ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2014 November 26; 6(11): 1135-1226

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

A peer-reviewed, online, open-access journal of Cardiology

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2014-2017

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WJC

World Journal of Cardiology

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Monthly Volume 6 Number 11 November 26, 2014

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World Journal of Cardiology is now indexed in PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

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PUBLICATION DATE
November 26, 2014

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DOI: 10.4330/wjc.v6.i11.1135

World J Cardiol 2014 November 26; 6(11): 1135-1139
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (1): Hypertension

Role of microparticles in endothelial dysfunction and arterial hypertension

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Received: May 30, 2014 Revised: August 29, 2014
Accepted: October 1, 2014
Published online: November 26, 2014

Abstract

Microparticles are small cell vesicles that can be released by almost all eukaryotic cells during cellular stress and cell activation. Within the last 1-2 decades it has been shown that microparticles are useful blood surrogate markers for different pathological conditions, such as vascular inflammation, coagulation and tumour diseases. Several studies have investigated the abundance of microparticles of different cellular origins in multiple cardiovascular diseases. It thereby has been shown that microparticles released by platelets, leukocytes and endothelial cells can be found in conditions of endothelial dysfunction, acute and chronic vascular inflammation and hypercoagulation. In addition to their function as surrogate markers, several studies indicate that circulating microparticles can fuse with distinct target cells, such as endothelial cells or leukocyte, and thereby deliver cellular components of their parental cells to the target cells. Hence, microparticles are a novel entity of circulating, paracrine, biological vectors which can influence the phenotype, the function and presumably even the transcriptome of their target cells. This review article aims to give a brief overview about the microparticle biology with a focus on endothelial activation and arterial hypertension. More detailed information about the role of microparticles in pathophysiology and disease can be found in already published work.

Key words: Microparticles; Arterial hypertension; Endothelial dysfunction; Biological vectors; Inflammation

Core tip: Microparticles are small cell vesicles which can be released from many cells (*e.g.*, endothelial cells, platelets, leukocytes) into circulation and that can be quantified with flow cytometry. Several studies have shown that specific microparticles subtypes are increased in conditions enhanced vascular inflammation and coagulation. Thereby, microparticles have become surrogate markers, which can be used to assess for example leukocyte and endothelial cell activation. Additionally, by fusion with other cells, microparticles transfer cellular components of their parental cells to their target cells, which often results in altered function of the target cells.

Helbing T, Olivier C, Bode C, Moser M, Diehl P. Role of microparticles in endothelial dysfunction and arterial hypertension. *World J Cardiol* 2014; 6(11): 1135-1139 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1135.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1135

INTRODUCTION

What are microparticles?

During cell activation, multiple eukaryotic cells, such as endothelial cells or leukocytes, but also prokaryotes, have the ability to shed little cell blebs, so called microparticles[1,2]. Microparticles consist of the cell membrane as well as of the cytoplasm of their maternal cells and can be classified by flow cytometry into for example endothelial microparticles (EMPs), leukocyte microparticles and

platelet microparticles (PMPs). When microparticles were first described by Wolf[3] over 40 years ago, it was suggested that they are only a kind of cellular debris. However, within the last couple of years microparticles have gained increasing interest in different medical fields and recent effort has been undertaken to investigate the biology of microparticles, as well as the impact of microparticles on different diseases[4-7]. It thereby has become evident that microparticles can be used as circulating surrogate markers for several pathophysiological conditions, such as inflammation, coagulation but also metastatic diseases and additionally are important circulating biological vectors[1].

Microparticles as biological vectors in circulation

The biology of microparticles is still incompletely understood, but it is evident that microparticles have far more functions than only activating inflammatory cells and the coagulation cascade. It recently has been shown that they bind to and fuse with distinct target cells, a process that is at least partly mediated by specific interactions of microparticles with surface receptors (such as Mac-1) of the target cell[8]. By fusion with their target cells, microparticles deliver cytoplasm as well as membrane anchored surface receptors to their destination cells. This process is frequently associated with changes of the target cells phenotype and function. Hence, microparticles are an own kind of biological vectors modulating the function of their target cells remote from the location where they initially had been released.

Elevated microparticle levels can often be found in pathological conditions which are associated with cell mediated inflammation and coagulation. To assess the inflammatory effect of platelet microparticles, which is the largest microparticle fraction in the blood, Jy *et al*[9] investigated the effect of PMPs on neutrophils. They found that microparticles released from platelets attach to neutrophils and activate those. Hence, platelet microparticles may in fact be an additional link between vascular coagulation and inflammation in cardiovascular disease.

Hypothesizing that microparticles might not only influence the phenotype but also the transcriptome of their target cells, Hunter *et al*[10] assessed whether microparticles from mononuclear cells contain microRNAs, which are small non-coding RNA molecules that regulate mRNA translation and thereby affect post transcriptional gene expression. In this ground breaking study, they found that microparticles indeed contain a broad spectrum of different microRNAs, which they might deliver to their target cells and presumably affect the target cells protein synthesis. Interestingly, when compared to microRNA patterns of their cells of origin, microparticles do not contain a random set of microRNAs of their paternal cells, but are loaded with a distinct, specific selection of miRNAs[11]. These findings suggest that microparticle release is a highly regulated process in which cell vesicles are "loaded" from their cells of origin with specific RNA molecules which might eventually be transferred to their target cells. However, to date the underlying molecular mechanisms of this loading process are not understood.

To what extent circulating microparticles are involved in intercellular signalling was demonstrated by a pivotal study of Janowska-Wieczorek *et al*[12]. They found that PMPs transfer the platelet surface receptor glycoprotein (GP) Ⅱb/Ⅲa to the surfaces of different lung cancer cell lines. As the GPⅡb/Ⅲa integrin has a high affinity to (sub)endothelial antigens, tumour cells that were pre-incubated with platelet microparticles also showed increased metastasization. Hence, PMPs might be directly involved in the progression of tumour diseases.

In summary, microparticles are small cell blebs that represent a novel way of intercellular communication, which seems to be particularly relevant for inflammatory and pro-coagulatory diseases. Due to the effects on their target cells, microparticles are able to change the phenotype, the function and presumably also the transcriptome of their target cells and might be involved in the pathogenesis of several cardiovascular diseases[1].

ARTERIAL HYPERTENSION

Arterial hypertension is a strong risk factor for atherosclerosis and vascular mortality and often starts with endothelial dysfunction[13,14]. Early diagnosis of impaired endothelial function is crucial to allow medical anti-inflammatory, endothelium-protective treatment at an early disease stage. Reflecting endothelial dysfunction, endothelial microparticles might be a valuable tool to assess endothelial dysfunction, particularly in asymptomatic patients.

Microparticles in endothelial dysfunction and arterial hypertension

Arterial hypertension is a multifactor disease that is strongly promoted by endothelial dysfunction[15,16]. Recent data indicate that altered, activated endothelial cells release endothelial microparticles into circulation. EMPs can be used as cellular surrogate markers for endothelial dysfunction and are increased in several diseases with an altered endothelial function, such as atherosclerosis, aortic valve stenosis and pulmonary hypertension[17-20]. It recently was published that endothelial microparticles are even associated with several cardiovascular risk factors in the Framingham Heart Study[21].

However, besides their role as surrogate markers, microparticles are furthermore involved in the progression of impaired endothelial function as well as in angiogenesis[22,23]. For example Burger *et al*[24] assessed the effect of microparticles on endothelial inflammation and found that microparticles themselves induce endothelial expression of vascular cell adhesion molecule 1, platelet endothelial cell adhesion molecule and adhesion of J774A.1 cells, which is a cell line with macrophage characteristics[24]. Along the same line of evidence, Boulanger *et al*[25] investigated the mechanisms how microparticles induce endothelial dysfunction and found that MPs from patients with myocardial infarction, but not from healthy

controls, induced endothelial dysfunction by impairing the endothelial nitric oxide transduction pathway. These data were confirmed by Martin *et al*[26] who discovered that T cell microparticles reduced endothelial nitric oxide- and prostacyclin mediated vasodilatation and decreased expression levels of endothelial nitric oxide synthase.

One of the few studies investigating the interconnection between microparticles and arterial hypertension was performed by Preston *et al*[20]. They assessed the abundance of endothelial microparticles in patients with untreated severe hypertension *vs* those with mild hypertension compared to normotensive individuals. It was found that microparticles released from endothelial cells and platelets were significantly increased in patients with severe arterial hypertension and that endothelial microparticles correlated strongly with the level of both systolic and diastolic blood pressures. Thus, it can be suggested that EMPs and PMPs can be used as circulating markers for endothelial injury in arterial hypertension. The findings described by Preston *et al*[20] are supported by studies, in which increased levels of circulating endothelial microparticles had been found in patients with pre-eclampsia, a disease that is characterized by vascular inflammation, altered endothelial function and arterial hypertension[27,28].

The Renin Angiotensin System (RAS) plays a key role in arterial hypertension and is the target for antihypertensive medical treatment. It has been supposed that angiotensin Ⅱ, which is the final effector of the RAS, not only affects the blood pressure but furthermore induces a pro-thrombotic state. Hypothesizing that the RAS might be involved in the generation of pro-thrombotic microparticles, Cordazzo *et al*[29] investigated the effect of angiotensin Ⅱ on the release of microparticles from mononuclear cells. They found that angiotensin Ⅱ indeed induces shedding of pro-thrombotic MP from mononuclear cells. The data of Cordazzo support the suggestion that microparticles might in fact be the link between the activation of the renin angiotensin system and a pro-thrombotic state, which can be found in patients suffering from arterial hypertension.

End-organ damage, such as hypertensive nephropathy with impaired kidney function, is a common complication of patients with arterial hypertension. To assess whether endothelial microparticles might be involved in impaired renal function under arterial hypertension, Hsu *et al*[30] measured endothelial microparticles, endothelial progenitor cells (EPCs) and the glomerular filtration rate in patients suffering from arterial hypertension. They found that elevated EMPs to EPCs ratios are associated with a decline of the glomerular filtration rate in hypertensive patients. These data underline the impact of endothelial damage assessed by the EMP to EPC ratio on the progression of impaired kidney functions in arterial hypertensive patients.

In conclusion, particularly endothelial microparticles can be found in several conditions that are associated with arterial hypertension. EMPs are not only valuable surrogate markers reflecting the extent of endothelial cell dysfunction but additionally might promote the progression of arterial hypertension and its complications.

WHAT BRINGS THE FUTURE?

Microparticles are promising surrogate markers for a variety of pathological conditions, particularly in conditions that are associated with impaired endothelial function and arterial hypertension (Table 1). However, a lack of standardization of microparticle definitions and methods used to quantify microparticles makes it difficult to compare results from different research groups. As microparticles have a highly complex molecular architecture, they are more fragile than for example blood proteins, which are often used as clinical surrogate parameters. Hence, the way how blood samples for microparticle measurements are taken, such as the diameter and the length of the needle that was used, is critical and can significantly influences flow cytometric analysis of microparticles. Finally, even technical characteristics of the flow cytometry used to analysis microparticles can influence measurement results. Therefore, the International Society on Thrombosis and Haemostasis (www.isth.org) and the *I*nternational *S*ociety for Extracellular Vesicles (http://www.isev.org) are working on recommendations for standardized protocols for microparticle measurements. Standardized studies will need to assess the diagnostic value of microparticles as surrogate markers in arterial hypertension.

As microparticles reflect a variety of different pathological changes in the vascular system (*e.g.*, inflammation, coagulation, activation of different cell types, *etc.*) they might represent a broader spectrum of cellular changes in circulation than measuring only one distinct soluble marker protein. Furthermore, besides their role as vascular surrogate markers, microparticle measurement can presumably be used to monitor the success of medical treatments of diseases that are associated with vascular inflammation. However, large clinical multicentre studies are necessary to assess whether microparticles of different cellular origin can be used as surrogate markers and as tools for drug monitoring in different cardiovascular diseases.

Until now, only very few studies have investigated the effect of different drugs on circulating microparticles. Nomura *et al*[31] found that eicosapentaenoic acid, which is an omega-3 fatty acid, reduces endothelial derived microparticles in patients suffering from type 2 diabetes. Tramontano *et al*[32] described that fluvastatin has a protective effect on endothelial cells and inhibits EMP release and Morel *et al*[33] reports that vitamin C reduces endothelial and platelet derived microparticles in patients with myocardial infarction. Even if these data are promising, their results need to be confirmed by randomized multicentre studies and it needs to be assessed whether a reduction of microparticle levels is associated with a beneficial patient outcome.

In conclusion, microparticles are small cell vesicles re-

Table 1 Overview about studies investigating the interrelation between microparticles and endothelial dysfunction/arterial hypertension

Study subjects	Flow cytometric MP characteristics	Findings	Ref.
Framingham offspring cohort	$CD144^+$ $CD31^+/CD41^-$	Increased $CD144^+$ MP correlate with Arterial hypertension Elevated triglycerides Metabolic syndrome Increased $CD31^+/CD41^-$ correlate with elevated triglycerides	Amabile *et al*[21]
MPs of AMI patients	Isolated blood MPs	MPs from AMI patients impair the endothelial nitric oxide pathway	Boulanger *et al*[25]
Ang Ⅱ stimulated mouse aortic endothelial cells	Annexin V^+	Ang Ⅱ induces EMP release	Burger *et al*[24]
	$CD144^+$	EMPs increase endothelial expression of VCAM-1, PCAM and adhesion of J774A.1 cells	
(Microparticles of) human mononuclear cells	Microparticles from mononuclear cells	Ang Ⅱ induces MP release of mononuclear cells	Cordazzo *et al*[29]
		Angiotensin receptor type 2 inhibitors reduce Ang Ⅱ induced MP release	
MPs of human lymphoid CEM T cell line	Isolated cell culture MPs	MPs decrease expression levels of eNOS	Martin *et al*[26]
		MPs induce endothelial dysfunction by altering the NO- and prostacyclin pathways	
EMPs of women with pre-eclampsia	$CD62E^+$ $CD31^+/42b^-$	Women with preeclampsia have higher EMP levels than those with gestational hypertension and controls	González-Quintero *et al*[28]
MPs levels of patients with art Hypertension	$CD31^+/CD42^+$	Increased EMPs and PMPs in patients with severe arterial hypertension	Preston *et al*[20]
	$CD41^+$	EMPs and PMPs levels correlate with blood pressure	

EMPs: Example endothelial microparticles; PMPs: Platelet microparticles; Ang Ⅱ: Angiotensin Ⅱ; MPs: Microparticles; eNOS: Endothelial nitric oxide synthase; VCAM-1: Vascular cell adhesion molecule 1; PCAM: Platelet endothelial cell adhesion molecule; AMI: Acute myocardial infarction; NO: Nitric oxide.

leased by a huge variety of cells reflecting the state of activation of their parental cells. Besides functioning as surrogate markers for example for endothelial dysfunction, recent evidence indicates that they additionally influence the progression of several cardiovascular diseases. Hence, circulating microparticles might not only be valuable surrogate markers for different pathological conditions but furthermore be novel therapeutic targets by which the progression of microparticle mediated diseases might be influenced.

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P- Reviewer: Beltowski J, Sicari R **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i11.1140

World J Cardiol 2014 November 26; 6(11): 1140-1148
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (2): Coronary artery disease

Bleeding risk stratification in an era of aggressive management of acute coronary syndromes

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Received: March 2, 2014 Revised: September 9, 2014
Accepted: October 1, 2014
Published online: November 26, 2014

Abstract

Major bleeding is currently one of the most common non-cardiac complications observed in the treatment of patients with acute coronary syndrome (ACS). Hemorrhagic complications occur with a frequency of 1% to 10% during treatment for ACS. In fact, bleeding events are the most common extrinsic complication associated with ACS therapy. The identification of clinical characteristics and particularities of the antithrombin therapy associated with an increased risk of hemorrhagic complications would make it possible to adopt prevention strategies, especially among those exposed to greater risk. The international societies of cardiology renewed emphasis on bleeding risk stratification in order to decide strategy and therapy for patients with ACS. With this review, we performed an update about the ACS bleeding risk scores most frequently used in daily clinical practice.

Key words: Bleeding; Acute coronary syndrome; Risk scores; Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; Acute Coronary Treatment and Intervention Outcomes Network

Core tip: Bleeding is the main non-thrombotic complication associated with acute coronary syndrome. Bleeding implies a worse prognosis due itself directly (fatal bleeding, for example, intracranial bleeding) and indirectly (discontinuation of antithrombotic therapy). For this it is important to do an adequate bleeding risk stratification in all patients with acute coronary syndrome. In this review we analyze the different risk factors for bleeding, along with the bleeding risk scores currently available.

Abu-Assi E, Raposeiras-Roubín S, García-Acuña JM, González-Juanatey JR. Bleeding risk stratification in an era of aggressive management of acute coronary syndromes. *World J Cardiol* 2014; 6(11): 1140-1148 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1140.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1140

INTRODUCTION

The classic aim of acute coronary syndrome (ACS) therapy was to reduce mortality and to prevent or minimize ischemic complications. This was possible with percutaneous coronary intervention and with antithrombotic drugs[1]; however, these therapies have led to an increased risk of bleeding complications[2]. Until the recent past, bleeding was thought to be inherent to the modern therapeutic approach in ACS and percutaneous coronary intervention (PCI)[3]. Nowadays this consideration has been changed. Clinical trials have demonstrated that major bleeding has a strong impact on the risk of death,

myocardial infarction and stroke in patients with ACS[4]. Therefore, a reduction in bleeding events translates into improved survival[1]. Because today we have a large arsenal of antiplatelet and anticoagulant drugs with different profile of efficacy and safety, it is important to make a proper selection of medication in order to balance the ischemic and hemorrhagic risk[5-8]. European and American Societies of Cardiology recommend bleeding risk stratification to guide ACS treatment[9-12].

INCIDENCE OF BLEEDING: THE PROBLEM OF THE DEFINITION

Hemorrhagic complications occur with a frequency of 1% to 10% during treatment for ACS and after PCI[13]. The National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry Get with the Guidelines (NCDR ACTION Registry-GWTG)[14] evaluated 72699 patients with non ST-segment elevation myocardial infarction (NSTEMI) and 48943 with ST-segment elevation myocardial infarction (STEMI). The reported major bleeding rate was approximately 9% among patients with NSTEMI and 12% among those patients with STEMI. Of note, the bleeding rates were significantly influenced by the presence of comorbidities, as well as by the use of invasive strategies in both NSTEMI and STEMI.

Bleeding rates depend mainly on the clinical setting and on the definition of bleeding events[15,16]. Since their initial development, both TIMI and GUSTO criteria have been applied to identify very significant bleeding in a wide range of clinical trials[17,18], but a myriad of other criteria have also been created[19] [the CURE[20], Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)[21], STEEPLE[22], OASIS[6] and acute catheterization and urgent intervention triage strategy (ACUITY)[8] bleeding definitions] (Table 1).

The Bleeding Academic Research Consortium (BARC) convened in 2010 was idealized with the intention of reviewing the existing definitions and developing standards for the analysis of hemorrhagic complications[13]. Among the recommendations of the panel, the consensus around the challenge of creating a single definition of major bleeding to be adopted stands out since the analyzed population is extremely variable as to its characteristics, clinical profile, follow-up time length, and due to the constant temporary modifications in clinical therapy and treatment strategies considered appropriate at its time. Basing on this, BARC participants proposed 5 bleeding types (Table 1)[6].

PREDISPOSING FACTORS

Major bleeding is currently one of the most common non-cardiac complications observed in the treatment of ACS patients. The identification of clinical characteristics and particularities of the antithrombin therapy associated with an increased risk of hemorrhagic complications would make it possible to adopt prevention strategies, especially among those exposed to greater risk[15].

In this way, different studies exposed the main predictors of major bleeding in the treatment of ACS. The Global Registry of Acute Coronary Events (GRACE) investigators developed a risk score of major bleeding, basing on a registry with 24045 ACS patients, of which 933 (3.9%) developed an episode of major bleeding during hospitalization[23]. They identified 7 independent predictors of bleeding: age, female gender, prior bleeding, kidney dysfunction, fibrinolysis, glycoprotein Ⅱb/Ⅲa inhibitors (GPI) use, and PCI. The most frequent bleeding sites were gastrointestinal (31.5%) and those related to the vascular access site (23.8%).

In the ACUITY study[22], authors identified 8 variables related to greater risk of bleeding were identified: female sex, anemia, advanced age, use of unfractionated heparin and Ⅱb/Ⅲa inhibitors instead of isolated bivalirudin, elevated serum creatinine, increased leukocyte count, absence of previous PCI, prior stroke, ST-segment elevation ≥ 1 mm, and routine use of GPI.

In an analysis of the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) database[1], with 89134 high-risk NSTEMI patients and with a incidence of major bleeding of 9.4%, 8 variables were identified as independent predictors of major bleeding: female sex, peripheral vascular disease, diabetes, systolic blood pressure, heart rate, congestive heart failure, creatinine clearance, and hematocrit.

In the REPLACE registry, female sex, anemia, and glomerular filtrate rate were also identified as independente predictor of bleeding[24]. Age > 55 years, low molecular weight heparin within 48 h pre-PCI, GPI, and intra-aortic balloon pump use were the other clinical variables associated with higher rate of major bleeding in the REPLACE trial.

In a global way, bleeding risk factors can be categorized into nonmodifiable and modifiable groups[25]. Commonly reported bleeding risk factors in patients with ACS are summarized in Figure 1.

According to the non-modifiable risk factors it is important to remarked 2 clinical variables: advanced age and female sex. Advanced age would predispose to a greater risk of bleeding due to injuries located in the vessels and systemic diffuse vessel disease. In the GRACE registry encompassing the whole spectrum of ACS, the adjusted odds of having a major hemorrhage prior to discharge increased by about 30% per decade of age (OR = 1.28, 95%CI: 1.21-1.37)[6,23,26]. In relation to female sex, within the GRACE registry, women had a 43% higher likelihood of developing major bleeds in-hospital compared with men (adjusted OR = 1.43, 95%CI: 1.23-1.66)[6,23]. It is believed that the smaller body size as well as the lower vessel size, reduced creatinine clearance, higher prevalence of comorbidities, higher risk of drug overdosing, older age at the moment of admission, and a lower threshold for transfusion due to lower baseline levels of hemoglobin would justify the relationship between female sex and

Table 1 Bleeding definitions

Trial	Definition
TIMI	Major bleeding: Intracranial hemorrhage or decrease of 5 g/dL in hemoglobin or 15% in hematocrit Minor bleeding: Decrease of 3 g/dL in hemoglobin with known source of blood los sor decrease of 4 g/dL in hemoglobin withoun known source of blood loss
GUSTO	Major bleeding: Fatal, intracranial, Retroperitoneal, intraocular leading to visión loss, or transfusion of 2 U Minor bleeding: any clinically significant bleeding not meeting major criteria leading to study drug interruption, surgery, or transfusion of 1 U of blood
ACUITY	Major bleeding: Intracranial or intraocular bleeding, hemorrhage at access site requiring intervention, hematoma ⩾ 5 cm, decrease ⩾ 4 g/dL of hemoglobin without overt bleeding source or ⩾ 3 g/dL with source, reoperation for bleeding, or transfusion of blood product Minor bleeding: any clinically significant bleeding not meeting major criteria
CRUSADE	Major bleeding: intracranial hemorrhage, documented retroperitoneal bleed, hematocrit drop ⩾ 12% (baseline to nadir), any red blood cell transfusion when baseline hematocrit was ⩾ 28%, or any red blood cell transfusion when baseline hematocrit was < 28% with witnessed bleed Minor bleeding: any clinically significant bleeding not meeting major criteria
GRACE	Major bleeding: Life-threatening bleeding requiring transfusion of ⩾ 2 U of packed red blood cells, bleeding resulting in absolute hematocrit decrease ⩾ 10% or death hemorrhagic/subdural hematoma Minor bleeding: any clinically significant bleeding not meeting major criteria
BARC	Type 0: No bleeding Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional Type 2: Any overt, actionable sign of bleeding (*e.g.*, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation Type 3a: Overt bleeding plus hemoglobin drop of 3-5 g/dL (provided hemoglobin drop is related to bleed), or any transfusion with overt bleeding Type 3b: Overt bleeding plus hemoglobin drop ⩾ 5 g/dL (provided hemoglobin drop is related to bleed), or cardiac tamponade, or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), or bleeding requiring intravenous vasoactive agents Type 3c: Intracranial bleeding (does not include microbleeds or hemorrhagic transformation, does include intraspinal), or subcategories confirmed by autopsy or imaging or lumbar puncture, or intraocular bleed compromising vision Type 4: Coronary artery bypass graft-related bleeding, or perioperative intracranial bleeding within 48 h, or reoperation after closure of sternotomy for the purpose of controlling bleeding, or transfusion of ⩾ 5 U whole blood or packed red blood cells within a 48-h period, or chest tube output ⩾ 2 L within a 24-h period Type 5 or fatal bleeding A: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious Type 5 or fatal bleeding B: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

ACUITY: Acute catheterization and urgent intervention triage strategy; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; GRACE: Global Registry of Acute Coronary Events; BARC: Bleeding Academic Research Consortium.

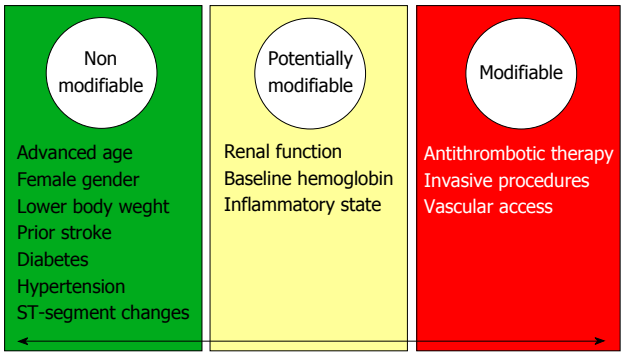

Figure 1 Bleeding risk factors in patients with acute coronary syndrome.

bleeding[15].

In relation with potentially modifiable factors, renal function is the most interesting. Santopinto *et al*[27] demonstrated that patients with moderate renal dysfunction were twice as likely to die (OR = 2.09, 95%CI: 1.55-2.81) and those patients with severe renal dysfunction are almost four times more likely to die (OR = 3.71, 95%CI: 2.57-5.37)[27]. Other potentially modifiable variable, with great interest in last years, is body mass index (BMI)[28]. Several epidemiologic studies have demonstrated that higher BMI was inversely associated with lower risk of mortality among patients with coronary artery disease (obesity-mortality paradox). As we know, the association between short-term death and BMI was affected not only by the ischemic risk but also by the major bleeding risk[25]. Recently, a meta-analysis have clarified the relationship between the risk of bleeding and BMI following PCI[29]. In this study, it was concluded that class I / II obese patients had the lowest risk of bleedings.

With regard to modifiable risk factors, two variables deserve a special mention: antithrombotic therapy and vascular access. Antithrombotic therapy would be influenced by pharmacodynamic and pharmacokinetic characteristics of the antithrombotic agents[15]. In this way, we can exemplify with the differences between fondaparinux, bivalirudin and enoxaparin, or the differences between clopidogrel, prasugrel, and ticagrelor. Fondaparinux and bivalirudin showed to reduce the rate of bleeding compli-

cations when compared with low molecular weight heparin and heparin sodium, with adequate antithrombotic ability (although fondaparinux have a slightly increased risk of catheter thrombosis in patients undergoing PCI). A critical aspect in the appropriate use of anticoagulant agents is dose adjustment according to the renal function. Current guidelines indicate dose reduction of enoxaparin to 1 mg/kg once daily in the case of severe renal failure (CrCl < 30 mL/min), and consider monitoring of anti-Xa activity[9,12]. Fondaparinux is contraindicated in severe renal failure (CrCl < 20 mL/min), ans is considered the drug of choice in patients with moderately reduced renal function (CrCl 30-60 mL/min). Regarding bivalirudin, patients with moderate renal impairment (30-59 mL/min) should receive an infusion of 1.75 mg/kg per hour, or 1 mg/kg per hour if the creatinine clearance is < 30 mL/min (0.25 mg/kg per hour if the patient is on haemodialysis). In presence of CrCl < 30 mL/min or eGFR is < 30 mL/min per 1.73 m^2, unfractionated heparin infusion adjusted to activated partial thromboplastin time is the recommended anticoagulant, albeit fondaparinux could be maintained until CrCl < 20 mL/min.

For the vascular access, the use of radial access significantly reduces bleeding complications in PCI compared with femoral access[30]. Importantly, vascular closure devices should be used in patients without significant arterial calcification in order to obtain satisfactory results.

In addition to these clinical factors, current research is focused on meeting new bleeding risk indicators. In this sense, genetic factors have been associated to bleeding[26]. For example, in clopidogrel-treated patients, the gain-function variant CYP2C19*17 was associated with higher bleeding rate[6,31]. This is an area with great projection in the near future.

CUANTITIVE EVALUATION OF BLEEDING RISK

The contemporary cardiology walks towards those predictive models that minimize as much as possible to morbidity and mortality resulting from cardiovascular disease[32]. This is to minimize the subjective component of clinical evaluation of a given patient. Therefore risk stratification is that characterizes modern clinical cardiologist[33]. Since patient's admission, there are many factors that determine the patient's prognosis in terms of mortality and morbidity. In this way, is necessary to go reassessing the patient risk at all times. Regarding acute coronary síndrome patient, particularly in relation to bleeding, there are a lot of variables that determine the hemorragic risk. The interaction between these variables is not easy to assess clinically. This is where lies the advantage of risk scores, which enable integration of all these variables providing a measure of risk that would not be possible otherwise. And this is the reason because of objective risk assessment provides superior risk discrimination when compared with physician-estimated risk[34]. Although there are several bleeding risk scores, there is no consensus about what is the best for bleeding risk assessment in daily clinical practice.

Contemporary bleeding risk scores (RS) (Table 2) in ACS comprise: REPLACE[24], CRUSADE[1], ACTION[35], and that derived by Mehran *et al*[36] from the combined dataset of ACUITY/HORIZONS-AMI trials. The CRUSADE risk score was developed to assess the in-hospital bleeding risk help during NSTEMI, whereas the ACTION and Mehran *et al*[36] models were derived from NSTEMI and STEMI patients. In addition to these risk models, the REPLACE proposes a stratification of the bleeding risk for patients submitted to PCI through femoral Access.

ADOPTION OF BLEEDING RISK SCORES

REPLACE

Using data from the multicenter studies REPLACE-1 e 2[37,38], Nikolsky *et al*[24] proposed a bleeding RS for patients submitted to PCI through femoral access (www.bleedingriskscore.org). In multivariate analysis performed in 5395 patients, seven variables were identified as predictors of major bleeding: age, female sex, chronic kidney dysfunction, anemia, use of low-molecular-weight heparin, administration of GPI, and the use of intra-aortic balloon pump. Based on them, a risk score was constructed, with an adequate discrimination (C-statistic = 0.62). The main limitation is that this risk score was derived from a highly selective population undergoing PCI using the femoral approach.

CRUSADE

More recently, investigators of the CRUSADE registry developed and validated a risk stratification tool for in-hospital major bleeding among NSTEMI patients[1]. Having a database constituted by 89134 patients, within 485 North American hospitals, the authors developed a bleeding risk score with those variables that resulted independent predictors of major bleeding: female sex, diabetes mellitus, peripheral artery disease, heart rate, systolic blood pressure, congestive heart failure, hematocrit, and creatinine clearance (www.crusadebleedingscore.org). Considering only the variables present at admission, the CRUSADE bleeding score is presented as an easily applicable and useful tool in predicting patient risk, in addition to the analysis of the risk of ischemic events, allowing a tailored therapeutic strategy, adapted to the individualized risk profile. Moreover, CRUSADE bleeding risk score was externally validated by Abu-Assi *et al*[39]. The CRUSADE score showed adequate calibration and excellent discriminatory powerful in the whole population and in the different treatment subgroups, except in patients treated with ≥ 2 antithrombotics who did not undergo cardiac catheterization (C-index = 0.56).

Mehran et al[36] bleeding risk score

Mehran *et al*[36] using data from the ACUITY and the HORIZONS-AMI trials (17421 patients) developed a bleeding risk score. Six independent baseline predictors

Table 2 Bleeding risk scores

Bleeding risk scores	Action		Mehran *et al*		CRUSADE	
variables	Values	Points	Values	Points	Values	Points
Sex	Male	0	Male	0	Male	0
	Female	4	Female	8	Female	8
Age (yr)	⩽ 40	0	< 50	0		
	41-50	1	50-59	3		
	51-60	2	60-69	6		
	61-70	3	70-79	9		
	71-80	4	⩾ 80	12		
	81-90	5				
	⩾ 91	6				
Weight (kg)	⩽ 50	5				
	51-70	4				
	71-100	3				
	101-120	2				
	121-140	1				
	⩾ 141	0				
Systolic blood pressure (mmHg)	⩽ 90	4			⩽ 90	10
	91-100	3			91-100	8
	101-120	2			101-120	5
	121-140	1			121-180	1
	141-170	0			181-200	3
	171-200	1			⩾ 201	5
	⩾ 201	2				
Heart rate (BPM)	⩽ 40	0			⩽ 70	0
	41-60	2			71-80	1
	61-70	3			81-90	3
	71-80	5			91-100	6
	81-100	6			101-110	8
	101-110	8			111-120	10
	111-120	9			⩾ 121	11
	121-130	11				
	131-150	12				
	⩾ 151	14				
Signs of heart failure	None	0			No	0
	Killip 2-3	3			Yes	7
	Cardiogenic shock	15				
Diabetes mellitus	No	0			No	0
	Yes	3			Yes	6
Prior vascular disease	No	0			No	0
	Yes	3			Yes	6
Home warfarin use	No	0				
	Yes	2				
Antithrombotic medications			Heparin plus GPI	0		
			Bivalirudin	-5		
ECG changes	No ST changes	0	No ST elevation	0		
	ST depresión	3	ST elevation	6		
	ST transient elevation	7				
	ST elevation					
Troponine I			Normal	0		
			Raised	6		
Serum creatinine (mg/dL)	< 0.80	0	< 1.00	0		
	0.80-1.59	1	1.00-1.19	2		
	1.60-1.99	2	1.20-1.39	3		
	2.00-2.99	4	1.40-1.59	5		
	3.00-3.99	6	1.60-1.79	6		
	4.00-4.99	8	1.80-1.99	8		
	5.00-5.99	10	⩾ 2.00	10		
	⩾ 6.00	11				
	On dialysis	11				
Creatinine clearance (mL/min)					⩽ 15.0	39
					15.1-30.0	35
					30.1-60.0	28
					60.1-90.0	17
					90.1-120.0	7
					> 120	0
Baseline hemoglobin (g/dL)	< 5.0	17				
	5.0-7.9	15				

	8.0-9.9	13				
	10.0-10.9	12				
	11.0-13.9	9				
	14.0-15.9	6				
	⩾ 16.0	2				
Baseline hematocrit (%)					< 31.0	9
					31.0-33.9	7
					34.0-36.9	3
					37.0-39.9	2
					⩾ 40.0	0
Anemia			No	0		
			Yes	6		
White blood cell count (giga/L)			< 10.0	0		
			10.0-11.9	2		
			12.0-13.9	3		
			14.0-15.9	5		
			16.0-17.9	6		
			18.0-19.9	8		
			⩾ 20.0	10		

CRUSADE: The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; GPI: Glycoprotein Ⅱb/Ⅲa inhibitors; ECG: Electrocardiography; BPM: Beats per minute.

for major bleeding were identified: female sex, age, creatinine, white blood cell count, anemia, ST-segment-elevation. The risk score differentiated patients with a 30-d rate of non-CABG-related major bleeding ranging from 1% to over 40%. As a difference with the other bleeding risk scores, this one includes white blood cell count as a risk factor for major bleeding.

ACTION

Using data from the ACTION trial in patients with STEMI and NSTEMI, an inhospital bleeding risk score was developed[35]. Twenty-two clinically variables were incorporated into the final regression model: heart rate, baseline hemoglobin, female gender, serum creatinine, age, electrocardiographic changes, heart failure or shock, diabetes, peripheral artery disease, body weight, systolic blood pressure, and home warfarin use. The rate of major bleeding in the overall population was 10.8%. The risk model discriminated well in the derivation (C-statistic = 0.73) and validation (C-statistic = 0.71) cohorts, with an optimal risk gradient: very low risk (3.9% of bleeding), low risk (7.3%), moderate risk (16.1%), high risk (29.0%), and very high risk (39.8%).

