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Heart failure and chronic obstructive pulmonary disease: Two for tea or tea for two?

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Abstract

A combination of chronic obstructive pulmonary disease (COPD) and heart failure (HF) is common yet it is inadequately and rarely recognized. Because of the similar clinical manifestations, comorbidity is frequently not considered and appropriate diagnostic tests are not performed. It is very important that a combination of COPD and HF is recognized as these patients have a worse prognosis than patients with an individual disease. When present, COPD should not prevent the use of life-saving therapy in patients with HF, particularly β -blockers. Despite clear evidence of the safety and tolerability of cardioselective β -blockers in COPD patients, these drugs remain grossly underprescribed and underdosed. Routine spirometry and echocardiography in HF and COPD patients, respectively, is therefore warranted to improve current clinical practice.

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EPIDEMIOLOGY

Epidemiological studies and registries have demonstrated that heart failure (HF) and chronic obstructive pulmonary disease (COPD) are highly prevalent across the globe and contribute markedly to the global burden of disease. It is also known that in clinical practice they frequently coexist but the comorbidity is not readily recognized nor adequately treated^[1-3]. Some of the estimates of the prevalence may not be accurate as they are based on hospital claims data, discharge diagnosis or medical prescription data. However, the coexistence of these two diseases should not be a surprise, as both diseases share smoking as the most common risk factor^[4]. Smoking is almost a prerequisite for the development of COPD, and is the second most important and independent risk factor for chronic HF (CHF). Cigarette smoking was associated with a 45% higher risk of CHF in men and an 88% higher risk of CHF in women after adjustment for other known risk factors for CHF, including coronary heart disease^[5].

SYMPTOMATOLOGY

Both COPD and HF have been intensively studied, but mostly on an individual basis. Consequently, clinicians should have sufficient knowledge to diagnose the condition and to deliver treatment as appropriate. Cardiologists and pneumologists, however, seem to focus primarily on a single organ and much too often fail to recognize the presence of COPD in patients with HF (cardiologists) and *vice versa* (pneumologists). Such ignorance extends even to large multinational or multicentric interventional trials where pulmonary function testing is exceptional in cardiology trials. Similarly, pneumologists seem to be satisfied with clinical parameters such as heart rate and blood pressure and did not consider simple diagnostic procedures, including echocardiography, in most of the conducted trials^[6-9].

Based on the current literature, it is appropriate to ask whether attending physicians or patients with HF and/or COPD come from two completely different worlds. It was frequently argued, that because of the similarities in clinical presentation it is difficult to differentiate between HF and COPD or diagnose co-existence. But are symptoms of HF and COPD indeed so similar? Is it really so difficult to perform a simple spirometry in patients with HF? Is it really so difficult to find physical signs of HF in patients with COPD? This can be disputed, but in a stable clinical condition, such a differentiation may not be too difficult. In dubious cases, differentiating HF from COPD is aided by measurement of natriuretic peptides (NP) as the presence of pulmonary hypertension and right ventricular dysfunction only rarely significantly increase NP levels and only a few patients with moderate COPD have a brain NP (BNP) > 100 pg/mL or N-terminal-proBNP levels > 350 pg/mL^[10].

Yet, in clinical practice, too many patients with HF had undiagnosed COPD and *vice versa*. Why such a paradox exists has not been investigated in detail. It seems unlikely that we are unaware of chronic lung and heart disease comorbidity. An overwhelming body of evidence is available and it is known that prognosis of patients with chronic cardiopulmonary conditions is poor^[11-14]. This holds true even if the physicians are not quite sure what the abbreviation COPD stands for^[15].

PATHOGENESIS

If so frequently associated, do HF and COPD share the same pathogenetic features? Chronic inflammation is certainly present in both conditions. It was hypothesized, that as a consequence of mutual mechanisms of systemic cellular and humoral inflammation, HF and COPD occur more commonly in the presence of each other^[16-18]. Such a “common inflammatory pathway” is by no means a splendid target for research or treatment. Although many studies demonstrated enhanced inflammatory activity, we still cannot provide convincing evidence for “bench to bedside” translation^[9,19], even with a very sophisticated and targeted approach^[20]. Other common mechanisms are the renin-angiotensin-aldosterone system and the sym-

thetic nervous system. In HF, there is no doubt about the efficacy of neurohormonal blockers^[21], whilst adequately designed trials in COPD are lacking^[22]. An interesting historical aspect is also a “prejudice” to β -blocker use in HF patients with coexistent COPD. It must be stressed, that nowadays differentiating asthma from COPD should not be a problem and that eligible COPD patients should not be withheld from life-saving therapy with β -blockers. On the other hand, however, is the warning that the safety of β -2 agonists in COPD is controversial^[23]. As stressed before, a simple office spirometer may perform the diagnosis in a majority of patients and only a few need to be referred to a pneumologist. The results from epidemiological studies, however, are promising^[24,25] and are likely to lead to adequately powered randomized trials. Much more important are clinical data from many studies of HF/COPD co-morbid patients.

DIAGNOSIS

A significant proportion of HF patients have not been undiagnosed or falsely diagnosed as having COPD, because pulmonary function tests were never performed or, if performed, they were falsely interpreted^[13]. As an obstructive or even restrictive pattern of pulmonary function impairment provides significant prognostic information for all-cause mortality in patients admitted with HF it should be concluded that pulmonary function testing should be considered as a part of routine work-up, along with electrocardiography (ECG), laboratory markers, chest X-ray investigation or echocardiography. A spirometer, as with a simple blood pressure monitor or ECG, should be present in every internal medicine ward and in every GP office, where most HF patients are managed. Nonetheless, it has to be underlined that relevant measurements have to be performed in clinically stable and acutely decompensated patients. The latter may be the reason for insufficient implementation in clinical practice.

CONCLUSION

Currently, we can conclude that a combination of COPD and HF is highly prevalent, but apparently frequently unrecognized. This is partly due to similar clinical manifestations but mainly due to lack appropriate diagnostic tests to diagnose HF and/or COPD. Comorbidity of COPD and HF is clinically of utmost importance as these patients have much worse prognosis in comparison with patients with one of the diseases. Furthermore, even patients with known comorbidity are very frequently not treated properly^[1,3,13]. Despite convincing evidence of cardioselective β -blocker safety and tolerability in COPD patients, β -blockers are grossly underprescribed to HF patients with concomitant COPD^[12,13,15]. To overcome current dilemmas, future research is warranted.

CURRENT STUDIES

The CIBIS-ELD^[26] multicenter, randomized, double-blind, double-dummy trial investigated the tolerability

of 2 pharmacologically distinct β -blockers, β -1 selective bisoprolol and nonselective carvedilol, in elderly patients with HF. Patients were included if they were β -blocker-naïve or under-dosed ($\leq 1/4$ of target daily dose). After randomization in a 1:1 manner β -blockers were uptitrated over 14-d interval according to patient condition. The primary end-point was tolerability after 4 wk of the achieved dose maintenance phase. Importantly, this is the first randomized, large scale β -blocker trial to have pulmonary function data. Spirometry was performed at baseline and after β -blocker titration. We expect to provide conclusive data on the prevalence of COPD and whether pharmacologically different β -blockers have any pulmonary effects in HF patients with or without COPD. Results of CIBIS-ELD, along with previously mentioned epidemiological studies are likely to set the stage for trials with angiotensin converting enzyme inhibitors and β -blockers in patients with COPD.

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Management and therapy of vasovagal syncope: A review

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Abstract

Vasovagal syncope is a common cause of recurrent syncope. Clinically, these episodes may present as an isolated event with an identifiable trigger, or manifest as a cluster of recurrent episodes warranting intensive evaluation. The mechanism of vasovagal syncope is incompletely understood. Diagnostic tools such as implantable loop recorders may facilitate the identification of patients with arrhythmia mimicking benign vasovagal syncope. This review focuses on the management of vasovagal syncope and discusses the non-pharmacological and pharmacological treatment options, especially the use of midodrine and selective serotonin reuptake inhibitors. The role of cardiac pacing may be meaningful for a subgroup of patients who manifest severe bradycardia or asystole but this still remains controversial.

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Key words: Vasovagal syncope; Midodrine; Adrenergic β -antagonists; Serotonin uptake inhibitors

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INTRODUCTION

Syncope is a common clinical problem challenging both cardiologists and general practitioners with an annual incidence of 1.3 to 2.7 events per thousand population^[1]. The aim of this review is to present a review on the management and treatment of vasovagal syncope. It covers new aspects presented in current guidelines for the diagnosis and management^[2], and new data for risk stratification^[3].

The main aim of the evaluation is to distinguish patients with a benign cause like vasovagal syncope from patients with life-threatening conditions like arrhythmias, severe cardiovascular diseases or neurological causes to minimize the risk of sudden cardiac death. There is still a high unexplained syncope rate in all settings, so new strategies for evaluation and diagnosis are crucial.

DEFINITIONS: SYNCOPE, PRESYNCOPE, REFLEX SYNCOPE, VASOVAGAL SYNCOPE

Syncope is defined as a transient and self-terminating loss of consciousness (LOC) with rapid onset, short duration combined with spontaneous, prompt and complete recovery. Syncope is characterized by global cerebral hypoperfusion^[2]. It is essential to discriminate syncope from other disorders with transient LOC, e.g. seizure, hypoglycemia, catalepsy or aborted sudden cardiac death. In most cases a detailed medical history and information about the trigger situation allows identification of cause. To avoid confusion, syncope should not be used as a synonym for transient loss of consciousness. The term 'pre-syncope' or 'near-syncope' is used to describe a state that resembles the prodrome of syncope but which is not followed by LOC^[2]. It is important to underline that doubts remain

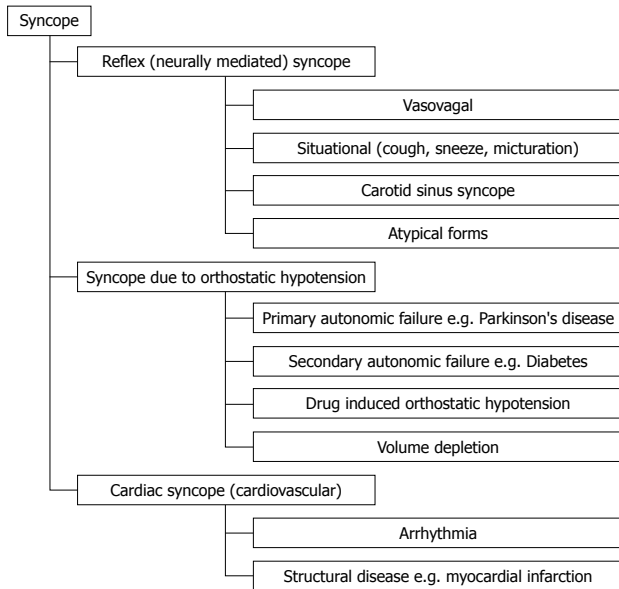


Figure 1 Classification of syncope.

as to whether the pathophysiological mechanisms of pre-syncope are the same as in syncope. Figure 1 displays a pathophysiological classification defined in the new guidelines: the first mechanism is a reflex causing bradycardia induced by typical triggers. The second is induced by inadequate venous return, due to volume depletion or venous pooling. The third is due to cardiovascular causes, such as arrhythmia and structural diseases^[2].

The reflex syncope includes different types of syncope which all show a typical trigger circumstance and an induction of cardiovascular reflexes. Activation of these sympathetic and parasympathetic reflex loops instigates either hypotension (vasodepressor type) or bradycardia (cardioinhibitory type) or both (mixed type)^[4]. The term neurocardiogenic syncope should not be used any longer.

Current guidelines subclassify reflex syncope into vasovagal, situational, carotid sinus syncope, and atypical reflex syncope^[2]. 'Vasovagal' syncope, also known as the 'common faint', is mediated by emotion or by orthostatic stress. It is usually preceded by prodromal symptoms of autonomic activation (sweating, pallor, nausea)^[2].

EPIDEMIOLOGY

Epidemiological studies indicate that up to 40% of the general population has experienced at least one episode of syncope in their lifetime^[5-9]. Savage *et al*^[1] reported an incidence of 1.3 per 1000 person-years for at least one syncopal episode and 1.0 per 1000 person-years in subjects with criteria for isolated syncope (likely vasovagal syncope). Soteriades *et al*^[7] reported an overall incidence of a first report of syncope in 6.2 per 1000 person-years. Recently a large database with reasons for encounters of general practitioners in the Netherlands revealed that 2 to 9 per 1000 encounters are due to blackouts or fainting^[10].

A reflex syncope is the most frequent cause of syncope

in any setting and age group^[2] representing 21% of all syncope in the general population^[7], 35%-48% of syncope presenting to the emergency department^[11] and 56%-78% of syncope in a specialized syncope unit^[11,12]. The vasovagal syncope is by far the most common reflex syncope in young patients. Clinical studies reveal a peak incidence between 10 and 30 years of age^[5,13]. The epidemiology of syncope is different in relation to age. In younger patients a neurally-mediated mechanism is the most common cause, while in older patients cardiovascular causes are more prevalent. The actual incidence and prevalence of vasovagal syncope in the elderly has not yet been established, but vasovagal syncope is now being diagnosed with increasing frequency in this age group, suggesting a bimodal age distribution of vasovagal syncope^[14]. In the elderly, cardiac causes, orthostatic and postprandial hypotension, and the effects of medications are common, whereas typical vasovagal syncope is less frequent^[10]. In the older patients the diagnostic work-up is more complex, the prognosis may not necessarily follow the benign course commonly observed in younger patients and therapy often remains uncertain. In this paper the management and treatment of vasovagal syncope focuses on patients with vasovagal syncope.

ETIOLOGY AND PATHOPHYSIOLOGY

The pathophysiology of the hypotension/bradycardia reflex responsible for vasovagal syncope is not completely understood. Central as well as peripheral mechanisms have been implicated in its pathogenesis; however their relative contribution is not fully elucidated. The different clinical presentation of vasovagal syncope, the variable outcome and the syncope tilt-induced with different drugs such as isoproterenol, nitroglycerin, or clomipramine, acting at very different levels of the reflex pathway, suggest that complex pathophysiological mechanisms may cause a vasovagal reaction.

The pathophysiology of vasovagal syncope is characterized by a reflex activation triggering a rapid decrease in heartbeat and a reduction of vascular tone^[15]. The concept of depressor reflexes originating in the heart was first described by von Bezold in 1867 and was later revised by Jarisch in 1937. The change to an upright position causes venous pooling: up to 800 mL of blood flows down to the legs. By activation of the autonomous system contractility and heartbeat increases to maintain sufficient circulating heart volume^[16]. In the first moments of a vasovagal syncope an empty heart is seen in echocardiographic investigations because of an acute loss of preload ('empty heart' syndrome)^[17].

Mechanoreceptors located in the wall of the left ventricle, the aorta and the pulmonary trunk were activated. Sensory receptors with non-myelinated vagal afferent pathways (found mainly in the left ventricle but also in the bladder, lungs or esophagus), detect and control cardiac filling to preserve a sufficient vascular tone. Stimulation of these inhibitory cardiac receptors by stretch forces, chemical substances or drugs heightens parasympathetic

activity and inhibits sympathetic activity^[18]. Vagal c-type nerve fibers connect the heart with the brainstem. Within the brainstem vagal neurons are stimulated and the activity of cells of the sympathetic nervous system is depressed.

Activation of this reflex mechanism provokes bradycardia, vasodilatation and hypotension. Furthermore, non-cardiac, humoral effects are part of the efferent leg of this reflex loop: e.g. renin, catecholamine and glucocorticoid secretion is augmented^[19]. Conversely, a decrease in the activity of these inhibitory sensory receptors stimulates an increase in sympathetic activity, vascular resistance, plasma renin activity and vasopressin. The main trigger for this reflex loops is a reduction in venous return during upright position. Factors which augment this reflex response include extravascular factors such as a warm environment or psychological stress^[20].

The different types of vasovagal syncope are explained by different degrees of activation or depression of the autonomous nervous system: a more intensive activation of the parasympathetic nervous system provokes bradycardia, the main symptom of cardioinhibitory vasovagal syncope. The primarily acute loss of sympathetic stimulation is the reason for the drop of blood pressure, the main symptom of the vasodepressive type. Nevertheless in most cases a combined mechanism is seen. Recent data in patients with vasovagal syncope undergoing tilt testing potentiated by intravenous clomipramine, suggested that the neurally-mediated syncope can not only be provoked by increased sympathetic nerve tone, but can also be initiated by some central nervous system triggers of the serotonergic system^[21]. In addition, in older subjects the mechanisms of tilt-induced syncope seems to be different than in younger subjects, justifying at least partially the different clinical pattern of neurally-mediated reflex syncope.

CLINICAL PRESENTATION

Although most patients display typical conditions and signs of a vasovagal syncope such as symptom onset during standing, light-headedness and full recovery after a few minutes, up to 30% have an atypical presentation. In some cases syncope occurs without any prodromal symptoms^[22]. The loss of consciousness is usually brief and fatigue is rarely seen. In the case of longer lasting cerebral hypoperfusion seizure-like movements are observed, imitating an epileptic seizure.

Symptoms before fainting are caused by reduced cerebral perfusion. The patients complain of fatigue, weakness, dizziness, wetness of the skin, a dimming of vision, and sometimes tinnitus and complete loss of vision. Some patients suffer trauma, though severe traumatic injuries are rare.

DIAGNOSTICS

Basic diagnostics

Many sophisticated tools, provocation tests and diagnostic methods have been introduced to diagnose vasovagal syn-

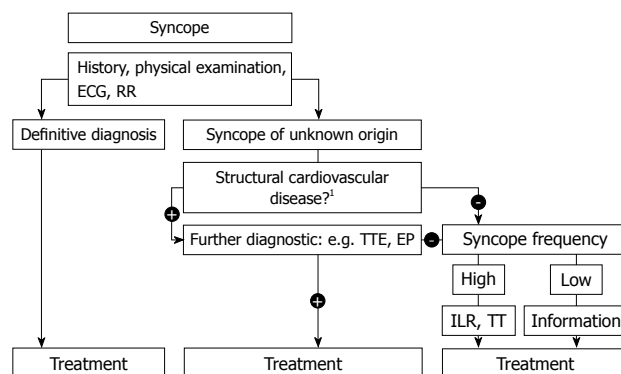


Figure 2 Diagnostic pathway in syncope. ¹Structural heart disease (e.g. valvular, myocardial infarction) or vascular diseases (e.g. pulmonary embolism, aortic disease). ECG: Electrocardiography; RR: Non-invasive blood-pressure; TTE: Transthoracic echocardiography; EP: Electrophysiologic study; ILR: Implantable loop recorder; TT: Head-up tilt table test.

cope though none are definitive. An exhaustive in-depth history and detailed examination are essential for diagnosis^[23,24]. The identification of life-threatening conditions in which syncope is only the indicator of an underlying cardiovascular disease is paramount.

Most experts recommend a standard 12-lead electrocardiography (ECG) as a routine investigation to rule out heart rhythm disturbances^[22]. In any patient with a history of cardiac disease and/or an abnormal examination, e.g. heart murmurs, echocardiography and/or stress-ECG is justified (Figure 2).

Special tests in suspected vasovagal syncope

Tilt table test: In patients with unexplained syncope and ambiguous history for a vasovagal syncope, a tilt table test may help to support a diagnosis^[2]. Fundamental to tilt testing is the ability to replicate the patient's symptoms, during which critical observations of heart rate and blood pressure are documented^[25]. A head-up tilt table test is a widely employed method in the diagnosis of syncopal disorders. Many investigations reported its usefulness in detecting neurally-mediated syncope^[26]. Different tilt table protocols are introduced with variations in the initial stabilization phase, duration of tilting (20 to 45 min) and application of pharmacological agents^[27,28]. Currently the most used protocols are the intravenous isoproterenol test, and the protocol using sublingual nitroglycerin^[29,30]. Some protocols use adenosine^[31], clomipramine^[32] or alcohol^[33] to provoke syncope. We use a method commonly known as the Westminster protocol, which was first introduced by Fitzpatrick *et al*^[34]. After maintaining a supine position of 10 min the patient is tilted to a head-up angle of 60°. If symptoms are not proved within a few minutes sublingual nitroglycerin is administered as additional provocation. Using the same protocol, Raviele *et al*^[35] observed a positive test response in 51% of patients with unexplained syncope; the test resulted in a specificity of 94%. In a recent analysis of pooled data published by Brignole, a positive head-up tilt table test was found in 62%-69% of patients with unexplained syncope, with a sensitivity of

94%^[36]. Due to a lack of a gold standard, sensitivity and specificity of the tilt table test for patients with vasovagal syncope is not exactly known. Furthermore, the tilt table test presents several disadvantages. First, the test is time-consuming and requires experienced medical staff and appropriate technical equipment such that small clinics and general practitioners cannot perform this investigation. Second, the reproducibility of a positive head-up tilt table test varies enormously. Foglia-Manzillo *et al.*^[37] could reproduce a first positive head-up tilt table test in 77% of 34 patients, whereas Ruiz *et al.*^[38] found a reproducibility rate for the positive and negative head-up tilt table test of 54.5% and 84.3%, respectively. Third, several studies have shown that the mechanism of syncope during a tilt table test is not equivalent to that of a spontaneous syncope. For this reason, the tilt table test is not a useful method to determine therapeutic strategies for patients with vasovagal syncope.

