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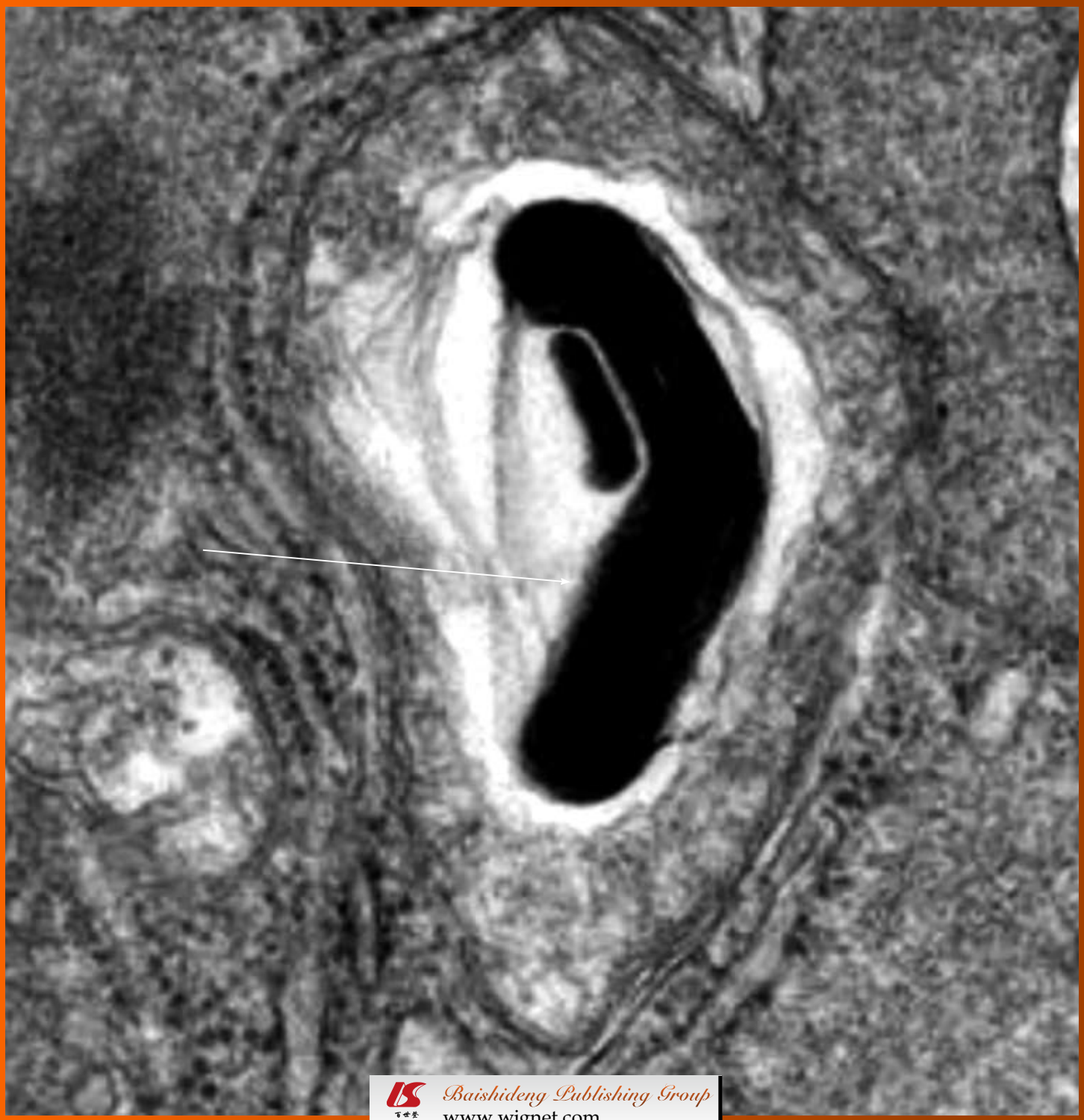

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EDITORIAL

Hypertension in the elderly

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Abstract

The elderly are the most rapidly growing population group in the world. Data collected over a 30-year period have demonstrated the increasing prevalence of hypertension with age. The risk of coronary artery disease, stroke, congestive heart disease, chronic kidney insufficiency and dementia is also increased in this subgroup of hypertensives. Hypertension in the elderly patients represents a management dilemma to cardiovascular specialists and other practioners. During the last years and before the findings of the Systolic Hypertension in Europe Trial were published, the general medical opinion considered not to decrease blood pressure values similarly to other younger patients, in order to avoid possible ischemic events and poor oxygenation of the organs (brain, heart, kidney). The aim of this review article is to highlight the importance of treating hypertension in aged population in order to improve their quality of life and lower the incidence of the cardiovascular complications.

Key words: Hypertension; Elderly; Pathophysiology; Treatment

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INTRODUCTION

Aging is an inevitable part of life and brings along two inconvenient events: physiologic decline and disease state[1]. Hypertension is an important risk factor for cardiovascular morbidity and mortality, particularly in the elderly. It is a significant and often asymptomatic chronic disease, which requires optimal control and persistent adherence to prescribed medication to reduce the risks of cardiovascular, cerebrovascular and renal disease[2]. Hypertension in the elderly patients represents a management dilemma to cardiovascular (CV) specialists and other practioners. Furthermore, with the wide adoption of multiple drug strategies targeting subgroups of hypertensive patients with specific risk conditions to lower blood pressure (BP) beyond traditional goals, difficult questions arise about how aggressive elderly patients should be treated. "Is hypertension in the elderly an emergency state or not?", "Does the BP control lower the risks associated with cardiovascular disease and death in the geriatric population?", "What are the general principles of hypertension management in this population?" The purpose of the following article is to answer those questions through a review of pathophysiology of aging, clinical assessment

and diagnosis of hypertension and finally recommendations for its management.

EPIDEMIOLOGY

As our population ages, the importance of cardiovascular disease (CVD) as the leading cause of death in adults becomes increasingly clear[3]. One major reason for this trend is the patterns of BP changes and increasing hypertension prevalence with age (about 1 billion people worldwide)[4]. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), hypertension occurs in more than two thirds of individuals after age of 65[5]. Data from the Framingham Heart Study, in men and women free of hypertension at 55 years of age indicate that the remaining lifetime risks for development of hypertension through 80 years are 93% and 91% respectively[6]. In other words, more than 90% of individuals who are free of hypertension at 55 years of age will develop it during their remaining lifespan.

From the standpoint of epidemiology and pathophysiology, there are some subgroups with particular characteristics such as elderly women and blacks that require additional focus. Hypertension prevalence is less in women than in men until 45 years of age, is similar in both sexes from 45 to 64 and is much higher in women than men over 65 years of age[3]. The severity of hypertension increases markedly with advancing age in women as well. After the age of 60 years, the majority of women (age 60-79 years: 48.8%; age ≥ 80 years: 63%) has stage 2 hypertension (BP ≥ 160/100 mmHg) or receives antihypertensive therapy[7-9]. Furthermore, BP control is difficult to achieve in elderly women[10]. Endothelial dysfunction, increased arterial stiffness, obesity, genetic factors, elevated total cholesterol and low high-density lipoprotein cholesterol levels have been implicated in menopause-related BP elevation rather than ovarian failure *per se*[11,12]. Hypertension among blacks is earlier in onset, more severe and uncontrolled and contributes to the highest coronary artery disease (CAD) mortality rates in the USA in addition to the highest morbidity and mortality attributable to stroke, left ventricular hypertrophy (LVH), heart failure (HF) and chronic kidney disease (CKD)[5]. Compared with whites, blacks are more likely to have hypertension, more likely to be aware of it and more likely to be pharmacologically treated, but less likely to achieve BP control[13]. Hypertension is an important factor in the disproportionate decreased life expectancy for blacks: African-American men 70.0 years *vs* 75.9 years for white men and African-American women 76.8 years *vs* 80.8 years for white women[14].

BP REGULATION

BP is regulated *via* several physiological mechanisms to ensure an adequate tissue blood flow. BP is determined by the rate of blood flow produced by the heart (cardiac output) and the resistance of the blood vessels to blood flow. The resistance is produced mainly in the arterioles and is known as the systemic vascular resistance. There are several physiological mechanisms that allow BP to maintain into normal range such as: (1) The autonomic nervous system is the most rapidly responding regulator of BP and receives continuous information from the baroreceptors situated in the carotid sinus and the aortic arch. This information is relayed to the vasomotor center. A decrease in BP causes activation of the sympathetic nervous system resulting in increased contractility of the heart (β receptors) and vasoconstriction of both arterial and venous side of the circulation (α receptors)[1]; (2) The capillary fluid shift mechanism refers to the exchange of fluid that occurs across the capillary membrane between the blood and the interstitial fluid. The fluid movement is controlled by the capillary BP, the interstitial fluid pressure as well as the colloid osmotic pressure of the plasma. Low BP results in fluid moving from the interstitial space into circulation, helping to restore blood volume and BP[6]; (3) Hormonal mechanisms exist both for lowering and raising BP. They act in various ways including vasoconstriction and vasodilation. The principal hormones raising BP are: (a) adrenaline and noradrenaline secreted from the adrenal medulla in response to sympathetic nervous system stimulation. They increase cardiac output and cause vasoconstriction; (b) renin-angiotensin-aldosterone production is increased in the kidney when stimulated by hypotension. Angiotensin is converted in the lung to Angiotensin Ⅱ which is a potent vasoconstrictor. In addition, these hormones stimulate the production of aldosterone from the adrenal cortex which decreases urinary fluid loss from the body (sodium retention-potassium loss). This system is responsible for the long-term maintenance of BP but is also activated very rapidly in the presence hypertension[5]; and (4) The kidneys help to regulate the BP by increasing the blood volume and also by the renin-angiotensin system (RAS) described above. They are the most important organs for the longterm control of the BP[5].

PATHOPHYSIOLOGY

Arterial stiffness

Elastic arteries show 2 major physical changes with age. They dilate and stiffen. Aorta and the proximal elastic arteries dilate by approximately 10% with each beat of heart in youth, while the muscular arteries dilate by only 3% with each beat[15]. Such difference in degree of stretch can explain differences in aging between proximal and distal arteries on the basis of fatigue[15]. Fracture of elastic lamellae is seen in the aorta with aging and can account for both dilation and for stiffening (through transfer of stresses to the more rigid collagenous components of the arterial wall)[15]. Autopsy studies of perfusion-fixed human arteries have shown that thickening is mostly confined to intimal hyperplasia[16]. The result is a stiff artery that has decreased capacitance and limited recoil and

is thus unable to accommodate the changes that occur during the cardiac cycle. Furthermore, during systole the arteriosclerotic arterial vessel exhibits limited expansion and fails to buffer effectively the pressures generated by the heart causing an increase in systolic BP (SBP). On the other hand, the loss of recoil during diastole results in reduction in diastolic BP (DBP)[17]. Thus, aging even in normotensive individuals is characterized by an increase pulse pressure, creating greater pulsatile stress on the arterial system[17]. Arterial stiffness is not only a product of structural changes in the arterial wall, but is also induced by endothelium-derived vasoactive mediators such as endothelin 1 and decreased bioavailability of nitric oxide (NO), which plays a key role in endothelial dysfunction[18,19]. According to a meta-analysis, aortic stiffness expressed as aortic pulse wave velocity (PWV) is a strong predictor for future cardiovascular events and all-cause mortality. The relative risk of total cardiovascular events, cardiovascular mortality and all-cause mortality were 2.26, 2.02 and 1.90, respectively for high *vs* low PWV subjects[20]. Aortic PWV is estimated noninvasively from the delay of pressure wave foot at the femoral site and from the distance traveled by the pulse. A typical value in a 20-year-old is 5 m/s and in an 80-year-old is 10-12 m/s (i.e., a 2, 4-fold increase over 60 years)[15]. In elderly individuals of 60-75 years old, an aortic PWV value below 10 m/s can be considered as a normal value. Values of 10-13 m/s can be considered as "high normal" or "borderline", whereas an aortic PWV above 13 m/s is frankly elevated[21]. In contrast to younger patients with hypertension in whom elevated BP is determined primarily by increased peripheral arterial resistance, the isolated systolic hypertension seen in elderly is due to increased arterial stiffness[22].

Neurohormonal and autonomic dysregulation

Neurohormonal mechanisms such as the renin-angiotensin-aldosterone system decline with age. Plasma renin activity at age of 60 years is 40% to 60% of the levels found in younger individuals[23]. This has been attributed to the effect of age-associated nephrosclerosis on the juxtaglomerular apparatus. Plasma aldosterone levels also decreases with age. Consequently, elderly patients with hypertension are more prone to drug-induced hyperkalemia[24]. In contrast, net basal sympathetic nervous system activity increases with advancing age. Peripheral plasma norepinephrine concentration in the elderly is double the level found in younger subjects[25]. The age-associated rise in plasma norepinephrine is thought to be a compensatory mechanism for reduction in β-adrenergic responsiveness with aging[25].

Decreased baroreflex sensitivity with age causes orthostatic hypotension in the elderly[26,27]. On the contrary, orthostatic hypertension, where BP increases with postural change, is also prevalent among the elderly[28]. The orthostatic hypertension is blocked by α-adrenergic blockade, indicating that α-adrenergic activity may be a predominant pathophysiological mechanism[28].

Table 1 Classification of blood pressure for adults according to JNC-7

Classification	SBP (mmHg)	DBP (mmHg)
Normal	⩽ 120	And ⩽ 80
Prehypertension	120-139	Or 80-89
Stage 1 hypertension	140-159	Or 90-99
Stage 2 hypertension	⩾ 160	Or ⩾ 100

SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 2 Classification of blood pressure for adults according to ESH/ESC 2007

Classification	SBP (mmHg)	DBP (mmHg)
Optimal	⩽ 120	And ⩽ 80
Normal	120-129	80-84
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	⩾ 180	⩾ 100
Isolated systolic hypertension	⩾ 140	⩽ 90

SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

The aging kidney

The aging kidney is characterized by progressive development of glomerulosclerosis and interstitial fibrosis, which is associated with a decline in GFR and reduction of other homeostatic mechanisms[29]. Age-associated decline in activity of membrane sodium/potassium and calcium adenosine triphosphate pumps lead to an excess of intracellular calcium and sodium, thereby increase of vasoconstriction and vascular resistance[30]. Increased salt sensitivity characterized by an increase in BP in response to sodium overload occurs in older and obese subjects as a result of the limited renal ability of these subjects to excrete sodium overload.

DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION

The JNC-7 has defined criteria for normal BP, prehypertension and stage 1 and 2 of hypertension[5] (Table 1). Guidelines from the European Society of Hypertension/European Society of Cardiology (ESH/ESC 2007 and 2009 update) stratify hypertension somewhat differently (Table 2). As with the previous ESH/ESC guidelines, the authors have again omitted the "prehypertension" category, as defined in JNC-7, because they believe that it implies that a large part of the population is "sick" and that this raises anxiety and leads to unnecessary physician visits. The authors also felt that the population of people who would fall into a prehypertension category would be so diverse to allow treatment recommendations for the whole group[31].

The diagnosis of hypertension should be based on at

Table 3 Causes of secondary hypertension

Hyperaldosteronism
Cushing syndrome
Coarctation of the aorta
Renovascular stenosis
Endocrine disorders (thyroid, parathyroid abnormalities)
Obstructive sleep apnea
Drugs (nonsteroidal antiinflammatory drugs, alcohol, estrogen)
Chronic kidney disease
Pheochromocytoma

Table 4 Causes of resistant hypertension

False positive or pseudoresistance
Incorrect technique in measuring blood pressure
Pseudohypertension
Lack of adherence to life style modifications
Lack of patient adherence to antihypertensive therapy
Suboptimal therapy
True resistant hypertension
Sleep apnea
Hypertension related to secondary etiology

least 3 different BP measurements taken on ≥ 2 separate office visits[5]. The majority of cases are due to essential hypertension. However, it is important to identify correctable causes of hypertension also known as secondary hypertension. History and examination may give clues to the presence of an underlying disease such as renal failure, renovascular disease, hyperaldosteronism, phaechromocytoma or Cushing syndrome. Other suggestive factors are lack of family history of hypertension, unusual course, early complications or resistance to therapy (Table 3).

Special definitions of hypertension

White-coat hypertension: A term reserved for those not on antihypertensive medications but with persistently elevated office BP (≥ 140/90 mmHg) together with a normal daytime ambulatory BP (≤ 135/85 mmHg), is also more common in the elderly and is more frequent among centenarians[32].

Masked hypertension: It is defined as normal BP at office associated with high BP at home, has been shown to be associated with an increased risk of cardiovascular events[33]. Masked hypertension is frequent in the elderly and is associated with a high vascular profile[34]. These results should encourage a more widespread use of home BP monitoring in this age segment.

Pseudohypertension: It is a falsely increased SBP caused by atherosclerotic and other vascular changes associated with age. The Osler maneuver (i.e. the presence of radial artery pulse that is still palpable after the cuff is inflated above the systolic pressure) should be performed if pseudohypertension is suspected, though it has low sensitivity and specificity[35]. Confirmation of pseudohypertension requires direct intraarterial measurement of BP[36].

Resistant hypertension: It is defined as BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts. Like the American Heart Association statement, the JNC 7 guidelines also include patients who are well controlled but require 4 or more medications as having resistant hypertension[5]. Resistant hypertension is prevalent across all ages, but is more prevalent in elderly patients[37]. Several factors have been identified as contributors to resistant hypertension. Poor patient adherence, physical inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, excess alcohol intake and sleep apnea are some of the most common causes of resistance. Secondary forms of hypertension represent another important contributor to drug resistance (Table 4).

Dipper or non-dipper patient: It is to say whether or not BP falls at night compared to daytime values. A night time fall is normal (nocturnal BP drop of 10%-20%, followed by an increase early in the morning). It correlates with variations in sympathetic activity but with other factors such as sleep quality, age, hypertensive status, marital status, and social network support[38]. In addition, nocturnal hypertension is associated with end organ damage and is a much better indicator than the daytime BP reading[39]. It should be noted that there is also a category of patients who, rather than non-dippers are extremely dippers (≥ 20% nocturnal BP fall) and this group may be at risk for silent and clinical cerebral ischemia through hypoperfusion during sleep[39]. The frequency of non-dippers is higher in the elder[40].

End-organ effects of hypertension in the elderly

Cerebrovascular disease and dementia: Hypertension in the elderly is a major risk factor for both ischemic stroke and cerebral hemorrhage. Isolated systemic hypertension (ISH) is an important component of BP-related stroke risk[41]. The benefit of BP reduction for stroke risk was demonstrated in Systolic Hypertension in the Elderly Program (SHEP), in which patients in the active treatment had reduced incidence of both ischemic (37%) and hemorrhagic stroke (54%)[42]. In the PROGRESS (Perindopril Protection Against Recurrent Stroke Study), patients under antihypertensive therapy had fewer recurrent ischemic strokes, 10% to 35% and hemorrhagic strokes 26% to 87% compared with placebo[43]. The Systolic Hypertension in Europe Trial (*Syst-Eur*), which comprised patients with ISH, confirmed stroke prevention with BP control using nitrendipine with possible addition of enalapril, hydrochlorothiazide (HCTZ) or both[44]. Patients in the aforementioned studies consisted of the "early elderly" (65-74 years). In Hypertension in the Very Elderly Trial (HYVET), patients in the "late elderly" group (≥ 80 years of age with elevated SBP) were randomized

to indapamide, with addition of perindopril if needed, or placebo. Patients in the indapamide group had a 30% risk reduction in fatal and non-fatal stroke[45]. It is unclear whether the benefits are related solely to BP reduction or whether there is additional benefit conferred by class of BP medication. Although there is consistent benefit in stroke reduction when drugs were compared with placebo, there is little difference between drug classes[46].

The prevalence of both hypertension and dementia increases with advancing age. Hypertension is an important risk factor for vascular dementia and Alzheimer's disease[47]. Poor BP control is associated with an even greater cognitive decline[48]. Four randomized studies evaluated dementia as an outcome with treatment of hypertension in elderly patients. In the Syst-Eur and PROGRESS, active treatment was associated with 50% and 19% reduction in dementia incidence respectively[43,49]. The SCOPE (Study on Cognition and Prognosis in Elderly) compared candesartan with placebo in 70 to 89 years old patients with hypertension and found no differences in cognitive outcome between the 2 groups[50]. The HYVET-COG trial found a non significant 14% decrease in dementia with active treatment *vs* placebo[51].

CAD: According to 2004 AHA statistics, 83% of CAD deaths occurred in persons ≥ 65 years of age[52]. Elderly patients with hypertension have higher prevalence of myocardial infarction than elderly patients without hypertension[53]. However, last recommendations to aggressively reduce BP in high risk patients, should be tempered particularly referring to myocardial infarction prevention. The old dogma "the lower the better" is not always true. This is what retrospective analysis of the International Verapamil-Trandolapril Study (INVEST) proved. The INVEST trial was designed to investigate two hypertension treatment strategies in patients with CAD. The study included a large number of individuals older than 80 years old and a secondary analysis of this group was performed to assess the effects of strict BP control by reporting a J-shaped mortality curve with BP control[54]. It is unclear whether the J-shaped mortality curve from this study is attributable to severe end stage disease alone or whether iatrogenesis plays a significant role. However, the data should cause one to be cautious in lowering BPs to below 130/70 mmHg in older patients, including those at high risk of adverse cardiovascular outcomes.

CKD: Hypertension and aging both impact renal function. Elderly patients are more likely to have CKD, usually defined by a measured estimated Glomerular Filtration Rate (eGFR) ≤ 60 mL/min per 1.73 m^2. 75% of the CKD population is ≥ 65 years of age[55]. SBP is a strong independent predictor of decline in kidney function among older patients with ISH[56].

Hypertension and age associated retinal changes: Retinal lesions prevalence increases with higher SBP, but not necessarily with DBP[57]. Persistent BP elevation produces intimal thickening, medial hyperplasia and hyaline degeneration (sclerosis)[58]. Aging itself is also associated with most of these changes which makes grading of retinal pathology in older patients less reliable *vs* younger patients[59]. Hypertension is an important risk factor for retinal artery occlusion and nonarteritic anterior ischemic optic neuropathy[60]. The final stages of retinal disease are caused by disruption of the retina/blood barrier and lipid exudates in severely elevated BP[61].

MANAGEMENT OF HYPERTENSION IN ELDERLY PATIENTS

The 2009 ESH/ESC update consider subclinical organ damage to be a very important component, because asymptomatic alterations of the cardiovascular system and the kidneys are important intermediate stages in the disease continuum that links risk factors such as hypertension to cardiovascular events and death. Moreover, multiple organ damage assessment is useful because of the evidence that in the presence of 2 signs of organ damage (even when present to the same organ), cardiovascular risk may be increased, upgrading the patient to the high cardiovascular risk category[62]. Reassessment of subclinical organ damage during treatment is also crucial because it offers information on whether the selected treatment is protecting patients from progressing organ damage and potentially from cardiovascular events[62]. Analysis of the data provided by some prospective studies indicate that in hypertensive patients, echocardiographic LVH is associated with an incidence of cardiovascular events equal or above 20% in 10 years[63,64]. Furthermore, the relationship of carotid intima-media thickness (IMT) and plaques with cardiovascular events, already discussed in the 2009 update, has been further reinforced by the European Lacidipine Study on Atherosclerosis trial, which have shown that IMT value at the bifurcations and the common carotid exerts an adverse prognostic effect in addition to that of high BP[65]. Finally, renal subclinical organ damage is associated with a 10-year risk of cardiovascular events of 20%. In a prospective cohort of Greek hypertensive patients, a low eGFR was associated with 20% incident cardiovascular event in 10 years[64].

A reappraisal of trials has underlined that no single trial on hypertension in the elderly has enrolled patients with grade 1 hypertension. Although not evidence based, the 2011 ACCF/AHA Expert Consensus Document suggest to initiate antihypertensive therapy in the elderly according to the same criteria used for younger adults and to use almost the same SBP goal as in younger patients[40]. Interestingly, although in almost all trials the groups of elderly patients randomized to treatment had lower incidence of cardiovascular outcomes, in no trial (except JATOS - the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients - with negative results[66]), the on-treatment SBP values were lowered to less than 140 mmHg. Thus, there is no randomized trial in support of lowering SBP to less than 140 mmHg[40].

Despite the known risk of uncontrolled hypertension in the elderly, there is poor adherence to guidelines. A meta-analysis in 2000 (largely from SHEP, Syst-Eur and Syst-China) pooled 15 693 patients older than 60 years (mean age 70 years) with ISH, SBP more than 160 mmHg, DBP less than 95 mmHg, analyzing the effect of hypertension treatment on cardiovascular outcomes[67]. Average BP was 174/83 mmHg and decrease in BP with treatment was 5.96% for SBP and 4.9% for DBP. Active treatment significantly reduced total mortality by 13%, chronic heart disease death by 18% and stroke by 26%. Clearly, we can conclude that treatment of hypertension in the elderly at least up to 70 years is beneficial to overall mortality. Treatment of hypertension in the elderly patients older than 80 years was not evaluated specifically in prospective trials until the HYVET study was published. The HYVET trial was a randomized prospective trial of 3845 participants older than 80 years[45]. The mean baseline BP was 173/91 mmHg (32% had ISH). Patients were randomized to diuretic or placebo. An angiotensin converting enzyme inhibitor (ACEI) was added if necessary to achieve a goal of BP of 150/80 mmHg. Active treatment was associated with a significant 30% relative risk reduction in fatal and non fatal stroke and 39% reduction in stroke death alone. CVD deaths were reduced by 23%. All cause mortality was also reduced by 23%. The HYVET trial answers a crucial question and gives an end to the dilemma whether hypertensive elderly patients should be treated or not. Physicians can feel comfortable prescribing anti-hypertensives for their elderly patients and know that there will be a mortality benefit. Another question regarding BP treatment in older individuals is whether severe hypertension constitutes an emergency and whether on the other hand there are levels that could be too low that might be associated with increases risk- known as the J-curve phenomenon.