COMPARISON OF BLEEDING RISK SCORES

As we have shown above, all bleeding RS have shown good discrimination and calibration. The question is: Which RS should be recommended for the management of patients with ACS? Perhaps for that question we first must be sure about the reliability of a given predictive model in our population. The REPLACE bleeding RS was designed for a femoral approach, so now, in times of radial access, its usefulness is less. The other 3 scores (CRUSADE, ACTION and Mehran *et al*[36]) were compared recently by the group of Abu Assi on a patient population with ACS (STEMI and NSTEMI)[40], being the greatest accuracy obtained with the CRUSADE method, even in patients with STEMI.

Although any score cannot replace the clinical evaluation, data from our study suggests that CRUSADE score represents an useful objective clinical tool which could lead to improvements in ACS care[40].

LONG-TERM BLEEDING RISK STRATIFICATION

The risk of developing bleeding complications continues after discharge. About 5% of patients develop bleeding complications throught the first yeart after hospital discharge being on dual antiplatelet therapy (DAPT)[41]. There is no risk model to estimate risk of bleeding after discharge in ACS patients. Using data from the REACH registry[42], a risk score was built although in a stable scenario (not in the ACS setting). Because the CRUSADE risk score performed well among patients taking DAPT, this risk model may be used for bleeding risk stratification in ACS on DAPT after hospital discharge.

PROGNOSTIC IMPLICATIONS OF BLEEDING RISK STRATIFICATION

The main clinical implication of RS is to pave the way for a decision concerning the best antithrombotic strategy to be used aiding individual evaluation for risk of ischemic or hemorrhagic events.

Collectively, innumerous studies have shown a robust association between the occurrence of major bleeding and the necessity of blood cell transfusion with greater mortality in patients admitted with ACS or submitted to PCI (Figure 2). Subherwal *et al*[1] demonstrated an association between bleeding and inhospital mortality. Mehran *et al*[36] showed that major bleeding was an independent predictor of a 3.2-fold increase in mortality.

Although it is coherent to justify the association be-

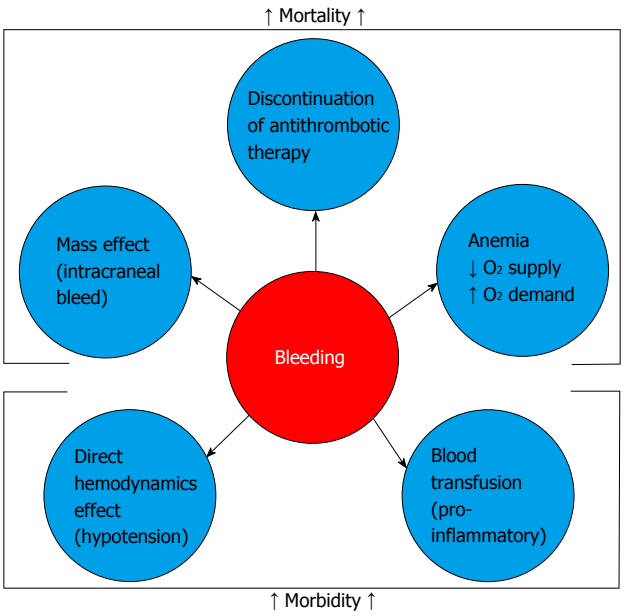

Figure 2 Different links between bleeding and morbidity and mortality in patients with acute coronary syndrome.

tween major bleeding and mortality by the coexistence of comorbidities and risk factors in the population common to the occurrence of these outcomes, today an accumulation of evidence is observed that points to direct or indirect influence of bleeding as a greater determinant of subsequent adverse ischemic events. The localization (intracranial) or the intensity (gastrointestinal, retroperitoneal) of the bleeding may itself result in death. However, other consequences may exhibit harmful effects to the ACS patients or those submitted to invasive coronary procedures[43].

CONCLUSION

The reduction of major bleeding, a relatively common complication in the current ACS scenario and possibly underestimated in randomized clinical trials, may be translated in better short- and long-term outcomes. Nowadays, its prevention represents a goal to be reached in the treatment of patients with ACS, through the balance between the risks and benefits of the pharmacological and invasive strategies offered. Appropriate risk stratification allows properly select those patients at increased risk of bleeding, focusing on them the efforts to reduce bleeding complications.

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P- Reviewer: Berenguer AB, Lin GM, Sethi A
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DOI: 10.4330/wjc.v6.i11.1149

World J Cardiol 2014 November 26; 6(11): 1149-1155
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (3): Cardiomyopathy

Infant with cardiomyopathy: When to suspect inborn errors of metabolism?

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Received: May 29, 2014 Revised: July 21, 2014
Accepted: September 4, 2014
Published online: November 26, 2014

Core tip: We highlight some very helpful red flags that, when present, should point physicians in the direction of doing a metabolic workup in patients with cardiomyopathy. Short case presentations will help readers to efficiently transfer metabolic diagnostic tools in their own practice. This article will be an essential reference for physicians as they evaluate patients with cardiomyopathy.

Byers SL, Ficicioglu C. Infant with cardiomyopathy: When to suspect inborn errors of metabolism? *World J Cardiol* 2014; 6(11): 1149-1155 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1149.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1149

Abstract

Inborn errors of metabolism are identified in 5%-26% of infants and children with cardiomyopathy. Although fatty acid oxidation disorders, lysosomal and glycogen storage disorders and organic acidurias are well-known to be associated with cardiomyopathies, emerging reports suggest that mitochondrial dysfunction and congenital disorders of glycosylation may also account for a proportion of cardiomyopathies. This review article clarifies when primary care physicians and cardiologists should suspect inborn errors of metabolism in a patient with cardiomyopathy, and refer the patient to a metabolic specialist for a further metabolic work up, with specific discussions of "red flags" which should prompt additional evaluation.

Key words: Cardiomyopathy; Inherited metabolic disorders; Inborn errors of metabolism

INTRODUCTION

Cardiomyopathy is rare in children (1.13 cases annually per 100000) but it often has catastrophic consequences including heart failure and death[1]. While the etiology of cardiomyopathy in infancy and childhood is varied, inborn errors of metabolism cause a substantial percentage of pediatric cardiomyopathies. Determining the etiology of cardiomyopathy presenting in the first year of life is critical to ensure optimal treatment and management, provide appropriate genetic counseling, and anticipate additional medical complications which may arise.

Previously, it was reported that approximately 5% of pediatric cardiomyopathies are due to an inborn error of metabolism[2], however a more recent study found a substantially higher percentage, with 26% of hypertrophic and 16% of dilated cardiomyopathies having a metabolic etiology[3]. A separate study found five out of 35 infants (13.5%) diagnosed in the first year of life had a metabolic etiology to their cardiomyopathy[4]. Over 40

Table 1 Red flags for inborn errors of metabolism associated with cardiomyopathy

Disorder	Pathognomonic biochemical abnormalities	Red flags
Mitochondrial disease	Elevated plasma lactate, elevated plasma alanine, proline	Hypotonia, developmental delays/ regression, other organ involvement
Barth syndrome	Urinary excretion of 3-Methylglutaconic acid	
VLCAD deficiency	Elevation of C14:1 acylcarnitine species	Hypoglycemia, elevated creatine kinase, liver dysfunction, metabolic decompensation with illness
LCHAD deficiency	Elevation of hydroxy compounds C14-OH, C16-OH, C18-OH	
Systemic primary carnitine deficiency	Very low plasma carnitine and elevated urinary carnitine extraction	
CPT2 deficiency	Elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1	
GSD deficiency Ⅱ (Pompe)	Decreased acid alpha-glucosidase enzyme activity	Hypotonia, enlarged tongue
MPS1 (Hurler, Hurler-Scheie, Scheie)	Elevated urine GAGs, decreased alpha-L-iduronidase enzyme activity	Dysmorphic features (coarse features), hepatomegaly, hernia, hearing loss, corneal clouding (MPS1) developmental delays/regression
MPS2 (Hunter)	Elevated urine GAGs, decreased iduronate-2-sulphatase enzyme activity	
Propionic aciduria	Urine organic acids: 3- hydroxypropionate, Methylcitrate, Tyglylglycine, Propionyl Glycine Plasma acylcarnitines: Elevated C3 (propionylcarnitine)	Hypotonia, high anion gap acidosis, hyperammonemia, metabolic decompensation with illness
Malonic aciduria	Plasma acylcarnitines: Elevated C3-DC (Malonyl carnitine). Urine organic acids: elevated malonic acid	Developmental delay/regression, hypotonia, hypoglycemia
Congenital disorders of glycosylation	Abnormal carbohydrate deficient transferrin, abnormal N- and O-glycosylation profiles (qualitative and/or quantitative)	Hypotonia, developmental delays/ regression hypoglycemia, liver dysfunction

VLCAD: Very long-chain acyl-CoA dehydrogenase; GAGs: Glycosaminoglycan; CPT2: Carnitine-palmitoyl transferase deficiency; LCHAD: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; GSD Ⅱ: Glycogen storage disease type 2; MPS1: Mucopolysaccharidosis type 1.

different metabolic disorders are known to cause cardiomyopathy[2]. Most commonly, disturbances of fatty acid oxidation, organic acidurias and storage disorders are implicated; however congenital disorders of glycosylation and mitochondrial disorders have more recently been identified in infants with cardiomyopathy[2,3,5,6].

This review article clarifies when primary care physicians and cardiologists should suspect inborn errors of metabolism in a patient with cardiomyopathy, and refer the patient to a metabolic specialist for a further metabolic work up. Short case presentations are designed to help readers efficiently transfer metabolic diagnostic tools into their clinical practice.

WHEN TO SUSPECT A METABOLIC DIAGNOSIS IN A CHILD PRESENTING WITH CARDIOMYOPATHY

Table 1 includes a summary of some of the more common metabolic disorders associated with cardiomyopathy along with pathognomonic biochemical abnormalities. Several "red flags" may be evident in the medical history and on initial physical examination. Identification of the following "red flags" should warrant a consultation with a metabolic specialist.

Medical history

A thorough medical history, including prenatal history, may give evidence of metabolic disease. Maternal history of acute fatty liver or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome during pregnancy may indicate that the fetus was affected with a fatty acid oxidation disorder. Newborn metabolic screening result should be obtained. A normal newborn screening is reassuring; however, many inborn errors of metabolism (IEM) such as storage disorders, mitochondrial disorders and congenital disorders of glycosylation are not included in the newborn screening panels; they could present with cardiomyopathy. Episodes of vomiting, lethargy, hypoglycemia, and metabolic decompensation in the context of poor feeding or illness are important clues of the potential presence of IEMs. A history of multisystem involvement, delayed developmental milestones, low muscle tone, developmental regression, coarse facial features, enlarged tongue, feeding difficulties and failure to thrive, recurrent ear and/or upper respiratory infections, rhabdomyolysis, muscle pain or spasms warrant consultation with a metabolic specialist.

Cardiomyopathy with hypoglycemia: Episodes of hypoglycemia, particularly nonketotic hypoglycemia, can be a red flag that there is a disturbance of energy production. In conjunction with cardiomyopathy, disorders of fatty acid oxidation are high on the list of differential diagnoses. Although some glycogen storage disorders may also be associated with episodic hypoglycemia, the hepatic glycogenoses are not generally associated with cardiomyopathy.

Family history

Family history of other closely related individuals with cardiomyopathy of unexplained etiology warrants further genetics evaluation. As most inborn errors of metabolism are inherited in an autosomal recessive manner, affected siblings and siblings who died at a young age from uncertain etiology should raise the suspicion for a metabolic etiology. X-linked disorders and many mitochondrial disorders are often inherited from the mother, thus family history should include second and third degree relatives,

Table 2 Biochemical testing recommendations for metabolic evaluation

Tier 1
Creatine kinase
Plasma acylcarnitine profile
Urine organic acids
Plasma lactate/pyruvate
Plasma amino acids
Enzyme analysis[1]
Tier 2
Carbohydrate deficient transferrin analysis
Urine glycosaminoglycans
Lysosomal storage disease enzyme panel (large panels are available through many laboratories)
Tier 3
Specific gene sequencing

[1]If there is a high suspicion for a single metabolic disease, for example Pompe disease.

particularly on the maternal side. Mitochondrial disorders may show considerable inter-individual variation, thus focus on maternal family history for other features of mitochondrial disorders, such as migraines, seizures, stroke-like episodes, developmental disabilities/regression, movement disorders, and exercise intolerance, may provide additional indication of mitochondrial dysfunction. Information regarding parental consanguinity and ethnic origins may also increase the suspicion of a metabolic etiology.

Cardiomyopathy with hypotonia: Hypotonia can be a key indicator of systemic muscle disease not limited to the heart. In an infant, hypotonia often results in the failure to meet developmental milestones on time. Hypotonia can also manifest as difficulty feeding and respiratory distress in an infant. For an infant with severe hypotonia and cardiomyopathy, Pompe disease should be excluded from the differentials. Congenital disorders of glycosylation and mitochondrial disorders may also present with cardiomyopathy and hypotonia due to an inability to produce and utilize energy in muscle. Lastly, due to the build-up of toxic waste products, organic acidurias may present in this manner.

Physical examination

Thorough examination of the patient should be performed and focused on the following: (1) Detection of hepatosplenomegaly, hypertrophic tonsils, joint contractures (indicative of lysosomal storage disorders); (2) Assessment of a neurologic function (may be abnormal in mitochondrial disorders, storage disorders, malonic aciduria); and (3) Identification of dysmorphic features such as coarsened facial features (pathognomonic for mucopolysaccharidosis).

Hearing and vision should always be included in the exam. Involvement of multiple organ systems in a child with cardiomyopathy should increase the suspicion for an IEM.

Cardiomyopathy with hepatomegaly: Hepatomegaly is a characteristic feature of storage disorders due to accumulation of waste materials in the liver. Liver biopsy may show characteristic storage materials. These waste materials may accumulate in other areas of the body, including soft tissues, joints and bones, which may be identified on physical examination. Coarse facial features in an infant with hepatomegaly should highly increase the suspicion of a storage disorder.

Laboratory studies

Confirmation of IEMs often relies on measuring the enzyme activity and/or identifying the genetic mutations responsible, but gene sequencing and copy number analysis may take weeks to months prior to having results. In an experienced laboratory, biochemical analysis can expeditiously determine whether a metabolic etiology warrants further investigation for some IEMs. In the absence of an obvious syndromic etiology, we recommend a biochemical evaluation as a standard of care for all infants with cardiomyopathy. Specifically, we recommend an acylcarnitine profile, plasma lactate/pyruvate, creatine kinanse and urine organic acids that could help in the diagnosis of fatty acid oxidation defects or malonic acidemia, which can be treated. Additional laboratory studies such as urine glycosaminoglycan quantification (for lysosomal storage disorders), N and O-glycans with carbohydrate deficient transferrin analysis (for congenital disorders of glycosylation) and specific enzyme analysis (for glycogen storage disorders and lysosomal storage disorders) may need to be performed to rule out some IEMs (Table 2).

MAJOR ETIOLOGICAL CATEGORIES

The major categories of inborn errors of metabolism associated with cardiomyopathy in infants are fatty acid oxidation disorders, lysosomal storage disorders, glycogen storage disorders, mitochondrial disorders and organic acidurias.

Fatty acids are used by the body as an alternative energy source when glucose is not available. Disorders of almost every step of the beta oxidation pathway, as well as disorders of fatty acid uptake and transport, have been identified and associated with cardiomyopathy. Carnitine-acylcarnitine translocase deficiency, carnitine palmitoyltransferase Ⅱ (CPT2) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein deficiency and glutaric acidemia type 2 are well known to be associated with cardiomyopathy[7]; however others such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency have also rarely been identified in infants with cardiomyopathy[8].

Lysosomal storage disorders (LSD) are an individually rare, but collectively common group of disorders in which waste materials accumulate in the lysosome. The accumulation of these materials in various organs and

tissues throughout the body is the main mode of pathogenesis for these disorders; however the exact mechanisms are unknown. Of the lysosomal storage disorders, Hurler syndrome (mucopolysaccharidosis type Ⅰ) and Hunter syndrome (mucopolysaccharidosis type Ⅱ) are the most well-known to be associated with cardiomyopathy in infancy and childhood. Maroteaux-Lamy syndrome (mucopolysaccharidosis type Ⅵ) has also been reported as presenting with cardiomyopathy in the infant period[9]. Inheritance is autosomal recessive, with the notable exception of Hunter syndrome and Fabry syndrome, which are both X-linked. LSDs are also notable in that enzyme replacement therapies (ERTs) are available for many of these disorders. ERTs halt the further accumulation of additional waste materials in the heart, but may not fully reverse the damage already done, further stressing the importance of early diagnosis.

Caused by many enzymes involved in the synthesis and breakdown of glycogen, glycogen storage disorders have primarily either hepatic or muscle involvement. Generally, muscle glycogenoses do not have symptoms of hypoglycemia. Pompe disease, a disorder which falls into both categories of lysosomal storage disorders and glycogen storage disorders, is one of the most common metabolic disorders associated with cardiomyopathy in infants. Infantile onset is associated with extreme hypotonia, failure to thrive, respiratory distress and cardiomyopathy. Although there are juvenile and adult-onset forms of Pompe disease, cardiomyopathy is not a feature of the later onset disorder. A similar disorder, Danon disease, is X-linked and affected males exhibit cardiomyopathy, intellectual disability and myopathy. ERT is available for Pompe disease, but not Danon disease at this time. Other glycogen storage disorders, which rarely present with cardiomyopathy in the infant period, include type Ⅲ (debranching enzyme deficiency)[10] and type Ⅳ (Andersen disease)[11].

Mitochondrial disorders typically have multisystem involvement, which can include hypertrophic or dilated cardiomyopathy, as well as left ventricular non-compaction[6]. Although mitochondrial disorders are estimated to have an incidence of 1 in 5000 births, these disorders are likely under diagnosed. Many of the well characterized mitochondrial disorders, including Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged-red fibers (MERRF), are known to include cardiomyopathy[6].

Congenital disorders of glycosylation (CDGs) are a heterogeneous group of disorders caused by enzymatic disturbances in the synthesis of glycoproteins. The spectrum of CDGs is ever expanding. Several case reports in the literature suggest that CDGs should be considered in infants with cardiomyopathy and multisystem disorders. Infants with CDG I a (phosphomannomutase 2 deficiency) are have been most often been reported to have hypertrophic cardiomyopathy[12-16] and infants with dolichol kinase deficiency have been reported to have dilated cardiomyopathy[17,18]. Case reports exist for cardiomyopathy associated with other CDGs[12,19].

Organic acidurias are the result of enzyme deficiencies characterized by the excretion of specific organic acids in the urine. Although this group is large, only a few have been associated with cardiomyopathy. Barth syndrome, characterized by urinary excretion of 3-methylglutaconic acid due to defects in the mitochondrial protein tafazzin, causes dilated cardiomyopathy in infant males, which is often severe[20]. Propionic acidemia is the most well known; however, individuals with propionic acidemia generally do not develop cardiomyopathy in the newborn period. Cardiomyopathy has rarely been reported in infants with methylmalonic acidemia[21].

NEWBORN SCREENING

With the advent and standardization of neonatal screening in the United States, many metabolic disorders associated with cardiomyopathy are identified within the first days of life. Fatty acid oxidation disorders, including VLCAD deficiency, LCHAD deficiency and carnitine uptake deficiency, as well as propionic acidemia are included in the disorders recommended by the American College of Medical Genetics as part of the core panel of disorders included on the newborn screen[22]. Despite the inclusion of several inborn errors of metabolism, this should not lead to a false sense of comprehensiveness. False negatives have been reported[23] and individuals with fatty acid oxidation disorders may have normal acylcarnitine profiles when they are not in a state of metabolic decompensation. Lysosomal storage disorders, congenital glycosylation defects, glycogen storage disorders and mitochondrial disorders are not screened. Although many states are moving towards screening for lysosomal storage disorders, it is uncertain whether there will be universal acceptance of neonatal screening for these disorders.

CASE PRESENTATIONS

The following cases represent several infants who presented in the newborn period with cardiomyopathy and a metabolic etiology was determined.

Patient 1

He is a male infant of Puerto Rican ethnicity. He presented to an emergency department in the setting of respiratory distress. Upon evaluation, the patient was found to have pneumonia. An echocardiogram was performed, which revealed dilated cardiomyopathy with severe dysfunction. The ejection fraction was estimated at 20%. The patient was transferred to our medical center for further evaluation and management of his cardiac dysfunction.

Physical examination of the patient showed an interactive male, with frontal bossing and dysmorphic features, including depressed nasal bridge, and low set, posteriorly rotated ears. He had developmental delays and had a history of failing his newborn hearing screen. Family history was significant for consanguinity, as the patient's parents are first cousins. Family history was also remarkable for a

sister who died at age 3 years 5 mo from unspecified cardiac dysfunction.

Red flags for IEM and final diagnosis: Patient 1

Red flags: (1) Family history of sibling death due to unspecified cardiac dysfunction. Further investigation revealed that she had coarse facial features and developmental delays as well; (2) Consanguinity; and (3) Coarse facial features, dysmorphic features, hearing loss, and developmental delay.

The deceased sibling had the same signs and symptoms as this patient, and the parents are consanguineous. This suggests autosomal recessive inheritance. The patient had many other clinical findings besides dilated cardiomyopathy so this was not simply an isolated cardiomyopathy. Based on coarse facial features, hearing loss, developmental delay, and cardiomyopathy, lysosomal storage disorders such as mucopolysaccharidosis were suspected first in the differential diagnosis. Leukocyte enzyme analysis showed alpha-iduronidase activity of 0 nmol substrate per hours per milligram per protein (normal 6-71.4). This was consistent with a diagnosis of Mucopolysaccharidosis type 1, or Hurler syndrome. Genetic testing confirmed this diagnosis with homozygous c.208C > T (p.Q70X) mutations in the *IDUA* gene. Urinary glycosaminoglycan quantitation showed elevation at 163.51 mg/nmol creatinine.

Following the diagnosis of mucopolysaccharidosis type 1, this patient started enzyme replacement therapy (Aldurazyme). The patient's cardiac function has stabilized at one year of age and he will continue to be followed for signs of cardiac dysfunction.

Patient 2

He is an 8-mo-old ex-full term male born to a 32-year-old G1P0 Haitian mother and Dominican father. Pregnancy was unremarkable except for hypertrophic cardiomyopathy noted on second trimester ultrasounds that was confirmed by fetal echocardiogram. He was initially asymptomatic, but echocardiogram at birth confirmed the presence of biventricular hypertrophy with increased trabeculation and decreased left ventricular function. Cardiac catheterization and endomyocardial muscle biopsy at three weeks of life revealed non-specific findings of cardiomyopathy with muscle disarray, and there was no evidence of glycogen accumulation. Additional metabolic evaluations were unremarkable, including acylcarnitine profile, urine and plasma amino acids, ammonia, cholesterol, urine and plasma carnitine and creatine kinase. Although the lactate level was normal, pyruvate was slightly low, which caused the lactate/pyruvate ratio to be elevated at 53 (normal 10-20). Pompe disease was ruled out based on normal enzyme activity.

Red flags for IEM and final diagnosis: Patient 2

Red flags: There was no clear explanation for this patient's hypertrophic cardiomyopathy. It appeared to be an isolated cardiomyopathy without significant neurologic or other organ involvement. Elevated lactate/pyruvate ratio was a red flag for mitochondrial disorders. This warranted further mitochondrial work up.

The patient had genetic testing for mutations in genes associated with mitochondrial disorders. The patient was found to have two predicted pathogenic variants in the *SLC25A3* gene, c.599T > G (p.L200W) and c.886-898delins7 (p.G296-S300delinsQIP). Parental testing indicated that the *SLC25A3* variants were in trans.

Mutations in *SLC25A3* are associated with mitochondrial phosphate carrier deficiency. There are only two papers in the literature describing five children from two families with mutations in this gene. Of the five children reported, three died in early infancy[24]. Two of the other children had difficult neonatal courses, but were living at age 9 and 17 as of 2011[25]. Mitochondrial phosphate carrier deficiency is characterized by hypertrophic cardiomyopathy, skeletal myopathy and lactic acidosis.

Patient 2 was listed for a cardiac transplant and received a heart at 8 mo of age. Following the surgery, this patient was observed to have new-onset seizures. Patient 2 continues to be followed by Cardiology, Metabolism, and Neurology at 10 mo of age.

Patient 3

He was previously reported[26] and is included with permission of the original author. A full term male of African American ethnicity presented at 5 mo of age in the setting of decreased oral intake, fatigue with feeds, cough and fever. His prenatal history was unremarkable. His first months were significant for poor head control and gross motor delays. Echocardiogram demonstrated left ventricular dilation, spongiform appearance of the left ventricular free wall and poor ventricular functioning. The ejection fraction was shortened at 21%.

Red flags for IEM and final diagnosis: Patient 3

Red flags: Hypotonia and developmental delay, in addition to cardiomyopathy, warrant additional testing to rule out an IEM. The metabolic tests such as plasma acylcarnitine profile, blood and urine carnitine levels, creatine kinase and urine organic acid analysis should be ordered as the first step tests.

Biochemical evaluation included urine organic acids [increased excretion of malonic acid (1060 mg/g creatinine) and methylmalonate (59 mg/g creatinine)], plasma acylcarnitine profile (elevated malonyl carnitine of 0.13 nmol/mL), lactate/pyruvate (normal), and creatine kinase (normal). The patient was neither acidotic nor hypoglycemic.

Malonyl-CoA decarboxylase enzyme assay showed 12% of normal activity. Retrospective analysis of the patient's newborn screening showed an elevated malonyl carnitine of 0.39 nmol/mL, which was not reported due to lack of routine screening for this compound and lack of established standards.

This patient was treated with carnitine supplementation, medium-chain triglyceride supplementation and a high-carbohydrate diet. After one year of treatment, the

patient did not have any further episodes of metabolic decompensation, but developmental delays persisted. Follow-up cardiac surveillance continued to show left ventricle dilation with a shortening fraction of 41%.

CONCLUSION

In conclusion, determining the etiology of cardiomyopathy in the infant is critical for determination of a treatment plan, accurate genetic counseling and discussion of prognosis. A significant proportion of infants with cardiomyopathy may have a metabolic etiology and some of these benefit greatly from diagnosis and follow up treatment. The efficacy of such treatments makes it important to exclude metabolic causes for all infants presenting with cardiomyopathy.

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P- Reviewer: Maleki AR, Peteiro J **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

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DOI: 10.4330/wjc.v6.i11.1156

World J Cardiol 2014 November 26; 6(11): 1156-1165
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (3): Cardiomyopathy

Importance of genetic evaluation and testing in pediatric cardiomyopathy

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Author contributions: Tariq M and Ware SM wrote and approved the manuscript.
Supported by The Children's Cardiomyopathy Foundation; Cincinnati Children's Hospital's Clinical and Translational Science Award, No. NIH-ULlRR026314 (Ware SM); and AHA Postdoctoral Fellowship Award, No. 12POST10370002 (Tariq M)
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Received: May 29, 2014 Revised: July 29, 2014
Accepted: September 4, 2014
Published online: November 26, 2014

Abstract

Pediatric cardiomyopathies are clinically heterogeneous heart muscle disorders that are responsible for significant morbidity and mortality. Phenotypes include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction and arrhythmogenic right ventricular cardiomyopathy. There is substantial evidence for a genetic contribution to pediatric cardiomyopathy. To date, more than 100 genes have been implicated in cardiomyopathy, but comprehensive genetic diagnosis has been problematic because of the large number of genes, the private nature of mutations, and difficulties in interpreting novel rare variants. This review will focus on current knowledge on the genetic etiologies of pediatric cardiomyopathy and their diagnostic relevance in clinical settings. Recent developments in sequencing technologies are greatly impacting the pace of gene discovery and clinical diagnosis. Understanding the genetic basis for pediatric cardiomyopathy and establishing genotype-phenotype correlations may help delineate the molecular and cellular events necessary to identify potential novel therapeutic targets for heart muscle dysfunction in children.

Key words: Pediatric; Mutation; Exome sequencing; Sarcomere

Core tip: Pediatric cardiomyopathy is a clinically and genetically heterogeneous heart muscle disease with five major phenotypes: hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. The genetic basis of these cardiomyopathies has been identified using traditional linkage analysis and sequencing. Novel gene discovery has been increased using modern next generation sequencing technologies, however the exact mechanisms of disease development are not fully known. In this review we focus on the current genetic knowledge of cardiomyopathies and their importance in diagnostic settings.

Tariq M, Ware SM. Importance of genetic evaluation and testing in pediatric cardiomyopathy. *World J Cardiol* 2014; 6(11): 1156-1165 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1156.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1156

INTRODUCTION

Cardiomyopathy is a clinically heterogeneous disease with a strong genetic component which affects heart muscle[1]. In the pediatric population, 40% of children progress to death or transplantation within 5 years of diagnosis[2-5]. The overall incidence of cardiomyopathy

Table 1 List of important genes involved in cardiomyopathy

Gene	Total coding exons	Encoded protein (AA)	NCBI GenBank accession #	Chromosomal location	Major phenotype
Sarcomere					
MYH7	38	1935	NG_007884	14q11.2	HCM, RCM, DCM, LVNC
MYBPC3	33	1274	NG_007667	11p11.2	HCM, DCM
TNNT2	15	295	NG_007556	1q32.1	HCM, RCM, DCM, LVNC
TPM1	9	284	NG_007557	15q22.2	HCM, DCM
MYL3	6	195	NG_007555	3q21.31	HCM, LVNC
MYL2	7	166	NG_007554	12q24.11	HCM, LVNC
ACTC1	6	377	NG_007553	15q14	HCM, RCM, DCM, LVNC
TNNI3	6	210	NG_007866	19q13.4	RCM
MYH6	37	1939	NC_000014	14q11.2	HCM, DCM
TNNC1	6	161	NG_008963	3p21.1	HCM, DCM, RCM
Desmosome					
JUP	9	563	NG_009090	17q21.2	ARVC
DSP	24	2871	NG_008803	6p24.3	ARVC
PKP2	14	881	NG_009000	12p11.21	ARVC
DSG2	15	1118	NG_007072	18q12.1	ARVC
DSC2	16	901	NG_008208	18q12.1	ARVC
Cytoskeleton, Z-disc, *etc.*					
ACTN2	21	894	NG_009081	1q43	HCM, DCM
DES	9	470	NG_008043	2q35	HCM, RCM, DCM, ARVC
LDB3	13	732	NG_008876	10q23.2	HCM, DCM, LVNC
CSRP3	5	194	NG_011932	11p15.1	HCM, DCM
TCAP	2	167	NG_008892	17q12	DCM
SGCD	8	290	NG_008693	5q33.3	DCM
TTN	311	33423	NG_011618	2q31.2	DCM
DMD	79	3385	NG_012232.1		DCM
MYPN	19	1320	NM_032578.2	10q21.3	HCM, DCM, RCM
PLN	1	52	NG_009082	6q22.31	HCM, DCM, ARVC
VCL	22	1134	NG_008868	10q22.2	HCM, DCM, LVNC
CRYAB	3	175	NG_009824	11q23.1	DCM
CAV3	2	151	NG_008797	3p25.3	HCM
BAG3	4	575	NM_004281.3	10q26.11	DCM
ANKRD1	9	319	NM_014391.2	10q23.31	HCM, DCM
Syndromic					
TAZ	11	292	NG_009634	Xq28	DCM, LVNC
ALMS1	23	4169	NG_011690	2p13.1	
PTPN11	15	593	NG_007459	12q24.13	HCM
RAF1	16	648	NG_007467	3p25.2	HCM, DCM
Others					
LAMP2	9	411	NG_007995	Xq24	HCM, DCM
LMNA	12	664	NG_008692	1q22	DCM, LVNC
EMD	6	254	NG_008677	Xq28	DCM
RYR2	105	4967	NG_008799	1q43	ARVC
ABCC9	38	1549	NG_012819	12p12.1	DCM
SCN5A	27	2015	NG_008934	3p22.2	DCM
TMEM43	12	400	NG_008975	3p25.1	ARVC

in children < 18 years of age in the United States is 1.13 cases per 100000 annually[6,7]. Cardiomyopathy in the pediatric population is diverse and may be caused by a number of different factors, including both genetic and non-genetic etiologies, posing an intense diagnostic challenge to clinicians. As a result, the majority of cases are still considered idiopathic. More than 100 genes have been identified causing cardiomyopathy related phenotypes and these genes belong to diverse molecular pathways, implicating the involvement of contractile proteins, intracellular calcium handling, and myocardial energetics as etiologies (Table 1)[8,9]. Identification of the underlying causes of cardiomyopathy may lead to improved outcomes with disease-specific treatments. A research-based pediatric cardiomyopathy registry (PCMR) identified familial, syndromic, neuromuscular or metabolic causes in 30% of children[10]. In the pediatric population, sarcomeric mutations, genetic syndromes, and other unique causes such as inborn errors of metabolism, mitochondrial disorders, myopathies and neuromuscular disorders all contribute (Table 1)[11]. However, the PCMR longitudinal outcome data on more than 3500 children with cardiomyopathy demonstrated that 60%-70% of these children are still classified as "idiopathic"[4,5,12]. Recently, Kindel *et al*[13] reported that classifying causes of cardiomyopathy can be increased to 70% with incorporation of evaluation by a geneticist and genetic testing. Because of the inclusion of syndromic, metabolic, and neuromuscular etiologies, genetic causes of pediatric cardiomyopathy are more heterogeneous than adult-onset

cardiomyopathy but also encompass the majority of genetic causes that result in isolated cardiomyopathy in adults (*e.g.*, sarcomeric or cytoskeletal gene mutations)[14]. In the pediatric population, the same genetic causes that result in isolated (also termed familial) cardiomyopathy in adults are prevalent, including causes of hypertrophic cardiomyopathy (HCM; > 35% yield with sarcomeric gene panel testing) or dilated cardiomyopathy (DCM; > 20% yield with current large DCM gene panels used for testing in adults). The genetic screening of these patients for known cardiomyopathy genes helps diagnostic screening of family members, family-based risk assessment, and disease-management[13,15,16]. Historically, this immense genetic and allelic heterogeneity has made molecular analyses difficult, expensive, and time-consuming due to low throughput of traditional sequencing technologies. However, recent advances in sequencing technologies provide rapid, accurate, and cost-effective DNA sequencing. The majority of the clinical diagnostic laboratories are now adopting next generation technologies for their routine gene testing in cardiomyopathy and focusing on coding regions. It is estimated that about 85% of disease-causing mutations lie within the protein-coding regions of the human genome[17-19].

Cardiomyopathy is classified into 5 clinical phenotypes: HCM, DCM, restrictive cardiomyopathy (RCM), left ventricular noncompaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC)[20,21]. Although these are clinically distinct entities, there is evidence for genetic overlap among them. For example, mutations in beta myosin heavy chain (*MYH7*) are most commonly associated with HCM and DCM but have also been reported in RCM[14,22] and LVNC[23-25]. The majority of pediatric cardiomyopathy cases exhibit dilated (50%) or hypertrophic (42%) phenotypes[6,26]. The PCMR is a valuable source for this population in terms of outcome and clinical features. In this review we will focus on the genetic causes of cardiomyopathy in the pediatric population.

HCM

HCM is the most prevalent inherited cardiac disorder and is defined as the presence of unexplained left ventricular hypertrophy (LVH), a primary myocardial process, with myocyte disarray and fibrosis. Fibrosis is a common endpoint in the pathological process of HCM. HCM was the first cardiomyopathy with a specific genetic etiology identified[27,28]. HCM is also considered the most common cause of sudden cardiac death in young, healthy and athletic individuals[29]. In adults, the diagnosis of HCM implies a sarcomeric gene mutation as the underlying etiology. However, in children, HCM is a heterogenous group of disorders encompassing conditions with diverse genetic origins and clinical phenotypes, including associations with inborn errors of metabolism, neuromuscular disorders, and malformation syndromes[6,10,13,30,31]. This is an important clinical distinction since patients classified in the metabolic, syndromic, or neuromuscular categories have additional medical management needs. At times, these conditions may require a high level of clinical suspicion in order to diagnose at early ages. For example, at our institution, the incorporation of genetic evaluation into the cardiomyopathy population led to the diagnosis of Noonan syndrome or Noonan syndrome with multiple lentigines in several adolescents and young adults who had been followed since early childhood with presumed isolated sarcomeric HCM and who had only very subtle features of a syndromic cause. These diagnoses also have substantial implications for family based cardiac screening recommendations.

