midventricular muscular apposition creating an hourglass-shaped LV^[35-40]. MVO is associated with an unfavorable prognosis in terms of end stage HCM, SCD and lethal arrhythmic events^[40,41]. A very challenging and distinct complication of midventricular obstruction is that of LV apical aneurysm formation associated with transmural myocardial scarring. Maron *et al.*^[42] and our team found a 2% prevalence of apical aneurysms in HCM patient cohorts. About 70% of patients with apical aneurysms had a midventricular, whereas the remaining 30% presented with an apical type of hypertrophy. More than 40% of patients with an apical aneurysm experienced cardiovascular complications, including SCD, appropriate implantable cardioverter-defibrillator (ICD) discharges, thromboembolic stroke and progressive heart failure-death, over a 4 years mean time of follow-up^[42].

Concerning therapeutic approaches for obstruction, interventional procedures should be applied in patients

who are severely symptomatic, with a maximal instantaneous gradient > 50 mmHg at rest or with physiological provocation despite optimal medical treatment (B-blockers, verapamil, disopyramide or combination thereof)^[4]. The major goal of pharmacological therapy in symptomatic patients with HCM is to alleviate symptoms of exertional dyspnea, palpitations and chest discomfort, which may reflect pathophysiological mechanisms such as LVOTO obstruction, reduced supply of myocardial oxygen, mitral regurgitation and impaired LV diastolic relaxation and compliance^[3,43]. Beta blockers accomplish that through their negative inotropic and chronotropic effects^[44] improving myocardial oxygen supply-demand relationships, prolonging the diastolic filling period, allowing for more efficient inactivation of myocardial contractile proteins and leading thus to LVOTO alleviation^[45,46]. Negative inotropic and rate lowering effects are the mechanism of action for verapamil and diltiazem, whereas negative inotropic action is also the pharmacological pathway of disopyramide^[4].

Surgical septal myectomy, accomplished through a transaortic approach and extended muscular resection (Morrow procedure), resulting in physical enlargement of the LV outflow has been fairly considered the gold standard of invasive therapies for relief of obstruction in severely symptomatic HCM patients^[47-54]. In a major retrospective study from the Mayo Clinic, surgical myectomy performed in severely symptomatic patients with obstructive HCM was associated with a long term survival equivalent to that of the US general population and superior to survival observed in patients with obstructive HCM without operation^[50]. In another study coming from the same center, surgical myectomy in patients carrying an ICD was associated with a significant reduction in the rate of appropriate ICD discharge and a reduction in the risk of SCD^[52].

Alcohol septal ablation *via* a percutaneous intracoronary approach uses administration of absolute ethanol to the septal perforator branch, inducing a localized infarction of the basal septum at the point of contact of the anterior mitral valve leaflet, reducing thereby the LV outflow tract gradient^[53-55].

Selection of the best interventional treatment should depend on demographic, anatomic-electrical and hemodynamic criteria. More specifically, the age of the patient, operator and institutional experience on each specific method, the presence of comorbidities (chronic kidney disease, coronary artery disease, chronic pulmonary or hepatic impairment, *etc.*) and, last but not least, patient's preference, are among the most crucial demographic factors influencing implementation of an interventional strategy. Additionally, the magnitude and extent of ventricular hypertrophy, dislocation of papillary muscles and their functionality, the presence of intrinsic mitral valve disease potentially demanding the need of additional surgical approaches, the complexity of coronary vasculature along with the existence or not of conduction abnormalities may influence final decisions based on an electro-anatomic and hemodynamic basis^[4].

Although long-term outcome studies comparing the effectiveness and mortality after alcohol septal ablation or septal myectomy are lacking, a recent meta-analysis reviewing 12 studies comparing the two interventional techniques found no significant differences concerning short and post-adjustment long term mortality, post-intervention functional status, improvement in New York Heart Association functional class, ventricular arrhythmia occurrence, re-interventions performed and post-procedure mitral regurgitation^[56]. However, septal ablation was connected to a higher post-procedure incidence of complete heart block requiring a permanent pacemaker (10%-20% *vs* 2% after surgery)^[4], while it was found to increase the risk of right bundle branch block (RBBB). Patients with left bundle branch block and RBBB are more likely to develop complete heart block with surgery and alcohol septal ablation, respectively^[4]. Finally, the percentage of patients showing a higher residual gradient was also deemed to be higher among patients having undergone septal ablation^[56].

Current evidence suggests that any attempt to conduct a double blind randomized study comparing the long term effects of the 2 main therapeutic options for LVOTO in HCM would be complicated, if not impossible. Furthermore, septal ablation and septal myectomy are 2 very different techniques; the former causing ischemia and generating a scar and the latter leading to myocardial resection. The myocardial scar caused by septal ablation has aroused concern of a potentially increased risk of malignant arrhythmias. Ventricular arrhythmias have been reported as an effect of ischemia in the early post procedural phase^[57,58]. However, no increased risk of malignant arrhythmias has been shown in patients who already had an ICD implanted because of a previously estimated high risk of SCD^[59,60]. In a recent report, various factors, including age ≥ 65 years, gradient < 100 mmHg, septal hypertrophy ≤ 18 mm and left anterior descending artery diameter < 4.0 mm, were the strongest patient characteristics that predicted clinical success after septal alcohol ablation^[61]. The increasing experience of involved tertiary centers and proper training of physicians providing both interventional treatments will diminish the rate of complications in future and significantly alter the natural course of the disease, especially among those patients presenting with more symptoms and eventually higher mortality.

RISK AND PREVENTION OF SCD

SCD is the most dramatic complication of HCM. Even although primary estimates of the SCD rate emanating from tertiary center based cohorts have been as high as 6% per year, true prevalence based on data coming from large scale community registries is significantly lower, approximately 0.7% annually^[3,4]. It is evident that the prevalence of SCD is higher in younger people, approximately before 35 years of age, even although according to other studies, longevity is not synonymous with immunity^[62,63]. HCM related SCD is the leading mortality cause among

Table 1 Risk factors for sudden cardiac death in hypertrophic cardiomyopathy

Established risk markers	Risk modifiers or novel risk factors
Prior resuscitated cardiac arrest (VF, sustained VT)	LGE in MRI
MWT > 30 mm	Marked LVOTO
FH of SCD	Severe or multiple sarcomeric mutations
Syncope	Certain phenotypic expressions: Apical aneurysms, midventricular obstruction
NSVT	Severe systolic or diastolic impairment, <i>e.g.</i> , burnt out HCM, restrictive pattern
ABPR	CAD
	Arrhythmic substrate: Atrial fibrillation

VF: Ventricular Fibrillation; VT: Ventricular tachycardia; MWT: Maximum Wall thickness; FH: Family history; SCD: Sudden cardiac death; NSVT: Non sustained ventricular tachycardia; ABPR: Abnormal blood pressure response to exercise; LGE: Late Gadolinium Enhancement; MRI: Magnetic resonance imaging; LVOTO: Left ventricular outflow tract obstruction; CAD: Coronary artery disease; HCM: Hypertrophic cardiomyopathy.

competitive athletes following different sport disciplines^[64,65]. The vast majority of SD (85%) occurs during daily activities (walking, rest, driving or during sleep), while 70% of patients dying suddenly are asymptomatic or have few symptoms (functional class I or II)^[62]. Despite the fact that SCD objectively affects a small minority of HCM patients, early recognition of predisposing factors and concomitant prevention still remains a major clinical challenge since SCD and associated lethal arrhythmic events may be fully prevented, either primarily or secondarily, by means of implantable ICDs.

Apart from personal history of ventricular fibrillation (VF), sustained ventricular tachycardia (SVT) or resuscitated cardiac arrest which has been found to represent the highest risk predisposing to new potentially lethal arrhythmic events (secondary prevention)^[66-68], 5 non interventional clinical factors have been identified up to now to represent risk markers for SCD in HCM: (1) Family history of SCD affecting at least one first degree relative < 40 years; (2) Syncope, without a known causal factor occurring in the recent past (< 6 mo); (3) Extreme left ventricular hypertrophy as this is represented by a maximum wall thickness of any myocardial segment > 30 mm; (4) Abnormal blood pressure response (ABPR) to exercise, defined as either a failure of systolic blood pressure to increase by at least 20 mmHg or a drop below baseline resting values during effort and even a drop of systolic pressure during maximal exercise; and (5) Non SVT (NSVT), defined as recording on ambulatory 24-h Holter of ≥ 3 consecutive ventricular ectopic beats at a rate of ≥ 120 beats lasting < 30 s^[69-73]. NSVT is considered a risk factor for SCD, primarily in patients under the age of 30^[74].

Recent HCM guidelines have suggested an escalation in risk stratification, suggesting that personal history of SVT or VF is Class I indication for ICD implantation^[4].

Existing literature suggests that these patients have 33% mortality in 7 years^[66] and that in 5 years 41% will experience SD or ICD-discharge^[67]. The presence of a family history of SCD, syncope or a maximal wall thickness > 30 mm confers a Class IIa indication for ICDs, whereas NSVT or ABPR alone probably could not justify ICD implantation needing reassessment of risk profile based on the rest of risk factors or potential arbitrators^[4]. Several clinical or laboratory aspects of HCM have been studied as potential risk modifiers for SCD, as shown in Table 1. Among them, 3 certain features of HCM may affect our decision in favor of ICD implantation based on evidence from published trials^[4,69]: the presence of LGE on MRI^[75]; certain mutations, especially coexistence of more than 1 sarcomere mutation^[22]; and marked LV outflow tract obstruction at rest^[4,29,31].

All of the above mentioned factors describe the very same phenomenon from a different point of view: extent of replacement and interstitial fibrosis leading to different conduction pathways in the myocardium, thus facilitating reentry events and finally malignant ventricular tachyarrhythmias^[76,77]. Based on the previous assumptions, detection of LGE by MRI could be the main pillar of SCD risk stratification since it reflects the extent of fibrosis, the main determinant of malignant arrhythmias. However, a recent meta analysis concluded that LGE showed a trend towards significance for predicting SCD/aborted SCD (pooled OR = 2.39; 95%CI: 0.87-6.58, $P = 0.091$), failing to accurately define individual patients with HCM reaching this end point^[75]. To date, there is no compelling published evidence that the extent is more important than just the presence of LGE for risk-prediction. Moreover, the 2011 current guidelines emphasize that it is the presence and not the extent of LGE that relates to adverse CV events. However, this is an interesting, controversial topic that should be addressed by future research [an ongoing multicenter trial with over 1000 HCM patients will probably show that the extent of LGE is also relevant (Martin Maron, ACC 2013)].

ICDs have proved to be effective in terminating life-threatening ventricular tachyarrhythmias in HCM, altering the natural course of the disease and prolonging life. ICDs should be offered after detailed discussion with the patient and his/her family and after benefits are anticipated to outweigh the potential risks. Data from retrospective analysis of sizeable cohorts of recipients have demonstrated that the number of risk factors prior to implantation for primary prophylaxis is disproportionate to the number and frequency of appropriate shocks delivered, while the time interval from ICD implant to first appropriate device discharge is quite variable in length since some patients have survived over 10 years after an initial episode of cardiac arrest without receiving appropriate ICD discharges^[78,79]. A careful evaluation of data coming from American and European registries could easily reveal that the annual rate of ICD adverse events (including inappropriate shocks and lead complications) may range between 8.6% and 25%, at least 2-fold higher than the rate of patients receiving appropriate shocks per

year^[78-80]. The rate of inappropriate shocks and lead dislodgment/fractures seems to be higher among younger populations (children, adolescents), mainly due to their increased activity levels and body growth^[81].

HCM AND BLUNTED MYOCARDIAL PERFUSION

For much of the past 50 years, HCM progression was mainly connected to LVOTO and diastolic dysfunction, under appreciating (or even worse, under recognizing) myocardial ischemia as an important pathophysiological component of the disease. Even now, assessment of myocardial ischemia is currently not part of routine clinical diagnostic or management strategies in HCM^[4].

Initial evidence that myocardial ischemia participates in the pathophysiological mechanism of HCM was based on post mortem studies of patients who had died suddenly and presented with extensive areas of myocardial damage. A spectrum of ischemic injury was observed, from an acute phase with coagulative necrosis and neutrophilic infiltrate to a chronic post-necrotic replacement-type fibrosis, always in the absence of atherosclerotic epicardial coronary artery disease^[82]. In addition to gross pathological evidence of myocardial scarring, autopsy studies in HCM patients have shown structural abnormalities of intramural coronary arterioles, characterized by thickening of the intima and/or medial layers of the vessel wall associated with a decreased luminal cross-sectional area. These morphological changes are the main substrate for functional decompensation, which translates to blunted myocardial blood flow during stress^[83-85].

Among contemporary non invasive imaging modalities that have been used for revealing impaired myocardial blood flow in HCM, PET with either ¹³N labeled ammonia or ¹⁵O-labeled water is the most reliable^[86]. The measurement of myocardial blood flow under basal conditions and in conditions of near-maximal vasodilatation (after intravenous adenosine or dipyridamole) permits the calculation of coronary flow reserve, that is, the ratio of maximum to basal blood flow. On the other hand, although SPECT myocardial perfusion imaging is widely available, this technique is limited by allowing only the assessment of relative changes in regional perfusion and by an inability to quantify absolute MBF^[87].

Similarly to PET, recent stress CMR studies in HCM showed blunted myocardial blood flow in response to stress. Importantly, areas of the myocardium in which fibrosis was present (as determined by LGE) were most often associated with reduced myocardial blood flow^[88], even although a small proportion of patients had LGE in the absence of perfusion abnormalities^[89]. Taken together, these CMR observations show an association between ischemia, myocardial fibrosis and LV remodeling, providing further support for the principle that abnormal blood flow caused by microvascular dysfunction is responsible for myocardial ischemia-mediated myocyte death and ultimately repair in the form of replacement

fibrosis^[87]. Traditional, noninvasive methods for detecting myocardial ischemia clinically, including ST-segment changes on 12-lead and ambulatory Holter electrocardiographic monitoring or exercise testing, have proved to be insufficiently sensitive or specific for detecting ischemia in HCM^[87].

Verapamil and beta-blockers may improve symptoms of chest pain and exertional dyspnea in HCM. This probably occurs *via* reduction in heart rate and oxygen consumption and possibly because of direct effects on the microvasculature and diastolic filling leading to improved perfusion, especially in the mostly “stressed” subendocardial regions^[87]. Also, since there is now evidence showing an improvement in myocardial perfusion after septal reduction therapy^[90], consideration should be given to these procedures to relieve severe chest pain refractory to drug therapy^[87].

Concerning the importance of revealing blunted myocardial blood flow in HCM, a previous study has shown that severe abnormalities in myocardial blood flow caused by microvascular dysfunction seemed to be a powerful determinant of impaired systolic function, whereas preserved myocardial blood flow identified the low-risk subgroup^[91]. Therefore, an impaired myocardial blood flow could possibly differentiate individuals with a higher risk for progression towards a “burnt out” phenotype (dilatation and severe systolic impairment). This has important clinical implications since HCM patients in the end stage experience a high rate of unfavorable disease consequences, including progressive heart failure (often requiring heart transplantation) and SCD (prompting consideration for prophylactic ICD).

In conclusion, blunted myocardial blood flow seems to be an important component of HCM physiology. However, many current controversies need to be clarified by future research. First of all, the dynamic interaction between fibrosis and ischemia needs further study so as to define which phenomenon precedes the other in the vicious circle set. This is extremely important since identifying the stage when active myocardial ischemia begins (with respect to the development of the HCM phenotype) answers the question of whether impaired myocardial blood flow could be considered an early therapeutic target. Secondly, future research should highlight optimal non-invasive imaging modalities as well as biomarkers with sufficient sensitivity and specificity to reveal HCM patients with ischemia predisposing to disease progression. Finally, future studies should not only discover novel therapies targeting myocardial ischemia in HCM (especially for those patients presenting refractory angina to common medication), but also define the groups of patients who should mostly benefit from anti-ischemic treatment.

AF

Patients with HCM are at increased risk of AF compared with age-matched cohorts, while AF is an important cause of symptoms, morbidity and even mortality in pa-

tients with HCM^[4,62]. The 2011 ACC/AHA guidelines for diagnosis and treatment of HCM recognize the importance of AF for HCM prognosis, extrapolating, however, AF diagnostic and therapeutic options recommended for the general population in HCM patients^[92].

The risk of systemic embolization is high in HCM patients with AF but does not seem to be related to the severity of symptoms^[4,62]. Risk scores that seem to be efficient and therapy guiding in the general population (like CHADS2-VASc) might be less effective in HCM where other risk factors may also play an important role in predisposing to embolic events. LVOTO, SAM and of course the magnitude of LA enlargement (a common morphological feature in many HCM patients) seem to be additional factors that increase the risk for stroke^[4,62]. Even although paroxysmal, persistent or chronic AF followed by a CHADS2-VASc score > 2 is a strong indication for anticoagulation with a vitamin K antagonist^[92], the threshold for AF that warrants anticoagulation remains unresolved. For example, should HCM patients with a sole AF episode receive anticoagulant treatment given the high risk of thromboembolism in HCM? Is a large LA volume or volume index sufficient as a risk factor for a vitamin K antagonist prescription in HCM patients prior to AF occurrence or in AF without the presence of other risk factors? Finally, could aspirin prevent embolic episodes in HCM patients with AF and low CHADS2-VASc score?

Contemporary developments in anticoagulation and rhythm control management in AF warrant a cautious assessment before their application in HCM patients. Unfortunately, few data exist concerning the safety and efficacy of dabigatran or activated X factor inhibitors in HCM. Accordingly, the long-term benefits of radiofrequency ablation *vs* antiarrhythmic drugs in patients with HCM remain to be established. Furthermore, there are no data regarding the efficacy of other class I antiarrhythmic agents, sotalol or dronedarone, in HCM^[4,93]. Overall, AF is an important feature of HCM pathophysiology and disease progression necessitating further research efforts to optimize existing treatment options.

NOVEL TREATMENT POTENTIALS

Five decades following the original description of HCM, there is still a dismal paucity of data supporting pharmacological treatment strategies for this complex disease. By comparison, device-based, percutaneous and surgical treatments of LVOTO obstruction have received significantly greater attention, although rarely in a double blind randomized fashion. This can be regarded as a paradox as only a minority of patients requires surgery or a device, whereas the large majority is treated pharmacologically^[94]. Additionally, few data exist concerning the therapeutic approach of HCM patients without obstruction (1/3 of the HCM population)^[94].

Treatment application in the preclinical phase of HCM may have a beneficial effect, whereas treatment during the mature phase of the disease could be rather

problematic since a possible regression of hypertrophy may lead to LV dilation and reduced EF^[95]. Taking into consideration the pathophysiological cascade of HCM progression, early treatment options could be simply divided into 3 categories: therapies targeting impaired calcium homeostasis and related disorders; drugs blocking the results of neurohumoral response secondary to sarcomere dysfunction; and anti-fibrotic agents.

With the knowledge that altered intracellular Ca²⁺ handling occurs early in disease pathogenesis, diltiazem, an L-type calcium channel blocker, inhibited the development of HCM phenotype when administered to young (pre-hypertrophic) mice carrying a pathogenic myosin heavy chain mutation (α MHC403/+)^[96]. Importantly, treatment initiated after the development of LV hypertrophy was unable to reverse the established phenotype in these animals^[96]. In an observational study enrolling a small number (6 patients) of genotype (+)/phenotype (-) HCM patients, oral daily administration of 240 mg of diltiazem led to normalization of early diastolic and systolic velocities about 8 wk after treatment initiation^[97]. Obviously, data on the actions of diltiazem in preclinical HCM patients are lacking, while an ongoing trial which is expected to terminate in December 2013 is testing the effects of diltiazem in preventing phenotypes in preclinical HCM, *i.e.*, in subjects with identified sarcomere mutation with no overt LVH^[98]. In a similar way, ranolazine is another factor that could possibly interrupt the vicious circle of calcium in preclinical HCM, deterring the establishment of an overt HCM phenotype. The drug is currently used as a metabolic modulator in ischemic heart disease^[99] but further insights suggested the role of this drug as a selective inhibitor of INaL in cardiomyocytes. Tomberli *et al*^[100] demonstrated the potential role of intracellular Na⁺ overload in inducing an altered Ca²⁺ homeostasis in HCM myocardial samples. This mechanism can play an important role in cardiac remodeling in HCM.