The implantable loop recorder: The main goal of the evaluation of patients with syncope is to rule out cardiac arrhythmia as a marker of a high risk for cardiac death^[15]. Continuous monitoring increases the likelihood of arrhythmia detection, with modern implantable loop recorders (ILRs) capable of continuous recording for up to 18 months. The ILR is implanted subcutaneously in the left hemithorax with automatic and patient-activated ECG-documentation modes available on most devices. Many studies have shown its value in detection of infrequent arrhythmias^[39-41]. Current guidelines suggest ILR implantation for unexplained syncopes. In patients with vasovagal syncopes a significant cardioinhibitory reaction is seen in 25% and a mild decrease of the heart rate in 50% of all falls. Even documented asystole does not necessarily indicate that an anti-bradycardic therapy would result in symptoms relief, if the setting is typical for vasovagal syncope. Particularly in young patients, the question “when to implant” and “whom to implant” a pacemaker is often far from clear even with current trial evidence. We believe that a conservative pacing policy in younger patients without any evidence for structural heart disease or conduction disease is justifiable. In contrast every patient with a history of structural heart disease, unexplained syncope or high risk for cardiac arrhythmia may benefit from an ILR or a pacemaker.

The value and cost-effectiveness of ILR is well documented^[42-44]. Implantation at an early stage in the investigation may reduce the costs of unnecessary investigations^[45].

What treatment options do we have?

Once the diagnosis is clear the next questions that arise include, who needs therapy and what kind? Every patient benefits from information and education; some patients need medical therapy and only a few people need a pacemaker.

As there are many causes of syncope, a specific treatment cannot be administered without knowing the exact mechanism responsible for syncope. The main therapeutic

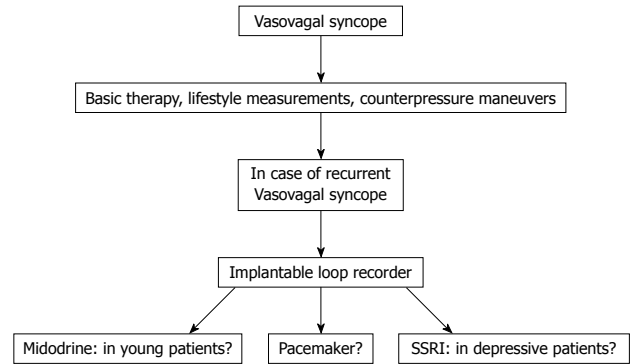


Figure 3 Treatment of vasovagal syncope. SSRI: Selective serotonin reuptake inhibitors.

innovations of the most recent years are isometric counter-pressure maneuver, lower limb compression bandage and therapy guided by external and ILR in patients with recurrent suspected neurally-mediated syncope. Most drugs are considered ineffective. However, some drugs such as midodrine and paroxetine showed positive results in patients with recurrent vasovagal syncope. The cornerstone of therapy for young patients with vasovagal syncope remains education and reassurance, except in rare and isolated cases of patients with a high frequency of recurrent episodes despite nonpharmacological measures. In the elderly, specific treatment is often necessary. In these patients, determination of the hemodynamic mechanism of spontaneous syncope by means of an external or implantable cardiac monitor seems to be the most advisable option for optimal management. Limited data exist for the role of drugs in the treatment of vasovagal syncope in older patients.

The main goal of treatment is to reduce syncope recurrence and physical trauma. However, patients with a single syncope without any high-risk occupations (e.g. professional drivers, pilots) may not necessarily need specific therapy. Clear education and counseling about the nature of the benign condition and how to avoid triggers may be sufficient. Patients with a high risk of recurrence or injury can be identified by risk scores and may require tailored treatment (Figure 3). Known risk factors for recurrent vasovagal syncope are the number of preceding syncopal spells and female gender^[3]. In contrast, the head-up tilt test response has no predictive value ($P = 0.881$)^[3].

Non-medical therapy

An informative and instructive talk with the patient about the benign nature and prognosis is the first step in the treatment of patients with vasovagal syncope. Conditions triggering vasovagal reflexes should be avoided such as a hot environment, humid atmosphere, prolonged standing, and reduced water intake^[2]. A reduction or cessation of vasoactive substances may be necessary^[46]. Discontinuation of hypotensive drug treatment for concomitant conditions is an important first line measure for the prevention of syncope recurrences in many subjects, especially in older patients. Substitution of salt and intake of isotonic

drinks expands the circulating blood volume and may improve venous return^[47].

Patients should be motivated to identify prodromals of syncope. Lying or sitting down when initial symptoms appear may avert or attenuate syncope or traumatic falls.

Furthermore counterpressure maneuvers such as hand-grip and leg crossing may inhibit vasovagal syncope by increasing the venous return^[48]. Leg crossing combined with tensing of muscles at the onset of prodromal symptoms can delay or even prevent vasovagal syncope^[48]. A more complex and time-consuming concept is that of tilt training: orthostatic training was found to significantly improve symptoms in adolescents with neurocardiogenic syncope^[49]. Twice-a-day training sessions of 40 min tilt positioning at home by standing against a wall significantly reduced the incidence of recurrence^[49]. However, the compliance in a tilt training program is rather low^[50,51] and no long-term data are available.

Pharmacological therapy

A number of drugs have been tested in the treatment of vasovagal syncope. These have included β -blockers, disopyramide, scopolamine, theophylline, ephedrine, etilefrine, midodrine, clonidine, and serotonin reuptake inhibitors (SRI)^[2]. Actually, no convincing data exist to support the use of one over another as a first line therapy. There is only limited data from placebo-controlled trials.

β -blockers: β -blockers have been the first choice for many years. Several small non-randomized, uncontrolled trials have shown a benefit, supporting the pathophysiological concept that β -blockers reduce sympathetic activity and avoid an “overshooting” vagal reaction^[52]. However, there was no positive outcome in randomized, long-term, controlled trials for metoprolol^[53], propranolol, nadolol^[54] or atenolol^[55]. According the guidelines of the European Society of Cardiology, β -blockers should not be used to treat reflex syncope^[2].

Midodrine: Midodrine, an alpha-agonist vasoconstrictor, affects smooth muscle cells both in arteries and veins without effecting heart rhythm or negative inotropy. There is no effect on the central nervous system. It is metabolized to the active drug desglymidodrine^[56]. It has to be administered 3 times per day starting with 5 mg, because of a half-life of only 2-3 h. In 3 small randomized, placebo-controlled trials, midodrine had a beneficial effect on symptom frequency, symptoms during head-up tilt, and quality of life^[57-59] (Table 1). Ward *et al.*^[57] evaluated 16 patients (mean age 56 years) in a 2 \times 2 crossover trial: group 1 received placebo for the first 28 d (period 1) and midodrine for the second 28 d (period 2); while group 2 received midodrine for period 1 and placebo for period 2. Patients treated with midodrine showed more symptom-free days ($P < 0.0001$), a higher quality of life and fewer positive tilt testing results ($P = 0.01$).

However, these patients probably had overlap with some forms of orthostatic hypotension. In an acute

Table 1 Midodrine: randomized placebo-controlled trials

Author, year	<i>n</i>	Follow-up period	Endpoint	<i>P</i>
Ward <i>et al.</i> ^[57] , 1998	16	1 mo	TT	0.01
Perez-Lugones <i>et al.</i> ^[58] , 2001	61	6 mo	Syncope recurrence	< 0.01
Kaufmann <i>et al.</i> ^[59] , 2002	12	1 wk	TT	< 0.02
Qingyou <i>et al.</i> ^[60] , 2006	26	42 mo	TT	< 0.05

TT: Head-up tilt table test.

Table 2 Selective serotonin reuptake inhibitors: randomized placebo-controlled trials

Author, year	<i>n</i>	Drug	Follow-up period	Endpoint	<i>P</i>
Theodorakis <i>et al.</i> ^[63] , 2006	96	Fluoxetine	6 mo	Time to vasovagal episode	< 0.05
				Well-being	0.01
				Syncope episodes	NS
Di Girolamo <i>et al.</i> ^[62] , 1999	68	Paroxetine	6 mo	TT	< 0.001
				Syncope recurrence	0.001

TT: Head-up tilt table test; NS: Not significant.

double-blind placebo-controlled tilt study performed in 12 patients with a history of neurally-mediated syncope, Kaufmann *et al.*^[59] (Table 1) reported that a positive tilt result was observed in 67% of patients in the placebo group *vs* 17% of patients in the active medication group. The patients were randomized to receive a nonpressor dose of midodrine (5 mg) or placebo on day 1 and the opposite on day 3. One hour after drug or placebo administration, patients underwent 60-degree head-up tilt lasting 40 min (unless hypotension or bradycardia developed first). Positive results were also obtained in one small randomized trial of pediatric patients. These data suggest that midodrine is more effective in the treatment of orthostatic hypotension caused by autonomic dysfunction than in the neurally-mediated syncope. The available data are still insufficient to prove an efficacy of midodrine in vasovagal syncope. Midodrine may be indicated in patients with frequent vasovagal syncope refractory to lifestyle measures (recommendation II B, level B)^[2] (Figure 3).

Serotonin reuptake inhibitors: In contrast to vasoconstrictors, SRI may reduce the central sympathetic nervous system activity^[61]. Some open-label studies and one randomized, placebo-controlled trial demonstrated that SRI may reduce recurrent vasovagal syncope: during a follow-up of 25 mo, 17.6% of patients who randomly received paroxetine had syncope recurrence compared to 52.9% of the placebo group ($P < 0.001$)^[62], although fluoxetine failed to show a significant reduction compared to propranolol^[63] (Table 2). However Takata *et al.*^[64] reported that

Table 3 Pacemaker-therapy: randomized trials

Author, year	Trial	n	Design	Follow-up period (yr)	Endpoint	P
Conolly <i>et al</i> ^[65] , 1999	VPS I	54	No placebo	1	Syncope recurrence	< 0.001
Sutton <i>et al</i> ^[66] , 2000	VASIS	42	No placebo	3.7	Syncope recurrence	< 0.001
Ammirati <i>et al</i> ^[67] , 2001	SYDIT	93	No placebo	1.5	Syncope recurrence	0.004
Conolly <i>et al</i> ^[68] , 2003	VPS II	100	Placebo	0.5	Syncope recurrence	NS
Raviele <i>et al</i> ^[69] , 2004	SYNPACE	29	Placebo	2 yr	Syncope recurrence	NS

NS: Not significant.

paroxetine does not prevent the vasovagal reaction associated with carotid sinus massage and/or lower body negative pressure in healthy volunteers. Until the result of the study is confirmed by other trials, use of this drug cannot be recommended.

Cardiac pacing

The role of cardiac pacing is controversial. Non-placebo-controlled trials (VPS I, VASIS, SYDIT) showed some benefit with dual-chamber pacing in reducing syncope recurrence^[65-67] (Table 3). However, placebo-controlled trials in which all patients received a dual-chamber pacemaker and were randomly assigned to DDD or DD0-Mode could not reproduce these results (VPS II, SYNPACE)^[68,69] (Table 3). A recently published meta-analysis of all studies suggested a non-significant 17% reduction in syncope from the double-blinded studies, and an 84% reduction in the studies where the control group did not receive a pacemaker^[70]. In conclusion, the results of small, initial trials have overrated the treatment effect of pacemakers due to a lack of blinding of physicians and patients. Blinded trials suggest that the apparent effect is due to a strong expectation response to pacing^[70].

ILRs may identify patients with severe cardioinhibitory vasovagal syncope and hence a better detection rate may identify responders to pacing more accurately. This is supported by the observation that patients with syncope associated with abrupt bradycardia displayed a better response to cardiac pacing therapy than those with gradual onset bradycardia^[71]. The syncope burden decreased from 2.7 per year to 0.45 per year ($P < 0.02$)^[71]. A larger trial, the ISSUE 2 study, hypothesized that spontaneous asystole and not tilt test results should form the basis for patient selection for pacemaker therapy. This study followed 392 patients with presumed reflex syncope with an ILR. Patients with ILR-guided therapy, predominantly pacing for asystole, experienced a reduction in recurrence of syncope compared to non-ILR-guided therapy (10% *vs* 41%, $P < 0.002$). It is noteworthy that ISSUE 2 was not a randomized trial in contrast to the ongoing ISSUE 3 study which will give new insights into ILR-guided pacemaker therapy in vasovagal syncope^[72].

Given a IIa/B classification by the European Society of Cardiology, pacemaker implantation may play a role in special circumstances. It should be considered in patients with frequent recurrent reflex syncope, e.g. when no prodromes occur, an age > 40 years and documented spontaneous bradycardia or asystole during monitoring^[2].

CONCLUSION

The management of vasovagal syncope is evolving. The pathophysiology of vasovagal syncope is not fully understood. Non-pharmacological treatment options are a fundamental first step of all treatment pathways. Only limited data exist showing a modest benefit using midodrine or SRI for recurrent vasovagal syncope. An ILR is a useful tool to detect or exclude hazardous cardiac arrhythmia.

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Contribution of oxidative stress to pulmonary arterial hypertension

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dase, and uncoupled endothelial nitric oxide synthase. As disease progresses circulating monocytes and bone marrow-derived monocytic progenitor cells are attracted to and accumulate in the pulmonary vasculature. Once established, these inflammatory cells generate ROS and secrete mitogenic and fibrogenic cytokines that induce cell proliferation and fibrosis in the vascular wall resulting in progressive vascular remodeling. Deficiencies in antioxidant enzymes also contribute to pulmonary hypertensive states. Current therapies were developed to improve endothelial function, reduce pulmonary artery pressure, and slow the progression of vascular remodeling in the pulmonary vasculature by targeting deficiencies in either NO (PDE-type 5 inhibition) or PGI₂ (prostacyclin analogs), or excessive synthesis of ET-1 (ET receptor blockers) with the intent to improve patient clinical status and survival. New therapies may slow disease progression to some extent, but long term management has not been achieved and mortality is still high. Although little is known concerning the effects of current pulmonary arterial hypertension treatments on RV structure and function, interest in this area is increasing. Development of therapeutic strategies that simultaneously target pathology in the pulmonary vasculature and RV may be beneficial in reducing mortality associated with RV failure.

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Abstract

Recent data implicate oxidative stress as a mediator of pulmonary hypertension (PH) and of the associated pathological changes to the pulmonary vasculature and right ventricle (RV). Increases in reactive oxygen species (ROS), altered redox state, and elevated oxidant stress have been demonstrated in the lungs and RV of several animal models of PH, including chronic hypoxia, monocrotaline toxicity, caveolin-1 knock-out mouse, and the transgenic Ren2 rat which overexpresses the mouse renin gene. Generation of ROS in these models is derived mostly from the activities of the nicotinamide adenine dinucleotide phosphate oxidases, xanthine oxi-

Key words: Pulmonary arterial hypertension; Rosuvastatin; Oxidative stress; Nicotinamide adenine dinucleotide phosphate oxidase; Statins

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INTRODUCTION

Pulmonary arterial hypertension (PAH), defined as mean pulmonary artery pressure (PAP) in excess of 25 mmHg at rest, is a rare and devastating disease that targets the endothelium of small pulmonary arteries resulting in vasoconstriction and profound vascular remodeling. Vasoconstriction results partly from endothelial dysfunction caused by an imbalance in bioavailability of dilators, such as nitric oxide (NO) and prostacyclin (PGI₂) *vs* excess in constrictors, such as, endothelin-1 (ET-1), thromboxane, serotonin, and angiotensin II (Ang II). The local imbalance in vasoactive mediators promotes proliferation, hypertrophy, and fibrosis within pulmonary arterioles. Early stages of vascular remodeling include medial hypertrophy and hyperplasia, whereas the arterioles of patients with advanced PAH are characterized by complex plexiform lesions resulting from intimal hyperplasia^[1]. These changes eventually lead to luminal occlusion and arteriolar pruning. The progressive increase in PAH increases afterload on the right ventricle (RV) which promotes right ventricular hypertrophy (RVH). During an initial period of compensation the RV may exhibit enhanced contractility in response to the increased afterload. With progressive increases in afterload the RV decompensates which results in RV failure. RV failure is marked by diminished myocardial perfusion and ischemia, increased end diastolic volume, RV dilation, reduced stroke volume, and reduced cardiac output. The factors contributing to the hemodynamic and structural abnormalities of the decompensating RV are likely due to neurohormonal signaling (Ang II, aldosterone, ET-1), natriuretic peptides, and adrenergic stimulation), oxidative stress (reactive oxygen and nitrogen species), inflammation (inflammatory cytokines), and myocardial cell death. One common cause of death in patients with PAH is right sided heart failure^[2].

Current therapies were developed to improve endothelial function, reduce PAP, and slow the progression of vascular remodeling in the pulmonary vasculature by targeting deficiencies in either NO (PDE-type 5 inhibition) or PGI₂ (prostacyclin analogs), or excessive synthesis of ET-1 (ET receptor blockers) with the intent to improve patient clinical status and survival^[3]. Although little is known concerning the effects of current PAH treatments on RV structure and function interest in this area is increasing^[4]. Important clinically relevant questions are raised in this regard because the simultaneous goals of reducing pulmonary vascular resistance and improving RV function may be challenging. Current therapies may reduce proliferation and increase apoptosis in cells in the pulmonary vascular wall and these same effects may be detrimental to cardiomyocytes in a decompensating RV. ET-1 receptor blockade may reduce PAP and slow pul-

monary vascular remodeling, yet the negative inotropic effects could be beneficial in some patients with compensated RVH and detrimental in patients with a decompensated RV. Therapeutic strategies that could be potentially beneficial to both the pulmonary vasculature and the RV would be those that reduce reactive oxygen species (ROS), reactive nitrogen species (RNS), inflammation, and fibrosis^[4].

The underlying causes of PAH are still largely unknown but, like many diseases, are likely to involve an interaction between genetic and environmental factors. Diagnosis usually occurs in patients with established disease because symptoms at presentation, such as dizziness, dyspnea, and syncope, are generally nonspecific. Despite modest therapeutic advancements in the last 15 years, PAH still results in high morbidity and mortality^[5]. Clearly, there is a critical need for further research to identify novel targets for treatment of PAH. Herein, we will review the contribution of oxidant stress to PAH and RV failure derived from several animal models of PH and the potential role of alternative strategies such as HMG co-A reductase class of drugs, referred to as statins, as adjunctive therapy.

OXIDATIVE STRESS IN THE VASCULAR WALL

Physiologically active levels of ROS, which can be generated in healthy endothelial, smooth muscle, and adventitial cells in the pulmonary and systemic vasculatures, are involved in the routine regulation of physiologic and cellular processes^[6-8]. ROS refer collectively to both unstable free radicals, such as superoxide anion (O₂•⁻), nitric oxide (NO), hydroxyl moiety (•OH), hypochlorite (ClO⁻), and peroxynitrite (ONOO⁻), and stable oxidants such as hydrogen peroxide (H₂O₂). Free radicals are short lived because they are highly reactive and are scavenged by a series of anti-oxidant moieties and enzymes. Oxidative stress occurs when there are repeated external insults that provoke excess ROS formation which overwhelms anti-oxidant systems, thus creating an imbalance in the redox state of the cell favoring oxidation. Excess synthesis of ROS can result in cell and tissue damage due to oxidation of a number of cell constituents such as proteins, lipids, carbohydrates, and DNA. Oxidative stress can contribute significantly to the pathogenesis of atherosclerosis^[9], heart failure^[10], ventricular hypertrophy^[11], respiratory distress^[12], ischemia-reperfusion injury^[13], and pulmonary and systemic hypertension^[14]. Oxidative stress *via* peroxynitrite-induced tyrosine nitration can damage endothelial nitric oxide synthase (eNOS) and prostacyclin synthase (PGIS) which impairs vasodilation by diminishing the capacity of vessels to synthesize the vasodilators, NO and PGI₂^[15]. Moreover peroxynitrite damage to eNOS redirects the synthase activity from NO to superoxide generation and superoxide synthesized in this manner has been implicated in eNOS-dependent tyrosine nitration of prostacyclin synthase^[16].

There are multiple enzymatic and metabolic sources known to generate superoxide within cells in the vascular wall^[17,18]. They include the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases^[19], the mitochondrial electron transport chain complexes, xanthine oxidase (XO)^[20,21], cytochrome P450, cyclooxygenase^[22], and uncoupled nitric oxide synthase^[23,24]. In mitochondria ROS are normally produced as byproducts of aerobic metabolism by the electron transport complexes, with 1%-2% of oxygen (O₂) being converted to O₂•⁻ at any given time. Normally, the activities of most oxidases are below a level that could influence signaling pathways, but the NADPH oxidases and mitochondria generate sufficient superoxide under basal conditions to activate signaling related to control of soluble guanylate cyclase and ion channels^[17]. In disease states such as hypertension the NADPH oxidases^[25], XO^[26], and nitric oxide synthases become major sources of ROS, especially in the vasculature and are activated by hormones, growth factors, cytokines, and shear stress^[27]. With disease mitochondria electron transport complexes can be disrupted and become a source of ROS that promote cellular senescence, necrosis, or apoptosis^[17]. Despite these varied sources of ROS, the consensus is that the NADPH oxidases are not only the principle generator of O₂•⁻ in the vasculature during disease^[9,28-30], but their activities regulate the activities of other ROS-generating oxidases such as, XO^[26] and eNOS, and are important in recruitment of ROS-generating phagocytic cells.

EVIDENCE OF OXIDATIVE STRESS IN THE PULMONARY HYPERTENSIVE LUNG

Most of the available animal models of pulmonary hypertension (PH) exhibit the two principal pathological features in the pulmonary vasculature common to most forms of PH, which include excessive vasoconstriction and remodeling of the pulmonary arteriolar wall, primarily by a mechanism of smooth muscle proliferation within the medial layer^[14,31,32]. Because ROS may promote vasoconstriction, smooth muscle cell proliferation, and vascular remodeling, they are likely to play a critical role in many forms of PH.