HCM is frequently inherited in an autosomal dominant manner with hundreds of mutations affecting more than 27 genes identified to date (Table 1). Over 1000 distinct mutations in sarcomeric genes (*MYBPC3, MYH7, TNNT2, TPM1, ACTC1, TNNI3, TTN, MYL2*) of the contractile apparatus are known to cause adult-onset HCM[32,33] leading to the paradigm that HCM is a disease of the sarcomere[34,35]. Mutations in *MYH7*, encoding beta-myosin heavy chain, and in *MYBPC3*, encoding cardiac myosin-binding protein C, are the most common, each accounting for approximately 40% of all cases and nearly 80% of all mutation positive cases; the remaining seven genes each account for less than 1% to 5% of cases and collectively 10% of cases[36]. Overall, pathogenic mutations have been identified in 50%-70% of HCM cases[37]. Mutations found in these genes are generally missense, incorporating a mutated protein into the sarcomere. An exception is the *MYBPC3* gene, in which half of the mutations are truncations causing haploinsufficiency of the protein[38,39]. Interestingly, in the pediatric population, *MYBPC3* truncating mutations are less common and missense mutations predominate. Until recently, mutations in the sarcomeric machinery were thought to cause HCM in adults only and not contribute significantly to the development of HCM in young children[40]. However, two independent reports have shown that as many as 50% of pediatric HCM cases harbor mutations in sarcomeric genes and 17% of patients with these sarcomeric mutations were diagnosed in the first year of life[14,41], suggesting that sarcomere gene mutations are important cause of HCM both in adults and pediatric populations. Following this, Kindel *et al*[13] reported sarcomeric gene mutations as the major cause of disease in pediatric HCM patients with a family history of the disease. Non-genetic causes rarely cause HCM in children although LVH can occur in response to some environmental triggers, such as transient LVH in infants of diabetic mothers[42]. Both RCM and HCM are characterized by diastolic dysfunction and some reports suggest a clinical overlap with distinct clinical outcomes for patients who exhibit HCM with restrictive physiology[43,44]. In some families, distinct HCM and RCM phenotypes segregate with the same disease causing sarcomeric mutation[45]. Recently, risk factors for the outcomes of death or transplantation were reported for the largest pediatric HCM cohort studied to date[26]. The

results demonstrated that risk was greatest for those who presented as infants, those with inborn errors of metabolism, or those with mixed HCM phenotypes (HCM and DCM or HCM with restrictive physiology). Interestingly, children with mixed HCM with DCM or RCM phenotype frequently have a family history of the disease including family members with isolated HCM or mixed phenotypes[26], suggesting that even in families with Mendelian inheritance of cardiomyopathy, more complex genetic interactions occur to determine phenotype, with genetic modifier factors involved.

In the pediatric population, if metabolic or syndromic causes are ruled out as etiologies, HCM is considered a familial disease caused by the same genes that are causal for isolated cardiomyopathy in adults. The diagnosis of HCM in a child with suspected isolated cardiomyopathy should prompt evaluation of the first-degree relatives[46,47]. Current guidelines indicate that cascade cardiac screening and genetic testing are indicated in this patient population. These cascade screening and testing approaches have been applied particularly successfully in the Netherlands, where a founder *MYBPC3* mutation results in an identifiable at risk population[48]. Miller *et al*[49], assessed the success of cascade cardiac screening and genetic testing in a pediatric population in the United States, the first study to examine this approach in the United States. Cardiac screening of at-risk relatives in HCM families identified disease in a subset of asymptomatic relatives (25%). Interestingly, the study found that the uptake of cardiac screening was significantly higher than the uptake of genetic testing. The reasons for this are unclear given that known familial mutation genetic testing is substantially less expensive than an echocardiogram in the Unites States and also takes less time for the actual procedure (blood draw as compared to echocardiogram). Additional studies are important to determine the best delivery methods of cost effective familial screening and appropriate genetic testing.

RCM

RCM is a rare and distinct form of cardiomyopathy characterized by diastolic dysfunction but intact systolic function until later stages of the disease. The main features are marked atrial enlargement, and normal ventricular wall thickness (no hypertrophy)[50]. It accounts for less than 5% of all cardiomyopathies in the United States and Europe[51,52]. RCM is also an uncommon cardiomyopathy in children, accounting for approximately 3%-5% of all cardiomyopathy cases. Among the different types of cardiomyopathies, RCM has the worst prognosis, especially in pediatric cases where heart transplantation is often the only effective treatment[44,52,53]. To date, dominant mutations causing pediatric RCM have been reported with *DES*, *ACTC1*, *TNNI3*, *TNNT2*, and *MYH7* genes, but the majority of cases are considered idiopathic[8,22,54]. Recently, a *de novo* mutation in titin (*TTN*) was reported causing familial RCM[55]. Webber *et al*[52] described the largest RCM cohort (n = 152; 4.5% of all pediatric cardiomyopathy cases within the PCMR cohort) with one-fourth with a family history of the disease, indicating a genetic contribution to the disease, and one-third (n = 51) with a mixed/overlapping phenotype of RCM/HCM, suggesting that additional shared genetic causes may exist. One of the interesting questions for future research will be to understand how mutations in the same gene can cause distinct phenotypes. For example, mutations in *MYH7* can cause HCM, RCM, DCM, or LVNC. Possible explanations include mutation location resulting in protein domain specific phenotypic effects or effects of genetic modifiers. Future research will further delineate the consequences of specific mutations by highlighting the effects on protein-protein interactions and more precisely delineating specific patterns of genetic network dysregulation in response to mutational change.

DCM

DCM is characterized by left ventricular dilation and systolic dysfunction. The estimated annual incidence of DCM in children is 0.57 cases per 100000, with overall poor prognosis, and with 40% of children undergoing cardiac transplant or dying before 5 years post-diagnosis[4,6,10,56,57]. Pediatric DCM is the commonest form of cardiomyopathy, accounting for approximately 60% of all cases[58]. While environmental causes (predominantly related to infections resulting in myocarditis) contribute substantially to DCM in the pediatric population, a significant family history of DCM is not uncommon in pediatric patients, and the same genes that cause DCM in adults have been shown to lead to earlier onset DCM as well[59,60]. DCM is the most genetically heterogeneous of all cardiomyopathies with all Mendelian patterns of inheritance represented (autosomal dominant, autosomal recessive, X-linked, and mitochondrial)[61,62]. Neuromuscular causes of DCM, such as Duchenne muscular dystrophy, are relatively common in the pediatric population. In addition, inborn errors of metabolism and mitochondrial disorders underlie up to 10%-15% of cases in the pediatric population[13]. Syndromic causes of DCM are rare but do occur and are likely under-recognized[63]. Genetic causes of familial DCM are identified in approximately 30% of cases. To date, more than 40 genes have been identified for non-syndromic forms of DCM in adults, though only 3 of them (*TNNI3, GATAD1* and *DOLK*) show autosomal recessive inheritance[64-66]. Genetic causes of autosomal recessive forms of DCM have rarely been identified, although they are thought to explain approximately 16% of familial DCM and contribute to sudden cardiac death and heart failure, especially in the pediatric population. DCM is predominantly caused by mutations in genes encoding cytoskeletal and sarcomeric proteins[67-69]. Recently, heterozygous truncating mutations in *TTN* were reported in 25% of DCM cases, suggesting that the diagnostic yield for DCM might increase substantially with the addition of *TTN* sequenc-

ing to current gene testing panels[70,71]. However, truncating *TTN* mutations have been also reported in 3% of a healthy control populations[70], raising the possibility of a complex genetic model for DCM and posing a problem for clinical interpretation of many *TTN* variants. The prevalence of mutations in *TTN* has not been reported in children with DCM, although clearly there are shared genetic causes. Identification of the genetic causation of DCM allows for appropriate surveillance in neonates, infants, and children with DCM.

The Heart Failure Society of America has published recommended guidelines for genetic evaluation of DCM including family history, periodic cardiovascular screening of at-risk family members, and consideration of genetic counseling for DCM patients, and, when applicable, their family members. Upon targeted gene testing, unaffected family members with positive genetic testing results should undergo cardiac screening once a year. If mutation testing in the proband is negative or not performed, first degree relatives should undergo cardiac screening every 3-5 years[62]. Gene panels for DCM are quite large with > 50 genes available. However, these panels do not typically include the most common neuromuscular, syndromic, and metabolic causes of DCM in childhood, making it important to identify a differential with regard to cause and perform the correct testing to address suspected cause. This requires an understanding of the most common causes of DCM, careful attention to phenotyping beyond the cardiac condition, and knowledge of different types of genetic testing in order to facilitate the most appropriate and/or tiered testing as applicable.

ARVC

ARVC is characterized by a high incidence of ventricular arrhythmia and sudden death with an estimated prevalence of 1:2000 to 1:5000 in the general population[72,73]. ARVC is an inherited disorder with a family history in 30% to 50% of the cases (Klauke, 2010). ARVC is predominately reported as autosomal dominant trait, though autosomal recessive cases have been observed, frequently with syndromic features including cutaneous findings. ARVC has been considered a desmosomal disease caused by mutations in five desmosomal genes (*PKP2*, *DSP*, *JUP*, *DSG2*, *DSC2*) in approximately 50% of total cases, however other non-desmosomal genes are known to be responsible for the disease (*TMEM43, PLN, RYR2, LMNA, TTN, CTNNA3, TBF-β3*)[74-80]. ARVC is not frequently found in the pediatric population, however a recent Danish nationwide study reported sudden cardiac death in children (n = 4) due to ARVC[81].

LVNC

LVNC is a distinct rare form of primary cardiomyopathy with a genetic origin which is characterized by excessive trabeculation of the left ventricular myocardium, progressive myocardial dysfunction, and early mortality. Clinical presentation includes arrhythmia and sudden cardiac death. Current studies in children estimate that LVNC accounts for approximately 9% of newly diagnosed cardiomyopathies[58,82]. Recently, Brescia *et al*[83] retrospectively reported a cohort of pediatric LVNC (n = 242) with a high mortality rate and a strong association with arrhythmias. Criteria for "excessive" trabeculation have been proposed, but the diagnosis of LVNC is often more controversial than other cardiomyopathy phenotypes. In addition, LVNC may present as a mixed cardiomyopathy seen in combination with DCM or HCM, or may present in conjunction with congenital heart defects[84].

LVNC is a genetically heterogeneous disease that may be inherited in an X-linked, recessive, or autosomal dominant pattern. To date, genetic causes of LVNC have been implicated in genes encoding sarcomeric, cytoskeletal, sodium channel and unknown function proteins, *i.e.*, tafazzin, *DTNA, LDB3, ACTC1, MYH7, TNNT2*, and *SCN5A*[84]. The identification of LVNC in patients with mitochondrial disorders is not uncommon, as was initially seen for patients with Barth syndrome, caused by mutations in tafazzin. Mitochondrial genome mutations have also been revealed in patients with isolated LVNC as evident by biopsies from patients with mitochondrial abnormalities[85]. These causes of LVNC are rare in the general population and the genetic basis of disease remains unknown in a large proportion of patients. We screened 31 cardiomyopathy genes (sarcomeric and non-sarcomeric) in 23 childhood isolated LVNC patients using a custom next generation sequencing platform. This identified 13 previously known and 10 novel disease-causing mutations in 18 patients, predominantly in the *MYBPC3* gene (unpublished results). Further extensive genetic analyses will unravel novel and previously associated with other types of cardiomyopathy cause for LVNC, supporting the hypothesis of shared genetic etiology of cardiomyopathies.

CLINICAL GENETIC TESTING IN CARDIOMYOPATHY

Progress in understanding the genetic basis of cardiomyopathy enhances the value of clinical genetic testing and provides the clinician an additional route to diagnose individuals at risk for cardiomyopathy and understand pathogenesis. Newer technologies are influencing cardiomyopathy genetic testing, where an increased number of genes are now routinely being tested simultaneously, and enhancing the diagnostic yield and utility. However, simple statistics dictate that the more genes that are tested, the more variants of uncertain significance (VUS) will be discovered. VUS results can present a clinical challenge for care providers not comfortable with genetic testing results and can also present challenges for discussion and interpretation for families. Targeted next-generation based sequencing for cardiomyopathy gene panels are available through various laboratories in the United States and worldwide (http://www.genetests.org

and http://www.ncbi.nlm.nih.gov/gtr). Genetic testing in HCM has the highest diagnostic yield and therefore clinical utility[86]. The yield of current testing is approximately approximately 60% for familial and approximately 40% for sporadic HCM cases[36]. The Heart Rhythm Society and European Heart Rhythm Association guidelines recommended the comprehensive screening of 5 sarcomere genes (*MYBPC3, MYH7, TPM1, TNNI3, TNNT2*) for HCM[87], although these recommendations pre-date the rapid expansion in the number of genes tested on current clinical gene panels. Currently, genotype-phenotype correlations in HCM are controversial although there is a general consensus that incorporation of the genetic testing results should be part of management discussions. The sophistication to provide a specific prognosis based on, for example, a mutation in the N-terminal *vs* C-terminal domain of *MYH7* is not currently present. However, genotype-phenotype correlations exist for certain genes. For example, mutations in *LMNA* may result in a number of extra-cardiac features that require surveillance and management, but patients with these mutations may present with isolated DCM. Genetic testing of HCM is particularly useful for screening potential at risk first-degree relatives and subsequent cascade testing of family members as indicated. In a recent Danish study, child relatives (< 18 years of age) of HCM families were assessed based on clinical and predictive genetic testing and 6% of the asymptomatic relatives at-risk of HCM were found to develop HCM after a 12-year follow-up[16]. Hofman *et al*[15] assessed the yield of genetic testing in 648 HCM families from the Netherlands and found a 46% yield for positive genetic testing in probands with cascade screening of mutation positive families revealing 489 mutation-positive subjects over a 15-year follow-up. In DCM, the mutation spectrum is broader and detection rates are less than HCM owing to higher locus and allelic heterogeneity. However recent novel gene discoveries (for example *BAG3, RBM20*) are resulting in continuous additions to DCM gene panels. Also, the recent discovery of the high contribution of *TTN* mutations (25% familial and 18% sporadic) to DCM may increase the mutation detection rates in genetic testing panels to closer to that of HCM although the rates of *TTN* mutations segregating with disease need to be validated in larger populations[70].

CHALLENGES INTO THE GENETICS OF PEDIATRIC CARDIOMYOPATHY

Despite the advancements in genetic and genomic technologies, multiple challenges remain in order to clearly delineate the complete genetic etiologies responsible for pediatric cardiomyopathy. Pediatric cardiomyopathy is a very heterogeneous entity with variable phenotypes are seen within and between families even with identical genetic causes. Another complicating factor is the complex genetics of the disease. Although the majority of known isolated cardiomyopathy cases are caused by single gene mutations, it is important to remember that variants in more than one gene may be involved in disease causation. Identifying genetic modifiers is the next important step in pediatric cardiomyopathy genetic research and may be important to identify the causes of phenotypic variability within members of the same family. The high cost of traditional sequencing technologies posed a severe limitation to the discovery of new disease genes and screening of known disease genes in the past. New technology circumvents this hurdle, but the current challenge is to provide accurate and clinically useful interpretation of the variants identified in order to maximize the clinical utility of testing. Of course, the reproducibility of the next generation sequencing such as exome sequencing, is very high, however we do not have a complete expertise to identify the causative culprits from thousands of genetic variants. Differentiation of pathogenic variants, disease modifiers, and rare, benign variants in the deluge of data emerging from increasingly accessible novel sequencing technologies (> 80 K variants per exome and approximately 3 million per whole genome) is a challenge. This requires another tier of extensive research to understand the nature of disease causing variants available from advanced high-throughput sequencers. In this context, the involvement of pediatric cardiologists is very important in order to provide careful and comprehensive phenotypic information before genetic testing and/or evaluation. Finally, delineating the complex interplay of genes and environment and their relative contribution to phenotypic presentation and disease course is important for management and prognosis.

CONCLUSION

Modern genomics and human genetics have the capability to decipher the complete genetic anatomy of heritable pediatric cardiomyopathy. Early diagnosis and identification of at risk individuals is important as the clinical implications and outcomes may vary depending on both the gene and mutation type. While next-generation sequencing technologies have increased the capacity of genetic testing by an order of magnitude, we need extensive phenotyping expertise in order to inform novel gene discovery and interpretation of identified variants. In addition, genetic counseling of affected families is critical to facilitate testing and ensure appropriate pre- and post-test understanding of testing implications and results. Identification of the genetic modifiers is an important step toward a personalized medicine approach, but will require analysis of large cohorts using newer sequence capture technologies. Identification of the molecular etiology will allow sub-classification of pediatric cardiomyopathy based on cause. Understanding rare variants and SNPs that modify disease presentation and progression hold the promise of allowing new therapies to be developed.

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P- Reviewer: Ciampi Q, Doevendans P, Satoh H, Winkel BG
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i11.1166

World J Cardiol 2014 November 26; 6(11): 1166-1174
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (3): Cardiomyopathy

Diagnosis and management of ischemic cardiomyopathy: Role of cardiovascular magnetic resonance imaging

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Received: May 23, 2014 Revised: July 2, 2014
Accepted: September 6, 2014
Published online: November 26, 2014

Abstract

Coronary artery disease (CAD) represents an important cause of mortality. Cardiovascular magnetic resonance (CMR) imaging evolved as an imaging modality that allows the assessment of myocardial function, perfusion, contractile reserve and extent of fibrosis in a single comprehensive exam. This review highlights the role of CMR in the differential diagnosis of acute chest pain by detecting the location of obstructive CAD or necrosis and identifying other conditions like stress cardiomyopathy or myocarditis that can present with acute chest pain. Besides, it underlines the prognostic implication of perfusion abnormalities in the setting of acute chest pain. Furthermore, the review addresses the role of CMR to detect significant CAD in patients with stable CAD. It elucidates the accuracy and clinical utility of CMR with respect to other imaging modalities like single-photon emission computed tomography and positron emission tomography. Besides, the prognostic value of CMR stress testing is discussed. Additionally, it summarizes the available CMR techniques to assess myocardial viability and describes algorithm to identify those patient who might profit from revascularization those who should be treated medically. Finally, future promising imaging techniques that will provide further insights into the fundamental disease processes in ischemic cardiomyopathy are discussed.

Key words: Coronary artery disease; Cardiovascular magnetic resonance imaging; Prognostic value; Stress testing; Viability

Core tip: Coronary artery disease (CAD) represents an important cause of mortality. This review highlights the role of cardiovascular magnetic resonance (CMR) in the differential diagnosis of acute chest pain. It underlines the prognostic implication of perfusion abnormalities in the setting of acute chest pain and addresses the role of CMR to detect significant CAD in patients with stable CAD. Besides, the prognostic value of CMR stress testing is discussed. Additionally, it summarizes the available CMR techniques to assess myocardial viability. This review describes a treatment algorithm and presents new imaging techniques that might give further insights into the fundamental disease processes in ischemic cardiomyopathy.

Doesch C, Papavassiliu T. Diagnosis and management of ischemic cardiomyopathy: Role of cardiovascular magnetic resonance imaging. *World J Cardiol* 2014; 6(11): 1166-1174 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1166.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1166

INTRODUCTION

Coronary artery disease (CAD) has a high prevalence in industrialized countries[1] and is therefore an important cause of mortality in the Western world[2]. Cardiac magnetic resonance (CMR) imaging offers the unique opportunity to non-invasively detect coronary artery stenoses and has become the gold standard for the assessment of viability. The detection of coronary artery stenoses can be performed using either vasodilator stressors like adenosine to detect myocardial ischemia or inotropic agents such as dobutamine to identify regional wall motion abnormalities. Due to its excellent temporal and spatial resolution, the possibility to assess myocardial perfusion without exposure to ionizing radiation and the independence of an acoustic window, CMR offers plenty advantages over other imaging modalities like stress echocardiography or single-photon emission computed tomography (SPECT).

CMR TESTING IN PATIENTS WITH ACUTE CHEST PAIN

The exclusion of coronary artery stenoses in patients presenting with acute chest pain in the absence of diagnostic electrocardiographic changes or negative cardiac enzymes still remains a challenge. In these low risk patients CMR has proved to be a reliable risk-stratification tool. Kwong *et al*[3] was the first to demonstrate the utility of CMR for triage of patients with acute chest pain in the emergency department. He showed that the combination of CMR rest perfusion and late gadolinium enhancement (LGE) in patients presenting at an emergency department with angina and non-diagnostic electrocardiogram (ECG) had a sensitivity of 100% for non-ST-segment elevation infarction and a sensitivity of 84% sensitivity for acute coronary syndrome (ACS) as well as a specificity of 85% (Figure 1). Besides, CMR proved to be the strongest predictor of ACS and had an independent diagnostic value over clinical parameters including ECG, initial troponin-I , and the thrombolysis in myocardial infarction risk score. In a further study by Ingkanisorn *et al*[4], adenosine stress CMR was performed in 135 patients with chest pain and excluded myocardial infarction who presented at the emergency department. In this setting, adenosine perfusion abnormalities had 100% sensitivity and 93% to predict CAD. Furthermore, none of the patients with a normal adenosine stress examination was diagnosed with significant CAD or suffered from an adverse outcome during a follow-up period of one year. In a retrospective study by Hartlage *et al*[5] using either adenosine or dobutamine stress CMR in 255 patients presenting at the emergency department with acute low-risk chest pain and no prior history of CAD the negative predictive value for the primary endpoint of cardiac death, nonfatal acute myocardial infarction, obstructive CAD on invasive coronary angiography or recurrent chest pain, was 100% and 99%, respectively. Therefore, adenosine and dobutamine stress CMR proved to be reliable modalities to exclude obstructive CAD and a negative stress study provides an excellent intermediate-term prognosis. Besides, in patients with intermediate risk presenting at the emergency department, stress CMR reduced cardiac-related costs of the index visit and over the first year without increasing major cardiac events[6].

In addition, CMR can identify the underlying cause of conditions that present like ACS. In stress cardiomyopathy [Takotsubo cardiomyopathy (CMP), Figure 2], patients present with acute chest pain and/or dyspnea, modest elevation in cardiac troponin level and new ECG abnormalities despite the absence of significant (> 50%) obstructive coronary artery disease or angiographic evidence of acute plaque rupture. In these patients with marked apical or midventricular ballooning the absence of myocarditis or typical ischemic transmural LGE on CMR confirms the diagnosis[7-11]. Myocarditis (Figure 3) is another differential diagnosis in patients with acute chest pain that can be addressed with CMR allowing to visualize the key features of myocarditis: inflammation, hyperemia, edema, necrosis, myocardial dysfunction as well as accompanying pericardial perfusion in a single study[12-16].

CMR STRESS TESTING IN PATIENTS WITH STABLE CAD

The feasibility of stress CMR to detect coronary artery stenosis in patients with known or suspected CAD is well established[17-21]. In a meta-analysis[22] comparing 114 SPECT, 15 positron emission tomography (PET) and 37 CMR myocardial perfusion imaging studies for the detection of angiographically detected coronary artery stenoses ⩾ 50%, all three imaging modalities proved to accurately detect obstructive CAD. Metaregression showed that CMR and PET have a significantly higher diagnostic accuracy than SPECT. In contrast to nuclear techniques, CMR perfusion is not affected by attenuation artifacts, has the highest spatial resolution and is therefore able to even subendocardial perfusion deficits[23]. The sensitivity and specificity to detect CAD ranged between 79%-88% and 81%-91% for dobutamine stress CMR or 67%-94% and 61%-85% for adenosine stress CMR, in meta-analysis[24-26] and a multicenter study[27]. The use of 3.0 T has shown to provide even higher diagnostic accuracy[28,29], however this technique is not widely available, yet and no data from multicenter studies exist so far.

However, CMR stress testing is not only able to detect CAD but also offers prognostic information. A study performing adenosine stress CMR using 1.5 and 3.0 T in 815 consecutive patients with stable CAD could show that the addition of inducible ischemia reclassified patient risk beyond standard clinical variables and improved discrimination of major adverse cardiac events[30]. These results were confirmed by another single center study[31] enrolling 1229 patients with stable angina. Recent meta-analysis[32,33] also proved that a negative adenosine or dobutamine stress CMR had a high negative predictive

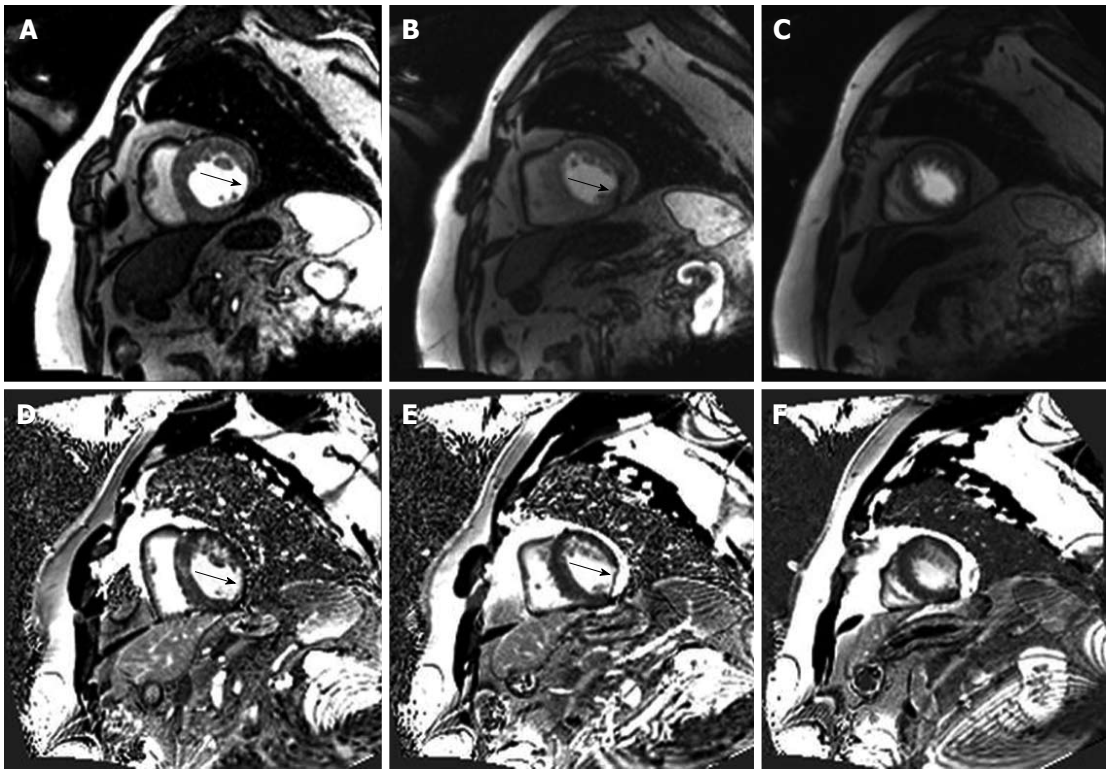

Figure 1 Patient presenting with an subacute non-ST-segment elevation infarction. Cardiovascular magnetic resonance (CMR) images of a 54-year-old man who presented with typical chest pain. Troponin was elevated to 1.9 μg/L. CMR rest perfusion (A-C) shows a subendocardial perfusion deficit inferolateral and lateral on the basal (A) and midventricular (B) short axis slice. The black arrow highlights the subendocardial perfusion deficit. Late gadolinium enhancement (D-F) of the representative short axis also revealed a hyperenhancement inferolateral and lateral (black arrow) indicative of a subacute myocardial infarction.

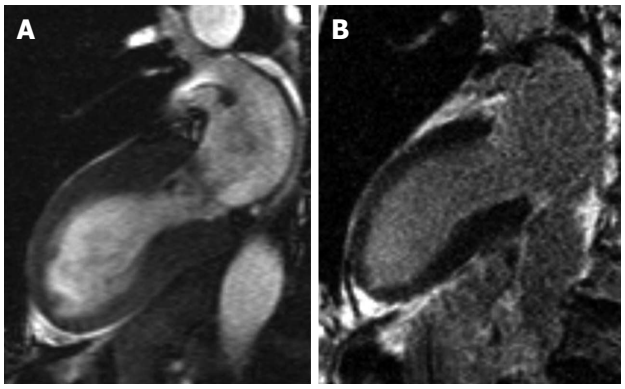

Figure 2 Patient with takotsubo cardiomyopathy. Example of a 45-year-old woman presenting with acute chest pain, anterior ST-segment elevation on electrocardiogram. Cardiovascular magnetic resonance cine images of showed a typical apical ballonning of the left ventricle (A). Late gadolinium enhancement images (B) could rule out myocardial infarction and did not show any fibrosis.

value for adverse cardiac events. Besides they showed that inducible perfusion defects as well as wall motion abnormalities had a comparable ability to identify low-risk patients.

Therefore, in the actual guidelines for the management of patients with stable CAD, stress imaging using either echocardiography, CMR or SPECT has become an integral part in the work-up of patients with a pretest probability (PTP) of CAD between 15%-65% and a left ventricular function (LVEF) ⩾ 50% as well as in patients with a PTP of 66%-85% or a LVEF < 50%[34]. An imaging study should also be considered in symptomatic patients with prior revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass graft][34]. In patients with coronary artery stenoses of angiographic intermediate severity causing a perfusion defect on CMR it could be shown that these patients are at higher risk for major adverse cardiac events (MACE) within the following 18 mo after the procedure, whereas deferring PCI in patients with intermediate coronary artery stenoses and no evidence of ischemia seemed to be save[18]. Thus, current guidelines suggest to consider an imaging stress test to assess the functional severity of intermediate lesions on coronary arteriography[34]. The decision to proceed to invasive angiography is not only based on symptoms and risk factors but also on the extent and severity of ischemia[34] (Figure 4).

GENDER-BASED PROGNOSTIC VALUE OF CMR STRESS TESTING

In women, CAD develops 7 to 10 years later than in men. However, it is still the major cause of death in women[35]. Moreover, the risk of heart disease in women is often underestimated. Due to the underrecognition of heart disease and differences in clinical presentation in women, treatment strategies are less straightforward in women. In a study by Coelho-Filho *et al*[36] performing adenosine

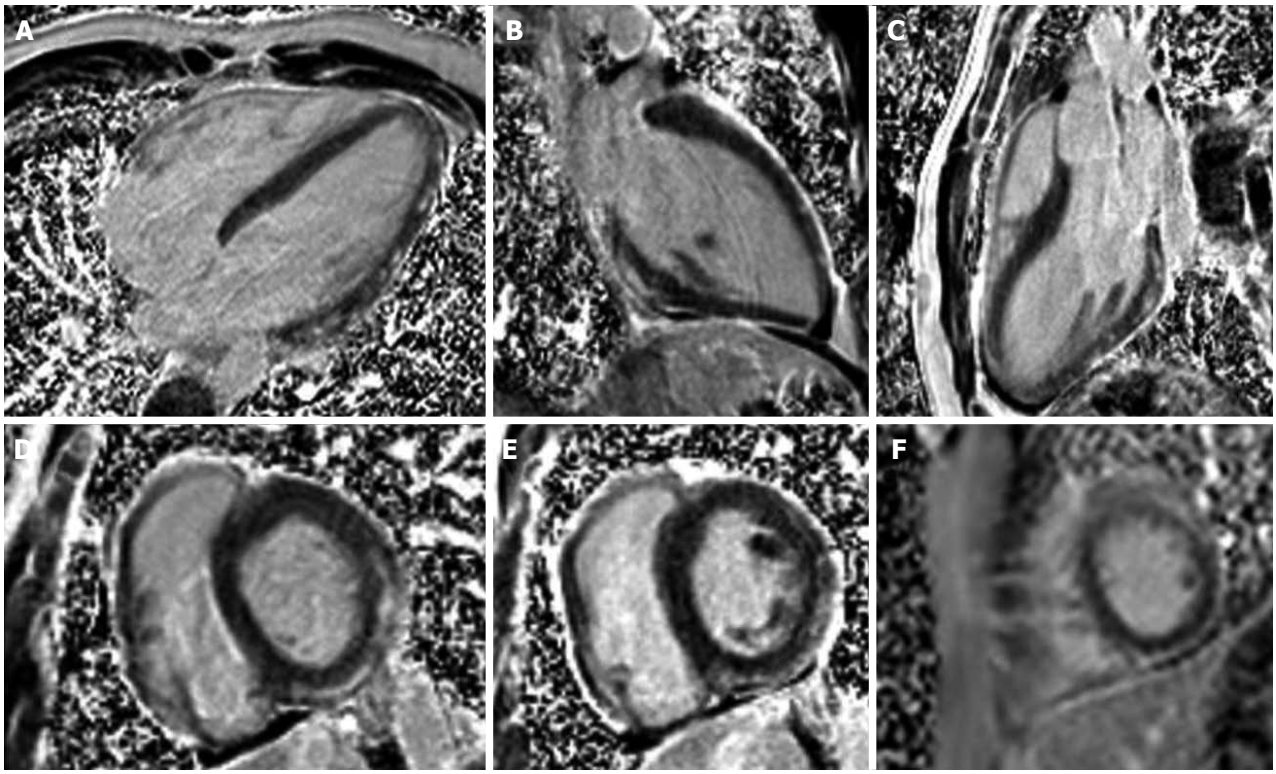

Figure 3 Patient with acute chest pain due to myocarditis. A 16-year-old boy who presented with acute chest pain and palpitations 1 wk after a gastrointestinal infection. Troponin was 2.4 μg/L. Late gadolinium enhancement cardiovascular magnetic resonance showed a patchy midmyocardial and epicardial hyperenhancement of the lateral, anterior and inferior wall. These findings are typical of acute myocarditis.

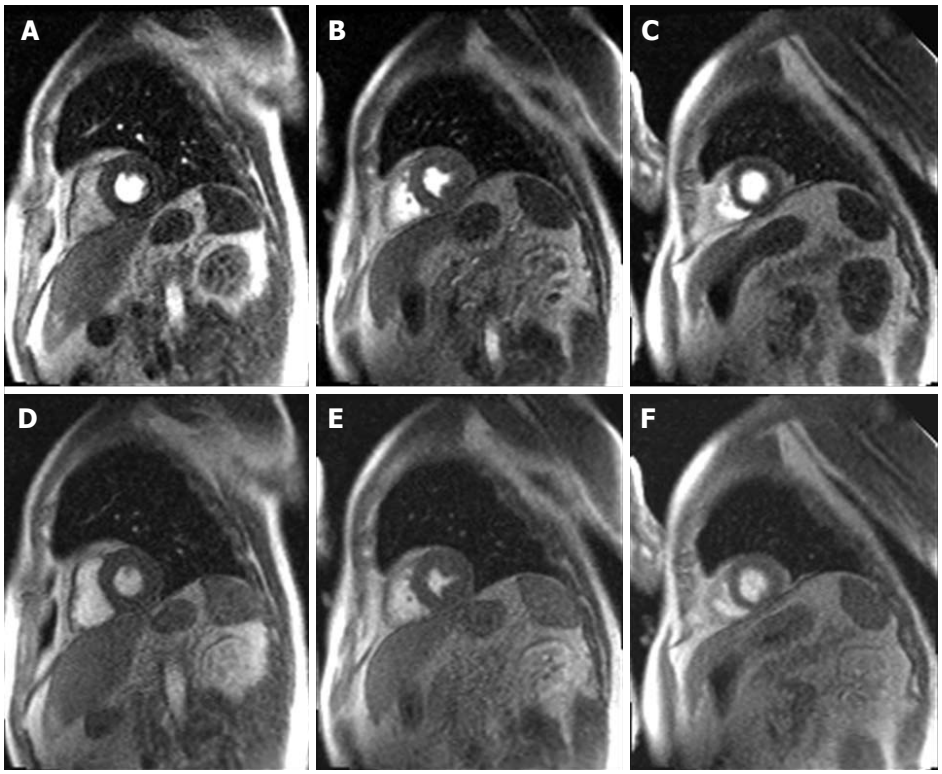

Figure 4 Adenosine stress perfusion imaging. A 63-year-old patient who presented with stable angina for more than 6 mo. Adenosine stress (A-C) *vs* rest perfusion (D-F) revealed myocardial ischemia only during stress perfusion of the basal inferior and lateral as well as midventriucular inferoseptal wall. The patient did not show a late gadolinium enhancement. Coronary angiography showed a 60% stenosis of the medial right coronary artery that was treated with percutaneous coronary intervention and stent implantation due to the detected ischemia.