Statins, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors and angiotensin II receptor blockers (ARBs) are demonstrated to inhibit angiotensin II-mediated cardiac hypertrophy^[101,102]. Senthil *et al*^[103] treated 15 pre-hypertrophic β MHC-Q403 rabbits with Atorvastatin, 2.5 mg/kg per day, *vs* a placebo group for 1 year. Rabbits treated with statins did not develop hypertrophy and showed a reduction in both the myocyte cross-sectional area and collagen volume fraction. Similarly, Teekakirikul *et al*^[104] treated pre-hypertrophic α -MHC^{719/+} mice with Losartan for 2 wk prior and during Cyclosporine A induction of hypertrophy which prevented the emergence of hypertrophy, non-myocyte proliferation and fibrosis. Although statins and ARBs seemed to be able to reverse hypertrophy and fibrosis and to prevent the development of the phenotype in HCM animal models, these results were not replicated in clinical trials^[105,106].

The rationale for using N-acetylcysteine and spironolactone in HCM comes from the demonstration of the anti-fibrotic effects of the drugs in several human tissues and animal models^[107-113]. However, there are no demonstrations of efficacy of the long term treatment on

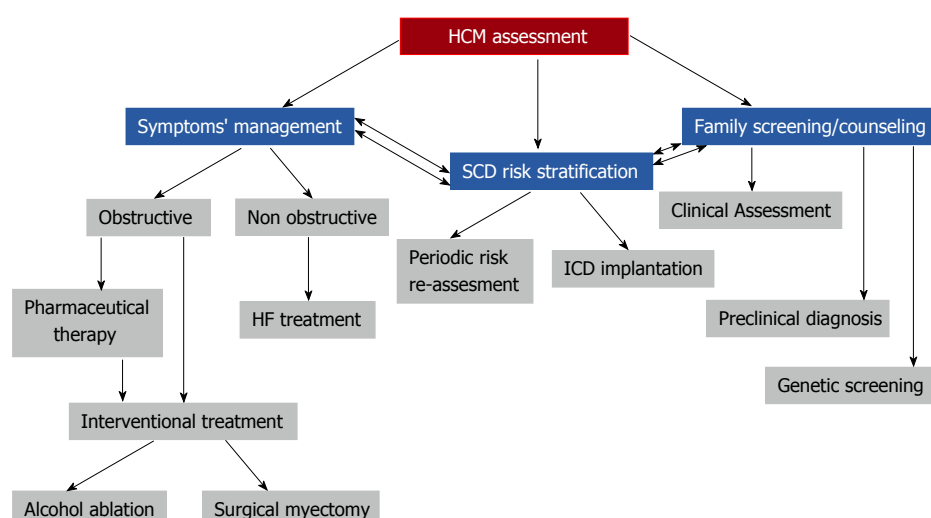


Figure 3 Hypertrophic cardiomyopathy assessment algorithm. A clinician dealing with a HCM patient should face 3 major issues: symptom management based on the existence or not of left ventricular outflow obstruction; sudden cardiac death risk stratification and prevention; and finally, family counseling and advice. HF: Heart failure; SCD: Sudden cardiac death; ICD: Implantable cardioverter defibrillator; HCM: Hypertrophic cardiomyopathy.

humans yet.

CONCLUSION

HCM assessment is based on a multilevel approach taking into consideration symptom (obstruction) management, SCD risk stratification and preclinical diagnosis/genetic screening/counseling (Figure 3). Could diagnostic evaluation and therapeutic approach be substantially improved over the next few years?

There has been a remarkable evolution during the last few years driven by the discovery of new mutations connected with the disease, expanding its known genetic database. Widespread adoption of genetic analysis, at least from tertiary referral centers, involving newer techniques such as next-generation sequencing along with the progress of bio-informatics, will help to better organize genetic bases by faster and more cost effective approaches of the responsible exons, thus bypassing the striking allelic and locus heterogeneity of the disease^[114]. Based on these achievements, differentiating no disease causing polymorphisms from disease causing mutations will become significantly easier, permitting genotype-phenotype correlations from thoroughly followed up patient cohorts. The introduction of proteomics will hopefully facilitate better definition of the molecular mechanisms of the disease, identifying the pathophysiological pathways from genetic mutations to phenotypic presentation and clinical course. All the above developments will certainly highlight new therapeutic targets, which may impede genotypic expression and disease progression, and may provide a more accurate risk assessment for SCD prevention based on an individual clinical-genetic assessment.

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The role of nutrition and nutraceutical supplements in the treatment of hypertension

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Abstract

Vascular biology, endothelial and vascular smooth muscle and cardiac dysfunction play a primary role in the initiation and perpetuation of hypertension, cardiovascular disease and target organ damage. Nutrient-gene interactions and epigenetics are predominant factors in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Macronutrients and micronutrients can prevent, control and treat hypertension through numerous mechanisms related to vascular biology. Oxidative stress, inflammation and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. There is a role for the selected use of single and component nutraceutical supplements, vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies which complement optimal nutrition, coupled with other lifestyle modifications.

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Key words: Hypertension; Nutrition; Nutritional supplements; Cardiovascular disease; Vascular biology

Core tip: Vascular biology and endothelial dysfunction play a primary roles in hypertension and subsequent

cardiovascular disease. Micronutrients, macronutrients and optimal nutrition and nutritional supplements can prevent, control and treat hypertension through numerous mechanisms related to vascular biology. These treatments are complementary to drug therapy. Oxidative stress, inflammation and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. There is a role for the selected use of single and component nutraceutical supplements, vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies which complement optimal nutrition, coupled with other lifestyle modifications.

Houston M. The role of nutrition and nutraceutical supplements in the treatment of hypertension. *World J Cardiol* 2014; 6(2): 38-66 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i2/38.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i2.38>

INTRODUCTION

Vascular disease is a balance between vascular injury and repair (Figure 1). The endothelium is in a strategic location between the blood and the vascular smooth muscle and secretes various substances to maintain vascular homeostasis and health (Figures 2 and 3). Various insults that damage the endothelium, lead to endothelial dysfunction (ED) and may induce hypertension and other cardiovascular diseases. Hypertension may be a hemodynamic marker of injured endothelium and vascular smooth muscle related to finite responses of inflammation, oxidative stress and immune dysfunction of the arteries leading to ED, vascular and cardiac smooth muscle dysfunction, loss of arterial elasticity with reduced arterial compliance and increased systemic vascular resistance. Hypertension is a consequence of the interaction of genetics and environment. Macronutrients and micronutrients are crucial in the regulation of blood pressure (BP) and subsequent

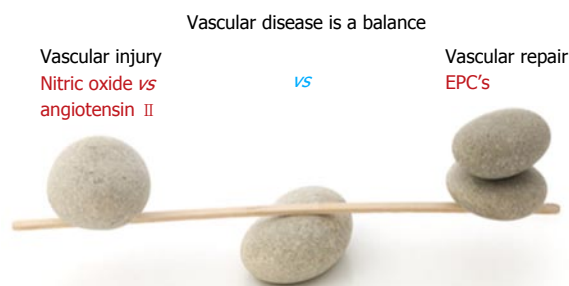


Figure 1 Vascular health is a balance of injury and repair. EPC's: Endothelial progenitor cells.

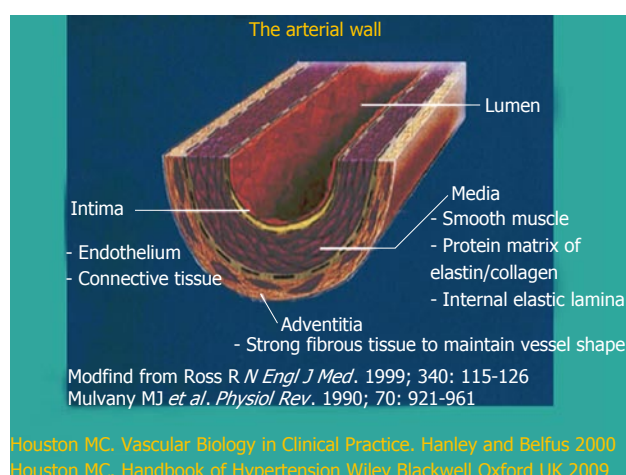
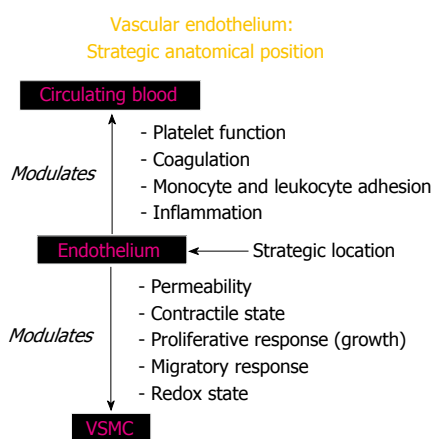


Figure 2 The blood vessel structure.



Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD

Figure 3 The role of the vascular endothelium to maintain vascular homeostasis and health. VSMC: Vascular smooth muscle cells.

target organ damage (TOD). Nutrient-gene interactions, subsequent gene expression, epigenetics, oxidative stress, inflammation and autoimmune vascular dysfunction have positive or negative influences on vascular biology in humans. Endothelial activation with ED and vascular smooth muscle dysfunction (VSMC) initiate and perpetuate essential hypertension.

Macronutrient and micronutrient deficiencies are very common in the general population and may be even

more common in patients with hypertension and cardiovascular disease due to genetics, environmental causes and prescription drug use. These deficiencies will have an enormous impact on present and future cardiovascular health outcomes such as hypertension, myocardial infarction (MI), stroke and renal disease. The diagnosis and treatment of these nutrient deficiencies will reduce BP and improve vascular health, ED, vascular biology and cardiovascular events.

EPIDEMIOLOGY

Epidemiology underscores the etiologic role of diet and associated nutrient intake in hypertension. The transition from the Paleolithic diet to our modern diet has produced an epidemic of nutritionally-related diseases (Table 1). Hypertension, atherosclerosis, coronary heart disease (CHD), MI, congestive heart failure (CHF), cerebrovascular accidents (CVA), renal disease, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS) and obesity are some of these diseases^[1,2]. Table 1 contrasts intake of nutrients involved in BP regulation during the Paleolithic Era and modern time. Evolution from a pre-agricultural, hunter-gatherer milieu to an agricultural, refrigeration society has imposed an unnatural and unhealthy nutritional selection process. In sum, diet has changed more than our genetics can adapt.

The human genetic makeup is 99.9% that of our Paleolithic ancestors, yet our nutritional, vitamin and mineral intakes are vastly different^[3]. The macronutrient and micronutrient variations, oxidative stress from radical oxygen species (ROS) and radical nitrogen species (RNS) and inflammatory mediators such as cell adhesion molecules (CAMs), cytokines, signaling molecules and autoimmune vascular dysfunction of T cells and B cells, contribute to the higher incidence of hypertension and other cardiovascular diseases through complex nutrient-gene interactions, epigenetic and nutrient-caveolae interactions and nutrient reactions with pattern recognition receptors [toll like receptors (TLR) and nod like receptors] in the endothelium^[4-9] (Figure 4). Reduction in nitric oxide bioavailability, increase in angiotensin II and endothelin coupled with endothelial activation initiate the vascular and cardiac dysfunction and hypertension. Poor nutrition, coupled with obesity and a sedentary lifestyle have resulted in an exponential increase in nutritionally-related diseases. In particular, the high Na⁺/K⁺ ratio of modern diets has contributed to hypertension, CVA, CHD, MI, CHF and renal disease^[3,10] as have the relatively low intake of omega-3 PUFA, increase in omega-6 PUFA, saturated fat and trans fatty acids^[11].

PATHOPHYSIOLOGY

Vascular biology assumes a pivotal role in the initiation and perpetuation of hypertension and cardiovascular TOD^[1]. Oxidative stress (ROS and RNS), inflammation (increased expression of redox-sensitive pro-inflammatory genes, CAMs and recruitment migration

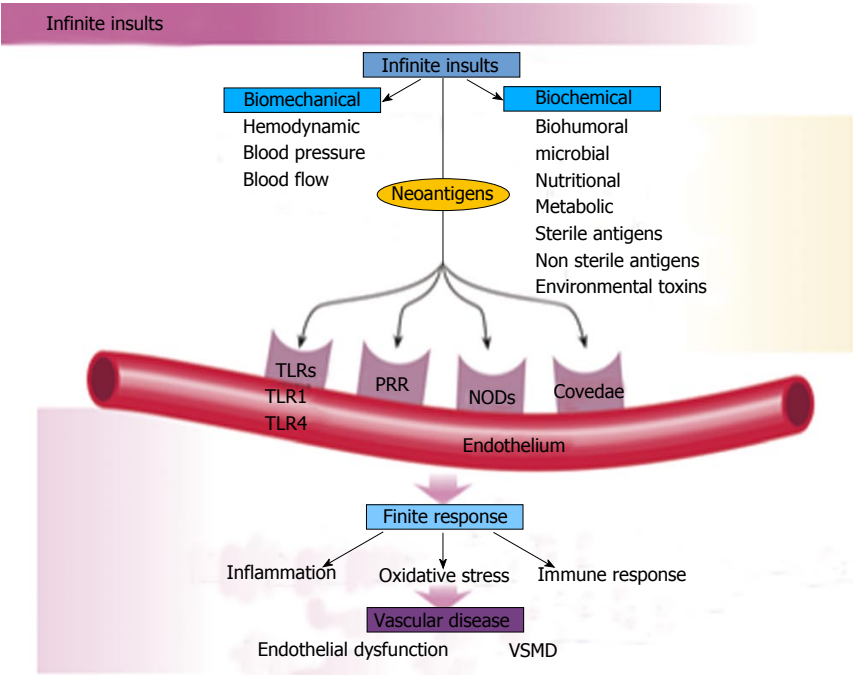


Figure 4 Infinite insults with three finite vascular responses. Biomechanical insults such as hypertension result in stimulation of pattern recognition receptors and caveolae that induce vascular inflammation, oxidative stress and immune dysfunction endothelial dysfunction and vascular and cardiac smooth muscle dysfunction. TLR: Toll like receptors.

Table 1 Dietary intake of nutrients involved in vascular biology: Comparing and contrasting the diet of paleolithic and contemporary humans

Nutrients and dietary characteristics	Paleolithic intake	Modern intake
Sodium	< 50 mmol/d (1.2 g)	175 mmol/d (4 g)
Potassium	> 10000 meq/d (256 g)	150 meq/d (6 g)
Sodium/potassium ratio	< 0.13/d	> 0.67/d
Protein	37%	20%
Carbohydrate	41%	40%-50%
Fat	22%	30%-40%
Polyunsaturated/saturated	1.4	0.4
Fat ratio		
Fiber	> 100 g/d	9 g/d

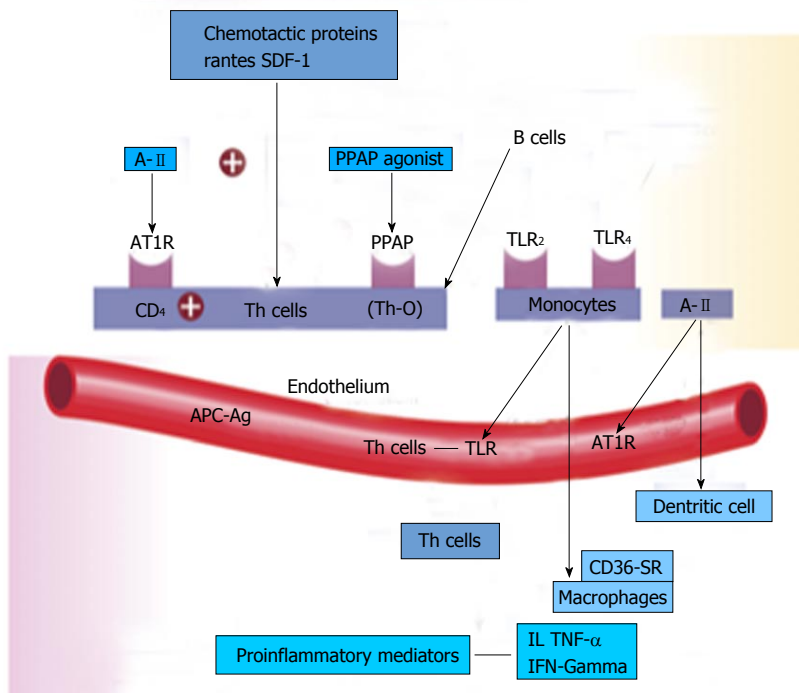
and infiltration of circulating cells) and autoimmune vascular dysfunction (T cells and B cells) are the primary pathophysiologic and functional mechanisms that induce vascular disease^[1,12-14] (Figure 5). All three of these are closely inter-related and establish a deadly combination that leads to ED, vascular smooth muscle and cardiac dysfunction, hypertension, vascular disease, atherosclerosis and CVD. Hypertension is not a disease but is the correct and chronically dysregulated response with an exaggerated outcome of the infinite insults to the blood vessel with subsequent environmental-genetic expression patterns and downstream disturbances in which the vascular system is the innocent bystander. This becomes a maladaptive vascular response that was initially intended to provide vascular defense to the endothelial insults (Figure 6)^[1,15-15]. Hypertension is a vasculopathy characterized by ED, structural remodeling, vascular inflammation, increased arterial stiffness, reduced distensibility and loss of elasticity^[13]. These insults are biomechanical (BP, pulse pressure, blood flow, oscillatory flow, turbulence, augmentation, pulse wave velocity and reflected

waves) and biohumoral or biochemical which includes all the non-mechanical causes such as metabolic, endocrine, nutritional, toxic, infectious and other etiologies^[1] (Figure 4). In addition to the very well established connections for endocrine and nutritional causes of hypertension, toxins and infections also increase BP^[16-20]. Various toxins such as polychlorinated biphenyls, mercury, lead, cadmium, arsenic and iron also increase BP and CVD^[16,17]. Numerous microbial organisms have been implicated in hypertension and CHD^[18-20]. All of these insults lead to impaired microvascular structure and function which manifests clinically as hypertension^[12-14]. The level of BP may not give an accurate indication of the microvascular involvement and impairment in hypertension. Hypertensive patients have abnormal microvasculature in the form of inward eutrophic remodeling of the small resistance arteries leading to impaired vasodilatory capacity, increased vascular resistance, increased media to lumen ratio, decreased maximal organ perfusion and reduced flow reserve, especially in the heart with decreased coronary flow reserve^[12-14]. Significant functional then structural microvascular impairment occurs even before the BP begins to rise in normotensive offspring of hypertensive parents evidenced by ED, impaired vasodilation, forearm vascular resistance, diastolic dysfunction, increased left ventricular mass index, increased septal and posterior wall thickness and left ventricular hypertrophy^[12,15]. Thus, the cellular processes underlying the vascular perturbations constitute a vascular phenotype of hypertension that may be determined by early life programming and imprinting which is compounded by vascular aging^[12-14].

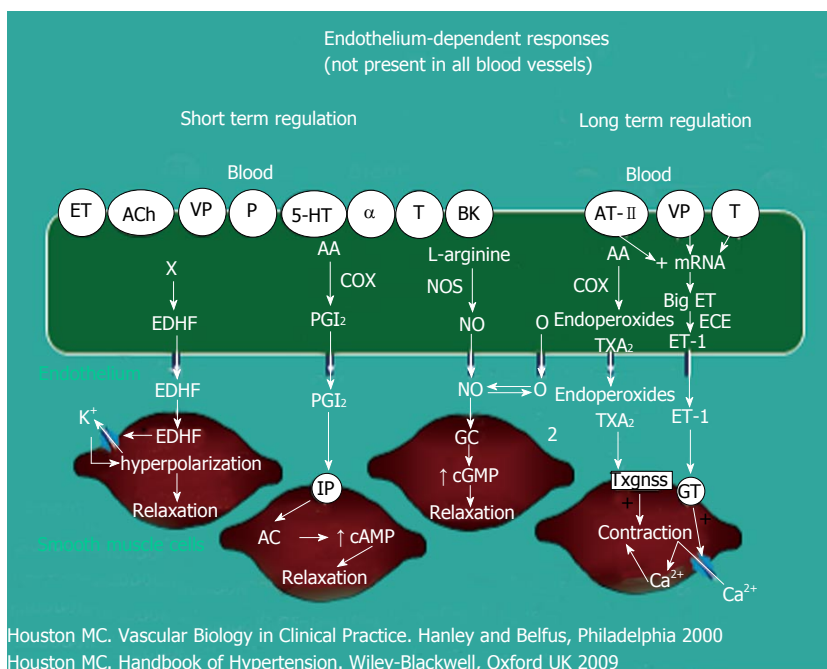
Oxidative stress

Oxidative stress, with an imbalance between ROS and RNS and the anti-oxidant defense mechanisms, contrib-

Autoimmune dysfunction in arteries

**Figure 5 Immune vascular dysfunction.**

Stimulation of the angiotensin receptor and toll like receptors and other and direct stimulation of T cells on the endothelium and vascular smooth muscle lead to immune dysfunction, inflammation and oxidative stress. TLR: Toll like receptors; IL: Interleukin; TNF- α : Tumor necrosis factor alpha.