Hypertensive emergency is defined as severely elevated BP in the setting of acute end organ damage[68]. Examples of hypertensive emergencies are acute myocardial infarction, pulmonary edema, cerebral ischemia or hemorrhage, aortic dissection, encephalopathy and progressive renal failure. Aside from the patient who has an obvious hypertensive emergency, how should patients who have asymptomatic severely elevated hypertension be treated? At what BP level does it become admirable to transfer the patient to the hospital? There is no evidence to support the idea that acute reduction of BP reduces cardiovascular events in the short or long term. In fact, many cases of harm have been documented. The mechanism by which acute reduction of BP leads to harm is related to auto regulation of blood flow. Patients, who have elevated BP, often have been present for many weeks or months. Any attempt to lower BP acutely may harm them by offsetting the patient's adaptive auto regulatory control[69]. Asymptomatic patients who do not have end-organ damage or significant comorbid illnesses should not have acute reduction of BP attempted. Instead, careful titration of antihypertensive medications should be undertaken with plans for close follow-up. Excessively lowering of the BP could be associated with poor outcome in long term (J-curve phenomenon). A Framingham Study in 2004 by Kannel *et al*[70] suggested that BP was responsible for the increased mortality and not DBP alone.

Table 5 Therapeutic strategies

Non-pharmacological strategy
Weight reduction
Dietary sodium reduction
Physical activity
Moderate alcohol consumption
Dash diet
Pharmacological strategy
Main Pharmacological agents
Thiazide diuretic: inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys →→ ↓ BP, ↓ stroke, ↓ CV mortality
ACEIs: block the conversion of angiotensin Ⅰ to angiotensin Ⅱ →→ ↓ SVR, ↓ BP, ↓ mortality in patients with MI and left ventricular dysfunction, ↓ progression of diabetic renal disease
ARBs: direct blockage of angiotensin Ⅱ receptors →→ vasodilation (↓SVR), ↓ secretion of vasopressin, ↓ aldosterone, ↓ BP, ↓ stroke. Generally, in patients who cannot tolerate ACEs
Calcium antagonists: disrupts the movement of calcium through calcium channels in cardiac muscle and peripheral arteries →→ vasodilation (↓ SVR), ↓ BP, ↓ CV complications in elderly patients with ISH
β blockers: ↓ heart rate, ↓ cardiac contractility, ↓ cardiac output, inhibit renin release, ↑ nitric oxide, ↓ vasomotor tone →→ ↓ BP
Other agents: direct renin inhibitors, aldosterone receptor antagonists, centrally acting agents, direct vasodilators, α-adrenergic blocking agents
Combination therapy
ACEIs or ARBs/Diuretic
ACEIs or ARBs/Calcium antagonist (especially in patients with high CV risk)

CV: Cardiovascular; BP: Blood pressure; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; SVR: Systemic vascular resistance.

The therapeutic strategies for hypertension in the elderly as well as the basic effects and the main cardiovascular benefits of the pharmacological agents are summurized in Table 5.

Non pharmacological management of hypertension in elderly patients

Non pharmacological management of hypertension is too often overlooked in the elderly. Lifestyle modifications may be the only treatment necessary for preventing or even treating milder forms of hypertension in the elderly. Weight reduction (results in a 5-20 mmHg decrease in SBP per 10kg less), dietary sodium reduction (2-8 mmHg decrease in SBP), physical activity (4-9 mmHg decrease in SBP), moderate alcohol consumption (2-4 mmHg decrease in SBP) and DASH (Dietary Approaches to Stop Hypertension) diet (8-14 mmHg decrease in SBP) should be the cornerstone of hypertension treatment in combination or not with active treatment[5].

Pharmacological management of hypertension in elderly patients

When lifestyle measures fail to lower BP to goal, pharmacotherapy should be initiated. The safety and efficacy of multiple medication classes has been studied in elderly patients over the last 30 years. Randomized controlled trials have consistently demonstrated that antihypertensive therapy in the elderly is effective in preventing total mortality, stroke and coronary events[5]. Another important consideration is that for most trials, the goal and achieved bp are higher than that recommended by JNC-7, while still showing a significant benefit of treatment.

General principles of pharmacological management: There is often a debate about which antihypertensive drug class should be used first in elderly patients with hypertension. Several classes of antihypertensive drugs are effective in preventing cardiovascular events. Treatment decisions should be guided by the presence of compelling indications such as diabetes mellitus, stroke or HF and by the tolerability of individual drugs or drug combinations. The initial antihypertensive drug should be started at the lowest dose and gradually increased depending on the BP response to the maximum tolerated dose[31]. If the antihypertensive response to the initial drug is inadequate after reaching full dose, a second drug from another class should be added. If the antihypertensive response in inadequate after reaching the full dose of 2 classes of drugs, a third drug from another class should be added[31].

A common question arising from current clinical practice refers to the threshold BP values for treatment initiation. As mentioned in the ESC 2007 document, the guidelines recommend to start drug treatment in grade 1 hypertensive patients at low or moderate risk when BP is equal or above 140/90 mmHg after lifestyle modifications. These thresholds which have been confirmed in the ESH 2009 update are similar in elderly hypertensives based on the results of the HYVET-trial[45]. Prompter treatment is recommended in grade 2 and 3 of hypertension[62]. In patients with high-normal BP ("pre-hypertension"), drug treatment should be delayed when overall cardiovascular risk is low. As far as goals of treatment are concerned, the ESH 2009 guidelines update document recommends to lower BP to values within the range 130-139 mmHg for systolic and 80-85 mmHg for diastolic, in all hypertensive patients[62]. Furthermore, the concept of lower BP goals in diabetics or very high risk patients is no longer recommended because there is no evidence of a greater benefit. On the other hand, the quantification of the total cardiovascular risk must also include a search for subclinical organ damage[62].

Pharmacological agents: The JNC-7 trial recommends a thiazide diuretic as initial drug therapy or in combination with other class[5]. Thiazide diuretics control hypertension by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter. The term "thiazide" is also often used for drugs with a similar action that do not have the thiazide chemical structure, such as chlorthalidone and metolazone. These agents are properly termed thiazide-like diuretics[71]. Thiazides are preferred because of an extensive volume of data showing that may decrease stroke and CV mortality in elderly patients with hypertension and because of their wide availability and low cost. These agents have benefits that are distinct from their effects on BP and CVD outcomes.

Their effect on calcium reabsorption constitutes the basis for their usefulness in preventing the formation of calcium containing renal stones and may also explain their protective effects on rates of bone mineral loss and prevention of hip fracture[72-74]. Unfortunately, thiazide treatment is associated with various metabolic side effects, including electrolyte abnormalities, dyslipidemia, insulin resistant and new-onset of diabetes mellitus[74]. Whether the metabolic effects of diuretics have adverse consequences for CVD outcomes has been questioned. In Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, there was no significant increase in any outcome (stroke, total mortality, CAD, HF, end stage renal disease) in subjects who developed incident diabetes mellitus[75]. In fact, thiazides remained unsurpassed in all clinical outcomes compared with the other drug classes[75]. Only the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial favored ACEI/CCB combination over the ACEI/THIAZIDE combination in patients with hypertension who were at high risk for cardiovascular events[76]. However, the hydrochlorothiazide dose used (12.5-25 mg/dL) was half the dose used in other trials, indicating the need to titrate to higher doses[76]. Data support the following dosages of thiazides: hydrochlorothiazide 25 to 50 mg/d, indapamide 2.5 mg/d, chlorthalidone 12.5-25 mg/d[31].

ACEIs can also be considered for first-line or combination therapy, especially if diabetes, HF, post myocardial infarction or chronic disease is present. ACEI block the conversion of angiotensin I to angiotensin Ⅱ in multiple tissues and thus lower total peripheral vascular resistance reducing BP without reflex stimulation of heart rate and cardiac output. As aging occurs, angiotensin levels are lower and theoretically ACEIs should not be as effective as other therapies, but multiple studies have shown otherwise[77]. Among ACEIs benefits reduction in mortality in patients with MI and left ventricular dysfunction as well as reducing progression of diabetic renal disease are the most important[78,79]. When combination therapies are needed, often for high risk patients, JNC-7 guidelines indicate a strong preference for a thiazide diuretic[5]. The superiority of the amlodipine-based therapy (ACCOMPLISH trial) with respect to the clinical outcomes in this trial suggests that approaches that do not include thia-

zides may be better for some populations[76]. Nevertheless, these results should not cast doubt on the efficacy of diuretics in reducing the risk of cardiovascular events. In the HYVET trial, mortality was reduced with therapy that combined a diuretic with an ACE inhibitor as compared with placebo[45]. Moreover,patients with or at risk of sarcopenia may particularly benefit, as ACEIs have been shown to improve muscle strength and working speed in older hypertensive individuals[80]. Therefore, this group of hypertensive may be a good choice for the frail elderly. Finally, the main adverse effects of ACEIs include hypotension, chronic dry cough and rarely angioedema or rash. Renal failure can develop in those with renal artery stenosis. Hyperkalemia can occur in patients with renal insufficiency. Rarely, neutropenia or agranulocytosis can occur[81]. Therefore, close monitoring is suggested during the first months of therapy.

Hypertensive patients with diabetes mellitus, angiotensin receptor blockers (*ARBs*) are considered first line treatment and as an alternative to ACEIs in patients with hypertension and HF who cannot tolerate ACEIs[82]. Blockage of angiotensin Ⅱ receptors directly causes vasodilation, reduces secretion of vasopressin and reduces production and secretion of aldosterone. The combined effect reduces BP[83]. The LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study compared losartan with atenolol in patients (age 55 to 80 years) with hypertension and LVH, showing reduced stroke rate in the losartan treated group despite comparable BP reduction in both treatment groups[84]. In MOSES (Morbidity and Mortality after Stroke-Eprosartan compared with Nitrindipine in Secondary Prevention) study, eprosartan reduced stroke by 25% in patients with mean age 68 years[85]. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) trial showed similar efficacy between telmisartan and ramipril in elderly hypertensive subjects[86].

The usefulness of β blockers (reduce the heart rate and cardiac output, inhibit renin release, generate NO, reduce vasomotor tone)[87] as first line treatment of hypertension in older persons has been questioned. Although β-blockers have been used for hypertension in the elderly for years, evidence for benefit has not been convincing. Two large randomized trials, the LIFE study and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, showed superiority of an angiotensin receptor antagonist and respectively an antihypertensive regimen of a calcium antagonist adding perindopril, over therapy initiated by a β-blocker as far as stroke (LIFE) or stroke and mortality (ASCOT) were concerned[84,88]. The 2 large trials have strongly influenced a recent meta-analysis which concluded that β-blocker should not remain first choice in the treatment of primary hypertension[89]. On the basis of a similar meta-analysis, the National Institute for health and Clinical Excellence in the United Kingdom has advised the use of β-blockers as fourth antihypertensive agent[90]. The adverse effects of β-adrenergic receptor blocking drugs can be divided in 2 categories: (1) those that result from known pharmacological consequences of β-adrenergic receptor blockade; and (2) other side-effect that do not appear to result from β-adrenergic receptor blockade. The first category includes bronchospasm, HF, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud's phenomenon. Neurological reactions include depression, fatigue, nightmares. Patient's age does not appear in itself, to be associated with more β-blocker side effects. Side effects of the second category are rare. They include an unusual oculomucocutaneous reaction and the possibility of oncogenesis[91].

In general, calcium antagonists appear well tolerated by the elderly. They are a heterogenous group of drugs with different effects on heart muscle, sinus node function, atrioventricular conduction, peripheral arteries and coronary circulation. Vascular smooth muscle is more dependent on external calcium entry for contraction whereas cardiac and skeletal muscles rely on a recirculating internal pool of calcium[92]. This preferential effect allows calcium antagonists to dilate coronary and peripheral arteries in doses that do not severely affect myocardial contractility and skeletal muscle. The Syst-Eur study investigated whether antihypertensive treatment could reduce cardiovascular complications in elderly patients with isolated systolic hypertension. It showed that antihypertensive drug-treatment, starting with the dihydropyridine calcium channel blocker nitrendipine, improves prognosis in elderly patients with isolated systolic hypertension[44].

Direct renin inhibitors, Aliskiren is an orally active direct rennin inhibitor approved for hypertension; 150 mg to 300 mg once daily appears as effective as ARBs and ACEIs for BP management[93]. Combining aliskiren with HCTZ, or amlodipine causes greater BP lowering than with either agent alone[94]. The major side effect is a low incidence of mild diarrhea[95]. Thus far, we know that dual RAS blockade with an ARB and an ACEI is not beneficial in patients like those in ONTARGET trial, and that it has questionable benefit in HF[86]. However, little was known about combining a direct renin inhibitor with either an ACEI or an ARB. The results of the halted ALTITUDE trial showed that the combination of aliskiren with ACEI or ARB in type 2 diabetic patients with high risk for cardiovascular and renal events is contraindicated because of the increased risk for non-fatal stroke, renal complications, hyperkalemia and hypotension in patients taking aliskiren after 18-24 mo[96,97].

Aldosterone receptor antagonists in hypertensive patients decrease BP to limit end-organ damage. Circulating aldosterone levels positively correlate with incident, resistant and obstructive sleep apnea-related hypertension[98]. Both spironolactone and eplerenone are each efficacious in reducing BP; however, there have been a limited number of comparison studies designed to establish drug superiority[99]. Eplerenone improves arterial compliance and reduces vascular stiffness by decreas-

ing the collagen to elastin ratio[100]. Both spironolactone and eplerenone have shown to decrease left ventricle mass[101]. In a small study of patients with resistant hypertension, 6 mo of spironolactone added to diuretic and ACEIs therapy reduced systolic and diastolic BP by 25 and 12 mmHg respectively and the magnitude of the response was not predicted by the plasma aldosterone level[102]. Spironolactone and eplerenone have different side effects profiles, although both share hyperkalemia as a serious side effect[103]. The incidence of spironolactone side-effect associated breast tenderness, gynecomastia, erectile dysfunction and menstrual irregularities increase the rates of medication non-compliance[104].

Centrally acting agents such as clonidine treats high BP by stimulating a2 receptors in the brain, which decreases cardiac output and peripheral vascular resistance, lowering thus BP. It has specificity towards the presynaptic a2 receptors in the vasomotor center in the brainstem. This binding decreases presynaptic calcium levels and inhibits the release of norepinephrine. The net effect is a decrease in sympathetic tone[105]. Reserpine is another centrally acting agent, whose antihypertensive action is a result of its ability to deplete catecholamines (among other monoamine neurotransmitter) from peripheral sympathetic nerve endings. Both clonidine and reserpine should not be used as monotherapy because they have been associated with a high incidence of adverse effects, including sedation, depression and constipation[106].

Direct vasodilators such as hydralazine (direct-acting smooth muscle relaxant, acting primarily in arteries and arterioles) and minoxidil may cause headache, fluid retention, tachycardia and angina pectoris[107]. Hydralazine may cause a lupus-like syndrome in 5%-10% of patients during longterm use[108]. Minoxidil (may act as a NO agonist), may cause hirsutism and pericardial effusion[109,110].

In the ALLHAT trial, an α-adrenergic blocking agent, the doxazosin (which inhibits the binding of noradrenaline to the α-1 receptors on the membrane of vascular muscle cells, leading to vasodilation and decreased BP) arm was stopped prematurely due to significant increases in HF (20%), stroke (19%), angina pectoris (16%)[111]. These drugs are used for prostate hypertrophy and caution should always be paid for orthostatic hypotension.

Monotherapy vs combination therapy

Both the 2009 updated ESH/ESC and the ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly recommend the combination of 2 drugs to be considered as initial treatment whenever hypertensive patients have high initial BP or are classified as being at high cardiovascular risk[40,62,76]. Trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an angiotensin receptor antagonist, and in recent trials for the ACE inhibitor/calcium antagonist combination (the angiotensin receptor antagonist/calcium antagonist combination also appears to be effective)[40,43,62,76]. Enhanced efficacy, reduced adverse effects, improved compliance as well as a potential organ protection are the key benefits of the combination therapy[40].

Medication compliance

Compliance is defined as the extent to which a patient takes medication as prescribed. Compliance rates are often reported as percentage of prescribed dose of medication taken over a period of time. Unfortunately, a large proportion of the elderly patients discontinues or takes the drugs inappropriately[112]. This noncompliance results in failing to reach guideline-recommended BP targets. Older age, low risk for cardiovascular events, competing health problems, low socioeconomic status, complexity (e.g., multiple dosing), side effects and cost of medication regimen predict noncompliance[113].

CONCLUSION

Hypertension is an important risk factor for cardiovascular morbidity and mortality, especially in the elderly. Multiple trials have been shown that not only is it safe to treat hypertension in the elderly, but also that will decrease stroke, HF, myocardial infarction and all-cause mortality. Hypertension treatment also reduces the incidence of cognitive impairment and dementia in the elderly. The adoption of a healthy lifestyle is one of the cornerstones of hypertension management. Evidence indicates that several classes of antihypertensive drugs are effective in preventing cardiovascular events, but usually no single drug is adequate to control BP in most elderly with hypertension. Individualization of the treatment should be guided by the presence of concomitant cardiovascular risk factors. The assessment of subclinical cardiovascular organ damage resulting to an earlier onset of antihypertensive therapy leads to a reduction of the total cardiovascular risk. For all those aforementioned reasons, physicians should treat hypertension in their patients regardless of their age.

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GUIDELINES FOR BASIC SCIENCE

Mitochondrial dysfunction and mitochondrial DNA mutations in atherosclerotic complications in diabetes

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Abstract

Mitochondrial DNA (mtDNA) is particularly prone to oxidation due to the lack of histones and a deficient mismatch repair system. This explains an increased mutation rate of mtDNA that results in heteroplasmy, e.g., the coexistence of the mutant and wild-type mtDNA molecules within the same mitochondrion. In diabetes mellitus, glycotoxicity, advanced oxidative stress, collagen cross-linking, and accumulation of lipid peroxides in foam macrophage cells and arterial wall cells may significantly decrease the mutation threshold required for mitochondrial dysfunction, which in turn further contributes to the oxidative damage of the diabetic vascular wall, endothelial dysfunction, and atherosclerosis.

Key words: Mitochondrial DNA; Mutation; Heteroplasmy; Atherosclerosis; Diabetes; Oxidative stress; Ultrastructure

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INTRODUCTION

Cardiovascular complications are mainly responsible for the high morbidity and mortality in diabetic patients. Diabetes itself is recognized as a strong independent risk factor for cardiovascular disease. According to the Framingham Heart Study, diabetes is associated with an odds ratio of 2-4 for cardiovascular mortality compared with nondiabetic subjects[1]. These results were confirmed in the recent Atherosclerosis Risk in Communities (ARIC) study[2].

There is a convincing evidence from epidemiological and pathophysiological studies that hyperglycemia *per se* is largely responsible for the harmful effects of diabetes. Today, evidence exists from long-term follow-up population-based studies in patients with type 1 and type 2 diabetes. This evidence clearly suggests that hyperglycemia is a key risk factor not only for diabetes-related disease, but also for cardiovascular and all-cause mortality. On the

basis of these long-term observations, one can assume an increase in the risk of cardiovascular disease by 18% for each unit (%) glycated hemoglobin HbA1c[3]. In the Glucose Tolerance in Acute Myocardial Infarction study of patients with acute coronary syndrome, abnormal glucose tolerance was the strongest independent predictor of subsequent cardiovascular complications and death[4]. In the Asian Pacific Study, fasting plasma glucose was shown to be an independent predictor of cardiovascular events up to a level of 5.2 mmol/L[5].

Glucose level fluctuations and hyperglycemia are triggers for inflammatory responses *via* increased mitochondrial superoxide production and endoplasmic reticulum stress[6]. Inflammation leads to insulin resistance and β-cell dysfunction, which further aggravates hyperglycemia[7]. The molecular pathways that integrate hyperglycemia, oxidative stress, and diabetic vascular complications have been most clearly described in the pathogenesis of endothelial dysfunction[8], which is considered as the first step in atherogenesis according to the response to injury hypothesis[9].

Mitochondria play a pivotal role in ATP production through oxidative phosphorylation (OXPHOS), a metabolic mechanism that utilizes up to 90% of pyruvate generated from glucose in the cytoplasm[10]. Indeed, mitochondria are directly involved in aerobic glucose metabolism. Accordingly, high blood glucose, through deleterious effects of glucotoxicity and hyperglycemia-induced oxidative stress, may result in the rapid progress of mitochondrial dysfunction[11]. Alterations in mitochondrial DNA (mtDNA), known as homoplasmic and heteroplasmic mutations, may influence mitochondrial OXPHOS capacity, and in turn contribute to the magnitude of oxidative stress in micro- and macrovascular networks in diabetic patients. In this review, we critically consider the impact of mtDNA mutations on the pathogenesis of cardiovascular diabetic complications.

HETEROPLASMY *VS* HOMOPLASMY

Compared with nuclear DNA repair, mtDNA repair mechanisms are significantly less efficient[12]. This results in increased vulnerability of mtDNA to oxidative stress, and significantly higher mutation rates in the mitochondrial genome compared with the nuclear genome. Indeed, mitochondrial genomes have a higher load of deleterious mutations than nuclear genomes[13].

When damage to mtDNA is not repaired, it can result in a cascade of events ultimately leading to a number of diseases. A mitochondrial disorder can result from the substitution, deletion, and duplication of mtDNA bases. To add to the complexity of mitochondrial disorders, they can arise from one mtDNA mutation or from a number of independent mutations that in turn can lead to more than one disease type.

The naturally occurring circle of mtDNA is also referred to as wild-type. The number of mutations can increase in a particular tissue, while not being reflected in other parts of the body. The mixtures of wild-type and mutant mtDNA coexisting in the same mitochondria are referred to as heteroplasmic mutations. Mitochondrial mutations can also be homoplasmic in nature when cellular mitochondria contain all of the same mutant mtDNA.

Repeated cell division leads to the separation of heteroplasmic and homoplasmic cell lines in a phenomenon of random segregation. Similar process can be observed in the atherosclerotic plaque due to the clonal proliferation of smooth muscle cells (SMCs)[14]. Mutant mtDNA increases with aging, and the cellular energy capacity can decrease. This decrease in turn affects the threshold of minimal cell function[15].

MUTATION THRESHOLD

Although cells may harbor mutant mtDNA, the expression of disease is dependent on the percent of alleles bearing mutations. Modeling confirms that an upper threshold level might exist for mutations beyond which the mitochondrial population collapses, with a subsequent decrease in ATP[16]. This decrease in ATP results in the phenotypic expression of disease[17]. It is estimated that in many patients with clinical manifestations of mitochondrial disorders, the proportion of mutant DNA exceeds 50%[18].

For the MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like syndrome)-causing mutation m.3243 A>G in the mitochondrial gene encoding $tRNA^{Leu}$, which is also associated with diabetes plus deafness[19], a strong correlation between the level of mutational heteroplasmy and documented disease has been found. Increased percentages of mutant mtDNA in muscle cells (up to 71%) can lead to mitochondrial myopathy[20]. Levels of heteroplasmy of over 80% may lead to recurrent stroke[21] and mutation levels of 95% have been associated with MELAS[18].

Regardless of the type of mutation or the level of heteroplasmy in affected mitochondria, unrepaired damage leads to a decrease in ATP, which in turn causes the phenotypic manifestation of disease. The manifestation of disease not only depends on the ATP level but also on the tissue affected. Various tissues have differing levels of demand on OXPHOS capacity. To evaluate a tissue threshold, Leber's hereditary optic neuropathy can be used as a model for mitochondrial neurodegenerative disease. For neural and skeletal muscle tissues, the tissue threshold should be as high as or higher than 90% of damaged (mutated) mtDNA[22]. To induce mitochondrial malfunctions, the tissue threshold of the cardiac muscle is estimated to be significantly lower (approximately 64%-67%)[23].

MUTATION THRESHOLD IN VASCULAR WALL TISSUE

For the vascular wall, the mutation threshold is thought to be high enough to induce acute mitochondrial dys-

function. For example, a heteroplasmy level of 95% of the MELAS mutation m.3243 A>G, was found in cytochrome C oxidase-deficient brain microvessels of patients who died from congestive heart failure[24]. Such a high level of mutated allele in brain microvessels is considered to be responsible for stroke-like episodes in the MELAS syndrome. Similarly, in a girl with severe mitochondrial encephalopathy, the vasculature of the affected left cerebral artery was almost homoplasmic for the m.3243A>T mutation in $tRNA^{Leu}$, but with a lower mutant load (about 50% heteroplasmy) in blood and skin fibroblasts[25].