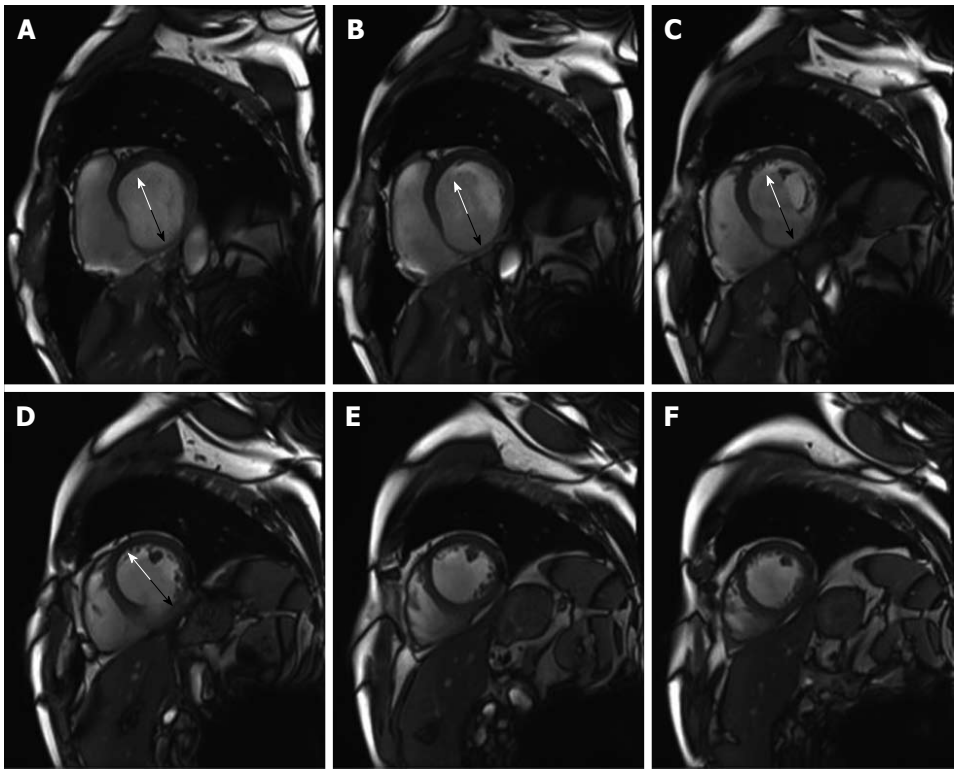

Figure 5 End diastolic wall thickness. Representative end diastolic short axis images from basal (A) to apical (F) of a patient with previous inferior myocardial infarction. The anterior, septal and lateral region (white arrow, A-D) show a preserved end diastolic wall thickness (EDWT) > 6 mm suggesting viable myocardium, whereas EDWT of the inferior wall (black arrow, A-D) is ≤ 6 mm indicating myocardial scarring.

stress imaging in 237 men and 168 women referred for ischemia assessment, myocardial ischemia was the strongest predictor of MACE in both sexes. In a large study[37] using a combined adenosine and dobutamine stress CMR protocol in 471 men and 208 women, Jahnke *et al*[37] could show that CMR perfusion and wall motion abnormalities are equally suited for cardiac risk stratification in both sexes. In women, a negative stress CMR resulted in very low event rates during the following 4 years whereas, the event rates in men increased after the second year. These results might suggest that it is feasible to prolong the generally proposed 2-year warranty period of a negative CMR stress test to 4 years in women.

ROLE OF CMR IN THE DETECTION OF MYOCARDIAL VIABILITY IN ISCHEMIC HEART DISEASE

In clinical practice myocardial viability is characterized by functional recovery 6 wk to 6 mo after successful revascularization. CMR offers 3 methods to assess myocardial viability: end-diastolic wall thickness, low dose dobutamin stress CMR and LGE.

The easiest technique is to evaluate the maximal end-diastolic wall thickness (EDWT) because it only requires to determine the maximal EDWT on the cine images at rest. In the course of acute myocardial infarction structural changes are associated with myocardial thinning in the core zone of the infarction. In a study comparing EDWT on resting CMR and[18] fluorodeoxyglocose positron emission tomography (FDG PET) in 35 patients with myocardial infarction, Baer *et al*[38] could prove that myocardial segments with an EDWT ≥ 5.5 mm showed a normal FDG uptake, whereas myocardial segments with an EDWT < 5.5 mm revealed a significantly FDG uptake. Several studies using either a cut-off of 5.5 mm[39,40] or 6 mm[41,42] in patients with chronic ischemic myocardial dysfunction could show that myocardial segments with wall thinning below the cut-off have a low likelihood of functional recovery after revascularization.

Overall these studies[39-42] proved that EDWT has a good sensitivity and negative predictive value but only reasonable positive predictive value and poor specificity to predict functional recovery.

Figure 5 shows an example of a patient with a previous inferior myocardial infarction with severe thinning of the inferior myocardial wall segments.

Low dose dobutamine (≤ 10 μg/kg per minute) stress CMR is another technique used to evaluate myocardial viability. At low doses, dobutamine supports coronary vasodilatation and increases myocardial contractility[43]. Viable myocardium is distinguished by the identification of improved contractility under low dose dobutamine infusion. Several studies[39-41,44-46] proved that a CMR-derived systolic wall thickening > 2 mm during low dose dobutamine stress is able to identify myocardial segments with functional recovery after revascularization. Accord-

Transmural extent of hyper-enhancement (%)	0	1-25	26-50	51-75	> 75
Improved contractility after revascularization (%)	78	60	42	10	< 2

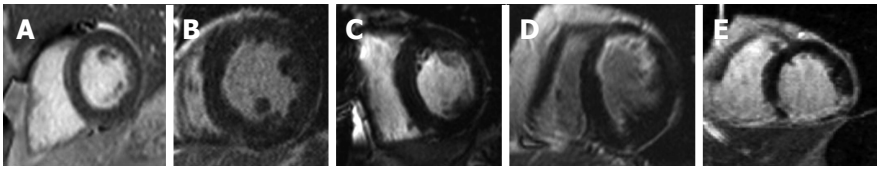

Figure 6 Late gadolinium enhancement imaging. Representative late gadolinium enhancement images of patients without scar (A), with a transmural extent of hyperenhancement of 1%-15% (B), 26%-50% (C), 51%-75% (D) and more than 75% (E) and the respective percentage of improved contractility according the study by Kim *et al*[51].

ing to these studies[39-41,44-46], the major strength of low dose dobutamine stress CMR is its high overall accuracy, specificity and positive predictive value.

LGE that was first applied by Kim *et al*[47] has now become the gold standard for the evaluation of myocardial viability in ischemic heart disease. In nonviable tissue, the extracellular contrast agent spreads in a larger volume of distribution which results in delayed washout kinetics[48]. Moreover, late enhancement imaging sequences suppress the signal derived from remote myocardium resulting in high image contrast. Hence, this technique allows the detection of even very small myocardial infarctions ($\geqslant$ 0.7 g of myocardial mass)[49]. In a meta-analysis by Romero *et al*[50] LGE with a cut-off of < 50% transmurality of scar tissue had a high sensitivity and a high negative predictive value to predict functional recovery. In patients with chronic ischemic heart disease the identification of viable myocardium is important to predict improvement of LVEF and survival after revascularization. In these patients the functional recovery was also linked to the transmural extent of scar[51]. Kim *et al*[51] could show that in segments without scar the functional recovery was 78% whereas in segments with a scar transmurality of more than 75%, the likelihood of contractility improvement after revascularization was less than 2% (Figure 6). As illustrated in Figure 6, the ability to predict functional recovery in segments with an intermediate scar transmurality between 1% and 75% ranged between 60% and 10%. In these patients with an intermediate scar transmurality an additional low-dose dobutamine stress examination helps to identify segments that show a contractile reserve. A combined approach of LGE enhancement imaging and low-dose dobutamin stress imaging proved to be the optimal approach to predict recovery after revascularization[44]. Therefore, in patients with wall motion abnormalities at rest the following algorithm as described by Nagel *et al*[52] should be applied. LGE imaging should be used as first line imaging modality to identify patients without a scar who should undergo revascularization. Patients with more than 50% LGE transmurality should be treated medically. In patients with less than 50% LGE transmurality an additional low dose dobutamine stress CMR should be performed to detect patients with an improved contractility who are likely to benefit from revascularization. Whereas patients with less than 50% LGE transmurality but without assessment of contractile reserve should be treated medically. This algorithm indicates that in patients without evidence of LGE or with a LGE > 50% transmurality, LGE imaging alone is sufficient. In case that an additional low dose dobutamin stress exam is required CMR allows to assess myocardial contractile reserve and LGE in a single comprehensive exam.

In patients with acute myocardial infarction and wall motion abnormalities CMR, Beek *et al*[53] could also proof that LGE CMR is able to detect hibernating myocardium that is able to functionally recover. Further studies[54,55] demonstrated that the transmural extent of delayed gadolinium enhancement correlates with the ability of functional improvement after acute myocardial infarction. Therefore, the distinction between reversible and irreversible dysfunctional myocardium in the acute setting after infarction also has a prognostic implication.

PROGNOSTIC ROLE OF LGE IN ISCHEMIC HEART DISEASE

Moreover, myocardial scar has been demonstrated to be the cause of malignant reentrant ventricular arrhythmias causing sudden cardiac death in patients after myocardial infarction[56]. In patients with ischemic cardiamyopathy, Kwon *et al*[57] revealed that a greater extent of myocardial scar was associated with a significantly increased mortality or the need for cardiac transplantation, improving further risk stratification. In patients undergoing ICD implantation with CAD, the extent of myocardial scarring visualized by LGE CMR was significantly associated with appropriate device therapy and identified a subgroup of CAD patients with an increased risk of life-threatening ventricular arrhythmias[58].

FUTURE INDICATIONS FOR CMR IN PATIENTS WITH CAD

Novel methods like precontrast T_1 maps enable the detection of acute and chronic myocardial infarction[59] and might represent a further field to establish the use of CMR as a key to tissue characterization. In a combined clinical protocol native T1 mapping was suggested to reveal area at risk in ACS[60,61].

Extracellular volume (ECV) maps as a CMR marker for myocardial fibrosis can be generated if pre and post contrast T_1 images are registered[62]. In contrast to LGE

CMR, ECV is also able to visualize very early fibrotic changes[63].

In the future, T1 mapping and ECV may provide more profound insights into fundamental disease processes of the myocardium. Both techniques might affect clinical decision making, but to date are not yet part of the routine work-up. Besides, the reproducibility of the results still needs to be shown in multi-centre studies[64].

CONCLUSION

CMR is a non invasive imaging for the workup of patients with known or suspected CAD. It allows the detection of significant coronary stenoses in patients with acute and chronic chest pain. Moreover, it offers the unique opportunity to detect myocardial ischemia and viability or wall motion abnormalities and fibrosis in one examination. Novel techniques like T1 mapping and ECV will further expand the scope of application in the future.

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P- Reviewer: Anan R, Fett JD, Toro R, Xiong XJ
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World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i11.1175

World J Cardiol 2014 November 26; 6(11): 1175-1191
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (4): Congestive heart failure

Positive airway pressure therapy for heart failure

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Supported by Grant-in-Aid for Scientific Research (C) Grant, Japan, No. 26507010; Grant to the Respiratory Failure Research Group from Ministry of Health, Labor and Welfare, Japan
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Received: May 30, 2014 Revised: July 16, 2014
Accepted: September 18, 2014
Published online: November 26, 2014

Abstract

Heart failure (HF) is a life-threatening disease and is a growing public health concern. Despite recent advances in pharmacological management for HF, the morbidity and mortality from HF remain high. Therefore, non-pharmacological approaches for HF are being developed. However, most non-pharmacological approaches are invasive, have limited indication and are considered only for advanced HF. Accordingly, the development of less invasive, non-pharmacological approaches that improve outcomes for patients with HF is important. One such approach may include positive airway pressure (PAP) therapy. In this review, the role of PAP therapy applied through mask interfaces in the wide spectrum of HF care is discussed.

Key words: Acute decompensated heart failure; Congestion; Continuous positive airway pressure; Non-invasive positive airway pressure ventilation; Sleep disordered breathing

Core tip: Less-invasive, non-pharmacological approaches may improve outcomes for patients with heart failure, and the role of positive airway pressure therapy is discussed in this review.

Kato T, Suda S, Kasai T. Positive airway pressure therapy for heart failure. *World J Cardiol* 2014; 6(11): 1175-1191 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1175.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1175

INTRODUCTION

Heart failure (HF) is a life-threatening disease and is a growing public health concern[1,2]. The prevalence of HF has increased along with the aging of the general population[3] and because of improved survival after acute myocardial infarction[4,5]. Indeed, a better understanding of the pathophysiology and medical management of myocardial infarction means that such patients are living longer with damaged hearts, and many of them go on to develop HF[5,6]. Despite recent advances in pharmacological management of HF, the morbidity and mortality from HF remain high[4,5]. Therefore, non-pharmacological approaches to HF, including cardiac resynchronization therapy, and left ventricular (LV) assist devices, are increasingly utilized. However, most non-pharmacological approaches are invasive, have limited indication and are considered only for advanced HF. Accordingly, the development of less invasive, non-pharmacological approaches that may improve outcomes for patients with HF is important.

Positive airway pressure (PAP) therapy represents a potentially beneficial non-pharmacological approach to the management of HF. PAP therapy involves the maintenance of positive airway pressure through invasive

(applied with endotracheal intubation or tracheostomy) or non-invasive (applied without endotracheal intubation or tracheostomy) means. Because we focused on less invasive approaches to the management of HF, we confined our discussion to non-invasive positive pressure ventilation, including continuous positive airway pressure (CPAP), in which PAP is applied through nasal masks, oro-nasal masks and face masks[7]. In the wide spectrum of HF care, PAP therapy can be used to improve oxygenation, decrease right ventricular (RV) afterload, alleviate hypoventilation and hypercapnia, improve lung and respiratory muscle functions, and normalize abnormal respiratory patterns. In this review, we discuss various types or modes, devices and equipment for PAP therapy, its effect on hemodynamics and respiration, and conditions for which PAP therapy should be considered in the care of HF patients. We also review the indications and evidence supporting the efficacy of PAP therapy in patients with HF.

EFFECT OF PAP ON HEMODYNAMICS AND RESPIRATION

All PAP therapies, which are considered for HF and mentioned later, adjunctively provide positive end-expiratory pressure. Therefore, the effect of PAP therapy, including positive end-expiratory pressure, on hemodynamics and respiration are described herein.

Effect on hemodynamics

PAP has several effects on hemodynamics. First, PAP diminishes systemic venous return and RV preload by increasing intrathoracic pressure[8-10]. Second, PAP alters pulmonary total vascular resistance (PVR), which is the major determinant of RV afterload, *via* an alternation in lung volume[11]. In the lungs, there are two types of vessels: the intra-alveolar vessels, which are compressed as lung volume increases, and the extra-alveolar vessels, which are exposed to dilating forces as lung volume increases. Thus, a change in total PVR is characterized by a U-shaped curve according to the alteration in lung volume (the lowest PVR can be observed in the lung volume around functional residual capacity)[12]. For example, when lung volume increases from residual volume to functional residual capacity, the effects of this increased volume on extra-alveolar vessels will predominate, and thus, vascular capacitance will increase. Consequently, total PVR will decrease. When the lung volume continues to increase from functional residual capacity to total lung capacity, the effects of this further increased volume on intra-alveolar vessels will predominate; vascular capacitance will therefore decrease, and total PVR will increase[12,13]. Although PAP without an excessive shift in lung volume does not cause a clinically important increase in RV afterload[12], it is possible that RV afterload can be increased by PAP[14]. Third, a decrease in RV preload (decrease in systemic venous return to RV) and an increase in RV afterload (increase in PVR) lead to a reduction in pulmonary venous return and limitations in LV inflow and filling. In addition, in cases with increased RV afterload, RV dilatation with a septal shift toward the LV can occur. This further limits the LV filling and causes reductions in cardiac output and overall organ perfusion[8,10,14-16]. Fourth, increased intrathoracic pressure relative to atmospheric pressure causes a pressure difference between the extrathoracic and intrathoracic cavities because most of the systemic circulation is at atmospheric pressure, which is lower than that of the LV and thoracic aorta[17]. Therefore, PAP therapy can reduce RV preload and increase RV afterload, whereas PAP therapy reduces LV preload and afterload (Figure 1). In general, subjects without HF are predominantly preload-dependent[18]. Therefore, in subjects without HF or in patients who manifest preload-dependent LV function, such as those with RV infarction or hypovolemia, a reduction in cardiac preload with PAP therapy may decrease cardiac output to a greater degree than decreasing afterload and its related increase in cardiac output[14].

Conversely, a failing heart is more sensitive to decreased afterload, and patients with HF are usually hypervolemic and thus insensitive to decreased preload. Therefore, patients with HF are predominantly afterload-dependent, and cardiac output can be increased by PAP therapy in those patients. Nevertheless, in HF patients, the preload- and afterload-dependent status will determine the cardiac output responses (increase or decrease) (Figure 1).

Effect on respiration

PAP also has several effects on respiration in HF. First, PAP maintains alveolar pressure and prevents the alveoli from collapsing at the end of expiration and thus improves gas exchange and oxygenation through the recruitment of alveolar units, counterbalance of hydrostatic forces leading to pulmonary edema, and maintenance of airway patency[19-22]. Particularly in HF patients with pulmonary congestion in whom lung compliance is impaired, PAP induces recruitment of collapsed alveoli, reversal of atelectasis, and induces a fluid shift from the alveoli and the interstitial space to the pulmonary circulation, consequently decreasing the amount of intrapulmonary shunting and improving oxygenation[21,23]. Second, PAP can reduce respiratory muscle load and the work of breathing[24-26] and can improve lung function through lung inflation and maintenance of functional residual capacity[27]. Third, PAP prevents upper airway narrowing and collapse and thereby functions as a "pneumatic splint"[28-30]. This is highly effective in the treatment of sleep-disordered breathing (SDB)[31], which is frequently observed in patients with HF[32]. Fourth, some PAP therapy provides pressure support during inspiration to maintain ventilation. This is particularly important in HF patients with hypoventilation. Fifth, if hypoxic pulmonary vasoconstriction occurs due to hypoxia in association with acute decompensated HF (ADHF) or HF accompanied by chronic obstructive lung disease (COPD)

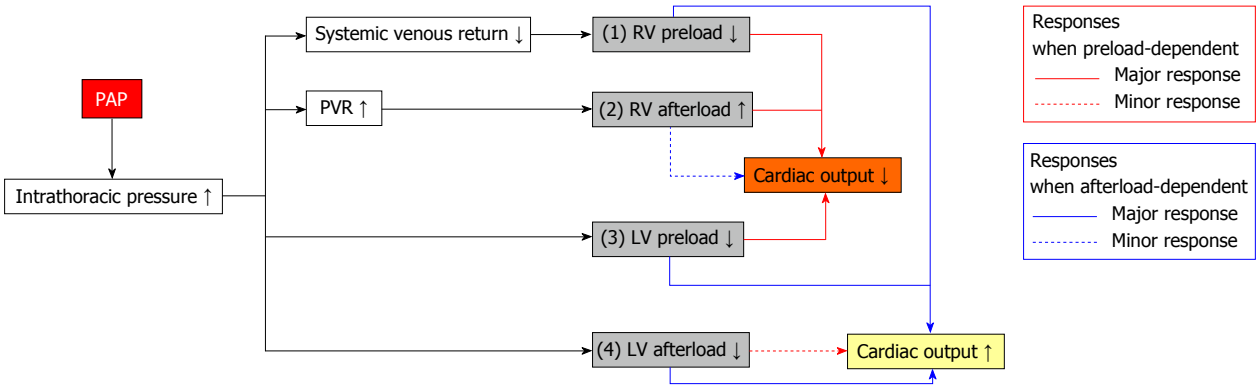

Figure 1 Effects of positive airway pressure on hemodynamics. First, PAP decreases systemic venous return and RV preload by increasing intrathoracic pressure; Second, PAP increases PVR by increasing lung volume. Thus, it is possible that RV afterload can be increased by PAP; Third, a decrease in RV preload and an increase in RV afterload lead to reductions in pulmonary venous return and limitations of LV inflow, filling and preload; Fourth, increased intrathoracic pressure relative to atmospheric pressure causes a pressure difference between the intrathoracic and extrathoracic cavities. Therefore, PAP may decrease LV afterload. In subjects without HF who are generally preload-dependent or in HF patients who manifest preload-dependent reduction, decreased RV and LV preload in addition to the increase in RV afterload may cause a net decrease in cardiac output, whereas a decrease in LV afterload may cause a minor response toward increasing cardiac output. Conversely, patients with HF are more sensitive to decreased afterload and are thus predominantly afterload-dependent. PAP therapy causes a net increase in cardiac output through decreases in RV preload, LV preload and afterload, whereas an increase in RV afterload may cause a minor response toward decreasing cardiac output. LV: Left ventricular; PAP: Positive airway pressure; PVR: Pulmonary vascular resistance; RV: Right ventricular; HF: Heart failure.

Table 1 Summary of equipped functions of each type/mode of positive airway pressure

	CPAP	Bi-level PAP	VAPS	ASV
Positive end-expiratory pressure	+	+	+	+
Pressure support during inspiration	-	+	+	+
Guarantee of tidal volume or minute ventilation	-	-	+	-
Servo-control of ventilation	-	-	-	+
Automated control of pressure level during expiration	+	-	-	+
Backup ventilation	-	±[1]	+[2]	+[2]

[1]Bi-level PAP devices that are only capable of spontaneous mode cannot provide back-up ventilation; [2]Most devices automatically provide a set backup ventilation rate based on their VAPS or ASV algorithm. ASV: Adaptive servo-ventilation; Bi-level PAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; VAPS: Volume assured pressure support.

and SDB, PAP can attenuate the increase in PVR by improving oxygenation through the abovementioned effect and by alleviating vasoconstriction. Consequently, such attenuation of increased PVR can be associated with improving hemodynamics. Finally, considering that the short-term servo-control of ventilation using adaptive servo ventilation (ASV) during wakefulness reduced muscle sympathetic nervous system activity in patients with chronic HF[33,34], keeping ventilation consistent with ASV may provide further beneficial effects on hemodynamics that are independent of the effects of PAP[35].

TYPES/MODES OF PAP IN HF TREATMENT

Several types or modes of PAP therapy can be considered for HF. Although each type or mode has different purposes, all of them apply positive pressure to the airway. In particular, all of them provide positive end-expiratory pressure. Thus, the benefits from the individual modes overlap. In this section, the types and modes of PAP generally applied for HF are described (Table 1).

CPAP

CPAP is the most widely used type/mode of PAP therapy in patients with HF. It provides a constant level of positive pressure to maintain airway patency during spontaneous breathing (Figure 2A). Because CPAP only provides a constant level of pressure during the entire respiratory cycle and because CPAP does not separately increase pressure during inspiration and thus does not directly support ventilation, sometimes CPAP is not classified as a form of non-invasive positive pressure ventilation. However, the International Consensus Conference in Intensive Care Medicine[7] defined non-invasive positive pressure ventilation as any form of PAP support applied without endotracheal intubation, in which the pressure is generated by the respiratory muscles only with a spontaneous support modality, such as CPAP, or by the ventilator only or by the ventilator and the respiratory muscles. Thus, we classify CPAP as non-invasive positive pressure ventilation unless otherwise indicated.

In general practice, CPAP is most commonly used for the management of SDB *via* specifically manufactured CPAP devices for home care. Some of these CPAP devices are designed to detect various degrees of upper airway obstruction and then adjust the pressure level to keep the airway open. Some of these systems can also provide information about the residual apneas or hypopneas while patients are on CPAP (*i.e.*, automated CPAP) (Figure 1B)[36,37]. Although treatment with automated CPAP improves patient satisfaction and compliance in a subset of patients with obstructive sleep apnea (OSA), the routine use of automated CPAP for OSA treatment provides limited benefit[38-40]. Furthermore, although

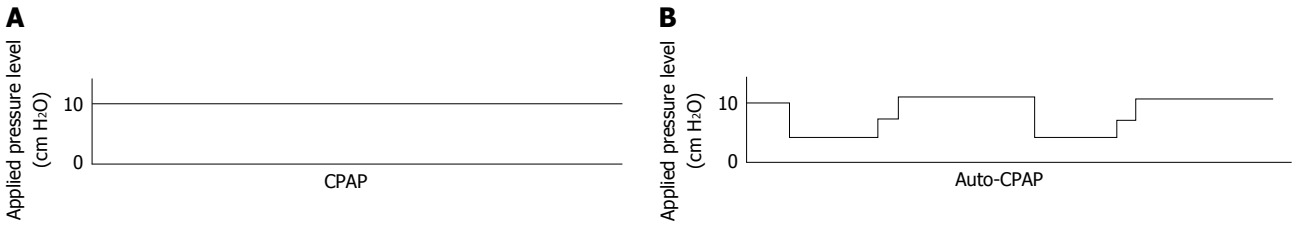

Figure 2 Differences between continuous positive airway pressure and automated continuous positive airway pressure. A: CPAP provides a constant level of positive pressure to the airway during spontaneous breathing; B: Automated CPAP devices are designed to detect various degrees of upper airway obstruction and consequently adjust the pressure level to keep the airway open. CPAP: Continuous positive airway pressure.

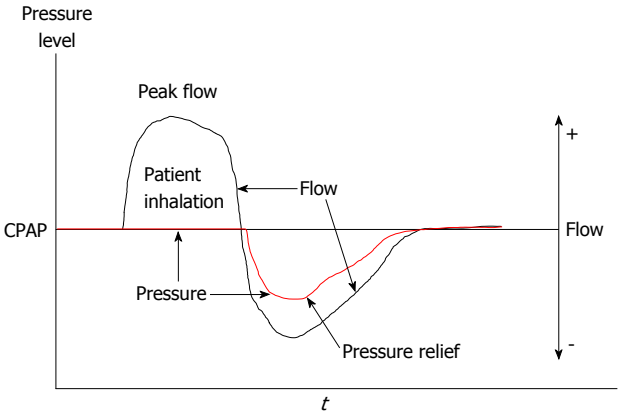

Figure 3 Algorithm of early expiratory phase pressure relief. The pressure is lowered in the early phase of expiration to enhance comfort, but the pressure returns to the critical pressure needed to keep the airway open before the next inspiration. CPAP: Continuous positive airway pressure.

more recent automated CPAP devices have an algorithm to detect central respiratory events, the accuracy of this algorithm remains to be elucidated. Thus, current guidelines do not recommend automated CPAP devices for the diagnosis of SDB or for the treatment of patients with HF, in which central respiratory events frequently coexist with OSA[41].

Some patients who cannot tolerate CPAP complain of difficulty while exhaling against the airway pressure generated by the CPAP device[42,43] especially in patients whose therapeutic pressure needed to eliminate OSA is fairly high (*e.g.*, > 10 cm H_2O). To resolve this issue, some CPAP devices use specific algorithms, such as early expiratory phase pressure-relief (Figure 2). Using these algorithms, the pressure is lowered in the early phase of expiration to enhance comfort, but the pressure returns to the critical pressure needed for keeping airway open before the next inspiration. Early expiratory pressure relief can be applied in combination with other modes of PAP therapy. Because patients with HF do not require such high pressures, even those with OSA, and because high-pressure CPAP might reduce cardiac output in some cases of HF, a pressure-relief algorithm is rarely used when treating HF patients.

Bi-level PAP

Bi-level PAP provides two fixed levels of PAP: a higher level of pressure during inspiration (inspiratory positive airway pressure (IPAP) and a lower level of pressure during expiration [expiratory positive airway pressure (EPAP)]. Its major difference from CPAP is that it provides pressure support during inspiration (Figure 3). The level of pressure support is determined as a difference between IPAP and EPAP, and the level of IPAP plays an important role in unloading respiratory muscles, reducing the work of breathing, controlling obstructive hypopnea or flow limitation, maintaining alveolar ventilation, and reducing the partial pressure of carbon dioxide ($PaCO_2$). EPAP produces respiration and hemodynamic effects that are similar to those provided by CPAP. In addition, most bi-level PAP devices have several modes for back-up ventilation, such as spontaneous breathing (S-mode), timed back-up ventilation, and spontaneous breathing with timed back-up ventilation (ST-mode). Bi-level PAP with S-mode can be used for patients who require high-pressure CPAP to control OSA or for those who cannot tolerate exhaling against high pressure CPAP[44]. However, patients with HF generally do not require high pressure, even those with OSA. Thus, the indication for bi-level PAP with S-mode in patients with HF is quite limited. When using CPAP, the airway pressure is increased at end-expiration but decreased during inspiration (Figure 4); because the net cardiac unloading effects during the respiration cycle are greater in bi-level PAP than in CPAP in association with an increased pressure level during inspiration and its unloading effects, bi-level PAP may be a better option for the treatment of HF[14,45]. In the care of HF, the purposes of treatment with bi-level PAP include the following: (1) reducing hypercapnia in some patients with acute decompensated HF or those with co-existing COPD and HF or those with obesity hypoventilation syndrome (OHS) and its related HF; (2) keeping ventilation consistent with a constant pressure support; and (3) back-up ventilation in patients with central sleep apnea (CSA). In patients with CSA, hypocapnia related to hyperventilation due to pulmonary congestion plays an important role in the development and maintenance of CSA[46]. Bi-level PAP sufficiently promotes ventilation and can reduce the carbon dioxide levels to below the apneic threshold during sleep.

Volume-assured pressure support

Volume-assured pressure support (VAPS) is an advanced mode of bi-level PAP developed for the treatment of pa-

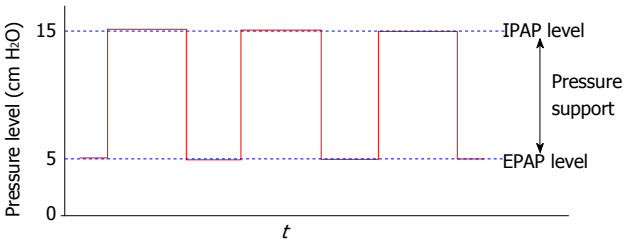

Figure 4 Bi-level positive airway pressure. Bi-level PAP provides two fixed levels of PAP, a higher level of pressure during inspiration (*i.e.*, IPAP) and a lower level of pressure during expiration (*i.e.*, EPAP), and thus provides pressure support during inspiration. EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PAP: Positive airway pressure.

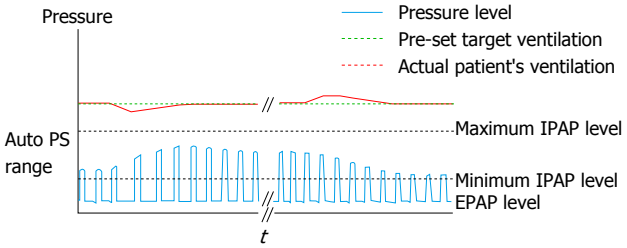

Figure 6 Volume assured pressure support. Using the volume assured pressure support mode, the device alters the level of pressure support from the minimum to maximum levels to maintain the pre-set ventilation or pre-set target tidal volume. This figure shows algorithm based on ventilation. EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PS: Pressure support.

tients with hypoventilation and hypercapnia[47-51]. In VAPS mode, the device alters the level of pressure support (*i.e.*, IPAP level) to maintain a pre-set target tidal volume. Devices with newer VAPS modes alter the respiratory rate in addition to the level of pressure support to maintain a pre-set minute ventilation. Nevertheless, VAPS mode guarantees a delivered tidal volume or minute ventilation despite patients' variable breathing effort, airway resistance, and lung or chest wall compliance (Figure 5).

ASV

ASV is an advanced mode of bi-level PAP developed for the treatment of Cheyne-Stokes respiration with CSA in patients with HF[52]. It is also used in the treatment of other forms of CSA, such as idiopathic CSA, CPAP-emerged CSA and opioid-induced CSA[53,54]. ASV devices automatically provide altering pressure support for each inspiration, ranging from a pre-set minimum level to a pre-set maximum level, to maintain moving target ventilation (determined based on volume or flow) determined by the patient's current breathing in addition to the back-up ventilation with variable respiratory rates (*i.e.*, servo-control of ventilation) (Figure 6). In addition, more recent devices provide altering EPAP levels that are sufficient for the control of upper airway narrowing or collapse, using an algorithm that is similar to that used by automated CPAP. The goals of ASV are to stabilize abnormal breathing patterns (*i.e.*, CSA with Cheyne-Stokes respiration) and to maintain the $PaCO_2$ level to prevent

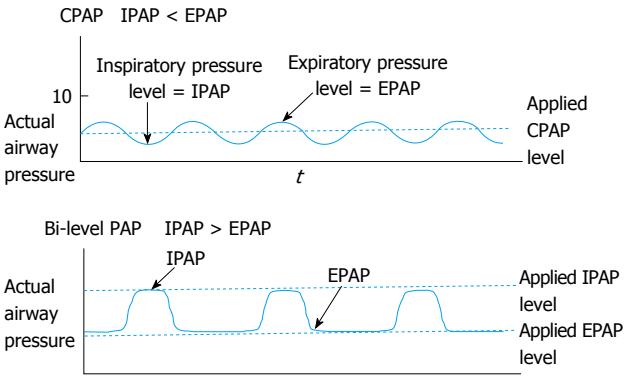

Figure 5 Differences in actual airway pressure between continuous positive airway pressure and bi-level positive airway pressure. While on CPAP, although a constant CPAP level is applied, actual airway pressure is not constant and oscillates. During inspiration, actual airway pressure decreases below the applied CPAP level, whereas during expiration, actual airway pressure increases above the applied CPAP level. Thus, the inspiratory pressure level in the airway (*i.e.*, IPAP) is lower than the expiratory pressure level in the airway (*i.e.*, EPAP). Conversely, while on bi-level PAP, the actual airway pressure increases during inspiration due to pressure support. Thus, IPAP is greater than EPAP according to the level of pressure support. CPAP: Continuous positive airway pressure; EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PAP: Positive airway pressure.

hypocapnia, which can trigger apnea reentry cycles[52] in addition to keeping the upper airway open (Figure 7).

There are two major ASV devices. In both products, pressure support is dynamically adjusted breath-to-breath as necessary to ensure that the patients' actual ventilation matches the target value in addition to the auto-titration of EPAP to maintain airway patency. The main points of difference are the mechanics used to assess the breathing status and to determine the target level. One type of device uses volume-targeted ASV, which sets a minute-ventilation target that is 90% of the recent average minute volume from a 3-min collection period and tries to maintain ventilation at the target level[52]. The other device uses flow-targeted ASV, which monitors the peak inspiratory flow of the patient over a recent moving 4-min window, calculating an average peak flow at every point within this window to set a target peak flow. It compares these data to an internal target and maintains a target peak inspiratory flow[55]. The other minor differences between volume-triggered and flow-triggered ASV devices are summarized in Table 2.

DEVICES, INTERFACE AND ADDITIONAL EQUIPMENT

In general, the equipment necessary for PAP therapy includes devices that provide PAP, tubing and several types of patient interfaces[56]. Ventilators that are used in standard critical care for invasive ventilation can also be used for non-invasive PAP therapy with specific patient interfaces. However, a few types of ventilators have specifically been designed to provide PAP noninvasively and are generally used during the acute phase of HF. Most of these non-invasive ventilators employ several of the

Table 2 Adaptive servo-ventilation devices

	Volume-triggered ASV	Flow-triggered ASV
Manufacturer	ResMed	Philips-Respironics
Target	90% of previous average ventilation (moving time window)	90% of average peak flow (moving time window)
EPAP/EEP	EEP automatically adjusted between min and max (4-20 cm H_2O) Cannot select auto EEP without PS	EPAP automatically adjusted between min and max (4-25 cm H_2O)
IPAP	Max pressure up to 30 cm H_2O IPAP changes within pre-set PS range from min (can be 0) to max Max PS can be limited by maximum pressure and current EEP	Max pressure up to 25 cm H_2O IPAP changes within pre-set PS range from min (can be 0) to max (21 cm H_2O) Max PS can be limited by pre-set maximum pressure and current EPAP level
Backup rate	Automatic 15 ± α breaths/min	Auto rate Fixed rate
Pressure wave form	Saw-tooth	Square shape
Inspiratory time	Automatic	Automatic in auto rate mode Set in manual rate mode

ASV: Adaptive servo-ventilation; EEP: End-expiratory pressure (*i.e.*, = EPAP); EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PS: Pressure support.