**Figure 6 Stimulation of the AT1R increases production of superoxide anion which neutralizes nitric oxide and also forms additional downstream radical oxygen species and radical nitrogen species that increase vascular oxidative stress.** AA: Arachidonic acid; NOS: Nitric oxide synthase.

utes to the etiology of hypertension in animals^[10] and humans^[11,12]. Radical oxygen species and RNS are generated by multiple cellular sources, including nicotinamide adenine dinucleotide phosphate hydrazine (NADPH) oxidase, mitochondria, xanthine oxidase, uncoupled endothelium-derived nitric oxide (NO) synthase (U-eNOS), cyclooxygenase and lipo-oxygenase^[11]. Superoxide anion is the predominant ROS species produced by these tissues, which neutralizes NO and also leads to downstream production of other ROS (Figure 3). Hypertensive patients have impaired endogenous and exogenous anti-oxidant defense mechanisms^[21], an increased plasma oxidative

stress and an exaggerated oxidative stress response to various stimuli^[21,22]. Hypertensive subjects also have lower plasma ferric reducing ability of plasma, lower vitamin C levels and increased plasma 8-isoprostanes, which correlate with both systolic and diastolic BP. Various single-nucleotide polymorphisms (SNP's) in genes that codify for anti-oxidant enzymes are directly related to hypertension^[23]. These include NADPH oxidase, xanthine oxidase, superoxide dismutase 3 (SOD 3), catalase, glutathione peroxidase 1 (GPx 1) and thioredoxin. Antioxidant deficiency and excess free radical production have been implicated in human hypertension in numerous

Table 2 Oxidative stress induces endothelial dysfunction, vascular disease and hypertension. Host protective factors include enzymatic and non-enzymatic defenses influenced by diet and nutrients

The cytotoxic reactive oxygen species and the natural defense mechanisms			
Reactive oxygen species		Antioxidant defense mechanisms	
Free radicals		Enzymatic scavengers	
O ₂ • ⁻	Superoxide anion radical	SOD	Superoxide dismutase
OH•	Hydroxyl radical		2O ₂ • ⁻ + 2H ⁺ → H ₂ O ₂ + O ₂
ROO•	Lipid peroxide (peroxyl)	CAT	Catalase (peroxisomal-bound)
RO•	Alkoxy		2H ₂ O ₂ → O ₂ + H ₂ O
RS•	Thiyl	GTP	Glutathione peroxidase
NO•	Nitric oxide		2GSH + H ₂ O ₂ → GSSG + 2H ₂ O
NO ₂ •	Nitrogen dioxide		2GSH + ROOH → GSSG + ROH + 2H ₂ O
ONOO ⁻	Peroxynitrite		
CCl ₃ •	Trichloromethyl		
Non-radicals		Nonenzymatic scavengers	
H ₂ O ₂	Hydrogen peroxide	Vitamin A	
HOCl	Hypochlorous acid	Vitamin C (ascorbic acid)	
ONOO ⁻	Peroxynitrite	Vitamin E (α-tocopherol)	
¹ O ₂	Singlet oxygen	β-carotene	
The superscripted bold dot indicates an unpaired electron and the negative charge indicates a gained electron. GSH, reduced glutathione; GSSG, oxidized glutathione; R, lipid chain. Singlet oxygen is an unstable molecule due to the two electrons present in its outer orbit spinning in opposite directions.		Cysteine	
		Coenzyme Q	
		Uric acid	
		Flavonoids	
		Sulphydryl group	
		Thioether compounds	

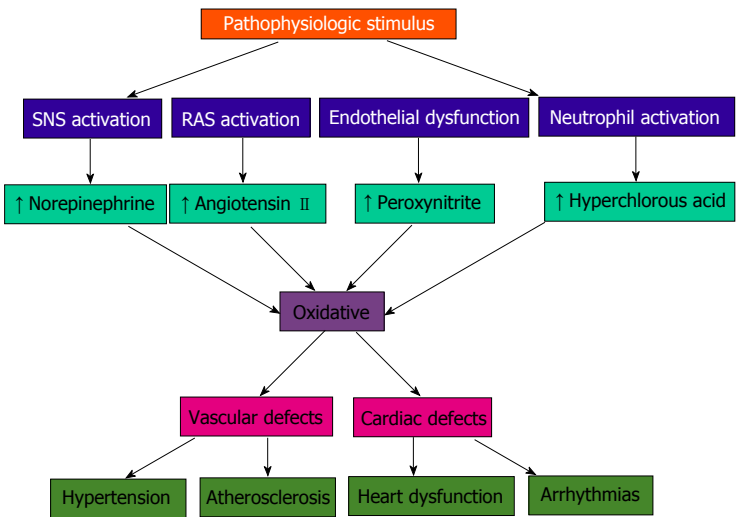


Figure 7 Neurohormonal and oxidative stress system interaction on cardiac and vascular muscle. SNS: Sympathetic nervous system; RAS: Renin angiotensin (aldosterone) system.

epidemiologic, observational and interventional studies (Table 2)^[21,22,24]. Radical oxygen species directly damage endothelial cells, degrade NO, influence eicosanoid metabolism, oxidize LDL, lipids, proteins, carbohydrates, DNA and organic molecules, increase catecholamines, damage the genetic machinery, influence gene expression and transcription factors^[1,21,22,25,26]. The inter-relations of neurohormonal systems, oxidative stress and cardiovascular disease are shown in Figures 6 and 7. The increased oxidative stress, inflammation and autoimmune vascular dysfunction in human hypertension results from a combination of increased generation of ROS and RNS, an exacerbated response to ROS and RNS and a decreased antioxidant reserve^[24-29]. Increased oxidative stress in the rostral ventrolateral medulla (RVLM) enhances glutamatergic excitatory inputs and attenuates GABA-ergic inhibitory inputs to the RVLM which contributes to increased sympathetic nervous system (SNS) activity from

the paraventricular nucleus^[30]. Activation of the AT1R in the RVLM increases NADPH oxidase and increases oxidative stress and superoxide anion, increases SNS outflow causing an imbalance of SNS/PNS activity with elevation of BP, increased heart rate and alterations in heart rate variability and heart rate recovery time, which can be blocked by AT1R blockers^[30,31].

Inflammation

The link between inflammation and hypertension has been suggested in both cross-sectional and longitudinal studies^[32]. Increases in high sensitivity C-reactive protein (HS-CRP) as well as other inflammatory cytokines such as interleukin-1B, (IL-1B), IL-6, tumor necrosis alpha (TNF-α) and chronic leukocytosis occur in hypertension and hypertensive- related TOD, such as increased carotid IMT^[33]. HS-CRP predicts future CV events^[32,33]. Elevated HS-CRP is both a risk marker and risk factor

for hypertension and CVD^[34,35]. Increases in HS-CRP of over 3 µg/mL may increase BP in just a few days that is directly proportional to the increase in HS-CRP^[34,35]. Nitric oxide and eNOS are inhibited by HS-CRP^[34,35]. The AT2R, which normally counterbalances AT1R, is down-regulated by HS-CRP^[34,35]. Angiotensin II (A-II) upregulates many of the cytokines, especially IL-6, CAMs and chemokines by activating nuclear factor Kappa B (NF-κB) leading to vasoconstriction. These events, along with the increases in oxidative stress and endothelin-1, elevate BP^[32].

Autoimmune dysfunction

Innate and adaptive immune responses are linked to hypertension and hypertension-induced CVD through at least three mechanisms: cytokine production, central nervous system stimulation and renal damage. This includes salt-sensitive hypertension with increased renal inflammation as a result of T cell imbalance, dysregulation of CD4⁺ and CD8⁺ lymphocytes and chronic leukocytosis with increased neutrophils and reduced lymphocytes^[36-38]. Leukocytosis, especially increased neutrophils and decreased lymphocyte count increase BP in Blacks by 6/2 mmHg in the highest *vs* the lowest tertile^[38]. Macrophages and various T-cell subtypes regulate BP, invade the arterial wall, activate TLRs and induce autoimmune vascular damage^[38,39]. Angiotensin II activates immune cells (T cells, macrophages and dendritic cells) and promotes cell infiltration into target organs^[39]. CD4⁺ T lymphocytes express AT1R and PPAR gamma receptors, and release TNF-α, interferon and interleukins within the vascular wall when activated^[39] (Figure 5). IL-17 produced by T cells may play a pivotal role in the genesis of hypertension caused by Angiotensin II^[39]. Hypertensive patients have significantly higher TLR 4 mRNA in monocytes compared to normal^[40]. Intensive reduction in BP to systolic BP (SBP) less than 130 mmHg *vs* SBP to only 140 mmHg lowers the TLR 4 more^[40]. A-II activates the TLR expression leading to inflammation and activation of the innate immune system. When TLR 4 is activated there is downstream macrophage activation, migration, increase metalloproteinase 9, vascular remodeling, collagen accumulation in the artery, LVH and cardiac fibrosis^[40]. The autonomic nervous system is critical in either increasing or decreasing immune dysfunction and inflammation^[41]. Efferent cholinergic anti-inflammatory pathways *via* the vagal nerve innervate the spleen, nicotine acetylcholine receptor subunits and cytokine producing immune cells to influence vasoconstriction and BP^[41]. Local CNS inflammation or ischemia may mediate vascular inflammation and hypertension^[39].

Aldosterone is associated with increased adaptive immunity and autoimmune responses with CD4⁺ T cell activation and Th 17 polarization with increased IL 17, TGF-β and TNF-α which modulate over 30 inflammatory genes^[42,43]. Increased serum aldosterone is an independent risk factor for CVD and CHD through non-hemodynamic effects as well as through increased

BP^[42,43]. Blockade of mineralocorticoid receptors in the heart, brain, blood vessels and immune cells reduces CV risk even with the persistence of hypertension^[42,43].

TREATMENT

Many of the natural compounds in food, certain nutraceutical supplements, vitamins, antioxidants or minerals function in a similar fashion to a specific class of antihypertensive drugs. Although the potency of these natural compounds may be less than the antihypertensive drug, when used in combination with other nutrients and nutraceutical supplements, the antihypertensive effect is additive or synergistic. Table 3 summarizes these natural compounds into the major antihypertensive drug classes such as diuretics, beta blockers, central alpha agonists, direct vasodilators, calcium channel blockers (CCB's), angiotensin converting enzyme inhibitors (ACEI's), angiotensin receptor blockers (ARB's) and direct renin inhibitors (DRI).

Dietary Approaches to Stop Hypertension diets

The Dietary Approaches to Stop Hypertension (DASH) I and II diets conclusively demonstrated significant reductions in BP in borderline and stage I hypertensive patients^[44,45]. In DASH I untreated hypertensive subjects with SBP < 160 mmHg and DBP 80-95 mmHg were placed on one of three diets for 4 wk, control diet, fruit and vegetable diet (F + V) and combined diet that added F + V and low fat dairy^[44]. DASH II added progressive sodium restriction in each group^[45]. The control diet consisted of sodium at 3 g/d, potassium, magnesium and calcium at 25% of the US average, macronutrients at US average of 4 servings per day, a sodium/potassium ratio of 1.7 and fiber at 9 g/d. The F + V diet increased the potassium, magnesium and calcium to 75%, macronutrients to greater than the US average, a sodium/potassium ratio of 0.7, 31 g of fiber and 8.5 servings of fruits and vegetables per day. The combined diet was similar to the F + V diet but added low fat dairy. At 2 wk the BP was decreased by 10.7/5.2 mmHg in the hypertensive patients in DASH I and 11.5/6.8 mmHg in the hypertensive patients in DASH II. These reductions persisted as long as the patients were on the diet. The DASH diet increases plasma renin activity (PRA) and serum aldosterone levels in response to the BP reductions^[46,47]. The mean increase in PRA was 37 ng/mL per day^[47]. There was an associated of response with the G46A polymorphism of beta 2 adrenergic receptor. The A allele of G46A had a greater BP reduction and blunted PRA and aldosterone. The arachidonic acid (AA) genotype had the best response and the GG genotype had no response. Adding an ARB, ACEI or DRI improved BP response to the DASH diet in the GG group due to blockade of the increase in PRA. A low sodium DASH diet decreases oxidative stress (urine F2-isoprostanes), improves vascular function (augmentation index) and lowers BP in salt sensitive subjects^[48]. In addition, plasma nitrite increased and pulse wave velocity

Table 3 Natural antihypertensive compounds categorized by antihypertensive class

Antihypertensive therapeutic class (alphabetical listing)	Foods and ingredients listed by therapeutic class	Nutrients and other supplements listed by therapeutic class
Angiotensin converting enzyme inhibitors	Egg yolk Fish (specific): bonito, dried salted fish, fish sauce sardine muscle/protein tuna garlic gelatin hawthorne berry Milk products (specific): casein sour milk whey (hydrolyzed) sake sea vegetables (kelp) sea weed (wakame) wheat germ (hydrolyzed) zein (corn protein)	Melatonin omega-3 fatty acids pomegranate pycnogenol zinc
Angiotensin receptor blockers	Celery fiber garlic MUFA	Coenzyme Q10 gamma linolenic acid N-acetyl cysteine oleic acid resveratrol potassium taurine vitamin C vitamin B6 (pyridoxine)
Beta blockers	Hawthorne berry	
Calcium channel blockers	Celery garlic hawthorn berry MUFA	Alpha lipoic acid calcium magnesium N-acetyl cysteine oleic acid omega-3 fatty acids: eicosapentaenoic acid docosahexaenoic acid taurine vitamin B6 vitamin C vitamin E
Central alpha agonists (reduce sympathetic nervous system activity)	Celery fiber garlic protein	Coenzyme Q 10 gamma linolenic acid potassium restriction of sodium taurine vitamin C vitamin B6 zinc Vitamin D
Direct renin inhibitors		
Direct vasodilators	Celery cooking oils with monounsaturated fats fiber garlic MUFA soy	Alpha linolenic acid arginine calcium flavonoids magnesium Omega-3 fatty acids potassium taurine vitamin C vitamin E
Diuretics	Celery hawthorn berry protein	Calcium coenzyme Q 10 fiber gamma linolenic acid l-carnitine magnesium potassium taurine vitamin B6 vitamin C Vitamin E: high gamma/delta tocopherols and tocotrienols.

MUFA: Monounsaturated fatty acids.

decreased at week two on the DASH diet^[49].**Sodium (Na⁺) reduction**

The average sodium intake in the US is 5000 mg/d with some areas of the country consuming 15000-20000 mg/d^[50]. However, the minimal requirement for sodium

is probably about 500 mg/d^[50]. Epidemiologic, observational and controlled clinical trials demonstrate that an increased sodium intake is associated with higher BP as well as increased risk for CVD, CVA, LVH, CHD, MI, renal insufficiency, proteinuria and over activity of the SNS^[1,50]. A reduction in sodium intake in hypertensive patients, especially the salt sensitive patients, will significantly lower BP by 4-6/2-3 mmHg that is proportional to the degree of sodium restriction and may prevent or delay hypertension in high risk patients and reduce future CV events^[51-53].

Salt sensitivity ($\geq 10\%$ increase in MAP with salt loading) occurs in about 51% of hypertensive patients and is a key factor in determining the cardiovascular, cerebrovascular, renal and BP responses to dietary salt intake^[54]. Cardiovascular events are more common in the salt sensitive patients than in salt resistant ones, independent of BP^[55]. An increased sodium intake has a direct positive correlation with BP and the risk of CVA and CHD^[56]. The risk is independent of BP for CVA with a relative risk of 1.04 to 1.25 from the lowest to the highest quartile^[56]. In addition, patients will convert to a nondipping BP pattern with increases in nocturnal BP as the sodium intake increases^[56].

Increased sodium intake has a direct adverse effect on endothelial cells^[57-61]. Sodium promotes cutaneous lymphangiogenesis, increases endothelial cell stiffness, reduces size, surface area, volume, cytoskeleton, deformability and pliability, reduces eNOS and NO production, increases asymmetric dimethyl arginine (ADMA), oxidative stress and TGF- β . All of these abnormal vascular responses are increased in the presence of aldosterone^[57-61]. These changes occur independent of BP and may be partially counteract by dietary potassium^[57-61]. The endothelial cells act as vascular salt sensors^[62]. Endothelial cells are targets for aldosterone which activate epithelial sodium channels (ENaCs) and have a negative effects on release of NO and on endothelial function. The mechanical stiffness of the cell plasma membrane and the submembranous actin network (endothelial glycocalyx) ("shell") serve as a "firewall" to protect the endothelial cells and are regulated by serum sodium, potassium and aldosterone within the physiologic range^[62]. Changes in shear-stress-dependent activity of the endothelial NO synthase located in the caveolae regulate the viscosity in this "shell"^[62]. High plasma sodium gelates the shell of the endothelial cell, whereas the shell is fluidized by high potassium. These communications between extracellular ions and intracellular enzymes occur at the plasma membrane barrier, whereas 90% of the total cell mass remains uninvolved in these changes. Blockade of the ENaC with spironolactone (100%) or amiloride (84%) minimizes or stop many of these vascular endothelial responses and increase NO^[58,63]. Nitric oxide release follows endothelial nanomechanics and not vice versa and membrane depolarization decreases vascular endothelial cell stiffness which improves flow mediated nitric-oxide dependent vasodilation^[64,65]. In the presence of vascular inflammation and increased HS-CRP, the effects of aldosterone on the

ENaC is enhanced further increasing vascular stiffness and BP^[66]. High sodium intake also abolishes the AT2R-mediated vasodilation immediately with complete abolition of endothelial vasodilation (EDV) within 30 d^[67]. Thus, it has become clear that increased dietary sodium has adverse effects on the vascular system, BP and CVD by altering the endothelial glycocalyx, which is a negatively charged biopolymer that lines the blood vessels and serves as a protective barrier against sodium overload, increased sodium permeability and sodium-induced TOD^[68]. Certain SNP's of salt inducible kinase I which alter Na⁺/K⁺ ATPase, determine sodium induced hypertension and LVH^[69].

The sodium intake per day in hypertensive patients should be between 1500 to 2000 mg. Sodium restriction improves BP reduction in those on patients that are on pharmacologic treatment and the decrease in BP is additive with restriction of refined carbohydrates^[70,71]. Reducing dietary sodium intake may reduce damage to the brain, heart, kidney and vasculature through mechanisms dependent on the small BP reduction as well as those independent of the decreased BP^[72-75].

A balance of sodium with other nutrients, especially potassium, magnesium and calcium is important, not only in reducing and controlling BP, but also in decreasing cardiovascular and cerebrovascular events^[3,72,73]. An increase in the sodium to potassium ratio is associated with significantly increased risk of CVD and all-cause mortality^[72]. The Yanomamo Indians consume and excrete only 1 meq of sodium in 24 h and consume and excrete 152 meq of potassium in 24 h^[73]. The Na⁺ to K⁺ ratio is 1/152 and is associated with elevated PRA, but BP does not increase with age. At age 50 the average BP in the Yanomamo is 100-108/64-69 mmHg^[73].