However, in chronic vascular disease such as atherosclerosis, a mutation threshold in the affected vessel wall (e.g., in the postmortem aortic atherosclerotic plaques) was observed to be significantly lower. For example, for mutations m.3256 C>T, m.12315 G>A, m.15059 G>A, and m.15315 G>A, the heteroplasmy range of 18%-66% in the atherosclerotic lesions was 2-3.5-fold that in normal vascular tissue[26]. What are the mechanisms leading to mitochondrial dysfunction in diabetic vascular pathology at mtDNA heteroplasmy levels that are considerably lower than those required, for example, to induce mitochondrial myopathy and/or neuropathy?

MITOCHONDRIAL STRESS AND INSULIN RESISTANCE

As noted above, due to its proximity to reactive oxygen species (ROS), the mitochondrial genome may be particularly susceptible to oxidative damage because of its lack of histones and a deficient mismatch repair system. This combination could be responsible for heteroplasmy levels, e.g., the ratio of both normal and mutated mtDNA in tissues[27].

Mitochondrial dysfunction may be involved in insulin resistance in diabetic skeletal muscle. Expression of genes critical for mitochondrial function, such as the gene encoding peroxisome proliferator-activated receptor-γ coactivator 1α, is decreased in humans with insulin resistance[28]. Energy production is impaired in the muscle of insulin-resistant subjects[29]. Recent findings also implicate mitochondrial dysfunction in atherosclerosis[30].

Insulin resistance causes circulating fatty acids to increase. Increased oxidation of fatty acids by aortic endothelial cells was recently reported to accelerate production of superoxide by the mitochondrial electron transport chain[31]. This effect was associated with proatherogenic vascular effects, and prevented by either blocking of release of fatty acids from adipose tissue or inhibition of mitochondrial fatty acid oxidation, consistent with a role for increased mitochondrial metabolism in vascular disease. In macrophage foam cells, oxidized fatty acids may be then widely esterified and form a pool of oxidized ethers containing cholesterol and 7-ketocholesterol, which exhibit high resistance to lysosomal esterases, and indeed accumulate within the lysosomes of foam cells[32]. The accumulation of oxidized lipids in foam cells subsequently aggravates atherogenesis through the recruitment of new monocytes and macrophages to the lesion site, inducing a local proinflammatory reaction and further proatherogenic events[33]. Elevated blood glucose was shown to significantly increase the amount of foam cells and accumulation of oxidized low density lipoproteins in cultivated arterial wall cells[34].

Human atherosclerotic samples obtained during vascular surgery show greater mtDNA damage than non-atherosclerotic samples obtained from age-matched transplant donors[35]. Mitochondrial damage precedes the development of atherosclerosis and tracks the extent of the lesion in apoE-null mice, and mitochondrial dysfunction caused by heterozygous deficiency of a superoxide dismutase increases atherosclerosis and vascular mitochondrial damage in the same model[35].

Blood vessels destined to develop atherosclerosis may be characterized by inefficient ATP production due to the uncoupling of respiration and OXPHOS. Blood vessels have regions of hypoxia[2], which lower the ratio of state 3 (phosphorylating) to state 4 (nonphosphorylating) respiration[36]. Human atherosclerotic lesions have been known for decades to be deficient in essential fatty acids[37], a condition that causes respiratory uncoupling[38] and atherosclerosis[39].

Vascular inducible expression of uncoupling protein 1 (UCP1), the prototypical inner mitochondrial membrane anion transporter found in brown fat, increases atherosclerosis and several markers of oxidative damage in apoE-null mice[40]. Mitochondrial dysfunction resulting from UCP1 expression in blood vessels causes renin-dependent hypertension[40], and a mitochondrial mutation m.4291 T>C associated with hypertension has been described in humans[41]. Uncoupling increases respiration, which might account for evidence of increased oxidative modifications.

Takagi *et al*[42] reported the anti-atherosclerotic effect of the presence of the minor allele A of the m.5178 C>A polymorphism (in fact, a homoplasmic mutation) of the MT-ND2 gene in a Japanese population. Matsunaga *et al*[43] observed significantly less frequent plaque formation in the bilateral carotid arteries of type 2 diabetic carriers of the allele m.5178A thereby suggesting an anti-atherogenic effect of this mtDNA variant. Kokaze *et al*[44] then showed significantly higher serum levels of high-density lipoprotein in males carrying 5178A compared with those having 5178C, and reduced concentrations of serum triglycerides in female carriers of 5178A than in those with 5178C. Therefore, the finding by Kokaze *et al*[44] helps to explain, at least in part, the anti-atherogenic effect of the allele m. 5178A due to its relation with the favorable lipid profile[45]. The nucleotide change causes leucine-to-methionine substitution at codon 237 (Leu-237Met) of the NADH dehydrogenase subunit 2 located in the loop between 7th and 8th transmembrane domains of the mitochondrial protein[42]. Given that this methionine residue is exposed at the surface of respiratory Complex I , this residue may be available as an efficient

oxidant scavenger. Complex I accepts electrons from NADH, transfers them to ubiquinone, and uses the energy released to pump protons across the mitochondrial inner membrane[46]. Thus, the Leu237Met replacement in the ND2 subunit might have a protective effect against oxidative damage to mitochondria.

In a pilot study performed in 192 unrelated participants taken randomly from a Russian population, 24 of whom (12.5%) were affected with type 2 diabetes, we observed that the level of m.14846 G>A heteroplasmy in circulating peripheral mononuclear blood cells was 1.3-fold higher in diabetic patients (34.5% *vs* 26.5%, P = 0.022) compared with non-diabetic subjects (unpublished data). This mutation occurs within the MT-CYB gene encoding cytochrome b and results in glycine-to-serine substitution at position 34, thus affecting the intermediate transfer of electrons in mitochondrial respiratory chains, reducing the enzymatic function of cytochrome B, and is thought to be associated with mitochondrial myopathies.

For reasons that are unclear, brown fat, the tissue defined by respiratory uncoupling, encases chest and neck blood vessels in humans[47]. Most fatty acid oxidation, which is promoted by peroxisome proliferator-activated receptor α (PPARα) activation, occurs in the mitochondria. Mitochondrial effects could explain why PPARα-deficient mice are protected from diet-induced insulin resistance and atherosclerosis[48] as well as glucocorticoid-induced insulin resistance and hypertension[49]. Caloric restriction, which improves features of insulin resistance, increases mitochondrial biogenesis and, surprisingly, enhances the efficiency of ATP production[50]. Dysfunctional mitochondria in cultured cells can be rescued by transfer of mitochondria from adult stem cells[51], raising the possibility of restoration of normal bioenergetics in the vasculature to treat atherosclerosis associated with insulin resistance.

GLUCOTOXICITY IN DIABETES AND MITOCHONDRIAL DYSFUNCTION

There are several reports suggesting a role for various mitochondrial mutations in diabetic complications. In a Japanese population, a total of eight mtDNA mutations, including m.3243 A>G, were found to be associated with reduced insulin secretion and increased risk of vascular diabetic complications[52]. Regarding the diabetes-associated mutation m.3243 A>G, a 4-fold higher accumulation of this mutation was observed in diabetic patients compared with non-diabetic subjects[53]. Furthermore, this mutation was associated with diabetes duration[54].

The mutant $tRNA^{Leu(UUR)}$ can recognize all four nucleotides at the third position of the codon, giving rise to the translation of not only the usual UUR (R = A or G) leucine codons but also UUY (Y = C or U) phenylalanine codons, which could eventually lead to the incorporation of leucine into phenylalanine sites at a certain rate[55]. The resulting synthesis of premature proteins due to this mistranslation could affect cells considerably, even if there is only a minor amount (usually, 0.02%-0.03%) of the 3243 A>G mutant mtDNA. Of interest, m.3243 A>G itself increases the intracellular production of ROS[56], which could in turn cause secondary somatic mutations[57]. An increased frequency of somatic transversion mutations in two segments of mtDNA (control region and gene encoding $tRNA^{Leu(UUR)}$) was found in diabetic patients compared to sex- and age-matched healthy subjects, and the mutation incidence correlated with hyperglycemia, e.g., level of glycated hemoglobin HbA1c[58].

In diabetic hyperglycemia, harmful effects on the vascular endothelial cells could be mainly realized through glucotoxicity and uncontrolled ROS production. Under hyperglycemic conditions such as diabetes, free radical production may arise from glucose self-oxidation[59], oxidative degradation of Amadori products[60], interaction of advanced glycation end-products (AGEs) and the AGE receptor[61], and an increase in the redox potential[62]. Glucose, in its aldehyde form, reacts with the amino groups of proteins to form a Schiff base which rearranges to a stable ketoamine adduct[63]. This process, called non-enzymatic glycation of protein, is particularly enhanced in diabetes and causes enzyme inactivation through oxidation, formation of AGEs, and protein-protein cross-linking[6]. Accumulation of AGEs in the vascular wall is accompanied by infiltration of the vasculature with macrophages, which engulf AGEs and actively contribute to inducing a local inflammation at the injury site[64].

In the diabetic vascular wall, oxidative stress causes numerous deleterious effects on mitochondrial function, including enhanced mtDNA damage (as reflected by increased levels of 7,8-dihydro-8-oxoguanine, a potential mutagen[65], in blood and urine of diabetic subjects), irreversible modification and inactivation of mitochondrial enzymes, uncoupling of the respiratory chain, reduced OXPHOS capacity, and mitochondrial superoxide overproduction by endothelial cells[66]. Indeed, due to the extensive oxidative stress and gluxotoxicity, even lower levels of heteroplasmy mtDNA mutations may be enough to induce atherogenic and atherosclerotic changes in diabetic vessels.

The 4977bp "common deletion", present in the mtDNA of patients with a variety of degenerative diseases, has been detected at low levels (an average of 0.35% of total mtDNA) in the SMCs in atherosclerotic lesions of the aorta of patients undergoing surgery for aneurysm, as well as in diseased aortas at autopsy[67]. There were no correlations observed between the amount of $mtDNA^{4977}$ deletion in atherosclerotic lesions and the levels of adducts and oxidative damage to nuclear DNA for each patient, except for a significant increase in $mtDNA^{4977}$ in subjects older than 72 years *vs* younger than 72 years[68]. The true physiological significance of age-dependent accumulation of this mitochondrial mutation is still unclear. However, the $mtDNA^{4977}$ deletion was shown to accumulate much faster in brain and heart tissue due to greater metabolic activity and minimal cell turnover compared to

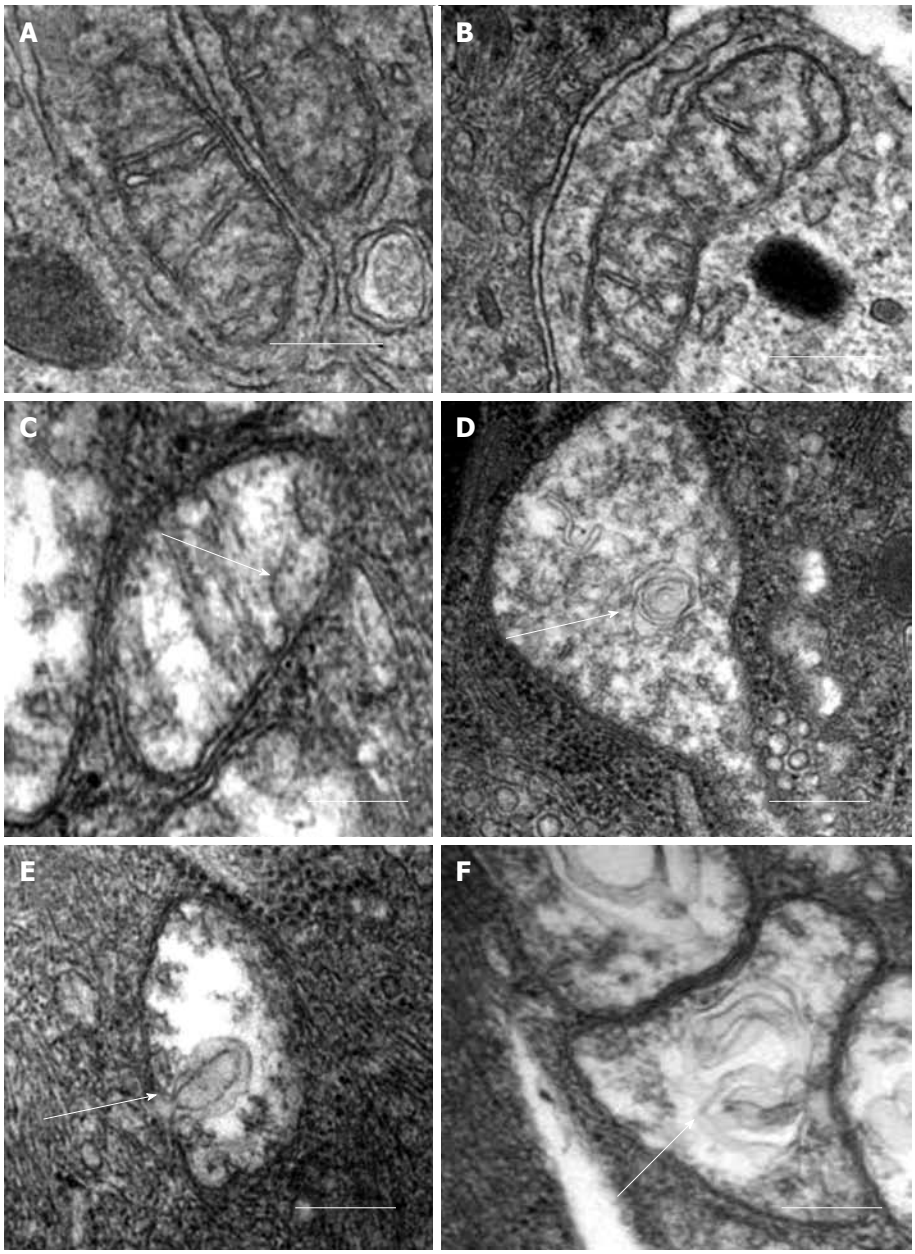

Figure 1 Different ultrastructural appearances of mitochondria in the arterial intima. A, B: "Intact" appearances of mitochondria with well-defined cristae and well-preserved surrounding membranes; C-F: Destructive alterations of cristae and the formation of vacuole-like structures (shown by arrows) in zones of edematous matrix of mitochondria. Electron microscopy, scale = 200 nm.

other tissues[69,70]. Indeed, it is reasonable to suppose that cardiac tissue of ischemic patients may be more susceptible to the accumulation of mtDNA damage that, in turn, can be an important cause of additional mitochondrial dysfunction and cardiac function decline. Indeed, these mutations could alter cellular energy capacity, increasing mitochondrial oxidative damage, which additionally can exacerbate the defects of electron transport in cardiac tissue and produce deleterious ROS. The reason that the mtDNA^{4977} deletion is not substantially elevated in arterial wall cells is thought to be the nature of the cells themselves. These cells did not have the energy demands/proliferation rate of cells such as cardiac myocytes, in which tissue the "common deletion" has been historically detected at higher frequency[67].

STRUCTURAL ALTERATIONS OF MITOCHONDRIA IN VASCULAR PATHOLOGY

It is impossible to exclude that mtDNA mutations in vascular diseases might be accompanied by structural changes in the mitochondria. Even though there are a large number of electron-microscopic studies that described structural changes of vascular cells in different vascular diseases[71-74], there is a paucity (if any) of ultrastructural studies devoted solely to examining morphological

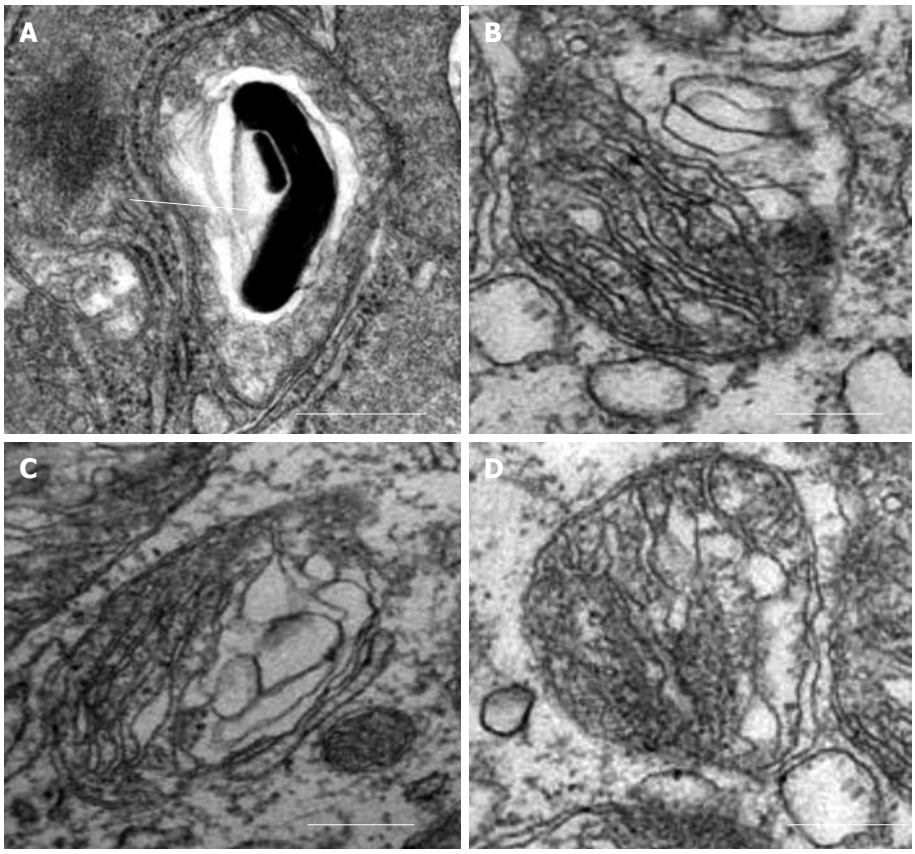

Figure 2 Alterations of mitochondria in intimal cells in atherosclerotic lesions. A: Myelin-like structure within a swollen mitochondrion (shown by arrow); B-D: Destruction of cristae and surrounding membranes of mitochondria. Electron microscopy, scale = 200 nm.

changes of mitochondria in vascular diseases.

Our recent electron microscopic study of human atherosclerotic lesions revealed marked structural alterations of intimal cell mitochondria (unpublished data). The study showed that in atherosclerotic lesions, mitochondria exhibited different appearances of their internal organization (Figures 1 and 2). While in some mitochondria, cristae were distinct and the surrounding membranes were well preserved (Figure 1A and B), others were characterized by disruption of cristae structures (Figure 1A-F). In mitochondria with disrupted cristae, the formation of vacuole-like structures was evident (Figure 1C-F). The zones where the formation of vacuole-like structures occurred were characterized by edema of the mitochondrial matrix (Figure 1C-F). In some intimal cells located in atherosclerotic lesions, the presence of myelin-like structures was observed in edematous mitochondria (Figure 2A). The fact that in the same arterial specimens, only some mitochondria were found to be swollen or showed destructive alteration while other were "intact" indicates that the structural alterations of mitochondria, observed in the present study, were not a reflection of autolysis degeneration which could occur in autopsy material, but rather represented *in situ* morphological heterogeneity of mitochondrial appearances in the arterial intima.

CONCLUSION

Overall, somatic heteroplasmic mtDNA mutations play a non-redundant role in the development of cardiovascular complications of diabetes. The mutation threshold required for phenotypic (pathogenic) expression of a mutation may be significantly reduced by the presence of diabetic hyperglycemia accompanied by uncontrolled oxidative stress, glucotoxicity, ROS production and abnormalities in lipid metabolism. Furthermore, due to the phenomenon of clonal proliferation of SMCs in the atherosclerotic lesion[75], mtDNA mutation whose heteroplasmy exceeds a threshold level may accumulate in the arterial wall and further contribute to mitochondrial dysfunction in the atheroma. To date, our knowledge about the role of somatic heteroplasmic mtDNA mutations in atherogenesis and other pathological changes in diabetic vessels is still in its infancy. Actually, each etiological mtDNA mutation has its own heteroplasmy threshold that needs to be measured. Evaluation of the true mutation threshold is seriously hampered by significant heterogeneity in heteroplasmy of a mutation of interest in neighboring tissues. In addition, little is known about the precise mechanism by which mutations potentially involved in vascular abnormalities in diabetes could contribute to the pathogenesis of diabetic vasculopathy. It is

also important to evaluate the functional consequences of each disease-associated mtDNA mutation depending on its heteroplasmy level. Substantial data obtained about the functionality of homoplasmic mtDNA mutations associated with maternally inherited forms of hypertension[76] may be helpful to select an optimal strategy for functional analysis of mutations associated with diabetic vascular complications.

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GUIDELINES FOR CLINICAL PRACTICE

Preventing radiocontrast-induced nephropathy in chronic kidney disease patients undergoing coronary angiography

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Abstract

Radiocontrast-induced nephropathy (RCIN) is an acute and severe complication after coronary angiography, particularly for patients with pre-existing chronic kidney disease (CKD). It has been associated with both short- and long-term adverse outcomes, including the need for renal replacement therapy, increased length of hospital stay, major cardiac adverse events, and mortality. RCIN is generally defined as an increase in serum creatinine concentration of 0.5 mg/dL or 25% above baseline within 48 h after contrast administration. There is no effective therapy once injury has occurred, therefore, prevention is the cornerstone for all patients at risk for acute kidney injury (AKI). There is a small but growing body of evidence that prevention of AKI is associated with a reduction in later adverse outcomes. The optimal strategy for preventing RCIN has not yet been established. This review discusses the principal risk factors for RCIN, evaluates and summarizes the evidence for RCIN prophylaxis, and proposes recommendations for preventing RCIN in CKD patients undergoing coronary angiography.

Key words: Acute kidney injury; Contrast media; Coronary angiography; N-acetylcysteine; Radiocontrast-induced nephropathy

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INTRODUCTION

Over the past decade there has been dramatic growth worldwide in contrast-enhanced imaging services, many involving exposure to iodinated contrast media[1,2]. Acute deterioration in renal function due to contrast media administration is a well-recognized complication after

coronary angiography, particularly for patients with pre-existing chronic kidney disease (CKD)[2-5]. Previous studies have shown that 12%-14% of patients who develop acute renal insufficiency during hospitalization do so after procedures involving radiographic contrast[6,7]. For patients with abnormal baseline renal function, the incidence of progressive deterioration can be as high as 42%[2,8].

Radiocontrast-induced nephropathy (RCIN), also called radiocontrast-induced acute kidney injury (AKI), is associated with increased health resource utilization, prolonged hospital stay, increased in-hospital and long-term mortality, and an acceleration in the rate of progression of CKD[6,9-13]. It has been associated with both short- and long-term adverse outcomes, including the need for renal replacement therapy (RRT), and major cardiac adverse events. Importantly, RCIN is associated with increased short- and long-term mortality[14-16].

RCIN has gained increased attention in the clinical setting, particularly during cardiac intervention, but also in many other radiological procedures in which iodinated contrast media are used. There are at least four factors explaining that the incidence of RCIN is likely to increase in the future[17,18]. First, CKD, which is a principal risk factor for RCIN, is likely to continue to grow in prevalence. Second, diabetes mellitus, which amplifies the risk for RCIN in patients with underlying CKD, is also increasing in prevalence. Third, the world population is aging, and more elderly patients are undergoing contrast-enhanced procedures. Fourth, patients with advanced CKD have been shown to be at risk for nephrogenic systemic fibrosis; a potentially debilitating disorder that is associated with the administration of gadolinium-based contrast agents[17]. As a result, many patients with CKD, who in recent years would have undergone contrast-enhanced magnetic resonance angiography, are now likely to undergo conventional angiography with iodinated contrast, thus, increasing the number of patients at risk for RCIN[18].

RCIN has been defined as the acute deterioration of renal function after parenteral administration of radiocontrast media in the absence of other causes[19]. Unfortunately, the definition of RCIN has not been consistent in the literature, which makes the comparison of data from various studies difficult. It is generally defined as an increase in serum creatinine concentration of 0.5 mg/dL (44 mmol/L) or 25% above baseline within 48 h after contrast administration[20-24]. There is no effective therapy once injury has occurred, therefore, prevention is the cornerstone for all patients at risk for AKI. There is a small but growing body of evidence showing that prevention of AKI is associated with a reduction in adverse outcomes[25]. The optimal strategy for preventing RCIN has not yet been established. This review discusses the principal risk factors for RCIN and current interventions, as well as evidence behind each intervention for preventing RCIN in patients with baseline renal dysfunction undergoing coronary angiography.

RISK FACTORS FOR RCIN

The pathophysiology of RCIN in humans is not clearly established, and is probably multifactorial. It is hypothesized that a combination of ischemia due to vasoconstriction and direct toxicity to the renal tubules mediated *via* reactive oxygen species leads to RCIN[26]. Intra-arterial infusion of contrast medium results in initial vasodilation, followed by vasoconstriction, accompanied by shunting of blood flow from the medulla to the cortex, with a net result of a 20% increase in blood flow to the cortex and a 40% decrease in blood flow to the medulla; the medullary ischemia that ensues is thought to contribute to tubular injury[27]. Direct cytotoxicity to the tubular epithelial cells has been demonstrated, as demonstrated by vacuolization and tubular epithelial cell death. In addition, production of reactive oxygen species and subsequent tubular damage have been demonstrated in several animal studies[27].