Ren2 model of PAH

We recently reported a new model of PAH and pulmonary vascular remodeling in the male TG(mRen2)27 rat^[14,33]. The Ren2 is a derivative of the Sprague-Dawley (SD) rat that expresses the mouse renin gene in renal and extrarenal sites resulting in increased tissue synthesis of Ang II *via* the local RAS, Ang II-dependent hypertension, and end organ damage. Thus, we investigated the possibility that an activated intrapulmonary RAS would result in PAH in the Ren2 due in part to oxidative stress. We based this notion on the well documented fact that Ang II stimulates NADPH oxidase-generated ROS in the vasculature (Ang II)^[27,34,35]. Ang II causes rapid induction of NADPH oxidase-dependent superoxide synthesis *via* pro-

tein kinase C (PKC)^[36] and more prolonged stimulation *via* transactivation of growth factors^[37,38]. Ang II also causes redox-sensitive XO activation and eNOS uncoupling leading to increases in superoxide levels in vascular tissue^[18,22]. In 8-9 wk old male Ren2 rats, we reported that the lung expresses mouse renin and other RAS components. We also showed increases in intrapulmonary NADPH oxidase activity, superoxide, right ventricular systolic pressure, and medial layer thickening of pulmonary resistance arterioles^[14]. Additionally, we found that the superoxide dismutase/catalase mimetic, tempol, reverses PAH and pulmonary vascular remodeling. Lastly, we showed that PAH developed prior to the onset of LV dysfunction and was not due to hypoxemia^[33]. Data from these studies in the Ren2 rat support the concept that PAH can occur as a consequence of NADPH oxidase-induced oxidative stress induced by activation of the local renin-angiotensin system (RAS) within the pulmonary vasculature and lung parenchyma. In support of this concept, other laboratories recently demonstrated the potential efficacy of gene therapy targeting the RAS for treatment of PAH^[39,40]. It is likely that therapies specifically targeting the RAS will reduce Ang II-induced activation of NADPH oxidases thereby limiting oxidative stress in the pulmonary vasculature, as well as in the RV.

Chronic hypoxia-induced PH

The rodent model of chronic hypoxia-induced PH (CH-PH) is one of the most frequently used animal models to study PH. Although clinical classification schemes categorize CH-PH separately from forms of PAH, both CH-PH and PAH share many pathophysiological features in common, including elevated PAP, medial thickening of pulmonary arterioles, and RVH. To induce CH-PH typically mice or rats are exposed 10% oxygen under normobaric or hypobaric conditions. CH-PH is reversible if animals are returned to normoxia. Hypoxia induces an immediate increase in PAP, initiates an inflammatory response within the first few hours of exposure^[41], and sustains the inflammatory response over time^[42]. There is a paradoxical increase in ROS during hypoxia which is likely due in part to the increase in numbers of inflammatory cells within the lung vasculature and parenchyma. Alveolar epithelial cells exposed to hypoxic gas signal vascular endothelial cells to release cytokines and chemokines that attract circulating macrophages. Hypoxia also induces the release of bone marrow-derived monocytic progenitor cells that are then attracted to and accumulate in the pulmonary vasculature. Once established, monocytes secrete mitogenic and fibrogenic cytokines that induce cell proliferation and fibrosis in the vascular wall resulting in progressive vascular remodeling.

As indicated above there is an increase in ROS in CH-PH. For instance, in a mouse model of CH-PH, intrapulmonary artery O₂•⁻ levels are elevated^[43-45]. Moreover, the pathological changes associated with exposure to chronic hypoxia, i.e. increased intrapulmonary artery superoxide, increased PAP, RVH, and pulmonary vascular remodeling,

are abolished by administration of the antioxidant, N-acetylcysteine or the XO inhibitor, allopurinol. Xanthine oxidase levels and enzyme activities of pulmonary artery endothelial cells can be dramatically increased by exposure to hypoxia resulting in significant $O_2^{\bullet-}$ generation^[20]. This implicates ROS, including ROS generated by the activity of XO, as important mediators of pathophysiological changes that occur in this model. Nox2 knockout mice fail to develop CH-PH which suggests a critical role for $O_2^{\bullet-}$ generated by Nox2 containing NADPH oxidases^[44]. It is possible that an activated intrapulmonary RAS induces NADPH oxidase and XO induced oxidative stress in CH-PH rodents. Angiotensin converting enzyme (ACE) levels are selectively increased in the wall of newly muscularized arterioles, but not in whole lung homogenates of CH-PH rats^[46]. Treatment of CH-PH rats with ACE inhibitors or AT₁R blockers prevent development of disease. Like the affected areas of the pulmonary vasculature, ACE expression is selectively elevated in affected areas of the RV, especially areas with pronounced fibrosis and treatment with ACE inhibitors or AT₁R blockers reduce development of RVH and fibrosis^[47]. This suggests that hypoxia induces local ACE activity which generates Ang II and that the remodeling in the pulmonary resistance arterioles and RV is mediated by local AT₁R signaling which induces several oxidant generating pathways.

Monocrotaline-induced PAH

Perhaps the most frequently used rodent model of PH is the rat monocrotaline model of PAH (MCT-PAH). MCT-PAH is often used to model the progression of RV failure^[10,48,49]. MCT is a pyrrolizidine alkaloid that is administered by one time IP injection, usually at a dose of 60 mg/kg. Although the precise mechanism of action of MCT is unknown there are several published longitudinal studies describing the details of the progression of PAH and RVH^[50-53]. Like CH-PH, rats injected with MCT experience a rapid intrapulmonary inflammatory response^[51] with notable increases in inflammatory monocytes in the adventitia of pulmonary resistance arterioles within 8-16 h after injection. Muscularization of nonmuscularized and muscularized arterioles leading to increased medial layer thickness is detectable as early as 3 and 7 d post injection, respectively and reaches significance by 10 and 14 d, respectively^[50]. A decrease in the normalized ratio of number of small arterioles to alveoli number is apparent by 21 d indicating arterial pruning. RVH is apparent by 21 d and becomes progressively more severe. A radiotelemetric monitoring study in conscious male Wistar rats showed that systolic PAP, which is normally around 35 mmHg, begins to increase by 12 d post MCT injection and rises progressively to 60-65 mmHg by 28 d^[52]. Consistent with earlier studies, RVH begins to become apparent by 21 d. If rats are left untreated mortality begins to occur due to RV failure beginning around 4 wk post injection and few rats survive beyond the 5th wk following MCT injection.

The MCT-PAH model is also characterized by elevated intrapulmonary and RV superoxide levels^[48,49,54-56] while

there is a notable absence of oxidative stress in the LV^[11]. Moreover, antioxidant therapy can attenuate development of MCT-PAH and RVH. For instance, intratracheal delivery of adenovirus containing the gene for human extracellular SOD acts as an antioxidant and ameliorates development of MCT-PAH^[54]. Intraperitoneal administration of EUK-134, an SOD/catalase mimetic, also reduces oxidative stress, interstitial fibrosis, and proapoptotic signaling in the RV and improves RV function^[11]. More recently it was reported that the antioxidant, resveratrol, decreased leukocyte infiltration into the pulmonary vasculature, pulmonary artery smooth muscle cell proliferation, NADPH oxidase-induced oxidative stress, and prevented the development of MCT-PAH and RVH^[56]. Thus, it appears that multiple antioxidant therapies are effective at reducing progression of MCT-PAH.

Caveolin-1 Knock Out (cav-1 ko) Mouse Model of PH

eNOS is abundant in caveoli and forms a heteromeric complex with cav-1. Cav-1 bound to eNOS is a negative regulator of eNOS activity in endothelial cells while binding of Ca^{2+} -calmodulin to eNOS disrupts the eNOS-cav-1 complex resulting in eNOS activation and NO synthesis^[57]. Disruption of cav-1 gene expression in cav-1 knockout mice (cav-1 ko) leads to global loss of caveoli resulting in hyperactive eNOS and excessive synthesis of NO^[58]. In the lung, endothelial cells and type I pneumocytes are rich in caveoli and several studies demonstrate that the loss of appropriate eNOS regulation by cav-1 ko causes multiple complications in the pulmonary vasculature and alveolar space. Cav-1 ko mice exhibit PH, endothelial cell proliferation, endothelial dysfunction, lung fibrosis, and biventricular hypertrophy^[58-60]. eNOS hyperactivation in pulmonary arterioles is marked by increased activation of Akt and eNOS leading to elevated cGMP and enhanced relaxation, as well as hyperactivation of the p42/p44ERK-MAPK pathways leading to cell proliferation and fibrosis. These fibrotic and proliferative responses are pronounced in alveolar septa and result in impaired gas exchange, arterial hypoxemia, and PH with RVH. Pulmonary defects can be reversed with either NOS blockade or targeted reexpression of cav-1 in endothelial cells^[61,62]. This animal model demonstrates the critical nature of the cav-1/eNOS interaction for normal lung and myocardial function, as well as the deleterious consequences to the lung of disruption of NOS function that leads to excessive synthesis of the free radical, NO.

Neonatal models of PAH

In two lamb models of persistent PH of the newborn caused by either prenatal placement of an aortopulmonary shunt^[24] or ductal ligation^[63], superoxide levels become elevated in pulmonary arterioles. Superoxide is the primary oxidant responsible for oxidative stress in these models and is derived mainly from NADPH oxidase and secondarily from uncoupled eNOS. Thus, it is increasingly apparent that activation of intrapulmonary superoxide generating systems, especially the NADPH oxidases, plays

a key role in development of diverse animal models of PH.

It should be noted that most animal models of PH do not faithfully reproduce the pathophysiology observed in human PH especially in the advanced stages. Thus, extrapolating the contribution of oxidative stress in the etiology of PH in humans from animal models may be premature. Recently, a novel rodent model of PAH was developed that exhibits similar lesions in the pulmonary vasculature as occur in advanced human PAH. Upon autopsy, the pulmonary arterioles of rats given a one-time injection of a VEGF receptor blocker, exposed to hypoxia for 3 wk and returned to normoxia for 10-11 wk, exhibit concentric neointimal and plexiform lesions, similar to those observed in humans. This novel rodent model may represent the most human-like model of PAH developed to date and offer new opportunities to examine mechanisms leading to development of plexiform and other complex lesions in PAH.

Oxidative stress in humans with PH

There is evidence of oxidative stress in the lungs of patients with PH. Recently, it was shown that patients with idiopathic PAH have elevated XO activity compared to control patients and that XO activity can be reversed with treatment^[64].

Immunohistochemical studies of lung biopsy samples of patients with severe PH demonstrate ubiquitous and profound elevation of 3-Nitrotyrosine. 3-Nitrotyrosine is a widely used biomarker of oxidative damage caused by reaction of peroxynitrite with tyrosine residues on proteins. 3-Nitrotyrosine is also considered evidence for scavenging of NO by superoxide. Indeed, these patients have lower levels of exhaled NO than normal patients and this may be due, in part, to loss of NO that reacts with superoxide. 8-Hydroxyguanosine staining is present within the endothelial cells within plexiform and concentric lesions from patients with PAH and is absent in the pulmonary vascular endothelium of control patients^[65]. 8-Hydroxyguanosine is a biomarker of oxidative damage caused by reaction of superoxide with guanine. In the lungs of the same PH patients the amount and activity of Mn-SOD was lower, indicating decreased capacity to scavenge superoxide. These data suggest that the lungs of patients with severe PH are under chronic oxidative stress^[65].

Pleiotropic effects of statins could be beneficial for treatment of PAH and RVH

Since antioxidant therapy appears to be beneficial for treatment of PAH and cor pulmonale in animal models it seems reasonable to incorporate strategies that reduce the excessive activity of oxidant generating systems as adjunctive therapy. Of interest in this regard are the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors (statins), originally developed for their cholesterol lowering/antiatherogenic effects. Statins exhibit diverse beneficial effects in the vascular wall independent of effects on cholesterol synthesis^[66,67]. Statins improve

cardiovascular outcomes/risk by restoring endothelial and smooth muscle cell function, inhibiting smooth muscle cell proliferation, reducing oxidative stress and inflammation in the vascular wall, and decreasing platelet thrombogenic activity. Many of the therapeutic benefits of statins in the vasculature are the likely consequence of reduced synthesis of $O_2^{\bullet-}$ which could result in more positive regulation of cell proliferation, apoptosis, growth, migration, inflammation, extracellular matrix synthesis and degradation, differentiation and contraction^[68]. Statins are associated with decreased expression of some of the NADPH oxidase subunit mRNAs and proteins, as well as increased expression of antioxidants, such as catalase^[69] or heme-oxygenase-1^[70]. Indeed, most statins increase lung heme-oxygenase activity in adult mice^[70]. One way in which statins act to inhibit NADPH oxidase activity is by blocking Rac1 geranylation which reduces the ability of Rac1 to translocate to the membrane and interact with the NADPH oxidase complex and signal properly^[71-73]. It has not been determined whether statins reduce oxidant stress in the pulmonary circulation or RV by blocking Rac1 geranylation.

Although statins display only minimal reductions in blood pressure in the hypertensive systemic circulation^[74,75], recent evidence suggests that these agents may be efficacious in treating PAH. For instance, in rat models of PAH statins attenuate the development of PH, pulmonary vascular remodeling, and RVH^[76-78] and in some reports reverse established PAH^[79]. In rodents, statins may improve endothelial function by reversing lung eNOS dysfunction during hypoxia-induced PH^[77,80] or increasing lung eNOS expression during monocrotaline-induced PAH^[78,81]. We showed that rosuvastatin reverses PAH in the Ren2 rat by reducing NADPH oxidase-mediated oxidative stress in the lungs^[33]. We also observed that the pulmonary arterioles of Ren2 rats have a thickened medial layer due to an increase in number, but not density, of smooth muscle cells. This raises the question whether rosuvastatin directly inhibits SMC proliferation in the pulmonary vasculature. Statins inhibit SMC proliferation through inhibiting RhoA activity by inhibiting isoprenylation of this protein which prevents translocation to the plasma membrane^[82]. Rho kinase inhibitors ameliorate PAH^[83]. Indeed, simvastatin reduces proliferation and increases apoptosis of neointimal and medial SMC in pulmonary arteries or rats with PAH^[79]. An observational study of adjunctive simvastatin therapy in patients with severe PH suggests functional improvements in symptoms^[84].

Statins are well known to improve cardiac function in animal models of heart disease^[85,86], as well as in patients^[87]. Although mechanistic studies suggest improved cardiac function following statin treatment is associated with improving NO signaling and reducing inflammatory mediators more recent interest focuses on a potential role for statins in promoting myocyte regeneration and myocardial repair. Statins are known to induce mobilization of endothelial progenitor cells (EPCs) which may, in part, explain their beneficial cardiovascular effects^[88-90].

One recent study demonstrates that pravastatin dose-dependently increases circulating bone marrow derived progenitor cells which help to facilitate regenerating myocardium in diseased heart^[90]. This is of importance because circulating bone marrow-derived EPCs are able to incorporate into the vascular wall where they may assist in repair of endothelial injury^[91]. EPCs can also migrate into the myocardium where they are able to differentiate into functional cardiomyocytes^[92]. Intravenous administration of syngeneic bone marrow derived-EPCs can prevent the development of MCT-PAH in rats^[93]. Delayed delivery of EPCs to rats with established MCT-PAH prevented further disease progression while disease was reversed in rats with established MCT-PAH that received EPCs transduced with eNOS. EPCs incorporated into the endothelial lining of distal pulmonary arterioles and restored microvascular structure and function. The efficacy of EPC delivery to the RV in MCT-PAH rats has not been examined. It seems reasonable to speculate that statin therapy may exhibit multiple beneficial effects in the RV that improve RV function and structure by reducing oxidative stress and promoting repair of the RV by mobilization of endothelial progenitor cells to the injured RV myocardium. Therefore, statins may be an attractive option for treatment of PAH and cor pulmonale because they may simultaneously prevent further tissue damage by decreasing oxidative stress and enhance repair to injured sites in both the pulmonary vasculature and RV.

A recent double-blind, randomized, placebo-controlled clinical trial of adjunctive simvastatin therapy in patients with PAH receiving conventional therapy demonstrated modest benefit in the form of a small and early reduction in RV mass and N-terminal pro-B-type natriuretic peptide levels, a marker of PAH; however, benefits were not sustained over a 12 mo period^[94]. Whether the reduction in RV mass was secondary to a reduction in PVR is unknown as PVR was not measured in this study. The authors also noted the potential for drug interactions as conventional therapies such as sildenafil and bosentan, like statins, are substrates of CYP3A4. This raises the possibility that combination therapies could enhance or reduce the exposure to one or both drugs.

CONCLUSION

In summary, PAH is associated with a generalized state of enhanced oxidative stress. Current clinical approaches which targeted the endothelial dysfunction and vasoconstriction have not produced long-lasting mortality benefit. Thus, alternative approaches to treating this complex disease are needed. In this review, we put forward that oxidative stress plays a significant role in the pathogenesis of this disease. Some studies suggest that improvement in physiological and micrographic parameters can occur when animals are treated early with statins. For significant improvement in this patient population to occur, it is critical that early recognition of the condition be increased. In addition, clinical trials which evaluate approaches to

preventing the deleterious effects of the oxidative stress which can lead to an irreversible state of pulmonary artery hypertension and resultant right ventricular failure and subsequently death must be conducted.

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Ischemia/reperfusion injury: The role of immune cells

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platelets and endothelial cells are discussed with reference to the complement cascade, toll-like receptors, cytokines, oxidative stress, renin-angiotensin system, and in reference to the microvascular system in the signaling mechanisms of I/R. Finally, the findings of the data summarized in this review are most important for possible translation into clinical cardiology practice and possible avenues for drug development.

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Abstract

Ischemia/reperfusion (I/R) injury is an inflammatory condition that is characterized by innate immunity and an adaptive immune response. This review is focused on the acute inflammatory response in I/R injury, and also the adaptive immunological mechanisms in chronic ischemic disease that lead to increased vulnerability during acute events, in relation to the cell types that have been shown to mediate innate immunity to an adaptive immune response in I/R, specifically myocardial infarction. Novel aspects are also highlighted in respect to the mechanisms within the cardiovascular system and cardiovascular risk factors that may be involved in the inflammatory response accompanying myocardial infarction. Experimental myocardial I/R has suggested that immune cells may mediate reperfusion injury. Specifically, monocytes, macrophages, T-cells, mast cells,

INTRODUCTION

In this special issue of the *World Journal of Cardiology* we have assembled a cosmopolitan group of expert faculty to address the role of inflammation in cardiovascular disease.

Inflammation plays a critical role in the pathophysiology of ischemia/reperfusion (I/R) injury as evidenced by the experimental and clinical studies published during the past 20 years. Several clinical syndromes are secondary to I/R injury: myocardial injury, stroke, organ transplantation, limb ischemia and multiple organ system dysfunction. The mechanisms involved are multifaceted and complex; however, several recent studies^[1-7] provide evidence that immune cells are involved in I/R injury, as well as wound healing.

ISCHEMIA/REPERFUSION INJURY: PATHOPHYSIOLOGY

I/R causes local cellular hypoxia that is accompanied by inflammatory responses that lead to the recruitment of leukocytes and subsequent peri-infarct damage, healing, and scar formation^[8-10]. Restoration of blood flow to the ischemic tissue may paradoxically exacerbate tissue injury. Elucidating the mechanisms of inflammation and their relationship to myocardial disease is of growing importance to basic and clinical cardiovascular scientists^[6,11-13]. Ischemic myocardial injury results in decreased oxygen tension with loss of oxidative phosphorylation and subsequent decreased generation of high energy phosphates (ATP); all leading to failure of the sodium pump, loss of potassium, influx of sodium and water, and cellular swelling. Ischemia leads to anaerobic metabolism, ATP depletion and accumulation of byproducts, like lactic acid, within seconds of ischemia. This leads to loss of contractility, and within minutes, reversible ultrastructural cardiomyocyte changes appear, including cellular and mitochondrial swelling and glycogen depletion. After 20-40 min of sustained ischemia, irreversible cardiomyocyte injury develops and is seen in disruption of sarcolemma and the presence of small amorphous densities in the mitochondria^[12].

Classically, ischemia has been shown to lead to endothelial dysfunction with an increase in permeability, increased expression of adhesion molecules, and recruitment of leukocytes. The activation of the innate immune response is considered an acute reaction to I/R, with several molecular mechanisms establishing links between this innate immunity and adaptive immunity. This review will focus on the cellular mediators of the molecular mechanisms involved in I/R with specific reference to the cardiovascular system.

HUMORAL MEDIATORS OF ISCHEMIA/ REPERFUSION INJURY: CYTOKINES AND CHEMOKINES, COMPLEMENT, AND TOLL-LIKE RECEPTORS

Several studies have shown increases in myocardial cytokines, in response to experimental I/R, and in human patients subsequent to myocardial infarction (MI), coronary bypass grafting, and chronic heart failure^[3]. Other humoral mediators of I/R include oxygen and nitrogen free radicals. All of these factors combined reflect the body's nonspecific innate immunity and regulate locomotion and trafficking of leukocytes in basal and inflammatory processes, such as I/R^[10-12,14-16]. Although the heart's macrophages are a rich source of several inflammatory cytokines^[5,12,17,18], other cell types affect inflammation in experimental models of I/R^[2,19-21] and may serve as potential candidate sources of cytokines following MI. Polymorphonuclear cells (PMNs) are the major leukocytes that are found in I/R injury with subsequent neutrophil accumulation and microvascular plugging and parenchymal damage leading to tissue destruction and necrosis. Monocytes and

macrophages will infiltrate the tissue at later time points during I/R injury; however, the direct role of these cells in injury *vs* repair mechanisms is still being investigated.