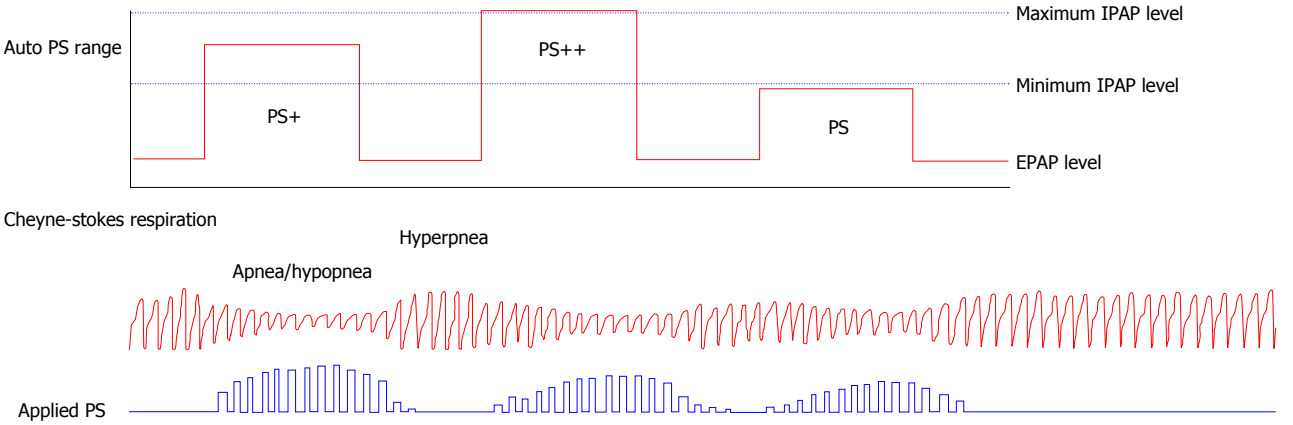

Figure 7 Adaptive servo-ventilation. Adaptive servo-ventilation devices automatically provide altering pressure support for each inspiration, ranging from a pre-set minimum level to a pre-set maximum level, to maintain moving target ventilation (determined based on volume or flow) determined by the patient's current breathing in addition to the back-up ventilation with variable respiratory rates. This stabilizes the abnormal breathing pattern (*i.e.*, cheyne-stokes respiration) and maintains the $PaCO_2$ levels to prevent hypocapnia, which can otherwise trigger apnea reentry cycles. EPAP: Expiratory positive airway pressure; IPAP: inspiratory positive airway pressure; $PaCO_2$: Arterial partial pressure of carbon dioxide; PS: Pressure support.

modes of PAP therapy mentioned earlier and can be used in many situations and conditions during the acute phase of HF. In addition, there are several smaller and more simplified devices that can provide only one or two modes for less intensive care in the general cardiology wards or for home care in patients with sub-acute or chronic phases of HF.

In terms of interface, various masks have been used for PAP therapy for HF; these include nasal masks, nasal pillows, oro-nasal (full-face) masks that cover the nose and mouth, and face (total-face) masks that cover the entire face[57], all of whose actual attachment portions to the face are made of silicone or other soft rubber-like materials to achieve a tighter air seal[58]. In acute HF, a disposable oro-nasal mask or face mask is usually used. In the home care setting, the choice of mask is the most important issue for patient comfort and tolerance to PAP therapy. Poorly fitted masks decrease the efficacy, compliance and adherence to PAP therapy. In addition to the mask itself, headgear or straps are used as a harness. Overly tight headgear may worsen the air leak and interfere with patient comfort and compliance.

Some patients receiving long-term PAP therapy complain of nasal oro-nasal dryness while on PAP devices[59]. For such patients, a heated humidifier can be used to maintain compliance with therapy[60]. One possible disadvantage of the use of heated humidifier includes the accumulation of condensate inside the tube, which can cause a decrease in inspiratory pressure and a delay of triggering when bi-level PAP is used. Condensation inside the tube is also frequently observed during the winter in the home care setting[61]. To resolve such condensate issues, heated tubing systems containing copper wire are now available for clinical use.

CONTRAINDICATION TO PAP THERAPY

There are several absolute contraindications to PAP therapy, such as the presence or absence of anatomic abnormalities for attaching the interface and recent

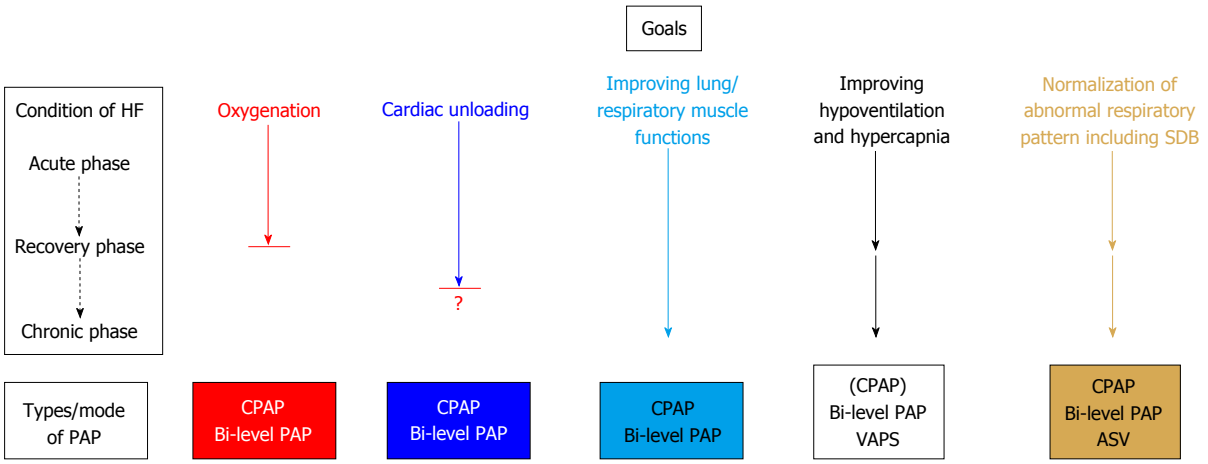

Figure 8 Importance of each goal of positive airway pressure therapy according to different heart failure conditions. In the wide spectrum of HF care, PAP therapy is used to help oxygenation, provide relief from cardiac load, improve lung and respiratory muscle function, reduce hypoventilation and hypercapnia, and normalize abnormal respiratory patterns, including SDB. The importance of each goal can differ according to the condition of HF. Improving oxygen is one of the most important goals in the acute phase. However, after recovery from acute decompensation, this goal becomes less important or is no longer considered. Providing cardiac unloading is another important goal in the acute phase to the recovery phase. However, the importance of this goal remains to be elucidated after recovery from acute decompensation. Improving lung and respiratory muscle function is sometimes important in the acute phase and after recovery. Improving hypoventilation is important in cases with hypercapnia in the acute phase. In addition, HF patients with hypoventilation and daytime hypercapnia can be treated by PAP therapy in the recovery or chronic phase. Normalization of abnormal respiratory patterns, particularly SDB suppression, is sometimes important in the recovery phase and is most important in the chronic phase. The specific types/modes of PAP that should be used differ according to each therapeutic purpose. ASV: Adaptive servo-ventilation; CPAP: Continuous positive airway pressure; HF: Heart failure; PAP: Positive airway pressure; SDB: Sleep disordered breathing; VAPS: Volume assured pressure support.

airway or gastrointestinal surgery. Relative contraindications include the need for the patient to be capable of airway protection, an increased risk of aspiration, swallowing impairment, excessive secretions, frequent coughing, severe hypoxemia (*i.e.*, $PaO_2/FiO_2 < 75$), acidemia, multiorgan failure, respiratory arrest, inability to fit the mask, or poorly motivated patient or family[62,63]. There is controversy regarding use of PAP therapy for patients with cardiogenic shock and hemodynamic instability[18]. In the care of HF, PAP therapy should be administered with caution in patients with severe right-side HF accompanied by severe liver congestion or cirrhosis, patients with hypertrophic obstructive cardiomyopathy and patients with severe aortic valvular heart disease because reductions in venous return to the heart may worsen liver congestion, ascites and edema, and because reductions in LV preload and afterload may cause further reduction in cardiac output unless these patients also have severe pulmonary congestion.

COMPLICATIONS

PAP therapy is generally safe, and only a few major complications can occur, including aspiration pneumonia[64,65], hypotension as a consequence of reduction of preload and afterload (see "Effect of positive airway pressure on hemodynamics"), and rarely, pulmonary barotraumas in association with excessive pressures. Because excessive pressures are not applied for patients with HF due to the risk of adverse reduction in cardiac output, actual applied pressures are much lower than such excessive pressure levels.

However, minor complications related to masks or pressures and air flows can occur. Fitting the mask too tightly for long periods of time may result in skin damage and ulceration, particularly around the nasal bridge[66]. Once established, such wounds may require artificial skin grafts, and of course, mask re-fitting should be considered. Furthermore, patients undergoing long-term PAP therapy with masks might have global facial flattening[67]. However, this may be a specific complication for children. Discomfort associated with pressures and air flows are common and can include dryness, pain in the nose or mouth and pneumophagia, all of which are usually resolved *via* the use of a humidifier or by a decrease in pressure levels.

CONDITIONS IN WHICH PAP THERAPY IS CONSIDERED FOR HF

In the wide spectrum of HF care, PAP therapy is used to improve oxygenation, reduce cardiac load, improve lung and respiratory muscle function, alleviate hypoventilation and hypercapnia, and normalize abnormal respiratory patterns, including SDB (Figure 8). In this section, specific conditions in which PAP therapy is frequently considered in the care of HF are described (Table 3).

Acute decompensated HF

Guidelines for ADHF generally recommend the use of PAP therapy if patients have breathing difficulty, signs of pulmonary edema, or hypoxia despite supplemental oxygen (Table 4)[5,68-71]. For patients with ADHF, the purposes of PAP therapy include augmentation of oxygenation through recruitment of collapsed alveoli, reversal of atelectasis, and induction of fluid shifts back from the alveoli

Table 3 Possible indication of each type/mode of positive airway pressure for each condition

	CPAP	Bi-level PAP	VAPS	ASV
Acute decompensated heart failure	o[1]	o	?[2]	?
Chronic HF with OSA	o	o	Δ[3]	Δ[4]
Chronic HF with CSA	Δ[5]	o	?	o
HF following acute decompensation	Δ[6]	o	?	Δ[7]
Chronic HF without SDB	×	?	?	Δ[8]
HF with hypoventilation (acute)	Δ[9]	o	o	×
HF with hypoventilation (chronic)	Δ[9]	o	o	?

[1]Bi-level PAP with S-mode for accompanying OSA; [2]Indicates that no clear data are available; [3]Can be used if accompanied by hypoventilation; [4]Can be used if Cheyne-Stokes respiration coexists; [5]Can be used if CSA is alleviated; [6]Can be used if OSA exists; [7]Can be used if CSA exists; [8]ASV may be useful for chronic HF patients with apnea-hypopnea index < 20 including those without SDB; [9]Can be used if hypoventilation is associated with OSA. ASV: Adaptive servo-ventilation; Bi-level PAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; CSA: Central sleep apnea; HF: Heart failure; OSA: Obstructive sleep apnea; SDB: Sleep disordered breathing; VAPS: Volume assured pressure support.

and the interstitial space to the pulmonary circulation, reducing respiratory muscle load and the work of breathing, and stabilizing hemodynamics *via* cardiac unloading.

In patients with ADHF, PAP therapy is usually administered by specifically designed ventilators for non-invasive PAP for acute or intensive care. The selection of modes (usually, CPAP or bi-level PAP) is dependent on whether patients require pressure support to ventilate appropriately. For example, patients with hypercapnia or respiratory muscle fatigue may require bi-level PAP. Otherwise, CPAP is used because most data suggest that there are no obvious clinical benefits to the use of bi-level PAP over CPAP[72,73]. In Japan, ASV is sometimes used for patients with ADHF, especially in institutions where specifically designed ventilators for non-invasive PAP for acute or intensive care are not available. The merits of using ASV for patients with ADHF may include the fact that devices for ASV are small, handy and mobile; ASV can be started in the emergency room, which allows PAP to be applied quite immediately upon presentation to the hospital; and ASV may synchronize patients' respiration more easily than typical bi-level PAP. However, these potential merits of ASV remain to be confirmed. It should be noted that ASV devices do not provide raw wave forms of parameters related to respiration, whereas specifically designed ventilators for non-invasive PAP for acute or intensive care do provide these data.

PAP therapy improves hemodynamics, respiratory function and oxygenation in patients with pulmonary edema in association with ADHF when compared with oxygen therapy alone[74-79]. Moreover, the use of PAP therapy in randomized prospective trials was associated with lower rates of intubation and improved 30-d mortality compared with oxygen therapy alone[74,76,77,79]. Thus, PAP therapy for ADHF is the universal standard.

SDB

SDB is frequently observed in patients with HF. In general, two types of SDB, OSA and CSA, can be observed in HF patients. Typically, CSA in HF patients is usually observed as Cheyne-Stokes respiration, which is a form of periodic breathing characterized by a crescendo-decrescendo pattern of breathing followed by central apnea or hypopnea[80].

OSA results from upper airway collapse and predisposes patients to the development and progression of HF *via* several mechanisms. For example, in patients with OSA, the blood pressure is frequently elevated as a result of overactivation of the sympathetic nervous system. Such high blood pressure may contribute to the development of HF in association with the direct deleterious effects of sympathetic overactivity. In addition, the generation of exaggerated negative intrathoracic pressure during obstructive apneas increases cardiac loads. Conversely, CSA appears to arise secondary to HF. In general, HF patients are likely to have chronic hyperventilation due to stimulation of the pulmonary vagal irritant receptors by pulmonary congestion and to increased chemosensitivity, which is characteristic of HF patients with CSA[46,81] and consequently results in hypocapnia. When $PaCO_2$ falls below the apneic threshold because of an increase in the apneic threshold during transition from wakefulness to sleep, CSA ensues[46,81]. Apnea persists until $PaCO_2$ rises above the apneic threshold; then, ventilation will resume; ventilatory overshoot occurs, and $PaCO_2$ will decrease below the apneic threshold in association with arousal during the ventilatory phase and increased chemosensitivity. This could also contribute to the pathogenesis of CSA with a Cheyne-Stokes respiration pattern by facilitating ventilatory overshoot and undershoot. Once triggered, the pattern of Cheyne-Stokes respiration will be sustained by the combination of increased respiratory chemoreceptor drive, pulmonary congestion, arousals, and apnea-induced hypoxia, which cause oscillations in $PaCO_2$ above and below the apnea threshold[46,81]. Nevertheless, CSA is also characterized by apnea, hypoxia, and increased sympathetic nervous activity and, when present in HF, is associated with an increased risk of death[46,81,82].

In patients with chronic HF, treatment of SDB alleviates underlying cardiac dysfunction. The standard treatment for OSA in patients with HF is CPAP. CPAP prevents upper airway narrowing and collapse and works as a "pneumatic splint"[28-30], thereby preventing obstructive apneas and hypopneas. It was reported that one night of CPAP resolved negative intrathoracic pressure swings in association with obstructive respiratory events and reductions in nocturnal blood pressure and heart rate[46,83]. Thus, HF patients with OSA may benefit from cardiac unloading by suppressing OSA *via* CPAP. Independent of OSA suppression, CPAP promotes reductions in LV preload and afterload in patients with HF. In fact, many studies regarding CPAP therapy for chronic HF patients demonstrated an improvement in LV systolic function in association with reductions in sympathetic nervous system activity and associated reductions in systemic arterial blood pressure and heart rate[46,84-87]. In terms of long-term clinical outcomes, two observational studies

Table 4 Recommendations for oxygen and bi-level positive airway pressure therapy for acute decompensated heart failure

Guidelines	Oxygen	PAP therapy
ACC/AHA (2009 updated)	To relieve symptoms related to hypoxemia: Class Ⅰ, level C	NA
ACCF/AHA (2013)	NA	NA
HFSA (2010)	Hypoxia+: Class Ⅰ, level C Hypoxia-: Class Ⅲ, level C	Dyspnea+ or pulmonary edema+: Class Ⅰ, level A
ESC (2012)	Hypoxemia+ (SaO_2 < 90% or PaO_2 < 60 mmHg): Class Ⅰ, level C	Dyspnea+ or pulmonary edema+ or RR > 20/min: Class Ⅱa, level B SBP < 85 mmHg: Class Ⅲ
JCS (2011)	Hypoxia+ (to keep SaO_2 > 95%, PaO_2 > 80 mmHg): Class Ⅰ, level C	Not responding to oxygen: Class Ⅰ, level A

ACC: American college of cardiology; ACCF: American college of Cardiology foundation; AHA: American heart association; ESC: European Society of Cardiology; HFSA: Heart failure society of America; JCS: Japanese Cardiology Society; NA: Not available; PaO_2: Arterial partial pressure of oxygen; RR: Respiratory rate; SaO_2: Oxyhemoglobin saturation; SBP: Systolic blood pressure; PAP: Positive airway pressure.

in chronic HF patients indicated that CPAP therapy for OSA results in a trend towards reduced mortality or a significant reduction in the composite endpoint of mortality and rehospitalization[88,89]. In addition, in one of those studies, the hospitalization-free survival rate in patients administered CPAP therapy was significantly higher in the more compliant group than in the less compliant group[89]. Therefore, good compliance with long-term CPAP therapy may provide better clinical outcomes in chronic HF patients with OSA.

Because HF patients with CSA have associated pulmonary congestion and increased LV filling pressures, CPAP has been applied to improve pulmonary congestion and increased LV filling through the cardiac unloading. However, studies regarding the effects of CPAP on the suppression of CSA in chronic HF patients produced inconsistent results, most likely due to the differences the application of CPAP. If CPAP was applied for a short period of time (*e.g.*, 1 night) at low pressure (*e.g.*, 5 cm and 7.5 cm H_2O), CSA was not alleviated[90,91]. However, if CPAP was applied for longer periods (*e.g.*, 7 d) at high pressure (8-12.5 cm H_2O), the severity of CSA decreased by > 50%[92-96]. In addition, CPAP with gradual titration alleviated CSA and was accompanied by an increase in $PaCO_2$[46,95,97,98]. reduction in sympathetic nervous system activity[99], and improvements in respiratory muscle function[100] and LV systolic function for 1-3 mo[46,95-98]. In terms of long-term clinical outcome, one small-randomized trial[97] showed that in chronic HF patients with CSA, CPAP produced a trend[90] toward a better outcome, and a sub-group of patients compliant with CPAP had significantly better outcomes. However, a large-scale randomized controlled study in chronic HF patients with CSA failed to demonstrate the benefits of CPAP in terms of long-term clinical outcomes (mean follow-up duration, 2-years)[101]. A post hoc analysis of this study suggested that patients whose apnea-hypopnea index (AHI) decreased below 15 in response to CPAP at 3 mo (*i.e.*, CPAP responder) had significantly better long-term clinical outcomes compared with the control groups. This implied that in approximately 50% of chronic HF patients, CPAP therapy suppressed CSA, but PAP therapy, which may suppress CSA more effectively and constantly, should be the focus.

One such PAP therapy is bi-level PAP[52]. A small randomized controlled trial comparing 10 HF patients with CSA on bi-level PAP without backup ventilation (*i.e.*, S-mode) and standard medical therapy versus 11 HF patients with CSA on standard medical therapy alone showed significant reduction in the AHI from 28.3 ± 12.3/h to 5.2 ± 3.8/h with one night of bi-level PAP with S-mode and significant improvement in LV ejection fraction at 3 mo with bi-level PAP with S-mode (20.3% ± 8.2% *vs* 3.2% ± 10.1% with standard medical therapy alone)[102]. Considering that bi-level PAP with S-mode may aggravate central apnea through hyperventilation, this is not a good option for all HF patients with CSA. Conversely, studies using bi-level PAP with spontaneous and timed backup ventilation mode (*i.e.*, ST-mode) in chronic HF patients showed sufficient reduction in the AHI with one night of bi-level PAP and significant improvement in LV ejection fraction at 3 mo with bi-level PAP with ST-mode[103-105]. In particular, in a study regarding the effects of bi-level PAP with ST-mode on the suppression of AHI and improvements in cardiac function in chronic HF patients with CSA that was not sufficiently suppressed by CPAP (*i.e.*, AHI ⩾ 15, non-responders), CSA sufficiently decreased in response to bi-level PAP with ST-mode (AHI, from 54.4 ± 7.8 at baseline to 30.3 ± 11.7 on CPAP to 8.4 ± 4.7 on bi-level PAP with ST-mode)[105]. Further, left ventricular ejection fraction (LVEF) and the plasma levels of B-type natriuretic peptide improved in chronic HF patients with CSA, even in patients deemed CPAP non-responders at 6 mo[105]. Another PAP therapy that is more effective at suppressing AHI in chronic HF patients with CSA is ASV[52]. Randomized and observational studies in which the effects of ASV on cardiac function were assessed showed that suppression of CSA *via* ASV reduced the levels of neurohumoral factors and improved LV systolic function and outcomes in chronic HF patients with CSA[106-109]. Furthermore, in studies on the effects of ASV on suppression of AHI and improvements of cardiac function in CPAP non-responders, CSA was sufficiently decreased in response to ASV, and cardiac functions and neurohumoral state were improved at 3 mo[110]. The effects of

ASV on long-term clinical outcomes in chronic HF patients with CSA will be clarified in an ongoing large-scale randomized controlled trial[111,112].

Both OSA and CSA can be observed in patients with chronic HF, and ASV can suppress OSA by modifying the EPAP levels in addition to suppressing CSA. Thus, ASV, particularly ASV with auto-titrating EPAP, may be a therapeutic option for SDB without the need to distinguish between OSA and CSA. Three randomized controlled trials assessed the effects of ASV on cardiac function in chronic HF patients with coexisting OSA and CSA[55,113,114]. These studies reported significant improvements in cardiac functions, especially reductions in neurohumoral factors. The effects of ASV for both types of SDB will be elucidated in an ongoing large-scale randomized controlled trial including chronic HF patients with either OSA or CSA[115].

HF patients following acute decompensation

Although patients with ADHF are frequently treated with PAP therapy, whether HF patients following recovery from acute decompensation remains unclear. In HF patients following recovery from acute decompensation, the presence or absence of SDB may play key roles in determining whether PAP therapy should be considered. Although most previous data regarding SDB in HF and its treatment with PAP mentioned earlier involve HF patients in the chronic phase, it was recently reported that hospitalized HF patients following ADHF frequently develop SDB and that the presence of SDB during hospitalization following ADHF is a predictor of readmission and mortality[116-118]. Thus, PAP therapy should be considered even for hospitalized HF patients, especially in the setting of symptomatic SDB. One study suggests a beneficial effect of in-hospital bi-level PAP (with S-mode) therapy for OSA on improvement of cardiac function following ADHF[117]. An ongoing study may elucidate whether PAP therapy improve outcomes in these patients[119]. However, there are no specific data regarding the effect of PAP therapy on hospitalized patients following ADHF who do not have SDB.

Chronic HF patients without SDB

Chronic HF patients even without SDB may also benefit from PAP therapy through its cardiac unloading effects. In fact, the short-term application of CPAP (*i.e.*, 5-10 cm H_2O) can increase cardiac output in stable HF patients with pulmonary congestion[120,121]. This possibility has been further assessed in a subgroup analysis of a small randomized trial regarding the effects of CPAP on cardiac function and clinical outcomes in HF patients with and without CSA[97]. In a subgroup analysis of patients without CSA, CPAP had no effect on either LVEF or the composite endpoint of mortality and cardiac transplantation rate. Bi-level PAP may be a better option for improving hemodynamics in HF patients with pulmonary congestion because net cardiac unloading effects during a respiration cycle may be greater in bi-level PAP than in CPAP (refer to the section regarding "Bi-level positive airway pressure")[14,45]. Furthermore, based on data showing the acute beneficial effects of short-term ASV application on sympathetic nervous system activity[33,34] and hemodynamics[35], ASV may be a more promising therapeutic option for chronic HF patients without SDB. In fact, Koyama *et al*[122] reported that ASV was associated with better clinical outcomes, regardless of the presence or absence of moderate CSA (*i.e.*, AHI < 20 or $\geqslant 20$). The possible benefits of ASV on cardiac function are being assessed in an ongoing randomized clinical trial in which HF patients with and without SDB are being randomized to either ASV treatment or medical therapy to assess the changes in LV ejection fraction at 6 mo[123].

Most acute hemodynamic effects of PAP therapy are more prominent in HF patients with pulmonary congestion or increased LV filling pressure *(i.e.*, pulmonary capillary wedge pressure $\geqslant 12$ mmHg)[45,121]. Patients with HF are more sensitive to decreased afterload and are usually hypervolemic and are thus insensitive to decreased preload. However, preload reduction may play a more prominent role in HF patients without hypervolemia. Therefore, chronic HF patients with low filling pressure and those without hypervolemia should not be treated with PAP therapy or at least should be treated with caution.

HF with hypoventilation and hypercapnia

Among patients with HF, there is a subset of patients who have hypoventilation and hypercapnia acutely or chronically. In the acute phase, it was reported that 35 of 80 patients with acute cardiogenic pulmonary edema had hypercapnia that was not associated with a previous history of COPD[124]. On the other hand, it was also reported that 25% of patients with ADHF had COPD[125]. Thus, PAP therapy can be considered in such HF patients with hypoventilation and hypercapnia in the acute phase. In general, specifically designed ventilators for non-invasive PAP for acute or intensive care are used, although small home-care devices can also be used. In terms of modes, bi-level PAP or VPAS, both of which can provide sufficient minute ventilation or tidal volume to reduce $PaCO_2$, should be used. ASV may also be considered. However, because ASV is designed to keep $PaCO_2$ consistent in patients with hypocapnia and $PaCO_2$ oscillation, its effects for the reduction in $PaCO_2$ will be insufficient.

In the chronic phase, hypoventilation and daytime hypercapnia are observed in some elderly HF patients with COPD or in obese HF patients with OHS. Some patients with COPD can suffer from hypoventilation and daytime hypercapnia in association with individual variations in chemoreceptor sensitivity to CO_2 and inspiratory muscle strength[126]. In addition, sleep-related hypoventilation and the initiation of long-term oxygen therapy can contribute to the development of hypoventilation and daytime hypercapnia in COPD patients. Mild physiologic hypoventilation during sleep, especially during rapid eye movement (REM) sleep, is exaggerated in patients with COPD. Hypoventilation and daytime hy-

percapnia can also be precipitated by supplemental oxygen therapy for hypoxia. Because both HF and COPD are more likely observed in elderly patients, the coexistence of HF and COPD has become more prevalent as the general population ages[127]. Although the use of PAP therapy in COPD patients with chronic hypoventilation has not been established, the potential benefits of PAP therapy in these patients generally include improvement in daytime and nighttime arterial blood gas parameters, increase in sleep duration, improvements in quality-of-life[128] and decreases in hospitalization rate[129,130]. For patients with HF and COPD, PAP therapy can be used for cardiac unloading. Furthermore, it was reported that OSA occurs in 10% to 15% of patients who have COPD (*i.e.*, overlap syndrome)[131]. In addition, HF patients frequently have OSA[32]. Hypoventilation and hypercapnia in patients with HF and COPD can be attributed to coexisting OSA. Another means of PAP therapy in patients with HF and hypoventilation and hypercapnia is to suppress coexisting OSA.

In patients with chronic HF with hypoventilation and hypocapnia, the selection of the mode of PAP therapy is dependent on the volume of ventilation required to reduce the $PaCO_2$ levels. In patients who only require alleviation of coexisting OSA to reduce $PaCO_2$, CPAP can be used during sleep. If patients require pressure support to reduce $PaCO_2$, bi-level PAP can be used. If patients require a guarantee on delivered tidal volume or minute ventilation to reduce $PaCO_2$, VAPS can be used. ASV may also be considered. However, it should be noted that the effects of ASV for the reduction of $PaCO_2$ will be insufficient.

In obese HF patients with hypoventilation and hypercapnia, the coexistence of OHS [defined as obesity (body mass index > 30 kg/m^2) and daytime hypoventilation with awake $PaCO_2$ > 45 mmHg in the absence of other causes of hypoventilation[29]] should be considered. Patients with OHS frequently have multiple risk factors for cardiovascular disease in association with comorbid obesity. OHS can cause LV hypertrophy and diastolic dysfunction, and longstanding OHS may promote LV systolic dysfunction[132]. In addition, OHS with severe hypoxia can cause pulmonary hypertension and subsequent right-sided HF. Therefore, OHS can induce the development and worsening of HF. Furthermore, approximately 90% of patients with OHS have OSA with and without REM sleep hypoventilation[133]. In OHS, hypercapnia is due to increased work of breathing, OSA, respiratory muscle impairment, decreased central ventilatory drive, and decreased response to leptin. Obesity *per se* can increase the work of breathing through the increased efforts required to move the rib cage and the diaphragm and through decreased lung compliance. In addition to mild physiologic hypoventilation during sleep, OSA contributes to hypoventilation during each obstructive respiratory event, especially for REM sleep during which apneas and hypopneas become more severe in both frequency and duration. Post-apnea (post-hypopnea) hyperpneas may not sufficiently compensate for hypoventilation to maintain eucapnia[134] and reduced pH level and bicarbonate excretion at night as well as progressive elevation in the serum bicarbonate level and subsequent depression of ventilation during the day[134,135]. Muscle impairment and decreased central ventilatory drive may play only a limited role in the pathogenesis of OHS[131]. Although it was reported that alterations in leptin levels and leptin resistance can cause hypoventilation[136], detailed mechanisms regarding these alternations in patients with OHS remain to be elucidated.

To treat HF patients with OHS, in addition to weight reduction, PAP should be considered to normalize ventilation and cardiac unloading. CPAP may be beneficial by preventing upper airway narrowing and hence improving alveolar hypoventilation, hypercapnia and oxygenation, and quality of life[28,137,138] in some patients with OHS. However, some OHS patients still have significant nocturnal oxygen desaturation, even on CPAP[139]. Providing pressure support with bi-level PAP should be considered for such patients and for those without OSA. Long-term bi-level PAP therapy improves hypercapnia, oxygenation, and increases lung volumes in patients with OHS[140]. In an observational study, the use of bi-level PAP in OHS patients was associated with reduced mortality compared with patients who were not treated with bi-level PAP[141]. Recent data suggest that VAPS may improve ventilation when compared with conventional bi-level PAP. However, the use of VAPS was associated with lower patient tolerance due to high pressure[47,48]. Therefore, VAPS can be considered in patients who do not tolerate CPAP or bi-level PAP.

CONCLUSION

PAP is a non-invasive and non-pharmacological therapy for HF in the acute setting and is now globally used. In addition, in chronic HF patients with SDB, PAP therapy should be used to alleviate SDB and to improve short-term cardiovascular outcomes. Similarly, in HF patients with hypoventilation and hypercapnia in association with COPD and OHS, PAP therapy should be used to improve hypoventilation and hypercapnia. However, it remains to be elucidated whether PAP therapy can improve cardiovascular outcomes in patients following ADHF, in chronic HF patients without SDB, and in those with hypoventilation and hypercapnia. In particular, whether PAP therapy can alter long-term outcomes is of great interest. Therefore, further research regarding these topics is needed.

Nevertheless, cardiologists and other clinicians should understand the benefits of PAP therapy, including the improvements in the control of respiration and cardiac unloading, as well as the indications, contraindications and complications of this therapy, as discussed in this review.

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P- Reviewer: Cheng XW, Gaetano S, Kolettis TM
S- Editor: Yu J **L- Editor**: A **E- Editor**: Liu SQ

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DOI: 10.4330/wjc.v6.i11.1192

World J Cardiol 2014 November 26; 6(11): 1192-1208
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (5): Myocardial infarction

Magnetic resonance imaging and multi-detector computed tomography assessment of extracellular compartment in ischemic and non-ischemic myocardial pathologies

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Received: April 25, 2014 Revised: August 15, 2014
Accepted: September 6, 2014
Published online: November 26, 2014

Abstract

Myocardial pathologies are major causes of morbidity and mortality worldwide. Early detection of loss of cellular integrity and expansion in extracellular volume (ECV) in myocardium is critical to initiate effective treatment. The three compartments in healthy myocardium are: intravascular (approximately 10% of tissue volume), interstitium (approximately 15%) and intracellular (approximately 75%). Myocardial cells, fibroblasts and vascular endothelial/smooth muscle cells represent intracellular compartment and the main proteins in the interstitium are types Ⅰ/Ⅲ collagens. Microscopic studies have shown that expansion of ECV is an important feature of diffuse physiologic fibrosis (*e.g.*, aging and obesity) and pathologic fibrosis [heart failure, aortic valve disease, hypertrophic cardiomyopathy, myocarditis, dilated cardiomyopathy, amyloidosis, congenital heart disease, aortic stenosis, restrictive cardiomyopathy (hypereosinophilic and idiopathic types), arrythmogenic right ventricular dysplasia and hypertension]. This review addresses recent advances in measuring of ECV in ischemic and non-ischemic myocardial pathologies. Magnetic resonance imaging (MRI) has the ability to characterize tissue proton relaxation times (T1, T2, and T2*). Proton relaxation times reflect the physical and chemical environments of water protons in myocardium. Delayed contrast enhanced-MRI (DE-MRI) and multi-detector computed tomography (DE-MDCT) demonstrated hyper-enhanced infarct, hypo-enhanced microvascular obstruction zone and moderately enhanced peri-infarct zone, but are limited for visualizing diffuse fibrosis and patchy microinfarct despite the increase in ECV. ECV can be measured on equilibrium contrast enhanced MRI/MDCT and MRI longitudinal relaxation time mapping. Equilibrium contrast enhanced MRI/MDCT and MRI T1 mapping is currently used, but at a lower scale, as an alternative to invasive sub-endomyocardial biopsies to eliminate the need for anesthesia, coronary catheterization and possibility of tissue sampling error. Similar to delayed contrast enhancement, equilibrium contrast enhanced MRI/MDCT and T1 mapping is completely noninvasive and may play a specialized role in diagnosis of subclinical and other myocardial pathologies. DE-MRI and when T1-mapping demonstrated sub-epicardium, sub-endocardial and patchy mid-myocardial enhancement in myocarditis, Behcet's disease and sarcoidosis, respectively. Furthermore, recent studies showed that the combined technique of cine, T2-weighted and DE-MRI technique has high diagnostic accuracy for detecting myocarditis. When the tomographic techniques are coupled with myocardial perfusion and left ventricular function they can provide valuable information on the progression of myocardial pathologies and effectiveness of new therapies.

Key words: Myocardial viability; Ischemic/non-ischemic

heart diseases; Magnetic resonance imaging; Multi-detector computed tomography; Cellular compartments; Contrast media

Core tip: This review addresses recent advances of measuring of extracellular volume (ECV) in ischemic and non-ischemic myocardial pathologies. The main approaches that are used for probing ECV are equilibrium contrast enhanced magnetic resonance imaging/multi-detector computed tomography and magnetic resonance imaging (MRI) longitudinal relaxation time mapping. These noninvasive techniques are currently used, but at a lower scale, as alternative to invasive endomyocardial biopsies to eliminate anesthesia, coronary catheterization and tissue sampling error. ECV measurements may aid in early detection of various myocardial pathologies. Delayed contrast enhanced-MRI (DE-MRI) and when T1-mapping demonstrated sub-epicardium, sub-endocardial and patchy mid-myocardial enhancement in myocarditis, Behcet's disease and sarcoidosis, respectively. Furthermore, recent studies showed that the combined technique of cine, T2-weighted and DE-MRI technique has high diagnostic accuracy for detecting myocarditis. When the tomographic techniques are coupled with myocardial perfusion and left ventricular function it can provide valuable information on the progression of myocardial pathologies and effectiveness of new therapies.