Many risk factors have been described for RCIN, among which pre-existing renal disease is the most important. The increasing levels of renal impairment have been associated with escalating levels of risk[28]. Among patients in the Minnesota Registry of Interventional Cardiac Procedures, RCIN was diagnosed in 22% of patients with serum creatinine > 2 mg/dL and in 30% of patients with serum creatinine > 3 mg/dL[16]. Diabetes, increased age, higher dose of contrast agent, route of contrast administration (intra-arterial *vs* intravenous), congestive heart failure (CHF), hypertension, periprocedural shock, baseline anemia, postprocedural drop in hematocrit, use of nephrotoxins, and nonsteroidal anti-inflammatory medications, volume depletion, increased creatine kinase-MB, and need for cardiac surgery after contrast exposure, have been associated with increased risk of RCIN[16,29]. Prior studies have shown that procedural issues such as the amount and type of contrast administered[30-32] could be the additional risk factors. Risk factor scoring (including both baseline comorbidity and procedural factors) has been used to predict the incidence of RCIN, need for RRT, and long-term mortality[33,34]. They have been developed to identify modifiable and nonmodifiable risk factors for RCIN. Mehran *et al*[33] have published a simple risk score of RCIN including both preprocedural and periprocedural risk factors. Mehran's model includes CHF, hypotension, intra-aortic balloon pump, age > 75 years, anemia, diabetes mellitus, contrast volume, and estimated glomerular filtration rate (eGFR)[33]. Brown *et al*[34] have developed a similar model but restricted it to only preprocedural risk factors that would be accessible for clinicians to ascribe risk of RCIN prior to the case. They found preprocedural serum creatinine, CHF, and diabetes accounted for > 75% of the predictive model, whereas other factors accounting for the remainder of the risk model were urgent and emergency priority, preprocedural intra-aortic balloon pump use, age ⩾ 80 years, and female sex[34,35]. Both models have identified potentially modifiable risk factors that include priority of the procedure, baseline renal function, diabetes, and contrast volume[35] (Table 1). The unfavorable prognostic

Table 1 Risk factors for radiocontrast-induced nephropathy

Modifiable risk factors
Higher dose of contrast agent used
Congestive heart failure
Periprocedural shock
Anemia or postprocedural drop in hematocrit
Use of nephrotoxins
Use of nonsteroidal anti-inflammatory medications
Dehydration
Hypertension or blood pressure control
Diabetes mellitus or sugar control
Increased CK-MB
Urgent or emergency priority of the procedure
Need for cardiac surgery after contrast exposure
Preprocedural intra-aortic balloon pump use
Non-modifiable risk factors
Age > 75 yr
Female sex
Baseline renal function

implications of RCIN make preventing the condition of paramount importance, especially in the performing of some targeted interventions focus on the modifiable risk factors to reduce this risk[35,36].

PREVENTION OF RCIN

Although the treatment of established RCIN is limited to supportive care and dialysis, the renal injury resulting from iodinated contrast exposure is potentially preventable[18]. Multiple interventions have been investigated for their capacity to prevent RCIN. The initial steps in reducing the risk of kidney injury are looking for risk factors and reviewing the indications for the administration of contrast medium. Most risk factors can be detected by history taking and physical examination. Factors such as dehydration can be at least partially corrected before exposure to the contrast medium[37]. According to the statement of Weisbord *et al*[18], efforts to find effective preventive interventions for RCIN have focused on four principal strategies: (1)administration of less nephrotoxic contrast agents; (2) provision of pre-emptive RRT to remove contrast from the circulation; (3) utilization of pharmacological agents to counteract the nephrotoxic effects of contrast media; and (4) expansion of the intravascular space and enhanced diuresis with intravenous fluids.

TYPE AND VOLUME OF CONTRAST MEDIA IN RCIN

Volume of contrast media

The correlation between the amount of contrast and risk of RCIN has been reported in several studies[6,12,30,31,33,38,39]. According to McCullough *et al*[6], the risk of RCIN is minimal in patients receiving < 100 mL contrast. In another study in the diabetic population, RCIN developed in approximately every fifth, fourth and second patient who received 200-400, 400-600 and > 600 mL contrast, respectively[38]. In one observational study[31] of 561 patients with ST-elevation myocardial infarction who were undergoing primary angioplasty, higher amounts of contrast volume were associated with higher rates of RCIN and mortality. Kane *et al*[40] have determined in a multivariate analysis that the only predictor of RCIN in patients with pre-existing CKD was volume of contrast administered. They found that very-high-risk patients undergoing coronary arteriography who received 14 ± 4 mL contrast had a 4.4% incidence of RCIN; whereas those receiving 61 ± 12 mL had a 29.8% incidence. Thus, minimizing contrast media amount is the key element in preventing renal function impairment in patients undergoing cardiovascular intervention[36].

Some researchers have studied the relationship between the maximum radiographic contrast dose (MCD), baseline renal function, and risk of RCIN after angiography[8,31,40-42]. The MCD was calculated using the following formula: 5 mL contrast medium/kg body weight (maximum 300 mL) divided by serum creatinine (mg/dL)[41]. This calculated MCD was validated in 115 patients with CKD (creatinine > 1.8 mg/dL) undergoing angiography over a 10-year period[8]. Liu *et al*[41] have used the ratio of contrast media volume/estimated glomerular filtration rate, or V/eGFR to evaluate the RCIN in patients with ST-elevation myocardial infarction who underwent primary PCI. They reported that a V/eGFR ratio ⩾ 2.39 was a significant and independent predictor of RCIN in their series. In another registry of > 16 000 percutaneous coronary interventions (PCIs) by Freeman *et al*[42], the strongest independent predictor of nephropathy requiring dialysis in patients undergoing elective coronary interventions was exceeding the calculated MCD. Patients who received a volume of contrast that exceeded the MCD were six times more likely to develop RCIN. Recently, Marenzi *et al*[31] have defined the contrast ratio as the ratio between the contrast volume administered and the MCD. They have demonstrated that patients who received more than the MCD had a more complicated in-hospital clinical course and a higher RCIN rate than patients administered less contrast volume than the MCD (35% *vs* 6%, $P < 0.001$). Serum creatinine, especially in the elderly and female populations, who have low muscle mass, is an inexact measure of renal function, therefore, it is more accurate, and should be routine, to estimate creatinine clearance by the Cockroft-Gault formula or eGFR calculated using the modification of diet in renal disease equation for adults[31]. According to Laskey *et al*[43], the ratio of the volume of contrast to creatinine clearance (V/CrCl) of > 3.7 is a good predictor of RCIN.

Type of contrast agents

Contrast media are classified by their osmolality: high osmolar contrast media (HOCM), 2000 mOsm/kg; low-osmolar contrast media (LOCM), 600-800 mOsm/kg; and iso-osmolar contrast media (IOCM), 290 mOsm/kg[44]. Over the past 40 years, the osmolality of available contrast media has been gradually decreased to physiological levels. In the 1950s, only HOCM (e.g., diatrizoate)

with osmolality 5-8 times that of plasma were available. In the 1980s, LOCM agents such as iohexol, iopamidol and ioxaglate were introduced with osmolality 2-3 times greater than that of plasma. In the 1990s, iso-osmolar nonionic iodixanol with the same physiological osmolality as blood was developed[45]. The impact of contrast media osmolality on the incidence of RCIN had been assessed in several randomized trials. In a meta-analysis of the relative nephrotoxicity of the HOCM and LOCM reported in 1993, the pooled OR for the incidence of contrast-induced AKI events in 25 trials was 0.61 (95% CI: 0.48-0.77) times that after HOCM, indicating a significant reduction in risk with LOCM compared to HOCM[46]. In a multicenter randomized controlled trial (RCT) of 1196 patients, Rudnick *et al*[47] demonstrated a reduction in the incidence of RCIN (as defined by an increase in serum creatinine > 1 mg/dL at 48-72 h post-procedure) with the use of LOCM iohexol (3%), as compared with HOCM diatrizoate (7%, $P < 0.002$) in patients with pre-existent renal insufficiency, independent of the presence of diabetes mellitus.

More recent studies have focused on the comparative nephrotoxicity of IOCM iodixanol, and various LOCM. Several studies have evaluated whether an IOCM might provide a similar benefit over LOCM agents, but no consensus has emerged. Some randomized trials have suggested a lower incidence of RCIN with iodixanol in high-risk patients[48-52], while some other clinical trials have failed to show a benefit from use of IOCM[53-60]. A recent multicenter trial (ACTIVE trial) even demonstrated favorable results for LOCM (iomeprol) compared to IOCM (iodixanol), and the authors concluded that LOCM appeared to have a protective effect compared to IOCM (0% *vs* 6.9%)[61]. Of particular interest, Wessely *et al*[57] randomized 324 patients with CKD undergoing coronary angiography with PCI to receive either iodixanol or the low osmolar agent iomeprol. The primary endpoint was the peak increase in serum creatinine during hospitalization for PCI. They found contrast-medium-induced nephropathy rates were lower with iodixanol (22.2% *vs* 27.8% for iomeprol), but this difference was not statistically significant ($P = 0.25$). However, subgroup analysis suggested a favorable outcome regarding nephrotoxicity in patients who received higher contrast volumes (> 340 mL) in the iodixanol group compared with the LOCM group ($P = 0.016$).

The disparate results of these previous 14 clinical trials led to a proliferation of systematic reviews and meta-analyses comparing the nephrotoxicity of IOCM iodixanol and various LOCM; five of which have now been published[32,62-66]. Among earlier meta-analyses by McCullough *et al*[62], pooled data from 2727 patients from 16 double-blind, RCTs have indicated that use of the IOCM iodixanol is associated with smaller rises in creatinine and lower rates of RCIN than LOCM (1.4% *vs* 3.5%, $P < 0.001$), especially in patients with CKD or CKD and diabetes mellitus. Solomon has published a systematic review of prospective, randomized, controlled studies of RCIN in 1365 renal impaired patients receiving intra-arterial doses of the IOCM, iodixanol, or other LOCM, and conducted a pooled analysis of the data from those studies to determine whether the osmolality of contrast media was predictive of RCIN incidence. This review[63] found a significant difference in RCIN rates between iopamidol and iohexol (11.3% *vs* 21.6%, $P = 0.0001$), and between iodixanol and iohexol (9.5% *vs* 21.6%, $P < 0.0001$). A multivariate logistic regression model showed that the risk of RCIN was similar with the IOCM iodixanol and the LOCM iopamidol. Heinrich *et al*[64] have found that iodixanol is not associated with a significantly reduced risk of RCIN compared with the LOCM. However, in patients with intra-arterial administration and renal insufficiency, iodixanol is associated with a reduced risk of RCIN compared with iohexol, whereas no significant difference between iodixanol and other LOCM was found. Reed *et al*[32] have compared iodixanol to several LOCM and found no difference in the incidence of RCIN when they compared iodixanol to all LOCM pooled together. However, iodixanol was associated with a lower incidence of RCIN compared with ioxaglate and iohexol, but not when compared with other LOCM. In the most recent meta-analysis, which included 36 trials encompassing 7166 patients, From *et al*[65] compared iodixanol to several LOCMs. They found that iodixanol had no statistically significant reduction in RCIN incidence below that observed with heterogeneous comparator agents ($P = 0.11$). Analysis of patient subgroups has revealed that there was a significant benefit of iodixanol when compared with iohexol alone (OR: 0.25, 95% CI: 0.11-0.55, $P < 0.001$) but not when compared with iopamidol. These results suggest that the LOCM agents cannot be thought of as a class when it comes to renal tolerability, and that the potential benefit ascribed to IOCM has been overestimated based on earlier trials[36]. These studies suggest a lower incidence of RCIN with the use of iodixanol compared with specific low-osmolality agents, namely iohexol and possibly ioxaglate, with no discernible difference when iodixanol is compared with iopamidol. On the basis of these data, guidelines from the American College of Cardiology/American Heart Association recommend the use of IOCM or LOCM other than iohexol and ioxaglate in patients with CKD undergoing angiography[44,67].

In summary, these data support a benefit of IOCM iodixanol compared to specific LOCM agents such as iohexol and ioxaglate among patients with CKD undergoing angiography, but not a benefit for iodixanol compared to other nonionic low osmolar agents. We suggest the use of either an iso-osmolal contrast agent or a low-molecular-weight contrast agent other than iohexol or ioxaglate.

TEMPORARY PROPHYLACTIC RRT

Hemofiltration and hemodialysis

Another important approach for prevention of RCIN is the early initiation of RRT during or after the adminis-

Table 2 Clinical trials comparing prophylactic renal replacement therapy and control group for radiocontrast-induced nephropathy after coronary angiography procedure (baseline chronic kidney disease stage 3)

Ref.	Time from contrast exposure to the start of RRT (modes of RRT and duration)	No. of patients (RRT:control)	Incidence of RCIN results (RR, 95% CI)	Permanent dialysis rate of RCIN	In-hospital mortality of RCIN
Lehnert *et al*[70] (1998) diagnostic procedures	63 ± 6 min (HD 3 h)	30 (15:15)	8/15 *vs* 6/15 (RR = 1.33, 0.61-2.91)	NA	NA
Sterner *et al*[72] (2000) diagnostic procedures	< 3 h (HD 3 h)	32 (15:17)	6/15 *vs* 4/17 (RR = 1.70, 0.59-4.90)	NA	NA
Berger *et al*[71] (2001) diagnostic procedures	106 ± 25 min (HD 2–3 h)	15 (7:8)	3/7 *vs* 1/8 (RR = 3.43, 0.45-25.93)	NA	NA
Vogt *et al*[73] (2001) diagnostic procedures	2 h (HD 3 h)	113 (55:58)	24/55 *vs* 20/58 (RR = 1.27, 0.80-2.01)	3/55 *vs* 2/58 (RR = 1.58, 0.27-9.11)	1/55 *vs* 1/58 (RR = 1.06, 0.06-17.30)
Frank *et al*[74] (2003) diagnostic procedures	0 (HD 4 h)	17 (7:10)	NA	2/7 *vs* 2/10 (RR = 1.43, 0.26-7.86)	NA
Reinecke *et al*[78] (2007) diagnostic procedures	< 20 min (HD 4 h)	273 (135:139)	22/135 *vs* 10/138 (RR = 2.28, 1.12-4.64)	2/135 *vs* 1/137 (RR = 2.03, 0.19-22.12)	3/135 *vs* 3 137 (RR =1.02, 0.20-5.12)

RRT: Renal replacement therapy; HD: Hemodialysis; CVVH: Continuous venovenous hemofiltration; RCIN: Radiocontrast-induced nephropathy; CKD: Chronic kidney disease; RR: Relative risk; 95% CI: 95% confidence interval; NA: Not assessed.

tration of contrast. The use of RRT to prevent RCIN is predicated on the premise that rapid removal of iodinated radiocontrast material from the circulation, limiting the filtered load at the glomeruli, will decrease the risk of renal injury. Although contrast can be effectively eliminated by hemodialysis and hemofiltration[68,69], it is still controversial whether RRT is able to reduce the incidence of RCIN. Several RCTs have investigated this issue[69-79], but the results have been inconsistent.

In an effort to reconcile the disparate clinical trial findings, systematic reviews and meta-analyses have been performed to analyze the collective results of relevant studies[80,81]. Cruz *et al*[80] conducted a meta-analysis of blood purification therapies for the prevention of RCIN. Considering data from eight clinical trials, six of which assessed hemodialysis and two of which assessed continuous RRT, the authors found that RRT did not reduce the incidence of RCIN compared with routine preventive care. Moreover, there was considerable inter-trial heterogeneity. In sensitivity analyses that included only those studies of hemodialysis, inter-trial heterogeneity was not statistically significant, yet there was a trend toward greater risk for RCIN with hemodialysis compared with standard preventive care[80].

In a recently published meta-analysis, Song *et al*[81] compared the different modes of RRT in assessing the efficacy of prophylactic RRT on RCIN in 751 patients. They found considerable heterogeneity across trials ($P < 0.00001$). RRT reduced the risk of RCIN by 26% compared with the control group by saline infusion, but statistical significance was not reached (risk ratio, RR: 0.74, 95% CI: 0.35-1.60, $P = 0.45$). Subgroup analysis of modality indicated that hemodialysis was ineffective in reducing the risk of RCIN (RR: 1.21, 95% CI: 0.63-2.32, $P = 0.57$), while continuous RRT decreased the incidence of RCIN (RR: 0.22, 95% CI: 0.07-0.64, $P = 0.006$). They also analyzed the effects in the subgroups of baseline CKD stage 3 and higher. Interestingly, heterogeneity was not found in these subgroups. Patients in the studies of Marenzi *et al*[75,76] and Lee *et al*[77] represented a more severely ill population compared with other trials (CKD stage 4/5 *vs* stage 3). Subgroup analysis according to the CKD stage did not record heterogeneity across trials. When analysis was restricted to studies involving CKD stage 3 patients, they recorded a significant increase in relative risk of hemodialysis (RR: 1.53, $P = 0.01$). This finding indicated that hemodialysis was ineffective, or even harmful for prevention of RCIN in CKD stage 3 populations. However, analysis of trials with patients involving CKD stage 4/5 revealed an overwhelming favorable effect of RRT over standard treatment in reducing the incidence of RCIN (RR: 0.19, $P < 0.001$)[80]. Clinical trials comparing prophylactic RRT and control group for RCIN after coronary angiography procedure (baseline CKD stage 3) are shown in Table 2. Clinical trials comparing prophylactic RRT and control group for RCIN after coronary angiography procedure (baseline CKD stage > 3) are shown in Table 3.

In summary, considering the greater cost and risk of RRT, temporary prophylactic hemodialysis or continuous RRT are not indicated for the prevention of contrast nephropathy in patients with stage 3 CKD. Although more data are needed in CKD, we consider the prophylactic use of hemodialysis in patients with stage 4/5 CKD when the functioning access is already available.

PHARMACOLOGICAL INTERVENTIONS

The mechanisms of pharmacological prophylaxis for CIN include antioxidant strategy, inhibition of renal vasoconstriction, and combination of these two effects. Currently, there are no approved pharmacological agents for the prevention of RCIN. Trials of pharmacological interventions, including furosemide, dopamine, fenoldopam, calcium channel blockers, and mannitol, have failed to demonstrate significant benefit for the prevention

Table 3 Clinical trials comparing prophylactic renal replacement therapy and control group for radiocontrast-induced nephropathy after coronary angiography procedure (Baseline chronic kidney disease stage 4-5)

Ref.	Time from contrast exposure to the start of RRT (modes of RRT and duration)	CKD stage, No. of patients (RRT: control)	Incidence of RCIN results (RR, 95% CI)	Permanent dialysis rate of RCIN	In-hospital mortality of RCIN
Marenzi *et al*[75] (2003) interventional procedures	0 (CVVH 22-30 h)	Stage 4, 114 (58:56)	4/58 *vs* 32/56 (RR = 0.12, 0.05-0.32)	2/58 *vs* 11/56 (RR = 0.18, 0.04-0.76)	1/58 *vs* 8/56 (RR = 0.11, 0.01-0.87)
Marenzi *et al*[76] (2006) diagnostic and interventional procedures	0 (CVVH 18-36 h)	Stage 4, 92 (62: 30)	9/62 *vs* 12/30 (RR = 0.36, 0.17-0.77)	NA	3/62 *vs* 6/30 (RR = 0.20, 0.05-0.88)
Lee *et al*[77] (2007) diagnostic procedures	81 ± 32 min (HD 4 h)	Stage 5, 82 (42:40)	2/42 *vs* 18/40 (RR = 0.11, 0.03-0.43)	0/42 *vs* 5/40 (RR = 0.09, 0-1.52)	No

RRT: Renal replacement therapy; HD: Hemodialysis; CVVH: Continuous venovenous hemofiltration; RCIN: Radiocontrast-induced nephropathy; CKD: Chronic kidney disease; RR: Relative risk; 95% CI: 95% confidence interval; NA: Not assessed.

Table 4 Clinical trials showing benefit of oral N-acetylcysteine for radiocontrast-induced nephropathy after angiography

Ref.	NAC dosing regimen (cumulated NAC dose)	No. of patients (NAC:control)	Hydration protocol	Contrast media type	Results
Shyu *et al*[88] (2002) coronary angiography	400 mg po *bid* before and after the procedure (1.6 g)	121 (60:61)	0.45% saline for 12 h pre- and 12 h postprocedure	LOCM iopamidol	3.3% *vs* 24.6% ($P < 0.001$)
Diaz-Sandoval[89] (2002) coronary angiography	600 mg po *bid* × 2, 1 dose before and 3 dose after the procedure (2.4 g)	54 (25:29)	0.45% saline for 2-12 h pre-and 12 h postprocedure	LOCM ioxilan	8.0% *vs* 45% ($P = 0.005$)
Kay *et al*[86] (2003) coronary angiography	600 mg po *bid* × 2, before and after the procedure (2.4 g)	200 (102:98)	0.9% saline for 12 h pre- and 6 h postprocedure;	LOCM iopamidol	3.9% *vs* 12.2% ($P = 0.03$)
MacNeill *et al*[90] (2003) coronary angiography	600 mg twice daily × 5 doses (3 g)	43 (21:22)	0.45% saline at a rate of 1 ml/kg per hour for 12 h for in-patients and 2 mL/kg per hour for 4 h for daycare patient	LOCM iopromide	5% *vs* 32% ($P = 0.046$)
Efrati *et al*[91] (2003) coronary angiography.	1000 mg po *bid* × 2, before and after the procedure (4 g)	49 (24:25)	0.45% saline hydration 1 mL/kg per hour for 12 h before and 12 h after coronary angiography	LOCM iopromide	0% *vs* 8%
Miner *et al*[92] (2004) coronary angiography	2000 mg po either 2 or 3 (4 g or 6 g)	180 (95:85)	0.45% intravenous saline	LOCM iohexol	9.6 % *vs* 22.2% ($P = 0.04$)
Briguori *et al*[87] (2004) cardiac/peripheral angiography	standard-dose 600 mg *bid* × 2 (2.4 g)	224 (110:114)	0.45% saline hydration 1 mL/kg per hour for 12 h before and 12 h after angiography	LOCM iobitridol	11.0% *vs* 3.5% ($P = 0.038$)

NAC: N-acetylcysteine; LOCM: Low-osmolar contrast media.

of RCIN and in some cases have been associated with harm[82-84]. Findings on the benefit of N-acetylcysteine (NAC), ascorbic acid (vitamin C), and statins are discussed below.

NAC for RCIN prevention

The rationale for the use of NAC for the prevention of RCIN relates to its capacity to scavenge reactive oxygen species, reduce the depletion of glutathione, and stimulate the production of vasodilatory mediators, including NO[18]. However, there has been ongoing debate over whether NAC is effective in preventing RCIN[18,29,36]. NAC is a potent antioxidant that scavenges a wide variety of oxygen-derived free radicals, and it may be capable of preventing RCIN by improving renal hemodynamics and by diminishing direct oxidative tissue damage.