Complement activation following myocardial ischemia was first described by Hill and Ward, with subsequent evidence suggesting that myocardial cell necrosis results in the release of subcellular membrane constituents that are abundant in the mitochondria and capable of triggering the complement cascade (C1, C4, C2 and C3)^[12,22-24]. Indeed, mRNA and proteins for all the components of the classical complement pathway are upregulated in areas of myocardial infarction (MI)^[25,26]. Furthermore, postischemic cardiac lymph is shown to possess leukocyte chemotactic activity, with neutralizing antibodies to C5a added *in vitro* completely abolishing the chemotactic activity^[27,28]. Several animal studies point to a possible beneficial role of complement depletion in the treatment of postischemic myocardial injury^[29-34]. Unfortunately, clinical studies focused on complement depletion in humans have not proven effective in the setting of MI^[35].

The toll-like receptors (TLRs) are emerging as the primary, non-antigen-specific defense innate immune mechanism, and represent a family of receptors that serve to recognize molecular patterns associated with pathogens and, upon binding of their ligands, induce activation of several kinases and nuclear factor (NF)- κ B. To date, 13 members of the TLR family have been identified in mammals; however, their role in cardiac pathology remains poorly understood^[11,36]. TLR2, -3, -4, and -6 are expressed in cardiac myocytes^[36]. TLR4 is expressed in the heart and is markedly induced in mouse and rat infarcts and in samples obtained from cardiomyopathic hearts with confined intense staining predominantly localized to cardiac myocytes *vs* the diffuse staining typified in healthy myocytes^[36,37]. TLR4 deficient mice have decreased infarct size and suppressed inflammation, and exhibit attenuated adverse remodeling following MI, identifying TLR4 as a key component of the innate immune response in the infarcted heart^[11,38,39]. In contrast, TLR2 null animals had similar infarct size and comparable inflammatory leukocyte infiltration with their wildtype littermates, but exhibited decreased fibrosis in the non-infarcted area and attenuated post-infarction ventricular remodeling^[40]. These findings suggest that TLR2 signaling may not critically affect the inflammatory response but may modulate fibrous tissue deposition. A role for TLRs in the activation of inflammatory cells after cardiac injury is now clearly established and warrants further elucidation.

CELLULAR MEDIATORS OF ISCHEMIA/ REPERFUSION INJURY: MONOCYTES, MACROPHAGES, DENDRITIC CELLS, T CELLS, MAST CELLS, PLATELETS, EN- DOTHELIAL CELLS

In patients who develop atherosclerosis or experience MI, several immune cell types are prevalent in clinically

relevant inflammatory conditions, not only in the acute inflammatory response to I/R injury, but also to adaptive immunological mechanisms in chronic ischemic disease that leads to increased vulnerability during acute events^[41]. This review will remain focused on monocytes, macrophages, T cells, mast cells, platelets and endothelial cells, as these are the most clinically relevant immune cell types in myocardial I/R, with specific focus on MI, classically regarded as an acute inflammatory response, as well as atherosclerosis, classically regarded as a chronic adaptive immune response.

After MI, monocytes, *via* CCR2 receptor for monocyte chemoattractant protein 1, extravasate into the injured tissue and can give rise to inflammatory dendritic cells or macrophages that accumulate at the target sites of injury^[42-46]. Alternatively, atherosclerosis is considered a chronic inflammatory state with distinct and possibly very different inflammatory pathways. The primary immune cell type involved in atherosclerosis is the macrophage. Many studies have supported a role for chemokine-mediated monocyte infiltration to atheromatous lesions^[43,47-51], however distinct subsets of monocytes have been shown to infiltrate during 1-4 d post MI (inflammatory phase) (Ly-6C^{high} monocytes) *vs* 4-8 d post-MI (reparative phase) (Ly-6C^{low} monocytes), thus linking the acute inflammatory responses to the adaptive immune responses seen in chronic atheromatous conditions^[43]. The most recent evidence to directly relate atherosclerosis to immune cell recruitment following MI, found that hypercholesterolemic mice recruit more Ly-6C^{high} monocytes in infarcts; and that these monocytes persist longer (prolonged inflammatory phase) and with compromised monocyte response and impaired infarct healing, leading to accelerated left ventricular remodeling^[52]. Indeed, monocyte biology requires additional investigation to determine the effects of these parallel but distinct inflammatory phases in the setting of atherosclerosis and MI.

Interestingly, atherosclerotic plaques are also rich in T cells and mast cells^[53-57], suggesting these cell types may mediate injury and/or repair. Several groups have shown that T cells and mast cells are capable of producing cytokines^[6,7,58-61] and that both are involved in inflammation in the heart^[5,8,11,12,19]. Indeed, it is these inflammatory cells that may bridge the innate immune response to the adaptive immune response in response to I/R. In addition to the innate immune response, T cells have other functions that may contribute to vascular dysfunction, with recent studies pointing toward additional functions with unresolved impact. For example, T cells contain components of the renin-angiotensin system (i.e. angiotensin converting enzyme, renin, renin receptor, and angiotensinogen) suggesting T cells may be able to mediate the production of angiotensin^[62]. Hoch *et al.*^[62] have shown that angiotensin II has direct action on T cells including the production of tumor necrosis factor (TNF)- α . Huang *et al.*^[63] masterfully outline several experimental studies with direct and indirect evidence of T cells modulating I/R injury in the kidney, liver or intestine. During myocardial I/R, Yang *et al.*^[64] found that myocardial infarct size was smaller in renin-angiotensin 1 (RAG1) deficient mice (RAG1^{-/-}) (*vs*

controls) following 45 min of left anterior descending artery occlusion^[6]. After adoptive transfer of CD4⁺ T cells, the infarct size of the reconstituted RAG1^{-/-} mice was significantly greater than the RAG1^{-/-} mice, however CD4⁺ T cells from interferon- γ ^{-/-} mice showed no increased myocardial infarct size. T cell subsets have also been studied in many organ systems and in experimental models of immunodeficiency with multiple cell types affected, e.g. severe combined immunodeficiency (SCID) mice or RAG1^{-/-} knockout mice. Specifically, Yilmaz *et al.*^[60,61] have evaluated and found protective roles of lymphocytes in experimental models of ischemic stroke. In the heart, CD4⁺ T cell depletion in mice, but not CD8⁺ depletion, showed significantly smaller infarct size *vs* control mice^[64]. Again, with specific attention to T cells and the vulnerable atherosclerotic plaque, Pryshchep *et al.*^[65] report that T cells from acute coronary syndrome patients have a defect in phosphorylating Lck at Tyr505, thus failing to deactivate the membrane-proximal Src kinase, and enabling T cells to respond in conditions that otherwise would be ignored by the adaptive immune system. CD4⁺ T cells from acute coronary syndrome patients produce proinflammatory cytokines and are cytotoxic toward vascular smooth muscle cells and endothelial cells, directly implicating them in vascular injury and plaque destabilization^[65-68]. Further complicating the role of T cell signaling in I/R, is the differential information among studies, with some data showing T cells are responsible for injury and some data showing T cells are required for recovery from injury subsequent to I/R. One study shows mycophenolate mofetil, an anti-proliferative immunosuppressive agent, to be protective in I/R injury of cardiac transplantation, and also accompanied by decreased leukocyte infiltration^[69].

The recruitment of leukocytes in post-ischemic microvessels is often accompanied by the accumulation of platelets^[70]. Platelet accumulation in post-ischemic post-capillary venules is dependent on leukocyte adhesion and required P-selectin. Platelets and leukocytes bind to one another on the vessel wall and potentially interfere with the binding of either platelets or leukocytes to the vessel wall, thereby potentially creating more injury after I/R by allowing the cell-cell complex to produce more superoxide and platelet-activating factor than either cell is capable of producing alone^[70-73]. Specifically, mice genetically deficient in CD4⁺ or CD8⁺ T cells exhibit a blunted platelet recruitment response to I/R, again, supporting a possible cell-cell interaction that may lead to microvascular dysfunction^[59,70].

Like T cells, mast cells are resident perivascular, multifunctional, inflammatory and pro-fibrotic mediators^[74-76] and are hypothesized to quickly respond to mechanical stimuli, such as vasoconstriction during ischemia or vasodilation during reperfusion. Several studies have implicated mast cells as possible mediators of cardiac injury^[77-79]. Frangogiannis *et al.*^[79] found that resident cardiac mast cells rapidly degranulate following infarction releasing large amounts of histamine and TNF- α , with similar findings from other groups^[74,75,80-82]. Mast cell degranulation is likely an early source of preformed histamine and TNF- α ,

modulating the inflammatory response. Later, there is more of an interaction of cells, cytokines, growth factors and extracellular matrix proteins mediating myocardial repair. TNF- α of mast cell origin may be a crucial factor in upregulating IL-6 in infiltrating cells and initiating the cytokine cascade responsible for myocyte ICAM-1 induction and subsequent neutrophil-induced injury seen in I/R^[79], thus providing a mechanistic link among cytokine-producing cell types in myocardial I/R. Histamine may induce surface expression of P-selectin in endothelial cells by facilitating recruitment of rolling leukocytes^[83].

Although many mast cell-derived mediators are capable of modulating cellular events critical to the healing infarct, the role of mast cells and their secretory products in cardiac injury and repair remain poorly understood. Experiments in a canine model of reperfused infarction demonstrated that mast cell stabilization using lodoxamide significantly reduced infarct size^[84]. An increase in mast cell numbers was noted in the healing myocardium and immature mast cell progenitors were found in the infarcted area. Although the contribution of mast cell proliferation cannot be ruled out, chemotaxis of circulating mast cell precursors in the healing myocardium secondary to stem cell factor (SCF) may be the predominant mechanism responsible for mast cell accumulation in the ischemic heart. Frangogiannis *et al.*^[76,77] hypothesize that the role of SCF in infarct healing may not be limited to its effects on mast cells and further suggest that SCF may promote recruitment and homing of primitive bone marrow-derived cells delivered into the infarct, with further differentiation into cardiomyocytes and vascular cells^[85,86].

Additionally, Ayach *et al.*^[87] found that c-kit mast cell deficient mice are protected from ventricular dilation and hypertrophy, and maintenance of cardiac function is preserved in these mast cell deficient mice with phenotypic rescue of cardiac repair after MI by bone marrow transplantation of wild-type hematopoietic stem/progenitor cells. Microarray analysis revealed the activation of natural killer (NK) cell-mediated mobilization after MI in rescued hearts. Nevertheless, the specific mediators responsible for the injurious effects of mast cell activation in the infarct were not investigated. In addition, elucidation of the role of mast cell-derived cytokines and growth factors in MI is difficult because many of these secretory products are produced by other cell types involved in cardiac repair. On the other hand, the proteases chymase and tryptase are specific mast cell products and may play unique roles in infarct healing. Chymase inhibition in a rat model of non-reperfused MI attenuated left ventricular interstitial fibrosis and diastolic dysfunction without affecting the dilative pattern of cardiac remodeling^[88]. Tryptase stimulates granulocyte recruitment, upregulates cytokine and chemokine synthesis, induces fibroblast proliferation and chemotaxis, and upregulates type I collagen production^[89-93]. Furthermore, mast cells are important sources of transforming growth factor- α , bFGF, and vascular endothelial growth factor (VEGF), factors that can regulate fibroblast growth, modulate extracellular matrix metabolism and stimulate

angiogenesis^[94-97]. Histamine has been shown to stimulate fibroblast growth and collagen synthesis *in vitro*^[98]. Mast cells may also influence healing and tissue remodeling by expressing gelatinases A and B, both implicated in extracellular matrix metabolism^[99,100].

Similar to T cells, mast cells may also produce renin following ischemia; however, this has been challenged by subsequent groups^[101,102]. Cardiac mast cell-derived renin has been shown to promote local angiotensin formation and norepinephrine release, and induce arrhythmia in excised heart preparations of I/R^[102]. Mast cell degranulation has also been proposed as a mechanism for the anti-arrhythmic effect of endothelin-1^[103].

Endothelial cells comprise the wall of blood vessels and show activation following I/R and assume an inflammatory phenotype following activation, characterized by the enhanced production of ROS, inflammatory cytokines, and expression of adhesion molecules that bind leukocytes and platelets *via* activation of NF- κ B^[104]. Blood cell-derived superoxide *via* NADPH oxidase is most likely produced by leukocytes, as this is the blood cell type with the highest capacity to generate superoxide^[105]. The superoxide generated can thereby contribute to endothelial barrier dysfunction and impaired vascular permeability subsequent to I/R. Indeed, anti-endothelial cell antibodies have been detected in a variety of disorders connected with endothelial damage, including patients with myocardial infarction^[106].

Recent work suggests a role for stem cells from systemic circulation and local tissue. These stem cells may allow for regeneration of endothelial cells and are common in transplant recipients with allograft rejection or I/R injury^[107]. This regenerative mechanism following ischemia is dependent on stem cell mobilization and homing with several mediators of this process, namely stromal-cell-derived factor 1 (SDF-1), which homes stem cells to bone marrow, found to be upregulated following MI and focal cerebral ischemia^[108]. Moreover, endothelial nitric oxide synthase (eNOS) also allows for mobilization of stem cells, with eNOS deficient mice showing reduced VEGF-dependent mobilization of endothelial progenitor cells and possibly impaired regeneration processes with reduced systemic NO bioactivity^[8,109].

CONCLUSION

Current therapeutic strategies are aimed at inhibiting oxygen radicals and inflammatory cytokines for the treatment of I/R injury, despite our limited understanding of the specific mechanisms responsible for repair. Study of the innate immune system and the activation of the adaptive immune system, with respect to which individual systems and cell types are mobilized and responsible for I/R injury *vs* repair, will likely uncover new mechanisms with results still requiring transference into clinical practice. The specific organs and tissues affected by I/R may then be targeted with specific therapies tailored to each individual system and cell type, with specific attention to the differ-

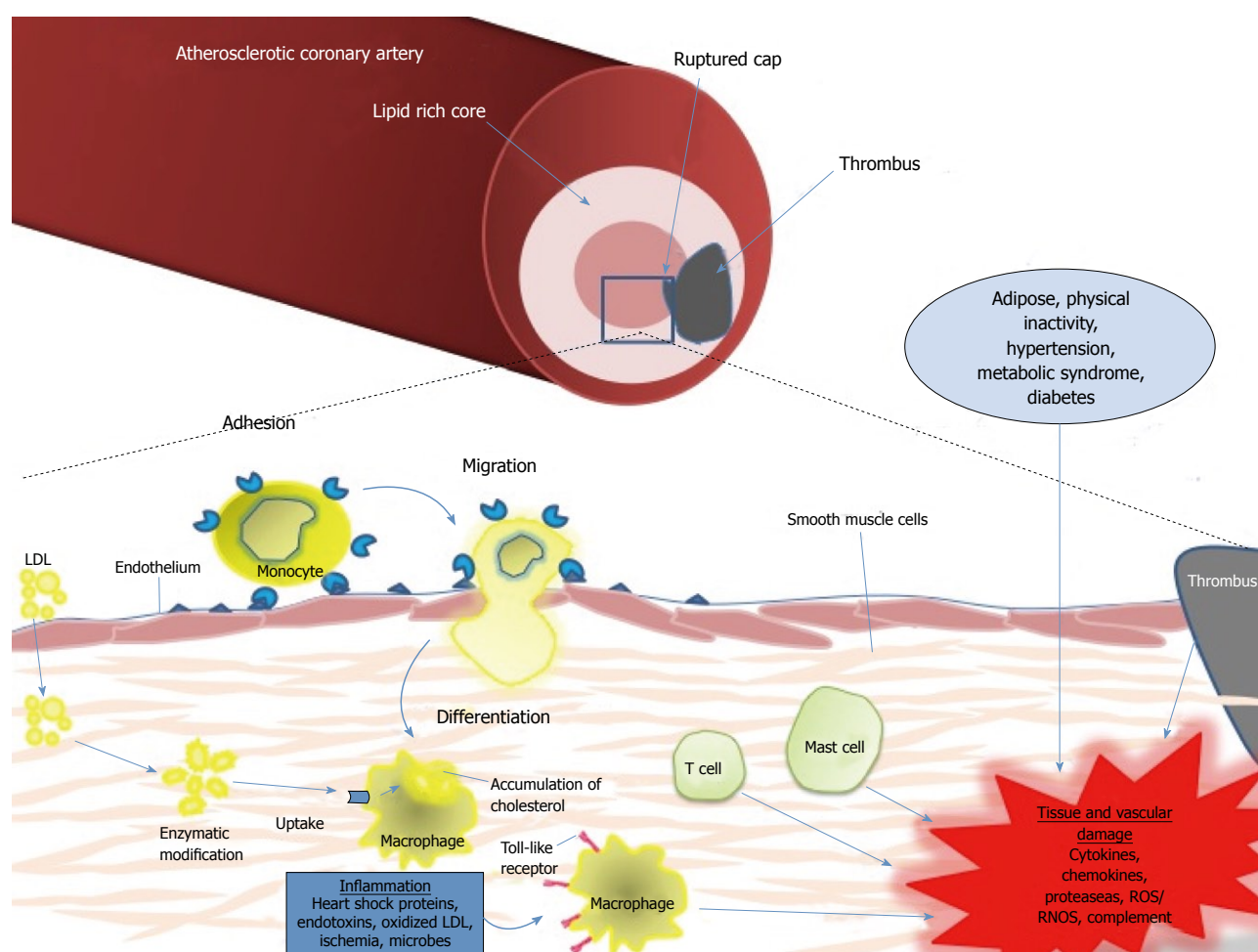


Figure 1 Mechanisms of immune cell-mediated injury following ischemia-reperfusion. Monocytes adhere to activated-endothelium at the site of thrombus formation or following ischemia in an atherosclerotic coronary artery. The adhesion of monocytes facilitates migration of the monocyte through the vessel wall. Differentiation of the cell and uptake of cholesterol particles then leads to inflammatory changes and tissue and vascular damage via macrophages, T cells and mast cells at the site of atherosclerosis. LDL: Low-density lipoprotein.

ences between immune systems of humans and experimental animal models.

Epidemiologic evidence from humans supports a clear relationship between cardiovascular risk factors and I/R injury. Hypertension, hypercholesterolemia, diabetes mellitus, obesity, and cigarette smoke all have the potential to individually or synergistically increase the sensitivity of the tissues to I/R injury, possibly through the induction of pro-inflammatory, pro-oxidative, and pro-thrombotic environments^[70]. Recent research supports the role of inflammation as a key player in coronary artery disease and manifestations of atherosclerosis (Figure 1). Immune cells dominate early atherosclerotic lesions, with effector molecules accelerating the progression of lesions, and activation of inflammation eliciting acute coronary syndrome^[110]. Pro-inflammatory cytokines stimulate the expression of leukocyte adhesion molecules on the endothelial surface that promote the binding of monocytes to their surface, with recruitment to the atheroma, and entrance to the arterial intima. Maturation of monocytes into macrophages within the arterial wall, along with recruitment of T-cells and mast cells, induce the expression of

scavenger receptors (TLRs) that permit lipid accumulation, foam cell formation, and apoptosis, and thrombogenic microparticles that allow for plaque rupture^[111]. Drugs that target immune cells may provide a novel therapeutic strategy for rescuing tissues and vessels from I/R injury in several clinically relevant syndromes, specifically MI.

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Multislice CT angiography in coronary artery disease: Technical developments, radiation dose and diagnostic value

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Abstract

Multislice computed tomography (CT) angiography has been increasingly used in the detection and diagnosis of coronary artery disease because of its rapid technical evolution from the early generation of 4-slice CT scanners to the latest models such as 64-slice, 256-slice and 320-slice CT scanners. Technical developments of multislice CT imaging enable improved diagnostic value in the detection of coronary artery disease, and this indicates that multislice CT can be used as a reliable less-invasive alternative to invasive coronary angiography in selected patients. In addition, multislice CT angiography has played a significant role in the prediction of disease progression and cardiac events. Despite promising results reported in the literature, multislice CT has the disadvantage of having a high radiation dose which could contribute to the radiation-induced malignancy. A variety of strategies have been currently undertaken to reduce the radiation dose associated with multislice CT coronary angiography while in the meantime acquiring diagnostic images. In this article, the author will review the technical developments, radiation dose associated with multislice CT coronary angiography, and strategies to reduce radiation dose. The diagnostic and prognostic value of multislice CT angiography in coronary artery disease is briefly discussed, and future directions of

multislice CT angiography in the diagnosis of coronary artery disease will also be highlighted.

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Key words: Coronary artery disease; Computed tomography; Diagnostic value; Radiation dose; Radiation risk

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in Western countries. Conventional coronary angiography is the gold standard technique for diagnosis of CAD, due to its superior spatial and temporal resolution. The diagnostic value of conventional coronary angiography has been challenged by the emergence and fast growing use of a less invasive imaging technique, multislice computerized tomography (MSCT) angiography^[1-3]. The diagnostic accuracy of MSCT angiography in CAD has been significantly augmented with the increased performance of MSCT from early generation of the 4-slice CT to 16-slice, 64-slice, dual-source CT and the latest models such as 256-slice and 320-slice CT scanners^[2-8]. This is mainly demonstrated by the improved spatial and temporal resolution from the latest MSCT scanners such as 64

or more slice scanners. In particular, MSCT angiography has been reported to demonstrate a very high negative predictive value (more than 95%), indicating that it can be used as a reliable technique for excluding patients suspected of CAD, thereby reducing the need for invasive coronary angiography.

While the number of MSCT examinations in cardiac imaging continues to increase, the potential risk of radiation exposure associated with CT should not be ignored, given the fact that CT is a high-radiation imaging modality. The radiation risks arising from cardiac CT angiography have raised serious concerns in the medical field as CT is associated with a non-negligible life attributable risk of cancer^[9]. Therefore, the benefit of the use of multislice CT angiography in the diagnostic workup and patient management must be weighed against the potential risks related to radiation exposure. In this review article, I will introduce the technical developments of MSCT in cardiac imaging, focusing on the diagnostic and prognostic value of MSCT angiography in CAD, followed by the strategies currently available to address radiation dose reduction. Future directions, including justification of use of MSCT in cardiac imaging, will be highlighted.