Saeed M, Hetts SW, Jablonowski R, Wilson MW. Magnetic resonance imaging and multi-detector computed tomography assessment of extracellular compartment in ischemic and non-ischemic myocardial pathologies. *World J Cardiol* 2014; 6(11): 1192-1208 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1192.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1192

INTRODUCTION

Ischemic and non-ischemic cardiomyopathies have become a worldwide epidemic of the 21st century with increasing impact on healthcare systems. The 2012 European Society of Cardiology and 2013 American College of Cardiology Foundation/American Heart Association guidelines have set the stage for current therapy to reduce mortality and morbidity[1,2]. Revascularization of coronary arteries in acute myocardial infarct (AMI) have become the treatment of choice and revascularization procedures have evolved significantly. Because X-ray coronary angiography-the clinically accepted reference standard for demonstrating coronary artery disease is invasive and provides information only on the anatomical status of coronary obstructive lesions several noninvasive methods have been developed to aid in the assessment of the functional status of myocardium, namely contraction and perfusion as well as microvascular and cellular integrity, including positron emission tomography and contrast-enhanced echocardiography. More recently, delayed contrast-enhanced (DE) magnetic resonance imaging (MRI)[3-13]. Extracellular MR contrast media identifies hyperenhanced infarct, hypoenhanced microvascular obstruction zone and a moderately enhanced peri-infarct zone in acute myocardial infarction[5,6]. Delayed contrast enhanced-MRI (DE-MRI) has sensitivity of 99% for measuring AMI/scar infarct extent and 94% for measuring the transmural enhancement[3,7,8]. Transmural enhancement was used to predict recovery of regional function in enhanced segments[9]. A cutoff of 50% transmural enhancement was the threshold of recovery of regional function after intervention, where < 50% transmural enhancement predicted recovery in 53% of segments, while > 50% transmural enhancement was associated with negligible recovery (8% of segments)[10]. Furthermore, < 25% transmural enhancement predicted residual viability in 82% of segments. DE-MRI has been clinically used to diagnose and specify different types of ischemic and non-ischemic cardiomyopathies based on the pattern and location of enhancement.

In ischemic cardiomyopathy the sub-endocardium is always enhanced on DE-MRI[3,7,8], while in dilated cardiomyopathy, a patchy mid-myocardial pattern of enhancement is seen[12]. Patients with mid-myocardial enhancement are at higher risk of sudden cardiac death and arrhythmias[13]. Furthermore, patients with restrictive cardiomyopathy showed delayed myocardial enhancement over the entire sub-endocardial circumference[14]. DE-MRI and T1-mapping demonstrated sub-epicardial, sub-endocardial and patchy mid-myocardial enhancement in myocarditis specific cardiomyopathies such as Behcet's disease and sarcoidosis, respectively. In Behcet's disease, enhancement of sub-endocardial fibrosis in the right ventricle is considered a feature of the disease. Vignaux[15] observed delayed enhancement in sarcoidosis patients in specific locations [basal interventricular septum, lateral left ventricular (LV) wall] and distribution patterns (patchy or striate that do not involve the sub-endocardium) and in advanced cases of diffuse and focal pathologies. In non-ischemic dilated cardiomyopathy, Assomull *et al*[13] showed that the presence of delayed myocardial enhancement was associated with a 3-fold increase of hospitalization for heart failure or cardiac death and a 5-fold increase of sudden cardiac death or ventricular arrhythmias. In hypertrophic cardiomyopathy, the extent of differentially enhanced myocardium assessed on DE-MRI was linked with progressive disease and markers of clinical risk for sudden death[16].

Other MRI studies showed discordant results about the relationship between infarct enhancement and regional LV function. Beek *et al*[17] reported that 25% of LV segments with transmural enhancement showed potential improvement in function at 13 wk. In another recent study, Dall'Armellina *et al*[18] found that AMI does not necessarily equate with irreversible injury and severely underestimate salvaged myocardium on DE-MRI. Accordingly, new strategies have been developed to quantify diffuse myocardial fibrosis and small infarcted areas using equilibrium contrast enhanced magnetic resonance imaging/multi-detector computed tomography (MRI/MDCT)

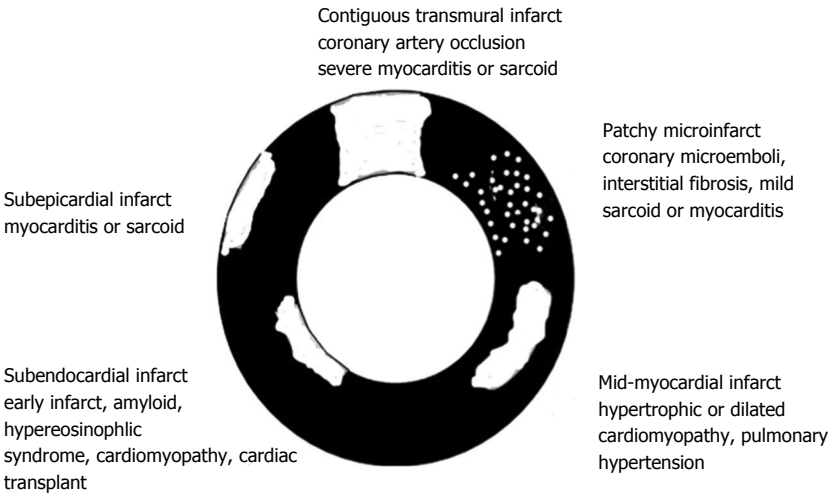

Figure 1 Schematic presentation of various types (patchy and contiguous) and locations (epicardium, midmyocardium and endocardiu) of myocardial infarct in different cardiac diseases. In acute myocardial infarct > 30% of the patients have a hypoenhanced microvascular zone in the core of contiguous infarct. Reactive interstitial fibrosis is seen in hypertension, valvular, diabetic and genetic diseases as well as aging, while infiltrative interstitial fibrosis is evident in amyloidosis and Anderson-Fabry disease. The replacement of myocardium with scar tissue is seen in inflammatory disease, chronic ischemia/coronary occlusion (contiguous), chronic renal insufficiency (patchy) and genetic and toxic diseases.

and T1-mapping techniques[19-27]. Lee *et al*[28] found that the extracellular volume (ECV) in healthy volunteers is stable between 8.5-23.5 min after gadolinium-based contrast media administration and in infarcted myocardium between 12-50 min[29]. These methods overcome the question of the relationship between myocardial enhancement, function and diffuse fibrosis on delayed enhancement. They also allowed for the detection of greater collagen content in the extracellular compartment of myocardium in aging, failing heart, congenital heart, infiltrative heart, hypertension and hypertrophic cardiomyopathy pathologies than normal myocardium[19,30-34].

Visualization of small infarcted areas, peri-infarct zone, patchy microinfarct and diffuse fibrosis remains difficult using existing DE-MRI and DE-MDCT because of low sensitivity, minor/vague alterations in tissue structure, nonspecific enhancement or overlapping with other confounding diseases. On the other hand, experimental studies have shown expansion of ECV in conditions where myocardial damage is invisible on MRI[26,27]. A clinical MRI study found that the ECV of AMI is higher than the ECV in non-ischemic cardiomyopathies, suggesting that the damage is greater damage in the former. The study also showed that the location and pattern of enhancement differs between non-ischemic and ischemic cardiomyopathies[35] (Figure 1).

MYOCARDIAL COMPARTMENTS

Microscopic studies revealed three fluid compartments in healthy myocardium, namely intravascular (approximately 10% of tissue volume), interstitial (approximately 15%) and intracellular (approximately 75%) compartment (Figure 2). It should be noted that the terms extracellular volume (ECV), volume of distribution, fibrosis index, and volume fraction of extravascular extracellular matrix share the same parameters for measuring the ECV by adjusting the contrast media partition coefficient with blood hematocrit[26,27,36].

Intracellular water accounts for 79% of total water or about 380 mL/100 g of dry tissue and varies between individuals and species[37]. The intracellular compartment includes myocardial cells, fibroblasts and vascular endothelial/smooth muscle cells. The main constituent proteins of the interstitial compartment are types I and Ⅲ collagens. Water permeable membranes separate these compartments. Blood plasma and interstitial fluid exchange through pores and intercellular clefts in capillary endothelium.

The fluid in the interstitial compartment consists of a water solvent containing sugars, salts, fatty acids, amino acids, coenzymes, hormones, neurotransmitters and cellular waste products. The exchange of fluid and accompanying solutes between compartments is governed by hydrostatic and oncotic forces. These forces are typically balanced to maintain a constant fluid volume in the compartments. The molecular pathways that contribute to extracellular compartment remodeling post-MI, however, are multifactorial and related to; (1) the increase in osmotic colloidal pressure resulting from the leakage of plasma proteins[38]; (2) the degradation of the extracellular matrix[39]; and (3) heterogeneous or homogeneous loss of membrane integrity of myocardial cells. Disturbance in microvascular permeability causes extravasation of plasma macromolecules that subsequently leads to water imbalance and interstitial edema. Loss of the membrane integrity of myocardial cells further expands the extracellular compartment; and that is the basis for assessing viability and fibrosis (Figure 2). Expansion of ECV in ischemic and non-ischemic heart diseases is strongly associated with adverse outcomes[40]. Expansion of ECV has been seen in myocarditis, hypertrophy, dilated cardiomyopathy, amyloidosis, congenital heart disease, aortic stenosis, restrictive cardiomyopathy, arrhythmogenic right

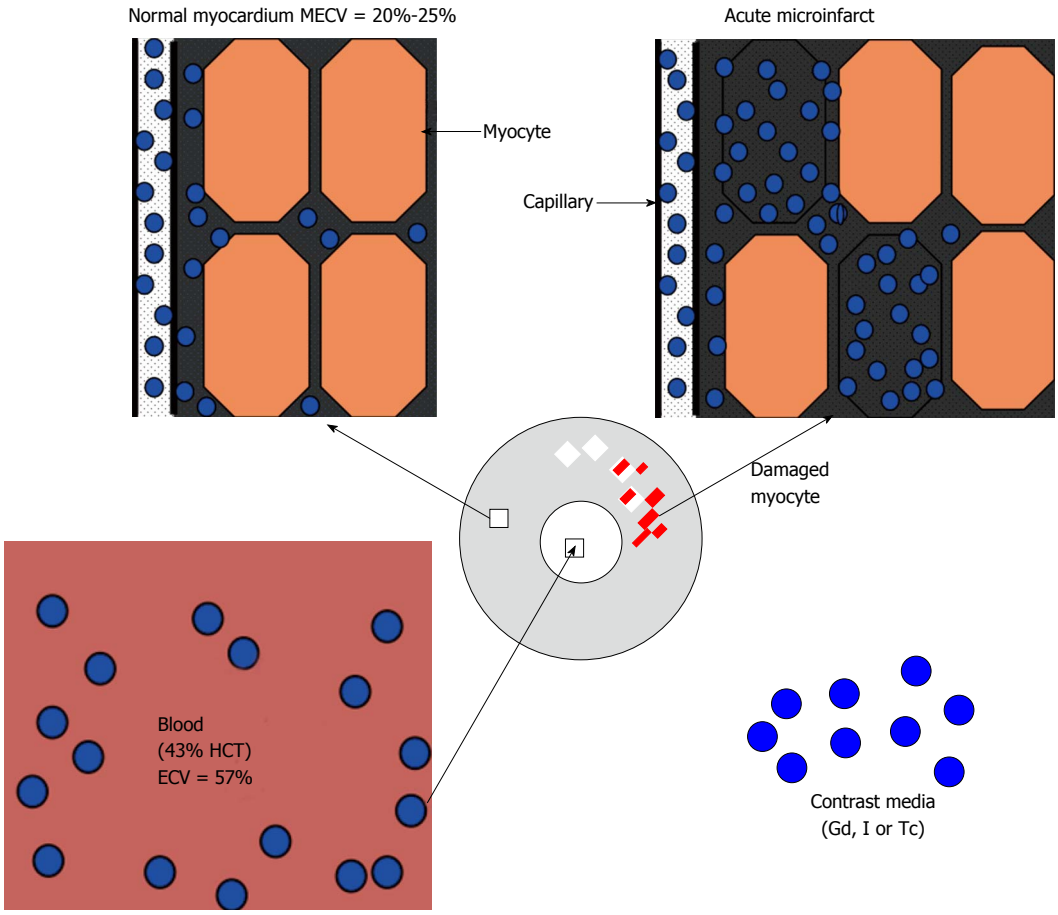

Figure 2 The three fluid compartments in healthy myocardium, namely intravascular (approximately 10% of tissue volume), interstitial (approximately 15%) and intracellular (approximately 75%) compartments. ECV: Extracellular volume; HCT: Hematocrit; Gd: Gadolinium; I: Iodine; Tc: Technetium; MECV: Myocardial extracellular volume.

ventricular dysplasia, hypertension and myocardial infarction (Figure 3).

Proton relaxation times (T1, T2, and T2*) reflect the composition of water protons in tissues. In 1992 several studies showed relationship between T1 change and extracellular MR contrast media content in myocardium[41-43]. Extracellular contrast media are rapidly distributed throughout the extracellular compartment in most tissues, but not in the brain, testis and retina. They are rapidly cleared from the circulation *via* the kidney. The quantity of contrast media distributed into a particular tissue is a function of physical extent of extracellular space and physiologic processes (blood flow, volume and diffusion) that distribute the agent into and remove it from the tissue. In myocardial infarct, investigators observed progressive alterations in structure and composition of the extracellular compartment[44,45]. Interstitial edema in infarcted myocardium causes increase in longitudinal (T1), transverse (T2) and T2* relaxation times[46] and administration of contrast media causes shortening[19,30-32]. The decrease in the T1 relaxation time is greater in infarcted than healthy myocardium, resulting in differential enhancement. T1 assessment has also been used to measure macromolecular content, water binding and water content in tissues. The T1 relaxation time is defined as the time when longitudinal proton magnetization recovers approximately 63% of its equilibrium value. T2* relaxation time refers to decay of transverse magnetization caused by a combination of spin-spin relaxation and magnetic field inhomogeneity. The differential attenuation of infarct and viable myocardium on MDCT relies on X-ray absorption by iodine.

STRATEGIES FOR ESTIMATION OF ECV

The gold standard method for estimation of ECV in patients has been sub-endocardial biopsy. This method, however, has relatively high inherent risk, is limited to small regions and is prone to sampling site error[47,48]. Visualization of large AMI and scar infarct on MRI and MDCT relies on the differences in signal intensity/attenuation between damaged and remote undamaged tissue to generate image contrast. It has been reported that undetected infarct account for at least 20% of all clinical cases of AMI and carry a prognosis as poor as detected ones[49]. Furthermore, signal intensity on DE-MRI is displayed on an arbitrary scale and tissue signals or contrast media concentration cannot be quantified. Patchy microinfarct and diffuse fibrosis in non-ischemic myocardial cardiomyopathies necessitate alternative techniques beyond current DE-MRI or DE-MDCT. Fast MRI and MDCT image acquisition, T1 sensitive sequences and

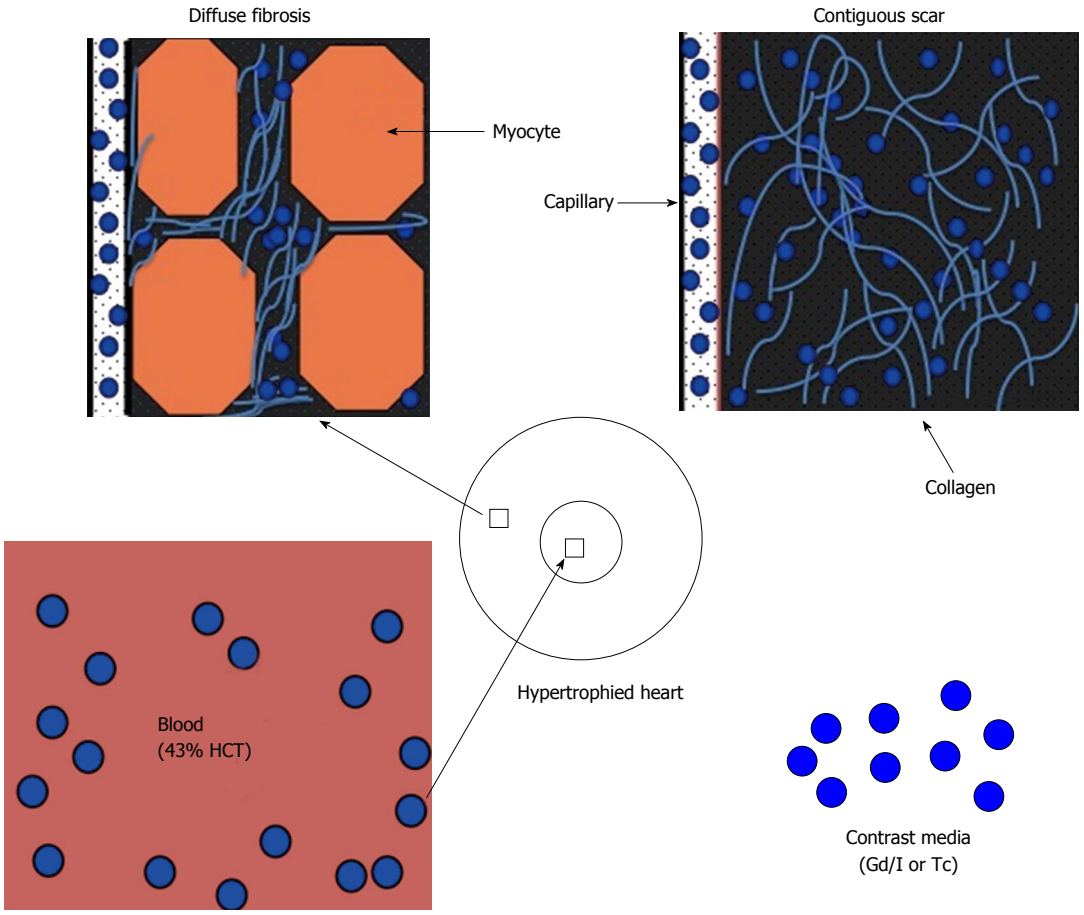

Figure 3 Schematic presentation of diffuse myocardial fibrosis in non-ischemic heart diseases (left) and contiguous chronic infarct (right) in ischemic heart disease. HCT: Hematocrit; Gd: Gadolinium; I: Iodine; Tc: Technetium.

contrast media allow the measurement of ECV. Look-Locker and echo planar MRI sequences as well as MDCT were used for non-invasive estimation of ECV. More recently, investigators have used MRI for T1 mapping and measuring ECV. The differences in regional T1 can be visualized as a grey-scale or color map[50-53]. Investigators also found that equilibrium contrast and T1 mapping methods provide information, beyond what is visually evident on DE-MRI/DE-MDCT[48,50]. These methods rely on three principles: (1) the measurement of global myocardial and blood T1 relaxation time/signal attenuation before contrast media administration; (2) a second measurement of T1 relaxation time/signal attenuation during contrast media equilibrium phase; and (3) a direct measurement of the blood contrast media volume of distribution. Extracellular inert gadolinium-based MR and iodinated computed tomography (CT) contrast media are crucial because they diffuse passively and rapidly between intravascular and extracellular compartments (Figure 4). Investigators have used longitudinal relaxation rate (1/longitudinal MR relaxation time; 1/T1) on MRI and myocardial signal attenuation on CT to quantify regional ECV[22,41-43,54]. The calculation of ECV is based on the ratio of the difference in signal attenuation or 1/T1 before and after administration of contrast medium in myocardium divided by the difference in signal attenuation or 1/T1 the blood pool. The increase in regional signal intensity on MRI and a decrease in attenuation on CT are attributed to the increase in ECV. Enhancement is expressed in Hounsfield or arbitrary units and employs tissue with lowest signal intensity as a reference for normality. The reason for using 1/T1 and not signal intensity on MRI is that signal intensity is not linearly correlated with contrast concentration. Unlike MR contrast media, signal attenuation after administration of CT contrast media is linearly correlated with contrast media concentration.

Our group was the first to find on MRI that the expansion in ECV is the mechanism for differential enhancement of infarct from healthy myocardium. We also demonstrated the peri-infarct zone[26,27,55]. Later, Klein *et al*[56] confirmed in patients with AMI that the partition coefficient is elevated in infarct compared to remote myocardium. Lee *et al*[28] found in healthy volunteers that the ECV is 27% ± 1% while Broberg *et al*[33] found it is slightly lower (22% ± 2%). Schelbert *et al*[29] claimed that similar ECV values can be obtained by bolus (21% ± 2%) and infusion (25% ± 2%) approaches.

Recent studies have also shown that MDCT allows for assessment of myocardial viability and visualization of coronary stenosis[57-59]. This imaging modality has been recently used for assessment of ECV in healthy volun-

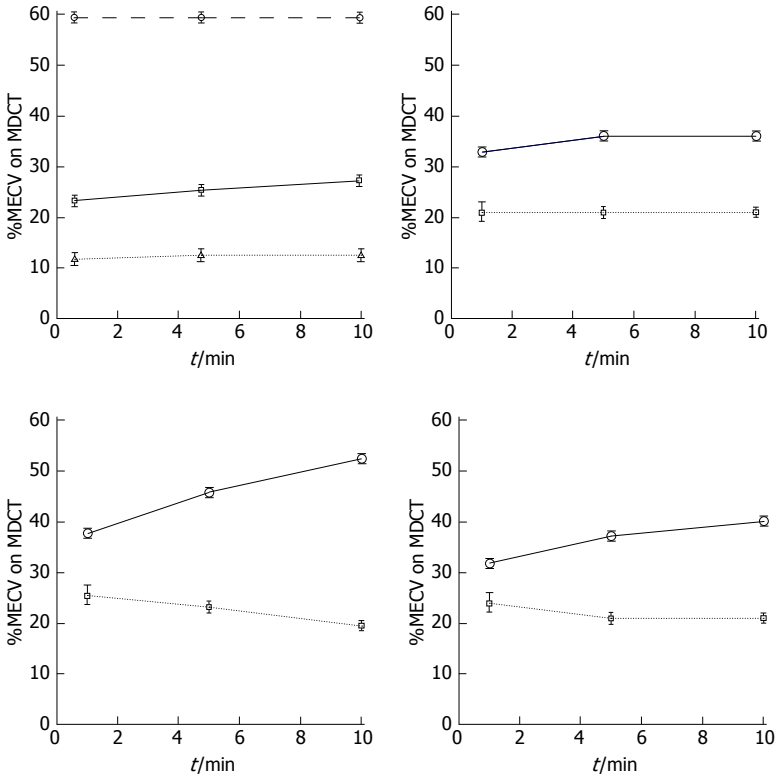

Figure 4 The top left plot shows the time course of equilibrium state of iodinated contrast media distribution in the extracellular volume of the blood (dashed line), healthy myocardium (solid line) and skeletal muscle (dotted line) over the course of 10 min using multi-detector computed tomography. The plots also demonstrate the remarkable difference in myocardial extracellular volume (MECV) in regions subjected to different insults. Differential increase in ECV was observed in ischemic myocardium after microembolization using 16 mm^3 (top right), 32 mm^3 (bottom left) or 90 min left anterior descending coronary artery occlusion/reperfusion (bottom right) compared with undamaged remote myocardium in all groups (dotted lines). MDCT: Multi-detector computed tomography.

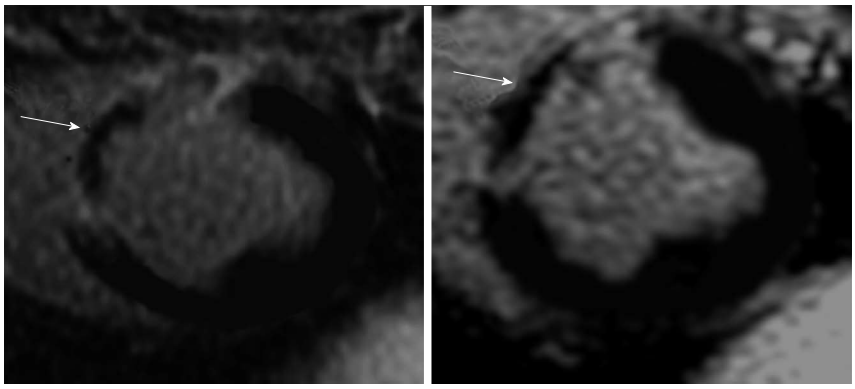

Figure 5 Delayed contrast enhanced magnetic resonance imaging of acute reperfused myocardial infarction (3 d) showing the hyperenhanced infarct and microvascular obstruction (arrows).

teers[60] and infarcted swine hearts[61]. Investigators found on MDCT that the ECV in healthy volunteers is between 23%-26%[62,63]. We found in swine model of AMI that the ECV of iodinated contrast media is 24% in normal and 68% in infarcted myocardium (Table 1). Furthermore, the distribution volume of iodinated contrast medium was lower at the peri-infarct zone than infarct, suggesting that this zone contains admixture of viable and nonviable myocardial cells. In chronic infarct, the ECV in remote undamaged myocardium decreased to 18% as a result of compensatory hypertrophy (Table 1). Schelbert *et al*[29] and Schmidt *et al*[64] also observed extensive heterogeneity in scar infarct, derangement in myocardial structure and accumulation of interstitial collagen that alters electrical activity and stiffens the myocardium. A clinical study showed that microvascular obstruction (MVO) occurs in > 30% of patients after ST segment elevation in myocardial infarction[65]. The presence of MVO in the infarct is problematic in the assessment of ECV, because the rate of contrast wash-in and wash-out is severely reduced in MVO zone and the equilibrium state condition takes 18 min post contrast injection[56]. Furthermore, the signal intensity of MVO zone is similar to remote undamaged myocardium (Figure 5).

Table 1 Multi-detector computed tomography quantification of extracellular volume in patchy microinfarct caused by microemboli, contiguous homogeneous infarct caused by left anterior descending coronary artery occlusion and remote undamaged myocardium

Intervention	Remote myocardium	Infarcted region
16 mm^3 and 3 d (AMI)	25 ± 4	33 ± 4[a]
32 mm^3 and 3 d (AMI)	24 ± 2	40 ± 1[a,c]
90 min LAD and 3 d (AMI)	24 ± 1	54 ± 4[a,e]
90 min LAD and 5 wk (scar)	18 ± 2[g]	68 ± 4[a,g]

[a]$P < 0.05$ *vs* remote myocardium; [c]$P < 0.05$ *vs* 16 mm^3 microemboli volume; [e]$P < 0.05$ *vs* 32 mm^3 microemboli volume; [g]$P < 0.05$ *vs* 90 min coronary artery occlusion/reperfusion at 3 d. AMI: Acute myocardial infarct.

MRI has inherent challenges that can be summarized as follows: (1) the presence of dental prostheses, orthopedic hardware or LV assist devices in the scanner; (2) slow acquisition time associated with high cost; (3) unsuitable for claustrophobic or uncooperative patients; (4) high technical and personnel requirements; and (5) MR contrast media provides a non-linear relationship between signal intensity and concentration[66]. On the other hand, MDCT has the potential to accommodate a growing population of patients who are counter indicated for MRI. MDCT has different challenges such as: (1) presence of radiation exposure precludes serial assessment; (2) low contrast between infarct and normal myocardium; (3) requires post imaging reconstruction of images; and (4) lack of sequences analogous to MRI that provide circumferential/longitudinal LV strain data (such as tagging, phase contrast velocity encoded cine) or information on interstitial edema and hemorrhage (such as T2-weighted and T2*-weighted imaging).

SPECIFIC CARDIOMYOPATHY

Myocardial fibrosis (scar) can be related to either ischemic MI, non-ischemic cardiomyopathy, or the combination[67]. For example, diffuse and contiguous fibrosis has been reported in heart failure, aortic valve disease and hypertrophic cardiomyopathy[29,68-70], while solely diffuse fibrosis has been observed in myocarditis, hypertrophic/dilated cardiomyopathy, amyloidosis, congenital heart disease, aortic stenosis, restrictive cardiomyopathy (hypereosinophilic and idiopathic types), arrythmogenic right ventricular dysplasia and hypertension.

ISCHEMIC MI

T1 mapping has been widely used to assess non-ischemic cardiomyopathies. Recent studies show that this technique also has the potential to assess ischemic MI. Klein *et al*[71] determined ECV in 11 patients with heart failure and found that the ECV is greater in the infarcted region (54% ± 1%) than remote myocardium (29% ± 2%). Ugander *et al*[20] measured ECV in 126 patients with myocardial infarct and non-ischemic myocardial fibrosis and detected sub-clinical abnormalities in remote myocardium using ECV measurements. They found that scar infarct has significantly higher ECV (51% ± 8%) than remote undamaged myocardium (27% ± 3%, $P < 0.001$, $n = 36$). In patients with non-ischemic cardiomyopathy, the ECV of atypically enhanced and remote myocardium were (37% ± 6% *vs* 26% ± 3%, $P < 0.001$, $n = 30$). They also observed in these patients that ECV of remote myocardium increased with the decrease of LV ejection fraction ($r = -0.50$, $P = 0.02$). A similar observation was reported in patients with heart failure[48]. It has been shown that beta-blockers and angiotensin-converting enzyme inhibitors reduce diffuse myocardial fibrosis in patients with heart failure and hypertensive heart disease, respectively[72,73], thus early measurement of ECV in suspected heart patients holds great promise for future clinical applications.

Coronary microembolization secondary to atherosclerotic plaque rupture occurs in spontaneously in patients with unstable angina/acute coronary syndromes[74-76] and accidentally during coronary interventions[77-83] with pathophysiological consequences, such as contractile dysfunction, perfusion-contraction mismatch, arrhythmias, myocardial ischemia and microinfarction[84-87]. Clinical studies showed that revascularization of an occluded coronary artery, using PCI, coronary artery stents, or bypass grafting, causes visible and invisible patchy microinfarct[88-91]. Both DE-MDCT and DE-MRI show promise in detecting patchy microinfarct caused by relatively large volumes of microemboli in a swine model (Figures 6 and 7)[92-99], while equilibrium contrast enhanced MDCT provides a quantitative estimation of ECV as a function of microemboli volumes and duration of coronary artery occlusion (Figure 8). Histologic examination reveals dislodged microemboli in blood vessels surrounded with microinfarct (Figure 9). Small particles cause MVO, patchy microinfarct[100], delayed infarct healing[101], perfusion deficits and disturbances in ECG signal conductivity[102,103]. ECV data derived from equilibrium contrast enhanced MDCT in a swine model are shown in Table 1.

NON-ISCHEMIC HEART DISEASES

Myocarditis

Myocarditis is the most frequent disease in patients with acute coronary syndrome and normal coronary arteries[104]. Acute myocarditis is associated with systemic viral disease[105,106]. At the early stage, there is myocardial injury/infarction, edema and regional/global LV dysfunction. On DE-MRI, myocardial injury is focal and located in the sub-epicardium and mid-myocardium (Figure 1). This method was also used for quantifying myocarditis[107,108]. Furthermore, T2-weighted MRI sequence was also useful in detecting acute myocarditis for detecting interstitial edema, as an integral part of the inflammatory response, in acute myocarditis. This non-invasive method is useful for patients with acute chest pain, positive serum troponin and angiographicallly normal coronary arteries[109,110]. Mahrholdt *et al*[110] speculated that the differential enhancement in the early phase is related to myocardial necrosis, but in the late phase to scar tissue. The sensitivity

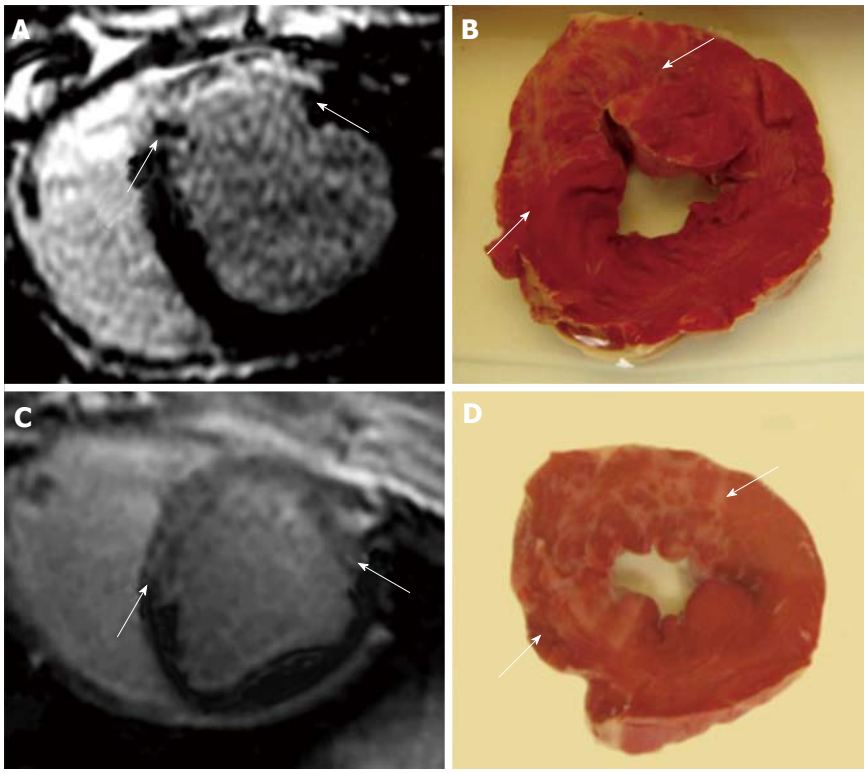

Figure 6 Delayed contrast enhanced magnetic resonance imaging (A and C) and histochemical triphenyltetrazplium chloride stain (B and D) show patchy microinfarct (arrows) 3 d after delivering 16 mm^3 (A and C) and 32 mm^3 (B and D) microemboli in the LAD coronary artery in a swine model.

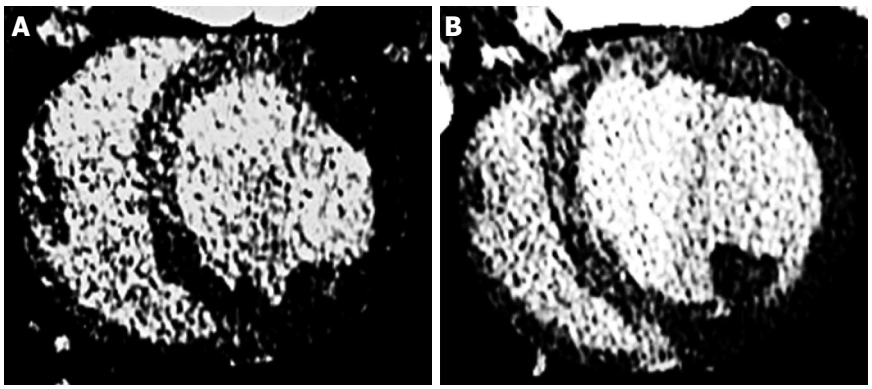

Figure 7 Delayed contrast enhanced multi-detector computed tomography 3 d after microembolization using 16 mm^3 (A) and 32 mm^3 (B) microemboli.

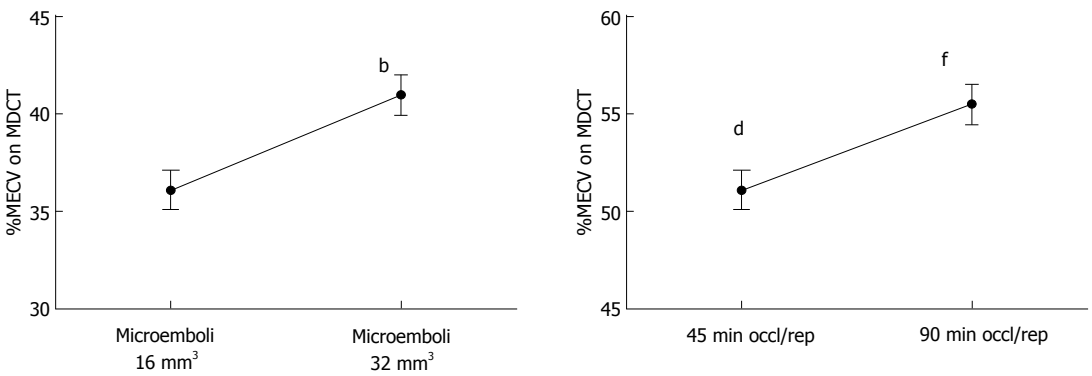

Figure 8 Gradient increase in myocardial extracellular volume as a function of microemboli volume (16 mm^3 *vs* 32 mm^3) and left anterior descending coronary artery occlusion time (45 min *vs* 90 min). $^{b}P < 0.01$ *vs* 16 mm^3, $^{d}P < 0.01$ *vs* 32 mm^3 and $^{f}P < 0.01$ *vs* 45 min left anterior descending coronary artery occlusion/reperfusion. MECV: Myocardial extracellular volume; MDCT: Multi-detector computed tomography.