Oral NAC treatment

The value of NAC for RCIN prevention has been the focus of many studies. The first study by Tepel *et al*[85] reported in 83 patients with CKD (serum creatinine > 1.2 mg/dL) undergoing applied computed tomography scanning with small amounts (75 mL) of LOCM. Administration of oral NAC at 600 mg twice daily on the day before and the day of the procedure (total dose: 2.4 g), in addition to an infusion of hypotonic saline, reduced the incidence of RCIN 10-fold[85]. Since the first publication of this initial study, many trials evaluating NAC for the prevention of RCIN have been performed and published in the literature but yielded highly conflicting results[85-100]. The clinical trials showing benefit of oral NAC for RCIN after angiography are shown in Table 4. Briguori *et al*[87] have concluded that the use of a double dose of NAC seems to be more protective in preventing contrast-induced renal dysfunction, especially in patients with high volumes of contrast medium. Similarly, in Marenzi's study[93], a 2.6-fold lower incidence of RCIN was shown in patients with ST-elevation acute myocardial infarction who were treated with isotonic saline and 1.2 g IV bolus of NAC, followed by 1.2 g oral NAC after emergency coronary

Table 5 Clinical trials comparing IV N-acetylcysteine and control after angiography procedure

Ref.	NAC dosing regimen (cumulated NAC dose)	No. of patients (NAC:hydration)	Hydration protocol	Contrast media type (mean dose)	Results
Baker *et al*[103] (2003) coronary angiography	150 mg/kg over 30 min before and 50 mg/kg over 4 h after (200 mg/kg)	41:39	0.9% NaCl 1 mL/kg per hour for 12 h pre- and post-procedure	IOCM iodixanol (253 mL)	5% *vs* 21% (RR = 0.28, *P* = 0.045)
Kefer *et al*[105] (2003) coronary angiography	1200 mg 12 h before 1200 mg immediately after the procedure (2.4 g)	53:51	0.9% NaCl 200 mL 12 h pre- and D5W 20 mL/h for 12 h pre and post-procedure	LOCM iopromide/ iohexol (199 mL)	3.8% *vs* 5.9 % (*P* = 0.98)
Rashid *et al*[107] (2004) peripheral angiography	2 doses of 1000 mg at 6-12 h before and after the procedure (2 g)	46:48	2 doses of 0.9% NaCl 500 mL over 4-6 h at 6-12 h before and after the procedure	LOCM iohexol (143 mL)	pts. CrCl < 70 mL/min 7.7% *vs* 8.8% (*P* = 1.0)
Webb *et al*[109] (2004) coronary angiography	500 mg in D5W/0.9% NaCl 50 mL for 15 min as a bolus within 1 h before the procedure (500 mg)	242:245	D5W/0.9% NaCl 50 mL as a bolus within 1 h before the procedure and 200 mL 0.9% NaCl	LOCM ioversol (136 mL)	23.3% *vs* 20.7% (*P* = 0.51)
Kotlyar *et al*[110] (2005) cardiac or peripheral angiography	Gr 1: 300 mg × 2 (600 mg) Gr 2: 600 mg × 2 (1.2 g)	41:19	0.9% NaCl 1 mL/kg per hour	LOCM iopromide	0% *vs* 0 %
Carbonell *et al*[104] (2007) coronary angiography	600 mg twice daily (2.4 g)	107:109	0.45% intravenous saline	LOCM iopromide (193 mL)	10.3% *vs* 10.1% (*P* = 0.5)
Koc *et al*[102] (2010) coronary angiography and/or PCI	600 mg twice daily before and on the day of the coronary procedure (total = 2.4 g)	80:80[1]:60[2]	0.9% saline	LOCM iohexol (138 ± 47 mL)	2.5% *vs* 16.3% *vs* 10.0% (*P* = 0.012)

[1]High-dose hydration group: IV 0.9% saline 1 mL/kg per hour before, on and after the day of coronary procedure (5334 ± 783 mL); [2]Standard hydration group: IV 0.9% saline 1 mL/kg per hour for 12 h (1893 ± 270 mL). NAC: N-acetylcysteine; RCIN: Radiocontrast induced nephropathy; RR: Relative risk; CrCl: Creatinine clearance; NaCl: Sodium chloride; D5W: 5% dextrose; IOCM: Iso-osmolar contrast media; LOCM: Low-osmolar contrast media; PCI: Percutaneous coronary intervention.

intervention compared with patients receiving 600 mg IV bolus of NAC before and 600 mg oral NAC after procedure. In contrast, the renoprotective effect of NAC was not supported by some other studies of orally administered NAC[94-100].

IV NAC treatment

NAC for RCIN prevention is usually started the day before the procedure requiring contrast agent, thus, it is not possible in situations requiring urgent catheterization[101]. Therefore, IV NAC treatment is suggested as a possible alternative in situations where oral NAC is unable to be given in advance. Another reason is the controversial data obtained from orally administered NAC[102]. As in the studies with oral NAC, the results with IV NAC have also been inconsistent[102-110]. The clinical trials comparing IV NAC and control groups for RCIN after angiography are shown in Table 5.

Systemic reviews and meta-analyses of the efficacy of NAC

A variety of factors may contribute to these inconsistencies of efficacy of NAC to prevent contrast-induced AKI. These may include the definition of contrast-induced acute renal failure, baseline risk for acute renal failure (e.g., severity of renal dysfunction, heart failure, and proportion with diabetes), NAC dose and route of administration (e.g., oral or IV), IV hydration protocols, amount and type of contrast given, and type of procedure performed[21,111,112].

The disparate results of these clinical trials have led to a proliferation of systematic reviews and meta-analyses comparing the overall prophylactic efficacy of NAC. To date, at least nine meta-analysis of NAC have shown beneficial treatment effects in reducing RCIN[113-121]. However, six meta-analyses were inconclusive[122-127]. In the largest meta-analysis that included 41 studies and encompassed 3393 patients, Kelly *et al*[118] found that oral or IV NAC significantly lowered the risk for RCIN by 38% when compared with hydration controls with saline alone (RR: 0.62, 95% CI: 0.44-0.88). Trivedi *et al*[121] conducted a meta-analysis of 16 trials that utilized high-dose NAC, defined as a daily dose > 1.2 g or one dose of > 600 mg within 4 h of contrast administration with a sample size of 1677 patients. Their results suggested that high-dose NAC was associated with a lower risk of RCIN compared with controls.

In summary, clinical data regarding the efficacy with NAC for RCIN prevention remains debatable. However, considering the very low toxicity and cost of this drug we recommend the use of oral NAC at a dose of 1.2 g twice daily on the day before and day of the procedure to patients at risk for contrast nephropathy.

Ascorbic acid for RCIN prevention

The rationale for the use of vitamin C for the prevention of RCIN relates to its antioxidant property; it has been shown to ameliorate renal damage in experimental post-ischemic stress, cisplatin, and aminoglycosides injury[128,129].

Spargias *et al*[130] conducted a randomized, double-blind, placebo-controlled trial of ascorbic acid in 231 patients with serum creatine > 1.2 mg/dL who underwent coronary angiography and/or intervention. Ascorbic

acid, 3 g at least 2 h before the procedure and 2 g in the night and the morning after the procedure, or placebo was administered orally. RCIN occurred in 11 of the 118 patients (9%) in the ascorbic acid group and in 23 of the 113 patients (20%) in the placebo group (OR: 0.38, P = 0.02). However, in another study by Boscheri *et al*[131], 143 consecutive patients with CKD (serum creatinine > 120 μmol/L) referred for coronary angiography intervention were randomly assigned to receive 1 g ascorbic acid or placebo in adjunct to saline hydration before and after angiography. They found there was no significant difference between the two groups (vitamin C 6.8%, placebo 4.3%, $P < 0.05$). No patient required dialysis. The authors concluded the prophylactic use of ascorbic acid in patients with renal dysfunction exposed to contrast dye is not justified. In the most recent randomized, double blinded, placebo-controlled, single-center study by Brueck *et al*[132], the prophylactic administration of the antioxidants NAC or ascorbic acid, along with prehydration, was not associated with a significantly reduced risk of RCIN compared with placebo in patients with chronic renal insufficiency. Thus, the role of ascorbic acid for RCIN prevention remains unclear.

Statins for RCIN prevention

The rationale for the use of statins for the prevention of RCIN relates to its antioxidative and anti-inflammatory properties. Given the potential role of oxidative stress in the pathophysiology of RCIN, statins might reduce contrast media nephrotoxicity by removing free radicals[133-135].

The possibility that statins might be beneficial in reducing the incidence of contrast-induced acute renal failure has been examined in several observational studies[136-138] and RCTs[139-142]. The earliest study by Attallah *et al*[130] reviewed a database of 1002 patients with renal insufficiency undergoing coronary angiography. Incidence of RCIN in patients receiving simvastatin or atorvastatin 24-72 h before catheterization was significantly lower than in those not receiving it. Khanal *et al*[137] similarly reported a significantly lower incidence of RCIN, based on a large database review of 29 409 patients undergoing emergency and non-emergency PCI, among patients receiving statins. Patti *et al*[138] prospectively evaluated 434 patients undergoing PCI to determine statin benefit in prevention of RCIN and long-term outcomes over 4 years. Statin-pretreated patients had a significantly lower incidence of RCIN and improved long-term outcomes including a significant decrease in cardiac death at 4 years. However, in the first prospective, randomized, double-blind, controlled study (PROMISS trial) to evaluate the use of a statin for RCIN prevention, short-term simvastatin pretreatment at high dose did not prevent renal function deterioration after administration of contrast medium in patients with baseline renal insufficiency undergoing coronary angiography[139]. Zhang *et al*[143] performed a systematic review and meta-analysis of published human cohort studies and RCTs to determine whether the administration of statins is protective against RCIN and to assess the magnitude of their effect on RCIN. In this most recently published systemic review, the investigators performed qualitative analysis of the cohort studies and quantitative analysis of the RCTs to estimate the pooled RRs for preventive effect of statins. Among six cohort studies, four showed chronic statin pretreatment had a preventive effect against RCIN. From six RCTs, 1194 patients were included in the meta-analysis. Under the fixed-effects model, an insignificant protective trend toward decreased incidence of RCIN with periprocedural short-term high-dose statin treatment was seen (RR: 0.70, 95% CI: 0.48-1.02). Current data are not conclusive as to whether statins are protective for RCIN due to the inherent limitations of the included studies[144]. In the future, large well-designed studies are needed to address the effect of this drug and its longer-term clinical outcomes.

Periprocedural hydration for preventing RCIN

The rationale for the prevention of RCIN by periprocedural hydration is through blocking its two complementary pathophysiological processes[144]. First, expansion of the intravascular space is thought to blunt the vasoconstrictive effect of contrast on the renal medulla. Second, intravascular fluids are believed to attenuate the direct toxic effect of contrast agents on tubular epithelial cells. The optimal hydration solution to prevent contrast nephropathy is unclear.

The optimal method and composition of the fluid administered remains to be established. To date, there are four types of periprocedural hydration: oral fluids, IV 0.45% saline, IV normal saline, and IV sodium bicarbonate. The positive effect of adequate periprocedural hydration in reducing rates of RCIN was first established in a randomized study by Solomon *et al*[83] in 1994. In that study, 78 patients with stable chronic renal failure (mean serum creatinine concentration 2.1 mg/dL) about to undergo coronary angiography were randomized to one of three regimens: (1) 0.45% (half-isotonic) saline at a rate of 1 mL/kg per hour for 12 h before and 12 h after the angiogram; (2) 0.45% saline plus 25 g of mannitol infused intravenously during the 1 h before the procedure; and (3) 0.45% saline plus 80 mg furosemide infused intravenously during the 30 min before angiography. The incidence of acute renal failure (defined as an increase in serum creatinine of at least 0.5 mg/dL) was lowest in the group treated with saline alone. However, this trial did not include a control group of patients who did not receive IV fluid. In another randomized study by Trivedi *et al*[145] who demonstrated a significantly lower incidence of RCIN in patients undergoing non-emergency coronary angiography who received IV normal saline (1 mL/kg per hour for 24 h starting 12 h before contrast exposure) compared with a protocol of unrestricted oral fluids (3.7% *vs* 34.6%, $P < 0.005$). Trivedi's study showed IV normal saline was better than unrestricted oral fluids. The randomized comparison of two hydration regimens in a total of 1620 patients undergoing PCI in a study by Mueller *et al*[146] showed the superiority of isotonic *vs*

Table 6 Clinical trials showing benefit of IV bicarbonate over saline to prevent radiocontrast-induced nephropathy after angiography

Ref.	Inclusion criteria	No. of patients	Hydration protocol	Contrast media type	Results: RCIN in bicarbonate group *vs* saline group	Dialysis and death rate
Merten *et al*[149] (2004) CT/coronary angiography	SCr ⩾ 1.1 mg/dL	119	0.9% NaCl 1 mL/kg per hour for 12 h pre- and post-procedure	Iopamidol	1.7% *vs* 13.6% (P = 0.02)	Dialysis rate 0%
Ozcan *et al*[152] (2007) coronary angiography/PCI	SCr > 1.2 mg/dL	264	0.9% NaCl 200 mL 12 h pre- and D5W 20 mL/h for 12 h pre and post-procedure	Ioxaglate	4.5% *vs* 13.6% (P = 0.036)	Dialysis rate 1%
Briguori *et al*[150] (2007) coronary/peripheral angiography	SCr ⩾ 2.0 mg/dL or eGFR < 40 mL/min per 1.73 m^2	326	0.9% NaCl 500 mL over 4-6 h at 6-12 h before and after the procedure	Iodixanol	1.9% *vs* 9.9% (P = 0.019)	Dialysis rate 1%
Masuda *et al*[151] (2007) emergency coronary angiography/PCI	SCr ⩾ 1.1 mg/dL or eGFR < 60 mL/min	59	D5W/0.9% NaCl 50 mL as a bolus within 1 h before the procedure and 200 mL 0.9% NaCl	Iopamidol	6.7% *vs* 34.5% (P = 0.01)	Dialysis rate 7%; death rate 3%
Recio-Mayoral *et al*[108] (2007) emergency PCI	None	111	Sodium bicarbonate 5 mL/kg per hour 1 h before the procedure and 1.5 mL/kg per hour for 12 h after the procedure	Iomeprol	1.8% *vs* 21.8% (P < 0.001)	Dialysis rate 4%; death rate 4.5%
Pakfetrat *et al*[153] (2009) coronary angiography/PCI	SCr > 1.2 mg/dL	192	Bicarbonate in dextrose infusion, normal saline infusion alone or combined with oral acetazolamide before procedure	Iodixanol	4.2% *vs* 12.5% (P < 0.001)	NA
Tamura *et al*[154] (2009) elective coronary angiography	SCr > 1.1 to < 2.0 mg/dL) undergoing an elective coronary	144	Single-bolus intravenous administration of sodium bicarbonate (20 mEq) immediately before contrast exposure	Iopamidol	10.3% *vs* 10.1% (P = 0.5)	NA
Ueda *et al*[155] (2011) emergent coronary procedures	SCr > 1.2 mg/dL	59	A bolus intravenous injection of 154 mEq/L of sodium bicarbonate or saline at the dose of 0.5 mL/kg, before CM, followed by infusion of 154 mEq/L sodium bicarbonate at 1 mL/kg per hour for 6 h in both groups	Iopamidol	3.3% *vs* 27.6% (P = 0.01)	NA

RCIN: Radiocontrast induced nephropathy; NaCl: Sodium chloride; D5W: 5% dextrose; PCI: Percutaneous coronary intervention; NA: Not assessed.

half-isotonic saline in reducing RCIN (0.7% *vs* 2%, respectively). Mueller's study showed the effect of tonicity of IV fluids on the development of RCIN. On the basis of this study, it has generally been accepted that isotonic saline is superior to hypotonic saline for the prevention of RCIN.

Sodium bicarbonate for RCIN prevention

One major underlying hypothesis for application of sodium bicarbonate is that the alkalinization of tubular fluid diminishes the production of free oxygen radicals and protects the kidney from oxidant injury[39,147]. Pretreatment with sodium bicarbonate is more protective than sodium chloride in animal models of acute ischemic renal failure[148]. Based on the above theory, the first study of sodium bicarbonate for RCIN prevention by Merten *et al*[149] was done in 2004. This study involved 119 patients with stable serum creatinine levels (⩾ 1.1 mg/dL) scheduled for contrast administration (coronary angiography, computed tomography, or radiographic procedures) and randomized to receive 3 mL/kg per hour 5% dextrose with 154 mEq/L sodium chloride or 5% dextrose with 154 mEq/L bicarbonate for 1 h before contrast administration, followed by an infusion at 1 mL/kg per hour for 6 h after contrast administration. The incidence of RCIN was 1.7% in patients receiving bicarbonate, compared with 13.6% (P = 0.02) in patients receiving saline[149].

Since the first publication of this initial study by Merten *et al*[149], many trials evaluating IV sodium bicarbonate for the prevention of RCIN have been performed and published in the literature, but yielded highly conflicting results[53,150-158]. Over the past 8 years, at least 12 clinical trials comparing the development of RCIN following the administration of either isotonic bicarbonate or isotonic saline have been published in the peer-reviewed literature; eight demonstrating a lower incidence of RCIN with bicarbonate administration[108,149-155], and four showing no significant benefit[53,156-158]. The clinical trials showing benefit of bicarbonate over saline for RCIN are shown in Table 6. In the most recently published study by Ueda *et al*[155], 59 patients with mild CKD were scheduled at admission to undergo an emergency coronary procedure. The patients were randomized to receive a bolus IV injection of 154 mEq/L sodium bicarbonate (n = 30) or sodium chloride (n = 29) at a dose of 0.5 mL/kg, before contrast administration, followed by infusion of 154 mEq/L sodium bicarbonate at 1 mL/kg per hour for 6 h in both groups. In the sodium bicarbonate group, the serum creatinine concentration remained unchanged within 2 d of contrast administration (from 1.32 ± 0.46 to 1.38 ± 0.60 mg/dL, P = 0.33). In contrast, it increased in the sodium chloride group (1.51 ± 0.59 to 1.91 ± 1.19 mg/dL, P = 0.006). The incidence of RCIN was significantly lower in the sodium bicarbonate group than in the sodium chloride group (3.3% *vs* 27.6%, P = 0.01).

In contrast to the above findings, several recently published studies have shown no significant benefit of isotonic bicarbonate over saline for lowering incidence

Table 7 Meta-analysis comparing the effectiveness of bicarbonate and saline to prevent radiocontrast-induced nephropathy

Ref.	Year of publication	No. of patients	No. of trials	Relative risk (95% CI) of RCIN of bicarbonate therapy compared with saline	Study heterogeneity and publication bias
Joannidis *et al*[160]	2008	2043	9	0.45 (0.26-0.79)	Heterogeneity detectable and publication bias was present
Hogan *et al*[161]	2008	1307	7	0.37 (0.18-0.714)	Evidence of heterogeneity
Ho *et al*[162]	2008	573	4	0.22 (0.11-0.44)	Significant heterogeneity
Meier *et al*[163]	2009	2633	17	0.52 (0.34-0.80)	Evidence of heterogeneity and publication bias
Navaneethan *et al*[166]	2009	1854	12	0.46 (0.26-0.82)	Heterogeneity and publication bias were detectable
Kanbay *et al*[165]	2009	2448	17	0.54 (0.36-0.83)	There are study heterogeneity and publication biases
Zoungas *et al*[168]	2009	3563	23	0.62 (0.45-0.86)	Evidence of heterogeneity and publication bias was present
Hoste *et al*[167]	2010	3055	18	0.66 (0.45-0.95)	Evidence of heterogeneity and publication bias was present
Trivedi *et al*[171]	2010	1090	10	0.57 (0.38-0.85)	No evidence of heterogeneity and no publication bias
Kunadian *et al*[170]	2011	1734	7	0.33 (0.16-0.69)	Heterogeneity and publication bias were detectable
Brown *et al*[164]	2009	1994	10	0.65 (0.40-1.05)	Significant heterogeneity
Brar *et al*[169]	2009	2290 (large trials, 1145; small trials, 1145)	14 (large trials 3; small trials 11)	large trials: 0.85 (0.63-1.16); small trials: 0.50 (0.27-0.93)	Evidence of publication bias; heterogeneity accounted for by trial size

RCIN: Radiocontrast-induced nephropathy; 95% CI: 95% confidence interval.

of RCIN[53,156-158]. In the largest randomized trial to date by Maioli *et al*[157], comparing isotonic saline (1 mL/kg per hour, started 12 h before and extended 12 h after the procedure) against isotonic sodium bicarbonate in dextrose (3 mL/kg per hour for 1 h before, followed by 1 mL/kg per hour for 6 h after contrast administration) given in addition to NAC in 502 CKD patients (eGFR < 60 mL/min) scheduled for non-emergency coronary angiography, there was no superiority of either treatment modality[157]. In addition, in a large retrospective analysis of the general population of patients undergoing coronary angiography, use of sodium bicarbonate alone was associated with an increased risk of contrast nephropathy compared with no treatment; whereas NAC alone or in combination with sodium bicarbonate was not associated with any significant difference in the incidence of contrast nephropathy[159].

Systematic reviews and meta-analyses comparing the effectiveness of bicarbonate and saline

The optimal hydration solution to prevent contrast nephropathy is unclear and the disparate results of these clinical trials, therefore, many systematic reviews and meta-analyses have been performed to analyze these collective results[160-171]. Of the 12 published meta-analyses, most have suggested a significant benefit of using sodium-bicarbonate-based hydration for prophylaxis of RCIN[160-169], although the magnitude of the benefit may have been overestimated by earlier studies. Two meta-analyses have shown no significant benefit[170,171]. Meta-analyses comparing the effectiveness of bicarbonate and saline to prevent RCIN are shown in Table 7.

Hoste *et al*[167] completed a comprehensive meta-analysis including 18 trials with a total of 3055 patients. The aggregate result demonstrated a benefit favoring sodium bicarbonate (RR: 0.66, 95% CI: 0.45-0.95,). This effect was most prominent in coronary procedures and in patients with CKD. In their subgroup analysis of nine published papers and nine unpublished abstracts, they found published papers demonstrated a beneficial effect, while abstracts did not. They also detected significant clinical and statistical heterogeneity between studies.

In another recent meta-analysis of 14 trials, encompassing 2290 patients, Brar *et al*[169] also found significant heterogeneity among the trials (P heterogeneity = 0.02, I^2 = 47.8%), and they found the heterogeneity was largely accounted for by trial size (P = 0.016). Therefore, the authors segregated the trials into two groups. Three trials were categorized as large (n > 1145) and 11 as small (n < 1145). Among the large trials, the incidence of RCIN for sodium bicarbonate and sodium chloride was 10.7 and 12.5%, respectively; the RR and 95% CI was 0.85 and 0.63-1.16, without evidence of heterogeneity (P = 0.89, I^2 = 0%). However, the pooled RR among the 11 small trials was 0.50 (95% CI: 0.27-0.93) with significant between-trial heterogeneity (P = 0.01, I^2 = 56%) and the small trials were more likely to be of lower methodological quality. As a result, the authors concluded there was no evidence of benefit for hydration with sodium bicarbonate compared with sodium chloride for the prevention of RCIN. The benefit of sodium bicarbonate was limited to small trials of lower methodological quality.

In summary, at this time, data on the comparative effectiveness of bicarbonate and saline for the prevention of RCIN are insufficient to warrant a recommendation for the routine use of a specific isotonic IV fluid. However, in the clinical setting when patients requiring emergency coronary procedures, there would not be enough time to administer sufficient IV fluids for hydration. The idea of a single bolus of sodium bicarbonate may be helpful.

CONCLUSION

RCIN is a predictable and perhaps partially preventable complication. Reasonable steps should be taken to mini-

mize risk. Novel diagnostic and therapeutic approaches are needed to manage the ever-increasing numbers of patients with baseline renal dysfunction undergoing coronary angiography. Clinicians should carefully evaluate the risks and benefits of prophylactic measures and apply them to individual patients. Large clinical trials that are based on clinically plausible effect sizes and examine serious, adverse, patient-centered outcomes are needed to define better the clinical utility of pharmaceutical agents for the prevention of this complication. Our current recommendations can be summarized as follows: (1) all patients should be stratified for RCIN risk prior to contrast exposure; (2) temporary withdrawal of the drugs which may affect the renal function; (3) dose of contrast medium should be limited to the minimum volume required to provide adequate clinical information; (4) high-risk patients should receive prophylaxis for modifiable factors; (5) consider using iso-osmolar or a nonionic, LOCM other than iohexol or ioxaglate; (6) unless contraindicated, consider using oral high-dose NAC at 1.2 g *bid* on the day before and the day of contrast exposure; (7) using periprocedural hydration, if no evidence of frank heart failure, either by isotonic saline at a dose of 1 mL/kg per hour for 12 h preceding and 12 h following the administration of contrast medium, or 154 mEq/L bicarbonate at a dose of 3.0 mL/kg for 1 h preceding and 1 mL/kg per hour for 6 h after contrast administration; (8) in an emergency setting, where preparation of the patient with IV hydration is not feasible, consider administration of isotonic sodium bicarbonate with high-dose oral NAC (2.4 g) 1 h before contrast; (9) consider the prophylactic use of hemodialysis in patients with stage 5 CKD, provided that a functioning access is already available; and (10) follow-up the serum creatinine 24-72 h after contrast exposure in high-risk patients.

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REVIEW

Investigation of cardiomyopathy using cardiac magnetic resonance imaging part 2: Rare phenotypes

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Abstract

Cardiac magnetic resonance imaging (CMRI) has emerged as a useful tertiary imaging tool in the investigation of patients suspected of many different types of cardiomyopathies. CMRI images are now of a sufficiently robust quality to enable high spatial and temporal resolution image acquisition. This has led to CMRI becoming an effective non-invasive imaging tool for many cardiomyopathies. In this two-part review we outline the typical sequences used to image cardiomyopathy and present the imaging spectrum of cardiomyopathy. Part Ⅰ focused on the current classification of cardiomyopathy, the basic CMRI sequences used in evaluating cardiomyopathy and the imaging spectrum of common phenotypes. Part Ⅱ illustrates the imaging spectrum of the more rare phenotypes.

Key words: Magnetic resonance imaging; Cardiomyopathies; Diagnosis; Ventricular dysfunction

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INTRODUCTION

A cardiomyopathy is described as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease or congenital heart disease sufficient to cause the observed myocardial abnormality[1]. It is estimated that cardiomyopathy cause over 26 000 deaths each year in the United States and follows coronary heart disease as the commonest cause of sudden death[2].

Cardiac magnetic resonance imaging (CMRI) has emerged as a useful non-invasive imaging modality capable of producing high-resolution images of the heart in any desired image plane and without ionizing radiation. As a result it has become a primary imaging modality for many cardiomyopathies[3,4]. In this two-part review, we outline the utility of CMRI in the investigation of cardiomyopathies. Part Ⅰ focused on the basic sequences used in characterizing the common cardiomyopathies, reviewed the commonest cardiomyopathy classification systems in use and illustrated the imaging spectrum of the common phenotypes. Part Ⅱ focuses on showing the imaging spectrum of the more rare phenotypes.