Potassium

The average U.S. dietary intake of potassium (K⁺) is 45 mmol/d with a potassium to sodium (K⁺/Na⁺) ratio of less than 1:2^[10,74]. The recommended intake of K⁺ is 4700 mg/d (120 mmol) with a K⁺/Na⁺ ratio of about 4-5 to 1^[10,74]. Numerous epidemiologic, observational and clinical trials have demonstrated a significant reduction in BP with increased dietary K⁺ intake in both normotensive and hypertensive patients^[10,74,76]. The average BP reduction with a K⁺ supplementation of 60 to 120 mmol/d is 4.4/2.5 mmHg in hypertensive patients but may be as much as 8/4.1 mmHg with 120 mmol/d (4700 mg)^[10,74,76,77]. In hypertensive patients, the linear dose-response relationship is 1.0 mmHg reduction in SBP and 0.52 mmHg reduction in diastolic BP per 0.6 g/d increase in dietary potassium intake that is independent of baseline dietary potassium ingestion^[10]. The response depends on race (black > white), sodium, magnesium and calcium intake^[10]. Those on a higher sodium intake have a greater reduction in BP with potassium^[10]. Alteration of the K⁺/Na⁺ ratio to a higher level is important for both anti-hypertensive as well as cardiovascular and cerebrovascular effects^[10,77]. High potassium intake reduces the incidence of cardiovascular (CHD, MI) and CVA independent of

the BP reduction^[10,74,76,77]. There are also reductions in CHF, LVH, diabetes mellitus and cardiac arrhythmias^[10]. If the serum potassium is less than 4.0 meq/dL, there is an increased risk of CVD mortality, ventricular tachycardia, ventricular fibrillation and CHF^[10]. Red blood cell potassium is a better indication of total body stores and CVD risk than is serum potassium^[10]. Gu *et al*^[77] found that potassium supplementation at 60 mmol of KCl per day for 12 wk significantly reduced SBP -5.0 mmHg (range -2.13 to -7.88 mmHg) ($P < 0.001$) in 150 Chinese men and women aged 35 to 64 years.

Potassium increases natriuresis, modulates baroreflex sensitivity, vasodilates, decreases the sensitivity to catecholamines and Angiotensin II, increases sodium potassium ATPase and DNA synthesis in the vascular smooth muscle cells and decreases SNS activity in cells with improved vascular function^[10]. In addition, potassium increases bradykinin and urinary kallikrein, decreases NADPH oxidase, which lowers oxidative stress and inflammation, improves insulin sensitivity, decreases ADMA, reduces intracellular sodium and lowers production of TGF- β ^[10].

Each 1000 mg increase in potassium intake per day reduces all cause mortality by approximately 20%. Potassium intake of 4.7 g/d is estimated to decrease CVA by 8% to 15% and MI by 6%-11%^[10]. Numerous SNP's such as nuclear receptor subfamily 3 group C, angiotensin II type receptor and hydroxysteroid 11 beta dehydrogenase (HSD11B1 and B2) determine an individual's response to dietary potassium intake^[78]. Each 1000 mg decrease in sodium intake per day will decrease all cause mortality by 20%^[10,73]. A recent analysis suggested a dose related response to CVA with urinary potassium excretion^[79]. There was a RRR of CVA of 23% at 1.5-1.99 g, 27% at 2.0-2.49 g, 29% at 2.5-3 g and 32% over 3 g/d of potassium urinary excretion^[79]. The recommended daily dietary intake for patients with hypertension is 4.7 to 5.0 g of potassium and less than 1500 mg of sodium^[10]. Potassium in food or from supplementation should be reduced or used with caution in those patients with renal impairment or those on medications that increase renal potassium retention such as ACEI, ARB, DRI and serum aldosterone receptor antagonists^[10].

Magnesium

A high dietary intake of magnesium of at least 500-1000 mg/d reduces BP in most of the reported epidemiologic, observational and clinical trials, but the results are less consistent than those seen with Na⁺ and K⁺^[74,80]. In most epidemiologic studies, there is an inverse relationship between dietary magnesium intake and BP^[74,80,81]. A study of 60 essential hypertensive subjects given magnesium supplements showed a significant reduction in BP over an eight week period documented by 24 h ambulatory BP, home and office blood BP^[74,80,81]. The maximum reduction in clinical trials has been 5.6/2.8 mmHg but some studies have shown no change in BP^[82]. The combination of high potassium and low sodium intake with increased magnesium intake had additive anti-hypertensive ef-

fects^[82]. Magnesium also increases the effectiveness of all anti-hypertensive drug classes^[82].

Magnesium competes with Na^+ for binding sites on vascular smooth muscle and acts as a direct vasodilator, like a CCB. Magnesium increases prostaglandin E (PGE), regulates intracellular calcium, sodium, potassium and pH, increases nitric oxide, improves endothelial function, reduces oxLDL, reduces HS-CRP, TBxA2, A-II, and nor-epinephrine. Magnesium also improves insulin resistance, glucose and MS, binds in a necessary-cooperative manner with potassium, inducing EDV and BP reduction, reduces CVD and cardiac arrhythmias, decreases carotid IMT, lowers cholesterol, lowers cytokine production, inhibits nuclear factor Kb, reduces oxidative stress and inhibits platelet aggregation to reduce thrombosis^[74,80-86].

Magnesium is an essential co-factor for the delta-6-desaturase enzyme that is the rate-limiting step for conversion of linoleic acid (LA) to gamma linolenic acid (GLA)^[74,80,81,83-85] needed for synthesis of the vasodilator and platelet inhibitor PGE₁. Altered TRPM7 channels, which are the transporter for magnesium occur in many hypertensive patients^[83].

A meta-analysis of 241378 patients with 6477 strokes showed an inverse relationship of dietary magnesium to the incidence of ischemic stroke^[84]. For each 100 mg of dietary magnesium intake, ischemic stroke was decreased by 8%. The proposed mechanism include inhibition of ischemia induced glutamate release, NMDA receptor blockade, CCB actions, mitochondrial calcium buffering, decrease in ATP depletion and vasodilation of the cerebral arteries^[84]. A meta-analysis showed reductions in BP of 3-4/2-3 mmHg in 22 trials of 1173 patients^[87].

Intracellular level of magnesium (RBC) is more indicative of total body stores and should be measured in conjunction with serum and urinary magnesium^[83]. Magnesium may be supplemented in doses of 500 to 1000 mg/d. Magnesium formulations chelated to an amino acid may improve absorption and decrease the incidence of diarrhea^[82]. Adding taurine at 1000 to 2000 mg/d will enhance the anti-hypertensive effects of magnesium^[82]. Magnesium supplements should be avoided or used with caution in patients with known renal insufficiency or in those taking medications that induce magnesium retention^[82].

Calcium

Population studies show a link between hypertension and calcium^[88], but clinical trials that administered calcium supplements to patients have shown inconsistent effects on BP^[88]. The heterogeneous responses to calcium supplementation have been explained by Resnick^[89]. This is the "ionic hypothesis"^[89] of hypertension, cardiovascular disease and associated metabolic, functional and structural disorders. Calcium supplementation is not recommended at this time as an effective means to reduce BP.

Zinc

Low serum zinc levels in observational studies correlate with hypertension as well as CHD, type II DM, hyperlipidemia, elevated lipoprotein a [Lp(a)], increased 2 h post-

prandial plasma insulin levels and insulin resistance^[90,91]. Zinc is transported into cardiac and vascular muscle and other tissues by metallothionein^[92]. Genetic deficiencies of metallothionein with intramuscular zinc deficiencies may lead to increased oxidative stress, mitochondrial dysfunction, cardiomyocyte dysfunction and apoptosis with subsequent myocardial fibrosis, abnormal cardiac remodeling, heart disease, heart failure, or hypertension^[92]. Intracellular calcium increases oxidative stress which is reduced by zinc^[92].

Bergomi *et al*^[93] evaluated Zinc (Zn^{++}) status in 60 hypertensive subjects compared to 60 normotensive control subjects. An inverse correlation of BP and serum Zn^{++} was observed. The BP was also inversely correlated to a Zn^{++} dependent enzyme-lysyl oxidase activity. Zn^{++} inhibits gene expression and transcription through NF- κ B and activated protein-1 and is an important cofactor for SOD^[90,92]. These effects plus those on insulin resistance, membrane ion exchange, RAAS and SNS effects may account for Zn^{++} antihypertensive effects^[90,92]. Zinc intake should be 50 mg/d^[1].

Protein

Observational and epidemiologic studies demonstrate a consistent association between a high protein intake and a reduction in BP and incident BP^[94,95]. The protein source is an important factor in the BP effect; animal protein being less effective than non-animal or plant protein, especially almonds^[94-97]. In the Inter-Salt Study of over 10000 subjects, those with a dietary protein intake 30% above the mean had a lower BP by 3.0/2.5 mmHg compared to those that were 30% below the mean (81 vs 44 g/d)^[94]. However, lean or wild animal protein with less saturated fat and more essential omega-3 fatty acids may reduce BP, lipids and CHD risk^[94,97]. A meta-analysis confirmed these findings and also suggested that hypertensive patients and the elderly have the greatest BP reduction with protein intake^[95]. Another meta-analysis of 40 trials with 3277 patients found reductions in BP of 1.76/1.15 mmHg compared to carbohydrate intake ($P < 0.001$)^[98]. Both vegetable and animal protein significantly and equally reduced BP at 2.27/1.26 mmHg and 2.54/0.95 mmHg respectively^[98]. Increased dietary protein intake is inversely associated with risk for stroke in women with hypertension^[99]. A randomized cross-over study in 352 adults with pre-hypertension and stage I hypertension found a significant reduction in SBP of 2.0 mmHg with soy protein and 2.3 mmHg with milk protein compared to a high glycemic index diet over each of the 8 wk treatment periods^[100]. There was a non-significant reduction in DBP. Another RDB parallel study over 4 wk of 94 subjects with prehypertension and stage I hypertension found significant reductions on office BP of 4.9/2.7 mmHg in those given a combination of 25% protein intake vs the control group given 15% protein in an isocaloric manner^[101]. The protein consisted of 20% pea, 20% soy, 30% egg and 30% milk-protein isolate^[101]. The daily recommended intake of protein from all sources is 1.0 to 1.5 g/kg body weight, varying with exercise level, age,

renal function and other factors^[1,70,71].

Fermented milk supplemented with whey protein concentrate significantly reduces BP in human studies^[102-106]. Administration of 20 g/d of hydrolyzed whey protein supplement rich in bioactive peptides significantly reduced BP over 6 wk by 8.0 ± 3.2 mmHg in SBP and 5.5 ± 2.1 mm in diastolic BP^[103]. Milk peptides which contain both caseins and whey proteins are a rich source of ACEI peptides. Val-Pro-Pro and Ile-Pro-Pro given at 5 to 60 mg/d have variable reductions in BP with an average decrease in pooled studies of about 1.28-4.8/0.59-2.2 mmHg^[71,100,104-107]. However several recent meta-analysis did not show significant reductions in BP in humans^[106,108]. Powdered fermented milk with *Lactobacillus helveticus* given at 12 g/d significantly lowered BP by 11.2/6.5 mmHg in 4 wk in one study^[104]. Milk peptides are beneficial in treating MS^[109]. A dose response study showed insignificant reductions in BP^[110]. The clinical response is attributed to fermented milk's active peptides which inhibit ACE.

Pins *et al*^[111] administered 20 g of hydrolyzed whey protein to 56 hypertensive subjects and noted a BP reduction of 11/7 mmHg compared to controls at one week that was sustained throughout the study. Whey protein is effective in improving lipids, insulin resistance, glucose, arterial stiffness and BP^[112]. These data indicate that the whey protein must be hydrolyzed in order to exhibit an antihypertensive effect, and the maximum BP response is dose dependent.

Bovine casein-derived peptides and whey protein-derived peptides exhibit ACEI activity^[102-111]. These components include B-caseins, B-Ig fractions, B2-microglobulin and serum albumin^[102-104,111]. The enzymatic hydrolysis of whey protein isolates releases ACEI peptides.

Marine collagen peptides (MCPs) from deep sea fish have anti-hypertensive activity^[113-115]. A double-blind placebo controlled trial in 100 hypertensive subjects with diabetes who received MCPs twice a day for 3 mo had significant reductions in DBP and mean arterial pressure^[113]. Bonito protein (*Sarda Orientalis*), from the tuna and mackerel family has natural ACEI inhibitory peptides and reduces BP 10.2/7 mmHg at 1.5 g/d^[114,116].

Sardine muscle protein, which contains Valyl-Tyrosine (VAL-TYR), significantly lowers BP in hypertensive subjects^[117]. Kawasaki *et al*^[117] treated 29 hypertensive subjects with 3 mg of VAL-TYR sardine muscle concentrated extract for four wk and lowered BP 9.7/5.3 mmHg ($P < 0.05$). Levels of A-I increased as serum A-II and aldosterone decreased indicating that VAL-TYR is a natural ACEI. A similar study with a vegetable drink with sardine protein hydrolysates significantly lowered BP by 8/5 mmHg in 13 wk^[118].

Soy protein lowers BP in hypertensive patients in most studies^[100,119-127]. Soy protein intake was significantly and inversely associated with both SBP and DBP in 45694 Chinese women consuming 25 g/d or more of soy protein over 3 years and the association increased with age^[119]. The SBP reduction was 1.9 to 4.9 mm lower and the DBP 0.9 to 2.2 mmHg lower^[119]. However, randomized clinical trials and meta-analysis have shown mixed

results on BP with no change in BP to reductions of 7% to 10 % for SBP and DBP^[121-125]. The recent meta-analysis of 27 trials found a significant reduction in BP of 2.21/1.44 mmHg^[120]. Some studies suggest improvement in endothelial function, improved arterial compliance, reduction in HS-CRP and inflammation, ACEI activity, reduction in sympathetic tone, diuretic action and reduction in both oxidative stress and aldosterone levels^[125-127]. Fermented soy at about 25 g/d is recommended.

In addition to ACEI effects, protein intake may also alter catecholamine responses and induce a natriuretic effect^[117,118]. Low protein intake coupled with low omega 3 fatty acid intake may contribute to hypertension in animal models^[128]. The optimal protein intake, depending on level of activity, renal function, stress and other factors, is about 1.0 to 1.5 g/kg per day^[1].

Amino acids and related compounds

L-arginine: L-arginine and endogenous methylarginines are the primary precursors for the production of NO, which has numerous beneficial cardiovascular effects, mediated through conversion of L-arginine to NO by eNOS. Patients with hypertension, hyperlipidemia, diabetes mellitus and atherosclerosis have increased levels of HSCRP and inflammation, increased microalbumin, low levels of apelin (stimulates NO in the endothelium), increased levels of arginase (breaks down arginine) and elevated serum levels of ADMA, which inactivates NO^[129-133].

Under normal physiological conditions, intracellular arginine levels far exceed the Km [Michaelis Menton constant(MMC)] of eNOS which is less than 5 μmol ^[134]. However, endogenous NO formation is dependent on extracellular arginine concentration^[134]. The intracellular concentrations of L-arginine are 0.1-3.8 mmol/L in endothelial cells while the plasma concentration of arginine is 80-120 $\mu\text{mol/L}$ which is about 20-25 times greater than the MMC^[135,136]. Despite this, cellular NO formation depends on exogenous L-arginine and this is the arginine paradox. Renal arginine regulates BP and blocks the formation of endothelin, reduces renal sodium reabsorption and is a potent antioxidant^[134]. The NO production in endothelial cells is closely coupled to cellular arginine uptake indicating that arginine transport mechanisms play a major role in the regulation of NO-dependent function. Exogenous arginine can increase renal vascular and tubular NO bioavailability and influence renal perfusion, function and BP^[132]. Molecular eNOS uncoupling may occur in the absence of tetrahydrobiopterin which stabilizes eNOS, which leads to production of ROS^[135].

Human studies in hypertensive and normotensive subjects of parenteral and oral administrations of L-arginine demonstrate an antihypertensive effect as well as improvement in coronary artery blood flow and peripheral blood flow in PAD^[129,136-140]. The BP decreased by 6.2/6.8 mmHg on 10 g/d of L-arginine when provided as a supplement or through natural foods to a group of hypertensive subjects^[136]. Arginine produces a statistically and biologically significant decrease in BP and improved met-

abolic effect in normotensive and hypertensive humans that is similar in magnitude to that seen in the DASH-I diet^[136]. Arginine given at 4 g/d also significantly lowered BP in women with gestational hypertension without proteinuria, reduced the need for anti-hypertensive therapy, decreased maternal and neonatal complications and prolonged the pregnancy^[137,138]. The combination of arginine (1200 mg/d) and N-acetyl cysteine (NAC) (600 mg bid) administered over 6 mo to hypertensive patients with type 2 diabetes, lowered SBP and DBP ($P < 0.05$), increased HDL-C, decreased LDL-C and oxLDL, reduced HSCR, ICAM, VCAM, PAI-1, fibrinogen and IMT^[139]. A study of 54 hypertensive subjects given arginine 4 g three times per day for four weeks had significant reductions in 24 h ABM^[140]. A meta-analysis of 11 trials with 383 subjects administered arginine 4-24 g/d found average reduction in BP of 5.39/2.66 mmHg ($P < 0.001$) in 4 wk^[141]. Although these doses of L-arginine appear to be safe, no long term studies in humans have been published at this time and there are concerns of a pro-oxidative effect or even an increase in mortality in patients who may have severely dysfunctional endothelium, advanced atherosclerosis, CHD, ACS or MI^[142]. In addition to the arginine-NO path, there exists a nitrate/nitrite pathway that is related to dietary nitrates from vegetables, beetroot juice and the DASH diet that are converted to nitrites by symbiotic, salivary, GI and oral bacteria^[143]. Administration of beetroot juice or extract at 500 mg/d will increase nitrites and lower BP, improve endothelial function, increase cerebral, coronary and peripheral blood flow^[143].

L-carnitine and acetyl-L-carnitine: L-carnitine is a nitrogenous constituent of muscle primarily involved in the oxidation of fatty acids in mammals. Animal studies indicate that carnitine has both systemic anti-hypertensive effects as well as anti-oxidant effects in the heart by up-regulation of eNOS and PPAR gamma, inhibition of RAAS, modulation of NF- κ B and down regulation of NOX2, NOX4, TGF- β and CTGF that reduces cardiac fibrosis^[144,145]. Endothelial function, NO and oxidative defense are improved while oxidative stress and BP are reduced^[144-147].

Human studies on the effects of L-carnitine and acetyl-L-carnitine are limited, with minimal to no change in BP^[148-153]. In patients with MS, acetyl-L-carnitine at one gram bid over 8 wk, improved dysglycemia and reduced SBP by 7-9 mmHg, but diastolic BP was significantly decreased only in those with higher glucose^[151]. Low carnitine levels are associated with a nondipping BP pattern in Type 2 DM^[153]. Carnitine has antioxidant and anti-inflammatory effects and may be useful in the treatment of essential hypertension, type II DM with hypertension, hyperlipidemia, cardiac arrhythmias, CHF and cardiac ischemic syndromes^[1,149,150,153]. Doses of 2-3 g twice per day are recommended.

Taurine: Taurine is a sulfonic beta-amino acid that is considered a conditionally-essential amino acid, which is not utilized in protein synthesis, but is found free or

in simple peptides with its highest concentration in the brain, retina and myocardium^[154]. In cardiomyocytes, it represents about 50% of the free amino acids and has a role of an osmoregulator, inotropic factor and anti-hypertensive agent^[155].

Human studies have noted that essential hypertensive subjects have reduced urinary taurine as well as other sulfur amino acids^[1,154,155]. Taurine lowers BP, SVR and HR, decreases arrhythmias, CHF symptoms and SNS activity, increases urinary sodium and water excretion, increases atrial natriuretic factor, improves insulin resistance, increases NO and improves endothelial function. Taurine also decreases A-II, PRA, aldosterone, SNS activity, plasma norepinephrine, plasma and urinary epinephrine, lowers homocysteine, improves insulin sensitivity, kinins and acetyl choline responsiveness, decreases intracellular calcium and sodium, lowers response to beta receptors and has antioxidant, anti-atherosclerotic and anti-inflammatory activities, decreases IMT and arterial stiffness and may protect from risk of CHD^[1,154-160]. A lower urinary taurine is associated with increased risk of hypertension and CVD^[160,161]. A study of 31 Japanese males with essential hypertension placed on an exercise program for 10 wk showed a 26% increase in taurine levels and a 287% increase in cysteine levels. The BP reduction of 14.8/6.6 mmHg was proportional to increases in serum taurine and reductions in plasma norepinephrine^[162]. Fujita *et al*^[155] demonstrated a reduction in BP of 9/4.1 mmHg ($P < 0.05$) in 19 hypertension subjects given 6 g of taurine for 7 d. Taurine has numerous beneficial effects on the cardiovascular system and BP^[156]. The recommended dose of taurine is 2 to 3 g/d at which no adverse effects are noted, but higher doses up to 6 g/d may be needed to reduce BP significantly^[1,70,71,154-162].