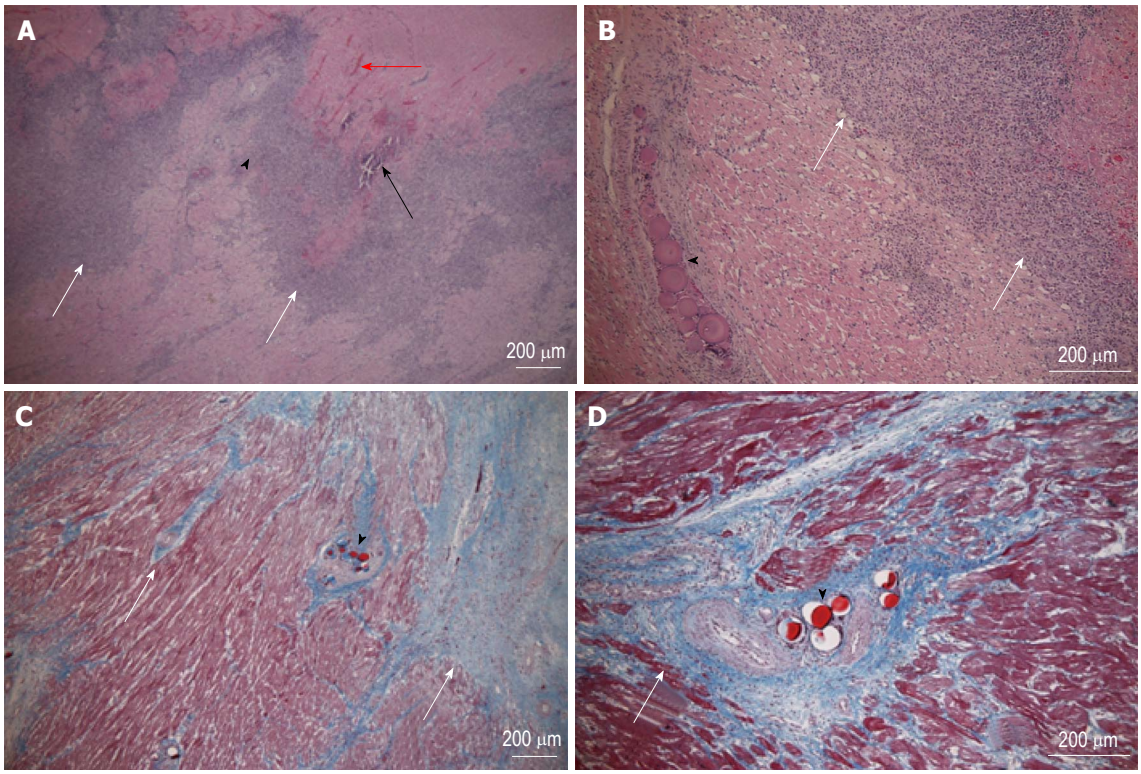

Figure 9 Acute (top row, hematoxylin and eosin stain) and chronic (bottom row, Masson trichrome stain) patchy microinfarct (white arrows) and microemboli (black arrowhead) distribution between viable myocardium at 3 d and 5 wk after embolization, respectively. Intramyocardial hemorrhage (red arrow) and calcium deposition (black arrow) are evident at 3 d on HE stain, but not at 5 wk. The magnifications are 40 × (A and C) and 100 × (B and D).

of DE-MRI in detecting myocarditis has been variable because of the different patterns (diffuse *vs* focal and acute *vs* chronic) of enhancement[111-115]. More recently, Kellman *et al*[52,116] found that ECV is significantly higher (44% ± 6%) in myocarditic tissue compared with remote myocardium using T1 mapping.

Hypertrophic cardiomyopathy

LV hypertrophy is an independent risk factor for sudden death[117,118]. Diffuse fibrosis is a common feature of hypertrophic cardiomyopathy and characterized by expansion of ECV and accumulation of interstitial collagen/fibrosis, which are hallmarks of pathologic remodeling[119]. Because ventricular hypertrophy prevalence estimates in the general population are as high as 16% the public health implications are significant[120].

DE-MRI in hypertrophic cardiomyopathy showed that both diffuse fibrosis and necrosis share mid-myocardium and sub-epicardium of the ventricular septum[3,16,121,122] (Figure 1). Díez *et al*[123] provided evidence for the role of fibrotic remodeling in hypertensive heart disease. Myocardial fibrosis in ventricular hypertrophy can impair the electrical coupling of myocardial cells by separating these cells with collagen and create a substrate of tissue heterogeneity from which re-entrant arrhythmias may arise[124].

Recently, Shiozaki *et al*[125] used MDCT to measure myocardial fibrosis in 26 patients with asymptomatic or mildly symptomatic hypertrophic cardiomyopathy. Myocardial fibrosis was present in 25 of 26 patients (96%) with mean fibrosis mass of 21 ± 16 g, while patients with appropriate implantable cardioverter defibrillator shocks for ventricular tachycardia/fibrillation had significantly greater myocardial fibrosis than patients without (29 ± 19 g *vs* 14 ± 8 g; $P = 0.01$). For a myocardial fibrosis mass of at least 18 g, sensitivity and specificity for appropriate implantable cardioverter defibrillator firing were 73% and 71%, respectively[125].

Clinical studies showed that myocardial fibrosis is reversible and treatable with timely intervention, therefore early detection and assessment is crucial. Investigators proposed that ECV measured on MRI may be useful in serially assessing the effects of therapies focused on proliferation of fibrosis in myocardium, such as the ACE-inhibitor (lisinopril)[73] and the angiotensin Ⅱ receptor antagonist losartan[73,123]. These therapies have been shown to reduce the LV wall stiffness and severity of myocardial fibrosis (measured on biopsy) and concomitantly improve diastolic function.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is an important cause of heart failure, sudden death and is the leading indication for cardiac transplantation in children and adults[126]. MRI provides accurate assessment of ventricular chamber size, wall thickness, and systolic function. The pattern of DE-MRI can differentiate ischemic *vs* non-ischemic heart dis-

ease[12]. For example, a sub-epicardial or mid-myocardial enhancement suggests non-ischemic cardiomyopathy. McCrohon *et al*[12] reported that specific patterns of enhancement have been purported in dilated cardiomyopathy to indicate a particular genetic association; however, these findings are nonspecific. Other investigators showed that 59% of patients with dilated cardiomyopathy and normal coronary arteries have no delayed enhancement. The other 28% of patients had mid-myocardial enhancement that is consistent with a non-ischemic cause and few patients had delayed endocardial enhancement that is consistent with ischemic cause. Others found in patients with dilated cardiomyopathy that the extent of fibrosis has been associated with increased risk of intraventricular systolic dyssynchrony[127].

CONGENITAL HEART DISEASE

Bandula *et al*[54] developed an equilibrium CT protocol, using iohexol at 300 mgI/mL delivered as a bolus of 1 mg/kg and a rate of 3 mL/s, followed immediately by an infusion of 1.88 mL/kg per hour with CT imaging before and at 25 min after injection of bolus of contrast agent. The ECV within the myocardial septum in 23 patients with severe aortic stenosis was measured using both equilibrium CT and equilibrium MRI in patients. Biopsy samples of the myocardial septum were collected during valve replacement surgery and used for histologic quantification of extracellular fibrosis. They found that the mean percentage of histologic fibrosis was 18% and a significant correlation between both equilibrium MDCT derived and equilibrium MRI derived ECV and percentage of histologic fibrosis (r = 0.71, P < 0.001 and r = 0.84[128], respectively). Equilibrium MDCT derived ECV was well correlated to equilibrium MRI derived ECV (r = 0.73). Broberg *et al*[33] also found the fibrosis index was significantly elevated in patients with congenital heart disease compared with normal controls (32% ± 5% *vs* 25% ± 2%; P = 0.001), ECV values were highest in patients with a systemic right ventricle (L-transposition of the great arteries or D-transposition with prior atrial redirection surgery) and cyanosis (35% ± 6%; P < 0.001 and 34% ± 6%; P < 0.001, respectively).

Ho *et al*[129] were unable to visualize diffuse myocardial fibrosis in the setting of dilated cardiomyopathy using DE-MRI, but by T1 mapping technique, they found that fibrotic tissue has lower T1 relaxation time compared with healthy myocardium. Nacif *et al*[22] successfully measured interstitial myocardial fibrosis in hypertrophied hearts using ECV measurement method. Others found that ECV is higher in subjects with hypertrophic cardiomyopathy (36% ± 3%) than control volunteers (27% ± 1%, P < 0.001). Furthermore, the ECV in hypertrophic hearts is heterogeneous and had substantially lower mean value than for scar infarct (69% ± 9%, P < 0.001)[116].

Neilan *et al*[130] studied patients with hypertension and recurrent atrial fibrillation referred for pulmonary vein isolation underwent a contrast-enhanced MRI for measurement of ECV and were followed up prospectively for a median of 18 mo. These patients had elevated LV volumes, LV mass, left atrial volumes, and increased ECV (patients with atrial fibrillation = 34% ± 3%; healthy control volunteers = 29% ± 3%; P < 0.001). They found positive associations between ECV and left atrial volume (r = 0.46, P < 0.01) and LV mass, but negative association between ECV and diastolic function (r = -0.55, P < 0.001). Furthermore, they demonstrated that each 10% increase in ECV is associated with a 29% increased risk of recurrent atrial fibrillation and concluded that ECV was the strongest predictor of the primary outcome of recurrent atrial fibrillation and the secondary composite outcome of recurrent atrial fibrillation, heart failure admission, and death.

AMYLOID

Amyloidosis refers to soluble proteins become insoluble, which are deposited in the extracellular compartment of various tissues, resulted in disrupting function[131]. Amyloid heart disease is a systemic infiltrative disorder[132]. It has been hypothesized that amyloidosis in myocardium is facilitated by hypoxia that results from capillary dysfunction. Endomyocardial biopsy has been considered to be the gold standard for demonstrating amyloid deposition in the heart. The most useful stain in the diagnosis of amyloid is Congo red, which, combined with polarized light, makes the amyloid proteins appear apple green on microscopy.

Noninvasive diagnosis of myocardial amyloidosis on MRI is difficult when this disease is accompanied with LV wall thickening related to hypertension[133]. Amyloid heart reveals small infarcted areas on unenhanced T1 and T2 MRI[134]. DE-MRI in myocardial amyloidosis is inherently challenging because amyloid infiltration within the extracellular compartment reduces the differences in contrast between LV chamber blood and myocardium such that the two regions may null simultaneously[133,135]. On the other hand, other investigators found that the appearance of global and subendocardial enhancement On DE-MRI, is a unique characteristic of cardiac amyloid and correlates with prognosis[136]. ECV was also measured in this disease using T1 mapping and gadolinium-based contrast media[34,137]. It was found that the median ECV is significantly higher in infiltrative diseases (49% of tissue volume) compared with non-amyloid cardiomyopathy patients (33%) and volunteers (24%). The ECV strongly correlated with visually assessed segmental DE-MRI (r = 0.80) and LV mass index (r = 0.69), reflecting severity of myocardial infiltration. Sado *et al*[35] reported that the ECV expansion is higher in systemic amyloidosis than in any other measured myocardial diseases, such as Anderson-Fabry disease, dilated cardiomyopathy, hypertrophic cardiomyopathy and hypertrophic cardiomyopathy, outside of the infarct zone. In another MRI study, Bandula *et al*[54] studied 40 healthy volunteers and 67 patients with systemic amyloid light-chain amyloidosis of the upper abdomen using equilibrium MRI. They found that ECV was measured in the liver, spleen, and paravertebral mus-

cle. ECV was highest in the spleen (34%), followed by liver (29%) and muscle (9%). In patients with amyloidosis ECVs measured within the spleen (39%), liver (31%), and muscle (16%) were significantly higher than in healthy controls.

DIABETES

Type 2 diabetes mellitus promotes the expansion of ECV and increase vulnerability to a variety of clinical problems. Expansion of ECV is associated with mechanical dysfunction[138-140] vasomotor dysfunction[141], arrhythmia[142] and mortality[40,142]. Several studies support the notion that expansion of ECV contributes to adverse outcomes in diabetic patients. This notion is based on medications blocking the renin-angiotensin-aldosterone system ameliorate expansion of ECV[143-145]. In a recent study, Wong *et al*[40] examined 1176 patients referred for MRI with and without diabetes. They found that diabetic patients (n = 231) had higher median ECV than non-diabetic patients (n = 945) (30.2% *vs* 28.1%, $P < 0.001$). More importantly, expansion of ECV measured by MRI appeared to be ameliorated with medications blocking the renin-angiotensin-aldosterone system. They concluded that diabetes is associated with increased ECV, which may be an important intermediate phenotype in diabetic individuals that is detectable by MRI-ECV and could be used as a biomarker to follow the effectiveness of diabetic treatment.

The ability to distinguish the sub-endocardial, mid-myocardium or sub-epicardial regions with true pathophysiology is a major limitation of ECV measurement. The presence of intra-myocardial fat also affects ECV measurements. The other major limitations of non-invasive MRI and MDCT in measuring ECV are the quality of the acquired images, presence of microvascular obstruction (may require continuous contrast infusion to reach equilibrium state of distribution)[23,146] and the binding of contrast media to serum albumin that increases the relaxivity of some extracellular contrast media and decreases its diffusion[147]. ECV measurement or T1 mapping are not intended to replace DE-MRI or DE-MDCT, which are excellent at depicting large infarction, but rather to be used in concert with cine and perfusion techniques. In tissues with a large intravascular compartment (such as the liver), the values of ECV may be overestimated by the equilibrium technique. The noise in the MDCT images stemming from beam-hardening artifacts originating from dense vertebral endplates is another limitation. Potential technical improvements in ECV measurements include faster processing of image data that reduce reliance on expert interpretation and increase the speed of image data processing.

Limitation

There are still multiple limitations in using MRI and MDCT for the assessment of ECV, such as the radiation dose, availability of experienced staff, extensive labor and the usage of contrast media. The side effects and cost of contrast media as well as costs of the scanner time should be considered. Monitoring patients with severe heart failure or acute myocardial infarct inside the MR scanner is a difficult task.

FUTURE APPLICATIONS OF ECV MEASUREMENTS

New drugs, transplantation of different stem cells and local injection of genes have been recently introduced as potential therapies for infarct healing and myocardial regeneration. Chronological estimation of ECV may be useful for documenting the effectiveness of these therapies to promote myocardial viability. Recent clinical and experimental studies have shown that stem cells reduce infarct size and improve LV function in both AMI and scar[148-151]. In a recent study Wong *et al*[40] described an association between measurements of ECV and clinical outcomes in a large patient cohort undergoing MRI. They analyzed 793 patients with known or suspected coronary artery disease, cardiomyopathy, or arrhythmias. They excluded patients with cardiac amyloidosis, infiltrative disease, hypertrophic cardiomyopathy and areas of delayed contrast enhancement consistent with classic pattern of myocardial infarction. They found that ECV ranged from 22%-26% in healthy volunteers, whereas it ranged from 21%-46% in the patients. Over a median follow-up period of 6 mo, 39 patients died, and 43 experienced a major adverse event (composite of death/cardiac transplant/LV assist device implantation). In multivariable modeling, ECV was associated with adverse cardiac events. For every 3% increase in ECV, there was a 50% increased probability of an adverse cardiac event. Furthermore, the potential of MRI/MDCT in guiding intramyocardial therapies and providing reliable and reproducible assessment of myocardial viability, perfusion and function has been recently reviewed[152-154]. Further improvement in image resolution and processing of data would promise early detection and better pathophysiological understanding of diffuse fibrosis, myocardial infarct and help in timely intervention and therapy[155].

In conclusion, since ischemic and non-ischemic myocardial diseases are characterized by an increase in the ECV, these pathologies can be characterized and may be differentiated on equilibrium contrast enhanced MRI/MDCT and T1 mapping. ECV data may provide a useful tool for diagnosis and treatment monitoring in ischemic and non-ischemic myocardial diseases (such as patchy microinfarct after percutaneous coronary intervention), compensatory hypertrophy, inflammation, heart failure and hypertrophic cardiomyopathy. The challenges lie in developing fast and sensitive imaging sequences, simple software for analysis, which will facilitate the ECV assessment approach into clinical routine practice.

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P- Reviewer: Kolettis TM, Lazzeri C, Lee TM **S- Editor**: Song XX
L- Editor: A **E- Editor**: Liu SQ

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v6.i11.1209

World J Cardiol 2014 November 26; 6(11): 1209-1217
ISSN 1949-8462 (online)

REVIEW

Blood glucose management in the patient undergoing cardiac surgery: A review

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Received: December 28, 2013 Revised: August 27, 2014
Accepted: September 16, 2014
Published online: November 26, 2014

Abstract

Both diabetes mellitus and hyperglycemia *per se* are associated with negative outcomes after cardiac surgery. In this article, we review these associations, the possible mechanisms that lead to adverse outcomes, and the epidemiology of diabetes focusing on those patients requiring cardiac surgery. We also examine outpatient and perioperative management of diabetes with the same focus. Finally, we discuss our own efforts to improve glycemic management of patients undergoing cardiac surgery at our institution, including keys to success, results of implementation, and patient safety concerns.

Key words: Blood glucose management; Glycemic management; Cardiac surgery; Cardiothoracic surgery; Diabetes; Diabetes mellitus; Hyperglycemia; Perioperative

Core tip: There is a growing body of evidence that moderate glycemic control (*e.g.*, 120-180 mg/dL, 6.7-10.0 mmol/L) is an appropriate goal in cardiac surgery. Achieving this goal can be accomplished by adopting a multidisciplinary approach, addressing the entire continuum of care, demanding a short project timeline, and identifying gaps in current management.

Reddy P, Duggar B, Butterworth J. Blood glucose management in the patient undergoing cardiac surgery: A review. *World J Cardiol* 2014; 6(11): 1209-1217 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1209.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1209

INTRODUCTION

Diabetes is a common comorbidity in patients who require cardiovascular surgery. Worldwide, the total number of people with diabetes is projected to increase from 171 million in 2000 to 366 million in 2030[1]. According to data from the National Diabetes Fact Sheet released in January of 2011, there are 25.8 million individuals with diabetes-which is more than 8% of the population-in the United States. In addition, based on fasting blood glucose and hemoglobin A1c levels, the authors of the National Diabetes Fact Sheet estimate that there are an additional 7 million people with undiagnosed diabetes and 79 million who are prediabetic and have a greatly increased risk of developing diabetes. The American Diabetic Association and the American College of Endocrinology classify prediabetics as those individuals with fasting blood glucose levels within the 100-125 mg/dL (5.5-6.9 mmol/L) range, while those with fasting blood glucose levels greater than 126 mg/dL (7.0 mmol/L) are considered to have diabetes mellitus[2]. An estimate of the total cost of diagnosed diabetes in the United States was $245 billion in 2012: $176 billion for direct medical costs and $69 billion in reduced productivity[3]. Clearly, diabetes represents a major medical-economic problem in the developed world and the presence of diabetes complicates the management of the patient undergoing cardiovascular surgery. In this

review we will provide an overview of current data on best practices, techniques, and outcomes of glucose management in patients undergoing cardiovascular surgery. In addition, we will discuss how physicians can incorporate these findings into their own practices based on our own experiences and those of others.

HYPERGLYCEMIA AND ADVERSE OUTCOMES

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia as a result of a deficiency in insulin secretion, an increase in insulin resistance, or a combination of both. Type 1 (or "juvenile") diabetes mellitus represents 5%-10% of all patients with the diagnosis of diabetes and is due to complete lack of insulin secretion by the pancreas. Type 2 diabetes mellitus, representing 90%-95% of all patients with the diagnosis of diabetes, is primarily due to insulin resistance resulting from multiple etiologies including genetic predisposition, unhealthy diet, lack of physical activity, and a characteristic central pattern of weight gain. Approximately 28% of diabetics will undergo coronary artery bypass grafting[4,5].

Patients with diabetes have increased morbidity and mortality following coronary artery surgery[6-8]. The incidence of stroke, renal failure, and sternal wound infections is greater in diabetic patients[9-11]. Diabetics have a 44% greater risk for readmission (following hospital discharge after coronary artery surgery) for any cause and a 24% greater risk for readmission for heart-related issues than comparable nondiabetic patients who have undergone coronary artery surgery[12,13].

DIABETES AND CARDIAC DISEASE

Hyperglycemia and insulin resistance lead to an alteration in free fatty acid metabolism, endothelial dysfunction, and resultant thrombogenesis[14,15]. Hyperglycemia-induced endothelial dysfunction is the result of imbalance between nitric oxide bioavailability and the accumulation of reactive oxygen species, the latter triggered by activation of protein kinase C. Hyperglycemia also induces the generation of superoxide anion which inactivates nitric oxide to form peroxynitrite which induces substrate nitration[16]. Diminished nitric oxide availability is a strong predictor of adverse nitric oxide outcomes[17]. Protein kinase C also triggers the production of endothelin-1, which causes vasoconstriction, vascular inflammation and platelet aggregation[18].

Hyperglycemia results in the production of advanced glycation products (AGE) and their cell surface receptor-RAGE. RAGE contributes to the inflammatory response by activating three key transcription factors: nuclear factor κB, activated protein-1, and early growth response, all three of which are suppressed by insulin under normal conditions[19-21]. Endothelial dysfunction also results from an increase in the synthesis of vasoconstrictors and prostanoids. Increased adiposity, a common feature in diabetics, is strongly associated with increased concentrations of inflammatory markers and free fatty acids[22]. Insulin resistance also promotes atherosclerosis by increasing triglycerides, apolipoprotein B, and low-density lipoproteins. In addition, concentrations of very low-density lipoproteins are generated in response to increased synthesis of apolipoprotein B[23]. Coronary events in diabetics result from a prothrombotic state. Under normal circumstances, circulating concentrations of insulin inhibit platelet aggregation and thrombosis by inhibiting tissue factor and inhibiting production of plasminogen activator inhibitor-1 (PAI-1). In contrast, insulin resistance promotes increased synthesis of PAI-1 and fibrinogen as well as reduced production of tissue plasminogen activator. These factors collectively result in atherothrombosis[24].

Key contributors to hyperglycemia-induced vascular damage include a newly identified class of RNAs termed micro RNAs (miRNAs) which regulate gene expression at the post-transcription level[25,26]. Diabetics display a significant deregulation of the miRNAs involved in angiogenesis, vascular repair, and endothelial function[27]. Ultimately, increased oxidative vascular stress causes thrombosis, impaired platelet function, and plaque rupture-all of which will result in reduced patency of grafts, reduced ischemic events, and a greater incidence of repeat revascularization in both coronary artery disease and diabetes[28].

Hyperglycemia is associated with worse outcomes after acute coronary syndrome, acute myocardial infarction, or coronary artery surgery. Capes and coworkers performed a meta-analysis of 15 studies of patients without the diagnosis of diabetes who had glucose concentrations more than or equal to 110 mg/dL (6.1 mmol/L). Such patients had a 3.9 fold higher risk of death than patients without diabetes who had lower glucose concentrations. In patients without diabetes, glucose concentrations greater than 180 mg/dL (10 mmol/L) on admission were associated with increased risk of congestive heart failure or cardiogenic shock. Diabetic patients with glucose concentrations equal to or greater than greater than 180 mg/dL (10 mmol/L) had a moderately increased risk of death[29]. Kosiborod *et al*[30] analyzed admission glucose concentrations in 141680 elderly patients who were hospitalized for acute myocardial infarction. Twenty-six percent of these patients having glucose levels > 240 mg/dL (13.3 mmol/L) did not have the diagnosis of diabetes. Increased glucose concentrations were associated with a greater risk of 30-d mortality in patients without a previous diagnosis of diabetes (10%-39%) as compared to those patients with a diagnosis of diabetes (16%-24%)[30]. In another review of 2127 patients with acute coronary syndrome, Foo *et al*[31] showed a strong relationship between elevated glucose concentrations and an increased incidence of left ventricular failure and death. Meier *et al*[32] analyzed data from 227 type 2 diabetics and 287 nondiabetics who were diagnosed with acute myocardial infarction. Hyperglycemia at the time of myocardial infarction was associated with shorter survival, larger infarct size, and an increased incidence of adverse outcomes in both diabetics and nondiabetics[32].

Kubal *et al*[11] analyzed the association of diabetes morbidity and mortality in 6033 patients undergoing isolated coronary artery bypass surgery. Insulin dependent diabetes was associated with an increased incidence of acute renal failure (adjusted OR = 4.5), deep sternal wound infection (adjusted OR = 2.96), and prolonged postoperative stay (adjusted OR = 1.60)[11]. Gandhi *et al*[33] analyzed glucose measurements and outcomes from 409 cardiac surgery patients and found that a 20 mg/dL (1.1 mmol/L) increase in mean intraoperative glucose concentration was associated with a 30% increase of an adverse event. Doenst *et al*[34] in a retrospective review of 6280 cardiac surgery patients showed that a peak glucose of > 360 mg/dL (20.0 mmol/L) was associated with an increased likelihood of adverse events and mortality. Ascione *et al*[35] in a retrospective review of 8727 cardiac surgery patients showed that glucose level > 200 mg/dL (11.1 mmol/L) at any time during the first 5 postoperative days was associated with an increased likelihood of in-hospital morbidity and mortality. Taken together, these studies suggest that hyperglycemia during acute coronary syndromes following cardiac surgery increases the likelihood of morbidity and mortality.

The Portland Diabetic Project as described in publications by Furnary *et al*[36] provides strong evidence for an adverse linkage between hyperglycemia in diabetics undergoing cardiac surgery. This nonrandomized but prospective interventional trial involved 4864 diabetics. These investigators focused on the relationship between the use of a continuous insulin infusion and the incidence of perioperative mortality or deep sternal wound infections, and on length of hospital stay. Hyperglycemia was found to be an independent factor for increasing the likelihood of perioperative mortality. Those patients in which blood glucose remained < 150 mg/dL (8.3 mmol/L) were less likely to experience mortality (57% less likely) or deep sternal wound infections (66% less likely) as compared to diabetic patients whose blood glucose were "out of range". Butterworth *et al*[37] conducted a prospective, randomized trial of 381 nondiabetic patients undergoing cardiac surgery, where one group received a continuous insulin infusion attempting to maintain intraoperative blood glucose level less than a target level of 100 mg/dL (5.5 mmol/L) while the other group received no insulin. There was no difference in neurological or neuropsychological morbidity or in mortality between the two groups despite the insulin-receiving group having significantly lower intraoperative glucose levels[37].

Hyperglycemia associates with adverse outcomes in patients with critical illness. Van den Berghe *et al*[38] conducted a landmark study of 1548 ventilated patients. One group received insulin only if blood glucose exceeded 215 mg/dL (11.9 mmol/L) and had a target range of 180-200 mg/dL (10.0-11.1 mmol/L) while the other group received a continuous insulin infusion to maintain a blood glucose level between 80-110 mg/dL (4.4-6.1 mmol/L). Although intensive insulin therapy significantly reduced mortality in those patients requiring more than five days in the intensive care unit (ICU), there was no difference in morbidity or mortality in those with ICU stays shorter than 3 d. Bhamidipati *et al*[39] studied 4658 patients with known diabetes or perioperative hyperglycemia who were undergoing isolated coronary artery surgery. Patients in this study were stratified into a "tight group" (blood glucose concentrations < 126 mg/dL, 7.0 mmol/L), a "moderate group" (blood glucose concentrations 127-179 mg/dL, 7.0-9.9 mmol/L), and a "liberal group" (blood glucose concentrations > 180 mg/dL, 10.0 mmol/L). The moderate group had the lowest mortality 2.0% *vs* 2.9% in the tight group. Risk adjusted incidence of major complications was also less in the moderate control group suggesting that moderate control of hyperglycemia may be ideal for those diabetics undergoing isolated coronary artery surgery[39].

OUTPATIENT DIABETES MANAGEMENT

Many patients who present for cardiac surgery have undiagnosed diabetes or metabolic syndrome. Such patients may have abnormally high blood glucose levels in the perioperative period and a significantly increased risk of adverse outcome. Of late, many institutions have formed multidisciplinary task forces involving the participation of representatives from pharmacy, anesthesiology, surgery, nursing, critical care, and endocrinology to provide better blood glucose control in patients undergoing and recovering from cardiac surgery. Some things are clear: diabetic care should be initiated in the preoperative period and not deferred until after the operation.

If possible, all cardiac surgical patients should have preoperative hemoglobin A1c (HbA1c) measurement. HbA1c levels reflect the adequacy of glycemic control in the 6-8 wk preceding the measurement. A HbA1c level of less than 7% indicates adequate glycemic control[40]. Halkos *et al*[41] found a significant association between HbA1c > 7.0% and a greater incidence of myocardial infarction, deep sternal wound infections, and mortality in patients undergoing coronary artery surgery. Some clinicians argue that elective coronary artery bypass surgery should be delayed when elevated HbA1c levels are detected to reduce the likelihood of perioperative complications. In a prospective study conducted by Lazar *et al*[42], preoperative HbA1c levels were not predictive of 30 d morbidity, length of stay, or mortality following coronary artery surgery if glycemic control was achieved. However, this was a small study (n = 167) and a larger cohort would be needed to establish a definite conclusion regarding negative outcome associations with an elevated preoperative HbA1c measurement[42].

The current recommendation from the Society of Thoracic Surgeons practice guideline is that oral hypoglycemics should be withheld for at least 24 h prior to surgery. Insulin dependent diabetics should not receive their nutritional insulins (regular, aspart, glulisine, lispro) once they have begun to fast after a meal the evening prior to surgery. neutral protamine hagedorn insulin (and other

intermediate or longer-acting insulins) should be reduced (on the day of surgery) from the usual dose to avoid intraoperative hypoglycemia. Many experienced clinicians will omit all subcutaneous insulin dosing on the day of surgery and substitute intravenous insulin infusion. Patients with a blood glucose concentration greater than 180 mg/dL (10.0 mmol/L) while awaiting elective surgery should receive a continuous insulin infusion to maintain their glucose concentration below 150 mg/dL (8.3 mmol/L). Once the patient is anesthetized we recommend that blood glucose be managed as if the patients were in the critical care unit (and we do not recommend "tight" control within the limits that would be used in ambulatory practice). Intraoperative blood glucose concentrations should be measured no less frequently than hourly. Patients with abnormal kidney function should be identified preoperatively since there is a greater incidence of perioperative hypoglycemia in these patients[43,44].

HISTORY OF PERIOPERATIVE BLOOD GLUCOSE MANAGEMENT

Perioperative management of diabetes mellitus has greatly evolved over the past several decades[45]. The scientific literature first recognized the importance of perioperative blood glucose control in the surgical patient in the early 1970s[46]. At that point, the primary concern for anesthesiologists was avoiding ketoacidosis and acute hypoglycemia. Dr. Jurgen Steinke described the common techniques employed at the time in his 1970 review. He described obtaining urine specimens every four hours perioperatively and administering "sliding scale" subcutaneous insulin based on urine glucose measurements (*e.g.*, 15 U for a 4+ urine specimen, 10 U for a 3+ urine specimen, *etc.*). Dr. Steinke recognized the many flaws of this technique, including the assumption of normal renal function and that treatment was reserved for glucosuria and not for hyperglycemia *per se*. While the deleterious effects of chronic hyperglycemia on the cardiovascular system were recognized at that time, the morbidity associated with perioperative hyperglycemia in cardiac surgery patients had not yet been appreciated. Thus, no special considerations were made for patients undergoing cardiac surgery.

Throughout the 1970s, infused insulin became more widely used in caring for the patient with critical illness[47-50]. Specifically, efforts to treat diabetic ketoacidosis with low-dose, continuous, infused insulin were met with considerable success[49]. Therefore, investigators began studying the potential role of continuous insulin in diabetic patients undergoing surgery[50]. In one report, Taitelman *et al*[50] described achieving better control of their diabetic surgical patients' blood glucose with continuous insulin infusion (as compared to conventional subcutaneous "sliding scale") as well as the unfortunate side effect of a more frequent incidence of hypoglycemia.

During the 1980s, a body of evidence was developed that linked poor glucose control in diabetics with poor wound healing and increased rates of infection[51,52]. The implications that this would have on diabetic patients undergoing surgery were clear, and by the late 1980s, algorithms for postoperative insulin infusions were widely available[53]. In 1987, Watts *et al*[53] advocated a target plasma glucose range of 120 to 180 mg/dL (6.7 to 10.0 mmol/L) at a time when ideal blood glucose ranges were not well established. As a result of the lack of consensus on so many issues related to diabetic management, there was marked variation in accepted clinical practice.

In the 1990s, a multitude of outcomes-oriented clinical trials addressing diabetes in cardiothoracic surgery patients was reported[12,54,55]. Now there was convincing evidence that diabetics were more likely to have wound infections, prolonged ICU length of stay, and mortality after cardiac surgery. Nevertheless, there remained no consensus on the ideal target range for blood glucose measurements. Consensus was reached (but only briefly) after Van den Berghe *et al*[38] 2001 prospective, randomized, controlled trial on intensive insulin therapy in 1548 critically ill patients. This study, which came to be known as the Leuven Surgical Trial, demonstrated reduced 12-mo mortality among critically ill patients when blood glucose levels were maintained in the 80-110 mg/dL (4.4-6.1 mmol/L) range as compared to 180-200 mg/dL (10.0-11.1 mmol/L). Mortality was 4.6% in the tight control group compared to 8.0% in the standard control group. The improved outcomes in the tight control group were attributed to fewer instances of multiple organ failure associated with sepsis. This led to an abrupt shift in how physicians cared for patients with critical illness. The publication of this study marked the beginning of the era of "tight control" in which standard care for critically ill patients, including those recovering from cardiothoracic surgery, mandated insulin infusion therapy.

Reports of several other important studies appeared during this time. For instance, the Portland Diabetic Project created and analyzed a large database of cardiac surgery patients (n = 5510) who underwent surgery between 1987 and 2005[56]. These authors concluded that postoperative hyperglycemia rather than presence or absence of the diagnosis of diabetes was the true driver of increased mortality risk in the cardiac surgery patient. Van den Berghe *et al*[57,58] also continued to study the role of intensive insulin therapy in the critically ill during this time. In 2006, the group published two studies confirming the benefits of intensive insulin therapy in reducing the risk of morbidity and mortality in both medical and surgical ICU patients. These findings reinforced the prevailing notion that the tight control [*i.e.*, the 80-110 mg/dL (4.4-6.1 mmol/L) range that is used for tight control in ambulatory, nonsurgical practice] was also the ideal range for surgical patients in the perioperative period.

The era of tight glucose control in patients with critical illness came to an abrupt end with the publication of the NICE-SUGAR Study[59]. These investigators were famously unable to reproduce the findings of the Leuven Surgical Trial. Here, 6104 patients were randomly assigned to either intensive control (target 81 to 108 mg/dL, 4.5

to 6.0 mmol/L) or standard control [target 180 mg/dL (10.0 mmol/L) or less]. Rather than experiencing the mortality benefit that Van den Berghe *et al*[38,57,58] found, the intensive control group actually experienced a greater incidence of all-cause mortality at 90 d after surgery (27.5% mortality in intensive group *vs* 24.9% in conventional group; 95%CI for the OR = 1.02-1.28; $P = 0.02$). These results caused physicians around the world to scale back the aggressive glycemic management protocols that were instituted during the era of tight control.

More recent studies were also unable to demonstrate a benefit of tight control[60]. In 2011, Lazar *et al*[60] compared aggressive glycemic control (90-120 mg/dL, 5.0-6.7 mmol/L) against moderate control (120-180 mg/dL, 6.7-10.0 mmol/L) in 82 patients undergoing coronary artery bypass graft surgery. In this report, there was no difference in the incidence of adverse events between the groups (17 events in the moderate group compared to 15 events in the aggressive group, $P = 0.91$). Furthermore, hypoglycemic events were more frequent in the aggressive group (4 events in the moderate group compared to 30 events in the aggressive group, $P < 0.0001$). These results support the conclusions of NICE-SUGAR and suggest that moderate control (*e.g.*, 120-180 mg/dL, 6.7-10.0 mmol/L) may provide an appropriate balance between preventing adverse outcomes associated with perioperative hyperglycemia and avoiding dangerous hypoglycemic events.

ONGOING STUDIES

Diabetes and glucose control in the patient undergoing cardiac surgery remain subjects of intense research interest. For example, ongoing studies include "improving neurologic outcomes in diabetics undergoing cardiac surgery," a clinical study ongoing at Wake Forest University (5R01HL089115). This study will address how genotype and phenotype interact to produce outcomes in patients with perioperative glucose intolerance. The hope is that with better classification of disease, management can be better tailored to meet the needs of individual patients. Ultimately, better perioperative management could lead to better perioperative glucose control and improved neurologic, neurobehavioral and other outcomes.