RARE CARDIOMYOPATHIES CHARACTERIZED BY HYPERTROPHY

Hypertrophic cardiomyopathy (HCM) is characterized by increased ventricular wall thickness or mass in the ab-

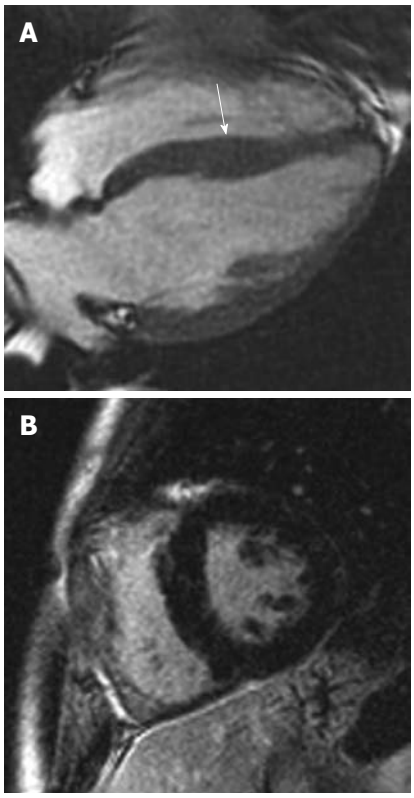

Figure 1 A 19-year-old man with Friedrich's ataxia who presented with sudden onset chest pain. A: Horizontal long-axis SSFP sequence showing circumferential hypertrophy (arrow, 14 mm thickness) of the anterobasal segment of the left ventricular; B: Late-enhanced sequence showing absence of high signal, characteristic of the hypertrophy seen in this disorder.

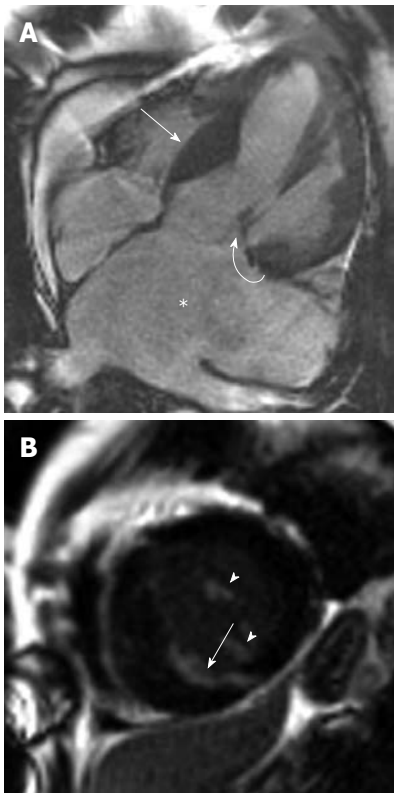

Figure 2 A 46-year-old man with Noonan's syndrome. A: Horizontal long-axis SSFP sequence showing septal hypertrophy (curved arrow) and a severely dilated left atrium secondary to severe mitral regurgitation (asterisk); B: Late-enhanced short axis sequence showing extensive late gadolinium enhancement (LGE) throughout the antero- and infero-septal myocardial segments (arrow). LGE was also noted in the papillary muscles (arrowheads).

sence of a loading condition such as valvular disease or hypertension. Loading conditions can be volume loading (aortic regurgitation) or pressure loading (aortic stenosis and chronic systemic hypertension).

Friedrich's ataxia

Friedrich's ataxia (FA) is the most common inherited ataxia syndrome. Reduced fraxetin synthesis causes an unstable expansion of a GAA trinucleotide repeat. Clinical features include progressive ataxia, dysarthria, sensory neuropathy, lower limb areflexia, extensor plantar response and weakness secondary to degeneration of dorsal columns and pyramidal tracts[5,6]. Glucose intolerance and various skeletal abnormalities may also be seen. Cardiac involvement in FA is commonly encountered and defined by concentric and symmetrical increased ventricular wall thickness and a normal or small left ventricular (LV) cavity. The systolic function is normal[7].

LV mass on CMRI has been shown to positively correlate with both the genotypic and phenotypic severity of the disease[8]. Increased trinucleotide repeats correlates with increasing LV mass[9]. In particular, septal and posterior wall hypertrophy is more severe in patients with more trinucleotide repeats[8,10]. Larger LV mass is seen with severe and early onset disease. Conversely longer disease duration is often associated with a smaller LV mass. Echocardiography has been the traditional primary imaging tool in FA cardiomyopathy. CMRI offers several additional advantages. It provides a more accurate assessment of the presence, extent and location of myocardial hypertrophy than echocardiography (Figure 1)[8]. It provides these parameters with lower interobserver variation. Perfusion and late contrast enhancement abnormalities indicating myocardial fibrosis can be detected with CMRI early in the pathogenesis of FA cardiomyopathy, earlier than the onset of measurable hypertrophy[11].

Noonan syndrome

Noonan syndrome occurs as a sporadic or autosomal dominant mutation with equal sex predominance[12]. Clinical features include congenital heart defects, bleeding diathesis and mental retardation. Phenotypical features include short stature, hypertelorism, down-slanting eyes, epicanthic folds, low-set posterior ears, micrognathia, a webbed neck and chest deformities[13,14]. Valvular disease is the most common cardiac abnormality. Pulmonary valve stenosis is the most common defect, affecting approximately 50% of patients[15]. Thus, it is important to acquire steady-state free precession sequences of the right ventricular outflow tract (RVOT) and pulmonary valve when evaluating patients suspected of cardiac involvement. Asymmetric septal hypertrophy is seen in 20% of patients with Noonan syndrome (Figure 2)[16,17]. Atrial sep-

tal defects occur in approximately 10%, persistent ductus arteriosus in 3% and ventricular septal defects in 5%[12]. A previous case report has described the CMRI appearances in a patient with Noonan syndrome[17]. In that 27-year-old female the presence of septal hypertrophy was detected with CMRI and shunts were excluded. Late gadolinium enhancement (LGE) manifested as patchy increased signal in the anterior, anteroseptal and lateral walls[17]. Echocardiography remains the primary imaging modality in Noonan's cardiomyopathy. In cases where imaging with echocardiography is equivocal or incongruent with other clinical parameters, CMRI can provide imaging confirmation of hypertrophy.

RARE CARDIOMYOPATHIES CHARACTERIZED BY DILATATION

Dilatation of the cardiac chambers with impaired contraction of the ventricles is characteristic of dilated cardiomyopathies.

Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a rare genetic disorder characterized by progressive loss of myocytes with fibro-fatty replacement of right, and more recently described, LV myocardium. Patients may present with ventricular arrhythmias and left bundle branch block, syncope or sudden cardiac death. It may be responsible for up to 5% of sudden deaths in young athletes[18], although it has a higher prevalence in some countries such as Italy (25% of sudden deaths in young athletes)[19]. Because of the subtlety of the phenotype, consensus criteria were developed based on structural, functional, and electrocardiographic (ECG) manifestations[20]. In these criteria, tissue characterization depicted on CMRI such as fatty infiltration has been removed and an increased emphasis placed on right ventricular wall motion, volume and ejection fraction abnormalities.

CMRI assessment of ARVD is now primarily based on functional and volume abnormalities of the right ventricle[20] although many centers still provide tissue characterization imaging of the right ventricle. Morphological abnormalities include intra-myocardial fat deposits, focal wall thinning (< 2 mm), wall hypertrophy (> 6 mm), moderator band hypertrophy and trabeculation disarray. Functional abnormalities include focal or global RV wall hypokinesis (dilatation, focal or global RV dilatation and in severe cases, focal aneurysms). The site of involvement most commonly occurs in the "triangle of dysplasia" found in the inferior sub-tricuspid area, RV apex and RV infundibulum. The major treatment implication in suspected cases of ARVD is implantable defibrillator placement.

Important CMRI sequences in ARVD

CMRI protocols for ARVD focuses particular attention on the right ventricle and RVOT (Figure 3). A thinner slice thickness and slice gap for this protocol (5-6 mm contiguous slices are typical) is recommended. Saturation bands above and below the heart help improve image quality by reducing flow artifacts related to slow-inflowing blood. A small field of view targeted to the right ventricle helps improve the spatial resolution further, at the cost of decreasing signal-to-noise ratio. Myocardial late enhancement has been used to demonstrate scarring of the RV wall[21].

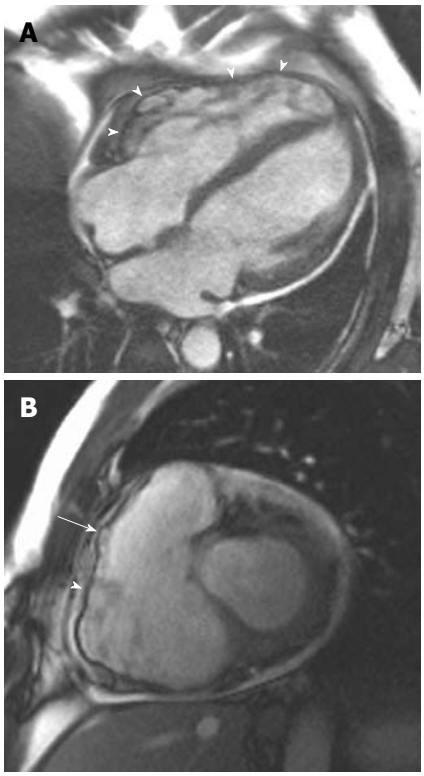

Figure 3 A 38-year-old man of Italian origin presented with palpitations and progressive shortness of breath during exercise. A: Horizontal long-axis SSFP shows a heavily trabeculated right ventricle with thickened trabeculae and increased right ventricular (RV) volume. The RV free wall is very thin, with multiple small aneurysms (arrowheads); B: Short-axis SSFP sequence showing further small aneurysms of the RV free wall. Note again the increased RV volume.

The diagnostic accuracy of CMRI for ARVD carries a high sensitivity but low specificity when compared with traditional Task Force criteria[22]. Modified criteria have been proposed, such that the presence of any minor criterion in a first-degree relative of a proven case of ARVD is regarded as clinical disease expression[20]. When CMRI is assessed using these modified criteria it is frequently abnormal, suggesting a role in depicting initial manifestations of disease[20,23]. It is important to emphasize that the interpretation of CMRI abnormalities should be made in a multidisciplinary approach involving ECG, arrhythmic, morpho-functional, histopathological, and clinical/molecular genetic analysis before making the diagnosis of ARVD[20,24].

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as heart failure occurring in the last month of pregnancy or with-

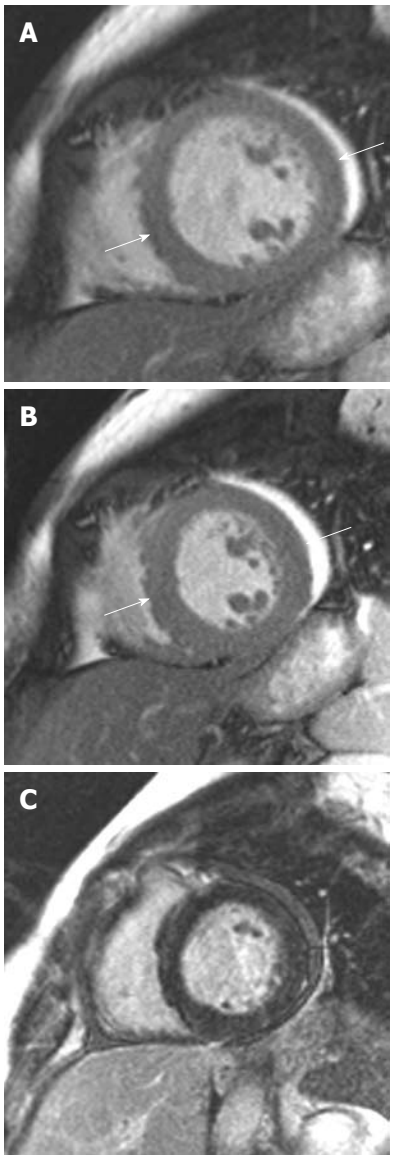

Figure 4 A 34-year-old woman 1 wk post-partum who developed progressive shortness of breath. A: Short-axis SSFP sequence showing dilation of the left ventricle (end-diastolic diameter = 62 mm); B: The systolic phase demonstrating moderate circumferential hypokinesis (left ventricular ejection fraction 45%); C: Late gadolinium enhancement sequence showing an absence of high signal in this case.

in 5 mo of delivery. The etiology of PPCM is multifactorial. Ntusi *et al*[25] and Baruteau *et al*[26,27] divided the etiology of PPCM into inflammatory and non-inflammatory causes. Inflammatory PPCM occurs secondary to viral myocarditis, an abnormal immune response to pregnancy, an abnormal response to hemodynamic stresses of pregnancy, increased myocyte apoptosis and cytokine-mediated myocardial inflammation. Non-inflammatory causes of PPCM include malnutrition, genetic factors, increased prolactin production, abnormal hormone function and increased adrenergic tone.

CMRI appearances: It is no surprise with such a multifactorial etiology that the reported CMRI appearances of PPCM are varied. The most common finding is a dilated left ventricle (Figure 4). Reported appearances post administration of gadolinium are more varied. Marmursztejn *et al*[28] described the CMRI appearances of two patients with PPCM. The first patient had a normal post-gadolinium CMRI and at clinical follow-up regained normal cardiac function. The second patient had several areas of myocardial LGE and had persistent LV dysfunction on clinical follow-up. Mouquet *et al*[29] evaluated eight patients with PPCM with CMRI and no LGE was seen in any patient. Kawano *et al*[30] described a case of PPCM with diffuse epicardial and midwall LGE in the left ventricle on CMRI performed at 2 mo with reduction in the LGE on follow-up CMRI at 10 mo. One explanation for the differing reports may lie in the differing inflammatory *vs* non-inflammatory etiologies for PPCM. Those with a predominantly inflammatory etiology demonstrate LGE in a similar fashion to other viral myocarditis as opposed to non-inflammatory etiologies which are not associated with a T2 hypersignal or LGE[27].

Muscular dystrophy

Duchenne and Becker muscular dystrophies are X-linked genetic mutations affecting the dystrophin gene. Dystrophin is totally absent or dysfunctional in Duchenne muscular dystrophy (DMD) and dystrophin is mildly dysfunctional or reduced in expression in Becker muscular dystrophy (BMD). DMD is associated with a more severe disorder and patients die of respiratory failure, rarely surviving past the third decade. In contrast, BMD is a milder form of dystrophy with patients surviving until the sixth decade; cardiomyopathy is the main cause of death[31]. Another important group of dystrophies that may exhibit cardiomyopathy are the limb girdle muscular dystrophies. The subtypes most commonly associated with cardiac involvement include those associated with a defect in the genes coding for the α (LGMD2D), β (LGMD2E), γ (LGMD2C), or θ (LGMD2F) subunits of the dystrophin associated sarcoglycan complex.

CMRI appearances: The subepicardium of the inferolateral wall is initially affected in BMD. This occurs in the third decade of life and increases in extent with age. There is a progressive loss of contractility and decrease in LV systolic dysfunction secondary to ongoing myocardial damage. Cardiac involvement is not commonly seen in patients under the age of 16 with BMD, but increases to 70% by the age of 40 years[32]. Yilmaz *et al*[33] demonstrated that patients with BMD and reduced LV ejection fraction were older, had heavier hearts and regional wall motion abnormalities. In DMD, almost all patients that survive to > 30 years of age demonstrate cardiomyopathy. LGE has been reported involving the inferolateral free wall, the basal inferior and anterolateral region of the left ventricle (Figure 5)[34,35]. The LGE likely occurs because of myocardial damage resulting from mechanical stress on top of a metabolically and structurally abnormal myocardium, although the precise mechanism remains to be elucidated. Whether the inferolateral wall is particularly vulnerable because of

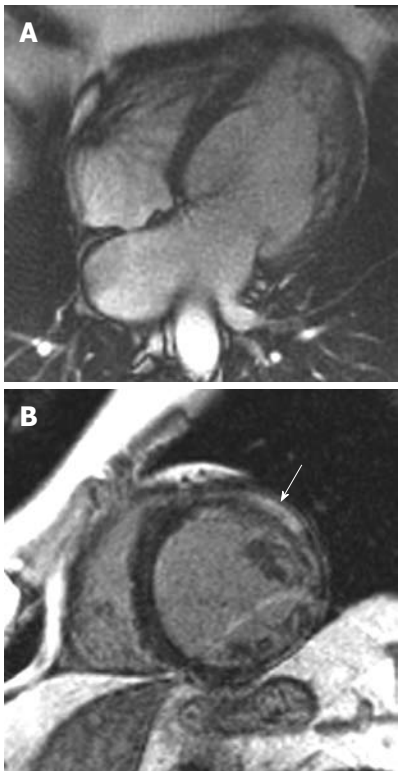

Figure 5 A 46-year-old man with progressive heart failure and Becker's muscular dystrophy. A: Short-axis SSFP sequence showing moderate dilation of the left ventricle; B: Late gadolinium enhancement (LGE) sequence showing extensive transmural LGE throughout the lateral segments (arrow).

regional molecular changes or from exposure to higher mechanical stress is unknown. It is interesting that the LGE pattern is remarkably similar to that of myocarditis, and that enterovirus infection has been shown to produce myocardial damage *via* cleavage of dystrophin[36]. Perhaps this explains the similarity in the LGE pattern between myocarditis and dystrophin-associated cardiomyopathy. Performing CMRI in DMD/BMD is useful because early commencement of standard heart failure therapy can delay the onset and progression of LV systolic dysfunction and possibly even reverse the remodeling process. Furthermore, myocardial fibrosis detected by LGE imaging may be observed in the presence of normal echocardiography[34]. For the limb-girdle muscular dystrophies, several authors have shown LGE in the basal interventricular septum in these cardiomyopathies before the onset of ventricular dilatation and systolic dysfunction[37].

RARE CARDIOMYOPATHIES CHARACTERIZED BY RESTRICTION

Carcinoid heart disease

Carcinoid tumors arise from neuroendocrine tumors and secrete vasoactive substances including 5-hydroxytryptamine, histamine and bradykinin. Clinical symptoms of carcinoid syndrome occur when there is metastatic disease in the liver and symptoms include episodic flushing, diarrhea and bronchospasm. Carcinoid heart disease occurs in two-thirds of patients with carcinoid syndrome[38]. Most cardiac lesions affect the right side of the heart, which is postulated to be due to paraneoplastic effects of the vasoactive substances secreted into the hepatic veins from liver metastases[39].

CMRI appearances: Right heart valvular dysfunction is the most common abnormality and the tricuspid valve is most commonly involved[40]. Right atrial and right ventricular enlargement are present in up to 90% of cases of carcinoid heart disease. One study of 252 patients with carcinoid heart disease demonstrated tricuspid valve involvement in 90%, pulmonary valve in 69%, mitral valve in 29% and aortic valve in 27%. Thirteen out of 15 (87%) patients with left-sided cardiac involvement had a patent foramen ovale. Myocardial metastases were seen in 3.8%[41]. Imaging appearances of carcinoid heart disease are of plaque-like deposits causing fibrous endocardial thickening, with retraction and fixation of the valvular cusps and the subvalvular apparatus (chordae and papillary muscles)[42]. Tricuspid valve regurgitation leads to volume overload, which in turn causes right atrial and RV dilatation. In contrast to the tricuspid valve involvement, pulmonary valve involvement typically causes pulmonary stenosis rather than regurgitation[40].

Post contrast delayed CMRI may also demonstrate myocardial fibrosis or scarring as areas of high signal intensity. Several case reports describe similar appearances of cardiac carcinoid on CMRI with right heart chamber dilatation and fixed retraction of the tricuspid valve leaflets. Post contrast images demonstrated enhancement of the tricuspid septal leaflet, most marked at the annulus[43,44].

Hypereosinophilic syndrome

Idiopathic hypereosinophilic syndrome is a syndrome of unknown cause characterized by peripheral eosinophilia and multiorgan dysfunction. Cardiac involvement is common and is characterized by endomyocardial fibrosis and thrombus formation. Three stages are recognized. Stage one is an acute necrotic stage and is clinically silent. There is thrombus formation in stage two. Stage three is characterized by endomyocardial fibrosis and a restrictive cardiomyopathy[45].

CMRI appearances: There are several case reports documenting the appearances of cardiac involvement in hypereosinophilic syndrome on CMRI. A two- or three-layered appearance post contrast is most commonly described, consisting of a normal appearing epicardium, a hyperintense subendocardium indicating eosinophilic infiltration and frequently a linear hypointense layer of thrombus in the endocardium (Figure 6)[46,47]. Histological evaluation has confirmed the presence of endomyocardial eosinophilic infiltration and areas of myocyte necrosis. Debl *et al*[48] have suggested the potential for CMRI to evaluate response to treatment, with a decrease in the

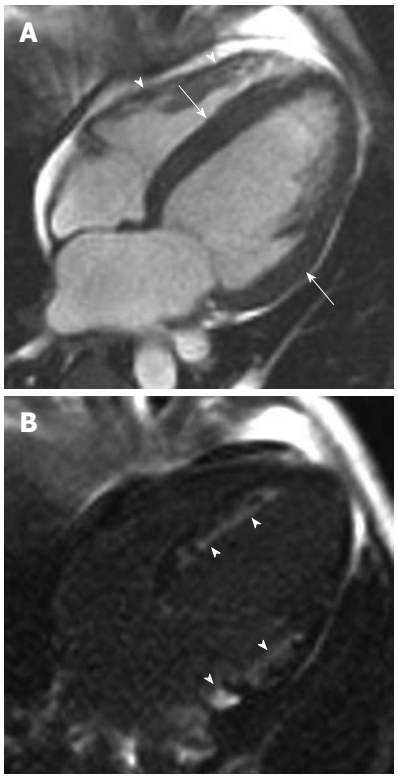

Figure 6 A 38-year-old man presented with progressive shortness of breath. Serum measurements demonstrated hypereosinophilia. A: Horizontal long-axis SSFP sequence showing mild circumferential hypertrophy of the left ventricle (arrows) Note the normal thin right ventricular free wall (arrowheads), a useful differentiating feature from cardiac amyloid; B: Late-enhanced horizontal long-axis sequence showing extensive high signal in the typical subendocardial distribution (arrowheads) of eosinophilic myocardial infiltration. Cardiac amyloid is the principal other cardiomyopathy that mimics this late gadolinium enhancement appearance.

extent of late enhancement occurring with successful steroid therapy. Syed *et al*[46] has also described severe hypertrophy of the LV myocardium and partial obliteration of the LV cavity in systole.

Metastatic disease

Metastatic disease to the heart and pericardium is more common than primary cardiac tumors[49]. Lung carcinoma, lymphoma, breast carcinoma, esophageal carcinoma and melanoma are the most common metastases to the heart[50,51]. Lung carcinoma typically involves the heart through direct invasion, sometimes by transvenous growth through the pulmonary veins. Cardiac metastatic involvement heralds a poor prognosis. "Charcoal heart" is the term peculiar to extensive cardiac melanoma metastases, in which the pathological appearance of the infiltrated myocardium is heavily pigmented.

CMRI appearances: Most cardiac tumors are low signal on T1-weighted sequences and higher signal on T2-weighted sequences (Figure 7)[52]. Typically, metastases enhance post contrast administration. A first pass perfusion sequence may be used to image the enhancement of the tumor with high temporal resolution. If this sequence is used, its duration should be for longer than the typical 30 s used for ischemic cases, as often the metastases take longer to demonstrate perfusion. Another useful sequence to differentiate metastases from a thrombus mass is the late-enhanced sequence in which the inversion time is set to 600 ms. Metastases enhance whilst a thrombus remains black (no signal).

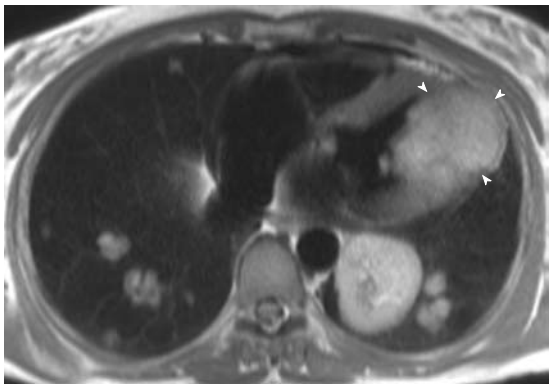

Figure 7 A 56-year-old woman with metastatic sarcoma. Note the diffuse metastatic infiltration of the left ventricle (arrowheads), resulting in restrictive pathophysiology. There are also diffuse pulmonary metastases throughout both lungs.

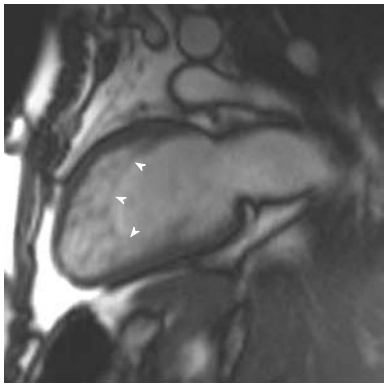

Figure 8 A 23-year-old man with Rubenstein-Taybi syndrome who presented with increasing shortness of breath. Vertical long-axis view demonstrating increased trabeculations at the apical ventricular level fulfilling cardiac magnetic resonance imaging criteria for left ventricular noncompaction.

UNCLASSIFIED CARDIOMYOPATHIES

LV non-compaction (LVNC) and Takotsubo cardiomyopathy (TTC) are unclassified cardiomyopathies.