Omega-3 fats

The omega-3 fatty acids found in cold water fish, fish oils, flax, flax seed, flax oil and nuts lower BP in observational, epidemiologic and in prospective clinical trials^[163-173]. The findings are strengthened by a dose-related response in hypertension as well as a relationship to the specific concomitant diseases associated with hypertension^[163-173].

Studies indicate that DHA at 2 g/d reduces BP and heart rate^[163,173]. The average reduction in BP is 8/5 mmHg and heart rate falls about 6 beats/min usually in about 6 wk^[1,70,71,91-175]. Fish oil at 4-9 g/d or combination of DHA and EPA at 3-5 g/d will also reduce BP^[1,168-173]. However, formation of EPA and ultimately DHA from ALA is decreased in the presence of high LA (the essential omega-6 fatty acid), saturated fats, trans fatty acids, alcohol, several nutrient deficiencies (magnesium, vitamin B6) and aging, all of which inhibit the desaturase enzymes^[163]. Eating cold water fish three times per week may be as effective as high dose fish oil in reducing BP in hypertensive patients, and the protein in the fish may also have antihypertensive effects^[1,163]. In patients with chronic kidney disease 4 g of omega 3 fatty acids reduced BP measured with 24 h ABM over 8 wk by 3.3/2.9 mmHg

compared to placebo ($P < 0.0001$)^[167].

The ideal ratio of omega-6 FA to omega-3 FA is between 1:1 to 1:4 with a polyunsaturated to saturated fat ratio greater than 1.5 to 2:0^[2]. Omega 3 fatty acids increase eNOS and nitric oxide, improve endothelial function, improve insulin sensitivity, reduce calcium influx, suppress ACE activity and improve parasympathetic tone^[1,163-171]. The omega-6 FA family includes LA, GLA, dihomo-GLA and AA which do not usually lower BP significantly, but may prevent increases in BP induced by saturated fats^[176]. GLA may block stress-induced hypertension by increasing PGE1 and PGI2, reducing aldosterone levels, reducing adrenal AT1R density and affinity^[175].

The omega-3 FA have a multitude of other cardiovascular consequences which modulates BP such as increases in eNOS and nitric oxide, improvement in ED, reduction in plasma nor-epinephrine and increase in paraSNS tone, suppression of ACE activity and improvement in insulin resistance^[176]. The recommended daily dose is 3000 to 5000 mg/d of combined DHA and EPA in a ratio of 3 parts EPA to 2 parts DHA and about 50% of this dose as GLA combined with gamma/delta tocopherol at 100 mg per gram of DHA and EPA to get the omega 3 index to 8% or higher to reduce BP and provide optimal cardioprotection^[177]. DHA is more effective than EPA for reducing BP and should be given at 2 g/d if administered alone^[163,173].

Omega-9 fats

Olive oil is rich in the omega-9 monounsaturated fat (MUFA) oleic acid, which has been associated with BP and lipid reduction in Mediterranean and other diets^[178-180]. Olive oil and MUFAs have shown consistent reductions in BP in most clinical studies in humans^[178-190]. In one study, the SBP fell 8 mmHg ($P \leq 0.05$) and the DBP fell 6 mmHg ($P \leq 0.01$) in both clinic and 24 h ambulatory BP monitoring in the MUFA treated subjects compared to the PUFA treated subjects^[178]. In addition, the need for antihypertensive medications was reduced by 48% in the MUFA group *vs* 4% in the omega-6 PUFA group ($P < 0.005$). Extra virgin olive oil (EVOO) was more effective than sunflower oil in lowering SBP in a group of 31 elderly hypertensive patients in a double blind randomized crossover study^[187]. The SBP was 136 mmHg in the EVOO treated subjects *vs* 150 mmHg in the sunflower treated group ($P < 0.01$). Olive oil also reduces BP in hypertensive diabetic subjects^[188]. It is the high oleic acid content in olive oil that reduces BP^[180]. In stage I hypertensive patients, oleuropein-olive leaf (*Olea Europaea*) extract 500 mg bid for 8 wk reduced BP 11.5/4.8 mmHg which was similar to captopril 25 mg bid^[189]. *Olea Europaea* L aqueous extract administered to 12 patients with hypertension at 400 mg qid for 3 mo significantly reduced BP ($P < 0.001$)^[181]. Olive oil intake in the EPIC study of 20343 subjects was inversely associated with both systolic and diastolic BP^[182]. In the SUN study of 6863 subjects, BP was inversely associated with olive oil consumption, but only in men^[183]. In a study of 40 hypertensive

monozygotic twins, olive leaf extract demonstrated a dose response reduction in BP at doses of 500 to 1000 mg/d in 8 wk compared to placebo^[184]. The low dose groups decreased BP 3/1 mmHg and the high dose 11/4 mmHg^[184]. A double blind, randomized, crossover dietary intervention study over 4 mo using polyphenol rich olive oil 30 mg/d decreased BP in the study group by 7.91/6.65 mmHg and improved endothelial function^[185]. The ADMA levels, oxLDL and HS-CRP were reduced in the olive oil group. Plasma nitrites and nitrates increased and hyperemic area after ischemia improved in the treated group. Olive oil inhibits the AT1R receptor, exerts L-type calcium channel antagonist effects and improves wave reflections and augmentation index^[191-193].

EVOO is also contains lipid-soluble phytonutrients such as polyphenols. Approximately 5 mg of phenols are found in 10 g of EVOO^[178,186]. About 4 tablespoons of EVOO is equal to 40 g of EVOO which is the amount required to get significant reductions in BP.

Fiber

The clinical trials with various types of fiber to reduce BP have been inconsistent^[194,195]. Soluble fiber, guar gum, guava, psyllium and oat bran may reduce BP and reduce the need for antihypertensive medications in hypertensive subjects, diabetic subjects and hypertensive-diabetic subjects^[1,70,71,194,195]. The average reduction in BP is about 7.5/5.5 mmHg on 40 to 50 g/d of a mixed fiber. There is improvement in insulin sensitivity, endothelial function, reduction in SNS activity and increase in renal sodium loss^[1,70,71,194].

Vitamin C

Vitamin C is a potent water-soluble electron-donor. At physiologic levels it is an antioxidant although at supra-physiologic doses such as those achieved with intravenous vitamin C it donates electrons to different enzymes which results in pro-oxidative effects. At physiologic doses vitamin C recycles vitamin E, improves ED and produces a diuresis^[196]. Dietary intake of vitamin C and plasma ascorbate concentration in humans is inversely correlated to SBP, DBP and heart rate^[196-210].

An evaluation of published clinical trials indicate that vitamin C dosing at 250 mg twice daily will significantly lower SBP 5-7 mmHg and diastolic BP 2-4 mmHg over 8 wk^[196-210]. Vitamin C will induce a sodium water diuresis, improve arterial compliance, improve endothelial function, increase nitric oxide and PGI2, decrease adrenal steroid production, improve sympathovagal balance, increase RBC Na/K ATPase, increase SOD, improve aortic elasticity and compliance, improve flow mediated vasodilation, decrease pulse wave velocity and augmentation index, increase cyclic GMP, activate potassium channels, reduce cytosolic calcium and reduce serum aldehydes^[208]. Vitamin C prevents ED induced by an oral glucose load. Vitamin C enhances the efficacy of amlodipine, decreases the binding affinity of the AT 1 receptor for angiotensin II by disrupting the ATR1 disulfide bridges and enhances the anti-hypertensive effects of medications in the elderly

with refractory hypertension^[1,70,71,200-205]. In elderly patients with refractory hypertension already on maximum pharmacologic therapy, 600 mg of vitamin C daily lowered the BP by 20/16 mmHg^[205]. The lower the initial ascorbate serum level, the better is the BP response. A serum level of 100 $\mu\text{mol/L}$ is recommended^[1,70,71]. The SBP and 24 ABM show the most significant reductions with chronic oral administration of Vitamin C^[200-205]. Block *et al*^[206] in an elegant depletion-repletion study of vitamin C demonstrated an inverse correlation of plasma ascorbate levels, SBP and DBP. In a meta-analysis of thirteen clinical trials with 284 patients, vitamin C at 500 mg/d over 6 wk reduced SBP 3.9 mmHg and DBP 2.1 mmHg^[207]. Hypertensive subjects were found to have significantly lower plasma ascorbate levels compared to normotensive subjects (40 $\mu\text{mol/L}$ vs 57 $\mu\text{mol/L}$ respectively)^[211], and plasma ascorbate is inversely correlated with BP even in healthy, normotensive individuals^[206].

Vitamin E

Most studies have not shown reductions in BP with most forms of tocopherols or tocotrienols^[1,70,71]. Patients with T2DM and controlled hypertension (130/76 mmHg) on prescription medications with an average BP of 136/76 mmHg were administered mixed tocopherols containing 60% gamma, 25% delta and 15% alpha tocopherols^[212]. The BP actually increased by 6.8/3.6 mmHg in the study patients ($P < 0.0001$) but was less compared to the increase with alpha tocopherol of 7/5.3 mmHg ($P < 0.0001$). This may be a reflection of drug interactions with tocopherols *via* cytochrome P 450 (3A4 and 4F2) and reduction in the serum levels of the pharmacologic treatments that were simultaneously being given^[212]. Gamma tocopherol may have natriuretic effects by inhibition of the 70pS potassium channel in the thick ascending limb of the loop of Henle and lower BP^[213]. Both alpha and gamma tocopherol improve insulin sensitivity and enhance adiponectin expression *via* PPAR gamma dependent processes, which have the potential to lower BP and serum glucose^[214]. If vitamin E has an antihypertensive effect, it is probably small and may be limited to untreated hypertensive patients or those with known vascular disease or other concomitant problems such as diabetes or hyperlipidemia.

Vitamin D

Vitamin D3 may have an independent and direct role in the regulation of BP and insulin metabolism^[215-225]. Vitamin D influences BP by its effects on calcium-phosphate metabolism, RAA system, immune system, control of endocrine glands and ED^[216]. If the Vitamin D level is below 30 ng/mL the circulating PRA levels are higher which increases angiotensin II, increases BP and blunts plasma renal blood flow^[221]. The lower the level of Vitamin D, the greater the risk of hypertension, with the lowest quartile of serum Vitamin D having a 52% incidence of hypertension and the highest quartile having a 20% incidence^[221]. Vitamin D3 markedly suppresses renin transcription by a VDR-mediated mechanism *via* the JGA ap-

paratus. Its role in electrolytes, volume and BP homeostasis indicates that Vitamin D3 is important in amelioration of hypertension. Vitamin D lower ADMA, suppresses pro-inflammatory cytokines such as TNF- α , increases nitric oxide, improves endothelial function and arterial elasticity, decreases vascular smooth muscle hypertrophy, regulates electrolytes and blood volume, increases insulin sensitivity, reduces free fatty acid concentration, regulates the expression of the natriuretic peptide receptor and lowers HS-CRP^[217-219,221].

The hypotensive effect of vitamin D was inversely related to the pretreatment serum levels of 1,25(OH) $_2$ D $_3$ and additive to antihypertensive medications. Pfeifer *et al*^[225] showed that short-term supplementation with vitamin D3 and calcium is more effective in reducing SBP than calcium alone. In a group of 148 women with low 25(OH) $_2$ D $_3$ levels, the administration of 1200 mg calcium plus 800 IU of vitamin D3 reduced SBP 9.3% more ($P < 0.02$) compared to 1200 mg of calcium alone. The HR fell 5.4% ($P = 0.02$), but DBP was not changed. The range in BP reduction was 3.6/3.1 to 13.1/7.2 mmHg. The reduction in BP is related to the pretreatment level of vitamin D3, the dose of vitamin D3 and serum level of vitamin D3, but BP is reduced only in hypertensive patients. Although vitamin D deficiency is associated with hypertension in observational studies, randomized clinical trials and their meta-analysis have yielded inconclusive results^[223]. In addition, vitamin D receptor gene polymorphisms may effect the risk of hypertension in men^[224]. A 25 hydroxyvitamin D level of 60 ng/mL is recommended.

Vitamin B6 (pyridoxine)

Low serum vitamin B6 (pyridoxine) levels are associated with hypertension in humans^[226]. One human study by Aybak *et al*^[227] proved that high dose vitamin B6 at 5 mg/kg per day for 4 wk significantly lowered BP by 14/10 mmHg. Pyridoxine (vitamin B6) is a cofactor in neurotransmitter and hormone synthesis in the central nervous system (norepinephrine, epinephrine, serotonin, GABA and kynurenine), increases cysteine synthesis to neutralize aldehydes, enhances the production of glutathione, blocks calcium channels, improves insulin resistance, decreases central sympathetic tone and reduces end organ responsiveness to glucocorticoids and mineralocorticoids^[1,70,71,228,229]. Vitamin B6 is reduced with chronic diuretic therapy and heme pyrollactams. Vitamin B6 thus has similar action to central alpha agonists, diuretics and CCB's. The recommended dose is 200 mg/d orally.

Flavonoids

Over 4000 naturally occurring flavonoids have been identified in such diverse substances as fruits, vegetables, red wine, tea, soy and licorice^[230]. Flavonoids (flavonols, flavones and isoflavones) are potent free radical scavengers that inhibit lipid peroxidation, prevent atherosclerosis, promote vascular relaxation and have antihypertensive properties^[230]. In addition, they reduce stroke and provide cardioprotective effects that reduce CHD morbidity and

mortality^[231].

Resveratrol is a potent antioxidant and antihypertensive found in the skin of red grapes and in red wine. Resveratrol administration to humans reduces augmentation index, improves arterial compliance and lowers central arterial pressure when administered as 250 mL of either regular or dealcoholized red wine^[232]. There was a significant reduction in the aortic augmentation index of 6.1% with the dealcoholized red wine and 10.5% with regular red wine. The central arterial pressure was significantly reduced by dealcoholized red wine at 7.4 mmHg and 5.4 mmHg by regular red wine. Resveratrol increases flow mediated vasodilation in a dose related manner, improves ED, prevents uncoupling of eNOS, increases adiponectin, lowers HS-CRP and blocks the effects of angiotensin II^[233-236]. The recommended dose is 250 mg/d of *trans* resveratrol^[234].

Lycopene

Lycopene is a fat-soluble phytonutrient in the carotenoid family. Dietary sources include tomatoes, guava, pink grapefruit, watermelon, apricots and papaya in high concentrations^[237-241]. Lycopene produces a significant reduction in BP, serum lipids and oxidative stress markers^[237-241]. Paran *et al*^[241] evaluated 30 subjects with Grade I hypertension, age 40-65, taking no antihypertensive or anti-lipid medications treated with a tomato lycopene extract (10 mg lycopene) for eight weeks. The SBP was reduced from 144 to 135 mmHg (9 mmHg reduction, $P < 0.01$) and DBP fell from 91 to 84 mmHg (7 mmHg reduction, $P < 0.01$). Another study of 35 subjects with Grade I hypertension showed similar results on SBP, but not DBP^[237]. Englehard gave a tomato extract to 31 hypertensive subjects over 12 wk demonstrating a significant BP reduction of 10/4 mmHg^[238]. Patients on various anti-hypertensive agents including ACEI, CCB and diuretics had a significant BP reduction of 5.4/3 mmHg over 6 wk when administered a standardized tomato extract^[239]. Other studies have not shown changes in BP with lycopene^[240]. Lycopene and tomato extract improve ED and reduce plasma total oxidative stress^[242]. The recommended daily intake of lycopene is 10-20 mg in food or supplement form.

Pycnogenol

Pycnogenol, a bark extract from the French maritime pine, at doses of 200 mg/d resulted in a significant reduction in SBP from 139.9 mmHg to 132.7 mmHg ($P < 0.05$) in eleven patients with mild hypertension over eight weeks in a double-blind randomized placebo crossover trial. Diastolic BP fell from 93.8 mmHg to 92.0 mmHg. Pycnogenol acts as a natural ACEI, protects cell membranes from oxidative stress, increases NO and improves endothelial function, reduces serum thromboxane concentrations, decreases myelo-peroxidase activity, improves renal cortical blood flow, reduces urinary albumin excretion and decreases HS-CRP^[243-247]. Other studies have shown reductions in BP and a decreased need for ACEI

and CCB, reductions in endothelin-1, HgA1C, fasting glucose, LDL-C and myeloperoxidase^[244,245,247].

Garlic

Clinical trials utilizing the correct dose, type of garlic and well absorbed long acting preparations have shown consistent reductions in BP in hypertensive patients with an average reduction in BP of 8.4/7.3 mmHg^[248,249]. Not all garlic preparations are processed similarly and are not comparable in antihypertensive potency^[1]. In addition, cultivated garlic (*allium sativum*), wild uncultivated garlic or bear garlic (*allium ursinum*) as well as the effects of aged, fresh and long acting garlic preparations differ^[1,70,71,248,249]. Garlic is also effective in reducing BP in patients with uncontrolled hypertension already on anti-hypertensive medication^[249,250]. A garlic homogenate-based supplement was administered to 34 prehypertensive and stage I hypertensive patients at 300 mg/d over 12 wk with a reduction in BP of 6.6-7.5/4.6-5.2 mmHg^[249]. Aged garlic at doses of 240 to 960 mg/d given to 79 hypertensive subjects over 12 wk significantly lowered SBP 11.8 ± 5.4 mmHg in the high dose garlic group^[249]. A time released garlic may reduce BP better than the shorter acting garlic^[249]. A Cochrane Database review indicated a net reduction in BP of 10-12/6-9 mmHg in all clinical trials with garlic^[249]. In a double-blind parallel randomized placebo-controlled trial of 50 patients, 900 mg of aged garlic extract with 2.4 mg of S-allylcysteine was administered daily for 12 wk and reduced SBP 10.2 mmHg ($P = 0.03$) more than the control group^[250].

Approximately 10000 mcg of allicin (one of the active ingredients in garlic) per day, the amount contained in four cloves of garlic (5 g) is required to achieve a significant BP lowering effect^[1,70,71,249,250]. Garlic has ACEI activity, calcium channel blocking activity, reduces catecholamine sensitivity, improves arterial compliance, increases bradykinin and nitric oxide and contains adenosine, magnesium, flavonoids, sulfur, allicin, phosphorous and ajoenes that reduce BP^[1,70,71].

Seaweed

Wakame seaweed (*Undaria pinnatifida*) is the most popular, edible seaweed in Japan^[251]. In humans, 3.3 g of dried Wakame for four wk significantly reduced both the SBP 14 ± 3 mmHg and the DBP 5 ± 2 mmHg ($P < 0.01$)^[252]. In a study of 62 middle-aged, male subjects with mild hypertension given a potassium-loaded, ion-exchanging, sodium-adsorbing, potassium-releasing seaweed preparation, significant BP reductions occurred at four weeks on 12 and 24 g/d of the seaweed preparation ($P < 0.01$)^[253]. The MAP fell 11.2 mmHg ($P < 0.001$) in the sodium-sensitive subjects and 5.7 mmHg ($P < 0.05$) in the sodium-insensitive subjects, which correlated with PRA.

Seaweed and sea vegetables contain most all of the seawater's 77I minerals and rare earth elements, fiber and alginate in a colloidal form^[251-253]. The primary effect of Wakame appears to be through its ACEI activity from at least four parent tetrapeptides and possibly their dipeptide

and tripeptide metabolites, especially those containing the amino acid sequence Val-Tyr, Ile-Tyr, Phe-Tyr and Ile-Try in some combination^[251,254,255]. Its long-term use in Japan has demonstrated its safety. Other varieties of seaweed may reduce BP by reducing intestinal sodium absorption and increasing intestinal potassium absorption^[253].