CURRENT GUIDELINES

After publication of the conflicting results from the Leuven Surgical Trial and the NICE-SUGAR Study, the ideal blood glucose range for patients with critical illness (and especially patients undergoing cardiac surgery) is once again ambiguous. Nevertheless, the 2009 Society of Thoracic Surgeons (STS) Guidelines are considered the current standard[61]. The following Class I recommendations are included among these guidelines: (1) Patients taking insulin should not receive their nutritional insulin (lispro, aspart, glulisine, or regular) after receiving their dinnertime dose the evening prior to surgery (level of evidence = B); (2) Scheduled insulin therapy, using a combination of long-acting and short-acting subcutaneous insulin or an insulin infusion, should be initiated to achieve glycemic control for in-hospital patients awaiting surgery (level of evidence = C); (3) All oral hypoglycemic agents and noninsulin diabetes medications should be withheld for 24 h prior to surgery (level of evidence = C); (4) All patients with diabetes undergoing cardiac surgical procedures should receive an insulin infusion in the operating room and for at least 24 h postoperatively to maintain serum glucose levels $\leqslant$ 180 mg/dL (10.0 mmol/L) (level of evidence = B); (5) Glucose levels > 180 mg/dL (10.0 mmol/L) that occur in patients without diabetes only during cardiopulmonary bypass may be treated initially with a single or intermittent dose of intravenous (*iv*) insulin as long as levels remain $\leqslant$ 180 mg/dL (10.0 mmol/L) thereafter. However, those patients with persistently elevated serum glucose (> 180 mg/dL, 10.0 mmol/L) after cardiopulmonary bypass should receive a continuous insulin drip, and an endocrinology consult should be obtained (level of evidence = B); (6) Patients (with or without diabetes) having persistently elevated serum glucose (> 180 mg/dL, 10.0 mmol/L) should receive *iv* insulin infusion to maintain serum glucose < 180 mg/dL (10.0 mmol/L) for the duration of their ICU care (level of evidence = A); and (7) Before intravenous insulin infusions are discontinued, patients should be transitioned to a subcutaneous insulin schedule using institutional protocols (level of evidence = B).

It is important to note that these guidelines were released before the publication of the NICE-SUGAR Study, so the information available at the time would not be considered complete today. The Guidelines Writing Group at the STS is currently working on updating these guidelines.

INSTITUTING A PERIOPERATIVE BLOOD GLUCOSE MANAGEMENT PROTOCOL

Instituting a new blood glucose management protocol can (and nearly always will) be a daunting task. While guidelines exist to define "guardrails" for insulin dosing and target glucose ranges, these guidelines provide little direction as to how best to implement the changes in practice and in culture that are so necessary to achieve those goals. Change management and the psychology of groups (particularly groups composed of "unequal" players) are beyond the scope of this manuscript[62]. These topics are covered well in any number of management textbooks and monographs. Yet, experienced clinicians will recognize the key importance of group dynamics and negotiation skills to achieving success with a new clinical strategy. In other words, these issues cannot be ignored if the new strategy will succeed. Success cannot be achieved without "buy in" from physicians on the relevant clinical services. Nevertheless, nurses will drive the protocol in the ICU and on the hospital units; nurses must be involved in program development from the start. We have seen new clinical pathways fail due to the opposition of

a single, influential, antagonistic physician. Conversely, pathway success always requires an influential, trusted, and respected champion.

McDonnell *et al*[40] published a primer in 2012 that provides some insight into the challenges that must be overcome when seeking to improve blood glucose management for cardiac surgery patients. At our institution, we encountered many of these temporary obstacles when we recently overhauled our perioperative glycemic management strategy in order to better comply with both STS Guidelines and Surgical Care Improvement Project (SCIP) requirements. We learned (or were reminded of) numerous lessons, a few of which are listed below:

Use a multidisciplinary approach

As previously noted, optimal glycemic control cannot be achieved through the efforts of a single physician or single medical discipline. We formed a process improvement team with representation from cardiac surgery, cardiac anesthesia, cardiac critical care, ICU nursing, endocrinology, clinical pharmacy, dietary, and the performance improvement department. Each discipline was responsible for a small subset of the project, and frequent meetings of the entire process improvement team allowed for ongoing progress updates and collaboration.

Address preoperative, intraoperative, and postoperative care at the same time

Glucose control in the preoperative, intraoperative and postoperative periods cannot be disentangled. Although it is tempting to address each stage of care in a piecemeal fashion, overall success requires the team to integrate these phases together. Having representation and periodic updates from those responsible for care at each point along the care continuum permits timely identification and remediation of persisting misconceptions or deviations from the plan.

Demand a relatively short project timeline (with well defined deadlines)

Process improvement projects can (and sometimes should) go on indefinitely. But, one will never see results if a strict timeline is not enforced. We recognize that the ideal approach to process improvement (since the time of Walter Shewhart and W. Edwards Deming) is a "plan-do-study-act" repetitive cycle, but also have seen that a team can get stuck on "plan" if the focus is on perfection rather than on improvement. The perfect course of action likely will never be determined; reaching a consensus can take an exorbitantly long time when discussion and debate are allowed to continue unchecked. We structured our discussions, allowing each discipline to take the lead on the facet of the project for which they were responsible. Our process improvement team met from May 2013 to August 2013.

Use flow charts to facilitate identification of "gaps"

Flow charts and process mapping were developed in industrial engineering to define precisely what is the desired "product," what are the individual steps in the process by which it is "made," who is responsible for each step, and how can we measure our success at "manufacturing" this "product?" The process improvement team "mapped" glycemic management from patient admission to discharge during its first meetings. Each discipline described in detail the manner in which care was provided within their domain. Once the entire care continuum had been described, "gaps" in ideal care were identified. For example, representatives from anesthesiology identified that they had no standard blood glucose management protocol for the intraoperative period. Representatives of the dietary department pointed out that patients who had an order for a diabetic diet could still request sugar-sweetened soft drinks during the postoperative period. Once dozens of these potential gaps had been identified, the team determined which gaps fell under the purview of which disciplines, and then voted on which gaps should be prioritized for correction. This process allowed for the systematic identification and elimination in barriers to optimal glycemic control.

OUR SUCCESS IMPLEMENTING CHANGE

We monitored several outcome measures to evaluate the success of our newly instituted blood glucose management practices. Detailed explanations of these results are not the focus of this article, but broad trends are described here. Briefly, intraoperative blood glucose values fell within our target range 63% of the time for 35 consecutive patients who underwent cardiac surgery prior to the adoption of our new protocol. Thirty-eight consecutive patients undergoing cardiac surgery after to the institution of the protocol were similarly evaluated, and their blood glucose values fell within our target range 81% of the time ($P < 0.05$ using nonparametric tests).

Compliance with SCIP 4 measures for postoperative day one and two 6 am blood glucose values was also monitored [SCIP 4 requires postoperative day (POD) 1 and POD 2 blood glucose levels to be below 200 mg/dL]. Suboptimal performance on these measures during 2012 served as the impetus for the formation of our process improvement team. For that year, we achieved 90% compliance but lost considerable potential revenue in the value based purchasing program. For the 38 consecutive patients analyzed after the overhaul of our blood glucose management practices, we achieved 99% compliance on this SCIP 4 measure.

It is important to note that Institutional Review Board (ethics committee) approval including a waiver of consent was obtained in order to perform the chart review necessary to include these results here.

PATIENT SAFETY AND INSULIN INFUSION

The potential dangers of insulin therapy are well known to providers, and insulin infusion in the perioperative

setting is no exception. We experienced an example of the "Swiss cheese" model of error in which a series of unexpected, sequential actions were taken; omission of any one of these actions would have prevented a protocol deviation. The individual actions leading up to this patient safety "near miss" are listed here: (1) The infusion pump was programmed for a "basic" infusion rather than using preprogrammed "guardrails" for insulin infusions. The "guardrails" settings have built-in safeguards that alert the provider when excessive doses of a drug are entered. Using the basic infusion setting circumvents these safeguards; (2) An insulin infusion was intended to be programmed for 1.5 U/h but was erroneously programmed for 105 U/h; (3) Fortunately, this programming error occurred toward the end of the case, and the error was noticed immediately upon arrival in the ICU. As a consequence, we made several changes to our intraoperative protocol: We removed decimal points from the protocol such that infusion rates are rounded to the nearest unit rather than the nearest half-unit. This allows most infusion rates to be entered as a single digit, reducing the likelihood that a three-digit infusion rate will be set accidentally; (4) The safeguards built into the "guardrails" setting are now more explicitly stated within the protocol; and (5) Initiation of insulin infusion in the operating room now requires a second provider to double-check the correctness of the infusion (just as is done prior to any blood transfusion).

Even with the most stringent safeguards in place, one must keep in mind that every time an insulin infusion is started, there is an opportunity for a life-threatening error. Despite our best intentions, human error will not soon be eliminated from health care delivery[63]. It is easy to point fingers and assign blame after a medical error, but it is far more productive to learn from mistakes and make whatever improvements are possible to the care pathways in which the error occurred.

CONCLUSION

The association between perioperative hyperglycemia and adverse outcomes after cardiac surgery is well established. It is less clear which clinical practices will optimize outcomes in these patients: efforts to tightly control blood glucose in cardiac surgery may lead to dangerous hypoglycemia. Van den Berghe *et al*[38,57,58] showed benefits of aggressive insulin therapy to maintain tight control in the perioperative period, but later studies including NICE-SUGAR demonstrated that tight control was actually associated with worse clinical outcomes[59]. As a result, tight control is no longer standard care for patients with critical illness. Even so, a consensus regarding the range of glucose concentrations for which clinicians should be aiming in these patients has remained elusive. There is a growing body of evidence that moderate control (*e.g.*, 120-180 mg/dL, 6.7-10.0 mmol/L) is an appropriate goal. The Society of Thoracic Surgeons is expected to update their 2009 practice guidelines on perioperative glycemic management in the near future, so more formal guidance will be available at that time.

Within a given institution, selecting a target glucose range is only the first step. Implementing a protocol to achieve that goal can be a challenging ordeal, and success is more often achieved when one addresses the entire continuum of care associated with blood sugar management. It is important to obtain buy-in from all those who will be involved in the care of patients undergoing cardiac surgery. Patient safety must be paramount throughout the design of a glycemic management protocol. Human error can never be completely eliminated. Wise clinicians will respond to patient safety events as opportunities for process improvement.

ACKNOWLEDGMENTS

We acknowledge the countless contributions of our process improvement team, the members of which were: Deblynn Austin, MSN, RN; John Clore, MD; Linda Currie, MSN, CNS; Laura Franklin, MSN, RN; Jeff Green, MD; Zirui Gu; Vigneshwar Kasirajan, MD; Raj Malhotra, DO; Kim Nelson, MSN, RN; Kathyrn Perkinson, MSN, RN; Edna Rensing, MSHA, RN; Jo Weller, MBA.

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DOI: 10.4330/wjc.v6.i11.1218

World J Cardiol 2014 November 26; 6(11): 1218-1222
ISSN 1949-8462 (online)

MINIREVIEWS

Surgical management of moderate ischemic mitral valve regurgitation: Where do we stand?

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Received: June 2, 2014 Revised: September 16, 2014
Accepted: October 1, 2014
Published online: November 26, 2014

Abstract

Ischemic mitral regurgitation (IMR) represents a common complication after myocardial infarction. The valve is anatomically normal and the incompetence is the result of papillary muscles displacement and annular dilatation, causing leaflets tethering. Functionally the leaflets present a restricted systolic motion due to tethering forces that displaces the coaptation surface toward the left ventricle apex. The patients present poor left ventricular function at the time of surgery and the severity of the mitral regurgitation increases the risk of mortality. Currently there is general agreement to treat surgically severe IMR nevertheless strong evidences for patient with moderate insufficiency remains poor and proper treatment debated. The most effective surgical approach for the treatment of IMR remains debated. Some authors demonstrated that coronary artery bypass graft (CABG) alone is beneficial in patients with IMR. Conversely, in most patients, moderate IMR will persist or worsen after CABG alone which translate in higher long-term mortality as a function of residual mitral regurgitation severity. A probable reason for this unclear surgical management of functional MR is due to the contemporary suboptimal results of reparative techniques. The standard surgical treatment of chronic IMR is CABG associated with undersized annuloplasty using complete ring. Though, the recurrence of mitral regurgitation remains high (> 30%) because of continous left ventricle remodeling. To get better long term results, in the last decade, several subvalvular procedures in adjunct to mitral anuloplasty have been developed. Among them, surgical papillary muscle relocation represents the most appreciated option capable to restore normal left ventricle geometry. In the next future new preoperative predictors of increased mitral regurgitation recurrence are certainly needed to find an individual time period of treatment in each patient with moderate IMR.

Key words: Anatomy; Surgery; Cardiology; Valve; Mitral; Echocardiography

Core tip: Moderate ischemic mitral regurgitation should always be considered in patients undergoing other cardiac surgery. Restrictive anuloplasty alone fails as valid treatment because often associated with persistence and high recurrence rate of mitral regurgitation due to continuous ventricular remodeling. Probably more aggressive repair procedures addressing the subvalvular mitral apparatus would help to find more durable results for this complex disease. In the next future new preoperative predictors of increased MR recurrence are certainly needed to find an individual time period of treatment in each patients with moderate ischemic mi-

tral regurgitation.

Fattouch K, Castrovinci S, Murana G, Moscarelli M, Speziale G. Surgical management of moderate ischemic mitral valve regurgitation: Where do we stand? *World J Cardiol* 2014; 6(11): 1218-1222 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1218.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1218

INTRODUCTION

Ischemic mitral regurgitation (IMR) occur in up to 40% of patients affected by myocardial infarction[1]. IMR affects the myocardium rather than the valve itself and valve incompetence is the result of papillary muscles (PPMs) displacement, leaflet tethering, and annular dilatation. Functionally the leaflets present a restricted systolic motion due to tethering forces that displaces the coaptation surface toward the left ventricle (LV) apex[2]. The patients present poor left ventricular function at the time of surgery and the severity of the mitral regurgitation increases the risk of mortality (lower among patients with mild IMR). Currently there is general agreement to treat severe IMR surgically, nevertheless evidences for patient with moderate insufficiency remain poor and proper treatment is debated.

ECHOCARDIOGRAPHIC CONSIDERATIONS

To define the severity of mitral regurgitation by Doppler echocardiography, the effective regurgitant orifice (ERO) area and the regurgitant volume (RV) are used. Organic MR is usually characterized by an ERO area > 0.4 cm^2 and RV > 60 mL/beat; these cut points are significantly lower for patients with functional MR (ERO area > 0.2 cm^2 and RV > 30 mL/beat, respectively)[3,4].

MR severity in any individual patient should not be defined exclusively on the basis of few quantitative parameters but on an integrative evaluation that assess supplementary helpful findings, such as the pulmonary vein flow pattern, the size of left atrial and LV chambers. Lastly, since functional MR is an essentially dynamic lesion, the severity of regurgitation varies as a function of LV loading conditions and heart rhythm. For that reason, stress echocardiography is an important adjunct to the noninvasive evaluation of appropriate patients[5].

OPEN CONTROVERSIAL ON SURGICAL MANAGEMENT

The most effective approach for the management of IMR remains discussed. Some authors demonstrated that coronary artery bypass graft (CABG) alone is beneficial in patients with IMR[6,7]. Conversely, in most patients moderate IMR will persist or worsen after CABG alone which translate in higher long-term mortality as a function of residual MR severity[8]. A probable reason for this unclear surgical management of functional MR is due to the contemporary suboptimal results of reparative techniques[9,10]. Undersized annuloplasty with complete ring, associated with CABG, presently is the most frequently performed surgical procedure to treat chronic IMR. However, recurrent MR can be expected in 1/3 of patients because of continued LV remodeling[11,12]. There are many reviews about of adding subvalvular procedures to mitral anuloplasty to reduce the tenting forces and improve the long-term repair results[13-15]. Recent experimental and clinical studies reported that displacement of the PPMs, due to LV remodeling, represents a key characteristic in the development of IMR; surgical papillary muscles relocation may represent a new precious instrument for surgeons[15-18]. On the other hand, some authors reported very good results after mitral valve replacement[19,20]. In a recent randomized trial[21]. The Cardiothoracic Surgical Trials Network evaluate the relative risks and benefits of replacement versus repair, with or without CABG, in patients with severe IMR. As regard left ventricular reverse remodeling and 12-mo survival the authors observed no significant difference between mitral valve annuloplasty and replacement. However, in more than 30% of the patients in the repair group, a significant recurrent IMR developed. These data suggest a large potential benefit of valve repair if the effects of recurrent IMR can be limited. Therefore, the timing of valve repair in IMR needs to be assessed and patients with moderate regurgitation could benefit from early mitral surgery in morbidity though prolonged survival has to be demonstrated[22].

FUTURE PERSPECTIVES

Currently there is general agreement to treat only severe IMR at the time of CABG. Conversely, according recent guidelines[23,24], mitral valve repair should be considered for patients with chronic moderate secondary MR who are undergoing other cardiac surgery (class of recommendation Ⅱb and Ⅱa respectively for American heart association/American college of cardiology and ESC guidelines). Consensus opinions regarding best practices rely on studies that are retrospective, observational, and most often single centered[25]. In 2009, the first trial on efficacy of adding mitral valves plasty to CABG for moderate IMR have been published by our group[26]. We demonstrated that the effectiveness of adding mitral valve plasty to CABG was well demonstrated by the improvement of NYHA class and percentage of LVEF and by the decrease of MR, left ventricular end-diastolic and end-systolic diameters, left atrial size and pulmonary artery pressure. In the same direction the Randomized Ischemic Mitral Evaluation Trial support the addition of MVR to CABG in patients with moderate ischemic MR undergoing CABG[27]. In this study, 73 patients referred for CABG with moderate IMR and an ejection fraction

> 30% were randomized to receive CABG plus mitral valve plasty (34 patients) or CABG only (39 patients). Moderate IMR was defined by an effective regurgitant orifice area of 0.20 to 0.39 cm^2, RV of 30 to 59 mL/beat, and vena contracta width of 0.30 to 0.69 cm. Mitral valve plasty was performed with insertion of a Carpentier-McCarthy-Adams ETlogix Ring (Edwards Lifesciences) in 85% of patients and a Carpentier-Edwards Physio Ring (Edwards Lifesciences) in 15% of patients. Mean mitral leaflet coaptation length was 7.1 ± 1.2 mm, and technical success was defined as no or trivial MR intraoperatively. The authors demonstrated that the addition of mitral valve repair by anuloplasty to CABG reduced MR severity, LV volumes, and BNP levels, with an improvement in functional capacity and symptoms at 1 year. Longer-term follow-up of MR severity in both treatment groups would be of interest because LV reverse remodeling continue for up to 2 years after coronary artery revascularization, and it is possible that patients in the CABG-only group may demonstrate greater reverse remodeling with time. Unfortunately, in both trials[26,27] there are no data on the use of cardiac resynchronization therapy when appropriate, strongly encouraged in guidelines. Another randomized, controlled multicenter trial in patients with moderate IMR is ongoing (ClinicalTrials.gov NCT00806988) designed to assess the effect of mitral valve repair added to CABG surgery on the combined end point of survival and re-hospitalization for heart failure in patients with moderate IMR followed for 5 years[28]. Moreover, the Cardiothoracic Surgery Network will shortly complete enrollment of 300 patients in a companion study of CABG plus mitral valve repair versus CABG alone in patients with moderate IMR[29]. Results from these trials will further elucidate the optimal treatment algorithm for patients with IMR; however, discrepancies in trial design, echocardiographic inclusion/exclusion criteria, and surgical technique suggest a continued role for large observational studies to facilitate a valid management of these patients. A key point could be to improve patient selection to identify more precisely which individuals will benefit from surgical intervention. In particular, stress tests could be very helpful to determine the precise time of intervention in this clinical setting. In particular, recent research efforts concentrated on exercise echocardiography[5,30]. Hung *et al*[11], for example, demonstrated as CABG alone left more patients with heart failure symptoms at rest and during exercise. This diagnostic tool should always be considered preoperatively because induced dyspnea, increased in MR severity and systolic pulmonary artery pressure are often disguised in patients with moderate IMR at rest. Only a proper preoperative evaluation would not leave patients un-correctly treated. Therefore, this new clinical strategy would maximize the beneficial effects of repair and neutralize the effects of recurrent IMR. In the next future, the research for preoperative predictors of increasing MR recurrence and for alternative reparative approaches are probably the two key points to find an individual treatment in each patients with this complex post-ischemic complication.

CONCLUSION

Moderate IMR should always be considered in patients undergoing other cardiac surgery. Restrictive anuloplasty alone fails as valid treatment because often associated with persistence and high recurrence rate of MR due to continuous ventricular remodeling. Probably more aggressive repair procedures addressing the subvalvular mitral apparatus would help to find more durable results for this complex disease. In the next future new preoperative predictors of increased MR recurrence are certainly needed to find an individual time period of treatment in each patient with moderate IMR.

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P- Reviewer: Ciaccio EJ, de Jong T, Hsiao SH, Ilgenli TF
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DOI: 10.4330/wjc.v6.i11.1223

World J Cardiol 2014 November 26; 6(11): 1223-1226
ISSN 1949-8462 (online)

CASE REPORT

Primary angioplasty for infarction due to isolated right ventricular artery occlusion

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Author contributions: Borg AN and Al-Najjar Y were involved in direct patient care; Chahal AA and Borg AN wrote the manuscript, including preparation of figures; Kim MY and Al-Najjar Y edited and referenced the manuscript; Kim MY acted as the corresponding author for publication process.

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Received: June 2, 2014 Revised: September 11, 2014
Accepted: October 28, 2014
Published online: November 26, 2014

Abstract

We report an unusual case of an isolated right ventricular infarction with haemodynamic compromise caused by spontaneous isolated proximal occlusion of the right ventricular branch of the right coronary artery (RCA), successfully treated by balloon angioplasty. A 58-year-old gentleman presented with epigastric pain radiating into both arms. Electrocardiograph with right ventricular leads confirmed ST elevation in V4R and a diagnosis of isolated right ventricular infarction was made. Urgent primary percutaneous intervention was performed which revealed occlusion of the right ventricular branch of the RCA. During the procedure, the patient's blood pressure dropped to 80/40 mmHg, and echocardiography showed impaired right ventricular systolic function. Despite aggressive fluid resuscitation, the patient remained hypotensive, continued to have chest pain and persistent electrocardiograph changes, and hence balloon angioplasty was performed on the proximal right ventricular branch which restored flow to the vessel and revealed a severe ostial stenosis. This was treated with further balloon angioplasty which restored TIMI 3 flow with resolution of patient's symptoms. Repeat echocardiography showed complete resolution of the ST-elevation in leads V4R and V5R and partial resolution in V1. Subsequent dobutamine-stress echocardiography at 4 wk showed good left and right ventricular contractions. The patient was discharged after a 3-d inpatient stay without any complications.

Key words: Right ventricular infarction; Right ventricular branch occlusion; Angioplasty; Myocardial infarction; Rare

Core tip: We describe an unusual case of an isolated right ventricular infarction caused by spontaneous proximal occlusion in the right ventricular branch of the right coronary artery (RCA), successfully treated by balloon angioplasty. Isolated right ventricular infarction (IRVI) is a rare presentation of occlusion of the right ventricular branch of the RCA. Most incidences of IRVI in the literature have been reported as complications to percutaneous intervention to the RCA.

Chahal AA, Kim MY, Borg AN, Al-Najjar Y. Primary angioplasty for infarction due to isolated right ventricular artery occlusion. *World J Cardiol* 2014; 6(11): 1223-1226 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i11/1223.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i11.1223

INTRODUCTION

Isolated right ventricular infarction (IRVI) is a rare presentation of occlusion of the right ventricular (RV) branch of the right coronary artery (RCA). Most incidences of IRVI in the literature have been reported as complications to percutaneous intervention to the RCA. There have been only two other reports describing spontaneous RV branch occlusion leading to IRVI. We describe an unusual case of IRVI caused by a spontane-

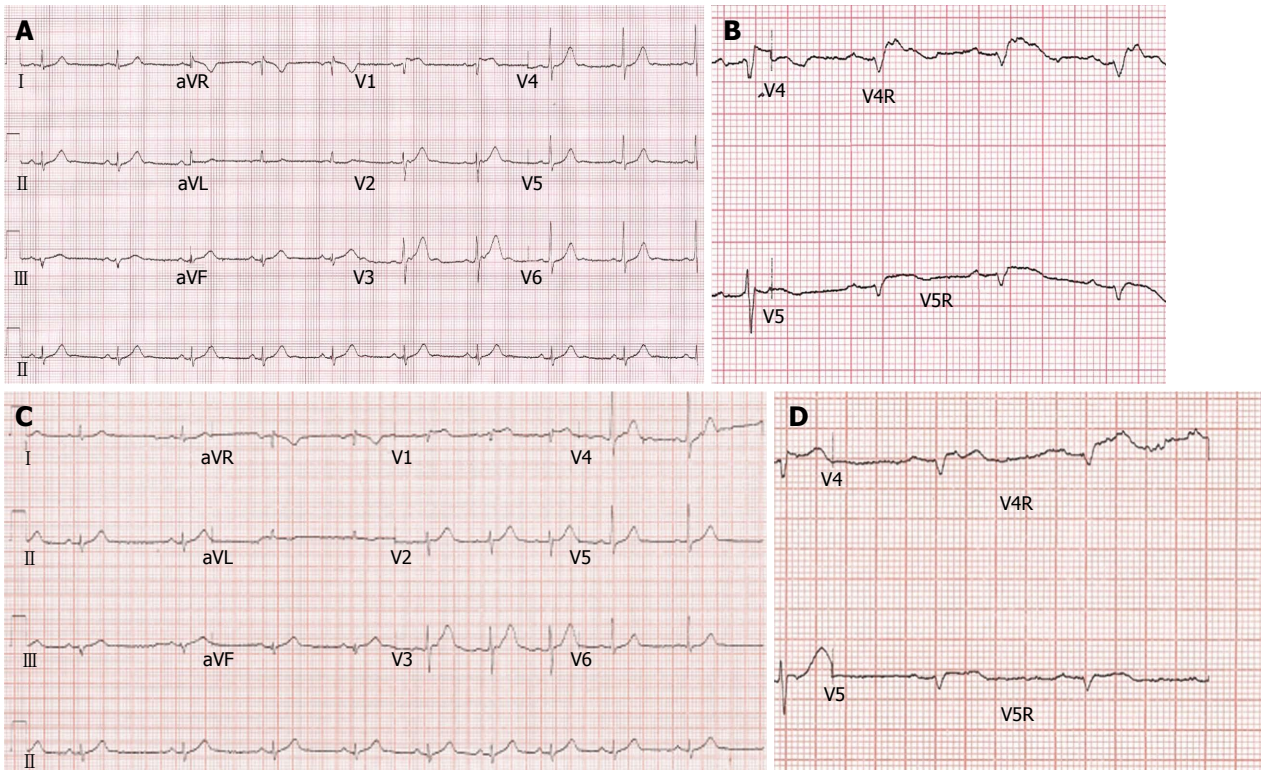

Figure 1 Electrocardiography. A: Standard 12-lead ECG at time of presentation showing ST elevation in lead V1; B: Right-sided ECG leads showing ST elevation in V4R and V5R; C: 12-lead ECG post-primary percutaneous intervention showing partial resolution of ST elevation in V1; D: Right-sided ECG post- percutaneous intervention showing resolution of ST elevation in V4R and V5R. ECG: Electrocardiography.

ous proximal occlusion in the RV branch of the RCA, successfully treated by balloon angioplasty.

CASE REPORT

A 58-year-old gentleman with no significant past medical history presented to the emergency department with sudden onset epigastric pain radiating to both arms. Initial electrocardiography (ECG) showed 3 mV ST elevation in lead V1 (Figure 1A). A subsequent ECG with right ventricular leads V4R and V5R confirmed ST elevation (Figure 1B) and a diagnosis of IRVI was made. Chest X-ray and clinical examination were unremarkable. The patient was given aspirin 300 mg, ticagrelor 180 mg, atorvastatin 80 mg and was transferred to our hospital for an urgent primary percutaneous intervention (PCI). The right radial artery was accessed using a 6F sheath (Glidesheath, Terumo) and angiography performed using a 5F Judkins left 3.5 diagnostic catheter and a Judkins right 4 guide catheter. The left main stem was free of significant atheroma. The left anterior descending artery had a 30% focal atherosclerotic plaque in the proximal vessel with a further mild mid-vessel stenosis. The circumflex artery and obtuse marginal branches did not have any significant atheromatous changes. The RCA was noted to be dominant and of moderate calibre. There was 40%-50% stenosis of the mid RCA and a moderate-severe ostial stenosis of the posterior descending artery (PDA) with TIMI 3 flow through the main vessel. Careful scrutiny of the images showed absence of the RV branch of the RCA (Figure 2A). At this point, the patient's blood pressure had dropped to 80/40 mmHg. Despite aggressive fluid resuscitation, there was little improvement in the BP and the patient had ongoing symptoms of chest pain with persistent ECG changes. Therefore, with Bivalirudin cover, the RV branch lesion was crossed with a hydrophilic Runthrough wire (Terumo) with an additional balance middle weight (Abbott Vascular) "buddy" wire to the distal RCA (Figure 3). This was followed by balloon angioplasty of the proximal RV branch with a 1.2 mm × 10 mm MINI TREK (Abbott Vascular) compliant balloon (Figure 4), which restored flow to the vessel and revealed a severe ostial stenosis. This was treated with further balloon angioplasty using a 2 mm × 6 mm non-compliant Quantum Apex (Boston Scientific) balloon. The final angiographic result showed restoration of TIMI 3 flow (Figure 2B) with resolution of chest pain. A bolus of Bivalirudin (a direct thrombin inhibitor) was administered, followed by an infusion.

The patient received routine post-MI care on the coronary care unit. The peak 12-h Troponin-I was 16628 ng/L from the initial 1115 ng/L (normal 0-59 ng) and creatine kinase was 632 IU/L (normal 25-175 IU/L). A transthoracic echocardiogram showed a normal sized left ventricle (LV) with preserved systolic function, but the RV had reduced radial systolic contraction of the basal and mid-segments of the free wall. The patient was discharged after an uncomplicated 3 d in-patient stay.

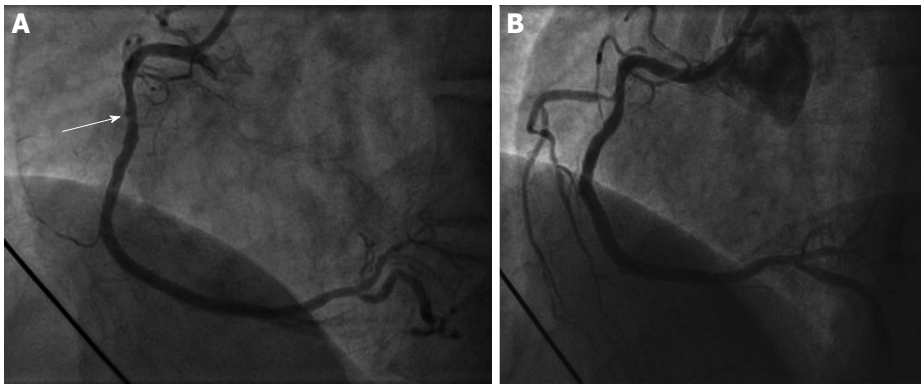

Figure 2 Balloon angioplasty for right coronary. A: Cranial view of right coronary artery showing occluded right ventricular branch (white arrow); B: Restoration of TIMI 3 flow in right ventricular branch after balloon angioplasty.

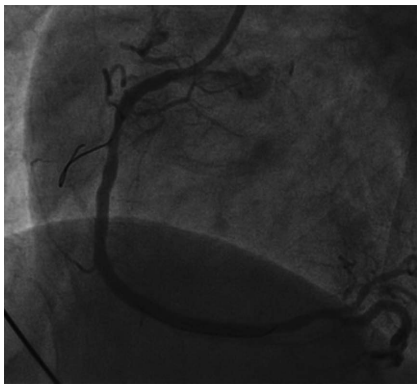

Figure 3 Right anterior oblique view of balance middle weight wire crossing the proximal lesion in the right ventricular branch. There is a "buddy" wire in the main right coronary artery vessel.

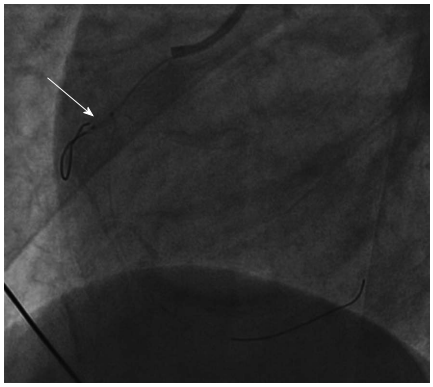

Figure 4 Same view as Figure 3 (right anterior oblique), showing balloon inflation in proximal right ventricular branch (white arrow).

Pre-discharge 12-lead ECG (Figure 1C) showed partial resolution of the ST segment elevation in lead V1 and complete resolution of ST-elevation in V4R and V5R (Figure 1D). After 4 wk, the patient was followed up with a high dose dobutamine stress echocardiography with intravenous ultrasonic contrast (SonoVue, Bracco). It showed good contractile reserve in the RV free wall and all LV segments. On this basis, we elected not to treat the residual PDA disease.

DISCUSSION

Significant RV infarction usually occurs with occlusion of the RCA, when it is accompanied by concomitant infarction of the LV segments supplied by the RCA. Smaller RV infarcts can occur with occlusion of the left circumflex and left anterior descending arteries. Involvement of the RV myocardium is common in infarction of the left ventricle. Conversely, IRVI is rare, accounting for less than 3% of all infarctions[1].

In patients with inferior MI, the presence of RV infarction is associated with a higher risk of arrhythmias and cardiogenic shock and death. Interestingly IRVI appears to have a relatively good long term prognosis, although immediate complications resulting in sudden death have been reported[2]. RV function tends to recover over the months following the acute event. This benign clinical course is most likely due to the thin muscular wall of this ventricle which provides a more favourable supply/demand ratio and the ample collateral supply from LV territory.

Isolated RV infarction has previously been attributed to occlusion of a non-dominant RCA or occlusion of an acute marginal artery, spontaneously or after PCI.

IRVI in the absence of the dominant current of injury from the LV posterior wall can present as ST elevation in the precordial leads V1-V3, similarly to an anterior MI. Obtaining right sided ECG may help to make this important distinction. ST elevation and Q waves in V4R is highly specific for IRVI. The ST elevation in the left precordial leads up to V5 are "dome-shaped"[3-5].

Echocardiographic features such as RV free wall hypokinesia, dilated RV chamber, leftward septal deviation provide a valuable non-invasive diagnostic aid in acute RV infarction. Cardiac magnetic resonance provides a more accurate assessment of RV size, ejection fraction and regional wall motion abnormalities. The MR pulse sequences applied to the LV can also be used to assess the area at risk and extent of infarction by T2 weighted oedema imaging and T1 weighted gradient echo late gadolinium enhancement images, respectively.

We believe PCI is a good option for IRVI when there

is haemodynamic compromise. Management should also include strict haemodynamic monitoring, avoidance of vasodilators and diuretics, inotropic support and treatment of arrhythmias.

COMMENTS

Case characteristics

A 58-year-old male presented with sudden onset epigastric pain radiating into both arms with no significant past medical history.

Differential diagnosis

Myocardial infarction, myo-pericarditis, aortic dissection, gastritis

Laboratory diagnosis

Troponin I on admission was 1115 ng/L (normal 0-59 ng) and the peak 12-h Troponin I was 16628 ng/L.

Imaging diagnosis

Electrocardiography showed ST-elevation in lead V1 and with right ventricular leads, ST-elevation was seen in V4R and V5R leading to the diagnosis of isolated right ventricular infarction. Echocardiography showed impaired right ventricular (RV) systolic function. Coronary angiography showed occlusion of the right ventricular branch of the right coronary artery (RCA) (TIMI 0).

Treatment

The patient was given aspirin 300 mg, ticagrelor 180 mg, atorvastatin 80 mg before transfer for urgent primary percutaneous intervention. Balloon angioplasty was performed at the proximal occlusion in the right ventricular branch of the RCA. Bivalirudin give peri-procedure.

Related reports

Reported cases comment on RV branch involvement with the main RCA and isolated occlusion usually as a complication of percutaneous intervention to the RCA. Anecdotal evidence and received wisdom favour a conservative approach, with the belief this small vessel can be sacrificed without little harm. However, each case demands a nuanced approach with an individualized risk-benefit analysis. An isolated branch occlusion can occur and can have dire consequences without prompt intervention.

Experiences and lessons

This is a rare case report that teaches the authors' to be "exsisto semper vigilans-to be ever vigilant". It is an infrequent case in their daily clinical practice that may be easily missed leading to a delay in diagnosis and management, which may lead to fatal consequences.

Peer review

This is a well written case report that offers useful clinical information.

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