MULTISLICE CT ANGIOGRAPHY IN CARDIAC IMAGING-TECHNICAL EVOLUTION OF CT SCANNERS

Traditionally, electron-beam CT (EBCT) with high temporal resolution (50-100 ms) makes this technique well suited for imaging the coronary tree, with capability of evaluating tiny abnormalities such as coronary calcium deposits and plaques, even with the motion of a rapidly beating heart. However, the inferior spatial resolution (1.5 mm) of EBCT limits its diagnostic value in the detection of CAD as the coronary artery is a very small structure ranging from 1.5 mm to 3.0 mm in diameter, thus, image quality of both normal and abnormal coronary arteries is degraded to a greater extent. The introduction of MSCT scanners in 1998 represented a significant technical improvement in the CT imaging technique because imaging of the heart was made possible with MSCT as multiple images could be acquired in a single breath-hold within a very short time^[10].

The significant application of 4-slice CT in clinical practice is in cardiac imaging with the aid of an electrocardiographic (ECG)-gating technique. The ability of 4-slice CT (gantry rotation time, 500 ms with temporal resolution of 250 ms) to image the coronary arteries and detect CAD less invasively has attracted much attention from physicians in the medical field, and this is represented by the increasing number of publications on 4-slice CT coronary angiography in the literature^[2,3,11,12]. Earlier studies with 4-slice CT were promising as a less-invasive technique in cardiac imaging, although the diagnostic value was insufficient to replace conventional coronary angiography in the diagnosis of CAD^[13]. With experience gathered, it was found that the image quality of coronary



Figure 1 Three-dimensional volume rendering of the left and right coronary arteries and their branches acquired with 64-slice computed tomography angiography in a 61-year-old diagnosed with coronary artery disease. Extensive calcification is present in the coronary artery wall which is shown as the white dots.

arteries was impaired in many cases with 4-slice CT due to limited spatial and temporal resolution, and the unassessable segments could be more than 20% in 4-slice studies^[13]. Thus 4-slice CT is unsuitable for imaging patients with heart rate higher than 60 bpm.

With the introduction of 16-slice and 64-slice CT, image quality in coronary MSCT has become more consistent with improved results^[14-18]. With gantry rotation times down to 330 ms for 64-slice CT, temporal resolution for cardiac ECG-gated imaging was further markedly improved, allowing evaluation of both the main coronary artery and its side branches, including the distal artery segments. In contrast to early generations, 64-slice CT showed improved diagnostic accuracy in CAD because of improved spatial and temporal resolution. Isotropic volume data (0.6 mm × 0.6 mm × 0.6 mm) is possible with 64-slice CT, and the scanning time is reduced to less than 15 s, allowing a decreased breath-hold time, better utilization of contrast medium with fewer enhancements of adjacent structures, and a lower dose of applied contrast medium^[15-18]. An improvement in image quality has also been reported in the visualization of all coronary artery branches, with high sensitivity and specificity achieved^[15-18] (Figure 1).

Further technical improvement in cardiac imaging was achieved with the development of dual-source CT (DSCT) due to its high temporal resolution of 83 ms, thus increasing visualization of coronary arteries in patients with high heart rate by reducing motion artifacts^[19,20]. Studies have shown that the cardiac CT image quality of the coronary artery is independent of heart rate, and high diagnostic accuracy is achieved with DSCT^[19,20] (Figure 2). There is no doubt that DSCT represents another technical development with its superior temporal resolution which contributes specifically to the assessment of patients with high heart rate.

Expansion of MSCT systems from 64-slice to the latest models of 256-slice and 320-slice systems has allowed whole heart coverage in one gantry rotation with a slice thickness of 0.5 mm^[6-8]. With 320-slice CT, 16 cm of cra-

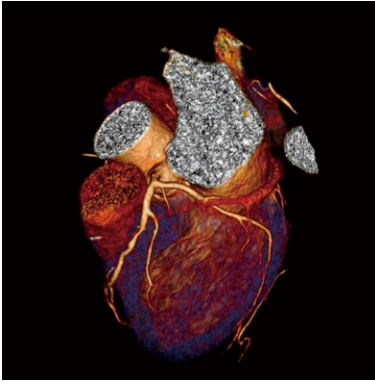


Figure 2 Three-dimensional volume rendering of the left coronary artery is acquired with dual-source computed tomography angiography in a 47-year-old woman suspected of coronary artery disease. Left anterior descending and left circumflex are clearly demonstrated without any sign of lumen stenosis or calcification.

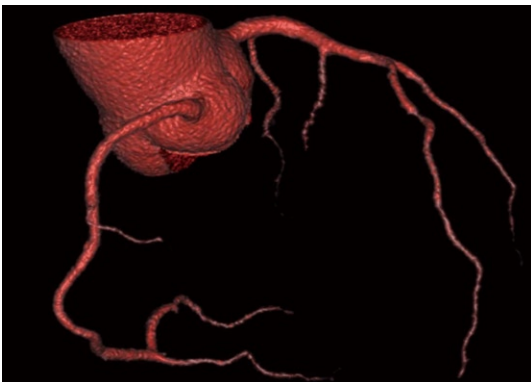


Figure 3 Three-dimensional volume rendering of the coronary arteries and side branches are clearly visualized with use of 320-slice computed tomography angiography in a 58-year-old man presenting with chest pain. Volumetric data were acquired within a single heartbeat with excellent image quality.

niocaudal coverage can be obtained in a single heartbeat, with excellent image quality and demonstration of the entire coronary arteries, and therefore, the entire cardiac volume data can be acquired within 1 s without of the need for patient movement during the scan^[7,8] (Figure 3). Table 1 lists the developments of MSCT scanners from 4-slice to 320-slice CT in terms of spatial and temporal resolution when compared to the gold standard technique, conventional coronary angiography.

MULTISLICE CT ANGIOGRAPHY IN CAD-RADIATION DOSE

Despite the above-mentioned promising results of MSCT angiography in CAD, MSCT has the disadvantage of requiring a high radiation dose. Conventional coronary angiography is effective at a radiation dose from 3 to 9 mSv, while MSCT coronary angiography delivers a radiation dose as high as 20 mSv according to early studies^[21,22]. Moreover, the average dose per site was reported to demonstrate

Table 1 Developments in multislice computed tomography scanners in terms of spatial and temporal resolution when compared to electron-beam computed tomography and invasive coronary angiography

Imaging modalities	Spatial resolution (mm)	Temporal resolution (ms)
EBCT	1.5-3.0	50-100
4-slice CT	1.0-1.25	250
16-slice CT	0.75	165-188
64-slice single-source CT	0.5-0.6	165
64-slice dual-source CT	0.5-0.6	75-83
256/320-slice CT	0.5-0.6	135-175
Invasive coronary angiography	0.2	20

CT: Computed tomography; EBCT: Electron-beam CT.

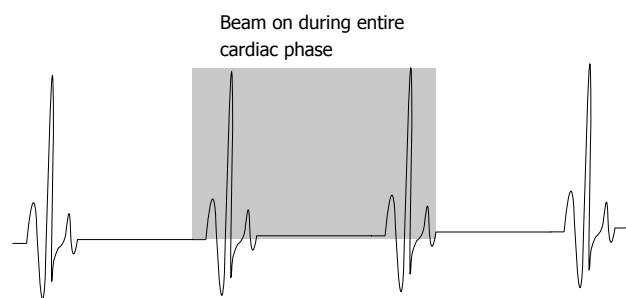


Figure 4 Diagram showing retrospective electrocardiogram-gating without tube current modulation in multislice computed tomography coronary angiography. An X-ray beam is turned on during the entire cardiac cycle without adjusting the tube current.

significant variability ranging from 5 to 30 mSv^[23]. Thus, reduction of the radiation dose in MSCT coronary angiography is of paramount importance to ensure that it is a safe technique for use in clinical application.

There are a number of strategies that have been undertaken to reduce the radiation dose from cardiac MSCT, and the most commonly used approaches include: adjustment of tube voltage (kVp) and tube current (mAs), increasing pitch value and choosing different ECG-gating methods (prospective *vs* retrospective gating). Effective reduction of radiation dose can be achieved by changing or selecting appropriate parameters without compromising diagnostic image quality.

MULTISLICE CT ANGIOGRAPHY IN CAD-RADIATION DOSE REDUCTION STRATEGIES

ECG-controlled tube current modulation

One of the most effective approaches for dose reduction is adjustment of the tube current according to ECG signal, which is defined as ECG-controlled tube current modulation. Traditionally, cardiac MSCT angiography is performed using a retrospective ECG-gating technique, which indicates that the volume data are acquired during the entire cardiac cycle within a single breath-hold helical

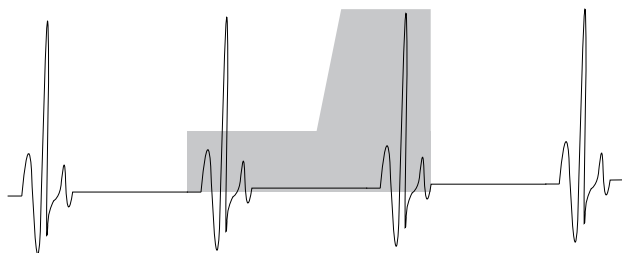


Figure 5 Diagram showing retrospective electrocardiogram-gating with the use of tube current modulation in multislice computed tomography coronary angiography. Normal tube current is applied only during the image reconstruction phase (late diastolic phase), while the tube current is reduced significantly during the systolic phase.

scan (Figure 4). This ensures acquisition of volumetric data during systolic and diastolic cardiac cycles, thus reconstruction of images at the diastolic phase allows us to generate images with the least motion artifacts. However, image reconstruction of the volume data only occurs in a specific phase of the cardiac cycle (end systole or mid diastole). Thus, not all of the data is used for diagnostic purposes, but the patient is exposed to X-rays during the entire cardiac cycle. This implies that the tube current can be adjusted in different cardiac phases so that high-quality diagnostic images of coronary arteries during the reconstruction window, and low-quality, higher noise images of the cardiac chamber and cardiac valves during the rest of cardiac cycle can be acquired (Figure 5).

ECG-controlled tube current modulation represents the most significant improvement in minimizing radiation exposure from CT technology and is the only one dedicated to cardiac imaging. It has been reported that radiation dose can be reduced by 30%-50% through modulation of the tube current output to decrease the dose given during the systolic phase^[24,25]. The estimated radiation dose reduction is similar to or less than that of a conventional coronary angiography examination with use of this dose-saving strategy^[24,26].

Automatic exposure control

Automatic exposure control (AEC) is regarded as another effective approach to reduce radiation dose for coronary cardiac CT examination. AEC takes this into consideration by automatically adjusting the tube current in the x, y plane (angular modulation) or along the scanning direction (z-axis modulation) or both (combined modulation) according to the anatomic geometry of the body region to be scanned to obtain diagnostic image quality while lowering radiation dose^[27,28]. Deetjen *et al*^[25] studied different groups of patients undergoing 16-slice and 64-slice coronary angiography examinations and showed significant reduction of radiation dose (42.8%) with AEC. This is consistent with a recent report involving a comparison of 4 different CT manufacturers with different AEC systems^[29]. Söderberg *et al*^[29] found that the magnitude of dose saving was considerable, ranging from 35% to 60%, with the use of AEC systems with similar performance

of tube current modulation dynamics among the different CT scanners.

Adjustment of tube voltage

Lowering the tube voltage is widely undertaken in clinical practice to reduce radiation dose, since radiation dose varies with the square of the kVp. Modern CT scanners include tube voltages of 120 or 140 kVp, reflecting the settings most often resulting in adequate image quality. However, cardiac CT acquisition with 100 kVp, or even lower, is possible and has been recommended as an effective means to reduce radiation dose in cardiac CT imaging^[30,31]. Previous studies have shown that decreasing the X-ray tube voltage from 120 to 100 kVp or 80 kVp resulted in up to a 70% reduction in radiation exposure for a constant tube current using 16-slice and 64-slice CT, with increased image noise and unchanged contrast-to-noise ratio^[30,31]. Studies utilizing dual-source CT compared a 100 kVp protocol to the routine 120 kVp for cardiac CT, and demonstrated a 25%-54% reduction in radiation dose, depending on the tube current time product^[32,33].

It should be emphasized that changing tube voltage needs to be correlated with patient's body mass index (BMI). Lowering tube voltage from 120 to 100 kVp can be performed when the patient's BMI is less than 25 kg/m². Reduction of the tube voltage to 80 kVp should be considered in children and slim young adults with BMI below 20 kg/m². It has been reported that the tube voltage can be lowered to 80 kVp without impairing image quality while the radiation dose was reduced by up to 80% in normal weight patients^[34]. Therefore, tube voltage can be adjusted in cardiac CT angiography without affecting diagnostic image quality, and this should be applied whenever possible in clinical practice.

High pitch value

It is well-known that radiation dose is inversely proportional to the pitch value. A high pitch (1.0-2.0) is recommended for helical CT angiography with the aim of reducing radiation dose without affecting image quality. However, for MSCT coronary angiography, a very low pitch (0.2-0.4) is routinely used to produce volume coverage without gaps in each phase of the cardiac cycle with multiple overlapping regions, thus resulting in high radiation exposure. Increasing pitch to a higher value is made possible with the development of a second generation of dual-source CT scanner^[35-39], which enables high detector coverage with the use of two 128-section detectors. This dual-source CT system allows coronary CT angiography to be performed at high pitch value of up to 3.4 with significant reduction of radiation dose. By combining high pitch and large detector coverage, the acquisition time of coronary CT angiography is reduced from the previous 5-10 s to a quarter of a second, allowing depiction of the entire heart within a single heartbeat. More than 90% of all coronary segments were assessable with dual-source CT coronary angiography at a high pitch of 3.4, result-

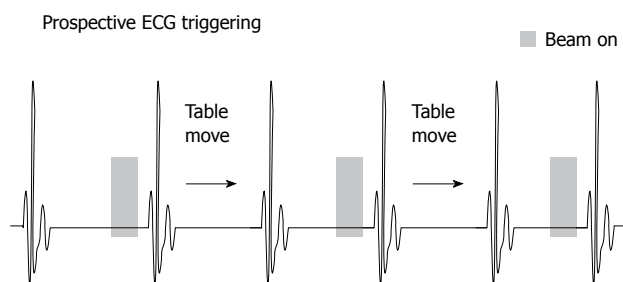


Figure 6 The diagram shows prospective electrocardiogram-triggering with X-ray beam on during a portion of the cardiac cycle, while in the remaining cardiac phase, the X-ray beam is turned off.

ing in a radiation dose less than 1 mSv^[35,36]. The new scan mode with a temporal resolution of 75 ms is regarded as an extremely attractive alternative to invasive coronary angiography because of the very low radiation dose and high image quality.

Prospective ECG-triggering

Prospective ECG-triggering with axial non-helical scan was used a long time ago with electron-beam CT for calcium scoring, but was proposed recently for cardiac imaging, and this imaging protocol is increasingly reported in the literature because of its very low radiation dose^[40-48]. The principle of prospective ECG-triggering is different from that of retrospective ECG-gating as the former is used to acquire data by selectively turning the X-ray tube on only in the selected cardiac phase, triggered by the ECG signal, and turning off during the rest of the R-R cycle (Figure 6). This is also referred to as sequential or step-and-shoot acquisition with prospective triggering, and the effective pitch is 1.0. The main advantage of this scanning protocol is the lower radiation dose as X-ray exposure only occurs during the selected cardiac phase rather than throughout the entire cardiac cycle. Therefore, a significant reduction in radiation dose can be achieved from prospective ECG-triggering, which is the most attractive side of this scanning protocol compared to retrospective ECG-gating.

Studies using prospective ECG-triggering showed significant dose reduction when compared to the conventional retrospective ECG-gating, with up to 90% dose reduction achieved in some studies^[46,47]. Even if the published results concerning image quality have generally been satisfactory, there is concern about the negative effect of low-dose scanning protocols which may affect image quality of cardiac CT examination. A “staged” protocol was recently introduced by researchers to address the situation when image quality may be suboptimal^[49]. Pflederer *et al*^[49] evaluated the staged low-dose methods for coronary CT angiography compared to standard protocols and reported an 86% reduction of the effective dose with use of a prospective triggering approach. However, a higher number of unevaluable coronary segments and impaired image quality was noticed in this group. An additional standard sequence was added to the patients with non-diagnostic

images and the overall radiation dose reduction still remained significant (1.5-3.4 mSv for low-dose protocols vs 9.8 mSv for the standard protocol). Thus, the staged strategy with an initial low-dose CT protocol should be encouraged to be used as a dose-saving algorithm.

DIAGNOSTIC VALUE OF MULTISLICE CT ANGIOGRAPHY IN CAD

Over the last decade much interest has been focused on imaging and diagnosis of CAD with MSCT as it is a less invasive and faster scanning technique with extended z-axis coverage when compared to single slice CT. Earlier studies with 4-slice CT showed moderate diagnostic accuracy with pooled sensitivity and specificity of 78% and 93%, respectively because the spatial and temporal resolution is limited, resulting in a high number of unassessable segments^[10]. With the introduction of 16-slice CT, the diagnostic value of MSCT angiography in CAD has been much improved, with more coronary segments assessable. Studies using 16-slice CT with acquisition and rotation times of < 400 ms have reported sensitivities between 83% and 98% and specificities between 96% and 98%^[14,15]. Despite improvement in both spatial and temporal resolution, isotropic volume data is still not possible with 16-slice CT. Moreover, the temporal resolution is insufficient to ensure acquisition of diagnostic images in patients with high heart rate.

MSCT examination times were reduced with further improvement in scanning techniques with 64-slice CT because of improved spatial and temporal resolution compared with 16-slice and 4-slice CT. Acquisition of isotropic volume data is possible with 64-slice CT, thus detection of main and side coronary artery branches is significantly improved when compared to earlier generations of MSCT scanners. Several meta-analyses of 64-slice CT studies reported sensitivities and specificities ranging from 86% to 99% and 88% to 97%, respectively^[50-53]. These studies indicated that MSCT, especially with 64-or more CT, has high diagnostic accuracy for detection of CAD and could be used as an effective alternative to invasive coronary angiography in selected patients.

One of the difficulties for MSCT cardiac imaging is that image quality highly depends on heart rate. Despite technical improvements in MSCT scanners with subsequent improvement in temporal resolution, the assessable segments and diagnostic accuracy are still higher in patients with a lower heart rate, and lower and deteriorated in patients with a higher heart rate. Therefore, an aggressive approach such as the use of β -blockers in patients with a heart rate more than 70 bpm has become a part of the routine procedure prior to CT scanning. With the advent of dual-source CT, temporal resolution has been increased to 83 ms, indicating that image quality is less dependent on the heart rate, thus potentially obviating the need for β -blockers before scanning.

In a recent study, Donnino *et al*^[54] compared dual-

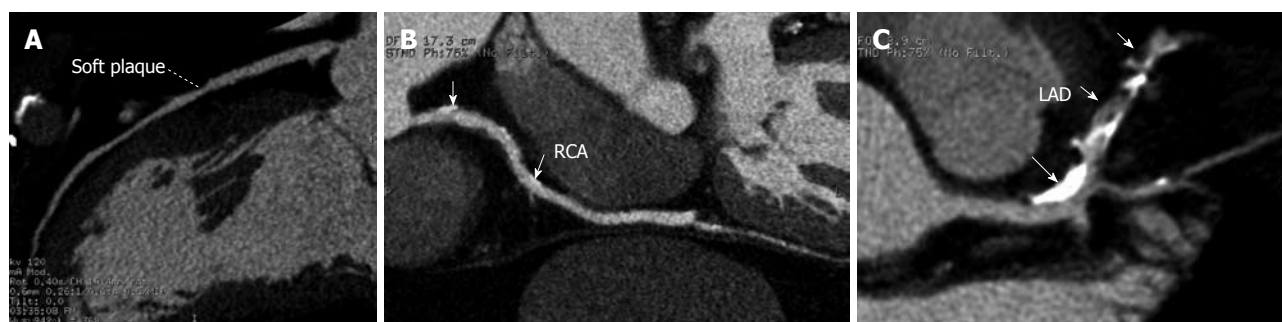


Figure 7 Characterization of coronary plaques. RCA-right coronary artery. A: Curved planar reformatted image acquired with 64-slice computed tomography angiography shows a non-calcified plaque at the mid-segment of the right coronary artery in a 57-year-old man suspected of coronary artery disease; B: Calcified plaques (arrows) are found at the proximal and middle segments of the right coronary artery; C: Mixed type plaques are shown in the left anterior descending (LAD) artery in a 59-year-old man suspected of coronary artery disease; the long arrow indicates the calcified plaque, while the short arrows indicate non-calcified components.

source with single-source CT for assessment of diagnostic image quality of coronary artery examinations. Their results showed a significant improvement in image quality with dual-source CT over single-source CT, in the absence of pre-examination use of β -blockers, and higher heart rate in the dual-source group. Reports by others also supported the improved diagnostic value of dual-source CT in cardiac imaging^[55,56]. Dual-source CT was reported to be superior to single-source 64-slice CT for the detection of CAD with a sensitivity and specificity of 100% for both in a small group of patients^[56], whereas the 64-slice scanner achieved a sensitivity of 100%, but a reduced specificity of 90%.