LV non-compaction

LVNC is a myocardial disorder characterized by prominent, excessive trabeculations and deep intratrabecular recesses (Figure 8). The intratrabecular recesses communicate with the ventricular cavity[53]. It is thought to be due to an arrest in the normal myocardial maturation process. The fetal myocardium has deep recesses between loosely interwoven fibers that communicate with the ventricular cavity. These trabeculations aid oxygen exchange by creat-

ing a larger surface area for diffusion. Once the coronary circulation develops, between the 5th to 8th weeks of life, these trabeculations are no longer needed and the loosely woven fibers undergo compaction[54]. Compaction moves from base to apex, epicardium to endocardium and from the septal to the lateral wall. The severity of LVNC will depend on the timing of the arrest in the myocardial maturation and compaction process. The apex and mid-ventricular lateral segments are more commonly involved in LVNC and this is explained by the compaction process as these areas are last to undergo compaction[55].

The recesses in LVNC are lined by ventricular endothelium that is in continuity with the ventricular cavity. There is focal ischemic necrosis within the trabeculations and endocardial layer, compensatory hypertrophy of the myocardium, interstitial fibrosis and scarring[56,57]. LVNC was originally described in association with other severe congenital abnormalities and can present as fetal hydrops, neonatal heart failure and ventricular fibrillation[54]. In adults, arrhythmias and thromboembolic events are seen more commonly than in pediatric patients. Cardiac failure is the most common finding in LVNC[53,58]. LVNC may also be seen in association with other congenital cardiac defects. The commonest association is ventricular septal defect, though subaortic obstruction, bicuspid aortic valve, coarctation of the aorta, Ebstein's anomaly, tetralogy of Fallot, pulmonary stenosis and pulmonary atresia are also seen in association with LVNC[59,60].

CMRI appearances: Three basic characteristics of LVNC on CMRI are described; trabeculations of the ventricular wall with deep recesses of the ventricular myocardium, extensive spongiform transformation of the LV myocardium and a dysplastic myocardium that is thinned with excessive trabeculations[61].

The end-diastolic non-compacted to compacted ratio (NC/C) is higher in patients with LVNC. A compaction ratio is calculated by measuring the thickness (in millimeters) of the non-compacted to compacted myocardium. The NC/C parameter separates out pathological non-compaction from less severe forms of non-compaction[62]. This measurement is typically obtained on SSFP sequences with high-resolution thin slices (4-5 mm) on radial slice projections with the fulcrum passing through the center of the left ventricle. The diastolic ratio of > 2.3 on CMRI is diagnostic of LVNC. Further imaging findings on CMRI in LVNC includes trabecular fibrosis, which is seen as delayed enhancement within the trabeculae. Interestingly, delayed enhancement can be seen in non-compacted segments indicating that fibrosis can also affect normal segments[61].

TTC

TTC, also called apical ballooning syndrome or stress cardiomyopathy, is characteristically accompanied by acute chest pain and when associated with ECG changes and elevated troponin, can be erroneously diagnosed as acute coronary syndrome. Clinical criteria for the diagnosis of

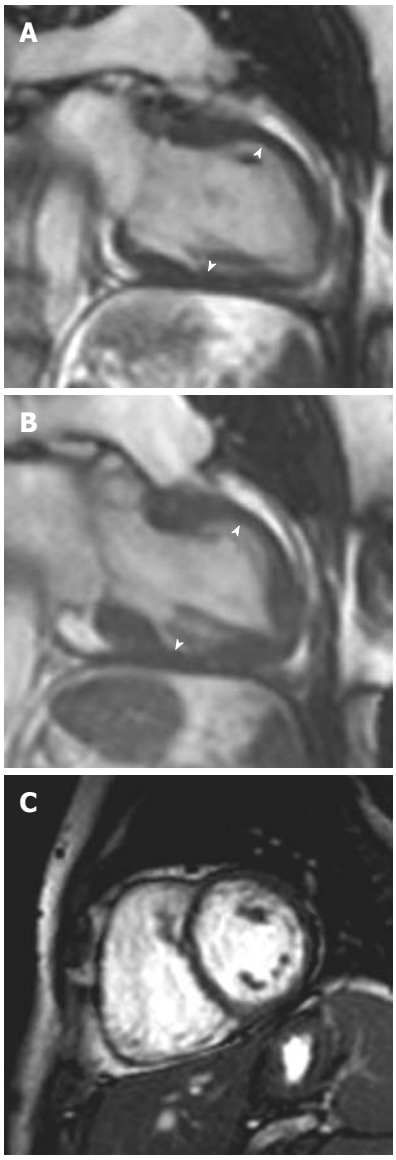

Figure 9 A 54-year-old woman with acute onset chest pain and palpitations following a road traffic accident. A, B: Vertical long-axis SSFP sequence in (A) diastole and (B) systole showed akinesis of the left ventricular myocardial segments at the midventricular level; C: Late gadolinium enhancement showing no myocardial enhancement in the involved segments. Subsequent echocardiography 1 mo later showed normal mid-wall contraction.

TTC include transient akinesia or dyskinesia of the LV apical, mid or basal segments beyond the distribution of a single coronary artery, new ECG abnormalities or an elevated troponin, no angiographic evidence of acute plaque rupture or obstructive coronary artery disease, no recent head trauma/intracranial bleeding, no HCM or pheochromocytoma[63,64].

The pathogenesis of TTC is not fully understood. Proposed etiologies include coronary spasm, coronary emboli with spontaneous fibrinolysis, regional myocarditis and abnormalities in the coronary microvascular function. Several studies have demonstrated an association with catecholamine excess. Emotional and physical stressors are often seen in patients with TTC. Plasma levels of neuropeptides and catecholamines in patients with TTC have

been found to be markedly elevated compared to patients with myocardial infarction[65]. One such study described TTC in nine patients, occurring after intravenous infusion of epinephrine or dobutamine[66]. Eitel *et al*[67] evaluated a large group of patients presenting with TTC. In 136 patients with TTC, 121 had significant stressful events 12 h preceding their TTC. Sixty-four patients had emotional stress and 57 had physical stress. Post-menopausal women were more commonly affected, 10% of patients were pre-menopausal, 10% were male and 10% did not recover LV function immediately. Endocardial biopsies in patients with TTC demonstrated changes consistent with catecholamine excess with contraction bands, increased inflammatory cells and interstitial fibrosis[68].

CMRI appearances: There are several patterns of regional wall motion abnormalities described in TTC[66]. An apical ballooning variant has apical akinesis with sparing of the base and mid-ventricle. A midventricular ballooning variant has midventricular akinesis with sparing of the apex and base (Figure 9). A basal ballooning variant has midventricular and basal akinesis but spares the apex. RV akinesia has also been described in some patients and is associated with lower LV ejection fractions[69]. LGE is seen in patients with myocardial infarctions and myocarditis but not typically in patients with TTC, making CMRI a valuable investigational tool in the work-up of patients suspected of TTC.

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BRIEF ARTICLE

Clinically unrecognized mitral regurgitation is prevalent in lone atrial fibrillation

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Abstract

AIM: To investigate the prevalence of clinically unrecognized mitral regurgitation (MR) in lone atrial fibrillation (AF).

METHODS: We studied the prevalence and severity of MR by transesophageal echocardiography (TEE) in patients with "lone" AF as compared to a matched cohort of patients in normal sinus rhythm (NSR) undergoing TEE for other indications besides recognized valvular heart disease.

RESULTS: A total of 157 subjects (57 in the AF group and 100 in the NSR group) with structurally normal cardiac valves were included in the study. In the AF group, moderate MR or more was noted in 66% of the patients, mild MR in 18%, trace or no MR in 16%. In the control group, moderate MR was noted in 6% of patients, mild MR 31%, trace or no MR in 63 % of patients. Moderate MR or greater was significantly more prevalent in the AF group compared to the NSR group (66% *vs* 6%, $P < 0.0001$).

CONCLUSION: Clinically unrecognized moderate MR is prevalent in "lone" AF -either as an etiologic factor leading to "lone" AF or developing after onset of AF.

Key words: Mitral regurgitation; Lone atrial fibrillation; Normal sinus rhythm

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INTRODUCTION

There is scant data regarding the prevalence of mitral regurgitation (MR) in lone atrial fibrillation (AF). Significant MR from structural valvular abnormality is associated with subsequent development of chronic AF. However, little is known regarding the relationship between lone AF and clinically unrecognized moderate MR in patients with

structurally normal valves. We noted that patients who were referred for transesophageal echocardiography (TEE) guided cardioversion for AF had an unusually higher prevalence of TEE evident moderate MR than a control group who underwent TEE for other indications. We sought to determine the exact prevalence of MR by TEE in patients with lone AF as compared to patients in normal sinus rhythm (NSR) by blinded observation in a cohort of consecutive patients who underwent TEE at our institution.

MATERIALS AND METHODS

Over a 50-mo period, 57 consecutive patients with a diagnosis of lone AF underwent TEE in our institution to exclude intra-cardiac thrombus prior to external direct current cardioversion. These patients comprised the AF group. Within the same period, a cohort of 100 patients in NSR who underwent TEE for a variety of indications (evaluation for suspected endocarditis, aortic dissection, and pulmonary hypertension) were enrolled as age- and sex-matched controls. At the time of the initial diagnosis, patients in the AF group were < 60 years and were without concomitant heart disease, hypertension or diabetes mellitus. Subjects from both groups were included if they had structurally normal mitral valves. Exclusion criteria included uncontrolled hypertension, heart failure, cardiomyopathy, structural abnormality of any of the valves (including valvular stenosis and mitral valve prolapse), history of cardiac surgery (including valve repair or replacement), and congenital or pericardial heart disease.

Standard TEE with doppler color flow mapping was employed to assess the variables. All measurements were in conformity with the American Society of Echocardiography guidelines, and were verified by two independent, blinded observers. The presence or absence of MR was verified, and its severity was graded semi-quantitatively as follows: 0 (none), 1 (trace), 2 (mild), 3 (moderate), 4 (severe). Any discordance of the severity of MR was resolved by joint reading by the two observers. The following variables were also measured: left ventricle (LV) ejection fraction, LV diameter, left atrial diameter (LA) and mitral annulus diameter in the 4 chamber views.

Patient demographics, severity of MR, and cardiac dimensions between groups were compared with the use of the Student's *t* test for continuous variables, and the Fisher's exact test for categorical variables. A two-sided *P* value of 0.05 or less was considered to indicate statistical significance.

RESULTS

A total of 157 subjects (57 in the AF group and 100 in the NSR group) with structurally normal cardiac valves were included in the analysis. Both groups were similar in terms of age, sex, and co-morbidities (hypertension, chronic kidney disease and cerebrovascular disease) except for a greater prevalence of diabetes and lung disease in the control group. Baseline characteristics of the subjects are listed in Table 1.

Table 1 Baseline characteristics of subjects

Demographic data	AF group (n = 57)	NSR group (n = 100)	P value (a = 0.05)
Age (mean ± SD)	50.2 ± 7.3	51.7 ± 6.1	0.17 NS
Male sex	39 (68)	66 (66)	0.86 NS
Comorbidities			
Hypertension (controlled)	8 (14)	19 (19)	0.51 NS
Diabetes mellitus	0 (0)	13 (13)	< 0.05
Chronic lung disease	0 (0)	9 (9)	< 0.05
Chronic kidney disease	0 (0)	6 (6)	0.08 NS
Cerebrovascular disease	0 (0)	3 (3)	0.55 NS

AF: Atrial fibrillation; NSR: Normal sinus rhythm; NS: Not significant.

Table 2 Chamber dimensions

Measurements	AF group (n = 57)	NSR group (n = 100)	P value (a = 0.05)
LV ejection fraction (%)	68 ± 6	66 ± 9	0.13 NS
LV end diastolic diameter (cm)	5.4 ± 0.7	5.5 ± 0.5	0.30 NS
LA diameter (cm)	3.7 ± 0.5	3.6 ± 0.6	0.28 NS
Mitral annulus diameter (cm)	4.0 ± 0.4	3.4 ± 0.5	< 0.0001

AF: Atrial fibrillation; NSR: Normal sinus rhythm; LV: Left ventricle; LA: Left atrial; NS: Not significant.

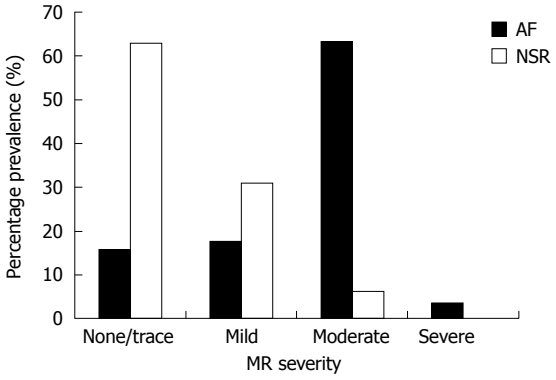

Figure 1 Percentage prevalence of mitral regurgitation severity between atrial fibrillation and normal sinus rhythm groups. AF: Atrial fibrillation; NSR: Normal sinus rhythm; MR: Mitral regurgitation.

The severity of MR noted in the patients in the AF and NSR cohorts is outlined in Figure 1. In the AF group (n = 57), moderate MR or more was noted in 38 patients (66%), mild MR in 10 patients (18%), trace or no MR in 9 patients (16%). In the control group (n = 100), moderate MR was noted in 6 patients (6%), mild MR 31 patients (31%), trace or no MR in 63 patients (63%). Moderate MR or greater was significantly more prevalent in the AF group compared to the NSR group (66% *vs* 6%, P < 0.0001). All of the subjects had left ventricular ejection fraction > 50%, and there was no difference in LV chamber sizes between groups. LA between the two groups was not statistically significant between the two groups. Mitral annular diameter was statistically greater in the AF group than the NSR group (Table 2).

DISCUSSION

AF is the most common cardiac rhythm disorder, affecting about 2% of the general adult population and is commonly associated with structural heart disease[1]. AF induces electrical, contractile and structural remodeling of the atrial myocardium that leads to AF progression and permanence[2]. However, lone AF (defined AF in the absence of demonstrable underlying cardiac disease or a history of hypertension in subjects < 65 years) is uncommon, comprising less than 3% of the total cases of AF[1-4]. Numerous mechanisms are postulated in pathogenesis of AF including acute atrial stretch, structural and electrophysiological alterations, systemic inflammation, oxidative stress, autonomic imbalance, atrial fibrosis, or localized atrial myocarditis, genetic predisposition, obesity, sleep apnea, metabolic syndrome, alcohol consumption, endurance sports suggest that apparently "lone" AF may not be necessarily idiopathic or "lone" in many patients[2-8].

In this study, we propose the possibility that clinically unrecognized moderate MR may predispose to occurrence of AF, or alternatively MR develops slowly in patients with AF related to mitral annular dilation as was noted in our subset of patients with AF. We cannot exactly pinpoint the time duration of the existence of AF in our subset of patients, since these patients were all recently or incidentally diagnosed with AF and were referred for TEE guided cardioversion to our clinic. Most of these subjects with lone AF had no transthoracic echocardiography carried out before since their TEE was scheduled essentially within the same week of their diagnosis.

Data are scant on the prevalence of MR in lone AF. In a previous report, using transthoracic 2-dimensional echocardiography, moderate or severe MR was not observed in patients with lone AF[9]. Some reports suggest that MR may arise from isolated annular dilatation secondary to lone AF and associated atrial remodeling[10-12]. Indeed, in our study, severe MR was not observed frequently. However, in our study utilizing TEE, which is more sensitive in evaluating MR, we noted that moderate MR was present in more than half of the subjects with lone AF, a prevalence that is significantly higher than that of the matched controls.

It is known that significant MR (from degenerative causes or organic valvular abnormalities) is associated with development of chronic AF, at a rate of about 5% per year[13,14]. The risk of AF is correlated with increase in LA dimension[15]. Even asymptomatic organic MR has been shown to increase the risk of AF and adverse cardiovascular outcomes. MR from organic causes enlarges the left atrium, but most patients are initially asymptomatic because atrial compliance may normalize left atrial pressure even in the presence of severe regurgitation[16]. In patients with lone AF, atrial compliance may remain abnormal even after restoration of NSR which could be related to atrial fibrosis in these patients[17-19].

In our study on subjects with structurally normal mitral valves, none of the subjects had any significant LA enlargement. However, mitral annular dilation was more frequent in the AF subgroup. It is conceivable that MR follows some mitral annular dilation and the left atrial dilation takes a longer time to develop and does not become apparent in the early stages of lone AF. Whether AF exerts some anatomical effect on the mitral annulus remains hypothetical, since the number of patients is small. It is also possible that the atrial dyssynchrony produces an anatomically variable contraction of the mitral annulus leading to varying degrees of mitral closure with an irregular R-R interval, possibly predisposing to slow development of MR. One study suggests development of "functional MR" in patients with AF that improves when sinus rhythm is restored[20].

Atrial hypertension and stretch induced by MR may also be a likely explanation for development of "lone" AF. In animal models, LA dilation of moderate severity has been shown to result in significant changes in the cellular action potential and calcium current in the atrial myocardium rendering the atria vulnerable to AF[21]. Chronic atrial dilation causes atrial conduction delays and a higher contribution of anatomically defined re-entrant circuits, creating a wider excitable gap during AF[22]. Increased left atrial size leads to greater recurrences of "lone" AF[23]. Treatment with ACE inhibitors prevents long term recurrences of "lone" AF and facilitates maintainence of sinus rhythm after cardioversion[24,25]. Cardioversion to NSR reverses the atrial enlargement in patients with AF and MR[26]. There is also an increased amount of atrial fibrosis in AF patients with mitral valve disease than in patients with lone AF[27].

Theoretically, it seems plausible that moderate MR may be a risk factor for the development of lone AF, primarily by causing mechanical stretch of the left atrium ("left atrial hypertension"). Or conversely, AF may predispose to slow development of "silent" MR that may progress with time. It is also conceivable that the MR is a transient atrial dyssynchrony predisposed phenomenon that resolves after NSR is restored; but we do not have longitudinal TEE follow-up on our patients to make that assumption. Lastly, it is conceivable that the greater degree of MR noted on TEE may be related to the greater sensitivity of TEE to evaluate MR; however the presence of a control group should have normalized for that observation bias. Our study suggests that clinically unrecognized moderate MR may be prevalent in patients with lone AF. Whether moderate unrecognized MR may be an etiologic factor related to development of "lone" AF or vice versa needs to be studied in long-term longitudinal studies.

This was a single-center, nonrandomized, retrospective, single time point observational study. Hence, it was not designed to prove causality. The basis of our study was to explore an association between "silent" unrecognized moderate MR and "lone" AF. Our observations are subject to the same limitations imposed by retrospective study designs, and it is possible for bias to exist during the review process. It is conceivable that AF, by induc-

ing atrial wall motion dyssynchrony, may by itself induce MR. Moderate MR may be a more likely explanation for development of "lone" AF. The etiologic basis of this hypothesis would require long term longitudinal follow-up studies of patients with moderate MR who are in NSR at the time of the initial diagnosis of moderate MR. Another limitation of our data relates to the greater sensitivity of recognizing moderate MR with TEE, though this bias was possibly neutralized by inclusion of the control group of patients who were in NSR.

In our study utilizing TEE, moderate MR is prevalent in patients with lone AF. Longitudinal studies may be required to explore whether "silent" unrecognized moderate MR leads to development of "lone" AF or vice versa.

COMMENTS

Background

Clinically significant mitral regurgitation (MR) often leads to development of atrial fibrillation (AF). However, whether a stage of clinically unrecognized moderate MR (preceding development of clinically obvious significant MR) in patients with structurally normal valves can also lead to development of AF is not known.

Research frontiers

MR and AF are common cardiac conditions that often co-exist. Moderate MR is often clinically unrecognized as it is asymptomatic. "Lone" AF often occurs in patients without any preceding established cardiac disease. Whether there is an etiologic relationship between moderate MR and "lone" AF has not been studied. In the present study the authors demonstrate that clinically unrecognized moderate MR often co-exists in patients with lone AF and there may be an etiologic relationship between these two entities.

Innovations and breakthroughs

The study highlights the relationship between the presence of AF without any clinically obvious cardiac disease and clinically unrecognized moderate MR. It highlights that a clinically unrecognized stage of moderate MR may be a preceding step before the clinical manifestations become obvious in the form of development of AF. It is also possible that atrial dyssynchrony induced by AF may make MR more manifest by echocardiography.

Applications

By understanding the relationship between moderate MR and lone AF, the study generates interest in whether a therapeutic strategy for preventing progression of MR by afterload reduction therapy may be of benefit in preventing onset of AF.

Terminology

"Lone" AF is defined as AF in the absence of demonstrable underlying cardiac disease or a history of hypertension. MR is the presence of leakage of the mitral valve that is present in trace-to mild degree almost universally on echocardiography. However, moderate or severe MR is more uncommon and is sometimes associated with presence of other heart disease.

Peer review

It is well written, concise paper and interesting.

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BRIEF ARTICLE

Measuring luminal esophageal temperature during pulmonary vein isolation of atrial fibrillation

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Abstract

AIM: To investigate the luminal esophageal temperature (LET) at the time of delivery of energy for pulmonary vein isolation (PVI).

METHODS: This study included a total of 110 patients with atrial fibrillation who underwent their first PVI procedure in our laboratory between March 2010 and February 2011. The LET was monitored in all patients. We measured the number of times that LET reached the cut-off temperature, the time when LET reached the cut-off temperature, the maximum temperature (T max) of the LET, and the time to return to the original pre-energy delivery temperature once the delivery of energy was stopped.

RESULTS: Seventy-eight patients reached the cut-off temperature. It took 6 s at the shortest time for the LET to reach the cut-off temperature, and 216.5 ± 102.9 s for the temperature to return to the level before the delivery of energy. Some patients experienced a transient drop in the LET (TDLET) just before energy delivery. Ablation at these sites always produced a rise to the LET cut-off temperature. TDLET was not observed at sites where the LET did not rise. Thus, the TDLET before the energy delivery was useful to distinguish a high risk of esophageal injury before delivery of energy.

CONCLUSION: Sites with a TDLET before energy delivery should be ablated with great caution or, perhaps, not at all.

Key words: Radiofrequency catheter ablation; Atrio-esophageal fistula; Esophageal injury; Real time luminal esophageal temperature monitoring; Open irrigation

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INTRODUCTION

Pulmonary vein isolation (PVI) by radiofrequency (RF) catheter ablation (CA) has become an established strategy for the management of patients with drug refractory, symptomatic atrial fibrillation (AF)[1-6]. However, in comparison to the CA of the other arrhythmias, there are many and varied complications[7,8]. Specifically, a left atrial esophageal fistula due to thermal injury of the esophagus is a rare but devastating complication after PVI[9,10]. Like-

wise, acute pyloric spasms and gastric hypomotility resulting from thermal damage to the periesophageal vagal nerves caused by CA for AF can be devastating as well[11].

A report exists that illustrates the potential for esophageal damage during the application of RF energy, and the ability to monitor luminal esophageal temperature (LET) by inserting a temperature probe in the esophagus[12,13]. However, there have been no reports on the detailed examination of the progress of the LET in PVI for AF. Therefore, we investigated progress of the LET at the time of the delivery of energy for PVI of AF, by real-time LET monitoring.

MATERIALS AND METHODS

Study population

This study included a total of 110 patients with drug-refractory AF (82 paroxysmal and 28 persistent) who underwent first PVI by CA in our laboratory between March 2010 and February 2011. Patient characteristics are shown in Table 1. All patients gave their written informed consent and antiarrhythmic drugs (AADs) were discontinued 7 d before the ablation session. All patients were effectively anticoagulated for > 4 wk, and a 64-slice multidetector computed tomography (MDCT) scan of the left atrium (LA) and/or transesophageal echocardiography was performed before the CA to exclude any atrial thrombi.

Ultracardiograph and cardiac CT

Transthoracic echocardiography was performed on all patients to measure LA diameter. MDCT was performed for electroanatomical mapping integration, pulmonary vein anatomy delineation, LA thrombi exclusion, measuring the PV ostium diameter, and LA volume estimation.

PVI

The procedures were performed during deep sedation/analgesia with the administration of propofol and dexmedetomidine with preservation of spontaneous breathing and continuous monitoring of the systemic arterial pressure and oxygen saturation.

A 6 Fr duo-decapolar three-site mapping catheter (EPstar SAC, Japan Lifeline Inc., Tokyo, Japan) was positioned in the coronary sinus for pacing, recording and internal cardioversion. Four venous sheaths (5, 8, 8 and 8.5 Fr) and one arterial sheath (4 Fr) were placed in the femoral veins/arteries. A 5 Fr catheter was introduced into the right ventricle. A single trans-septal puncture was performed. After the trans-septal puncture, two non-steerable long sheaths (LAMP 45; St Jude Medical, St Paul, MN, United States; Preface; Biosense-Webster, Diamond Bar, CA, United States) and a steerable introducer (Agilis NxT Steerable Introducer Small Curl; St Jude Medical) were introduced into the left superior pulmonary vein, left inferior pulmonary vein (LIPV) and right superior pulmonary vein, respectively. Left arteriography by injection of contrast medium *via* the three long sheaths was simultaneously performed to obtain the anatomical relationship between the area around the PV ostium and the esophagus (Figure 1).