Sesame

Sesame has been shown to reduce BP in a several small randomized, placebo controlled human studies over 30-60 d^[256-264]. Sesame lowers BP alone^[257-261] or in combination with nifedipine^[256,260] diuretics and beta blockers^[257,261]. In a group of 13 mild hypertensive subjects, 60 mg of sesamin for 4 wk lowered SBP 3.5 mmHg ($P < 0.044$) and DBP 1.9 mmHg ($P < 0.045$)^[258]. Black sesame meal at 2.52 g/d over 4 wk in 15 subjects reduced SBP by 8.3 mmHg ($P < 0.05$) but there was a non-significant reduction in DBP of 4.2 mmHg^[259]. Sesame oil at 35 g/d significantly lowered central BP within 1 h and also maintained BP reduction chronically in 30 hypertensive subjects, reduced heart rate, reduced arterial stiffness, decreased augmentation index and pulse wave velocity, decreased HSCRP, improved NO, decreased endothelin-I and improved antioxidant capacity^[264]. In addition sesame lowers serum glucose, HgbA1C and LDL-C, increases HDL, reduces oxidative stress markers and increases glutathione, SOD, GPx, CAT, vitamins C, E and A^[256,257,258-261]. The active ingredients are natural ACEI's such as sesamin, sesamol, sesaminol glucosides, furofuran lignans which also suppressors of NF- κ B^[262,263]. All of these effects lower inflammation and oxidative stress, improve oxidative defense and reduce BP^[262,263].

Beverages: Tea, coffee, and cocoa

Green tea, black tea and extracts of active components in both have demonstrated reduction in BP in humans^[265-271]. In a double blind placebo controlled trial of 379 hypertensive subjects given green tea extract 370 mg/d for 3 mo, BP was reduced significantly at 4/4 mmHg with simultaneous decrease in HS CRP, TNF- α , glucose and insulin levels^[268].

Dark chocolate (100 g) and cocoa with a high content of polyphenols (30 mg or more) have been shown to significantly reduce BP in humans^[272-283]. A meta-analysis of 173 hypertensive subjects given cocoa for a mean duration of 2 wk had a significant reduction in BP 4.7/2.8 mmHg ($P = 0.002$ for SBP and 0.006 for DBP)^[276]. Fifteen subjects given 100 g of dark chocolate with 500 mg of poly-phenols for 15 d had a 6.4 mmHg reduction in SBP ($P < 0.05$) with a non significant change in DBP^[273]. Cocoa at 30 mg of poly-phenols reduced BP in pre-hypertensive and stage I hypertensive patients by 2.9/1.9 mmHg at 18 wk ($P < 0.001$)^[274]. Two more recent meta-analysis of 13 trials and 10 trials with 297 patients found a significant reduction in BP of 3.2/2.0 mmHg and 4.5/3.2 mmHg respectively^[276,279]. The BP reduction is the greatest in those with the highest baseline BP and those with at least 50%-70% cocoa at doses of 6 to 100 g/d^[280,282]. Cocoa may also improve insulin resistance and

endothelial function^[276,279,281].

Polyphenols, chlorogenic acids (CGAs), the ferulic acid metabolite of CGAs and di-hydro-caffeic acids decrease BP in a dose dependent manner, increase eNOS and improve endothelial function in humans^[284-286]. CGAs in green coffee bean extract at doses of 140 mg/d significantly reduced SBP and DBP in 28 subjects in a placebo-controlled randomized clinical trial. A study of 122 male subjects demonstrated a dose response in SBP and DBP with doses of CGA from 46 mg/d to 185 mg/d. The group that received the 185 mg dose had a significant reduction in BP of 5.6/3.9 mmHg ($P < 0.01$) over 28 d. Hydroxyhydroquinone is another component of coffee beans which reduces the efficacy of CGAs in a dose-dependent manner which partially explains the conflicting results of coffee ingestion on BP^[284,286]. Furthermore, there is genetic variation in the enzyme responsible for the metabolism of caffeine modifies the association between coffee intake, amount of coffee ingested and the risk of hypertension, heart rate, MI, arterial stiffness, arterial wave reflections and urinary catecholamine levels^[287]. Fifty-nine percent of the population has the I F/ I A allele of the CYP1A2 genotype which confers slow metabolism of caffeine. Heavy coffee drinkers who are slow metabolizers had a 3.00 HR for developing hypertension. In contrast, fast metabolizers with the I A/ I A allele have a 0.36 HR for incident hypertension^[288].

Additional compounds

Melatonin demonstrates significant anti-hypertensive effects in humans in a numerous double-blind randomized placebo controlled clinical trials at 3-5 mg/d^[289-299]. The average reduction in BP is 6/3 mmHg. Melatonin stimulates GABA receptors in the CNS and vascular melatonin receptors, inhibits plasma A II levels, improves endothelial function, increases NO, vasodilates, improves nocturnal dipping, lowers cortisol and is additive with ARBs. Beta blockers reduce melatonin secretion^[300].

Hesperidin significantly lowered DBP 3-4 mmHg ($P < 0.02$) and improved microvascular endothelial reactivity in 24 obese hypertensive male subjects in a randomized, controlled crossover study over 4 wk for each of three treatment groups consuming 500 mL of orange juice, hesperidin or placebo^[301].

Pomegranate juice is rich in tannins and has numerous other properties that improve vascular health and reduces the SBP by 5%-12%^[302,303]. A study of 51 healthy subjects given 330 mg/d of pomegranate juice had reduction in BP of 3.14/2.33 mmHg ($P < 0.001$)^[303]. Pomegranate juice also suppresses the postprandial increase in SBP following a high-fat meal^[303]. Pomegranate juice reduces serum ACE activity by 36%, and has anti-atherogenic, antioxidant and anti-inflammatory effects^[302,303]. Pomegranate juice at 50 mL/d reduced carotid IMT by 30% over one year, increased PON 83%, decreased oxLDL by 59%-90%, decreased antibodies to oxLDL by 19%, increased total antioxidant status by 130 %, reduced TGF- β , increased catalase, SOD and GPx, increased eNOS and NO and improved endothelial function^[304,305].

Pomegranate juice works like an ACEI.

Grape seed extract (GSE) was administered to subjects in nine randomized trials, meta-analysis of 390 subjects and demonstrated a significant reduction in SBP of 1.54 mmHg ($P < 0.02$)^[304,305]. Significant reduction in BP of 11/8 mmHg ($P < 0.05$) were seen in another dose response study with 150 to 300 mg/d of GSE over 4 wk^[306]. GSE has high phenolic content which activates the PI3K/Akt signaling pathway that phosphorylates eNOS and increases NO^[306,307].

Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 has consistent and significant antihypertensive effects in patients with essential hypertension^[1,308-317]. The literature is summarized below: (1) Compared to normotensive patients, essential hypertensive patients have a higher incidence (6 fold) of coenzyme Q10 deficiency documented by serum levels^[1]; (2) Doses of 120 to 225 mg/d of coenzyme Q10, depending on the delivery method or the concomitant ingestion with a fatty meal, are necessary to achieve a therapeutic level of 3 ug/mL^[1,313,314]. This dose is usually 3-5 mg/kg per day of coenzyme Q10. Oral dosing levels may become lower with nanoparticle and emulsion delivery systems intended to facilitate absorption^[315]. Adverse effects have not been characterized in the literature; (3) Patients with the lowest coenzyme Q10 serum levels may have the best antihypertensive response to supplementation; (4) The average reduction in BP is about 15/10 mmHg and heart rate falls 5 beats/min based on reported studies and meta-analysis; (5) The antihypertensive effect takes time to reach its peak level at 4 wk. Then the BP remains stable during long term treatment. The antihypertensive effect is gone within two weeks after discontinuation of coenzyme Q10. The reduction in BP and SVR are correlated with the pretreatment and post treatment serum levels of coenzyme Q10. About 50% of patients respond to oral coenzyme Q10 supplementation for BP^[309]; (6) Approximately 50% of patients on antihypertensive drugs may be able to stop between one and three agents. Both total dose and frequency of administration may be reduced. (7) Patients administered coenzyme Q10 with enalapril improved the 24 h ABM better than with enalapril monotherapy and also normalized endothelial function^[310]; and (8) Coenzyme Q10 is a lipid phase antioxidant and free radical scavenger, increases eNOS and NO, reduces inflammation and NF- κ B and improves endothelial function and vascular elasticity^[1,311,312].

Other favorable effects on cardiovascular risk factors include improvement in the serum lipid profile and carbohydrate metabolism with reduced glucose and improved insulin sensitivity, reduced oxidative stress, reduced heart rate, improved myocardial LV function and oxygen delivery and decreased catecholamine levels^[1,311,312].

Alpha lipoic acid

Alpha lipoic acid (ALA) is known as thioctic acid in Europe where it is a prescription medication. It is a sulfur-containing compound with antioxidant activity both in

water and lipid phases^[1,70,71]. Its use is well-established in the treatment of certain forms of liver disease and in the delay of onset of peripheral neuropathy in patients with diabetes. Recent research has evaluated its potential role in the treatment of hypertension, especially as part of the MS^[318-321]. In a double-blind cross over study of 36 patients over 8 wk with CHD and hypertension, 200 mg of lipoic acid with 500 mg of acetyl-L-carnitine significantly reduced BP 7/3 mmHg and increased brachial artery diameter^[320]. The QUALITY study of 40 patients with DM and stage I hypertension showed significant improvements in BP, urinary albumin excretion, FMD and insulin sensitivity over 8 wk with a combination of Quinapril (40 mg/d) and lipoic acid (600 mg/d) that was greater than either alone^[320]. Lipoic acid increases levels of glutathione, cysteine, vitamin C and vitamin E, inhibits NF- κ B, reduces endothelin-1, tissue factor and VCAM-1, increases cAMP, downregulates CD4 immune expression on mononuclear cells, reduces oxidative stress, inflammation, reduces atherosclerosis in animal models, decreases serum aldehydes and closes calcium channels which improves vasodilation, increases NO and nitrosothiols, improves endothelial function and lowers BP^[1,318-321]. Lipoic acid normalizes membrane calcium channels by providing sulfhydryl groups, decreasing cytosolic free calcium and lowers SVR. In addition, lipoic acid improves insulin sensitivity which lowers glucose and advanced glycosylation end products which improves BP control and lowers serum triglycerides. Morcos *et al*^[321], showed stabilization of urinary albumin excretion in DM subjects given 600 mg of ALA compared to placebo for 18 mo ($P < 0.05$).

The recommended dose is 100 to 200 mg/d of R-lipoic acid with biotin 2-4 mg/d to prevent biotin depletion with long term use of lipoic acid. R-lipoic acid is preferred to the L isomer because of its preferred use by the mitochondria^[1,32,71].

NAC: NAC and L arginine (ARG) in combination reduce endothelial activation and BP in hypertensive patients with type 2 DM^[141]. Over 6 mo 24 subjects given placebo or NAC with ARG, significantly reduced both systolic and diastolic BP ($P = 0.05$)^[141]. In addition, ox LDL, HSCRP, ICAM, VCAM, fibrinogen and PAI-1 were decreased while HDL, NO and endothelial postischemic vasodilation increased^[141]. NAC increases NO *via* IL-1b and increases iNOS mRNA, increases glutathione by increasing cysteine levels, reduces the affinity for the AT1 receptor by disrupting disulfide groups, blocks the L type calcium channel, lowers homocysteine, and improves IMT^[141,322-324]. The recommended dose is 500 to 1000 mg bid.

Hawthorne extract has been used for centuries for the treatment of hypertension, CHF and other cardiovascular diseases^[325-329]. A recent four-period crossover design, dose response study in 21 subjects with prehypertension or mild hypertension over 3^{1/2} d, did not show changes in FMD or BP on standardized extract with 50 mg of oligomeric procyanidin per 250 mg extract with 1000 mg, 1500 or 2500 mg of the extract^[325]. Hawthorne showed non inferiority of ACEI and diuretics in the treatment of

Table 4 Integrative approach to the treatment of hypertension

Intervention category	Therapeutic intervention	Daily intake
Diet characteristics	DASH I , DASH II-Na ⁺ or premier diet	Diet type
	Sodium restriction	1500 mg
	Potassium	5000 mg
	Potassium/sodium ratio	> 3:1
	Magnesium	1000 mg
	Zinc	50 mg
Macronutrients	Protein total intake from non-animal sources, organic lean or wild animal protein, or coldwater fish	30% of total calories, which 1.5-1.8 g/kg body weight
	Whey protein	30 g
	Soy protein (fermented sources are preferred)	30 g
	Sardine muscle concentrate extract	3 g
	Milk peptides	30-60 mg
	Fat	30% of total calories
	Omega-3 fatty acids	2-3 g
	Omega-6 fatty acids	1 g
	Omega-9 fatty acids	2-4 tablespoons of olive or nut oil or 10-20 olives
	Saturated fatty acids from wild game, bison, or other lean meat	< 10% total calories
	Polyunsaturated to saturated fat ratio	< 2.0
	Omega 3 to omega 6 ratio	1.1-1.2
	Synthetic trans fatty acids	None (completely remove from diet)
	Nuts in variety	Ad libitum
	Carbohydrates as primarily complex carbohydrates and fiber	40% of total calories
	Oatmeal or	60 g
	Oatbran or	40 g
	Beta-glucan or	3 g
	Psyllium	7 g
Specific foods	Garlic as fresh cloves or aged kyolic garlic	4 fresh cloves (4 g) or 600 mg aged garlic taken twice daily
	Sea vegetables, specifically dried wakame	3.0-3.5 g
	Lycopene as tomato products, guava, watermelon, apricots, pink grapefruit, papaya or supplements	10-20 mg
	Dark chocolate	100 g
	Pomegranate juice or seeds	8 ounces or one cup
	Sesame	60 mg sesamin or 2.5 g sesame meal
Exercise	Aerobic	20 min daily at 4200 kJ/wk
	Resistance	40 min/d
Weight reduction	Body mass index < 25	Lose 1-2 pounds per week and increasing the proportion of lean muscle
	Waist circumference:	
	< 35 inches for women	
	< 40 inches for men	
	Total body fat:	
	< 22% for women	
	< 16% for men	
Other lifestyle recommendations	Alcohol restriction:	< 20 g/d
	Among the choice of alcohol red wine is preferred due to its vasoactive phytonutrients	Wine < 10 ounces
		Beer < 24 ounces
		Liquor < 2 ounces
	Caffeine restriction or elimination depending on CYP 450 type	< 100 mg/d
	Tobacco and smoking	Stop
Medical considerations	Medications which may increase blood pressure.	Minimize use when possible, such as by using disease-specific nutritional interventions
Supplemental foods and nutrients	Alpha lipoic acid with biotin	100-200 mg twice daily
	Amino acids:	
	Arginine	5 g twice daily
	Carnitine	1 to 2 g twice daily
	Taurine	1 to 3 g twice daily
	Chlorogenic acids	150-200 mg
	Coenzyme Q10	100mg once to twice daily
	Grape seed extract	300 mg
	Hawthorne extract	500 mg twice a day
	Melatonin	2.5 mg
	N-acetyl cysteine	500 mg twice a day
	Olive leaf extract (oleuropein)	500 mg twice a day
	Pycnogenol	200 mg
	Quercetin	500 mg twice a day

Resveratrol (<i>trans</i>)	250 mg
Vitamin B6	100 mg once to twice daily
Vitamin C	250-500 mg twice daily
Vitamin D3	Dose to raise 25-hydroxyvitamin D serum level to 60 ng/mL
Vitamin E as mixed tocopherols	400 IU

102 patients with NYHC II CHF over 8 wk^[327]. Patients with hypertension and type 2 DM on medications for BP and DM were randomized to 1200 mg of hawthorne extract for 16 wk showed significant reductions in DBP of 2.6 mmHg ($P = 0.035$)^[328]. Thirty six mildly hypertensive patients were administered 500 mg of hawthorne extract for 10 wk and showed a non significant trend in DBP reduction ($P = 0.081$) compared to placebo^[329]. Hawthorne acts like an ACEI, BB, CCB and diuretic. More studies are needed to determine the efficacy, long term effects and dose of hawthorne for the treatment of hypertension.

Quercetin is an antioxidant flavonol found in apples, berries and onions that reduces BP in hypertensive individuals^[330,331] but the hypotensive effects do not appear to be mediated by changes in HSCR, TNF- α , ACE activity, ET-1, NO, vascular reactivity or FMD^[330]. Quercetin is metabolized by CYP 3A4. Quercetin was administered to 12 hypertensive men at an oral dose of 1095 mg with reduction in mean BP by 5 mmHg, SBP by 7 mmHg and DBP by 3 mmHg^[330]. The maximal plasma level at 10 h was $2.3 \pm 1.8 \mu\text{mol/L}$, with return to baseline levels at 17 h. Forty one pre-hypertensive and stage I hypertensive subjects were enrolled in a randomized, double-blind, placebo-controlled, crossover study with 730 mg of quercetin per day *vs* placebo^[331]. In the stage I hypertensive patients, the BP was reduced by 7/5 mmHg ($P < 0.05$) but there were no changes in oxidative stress markers^[331]. Quercetin administered to 93 overweight or obese subjects at 150 mg/d (plasma levels of 269 nmol/L) over 6 wk lowered SBP 2.9 mmHg in the hypertensive group and up to 3.7 mmHg in SBP in the patients 25-50 years of age^[332]. The recommended dose of quercetin is 500 mg bid.

CLINICAL CONSIDERATIONS

Combining food and nutrients with medications

Several of the strategic combinations of nutraceutical supplements together or with anti-hypertensive drugs, have been shown to lower BP more than the medication alone: (1) Sesame with beta blockers, diuretics and nifedipine; (2) Pycnogenol with ACEI and CCB; (3) Lycopene with ACEI, CCB and diuretics; (4) ALA with ACEI or acetyl-L Carnitine; (5) Vitamin C with CCB's; (6) NAC with arginine; (7) Garlic with ACEI, diuretics and beta blockers; (8) Coenzyme Q10 with ACEI and CCB; (9) Taurine with magnesium; (10) Potassium with all anti-hypertensive agents; and (11) Magnesium with all anti-hypertensive agents.

Many anti-hypertensive drugs may cause nutrient depletions that can actually interfere with their anti-hypertensive action or cause other metabolic adverse effects

manifest through the lab or with clinical symptoms^[333]. Diuretics decrease potassium, magnesium, phosphorous, sodium, chloride, folate, vitamin B6, zinc, iodine and coenzyme Q10; increase homocysteine, calcium and creatinine; and elevate serum glucose by inducing insulin resistance. Beta blockers reduce coenzyme Q10. ACEI and ARB's reduce zinc.

Vascular biology such as endothelial and VSMD plays a primary role in the initiation and perpetuation of hypertension, CVD and TOD. Nutrient-gene interactions and epigenetics are a predominant factor in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Food and nutrients can prevent, control and treat hypertension through numerous vascular biology mechanisms. Oxidative stress, inflammation and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. There is a role for the selected use of single and component nutraceutical supplements vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies as a complement to optimal nutritional, dietary intake from food and other lifestyle modifications^[333]. A clinical approach which incorporates diet, foods, nutrients, exercise, weight reduction, smoking cessation, alcohol and caffeine restriction, and other lifestyle strategies can be systematically and successfully incorporated into clinical practice (Table 4).

CONCLUSION

Vascular biology, endothelial and vascular smooth muscle and cardiac dysfunction play a primary role in the initiation and perpetuation of hypertension, cardiovascular disease and TOD. Nutrient-gene interactions and epigenetics are predominant factors in promoting beneficial or detrimental effects in cardiovascular health and hypertension. Macronutrients and micronutrients can prevent, control and treat hypertension through numerous mechanisms related to vascular biology.

Oxidative stress, inflammation and autoimmune dysfunction initiate and propagate hypertension and cardiovascular disease. There is a role for the selected use of single and component nutraceutical supplements, vitamins, antioxidants and minerals in the treatment of hypertension based on scientifically controlled studies which complement optimal nutrition, coupled with other lifestyle modifications.

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Therapeutic interventions for heart failure with preserved ejection fraction: A summary of current evidence

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(HFPEF) is common and represents a major challenge in cardiovascular medicine. Various pharmacological interventions available for heart failure with reduced ejection fraction have not been supported by clinical studies for HFPEF. This article presents a brief overview of the currently recommended therapeutic strategies for HFPEF.

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Abstract

Heart failure with preserved ejection fraction (HFPEF) is common and represents a major challenge in cardiovascular medicine. Most of the current treatment of HFPEF is based on morbidity benefits and symptom reduction. Various pharmacological interventions available for heart failure with reduced ejection fraction have not been supported by clinical studies for HFPEF. Addressing the specific aetiology and aggressive risk factor modification remain the mainstay in the treatment of HFPEF. We present a brief overview of the currently recommended therapeutic options with available evidence.