Latest models such as 256-slice and 320-slice CT scanners allow for longer z-axis coverage ranging from 12.8 to 16 cm on one gantry rotation, so it is possible to achieve full cardiac coverage in one gantry rotation within a very short period, thus eliminating the restrictions and limitations associated with 64-slice CT scanners^[57,58]. de Graaf *et al*^[57] reported that a high diagnostic value, especially a 100% negative predictive value (including the non-diagnostic images) and diagnostic accuracy of 95%, was achieved with 320-slice CT angiography for detection of significant coronary stenosis in a patient-based analysis. This indicated that 320-slice CT angiography is a highly sensitive modality for the detection of significant CAD. Pasricha *et al*^[58] compared image quality of 320-slice CT in patients with atrial fibrillation with that acquired from the group with sinus rhythm. In this study, 96% of the coronary segments were assessable with sufficient quality for diagnosis in patients with atrial fibrillation, and this showed the potential application of 320-slice CT in this patient group. Although 320-slice CT shows very promising results, more data are needed to confirm its diagnostic accuracy in CAD.

PROGNOSTIC VALUE OF MULTISLICE CT ANGIOGRAPHY IN CAD

MSCT is not only able to evaluate the coronary luminal changes, but also visualize the coronary artery wall mor-

phology, identify and characterize coronary plaques, especially the non-stenotic plaques that may be undetected by conventional coronary angiography. Thus, MSCT could be used as a non-invasive technique to provide prognostic information in patients suspected of having CAD.

MSCT also allows for non-invasive detection of plaque morphology and composition (calcified *vs* non-calcified atherosclerotic plaques), as well as the assessment of the extent of vascular remodeling^[59]. Atherosclerotic plaque size and geometry play an important role in the natural progression of the disease process and may have important clinical predictive value. Schmid *et al*^[59] in their study concluded that a significant increase in the amount of noncalcified plaque was observed with 64-slice CT over a mean interval follow-up of 17 mo, and their results indicated that MSCT may be used as a tool to study the progression of coronary atherosclerosis.

Coronary artery plaque is characterized into 3 types based on the CT attenuation^[60]: non-calcified plaques refer to plaques having lower density compared with the contrast-enhanced vessel lumen (Figure 7A); calcified plaques indicate plaques with high density (Figure 7B); mixed plaques refer to plaques with non-calcified and calcified components within a single plaque or within a segment of the coronary artery (Figure 7C). Accurate identification of the type of plaques as well as demonstration of coronary luminal changes is important for prediction of disease progress based on 2D and 3D CT visualizations. In contrast to conventional 2D or 3D extraluminal visualizations, the 3D virtual intravascular endoscopy has been reported to provide additional information about the intraluminal appearance of coronary plaques (Figure 8), and corresponding luminal changes due to the presence of plaques in the artery wall^[61]. Virtual intravascular endoscopy also helps to confirm the degree of coronary stenosis as severe calcification sometimes results in a false positive sign of lumen occlusion on 2D views (Figure 9).

Preliminary reports have shown that MSCT angiography is able to provide independent prognostic information for predicting cardiac events and mortality in patients with known or suspected CAD at short-term follow-up.

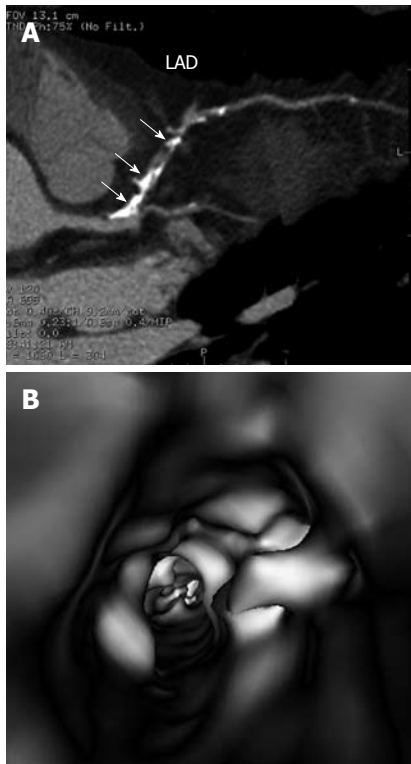


Figure 8 Virtual endoscopy visualization of coronary plaques. A: Extensive calcified plaques in the left anterior descending (LAD) are observed on curved planar reformatted view with more than 70% luminal stenosis in a 52-year-old man with chest pain; B: Corresponding virtual intravascular endoscopy visualization demonstrates irregular intraluminal appearance with significant stenosis of the coronary artery.

Gilard *et al*^[62] reported that a normal MSCT in a population of 141 patients with suspected CAD was associated with a low rate of cardiac events (mortality 0%, myocardial infarction 0.7%, coronary angiography 3.5%) at 1-year follow-up. Similar results were reported by other studies demonstrating that obstructive plaque, particularly in the left main or left anterior descending arteries, had the highest risk (up to 34% cardiac event rate), while in contrast, a normal coronary CT angiography was associated with a 0% event rate^[63-65]. However, these studies have been largely limited by small sample sizes, single centre evaluations and short follow-up periods. Two recent studies based on a large cohort of patients offered independent and additional prognostic information of MSCT angiography for the prediction of incidence of cardiac events^[66,67].

Hadamitzky *et al*^[66] in their recent report assessed the prognostic value of MSCT angiography in the prediction of cardiac events in asymptomatic patients. They retrospectively analyzed 451 asymptomatic patients with 16-slice and 64-slice CT angiography during a median follow-up of 27.5 mo. Their study confirmed that MSCT angiography could be reliably used to predict further cardiac events, despite the low cardiac event rate in asymptomatic patients. Min *et al*^[67] in a large cohort of 5330 patients without known CAD determined the prognostic value of MSCT angiography by measuring the left ven-

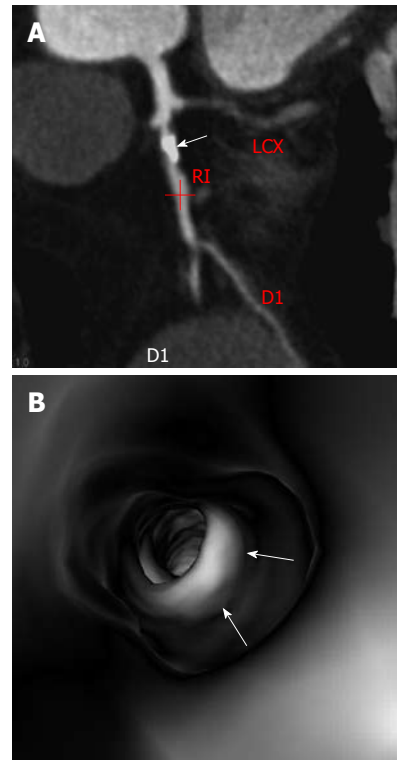


Figure 9 Virtual endoscopy confirmation of plaque stenosis. A: A calcified plaque (arrow) is present in the left anterior descending with more than 90% lumen stenosis in a 51-year-old man presenting with symptoms of chest pain; B: Corresponding virtual intravascular endoscopy shows intraluminal protrusion caused by the plaque, but the luminal stenosis is less than 70%; arrows indicate the intraluminal appearance of calcified plaque. RI: Ramus intermedius; LCX: left circumflex; D1: Diagonal branch.

tricular ejection fraction (LVEF) in addition to the traditional criterion of presence of obstructive CAD. Their study demonstrated that MSCT angiography successfully identified individuals at higher risk of all-cause death at a follow-up of 2.3 years. The presence of obstructive CAD in an increasing number of coronary arteries indicated a particularly poor prognosis. In addition, measures of LVEF were found to add incremental prognostic values above and beyond CAD detection with patients without obstructive CAD or with normal LVEF and a low risk of death.

MULTISLICE CT ANGIOGRAPHY IN CAD-FUTURE DIRECTIONS

Future directions of MSCT angiography in the diagnosis of CAD lie in 3 main aspects: improvement of temporal resolution, reduction of radiation dose and judicious use of MSCT. The MSCT scanning technique has improved significantly over the last decade, with acquisition of isotropic volume data in patients with high heart rate. However, the current temporal resolution of MSCT imaging (75-83 ms with dual-source CT, 135-175 ms with 256-slice and 320-slice CT) is still inferior to that of invasive coronary angiography (20 ms), thus further technical improve-

ment in temporal resolution is necessary so that MSCT can be applied in more patients, especially for those with high or irregular heart rate. Control of high heart rate with the use of β -blockers is still commonly performed in many cardiac MSCT examinations, including scans with the use of 320-slice CT, and further improvement in temporal resolution will contribute to the elimination of the aggressive procedure of heart rate control in patients with heart rate more than 70 bpm.

As already discussed above, radiation exposure associated with MSCT angiography is relatively high and poses a potential risk of radiation-induced malignancy. Although dose-saving strategies have been recommended to reduce the radiation dose from MSCT angiography, CT scanning protocols across institutions are widely variable and could contribute to the high radiation exposure to patients. Two recent studies highlighted the importance of standardization of common CT scans including cardiac CT imaging, as well as the cancer risk associated with the radiation^[68,69]. Smith-Bindman *et al*^[68], in their prospective study involving 4 institutions, collected data on radiation doses for the most common CT scans and found a significant variation in radiation dose, a mean 13-fold variation between the highest and lowest dose for each CT type studied (range, 6- to 22-fold difference across study types). They estimated that 1 in every 270 40-year-old women undergoing CT coronary angiography will develop cancer from the procedure. In another study, Berrington de González *et al*^[69] estimated that CT scans performed in 2007 could have led to 29 000 excess cancers, which will appear in the next 20 to 30 years and by the authors' estimates, at a 50% mortality rate, will cause approximately 15 000 deaths annually.

There is no doubt that, with increasing technological improvements, MSCT will continue to play an important role in the diagnosis of CAD. Judicious use of MSCT in cardiac imaging is essential to maximize its clinical applications while minimizing the potential risk of radiation exposure. This is particularly important for young individuals, especially women, for whom alternative diagnostic modalities that do not involve the use of ionizing radiation should be considered, such as echocardiography, or magnetic resonance imaging^[23]. Physicians need to be aware of the potential risk of radiation dose associated with CT cardiac imaging. It has been reported that 47% of radiologists and 9% of emergency department physicians believed that there was an increased risk of cancer associated with CT scans^[70]. Thus, there is an urgent need for physicians to educate themselves and increase their awareness about ionizing radiation from CT and its associated risks^[71]. The benefit-to-risk ratio for imaging patients suspected of CAD must be driven by the benefit and appropriateness of the cardiac MSCT examination requested by the cardiologists. The main purpose of utilizing MSCT imaging is to address specific medical questions without allowing concerns about radiation exposure to dissuade cardiologists or their patients from obtaining or undergoing the needed MSCT examination^[72].

CONCLUSION

Multislice CT angiography, as a less-invasive imaging modality has demonstrated high diagnostic value in the detection and diagnosis of CAD. In particular, the very high negative predictive value of MSCT angiography allows it to be used as a reliable technique for screening purposes. With continued technical improvements in the scanning technique, MSCT will play an increasing role in the detection and characterization of coronary plaques. Moreover, MSCT is regarded as a reliable modality for prediction of disease prognosis in patients suspected of CAD.

Serious concerns have recently been raised about the radiation dose from MSCT angiography in clinical practice, as it has been confirmed to be related to a potential risk of inducing cancer. MSCT coronary angiography should be performed with dose-saving strategies whenever possible to reduce the radiation exposure to patients. Multislice CT scanning protocols in cardiac imaging should be standardized across institutions with the aim of reducing dose variation across patients and facilities. Utilization of coronary MSCT angiography must be considered with care as to whether it leads to an overall benefit or whether the radiation risk may be greater than the benefit expected from the CT examinations. Physicians, especially cardiologists, should be aware of the potential risk from CT scans, and consider reducing unnecessary CT examinations or replacing CT with other alternative modalities, such as ultrasound or magnetic resonance imaging.

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Clinical use of nuclear cardiology in the assessment of heart failure

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Abstract

A nuclear cardiology test is the most commonly performed non-invasive cardiac imaging test in patients with heart failure, and it plays a pivotal role in their assessment and management. Quantitative gated single positron emission computed tomography (QGS) is used to assess quantitatively cardiac volume, left ventricular ejection fraction (LVEF), stroke volume, and cardiac diastolic function. Resting and stress myocardial perfusion imaging, with exercise or pharmacologic stress, plays a fundamental role in distinguishing ischemic from non-ischemic etiology of heart failure, and in demonstrating myocardial viability. Diastolic heart failure also termed as heart failure with a preserved LVEF is readily identified by nuclear cardiology techniques and can accurately be estimated by peak filling rate (PFR) and time to PFR. Movement of the left ventricle can also be readily assessed by QGS, with newer techniques such as three-dimensional, wall thickening evaluation aiding its assessment. Myocardial perfusion imaging is also commonly used to identify candidates for implantable cardiac defibrillator and cardiac resynchronization therapies. Neurotransmitter imaging using ^{123}I -metaiodobenzylguanidine offers prognostic information in patients with heart failure. Metabolism and function in the heart are closely related, and energy substrate metabolism is a potential

target of medical therapies to improve cardiac function in patients with heart failure. Cardiac metabolic imaging using ^{123}I -15-(p-iodophenyl)3-R, S-methylpentadecanoic acid is a commonly used tracer in clinical studies to diagnose metabolic heart failure. Nuclear cardiology tests, including neurotransmitter imaging and metabolic imaging, are now easily performed with new tracers to refine heart failure diagnosis. Nuclear cardiology studies contribute significantly to guiding management decisions for identifying cardiac risk in patients with heart failure.

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Key words: Quantitative gated single photon emission computed tomography; Metaiodobenzylguanidine; β -methyl-p-iodophenyl-pentadecanoic acid; Diastolic function; Prognosis

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INTRODUCTION

Congestive heart failure is a specific term that is used to define the clinical syndrome that describes the situation when the heart is unable to pump enough blood for the metabolic needs of the body. Systolic and diastolic heart failure have been commonly used in clinical settings to describe a category of congestive heart failure^[1]. There are several conditions that can lead to heart failure, including

coronary artery disease and cardiomyopathy. It is helpful for the clinician to identify non-invasively the underlying cause of heart failure by means of nuclear cardiology studies. A substantial proportion of patients with symptomatic heart failure have been known to have relatively normal or preserved left ventricular ejection fraction (LVEF)^[1,2]. Diastolic heart failure has been found to play an important role in cardiac morbidity and mortality in patients with preserved systolic function. Diastolic function is influenced by myocardial relaxation, ventricular filling and ventricular elastic properties. Moreover, in cases of ischemic heart disease, hypertension, and cardiomyopathy, myocardial involvement has been detected early by evaluation of diastolic abnormalities by means of a nuclear technique. Recently, electrocardiography (ECG)-gated single photon emission computed tomography (SPECT) has become a common procedure in patients with ischemic heart disease. A nuclear cardiology test, including the quantitative ECG-gated SPECT (QGS), sympathetic and metabolic imaging, is well suited for serial follow-up of changes in the myocardium^[3]. The aim of the present review is to describe the measurement of cardiac function and the evaluation of patients' risk, including diastolic properties, by means of a nuclear technique, and to provide an overview of the state of the art of nuclear cardiology and physiology of the heart.

CLINICAL APPLICATION

Diagnosis of coronary artery disease

Myocardial perfusion imaging is an established method for the primary detection of coronary artery disease^[4-10]. The development of ischemia or coronary flow heterogeneities is then used to represent physiological coronary stenosis as shown in Figure 1. The myocardium can increase coronary flow from its basal levels to a maximal flow in response to physiological or pharmacological stress. Nitric oxide and other metabolic mediators increase blood flow^[11,12]. Coronary arteries without focal stenosis are generally considered non-flow-limiting. However, the levels of coronary flow reserve in non-obstructive coronary arteries vary in each subject^[13,14]. Diffuse coronary atherosclerosis also accounts for persistently abnormal myocardial perfusion imaging studies without obstructive coronary artery segments. Physiological information from nuclear cardiology tests is essential for the assessment and management of heart disease, which might not otherwise be obtained by anatomical imaging such as CT.

Left ventricular function analysis

A number of studies have shown that ECG-gated SPECT can provide accurate and reproducible values for ejection fraction, regional wall motion, and wall thickening^[15-17], and dyssynchrony^[18]. Left ventricular function can be quantitatively analyzed with QGS software. QGS software has often been used to evaluate wall ejection fraction and left ventricular volume^[19]. For data analysis, the QGS program has been applied to process short-axis tomograms to determine LVEF, end-systolic volume (ESV), and end-di-

astolic volume (EDV)^[5]. The reproducibility in LVEF and volumes within each work station has been validated^[20,21], even although the gated SPECT preferences have varied. Normal limits for gated SPECT and QGS software have been determined based on a Japanese database, including the Japanese Assessment of a Cardiac Event Survival Study (J-ACCESS)^[8]. The study defined ESV in a normal range when it was ≥ 60 mL in male subjects, or when it was ≥ 40 mL in female subjects. The study therefore defined gated SPECT images as normal when LVEF in men was $\geq 49\%$, or when LVEF in women was $\geq 55\%$ ^[8].

To evaluate left ventricular regional wall motion, wall thickening seems to be more appropriate for the evaluation in many cases, including evaluation of patients with left bundle branch block or coronary artery bypass graft. Normal standard values of myocardial wall thickening were created by the database of the Japanese Society of Nuclear Medicine (JSNM). Myocardial wall thickening in the apex was higher than that in the mid and basal regions. The wall thickening of the left ventricle was higher in women than in men^[17].

Post-stress dysfunction

Post-ischemic stunning has been well documented in animal models and in humans^[4,21,22]. In detecting multi-vessel coronary artery disease, post-stress dysfunction using SPECT imaging provides critical diagnostic information as shown in Figure 2. Transient ischemic dilatation (TID) of the left ventricle refers to an imaging pattern in which the left ventricle cavity appears to be larger on the stress image than on the rest image. The phenomenon of TID is considered to be a sensitive marker of extensive ischemia and prolonged post-ischemic systolic dysfunction, which results in a dilated, dysfunctional left ventricle during stress acquisition relative to rest acquisition. Patients with TID are considered to be high risk for future cardiac events. Patients with multi-vessel or left main coronary artery disease have reduced left ventricular systolic and diastolic function, especially in stressed conditions. The phenomenon of post-ischemic stunning consists of the presence of abnormal regional function in the absence of necrosis. Therefore, functional information after stress might be associated with severe and extensive ischemia in the myocardium. Persistence of functional abnormalities is certainly proportional to the degree of ischemia induced by exercise or pharmacological stress. An exercise stress perfusion thallium-201 (²⁰¹Tl) study can identify patients at high risk^[4]. In previous studies using ^{99m}Tc-sestamibi (MIBI) gated SPECT, LVEF after stress was depressed in patients with reversible myocardial ischemia compared to those at rest^[18,19]. Assessment of post-stress left ventricular function by gated SPECT provides incremental prognostic information and is useful in predicting cardiac events in patients with coronary artery disease^[23,24].

Risk stratification using myocardial perfusion imaging

Assessment of prognosis by a nuclear cardiology study contributes significantly to guiding management decisions

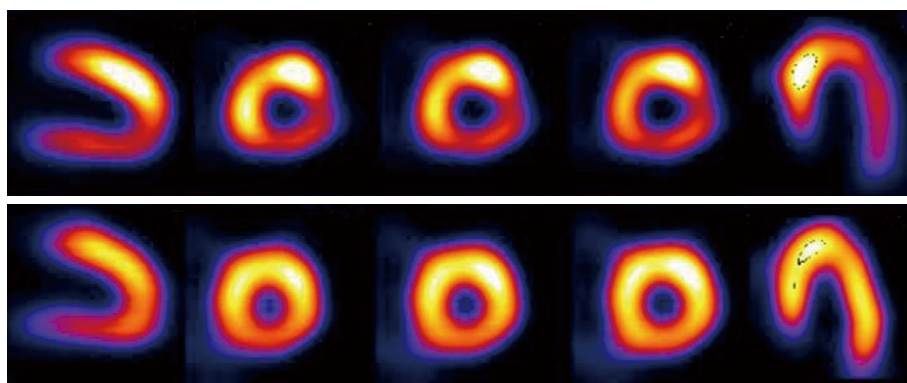


Figure 1 Single photon emission computed tomography image of exercise ^{201}Tl scintigraphy in a 70-year-old man. The stress image (upper panel) shows decreased perfusion in the infero-lateral region. There is a redistribution of the tracer in the rest image (lower panel), which indicates exercise-induced myocardial ischemia in the infero-lateral region of the left ventricle.