A 5000-U intravenous bolus of heparin was administered after the successful trans-septal puncture. The activated clotting time (ACT) was measured every 30 min, and the heparin dose was adjusted to maintain a target ACT of 300 s.

Table 1 Baseline characteristics of the patients (mean ± SD)

Age (yr)	63.8 ± 11.2
Male sex, *n* (%)	79 (71.8)
BMI (kg/m^2)	24.1 ± 3.4
Paroxysmal/persistent AF	82/28
Ineffective drugs, n	1.9 ± 1.1
LA diameter (mm)	43.1 ± 6.7
LA volume (cm^3)	124.8 ± 43.3
LA volume index (cm^3/m^2)	73.5 ± 25.6
Ejection fraction (%)	65.4 ± 11.9
LSPV diameter (mm)	20.7 ± 4.7
LIPV diameter (mm)	16.3 ± 2.4
RSPV diameter (mm)	20.4 ± 4.7
RIPV diameter (mm)	17.1 ± 3.5

BMI: Body mass index; AF: Atrial fibrillation; LA: Left atrium; LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein; RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein.

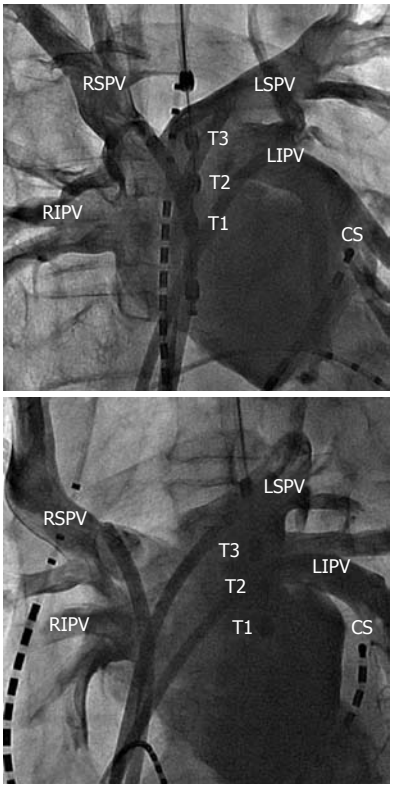

Figure 1 Left arteriography. Fluoroscopy of left arteriography using the trans-septal sheath after short iatrogenic complete AV-block using high-frequency right ventricular stimulation. The relationship is shown of the eso-temperature probe (Eso) with three thermistor electrodes (T1-T3) to the ostium of the pulmonary veins. Upper: Right anterior oblique; Lower: Left anterior oblique. LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein; RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein.

Two circular mapping catheters (EPstar Libero; Japan Lifeline Inc.) were placed in the superior and inferior pulmonary veins, respectively, and the left- and right-sided ipsilateral PVs were circumferentially and extensively ablated, respectively, with use of an electromagnetic mapping system (CARTO, Biosense Webster, United States) and electrophysiologic guidance. The LA posterior wall, at a distance of 1 to 3 cm from the left- or right-sided ostia of the PVs, was anatomically ablated. The distal edges of the anterior aspect of the PVs with early PV potentials or continuous PV and LA potentials were targeted for ablation. Isolation of the left sided PVs was performed during distal coronary sinus pacing and isolation of the right-sided PVs during sinus rhythm.

Ablation was performed with an open irrigated tip catheter (ThermoCool; Biosense Webster). A generator was used to deliver 25 W of RF energy to the catheter tip and finished delivery in 20-25 s at all sites. The irrigation flow rate was set to 17 mL/min. For safety, the generator was set to reduce the power if the temperature of the catheter exceeded 43 ℃. The ablation catheter was irrigated for 2 s just before and just after delivering the energy. A cut-off LET of 42 ℃ was defined for the termination of the energy delivery. Even if an ablation catheter was near to the temperature probe in fluoroscopy, we delivered energy if the LET did not rise. After the LET normalized, the ablation was continued with less power and/or an alternative ablation course was chosen to prevent further temperature rises. The endpoint of the ablation was the elimination of all PV potentials and pacing maneuvers performed inside the PVs to test for any remaining PV conduction or complete PVI with bidirectional block[14].

After completing the PVI, the cavotricuspid isthmus was also ablated to create bidirectional conduction block[15]. Following the PVI and cavotricuspid isthmus ablation, decremental pacing was performed from the coronary sinus or LA appendage starting at a cycle length of 300 ms and ending with loss of 1:1 atrial capture, which was repeated two times. If burst pacing from the coronary sinus or LA appendage was able to induce sustained AF lasting > 5 min, the LA roof line and the mitral isthmus between the LIPV and mitral annulus were also ablated to achieve bidirectional conduction block. Finally, in the presence of sustained AF induced by burst pacing, ablation-targeting complex fractionated atrial electrography (CFAE) was performed within the LA including the coronary sinus.

LET monitoring

In all patients, an LET monitoring probe (Esotherm; FIAB SpA, Florence, Italy) with three olive-shaped metal thermocouple electrodes (distance 10 mm) was placed within the esophagus under fluoroscopic guidance directly posterior to the LA. The temperature probe was adjusted to equal heights of the PV ostium after left arteriography and selective cannulation of the PVs with the ablation catheter. The temperature probe was connected to three precision thermometers allowing continuous measurement, recording and display of the LET.

We measured the number of times the LET reached the cut-off temperature, the time when the LET reached the cut-off temperature, the maximum temperature (T max) of the LET, the time to reach T max after the LET reached the cut-off temperature, and the time for the temperature to decrease to the following values after stopping delivery of energy: 42, 41, 40, 39, 38 and 37 ℃ and the temperature before the delivery of energy. We also measured the temperature before the delivery of energy at the site where the LET reached the cut-off temperature (Figure 2).

Follow-up

After 3-6 mo, in the absence of any AF recurrence, anticoagulant treatment was discontinued unless other major risk factors were present. AADs were not prescribed for patients with paroxysmal AF, but were prescribed for 3 mo following the ablation in patients with persistent AF. All patients were scheduled to visit our clinic at 1, 3 and 6 mo after discharge. In the case of nonappearance at the follow-up dates, patients were contacted by telephone. A recurrence of AF was defined according to the patient's symptoms and electrocardiogram. All patients took proton pump inhibitors (PPIs) after ablation for at least 2 wk.

Statistical analysis

Continuous variables are expressed as the mean ± SD except for the count and time variables. Statistical significance was assessed using the unpaired Student's *t* test or Mann-Whitney test if necessary. Categorical variables, expressed as numbers or percentages, were analyzed with the χ^2 test or Fisher's exact test. All tests were two-tailed and a P value < 0.05 was considered statistically significant.

Study approval

The study was approved by the Institutional Review Board of Takeda Hospital (Kyoto, Japan).

RESULTS

A total of 229 RF energy deliveries (in 78 out of 110 patients) reached the cut-off temperature. Most of these sites were located on the LA posterior wall near the left PVs, and in particular around the LIPV ostium. The LET also increased on the left side of the right PVs, whereas there were only five sites with an LET > 42 ℃ (Figure 3).

There was no atrio-esophageal fistula formation. There was no significant difference in the age, sex, body mass index, LA diameter, LA volume, LA volume index, and diameter of the PVs between the LET increase and non-LET increase groups (Table 2).

The time for the LET to reach the cut-off temperature was 12.2 ± 4.5 s (280.8 ± 103.7 J). The LET reached the cut-off temperature within 10 s in 32 of 110 (29.1%) patients. The shortest time was 6 s. It was 4.1 ± 1.9 s to

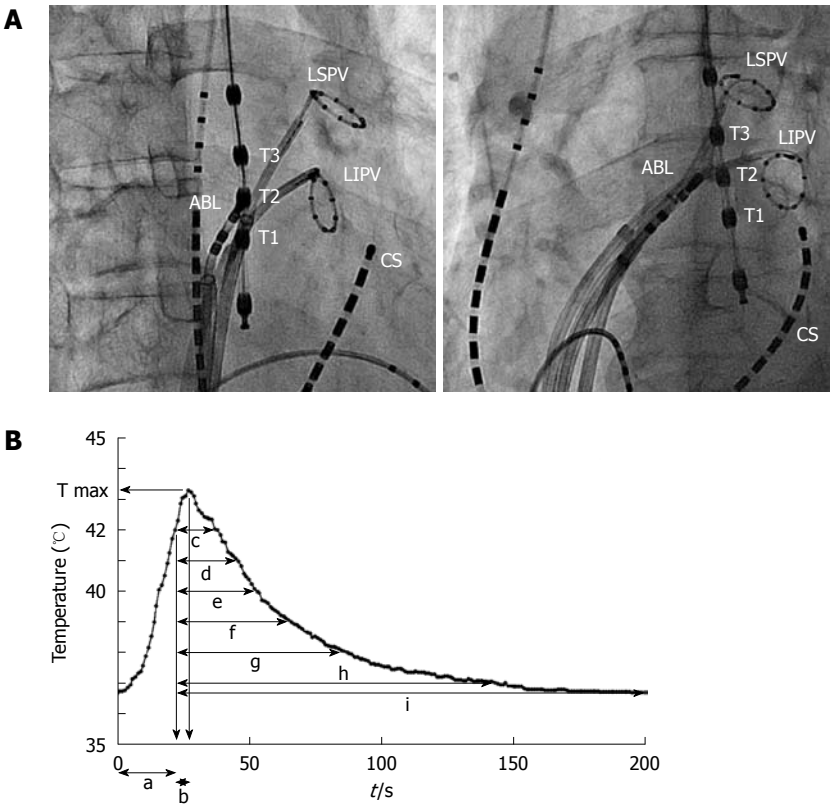

Figure 2 Position of ablation catheter (A) (left: right anterior oblique, right: left anterior oblique) and luminal esophageal temperature monitoring graph (B). We measured the time when luminal esophageal temperature (LET) reached the cut-off temperature (a), the maximum temperature (T max) of LET, the time to reach T max after the LET reached 42 ℃ (b) and the time to come back from the delivery of energy end to 42 ℃ (c), 41 ℃ (d), 40 ℃ (e), 39 ℃ (f), 38 ℃ (g) and 37 ℃ (h), and the temperature before the delivery of energy (i). LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein; RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein.

Table 2 Comparison between non-luminal esophageal temperature and luminal esophageal temperature increase groups (mean ± SD)

	Non-LET increase (n = 32)	LET increase (n = 78)	P value
Age (yr)	65.3 ± 11.9	63.2 ± 10.9	0.395
Male sex, n (%)	21 (65.6)	58 (74.4)	0.355
BMI (kg/m^2)	24.3 ± 3.6	24.0 ± 3.3	0.619
Paroxysmal/persistent AF	24/8	58/20	0.944
LA diameter (mm)	43.7 ± 6.1	42.9 ± 6.9	0.582
LA volume (cm^3)	127.7 ± 42.7	123.2 ± 43.3	0.658
LA volume index (cm^3/m^2)	77.5 ± 27.0	71.7 ± 24.8	0.334
Ejection fraction (%)	62.9 ± 12.3	66.5 ± 11.7	0.155
LSPV diameter (mm)	21.2 ± 5.1	20.5 ± 4.5	0.972
LIPV diameter (mm)	15.9 ± 2.5	16.5 ± 2.3	0.295
RSPV diameter (mm)	20.8 ± 5.6	20.2 ± 4.4	0.548
RIPV diameter (mm)	17.0 ± 4.5	17.1 ± 3.1	0.972

LET: Luminal esophageal temperature; BMI: Body mass index; AF: Atrial fibrillation; LA: Left atrium; LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein; RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein.

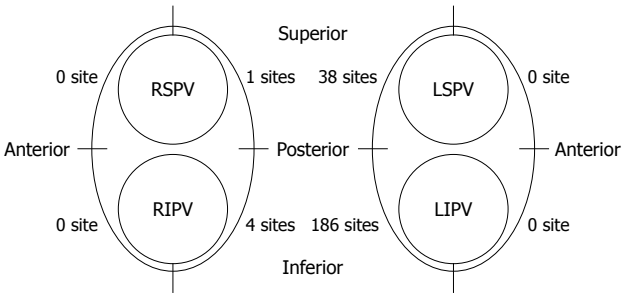

Figure 3 Position of sites where luminal esophageal temperature reached the cut-off temperature. Most of the sites were located along the posterior side of the LPV, especially around the left inferior pulmonary vein (LIPV), while only five sites were observed near the RPVs. LSPV: Left superior pulmonary vein; RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein.

reach T max after the LET reached the cut-off temperature. The time for the temperature to decrease to the following values after stopping delivery of energy: 42, 41, 40, 39, 38 and 37 ℃, and the temperature before the delivery of energy was 16.4 ± 6.3, 23.3 ± 8.3, 31.9 ± 9.9, 45.0 ± 15.8, 61.3 ± 22.9, 126.7 ± 54.5 and 216.5 ± 102.9 s (Figure 4A).

LET often overshot the cut-off temperature after cessation of energy delivery. A temperature overshoot was observed in all patients. The average T max was 43.8 ± 0.8 ℃ and the maximal registered temperature was 45.6 ℃.

There was a transient drop in the LET (TDLET) just before the delivery of energy. We defined TDLET as a

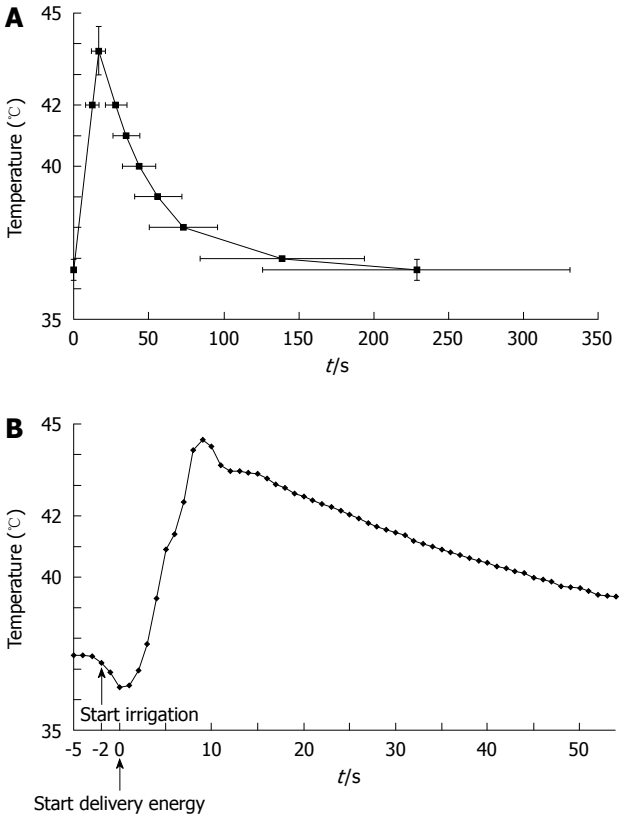

Figure 4 Luminal esophageal temperature. A: Graph of luminal esophageal temperature (LET); B:Transient drop in the LET. After having caused a transient drop in the luminal esophageal temperature just before delivering energy, the luminal esophageal temperature reached the cut-off temperature.

decrease of > 0.5 ℃ for 2 s just before energy delivery. TDLET was observed in 34 of 110 (30.9%) patients (Figure 4B). The LET decreased (0.82 ± 0.35 ℃) before delivery of energy with a TDLET. The maximum temperature decrease was 1.89 ℃. The site that caused a TDLET before energy delivery always reached the cut-off temperature within 9.2 ± 3.2 s. Most of these sites were located near the LIPV. TDLET was not observed at sites where the LET did not increase.

Clinical follow-up

Twenty-nine patients underwent a second ablation procedure and eight underwent a third involving treatment for reconduction of the PVs, the LA roof line, the mitral isthmus line, ablation of new atrial premature contraction foci, or additional CFAE ablation. The final success rate, evaluated at 6 mo after the first session, was 89% (73 of 82, including eight patients with AADs) for the paroxysmal AF patients and 79% (22 of 28, including 10 with AADs) for the persistent AF patients.

DISCUSSION

The LET rose by 70.9% in all cases. There was no significant difference in the various parameters between the LET increase and non-LET increase groups. Thus, there was no parameter that could predict an LET rise before ablation.

The shortest time for LET to reach the cut-off temperature was 6 s, and the maximum time for the temperature to decrease to the pre-energy application value after energy delivery was stopped was 216.5 s. Most of the sites were located along the posterior side of the LPV, especially around the LIPV.

It was determined that 30.9% of all patients in this study had a TDLET just before energy delivery. It was also determined that the TDLET was affected by the cooling of the irrigation catheter and the close proximity of the esophagus prior to energy delivery. In addition to causing the cooling effect, it was believed that the TDLET could easily be affected by the energy delivery and the location could more easily cause esophageal injury. In fact, the site that caused a TDLET before the energy delivery reached the cut-off temperature in all cases. TDLET was not observed at sites where the LET did not increase. Thus, the TDLET before energy delivery was useful to distinguish a high risk of esophageal injury before delivery of energy. We should avoid performing CA at sites with a TDLET. The upper limit of LET in PVI is important to prevent esophageal injury[16]. Similarly, the lower limit of LET in PVI is important to prevent esophageal injury by discovering TDLET.

Reports in the literature have attested to the utility of methods for visualizing the esophagus during AF ablation[17]. In this study, we were able to establish the position of the esophagus to some extent because a probe was inserted. However, even if an ablation catheter was near to the temperature probe in fluoroscopy, we delivered energy. We might affect the LET if we avoided using an esophagus probe and delivered energy.

We set the safety limit of the LET to 42 ℃ because it was shown that cells exposed to that temperature underwent morphological changes, including disruption and fragmentation of the Golgi complexes and swelling of the mitochondria[18]. In addition, metabolic studies have revealed the inhibition of both respiration and glycolysis in tumor tissue and cultured tumor cells exposed to temperatures of 42-43 ℃[19]. There was no atrio-esophageal fistula formation. There is a report that esophageal damage is not caused at 42 ℃[20]. However there is also a report that asymptomatic esophageal damage is observed in 14.6% of cases with endoscopy[16]. We did not perform upper gastrointestinal endoscopy, and asymptomatic esophageal damage may have been overlooked. Actually, the LET often overshot 42 ℃ after the cessation of RF energy delivery. LET > 42 ℃ was within 5 ℃ and persisted for a relatively short duration. Such slight and short overshooting of the LET did not seem to cause any serious esophageal damage. It is thought that the maximum temperature is the most important factor influencing esophageal injury and we should use lower temperature settings so that the T max remains within 42-43 ℃.

This study had several limitations. In a large survey of the incidence and causes of death during or as a con-

sequence of CA of AF, atrio-esophageal fistula occurred in 0.01%-0.02% of patients[20,21]. Atrio-esophageal fistula due to thermal injury of the esophagus is rare. This was possibly because atrio-esophageal fistula did not occur at a high frequency and the population of this study was not large enough. All patients took PPIs after CA, which may have resulted in an absence of gastrointestinal symptoms. Therefore, we might have underestimated gastrointestinal dysfunction. We used a non-deflectable temperature probe. This probe may not have been able to be accurately placed just posterior to the ablation catheter. Lesion formation was also related to the contact force[22]. It is also likely the LET was related to the contact force as well. However, the contact force was not evaluated in this study. Furthermore, this study was performed in a clinical setting, therefore, no estimation of the intramural tissue temperature or thrombus formation on the electrode-tissue interface was carried out, which would have been of great value.

We discovered TDLET by investigating the LET at the time of delivery of energy for PVI. The lower limit of LET in PVI is important to prevent esophageal injury by discovering TDLET. Sites with a TDLET before energy delivery should be ablated with great caution or, perhaps, not at all.

COMMENTS

Background

A left atrial esophageal fistula due to thermal injury to the esophagus is a devastating complication after pulmonary vein isolation (PVI). A report exists that illustrates the potential for esophageal damage during the application of radiofrequency (RF) energy, and the ability to monitor luminal esophageal temperature (LET) by inserting a temperature probe in the esophagus. However, there have been no reports on the detailed examination of the progress of the LET in PVI for atrial fibrillation (AF).

Research frontiers

This study reports on the detailed examination of the progress of the LET in PVI for AF. Specifically, this is the first study to report on transient drop in the LET (TDLET) just before the delivery of energy.

Innovations and breakthroughs

A report exists that illustrates the potential for esophageal damage during the application of RF energy, and the ability to monitor LET by inserting a temperature probe in the esophagus. However, nobody was able to anticipate whether LET increased before delivering energy. The TDLET before energy delivery may be useful to distinguish a high risk of esophageal injury before delivery of energy.

Applications

Detecting TDLET before energy delivery is useful for identifying a higher risk of esophageal injury. Therefore, the lower limit of LET in PVI is important to prevent esophageal injury by discovering TDLET.

Peer review

The study shows a new aspect of the LET monitoring during AF ablation. It shows, that the esophageal sites with the highest increase of temperature during ablation can be predicted by measuring the degree of lowering the intraluminal temperature shortly prior starting ablation. The decrease of LET is caused by proximity of the irrigated catheter tip in the posterior left atrium. It seems to be evident, that the cooling effect of the catheter is more pronounced on sites that are anatomically closer, than on sites that are more distant. This finding has not been described yet in a peer reviewed journal. This is an interesting manuscript with considerable merit.

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Events Calendar 2012

January 18-21, 2012
Ninth Gulf Heart Association Conference
Muscat, Oman

January 27, 2012
ESC Global Scientific Activities at the 23rd Annual Conference of the Saudi Heart Association
Riyadh, Saudi Arabia

January 29–31, 2012
Integrated management of acute and chronic coronary artery disease
Innsbruck, Austria

January 30, 2012
Webinar on "Best of Euroecho 2011"
Sophia Antipolis, France

February 1-3, 2012
American Heart Association and American Stroke Association International Stroke Conference 2012
New Orleans, Louisiana, United States

February 3-5, 2012
6th Asian-Pacific Congress Of Heart Failure 2012
Chiang Mai, Thailand

February 9, 2012
4th British Society for Heart Failure Medical Training Meeting
London, United Kingdom

February 23–25, 2012
Advanced Invasive Cardiac Electrophysiology
Sophia Antipolis, France

February 24–26, 2012
International Congress of Cardiology
Hong Kong, China

February 28, 2012
Echocardiography evaluation of patient with multivalvular disease
Sophia Antipolis, France

February 29-March 3, 2012
Winter ISHNE 2012
Zakopane, Poland

March 8–10, 2012
Cardiac Pacing, ICD and Cardiac Resynchronisation
Vienna, Austria

March 8–10, 2012
24th Colombian Congress of Cardiology and Cardiovascular Surgery
Cali, Colombia

March 10-11, 2012
23rd International Meeting "Cardiology Today"
Limassol, Cyprus

March 14-18, 2012
Ninth Mediterranean Meeting on Hypertension and Atherosclerosis
Antalya, Turkey

March 15-17, 2012
e-Cardiology 2012
Osijek, Croatia

March 15-18, 2012
China Interventional Therapeutics 2012-CIT
Beijing, China

March 16-17, 2012
12th Annual Spring Meeting on Cardiovascular Nursing
Copenhagen, Denmark

March 16-17, 2012
3rd European Meeting: Adult Congenital Heart Disease
Munich, Germany

March 16-18, 2012
JCS2012 - The 76th Annual Scientific Meeting
Fukuoka, Japan

March 20–23, 2012
32nd International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium

March 25-29, 2012
16th International Symposium On Atherosclerosis 2012
Sydney, Australia

March 28–31, 2012
Rome Cardiology Forum 2012
Rome, Italy

March 28–31, 2012
Annual Spring Meeting of the Finnish Cardiac Society 2012
Helsinki, Finland

March 30-April 1, 2012
Frontiers In CardioVascular Biology 2012
London, United Kingdom

April 5-7, 2012
EAE Teaching Course on New echocardiographic techniques for myocardial function imaging
Sofia, Bulgaria

April 12-14, 2012
Cardiovascular Risk Reduction: Leading The Way In Prevention 2012
National Harbor, MD, USA

April 12-15, 2012
NHAM Annual Scientific Meeting 2012
Kuala Lumpur, Malaysia

April 18-21, 2012
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April 19-21, 2012
Delivering Patient Care in Heart Failure
Sophia Antipolis, France

April 20-22, 2012
7th Clinical Update on Cardiac MRI and CT
Cannes, France

April 25-27, 2012
Angioplasty Summit 2012
Seoul, South Korea

April 25-28, 2012
The 61st International Congress of the European Society of Cardiovascular and Endovascular Surgery
Dubrovnik, Croatia

April 28-29, 2012
24th Annual Scientific Meeting of the SCS
Singapore, Singapore

May 3–5, 2012
EuroPRevent 2012
Dublin, Ireland

May 15–18, 2012
EuroPCR Congress 2012
Paris, France

May 17-20, 2012
2nd International Meeting On Cardiac Problems In Pregnancy 2012
Berlin, Germany

May 19-22, 2012
Heart Failure 2012
Belgrade, Serbia

May 23-26, 2012
46th Annual meeting of the Association for European Pediatric and Congenital Cardiology
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May 26-27, 2012
Cardiovascular Spring Meeting 2012
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World Journal of Cardiology

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INSTRUCTIONS TO AUTHORS

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

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

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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