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Key words: Heart failure; Diastolic dysfunction; Heart failure with preserved ejection fraction; Heart failure with normal ejection fraction

Core tip: Heart failure with preserved ejection fraction

INTRODUCTION

Prevalence of diastolic heart failure (HF) has been rising steadily in the recent past. It is now well established that at least half of patients presenting with symptoms and signs of HF have preserved left ventricular (LV) ejection fraction, *i.e.*, heart failure with preserved ejection fraction (HFPEF), and that this portion of the HF population consists predominantly of women, older age group, and people with hypertension and other cardiovascular risk factors^[1-3]. The prevalence of HFPEF varies from 1.1%-5.5%, depending on the age and other variables, *e.g.*, diagnostic criteria and methods, and rises to 3.1%-5.5% when studies are confined to a older population aged 65 years or above^[6-9]. Chronic hypertension is the most common cause in addition to age, with suggestion of up to 60% of patients with HFPEF being hypertensive^[10,11]. Obesity and Diabetes also contribute independently to the development of diastolic dysfunction^[12-15]. Other conditions associated with diastolic dysfunction are Coronary artery disease and hypertrophic or restrictive cardiomyopathies.

It is observed that the morbidity and mortality associated with HFPEF is much higher than the normal population^[16]. Several studies have reported an annual mortality rate ranging from 5% to 8% in this population^[17-19], much higher than the age-matched controls^[20-22]. Given the accumulated data of various studies, it appears that all-cause mortality of HF patients in the community is similar whether their contractility is preserved or not.

Most of the current treatment of HFPEF is based on morbidity benefits and symptom reduction. Various pharmacological interventions available for heart failure with reduced ejection fraction (HFREF) have not been supported by clinical studies for HFPEF. Addressing the specific aetiology and aggressive risk factor modification remain the mainstay in the treatment of HFPEF. Current guidelines recommend the management should involve treatment of hypertension, control of heart rate, venous pressure reduction, and prevention of myocardial ischemia^[23-25]. Here we present a brief overview of the currently recommended therapeutic options with available evidence.

TREATING THE HYPERTENSION

Treatment of hypertension remains one of the most important factors in the management of diastolic dysfunction^[23,25]. Effective management of increased blood pressure can reduce left atrial and LV end diastolic pressures, and enhance the LV filling by improving relaxation. It can further benefit by reduction of LV hypertrophy (LVH) and hence reducing the risk of development or progression of HF. Studies of hypertensive subjects indicate that diastolic dysfunction improves with LVH regression^[26]. Angiotensin converting enzyme inhibitors (ACEi) inhibitors or aldosterone antagonists such as spironolactone can have protective effect against the exaggerated fibrous tissue response^[27,28]. Thus theoretically, there may be benefits to inhibit renin-angiotensin-aldosterone system (RAAS) beyond blood pressure reduction.

In the Systolic Hypertension in the Elderly Program study^[29], a good control of isolated systolic hypertension with chlorthalidone and atenolol in a population of 4736 patients aged 60 years and older during an average of 4.5 years of follow-up led to significant reduction in the risk of HF {55 *vs* 105 in placebo group; RR = 0.51; 95%CI: 0.37-0.71, *P* < 0.001; number needed to treat to prevent 1 event [number needed to treat (NNT)], 48} and LV mass index, by 13%. In particular, among patients with prior MI, an 80% risk reduction was observed.

The Valsartan In Diastolic Dysfunction^[30] studied the effects of blood pressure reduction on the myocardial relaxation on Doppler tissue imaging after a 38 wk of exposure to different anti hypertensive agents, including renin-angiotensin system inhibitor Valsartan in one group matched with placebo in the other. The difference in blood pressure reduction between the two groups was not significant ($12.8 \pm 17.2/7.1 \pm 9.9$ mmHg reduction in the valsartan group *vs* $9.7 \pm 17.0/5.5 \pm 10.2$ mmHg in the placebo group). Diastolic relaxation velocity was in-

creased by 0.60 ± 1.4 cm/s from baseline in the valsartan group (*P* < 0.0001) and 0.44 ± 1.4 cm/s from baseline in the placebo group (*P* < 0.0001) by week 38. However, there was no significant difference in the change in diastolic relaxation velocity between the two groups (*P* = 0.29). This suggested that lowering blood pressure improves diastolic function irrespective of the type of antihypertensive agent used.

Effects of blood pressure reduction on LVH have also been studied. Beta-blockers and diuretics are well established interventions for prevention of cardiovascular morbidity and death in patients with hypertension. In the Losartan Intervention For Endpoint reduction in hypertension study^[31], regression of LVH after a year of anti-hypertensive therapy was associated with improvement of various LV diastolic filling parameters on echocardiography. In this trial, Dahlöf *et al*^[31] demonstrated superiority of an angiotensin receptor blocker (ARB), losartan, to β -blockade in reducing the composite primary endpoint (cardiovascular death, myocardial infarction or stroke; *P* = 0.021) and in regression of LVH (*P* < 0.0001), suggesting that besides blood pressure reduction, blockade of the AT1 receptor by losartan offers additional benefits for cardiovascular morbidity and mortality as compared to β -blockade, for a similar reduction in blood pressure, and was better tolerated.

The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Preserved (CHARM-Preserved) trial^[32] comparing the effects of candesartan *vs* placebo in HFPEF (EF > 40%) in 3023 patients (1514 in candesartan and 1509 in placebo group) reported a moderate impact of candesartan in preventing admissions for HF (230 *vs* 279, *P* = 0.017) over a period of 36.6 mo. There was however no difference in mortality between the two groups (170 *vs* 170 cardiovascular deaths). Similar results were observed in Perindopril In Elderly People With Chronic Heart Failure (PEP-CHF) trial^[33] in which a total of 850 patients aged ≥ 70 with HFPEF were randomized to perindopril 4 mg or placebo. The mean follow up period was 26.2 mo. In the first year of treatment, the hospitalizations for HF were less frequent in the perindopril group (*P* = 0.033), and significant improvement in the New York Heart Association (NYHA) class and functional capacity on 6-min walk test was observed in patients receiving perindopril (*P* < 0.030), however the mortality rate in both groups was similar. This study had insufficient power for its primary endpoint, which may be attributable to the non significant results of perindopril effects on long-term (> 1 year) morbidity and mortality of these patients. Differential Effects of Antihypertensive Treatment on LV Diastolic Function^[34] suggested that patients receiving treatment with an amlodipine-based regimen had better diastolic function than patients treated with the atenolol-based regimen, independent of blood pressure reduction and other factors that are known to affect diastolic function.

It has been suggested that aggressive blood pressure lowering with a combination of an ARB, valsartan; a calcium channel blocker (CCB), amlodipine; and potential

additional therapy with diuretics or β -blockers was associated with improved annular relaxation velocity (e') on tissue doppler imaging, a measure of diastolic function, in patients with hypertension and diastolic dysfunction^[35]. In this study, the patients who achieved the greatest blood pressure reduction had the best improvement in diastolic function, which supports that lower blood pressure targets may be an effective means to improve this measure of myocardial target-organ damage in hypertension.

CONTROLLING THE HEART RATE

Tachycardia is poorly tolerated in the presence of diastolic dysfunction and the guidelines recommend beta-blockers or CCB for decreasing heart rate^[23]. These drugs may also be helpful in stabilising rhythm and preventing atrial arrhythmias [*e.g.*, atrial fibrillation (AF)], which can cause substantial increase in diastolic and atrial filling pressures, leading to abrupt hemodynamic deterioration due to loss of the atrial contribution to diastolic filling. AF is common in HFPEF patients with a prevalence of up to 41%^[36] and a recent meta-analysis^[37] of 16 studies for the prognostic significance of AF in HF involving 53969 patients suggested that the presence of AF is associated with an adverse prognosis in HF irrespective of LV systolic function.

The diastole accounts for nearly 70% of the cardiac cycle at a heart rate of 60 bpm, slightly over 50% at 120 bpm, and only 40% at 180 bpm. The LV filling time is therefore considerably shortened with increased heart rate because the relaxation between beats is incomplete. In addition, in people with HFPEF tachycardia results in delayed relaxation and increased diastolic pressure. Things get further complicated during exercise. In patients with HFPEF, the heart is unable to take advantage of the Frank-Sterling mechanism during exercise. A stiff ventricle, despite elevated filling pressure, does not increase in volume. As a consequence filling pressure increases but cardiac output does not.

Therefore, decreasing heart rate would result in reduced pressure in the early period of the diastole by improving relaxation. Similarly increasing the ventricular filling time would improve cardiac output, and reduce symptoms during exercise.

The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors With Heart Failure (SENIORS) demonstrated that nebivolol reduces the composite risk of all-cause mortality and cardiovascular hospital admission in elderly patients with chronic HF and, importantly, that ejection fraction does not influence the clinical effects of nebivolol^[38]. This trial randomized 112 patients in 29 European centres, of whom 104 were evaluable for the study; 43 with EF \leq 35% and 61 with an EF $>$ 35%. LV end-systolic volume (ESV), EF, mitral valve E/A ratio, and E-wave deceleration time were assessed at baseline and after 12 mo. In the group with EF \leq 35%, nebivolol reduced ESV and improved EF; no changes were observed in the E/A ratio or E-wave deceleration time. In EF $>$ 35% group, no significant changes

in either systolic or diastolic parameters were observed. This absence of detectable changes with standard echocardiography in patients with predominant diastolic HF questions the mechanism of benefit on morbidity/mortality in this population. In the separate analysis of patients with an EF cut off greater than 40%, there was no noted statistical interaction, suggesting that nebivolol was of comparable benefit in reduced EF and preserved EF patients.

VENOUS PRESSURE REDUCTION

Diuretics remain the mainstay of symptomatic treatment for venous congestion similar to the management of systolic dysfunction. However, in patients with HFPEF optimising the volume status may be complicated by a narrow therapeutic margin given that in this group of patients the pressure/volume curve differs from the physiological curve and even a small decrease in filling pressure can result in a marked reduction of LV diastolic volume, which may lead to a significant reduction of cardiac output, risk of hypotension and renal impairment^[39,40]. The doses of diuretics in this group of patients are therefore much lower than those in patients with systolic dysfunction. Diuretics do not directly affect the myocardium, while nitrates improve the ability of the left ventricle to increase its volume by releasing nitric oxide (NO).

Spironolactone combines diuretic action with beneficial effects on the structure of the left ventricle. The results of Treatment of Preserved Cardiac Function Heart failure with an Aldosterone Antagonist^[41] was however a negative study, failing to show benefit for the clinical composite primary end point despite significantly fewer heart-failure hospitalisations, a part of the primary end point, over the average follow-up of 3.3 years. Aldosterone Receptor Blockade in Diastolic Heart Failure study^[42] suggested that long-term aldosterone receptor blockade with spironolactone improved diastolic function but did not affect clinical symptoms or exercise capacity. Therefore, further investigation into the clinical significance of these echocardiographic findings will be required in larger studies.

PREVENTION OF MYOCARDIAL ISCHEMIA

Myocardial ischemia is one of the most important mechanisms underlying HFPEF. Improved myocardial oxygen balance leads to better LV relaxation, reduced LVEDP, reduced risk of cardiac arrhythmias and stabilises the heart rate. It is therefore vital to use drugs that reduce oxygen consumption by the myocardium (beta-blockers, CCB, nitrates) and revascularization to improve oxygen supply to the myocardium. Flash pulmonary oedema frequently reoccurs in association with marked systolic hypertension, even after coronary revascularisation, suggesting that control of hypertension is important and that coronary revascularisation may not be adequate to

prevent reoccurrence of flash pulmonary oedema^[43].

SPECIFIC THERAPEUTIC AGENTS

Given the limited evidence regarding directed therapy for HFPEF, treatment of factors known to exacerbate diastolic dysfunction plays a vital role. All patients with diastolic dysfunction should get adequately treated for associated conditions, *i.e.*, diabetes, obesity, primary myocardial disease, or pericardial disease in addition to above mentioned hypertension, myocardial ischemia.

ACE inhibitors

The theoretical benefits of ACE inhibitors specifically in HFPEF rest on the basis that angiotensin II contributes to LV myocardial hypertrophy and fibrosis, impairs LV relaxation, and increases the stiffness of the left ventricle^[44]. All of these factors, potentially improved by ACE inhibitors, will therefore improve diastolic function. Clinical studies evaluating ACE inhibitors in HFPEF have shown contradicting results. Secondary endpoints of reduced hospitalisation and improved exercise tolerance has been suggested by few^[33,45] while other studies demonstrated no benefit except in patients with previous myocardial infarction^[46].

A small study assessed the effect of enalapril on 21 elderly patients with HFPEF (LVEF > 50%) and history of myocardial infarction^[45]. These patients had received furosemide for 2 wk or greater before the initiation of the study, and were on a constant dose of furosemide, were randomized to receive enalapril, titrated up to 20 mg daily as tolerated, and followed for 3 mo. There was a significant difference from baseline to study termination in the study outcomes in the treatment group: NYHA class improved from 3 to 2.4 ($P = 0.005$) and exercise time with the modified Bruce protocol increased from 224 to 270 s, versus no significant difference in the placebo group. Another small prospective study in France enrolled 358 subjects who were admitted for a first episode of HF but had ejection fractions $\geq 50\%$. Patients were separated into 2 groups based on whether or not they were prescribed an ACEi at discharge; lisinopril (32.3%), ramipril (25.6%), perindopril (23.8%), or enalapril (5.5%). The authors attempted to adjust for selection bias by developing a propensity score and comparing matched controls. Patients who had been prescribed ACEIs had a 10% reduction in 5-year mortality (NNT = 10). The largest and most well-designed study (PEP-CHF)^[33] demonstrated no significant difference in the primary endpoint but showed significant reduction in the secondary endpoint of hospitalization for HF.

ARB

Although well understood association of RAAS with many of the underlying processes behind HFPEF, various studies involving ARB use in HFPEF did not demonstrate significant benefits, except CHARM-Preserved, which relates reduced hospitalization with candesartan^[32].

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction trial compared irbesartan with placebo I 4128 patients with HFPEF^[47]. It did not improve the outcomes of patients.

β -blockers

The mechanism behind β -blockers' potential in improving diastolic function in patients with HFPEF is believed to be associated with the drugs' negative chronotropic and inotropic properties in stabilising the heart rate and helping the ventricle to relax^[44]. SENIORS study was the largest trial evaluating the effect of nebivolol on the composite of all-cause mortality or hospitalization for a cardiovascular cause^[48], which reported that nebivolol, a beta-blocker with vasodilation properties, is an effective and well-tolerated treatment for HF in the elderly. The subgroup with ejection fraction > 35% was analysed in a pre-specified analysis. The interaction test showed that ejection fraction did not modify the effect of nebivolol in terms of the primary outcome (all-cause mortality or cardiovascular hospitalization) (HR = 0.86; 95%CI: 0.74-0.99, $P = 0.039$ in the main analysis), implying that the effect of nebivolol is similar in patients with HF and an ejection fraction $\leq 35\%$ and > 35%. However, when the ejection fraction threshold of 40% was used instead of 35% (which was not a pre-specified subgroup), there was no significant difference between those treated with nebivolol and those given placebo (HR = 0.83; 95%CI: 0.62-1.11, $P = 0.203$).

Another study, conducted in elderly patients (mean age 81 years), enrolled patients 62 years and older with NYHA class II or III HF, prior Q-wave MI, and EF $\geq 40\%$ who had also been on ACE inhibitors and diuretics for 2 mo^[49]. This trial analysed the effect of propranolol on all-cause mortality and the composite of all-cause mortality and nonfatal MI after a follow-up period of 32 mo. All patients were on ACE inhibitors and diuretics during the study and digoxin was administered only in cases of atrial fibrillation. There was a significant difference between the groups in all-cause mortality (56% *vs* 76%; $P = 0.007$) and all-cause mortality plus nonfatal myocardial infarction (59% *vs* 82%; $P = 0.002$) favouring the patients treated with propranolol compared with those patients who were only on conventional therapy and no propranolol. The reduction in total mortality began 1 year after treatment initiation and the beneficial effects lasted until the end of the study. However, the percentage of deaths due to cardiac causes in each group did not differ significantly. Overall, studies that assessed the role of β -blockers in HFPEF have all found β -blockers to positively impact study outcomes (mortality in post myocardial infarction patients specifically and morbidity in others).

Digoxin

The use of digoxin has beneficial effect on hospitalization in HFPEF^[50]. This effect however has not been shown in HFPEF^[51]. Furthermore, digoxin has not shown any

impact on mortality in either HFREF or HFPEF.

OVERALL EFFECTS OF COMBINED PHARMACOTHERAPY ON EXERCISE TOLERANCE, CARDIAC FUNCTION, AND MORTALITY IN HFPEF

A recent meta-analysis was sought to determine whether pharmacologic interventions changed exercise capacity, diastolic function, and mortality in HFPEF^[52]. Data from 53878 patients enrolled in 30 published reports were collated including 18 randomized controlled trials ($n = 11253$) and 12 observational studies ($n = 42625$). A combined pharmacotherapy for HFPEF demonstrated a quantifiable improvement in exercise tolerance but failed to show a mortality benefit.

ROLE OF EXERCISE TRAINING

Exercise training is now widely used as an adjunct therapy for the stable HF patient. It is recommended by the American College of Cardiology and the American Heart Association at a Class 1 level^[24]. Many physical activity benefits for HF patients have been documented, such as improvements in physical capacity (an increase of 10%-30% of the maximum physical capacity)^[53,54], improvements in quality of life^[55], endothelial dysfunction^[56], circulating catecholamine levels^[57], morbidity and hospital admissions^[58]. However most of the studies have focused on patients with HFREF. Since the patients with HFPEF also experience exercise intolerance, dyspnoea, early fatigue, and similar mortality risk and re-hospitalization rates, a case can be made for exercise to be part of the management of people with HFPEF. In a recent study, 3 years of exercise-based lifestyle intervention was not effective in reducing progression of subclinical diastolic dysfunction in patients with type 2 diabetes mellitus^[59]. Other studies have suggested an improvement in exercise tolerance, quality of life and depression scale with low-to-moderate intensity exercise^[60-62].

Effects of exercise training on LV diastolic function in patients with systolic dysfunction have included a significant reduction in LV diastolic wall stress at low work rates resulting in a 30% increase in peak oxygen consumption after 2 mo^[63]. Belardinelli *et al.*^[64] evaluated patients with dilated cardiomyopathy and a Doppler mitral inflow profile suggestive of concomitant abnormal diastolic LV function. Only people with delayed relaxation improved their functional capacity after training. In these patients, the diastolic filling pattern normalised after training. Those with a restrictive filling pattern, however, were found to have a worse prognosis and did not improve functional capacity or diastolic filling pattern after training.

The standard recommendations for exercise training in general include aerobic activity performed at least 30 min, 5 or more days/week. Exercise intensity in HF train-

ing has varied between studies, and some study protocols have used interval or variable intensity training. In most clinical settings, an intensity range of 70%-80% of peak HR determined from a symptom-limited exercise test is used. Although aerobic exercise remains the mainstay of clinical training programs, resistance training has also shown benefits, including improved muscle strength, endurance, and blood flow associated with a lower VO₂ at submaximal workloads^[65-67]. While beta blockers have numerous benefits in patients with HF, they blunt heart rate responses to exercise. It has therefore been suggested that heart rates should not be used to determine exercise capacity in these patients^[68,69]. Exercise tolerance for CHF patients may be affected by the dose changes of some medications used for CHF, and exercise prescription may need to be modified accordingly. Generally self perceived exercise workload is more practical way of determining exercise intensity than parameters like maximum heart rate^[70].

EMERGING THERAPIES

Alagebrium chloride

A thiazolium derivative, Alagebrium chloride (ALT-711) is a novel compound that breaks advanced glycation end products (AGE) crosslinks and may improve ventricular distensibility and arterial compliance. A recent prospective, open-label trial of alagebrium in elderly patients found that in clinically stable HFPEF, the 16-wk treatment with alagebrium caused regression of LVH, improved Doppler indices of diastolic function, and enhanced quality of life without altering blood pressure, arterial stiffness, or exercise tolerance^[71]. A more recent however did not support these findings^[72]. Prevention of the formation of new AGEs with exercise and breakdown of already formed AGEs with ALT may represent a therapeutic strategy for age-related ventricular and vascular stiffness^[73].