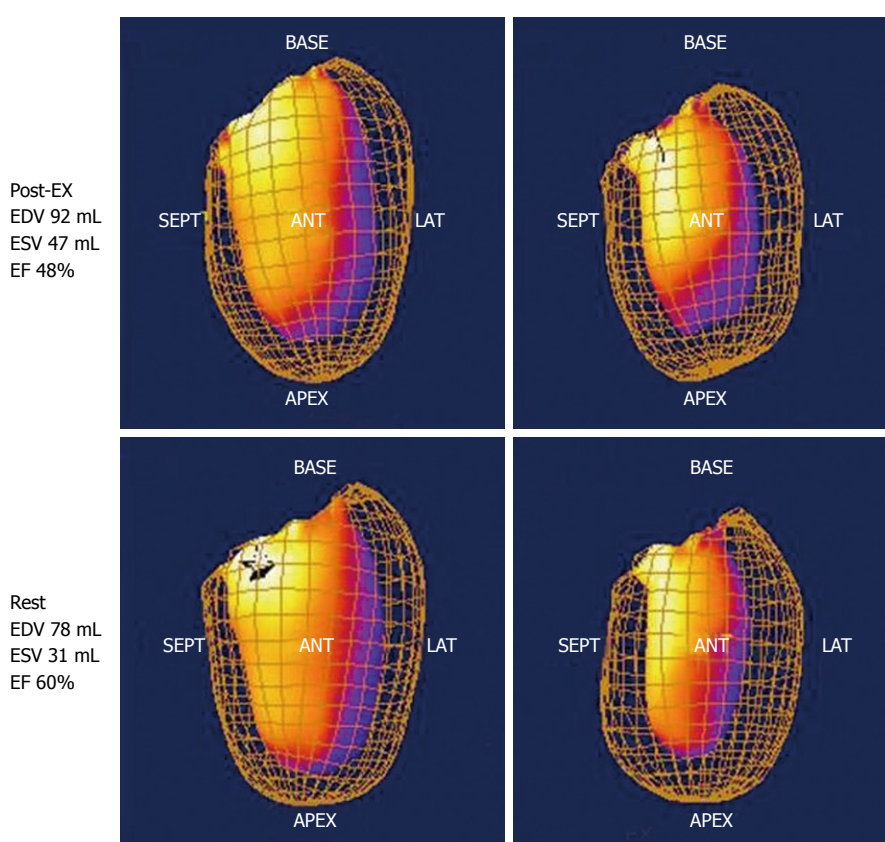


Figure 2 Post-stress left ventricular dysfunction detected by quantitative gated single positron emission computed tomography analysis. Transient ischemic dilatation was observed in a patient with multi-vessel disease. ESV: End-systolic volume; EDV: End-diastolic volume; EF: Ejection fraction.

for identifying patients with suspected or documented coronary artery disease. A multicenter nuclear cardiology study of > 45 000 subjects was conducted in Japan. J-ACCESS has demonstrated the low risk associated with normal SPECT images^[4,25]. Many studies have revealed important findings that have demonstrated that stress SPECT images alone have incremental information^[25-28]. Moreover, cardiac function analysis by QGS adds incremental prognostic information^[4,25]. It has been found that patients with normal SPECT have a low major cardiac event rate (< 1% per year)^[8,26]. These findings have im-

portant clinical implications because these patients can be exempted from further invasive procedures. A policy of proceeding directly with coronary angiography in suspected coronary artery disease without performing stress nuclear cardiology tests would result in subjecting patients to expensive and invasive procedures, with an expected good prognosis without interventions. The use of normal SPECT images needs no further invasive procedure. This type of management strategy results in cost efficiency and substantial cost savings compared with a more aggressive, invasive diagnostic workup strategy that includes diagnos-

tic cardiac catheterization^[29]. The patients undergo no further testing after a normal SPECT image, although studies of long-term outcome after a normal stress radionuclide study are scarce^[8,26]. As a result of greater frequency in atypical presentation, physicians rely more often on imaging results to guide management decisions. Thus, in clinical practice, SPECT imaging is frequently being employed as a first-line test. Risk stratification is essential to the development of evidence-based strategies for improved patient care in medicine^[30-35]. For patients with normal SPECT images, no additional testing is required because of the projected benign course. J-ACCESS has shown that patients with normal perfusion imaging require a watchful waiting approach to care^[8]. These results indicate that using stress myocardial SPECT images can be used as a gate-keeper for selective catheterization. Patients with type 2 diabetes mellitus have a higher risk of cardiovascular events and death than those without. Moreover, coronary artery disease in diabetic patients is frequently silent. It is important to identify coronary artery disease objectively in asymptomatic diabetic patients in a noninvasive way as early as possible. A risk-based approach is also essential in the management of diabetic patients with atherosclerosis^[26]. Screening coronary artery disease in diabetic patients using SPECT has been proven to be beneficial to determine the therapeutic strategy. Focusing on cardiovascular disease in diabetes, J-ACCESS-2 study is the first large-scale prospective study in diabetic patients to evaluate the prognostic value of ECG-gated SPECT imaging in Asia^[26,30]. Cardiac event rates associated with normal or low-risk myocardial perfusion SPECT imaging with ^{99m}Tc-tetrofosmin have been shown by the study. Results from J-ACCESS-2 provide further supportive evidence that the excellent prognosis associated with a normal SPECT scan does not require invasive therapy^[26]. In patients with documented coronary stenosis, the extent of stress myocardial perfusion imaging perfusion defects is reportedly related to increased risk of cardiac death^[33]. Myocardial perfusion imaging can be a significant predictor of sudden cardiac death^[35]. Summed stress scores provide incremental prognostic power to clinical history, and the LVEF can be the current gold standard for the risk stratification of sudden cardiac death^[35].

Assessment of myocardial viability and prediction of functional recovery

The aim of assessing myocardial viability is to optimize selection of patients with heart failure, whose symptoms and natural history might improve following revascularization. The presence of ²⁰¹Tl after redistribution indicates preserved cellular viability. However, the absence of ²⁰¹Tl uptake on the redistribution image is not sufficient to assert no viability^[27]. Myocardial uptake of ^{99m}Tc-MIBI is associated with regional perfusion and provides adequate information for the detection of coronary artery disease^[33]. The uptake and retention of ^{99m}Tc-MIBI is also dependent on cell membrane integrity and mitochondrial function (membrane potential), therefore, the uptake

of ^{99m}Tc-MIBI in the myocardium might reflect cellular viability. Many studies have compared ^{99m}Tc-MIBI imaging with other scintigraphic modalities, including ²⁰¹Tl stress-redistribution-reinjection, ²⁰¹Tl rest, ²⁰¹Tl rest-redistribution and ¹⁸F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET), and ¹²³I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP)^[32]. In patients with chronic total occlusion and viable myocardium, successful revascularization of chronic total occlusion can have a favorable outcome for left ventricular perfusion and function. Viable myocardium should be identified, particularly in such patients before percutaneous coronary intervention. Gated SPECT myocardial perfusion imaging with ^{99m}Tc-MIBI might be useful for monitoring long-term functional outcome of percutaneous coronary intervention in patients with chronic total occlusion^[36].

Assessment of myocardial viability with PET also improves the potential benefit of revascularization. A previous study has shown that patients with preserved myocardial viability who underwent revascularization had a significant reduction in the risk of cardiac death during follow-up^[37]. The mismatch pattern (enhanced FDG uptake relative to blood flow) can be related to the magnitude of improvement in left ventricular function after revascularization in patients with heart failure. On the other hand, the matched pattern (severe FDG uptake reduction and severely decreased myocardial perfusion) can be a sign of unfavorable outcome of revascularization and will unlikely lead to functional recovery.

Assessment of diastolic function with nuclear techniques

Systolic and diastolic heart failure have been commonly used in clinical settings to describe a category of congestive heart failure^[1]. There are several conditions that can lead to heart failure, including coronary artery disease and cardiomyopathy. It is helpful for the clinician to identify non-invasively the underlying cause of heart failure by means of a nuclear cardiology study. A substantial portion of patients with symptomatic heart failure are known to have relatively normal or preserved LVEF. In patients with symptomatic or suspected heart failure, determination of the presence and severity of diastolic dysfunction becomes increasingly important. Diastolic function analysis is often made by echocardiography, including tissue Doppler imaging and tracking techniques. Recent cardiac magnetic resonance techniques like strain-encoded cardiac magnetic resonance might provide accurate information of inducible ischemia and cardiac diastolic function^[38]. Diastolic heart failure, also termed as heart failure with preserved LVEF, is readily identified by nuclear cardiology techniques, and it can accurately estimate LV filling velocity rate and one third filling fraction. The reliability of diastolic function has been established in gated blood-pool studies but not in gated myocardial SPECT, especially in a ²⁰¹Tl study^[16]. The diastolic function determined for the Japanese population using a 16-frame format is summarized in Table 1, using the JSNM database^[10]. Although a 32-frame division of

Table 1 Normal values of diastolic parameter using ^{99m}Tc tracers

	JSNM WG
No. of subjects	60
Age (yr)	58 ± 15
Heart rate (beats/min)	66 ± 12
PFR (/s)	2.69 ± 0.57
1/3 mean filling rate (per s)	1.60 ± 0.39
TTPF (ms)	167 ± 38
TTPF/RR interval	0.18 ± 0.03
EF (%)	68 ± 6

JSNM WG: Japanese Society of Nuclear Medicine Working group; PFR: Peak filling rate; TTPF: Time to PFR; EF: Ejection fraction.

a cardiac cycle can provide better correlation with those determined by radionuclide ventriculography^[39], diastolic functional parameters can be analyzed in a more practical way by using a 16-frame acquisition per RR interval^[16,40-42]. Using the QGS software algorithm, abnormal thresholds in an American population have included peak filling rate (PFR) < 1.70/s and time to PFR (TTPF) > 208 ms^[41]. Multivariable analysis has shown that age, sex, LVEF and heart rate are strong predictors for PFR, whereas TTPF is not influenced by any clinical or systolic function variables. The Japanese population also has shown comparable normal values (Table 1). When patients were classified into two age groups of < 60 and ≥ 60 years, standard deviations of peak filling rate, one third mean filling rate, TTPF and TTPF/RR were larger in the older group than in the younger group. Because age-related differences were observed, it should be kept in mind that diastolic dysfunction in elderly patients and in those with LVEF < 50% are more common. Quantitative measurement depends on the tracers used, therefore, diastolic function analysis using ^{201}Tl requires further investigation^[16].

Evaluation of severity in patients with non-ischemic cardiomyopathy

Determination of left ventricular dysfunction due to non-ischemic cardiomyopathy is crucial in the management of heart failure. Cardiomyopathy constitutes a group of disorders in which the dominant feature is direct involvement of the cardiac myocardium itself. Hypertrophic cardiomyopathy and dilated cardiomyopathy are characterized by the presence of many alterations of adrenergic nerve function, such as decreased cardiac norepinephrine uptake, increased norepinephrine release, and decreased norepinephrine cardiac content and partial denervation. Myocardial damage or dysfunction leads to symptomatic heart failure^[43-46]. Non-ischemic cardiomyopathy can be evaluated also by metabolic imaging. The evaluation of metabolic status in addition to perfusion can offer clues to the underlying pathophysiology of the disease.

^{123}I -MIBG scintigraphy

^{123}I -MIBG scintigraphy is now used as an important technique for studying cardiac neuronal function^[43-49]. ^{123}I -MIBG, an analog of guanethidine, is taken up and stored

similarly to norepinephrine. It is taken up by sympathetic efferent nerve terminals, which are most abundant in the left ventricle. Distribution of ^{123}I -MIBG uptake is heterogeneous in normal subjects, with a relatively low uptake in the inferior and apical regions^[44]. ^{123}I -MIBG shares the same uptake and storage mechanisms as norepinephrine. It is reported that the uptake-1 system is mediated by the norepinephrine transporter, and the uptake-2 system is an extra-neuronal system. Planar imaging of the heart-mediastinum count ratio (H/M) of ^{123}I -MIBG is a simple method that allows comparison of inter-individual and institutional results by correcting for differences in body geometry and attenuation between individual subjects. In MIBG SPECT, a regional heterogeneity of ^{123}I -MIBG uptake exists, especially in the inferior and apical lesion in normal subjects^[9,44]. ^{123}I -MIBG uptake can vary depending on age or sex^[9]. Diabetes can affect the less inferior uptake of ^{123}I -MIBG.

^{123}I -MIBG scintigraphy has been accepted for routine use in many countries, and the standardization of ^{123}I -MIBG parameters among various collimators has been crucial. It has been shown that the H/M ratios obtained with low-energy high-resolution (LEHR) collimators with the ^{123}I dual energy (IDW) method are similar to those obtained with a medium-energy collimator^[50]. The scatter-correction IDW method could make it possible to standardize planar imaging of the H/M ratio among various collimators in clinical settings^[50].

Assessment of severity and prognosis of patients with heart failure, using MIBG imaging

Cardiomyopathy is a myocardial disease that often manifests as cardiac dysfunction and reduced ^{123}I -MIBG uptake, which could reflect associated abnormalities in sympathetic nerve function. This results in decreases in ^{123}I -MIBG uptake in patients with hypertrophic cardiomyopathy^[43,45]. The early and delayed images of ^{123}I -MIBG provide information about the ^{123}I -MIBG washout rate. The delayed image in patients with hypertrophic cardiomyopathy is significantly lower than that in control subjects, and the washout rate of ^{123}I -MIBG is significantly higher^[43]. ^{123}I -MIBG imaging shows that the cardiac sympathetic nerve function is impaired in hypertrophic cardiomyopathy, and the impairment might reflect progression of myocardial damage or dysfunction^[43]. The increased wall thickness of the left ventricle in hypertrophic cardiomyopathy is closely related to the perfusion defect based on a ^{201}Tl study, which is suggestive of myocardial damage, including myocardial hypertrophy, disarray or fibrosis^[43]. Furthermore, in patients with left ventricular dysfunction, decreased uptake-1 function has been found to be related to both myocardial overexposure to norepinephrine and decreased myocardial β -receptors^[46]. The norepinephrine levels that are required to inhibit ^{123}I -MIBG uptake in these conditions seem to be much higher than those in patients with hypertrophic cardiomyopathy. Cardiac sympathetic abnormalities are observed in hypertrophic cardiomyopathy patients with coronary

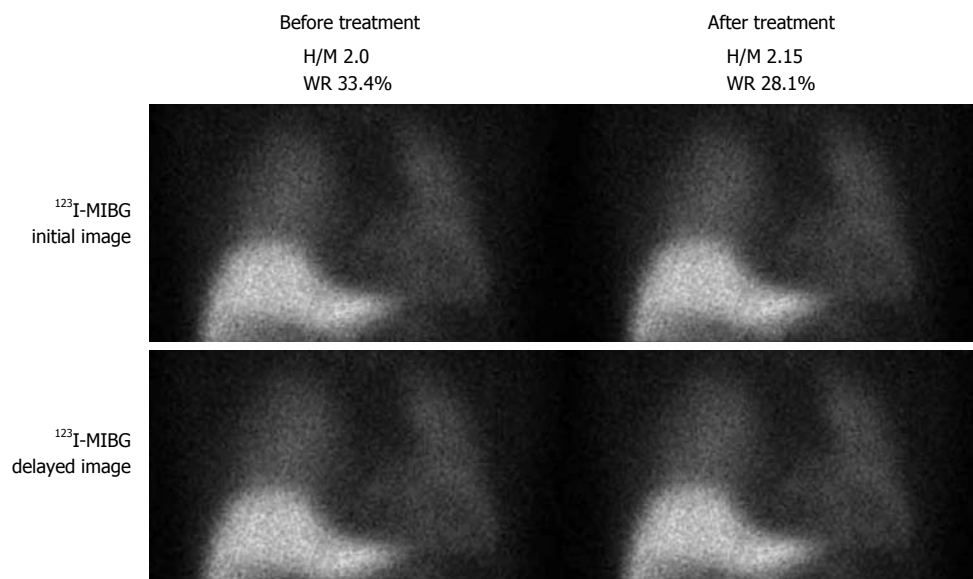


Figure 3 A patient with heart failure had ¹²³I-MIBG imaging and was treated with β -blockers. After treatment, ¹²³I-MIBG H/M ratio and washout rate (WR) were improved.

vasospasm, which suggests that the impaired sympathetic nerve function is associated with coronary vasospasm and diminished coronary blood flow reserve in hypertrophic cardiomyopathy^[43].

Dilated cardiomyopathy is also characterized by the presence of many alterations of adrenergic nerve dysfunction^[46]. The myocardial responsiveness of β -adrenergic agonists is blunted because of the increase in circulating catecholamines. A study of dilated cardiomyopathy has shown that ¹²³I-MIBG uptake is a predictor of life duration, and that impaired cardiac sympathetic nerve innervation, as assessed by ¹²³I-MIBG images, is strongly related to mortality in patients with heart failure^[49]. The delayed H/M ratio might reflect the myocardial contractile reserve in dilated cardiomyopathy patients^[51,52]. Cardiac resynchronization therapy has proven beneficial in dilated cardiomyopathy patients with advanced chronic heart failure or bundle branch block^[53,54]. Baseline cardiac sympathetic activity evaluated by ¹²³I-MIBG scintigraphy offers additional information for patients with dyssynchrony^[53], as well as both systolic and diastolic function^[54].

Merlet *et al.*^[47] have documented that there is a strong relationship between sympathetic nerve dysfunction and prognosis. Patients with the lowest uptake of ¹²³I-MIBG have the poorest prognosis^[48]. Sympathetic activity is enhanced with increasing severity of heart failure, therefore, the severity and prognosis of congestive heart failure can be evaluated based on two parameters that are determined by ¹²³I-MIBG scintigraphy. Previous studies have shown that delayed H/M ratio is the best predictor of survival in patients with heart failure with reduced cardiac function^[47,48]. Others have reported that the washout rate of ¹²³I-MIBG seems to be the most powerful predictor of subsequent mortality and morbidity in patients with heart failure. ¹²³I-MIBG imaging can be a useful tool in the evaluation of response to pharmacological treatment^[46,49].

On the basis of the parameters of ¹²³I-MIBG such as H/M and washout rate, treatment for congestive heart failure with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β -blockers, spironolactone, or torsemide can be monitored and evaluated for its efficacy in improving cardiac sympathetic nerve activity (Figure 3)^[56,57]. In ischemic patients with heart failure, an ¹²³I-MIBG study can also be predictive of improvements. Medical therapy can be effective when the H/M ratio on the initial image is maintained and the washout rate is increased on MIBG myocardial scintigraphy^[57-60]. Patients with heart failure can be good candidates for β -blocker treatment. The evaluation of severity and prognosis of heart failure is considered as class I evidence for nuclear cardiology based on the Japanese Circulation Society guidelines. Parameters obtained with delayed ¹²³I-MIBG scintigraphy images such as delayed H/M ratio and washout rate can be used as indicators of sympathetic activity^[59].

Following studies in Japan and European countries, the use of ¹²³I-MIBG imaging has also been validated by a large prognostic multicenter trial in patients with heart failure of NYHA functional class II/III and LVEF of $\leq 35\%$. The 2-year event rate in this trial was 15% for H/M > 1.60 and 37% for H/M < 1.60 . The authors found that ¹²³I-MIBG provided additional discrimination in analyses of interactions between B-type natriuretic peptide, LVEF and H/M ratio^[61].

A previous study has reported that there is no accumulation in the heart within 1 year after heart transplantation, and that the accumulation begins to recover in the anterobasal site during the subsequent course^[48,58]. An ¹²³I-MIBG study can be used to monitor the course of sympathetic re-innervation in the transplanted heart.

Cardiac metabolic imaging with ¹²³I-BMIPP

Glucose and fatty acids are the major energy sources in

the myocardium. Under normal conditions, approximately two-thirds or more of the total energy produced by the myocardium is derived from fatty acid oxidation. Fatty acid oxidation is the most efficient method of energy production^[62-64]. This process requires a large amount of oxygen. Therefore, under hypoxic or ischemic conditions, oxidation of long-chain fatty acids is greatly suppressed, and glucose metabolism, which requires less oxygen consumption, plays a major role in residual oxidative metabolism. Thus the evaluation of fatty acid metabolism is considered to be a sensitive marker of ischemia and myocardial damage. ¹²³I-BMIPP distribution in normal subjects is homogeneous^[9]. Initial myocardial ¹²³I-BMIPP uptake depends heavily on regional perfusion. Therefore, accurate reading of a ¹²³I-BMIPP image in comparison with a perfusion image is very important. In interpreting ¹²³I-BMIPP regional images, we should take into consideration the fact that ¹²³I-BMIPP uptake in the septal wall is higher than that of ^{99m}Tc tracer, and apical inferior uptake is higher in women than in men^[9].

Heart failure with metabolic imaging

In heart failure derived from cardiomyopathy, myocardial substrates can change significantly. Therefore, evaluation of metabolic status in addition to perfusion can offer clues to the underlying pathophysiology of cardiomyopathy. Currently available tracers for metabolic imaging comprise several fatty acid tracers^[64-67], ¹⁸F-FDG for the evaluation of glucose metabolism and ¹¹C-acetate for the assessment of oxygen consumption. Animal experiments with autoradiography using methyl-branched fatty acids in cardiomyopathic hamsters and hypertensive rats have demonstrated that fatty acid uptake is heterogeneous and lower than thallium uptake in the endocardium. ¹²³I-labelled 15-(p-iodophenyl)3-R, S-methylpentadecanoic acid (BMIPP) is the most commonly used tracer in clinical studies. It has been reported that less ¹²³I-BMIPP than ²⁰¹Tl uptake (disparity) is occasionally observed in patients with myocardial infarction, and such disparity segments tend to show redistribution in a stress ²⁰¹Tl study and increased FDG uptake in a PET study^[68]. In patients with cardiomyopathy, discordant ¹²³I-BMIPP uptake less than thallium uptake is a general finding, especially in patients with hypertrophic cardiomyopathy^[64]. Several studies using ²⁰¹Tl scintigraphy in patients with hypertrophic cardiomyopathy have revealed that, despite a normal epicardial coronary artery, a reversible perfusion defect on stress-distribution is often observed^[64]. A recent study has demonstrated that decreased myocardial ¹²³I-BMIPP uptake is observed in the area of stress-induced ischemia on ²⁰¹Tl imaging, which indicates the exercised-induced metabolic changes that occur even in a resting state^[64]. Similarly, exercise-induced abnormal blood pressure response is related to subendocardial ischemia in hypertrophic cardiomyopathy^[69]. Disparity of two tracers has frequently been observed in hypertrophic regions^[70,71]. This discrepancy could have been due to the multifactorial etiology of hypertrophic cardiomyopathy. It has been reported that

patients with hypertrophic cardiomyopathy show substantial heterogeneity in the distribution of ¹²³I-BMIPP, and accelerated washout of ¹²³I-BMIPP. Nishimura^[72] have suggested that impairment of myocardial fatty acid metabolism precedes a decrease in myocardial perfusion in hypertrophic cardiomyopathy because decreased ¹²³I-BMIPP uptake and normal ²⁰¹Tl perfusion are frequently observed. An ¹⁸F-FDG study has shown that the reduction in ¹²³I-BMIPP uptake is followed by oxidative metabolism and ¹⁸F-FDG uptake. Although most patients with hypertrophic cardiomyopathy have an excellent prognosis, some might progress to dilated cardiomyopathy or a poor prognostic course^[73]. ¹²³I-BMIPP imaging might be a tool to identify a subgroup of patients at risk of future cardiac events. Ishida *et al.*^[70], however, have failed to reveal abnormal distribution on ¹²³I-BMIPP images from patients with dilated cardiomyopathy despite severe left ventricular dysfunction. Myocardial fatty acid metabolism is impaired in heart failure patients with cardiomyopathy. In patients with congestive heart failure, myocardial metabolic abnormality evaluated by ¹²³I-BMIPP scintigraphy is related to the severity of congestive heart failure. Furthermore, it might be useful as a predictor of cardiac events^[62].

Metabolic abnormality observed as decreased ¹²³I-BMIPP uptake is related to myocardial creatine depletion by means of magnetic resonance spectroscopy^[74]. The detection of myocardial damage and prediction of prognosis can be achieved by metabolic imaging^[75,76], which might precede myocardial scarring that is detected by gadolinium-enhanced cardiovascular magnetic resonance imaging in patients with hypertrophic cardiomyopathy^[77].

An important feature of metabolic imaging is to provide a treatment strategy for patients with dilated cardiomyopathy. The decrease in ¹²³I-BMIPP uptake in patients with dilated cardiomyopathy might be a poor indicator for β -blocker therapy, whereas patients with relatively preserved ¹²³I-BMIPP uptake might respond well to therapy.

Metabolism and function of the heart are closely related, therefore, energy substrate metabolism is a potential target of medical therapy to improve cardiac systolic and diastolic function in patients with heart failure^[78]. PET imaging with recent advanced techniques offers good potential to evaluate cardiac stem-cell therapy by means of ¹⁸F-FDG-labeled bone marrow cells^[79]. Metabolic imaging with PET, including ¹¹C-acetate, ¹⁸F-FDG and new tracers, can be a tool to evaluate the efficacy of new therapies to improve cardiac function in heart failure.

Mitochondrial function imaging

^{99m}Tc-sestamibi (MIBI) is a lipophilic cation. Myocardial uptake and retention of ^{99m}Tc-MIBI involve passive diffusion across the plasma and mitochondrial membranes^[3]. Cellular influx of the tracer is driven by the inside negative plasma membrane and mitochondrial inner membrane potentials, which concentrates on the tracer within the cytosol and mitochondria^[3]. The retention of ^{99m}Tc-MIBI in the mitochondria is related to mitochondrial function. In the analysis of the ^{99m}Tc-MIBI images, the

regions of interest are placed on planar images to quantify cardiac ^{99m}Tc -MIBI uptake and calculate the H/M count ratio. The washout rate of ^{99m}Tc -MIBI is calculated from the segmental counts in the early and delayed images. Ischemia reportedly causes increased clearance of ^{99m}Tc -MIBI^[76]. In patients with heart failure, recent human studies have shown that the myocardial washout rate of ^{99m}Tc -MIBI is thought to be a novel marker for the diagnosis of myocardial damage or dysfunction, which provides prognostic information in patients with congestive heart failure^[3]. ^{99m}Tc -MIBI washout is increased in patients with anthracycline-induced cardiomyopathy. ^{99m}Tc -MIBI washout can be a marker of mitochondrial dysfunction^[3].

Restrictive cardiomyopathy can be idiopathic or secondary to heart muscle disease that manifests itself as restrictive physiology^[55]. The most common hemodynamic disturbance is impairment of ventricular filling due to the thickening and increased rigidity of the endocardium and myocardium secondary to infiltration by amyloid tissue or fibrosis. One study has shown the case of restrictive cardiomyopathy in which sympathetic and metabolic abnormalities and normal perfusion imaging were demonstrated^[55]. These findings of scintigraphic studies have shown us that restrictive physiology seems to cause metabolic and sympathetic abnormality with normal perfusion. Alcoholic cardiomyopathy, as a result of chronic alcohol abuse, results in heart failure. Up to 45% of all dilated cardiomyopathy appears to be due to alcohol abuse^[76]. The first sign of myocardial dysfunction is decreased diastolic function. Systolic dysfunction can appear later in these patients. Thereafter, cardiac enlargement is seen as a part of a compensatory mechanism. In our previous study, cardiac metabolic abnormalities were demonstrated in a patient with alcoholic cardiomyopathy^[76]. ^{123}I -MIBG identified myocardial damage in the inferior wall of the left ventricle, and mild heterogeneity of ^{123}I -MIBG uptake was observed in the myocardium. ^{123}I -BMIPP showed low uptake in the inferior wall of the myocardium, concordant with perfusion. These scintigraphic findings suggest that chronic alcoholism can cause myocardial damage, which results in metabolic and sympathetic neuronal abnormalities^[76]. Mitochondrial disorders are a heterogeneous group of diseases that result from abnormalities in mitochondrial DNA and function. In mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), cardiac involvement manifested as hypertrophic (symmetrical or asymmetrical) or dilated cardiomyopathy is frequently observed^[77]. In a patient with MELAS, decreased ^{99m}Tc -MIBI uptake and increased ^{99m}Tc -MIBI washout, which correlate inversely with LVEF, is observed. In addition, increased ^{123}I -BMIPP uptake is observed in the region of decreased ^{99m}Tc -MIBI uptake. ^{123}I -BMIPP is an analog of free fatty acid, which enters the intracellular triglyceride pool. In mitochondrial respiratory chain failure, energy production shifts from aerobic to the anaerobic pathway (glycolytic pathway), which results in increased lactic acid formation and increased ^{123}I -BMIPP uptake^[77].

Various etiologies of heart failure

Less common forms of cardiomyopathy are recognized: arrhythmogenic right ventricular cardiomyopathy (ARVC) and unclassified; the latter includes fibroelastosis, systolic dysfunction with minimal dilation, and isolated ventricular non-compaction; an unusual disease marked by prominent endocardial thickening with prominent trabeculations and deep recesses. ARVC is a condition in which the right ventricle is partially or totally replaced by adipose tissue^[80,81]. The involved myocardium provokes ventricular arrhythmias of a right ventricular origin that might lead to sudden death. Pathological abnormalities mostly affect the right ventricle, particularly the epimyocardium, but left ventricular involvement has been reported in up to 76% of patients with ARVC. The origin of ventricular tachycardia is related to the decreased accumulation of ^{123}I -MIBG^[82,83].

There are unusual types of cardiomyopathy that are recognized by nuclear techniques. Takotsubo cardiomyopathy is a newly defined syndrome that was first described in Japanese patients in 1991, and is characterized by transient, left ventricular apical ballooning. This name is related to the peculiar shape of the left ventricle, which can be visualized by end-systolic left ventriculograms, and it resembles an octopus-trapping pot, which is referred to as "Takotsubo" in Japanese^[84,85]. It is also referred to as stress cardiomyopathy, ampulla cardiomyopathy, apical ballooning syndrome, or broken heart syndrome. The mental stress due to earthquakes or train accidents could be one of the causes of the disease. This cardiomyopathy is now becoming recognized around the world and needs to be included in the differential diagnosis of acute coronary syndrome. It is recognized as a reversible left ventricular dysfunction with symptoms similar to those of acute myocardial infarction, but without coronary artery lesions, even during the acute phase of ST segment elevation. ^{123}I -MIBG and ^{123}I -BMIPP show reduced uptake in the apical segment of the myocardium in the acute phase, which indicates impairment of fatty acid metabolism and sympathetic nerve abnormalities. ^{99m}Tc -tetrafosmin uptake abnormality and apical wall motion dysfunction in the acute phase rapidly recover at the sub-acute stage, however, ^{123}I -BMIPP abnormalities persist for a longer period. These findings suggest that transient ventricular dysfunction might essentially be in stunned myocardium. ^{123}I -MIBG seems to be a specific diagnostic modality which is useful in the diagnosis of neurogenic myocardial stunning in Takotsubo cardiomyopathy, as shown in Figure 4.

Other forms of cardiomyopathy include sarcoidosis^[86], cardiomyopathy related to inflammatory disease^[87], and cardiac sympathetic dysfunction in the hearts of athletes^[88], all of which can be diagnosed by ^{123}I -MIBG imaging. Athlete's hearts are commonly characterized by an increase in left ventricular mass because of an increase in the left ventricular diastolic cavity dimension and/or wall thickness. Endurance exercise also increases numerous cardiovascular adaptations, such as increased vagal tone. Prolonged exercise training can alter cardiac sympathetic function, which can be detected by ^{123}I -MIBG imaging^[88].

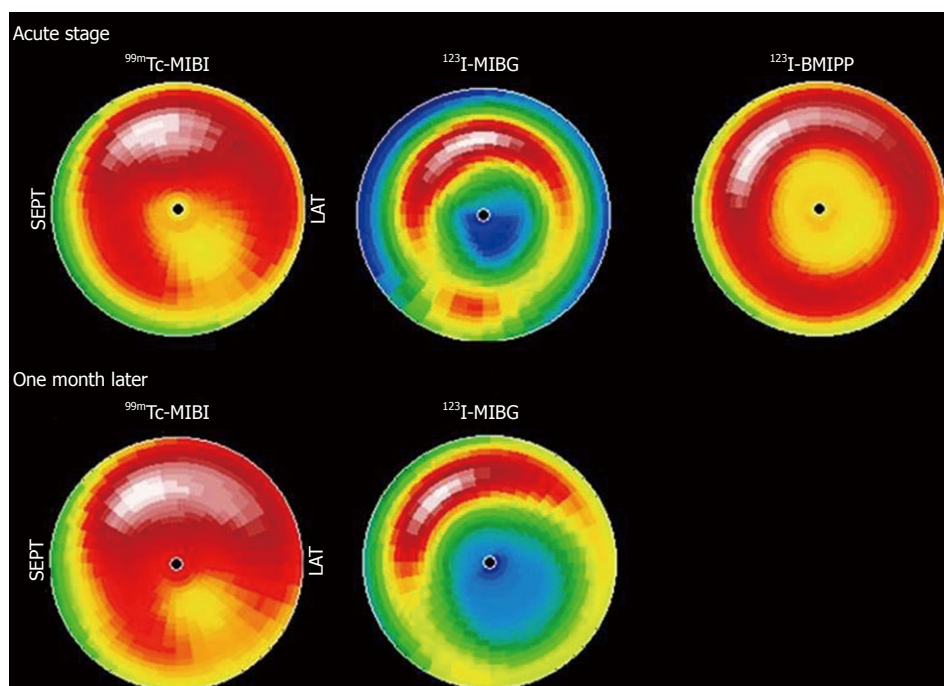


Figure 4 Scintigraphic features of Takotsubo cardiomyopathy are depicted. Bull's eye maps of ^{99m}Tc -sestamibi (MIBI), ^{123}I -MIBG and ^{123}I - β -methyl-p-iodophenyl-pentadecanoic acid (BMIPP) are shown. Both ^{123}I -MIBG and ^{123}I -BMIPP images show reduced uptake in the apical segment of the myocardium, which are typical features of the disease.

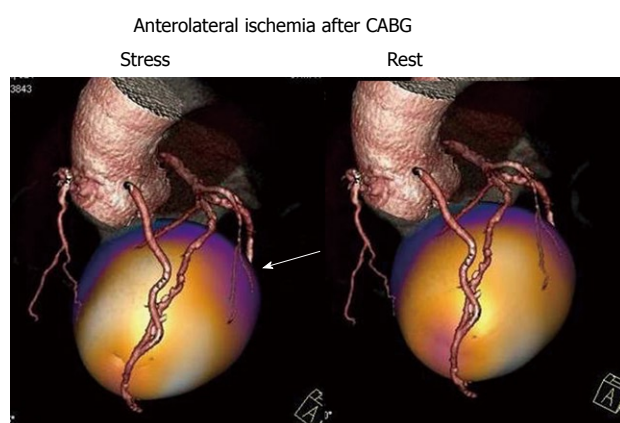


Figure 5 Fusion image reveals that the ischemic area in the basal anterolateral region shown by single photon emission computed tomography image is perfused by small vessels or has no corresponding artery assessed as imaging artifacts. Thus, the fusion image has increased diagnostic confidence for the detection of the culprit lesion in patients with coronary artery bypass grafting.

Advancement of technology with SPECT/CT

In the recent advances of fusion technology using X-ray CT angiography and myocardial perfusion imaging, SPECT/CT fusion imaging provides additional information about hemodynamic relevance and exact allocation of perfusion abnormalities to the subtending coronary artery. Software-based fusion imaging between SPECT and CT coronary angiography can offer better diagnostic information even if the culprit lesion is not identified by SPECT alone. The creation of the SPECT/CT fusion imaging by

different manufacturers has made these techniques more available to clinicians^[89,90]. In patients with coronary bypass graft surgery, the culprit lesion is difficult to determine, as shown in Figure 5. Fusion imaging has made it possible to diagnose more confidently the culprit region of ischemia using SPECT/CT imaging. Quantitative accuracy could be further improved by anatomical and functional correlation using fusion imaging.

Radiation exposure could be an issue with nuclear medicine imaging and CT. A number of techniques can be used to minimize the dose from CT^[91]. Also, the protocol to obtain CT images should be performed in a way in which the dose can be minimized. In terms of radiation dose reduction, ^{99m}Tc agents are more favorably used than ^{201}Tl .

Future perspective on nuclear imaging

The most important area of application of nuclear cardiology is risk stratification in the management of patients. A risk-based approach in patients with heart failure is clinically more important than simple diagnosis. The basic concept in the use of a nuclear cardiology test in myocardial perfusion imaging is that it can be applied to patients with an intermediate risk of death. With the use of sympathetic nerve imaging, prognostic evaluation of heart failure might be possible. Metabolic imaging also has prognostic information, including ischemic, myocardial damage and fibrosis. These nuclear techniques contribute significantly to guiding management decisions for identifying patients with heart failure.

CONCLUSION

There are several conditions that can lead to heart failure, including coronary artery disease and cardiomyopathy. It would be helpful for the clinician to identify non-invasively the underlying cause of heart failure. Physicians should rely more often on myocardial perfusion imaging to evaluate non-invasively cardiac function and ischemic conditions in patients with heart failure. Nuclear cardiology tests, including neurotransmitter imaging and metabolic imaging, are now easily performed with new tracers to refine heart failure diagnosis. Nuclear cardiology studies contribute significantly to guiding management decisions for identifying patients with heart failure.

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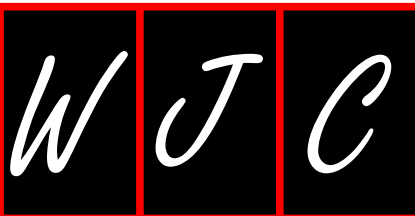
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Meetings

Events Calendar 2010

January 12-13
Riyadh, Saudi Arabia
1st International Cardiovascular
Pharmacotherapy Conference

January 17-21
Hollywood, United States
22nd Annual International
Symposium on Endovascular Therapy

January 20-23
Sao Paulo, Brazil
World Cardiology, Metabolism and
Thrombosis Congress

January 21-24
Phoenix, United States
13th Society for Cardiovascular
Magnetic Resonance Annual
Scientific Sessions

January 28-30
Brussels, Belgium
29th Belgian Society of Cardiology
Annual Scientific Meeting

January 28-31
Nashville, United States
31st Annual Meeting of
The American Academy of
Cardiovascular Perfusion

February 3-6
Snowbird, United States
35th Annual Cardiovascular
Conference at Snowbird

February 4-5
Leuven, Belgium
Leuven Symposium on Myocardial
Velocity and Deformation Imaging

February 6-9
St. Petersburg, United States
10th Annual International
Symposium on Congenital Heart
Disease

February 8-10
Tel Aviv, Israel
10th International Dead Sea
Symposium on Cardiac Arrhythmias
and Device Therapy

February 11-12
London, United Kingdom
2nd National Chronic Heart Failure
and Hypertension

February 18-21
Istanbul, Turkey
The 2nd World Congress on
Controversies in Cardiovascular
Disease (C-Care)

February 22-25
Maui, United States
Arrhythmias & the Heart
Symposium

February 22-26
Cancun, Mexico
15th Annual Cardiology at Cancun-
Advances in Clinical Cardiology and
Multi-Modality Imaging

February 25-28
Valencia, Spain
First International Meeting on
Cardiac Problems in Pregnancy

February 26-28
Hong Kong, China
International Congress of
Cardiology

February 28-March 4
Scottsdale, United States
International Congress XXIII on
Endovascular Interventions

February 28-March 5
Keystone, United States
Keystone Symposia: Cardiovascular
Development and Repair (X2)

March 3-5
Kish Island, Iran
Islamic Republic of 4th Middle East
Cardiovascular Congress

March 4-7
Newport Beach, United States
30th Annual CREF: Cardiothoracic
Surgery Symposium

March 7-12
Snowmass Village, United States
Interventional Cardiology 2010: 25th
Annual International Symposium

March 14-16
Atlanta, United States
American College of Cardiology
59th Annual Scientific Session

March 18-20
Rome, Italy
VIII Congress of the Italian Society
of Cardiovascular Prevention

March 18-20
Prague, Czech Republic
XI International Forum for the
Evaluation of Cardiovascular Care

March 24-25
Jeddah, Saudi Arabia
12th KFAFH Cardiovascular
Conference: A balanced approach to
treatment of cardiovascular diseases

April 8-11
Guangzhou, China
The 12th South China International
Congress of Cardiology

April 14-15
Tel Aviv, Israel
The 57th Annual Congress of the
Israel Heart Society in Association
with The Israel Society of
Cardiothoracic Surgery

April 15-18
Izmir, Turkey
59th European Society for
Cardiovascular Surgery
International Congress

May 5-7
Prague, Czech Republic
EuroPrevent 2010-Cardiovascular
Prevention: a Lifelong Challenge

May 8-9
St. Paul, United States
Controversies in Cardiovascular
Disease: Practical Approaches to
Complex Problems: Medical and
Surgical

May 12-16
Marrakesh, Morocco
7th Metabolic Syndrome, type
II Diabetes and Atherosclerosis
Congress

May 17-20
Whistler, Canada
6th IAS-Sponsored HDL Workshop
on High Density Lipoproteins

May 21-22
Sydney, Australia
3rd Cardiovascular CT, Concord
Conference 2010

May 29-June 1
Berlin, Germany
Heart Failure Congress 2010

June 1-4
Seoul, Korea, Republic of
9th Asian-Pacific Congress of
Cardiovascular & Interventional
Radiology (APCCVIR 2010)

June 16-19
Beijing, China
World Congress of Cardiology
Scientific Sessions

June 17-19
Port El Kantaoui, Tunisia
The 7th Tunisian and Europeans
Days of Cardiology Practice

July 1-3
Singapore, Singapore
6th Asian Interventional
Cardiovascular Therapeutics
Congress

July 16-19
Berlin, Germany
Frontiers in CardioVascular Biology
2010-1st Meeting of the CBCS of the
ESC

July 24-27
Vancouver, Canada
15th World Congress on Heart
Disease, Annual Scientific Sessions
2010

August 13-15
Krabi, Thailand
East Meets West Cardiology 2010

September 16-18
Athens, Greece
5th International Meeting of the
Onassis Cardiac Surgery Center

September 25-29
Belo Horizonte, Brazil
65th Brazilian Congress of
Cardiology

September 30-October 2
Berlin, Germany
5th International Symposium
on Integrated Biomarkers in
Cardiovascular Diseases

October 10-13
Rochester, United States
26th Annual Echocardiography
in Pediatric and Adult Congenital
Heart Disease Symposium

October 16-19
Copenhagen, Denmark
Acute Cardiac Care 2010

October 20-23
Boston, United States
2010 Cardiometabolic Health
Congress

November 25-26
London, United Kingdom
13th British Society for Heart Failure
Annual Meeting

December 9-11
Lisbon, Portugal
Heart, Vessels & Diabetes-The
European Conference



Instructions to authors

GENERAL INFORMATION

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 350 experts in cardiology from 41 countries.

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The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systematically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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Instructions to authors

stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

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DUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312194155.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: <http://www.wjgnet.com/1007-9327/13/4520.pdf>; <http://www.wjgnet.com/1007-9327/13/4554.pdf>; <http://www.wjgnet.com/1007-9327/13/4891.pdf>; <http://www.wjgnet.com/1007-9327/13/4986.pdf>; <http://www.wjgnet.com/1007-9327/13/4498.pdf>. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ... *etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Data that are not statistically significant should not be noted. ^a $P < 0.05$, ^b $P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, ^c $P < 0.05$ and ^d $P < 0.01$ are used. A third series of *P* values can be expressed as ^e $P < 0.05$ and ^f $P < 0.01$. Other notes in tables or under illustrations should be expressed as ¹F, ²F, ³F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua 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 PMID: 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. *HRS A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary 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**, Schorfeide AM. Adolescent pregnancy. 2nd ed. Wiecezorek 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 \pm SD or mean \pm 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 *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 \pm 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1949-8462/g_info_20100312200347.htm.

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Italics

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

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, etc.

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, etc.

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Topic highlight: http://www.wjgnet.com/1949-8462/g_info_20100312192932.htm

Observation: http://www.wjgnet.com/1949-8462/g_info_20100312193224.htm

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