Statins

Statins have a variety of potential benefits in addition to lipid reduction that may more directly impact diastolic function. Statins may exert beneficial effects on LVH and fibrosis, and thus may directly impact HFPEF^[74]. It appears to be associated with improved survival in HFPEF^[74,75]. A study involving 270 patients with HFPEF and a follow up of 5 years demonstrated improved survival compared to patients without statin therapy (HR = 0.65; 95%CI: 0.45-0.95, $P = 0.029$)^[75]. The survival benefit was maintained after adjusting for differences in baseline characteristics, comorbidities, and other medications.

Growth differentiation factor 11

A protein belonging to the TGF- β family, growth differentiation factor 11 (GDF-11) can reverse age-related cardiac hypertrophy in mice^[76]; a finding with implications for the experimental treatment of HFPEF^[77]. Although functional benefits as measured by means of echocar-

diography were not detected after GDF-11 treatment, the results suggest that the reversal of age-related cardiac hypertrophy by pharmacologic means is potentially feasible^[76].

Gene therapy

Calcium mishandling is implicated in heart disease. Efforts are ongoing in a number of gene therapy approaches to address the calcium mishandling issue, *e.g.*, by normalising the function of calcium handling proteins such as sarcoplasmic reticulum calcium ATPase, or to introduce calcium buffers to facilitate relaxation of the heart^[78].

Parvalbumin is a calcium binding protein found in fast-twitch skeletal muscle and not normally expressed in the heart. Gene transfer of parvalbumin into normal and diseased cardiac myocytes increases relaxation rate but also markedly decreases contraction amplitude^[78]. Szatkowski *et al*^[79] have shown that parvalbumin gene transfer to the heart *in vivo* produces levels of parvalbumin characteristic of fast skeletal muscles, causes a physiologically relevant acceleration of heart relaxation performance in normal hearts, and enhances relaxation performance in an animal model of slowed cardiac muscle relaxation. They suggested that parvalbumin may offer the unique potential to correct defective relaxation in energetically compromised failing hearts because the relaxation-enhancement effect of parvalbumin arises from an ATP-independent mechanism.

NO donors

In patients with dysfunctional endothelium, the constrictor effects of catecholamines can act unopposed, which may contribute to impaired dilator responses of epicardial and resistance vessel and thereby to myocardial ischemia, which slows ventricular relaxation and increases myocardial wall stiffness. Studies have suggested that diastolic function of the heart appears to benefit from exogenous NO whereas its endogenous production does not play a major role in myocardial relaxation^[80]. Similarly, NO donors have been shown to exert a relaxant effect on the myocardium which is associated with a decrease in LV end-diastolic pressure^[80].

Ranolazine

Ranolazine is a new anti-ischemic and antianginal agent that inhibits the late sodium current, reducing the Na-dependent Ca-overload, which improves diastolic tone and oxygen handling during myocardial ischemia^[81]. In addition, ranolazine seems to exert beneficial effects on diastolic function. Most of the experimental studies performing acute exposure to ranolazine in HF report on positive effects on diastolic performance^[81]. A recent proof-of-concept study however revealed that ranolazine improved measures of hemodynamics but there was no improvement in myocardial relaxation parameters^[82].

Angiotensin receptor neprilysin inhibitor

LCZ696, a first-in-class angiotensin receptor neprilysin

inhibitor, has been assessed in patients with HFPEF in PARAMOUNT trial^[83], a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with NYHA)class II-III HF, LV ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. In comparison with Valsartan, LCZ696 reduced NT-proBNP to a greater extent at 12. Whether these effects would translate into improved outcomes needs to be tested prospectively.

Phosphodiesterase-5 and endothelin inhibition

Despite initial encouraging results for a commonly used erectile dysfunction drug “sildenafil” to treat patients with HFPEF, the large multicentre trial “RELAX Study” failed to show any significant improvement in exercise capacity or clinical status when compared with placebo after 24 wk^[84].

Preliminary findings have suggested that cardiac endothelin-1 overexpression in a status of NO deficiency may have a role in oxidative stress, myocytes contractility, and energy metabolism^[85].

Ivabradine

Animal studies have suggested that long-term heart rate reduction induced by ivabradine may improve diastolic LV function probably involving attenuated hypoxia, reduced remodelling, and/or preserved NO bioavailability^[86]. This however is yet to be translated in human beings.

CONCLUSION

HFPEF is common and represents a major challenge in cardiovascular medicine. In contrast to advances in therapeutic options for systolic HF, there is no definitive evidence that ACE inhibitors, ARBs, beta-blockers, or aldosterone antagonists may improve outcomes in these patients. Addressing the specific aetiology and aggressive risk factor modification currently remains the mainstay in the treatment of HFPEF.

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Infiltrative cardiac lymphoma with tricuspid valve involvement in a young man

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large B-cell lymphoma involving the heart, in particular affecting the tricuspid valve. The clinical features in this case are clearly illustrated. The peculiarity of this case report is that besides the involvement of the right ventricle and atrium, the tricuspid valve was also infiltrated. Secondary valvular metastasis is unusual and the patient remained in remission after a course of chemotherapy.

Ngow HA, Wan Mohd Nowalid WK. Infiltrative cardiac lymphoma with tricuspid valve involvement in a young man. *World J Cardiol* 2014; 6(2): 77-80 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i2/77.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i2.77>

Abstract

Cardiac metastases are among the topics with limited systematic reviews. Theoretically, the heart can be infiltrated by any malignancy with the ability to spread to distant structures. Thus far, no specific tumors are known to have a predilection for the heart, but some do metastasize more often than others, for example, melanoma and primary mediastinal tumors. We report a case of cardiac metastasis from a diffuse large B cell lymphoma in a young man. The peculiarity of this case is that besides the involvement of right ventricle and atrium, the tricuspid valve was also infiltrated. Valvular metastasis is rarely reported in the medical literature.

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Key words: Cardiac metastases; Cardiac lymphoma; Non-Hodgkin's lymphoma; Tricuspid valve

Core tip: This manuscript describes a case of diffuse

INTRODUCTION

Primary cardiac tumors are extremely uncommon, with a reported prevalence of 0.001% to 0.28%^[1]. On the other hand, the incidence of secondary cardiac tumors is not as low as expected, ranging from 2% to 18.3%^[2]. There is growing awareness of the pathological and clinical effects of cardiac metastasis. Although metastatic heart tumors occur comparatively more frequently than primary tumors of the heart, they rarely gain clinical attention. Antemortem diagnosis of cardiac metastasis is seldom made because more than 90% are clinically silent^[1]. Besides, the signs of cardiac involvement may be overlooked when the tumors are advanced with widespread involvement of other organs. The clinical manifestations may be due to the valvular involvement or diminished cardiac function, which can be similar to a primary cardiac tumor, although intramural growth of secondary cardiac tumors is unusual. In addition, cardiac rhythm disturbances, conduction defects, syncope, distant embolism and pericardial effusion can occur. Not uncommonly, cardiac infiltration contributes to the mechanism of death in the affected person. The ability to metastasize to the heart depends

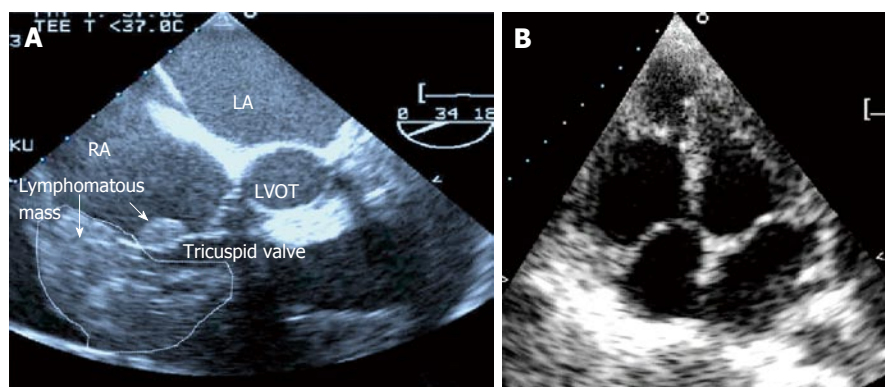


Figure 1 Transesophageal and transthoracic echocardiography before and after chemotherapy. A: Transesophageal echocardiography showed the appearance of the lymphomatous infiltration (dotted line) and a neoplastic infiltration on the tricuspid valve (short arrow). A moderate pericardial effusion is seen; B: This transthoracic echocardiography performed after 6 cycles of rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone regime showed the resolution of the tumor mass and the disappearance of the tricuspid valve tumor infiltration; RA: Right atrium; LA: Left atrium; LVOT: Left ventricular outflow tract.

on several factors, including the biological characteristics and histological subtype of the primary neoplasm, as well as the functional status of the cardiovascular system^[2,3]. Myocardial contractility may have a dual effect of both hindering and promoting the formation of cardiac metastasis; good contraction hinders the spreading of intramural tumor metastasis by facilitating lymph and blood drainage and therefore displacing any cardiac tumor-produced emboli, but on the other hand it helps neoplastic cells diffuse along the epicardial surface. Poor myocardial contractility would therefore create an opposite mechanism^[2].

CASE REPORT

A 46-year-old man was admitted with symptomatic decompensated heart failure. He complained of progressive bilateral pitting edema with dyspnea on exertion and reduced effort tolerance of 3 wk duration. However, he denied orthopnea and paroxysmal nocturnal dyspnea. He had anorexia and weight loss for the past 3 mo. He had a 5 year history of hypertension which was well-controlled with oral antihypertensives. He had multiple admissions for angina but the coronary angiogram showed no stenosis. His previous echocardiography examination was normal. He was not a smoker. There was no family history of hematogenous malignancy or exposure to radiation at a young age.

He was thin with obvious muscle wasting. His conjunctiva was pink and there was no jaundice. The jugular venous pressure was elevated and he had gross leg edema. There was multiple small shotty cervical lymphadenopathy as well as several others in the axillary and inguinal region. The apex beat was displaced but the heart sounds were normal. There was no sign of cardiac tamponade. The chest examination was insignificant. There was no hepatosplenomegaly and ascites.

The hemoglobin level was 125 g/L. The total white cell count was $8.7 \times 10^9/\text{L}$ and the platelet count was $360 \times 10^9/\text{L}$. The liver function test was normal with serum albumin of 47.1 g/L and serum globulin of 35.7 g/L. Serum transaminases were normal. The renal profile was impaired with calculated GFR of 27.5 mL/min per 1.73 m². Serum lactate dehydrogenase was 268 U/L. Other hematology parameters were within normal range.

The transthoracic echocardiogram showed global

pericardial effusion measuring 1.2-1.8 cm. The left ventricular function was 63% with mild tricuspid incompetence. An incidental finding of a right atrium and right ventricular mass was also made. An infiltrating tumor was also seen on the annulus of the anterior tricuspid valve and endocardium. The right ventricle was dilated with poor function. The right ventricle and atrium was not collapsing in systole to suggest cardiac tamponade. A repeat transesophageal echocardiography confirmed the diagnosis (Figure 1A).

Biopsy of the left axillary lymph node was performed and the histopathological examination showed diffuse malignant, large lymphoid cells consisting of centroblasts, immunoblasts and large centrocyte-like cells with occasional multinucleated cells. The large lymphoid cells were positive for CD20, weakly positive for Bcl-2 and negative for T-cell markers CD3 and CD5, and CD10. The diagnosis was diffuse large B-cell Non-Hodgkin's lymphoma (Figure 2). Computed tomography of the neck, thorax and abdomen showed multiple supra and infra-diaphragmatic enlarged lymph nodes which were suggestive of lymphoma.

The patient underwent 7 cycles of monthly chemotherapy consisting of rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone (R-CHOP). He acquired clinical remission after the chemotherapy and has remained well for the past 4 years. Clinically, there was resolution of the multiple lymphadenopathies and a repeat transthoracic and transesophageal echocardiography showed complete resolution of the tumor bulk with disappearance of the tumor infiltration on the tricuspid valve leaflet (Figure 1B). A fluorodeoxyglucose positron emission tomography (CT/FDG-PET) scan done 6 mo after the completion of chemotherapy showed no evidence of active lymphoma. The patient has remained in good health 4 years after the diagnosis and currently still under our follow up.

DISCUSSION

Cardiac metastases refer to distant spread of tumor to any structures of the cardiovascular system, including the pericardium, epicardium, myocardium, endocardium, great vessels and coronary arteries, as well as tumors affecting the heart cavities or producing intramural neoplastic thrombi. Cardiac metastases are commoner than a

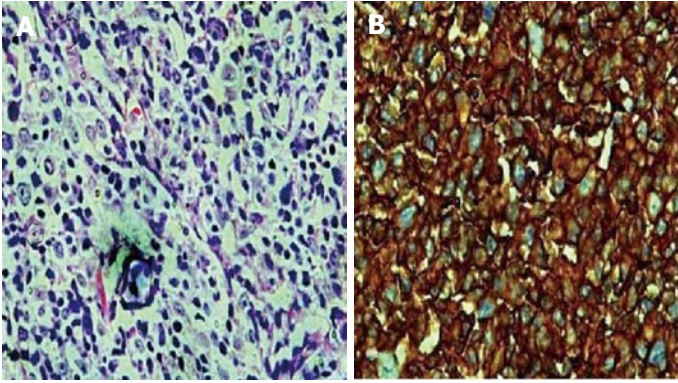


Figure 2 Histopathological staining of the left axillary lymph node.

A: The H E slide showing diffuse malignant large lymphoid cells consisting of centroblasts, immunoblasts and large centrocyte-like cells with occasional multinucleated cells (HE stain, $\times 40$); B: The tumor cells are positive for CD20 (Immunohistochemistry staining, $\times 10$).

primary tumor of the heart. The incidence from autopsy study varies between 2% and 18.3%^[1]. Common primary tumors are bronchus and breast cancers, although lymphomas, leukemia and malignant melanoma may sometimes give rise to cardiac metastasis^[4]. In a recent study from Italy by Bussani *et al.*^[2], the tumors that commonly metastasize to the heart are pleural mesothelioma (48.4%), melanoma (27.8%), lung adenocarcinoma (21%), undifferentiated carcinoma (19.5%), lung squamous cell carcinoma (18.2%), breast carcinoma (15.5%), ovarian carcinoma (10.3%), lymphoproliferative neoplasm (9.4%), bronchoalveolar carcinomas (9.8%), gastric carcinoma (8%), renal carcinomas (7.3%) and pancreatic carcinoma (6.4%)^[2]. The prevalence was somewhat different from an earlier study^[4].

Tumors can spread to the heart *via* four mechanisms, including direct tumor extension, hematogenous spread, retrograde lymphatic system dissemination and intracavitary diffusion *via* either the inferior vena cava or pulmonary vein. The different mechanisms result in specific involvement of the structure in the heart. In our patient, we postulated that the initial metastases involved the myocardium *via* one of the mechanisms above and later spread to the pericardium, resulting in moderate pericardial effusion.

Cardiac involvement in lymphoma is rare but in a recent autopsy study of malignant lymphoma, cardiac metastasis was found in 16% of the cases^[3]. Neoplastic infiltration by lymphoma typically tends to replace the myocardial tissue. Large areas of the heart are replaced by homogenous grayish white tissue with the typical “fish-meat” appearance. Despite the massive involvement of the myocardial contractile tissue, cardiac symptoms may be absent or non-specific. In the few existing cases in the medical literature, the heart seems to be more often involved in non-Hodgkin’s lymphoma, whereas the pericardium is more often metastasized by Hodgkin’s lymphoma^[5].

Clinical presentations of cardiac metastasis by lymphoma are extremely variable. They are determined by the location, size, growth rate, degree of invasiveness and friability of the neoplasm. The tumor can block the blood flow or valvular structures, leading to cardiac and valvular dysfunction. The involvement of the tricuspid valve in our patient did not give rise to severe tricuspid regurgitation and the right ventricle metastasis rather contributed

to the right heart failure. Invasion of the electrical pathways can cause arrhythmias and pericardial seeding may lead to malignant pericardial effusion or tamponade. The tumor may also cause distant embolization. In addition, sudden death may occur as a result of myocardial rupture, ventricular arrhythmias or acute myocardial infarction. Constitutional symptoms include fever, weight loss, palpitations, dyspnea and poor appetite. Lymphomatous infiltration of the heart may remain clinically silent and is often not detected until death occurs^[6].

Lymphomatous cardiac metastases are usually small and multiple, although a single large tumor mass is also observed. Focal or diffuse tumor infiltrations of the pericardium, myocardium or endocardium have been observed in lymphoma as well. In contrary to leukemic infiltration, lymphoma depositions are usually grossly discernible. The right side of the heart has been found to be more frequently involved than the left heart. This was apparent in our patient where the tumor mass was located in the right atrium and at the atrioventricular junction. Heart valves are unusual targets for tumor metastases and thus tricuspid valve involvement, as seen in our patient, is uncommon. Thus far, there is only one reported case of valvular involvement due to “neoplastic” thrombotic endocarditis by Bussani *et al.*^[7]. In our patient, the tricuspid valve involvement is most likely due to direct tumor metastasis as it completely resolved with chemotherapy, without the need for anticoagulation. Although one may argue that the valvular lesion could be due to vegetation and thrombus, they are often associated with other complications such as atrial fibrillation, ventricular aneurysm, cardiomyopathy or infective endocarditis. In the absence of these complications in our patient, the possibility of thrombosis and vegetation is less likely.

A multimodality imaging may be used to diagnose a cardiac metastasis. A plain chest radiograph lacks sensitivity and specificity as an initial diagnostic tool. Transthoracic echocardiography may be the first non-invasive screening tool but the restricted acoustic window remains a significant limitation, making transesophageal echocardiography a more sensitive technique. Computed tomography adequately demonstrates morphology, location and extent of a cardiac neoplasm with a larger view, while magnetic resonance signal intensity with contrast enhancement results in superior images identifying anatomy, blood flow, cardiac function and tissue characteriza-

tion of the mass. CT/ FDG-PET scan has recently been reported to be useful in monitoring the disease response to chemotherapy^[8,9].

Treatment options are usually aggressive chemotherapy and/or radiotherapy but the results are usually dismal. This may be due to late diagnosis or the aggressiveness of the tumor. Thus far, there is no evidence that surgical resection improves survival and furthermore it is often difficult to resect such tumors. The commonest type is B-cell lymphoma which usually responds well to chemotherapy. Chemotherapy regimens such as R-CHOP have been shown to be effective and prolong survival in the few reported cases^[10]. Without therapy, the median survival of patients is often less than 6 mo, while patients treated with chemotherapy or radiation have median survival of about 1 year. Our patient underwent 7 cycles of chemotherapy with the R-CHOP regime. The patient remained in clinical remission when he was last seen in the clinic recently.

In conclusion, cardiac involvement in lymphomatous infiltration is rare but early diagnosis is crucial in improving the prognosis. The institution of effective chemotherapy may cure the disease, avert invasive debulking surgery and maintain long term clinical remission.

COMMENTS

Case characteristics

A 46-year-old man was admitted with symptomatic decompensated heart failure.

Differential diagnosis

The peculiarity of this case is that besides the involvement of right ventricle and atrium, the tricuspid valve was also infiltrated.

Imaging diagnosis

The transthoracic echocardiogram showed global pericardial effusion measuring 1.2-1.8 cm.

Treatment

The patient underwent 7 cycles of monthly chemotherapy consisting of rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone (R-CHOP).

Related reports

Chemotherapy regimens such as R-CHOP have been shown to be effective and prolong survival in the few reported cases.

Experiences and lessons

The institution of effective chemotherapy may cure the disease, avert invasive

debulking surgery and maintain long term clinical remission.

Peer review

The manuscript describes a case of diffuse large B-cell lymphoma involving the heart, in particular affecting the tricuspid valve. Clinical features were clearly illustrated.

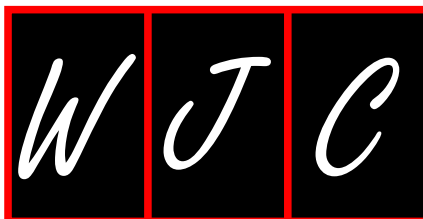
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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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