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EDITORIAL

Central and peripheral testosterone effects in men with heart failure: An approach for cardiovascular research

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Abstract

Heart failure (HF) is a syndrome recognized as a health problem worldwide. Despite advances in treatment, patients with HF still have increased morbidity and mortality. Testosterone is one of the most researched hormones in the course of HF. Growing interest regarding the effect of testosterone, on a variety of body systems, has increased the knowledge about its mechanisms of action. The terms central and peripheral effects are used to distinguish the effects of testosterone on cardiac and extracardiac structures. Central effects include influences on cardiomyocytes and electrophysiology. Peripheral effects include influences on blood vessels, baroreceptor reactivity, skeletal muscles and erythropoesis. Current knowledge about peripheral effects of testosterone may explain much about beneficiary effects in the pathophysiology of HF syndrome. However, central, *i.e.*, cardiac effects of testosterone are to be further explored.

Key words: Cardiomyocytes; Exercise; Electrophysiology; Heart failure; Vasodilation; Testosterone

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Core tip: Patients with heart failure often have a lower endogenous testosterone level. Testosterone has a number of effects on cardiac and extracardiac structures *via* genomic and non-genomic mechanisms. We summarize current knowledge about the involvement of testosterone in heart failure syndrome.

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INTRODUCTION

Despite many advances in medicine, heart failure (HF) remains one of the leading causes of increased morbidity and mortality among adult population. In recent years, there has been growing interest in

Table 1 Effects of nonphysiological testosterone levels

	Supraphysiological	Subphysiological
Cardiomyocytes	Hypertrophy	Hypotrophy
QT interval	Shortening	Prolongation
Vasculature	Vasodilation	Not known
Skeletal muscles	Hypertrophy	Hypotrophy
Exercise capacity	Increased	Decreased
Baroreceptor sensitivity	Increased	Attenuated

hormonal disturbances that accompany HF. A body of evidence suggests that several hormones and a variety of metabolic signals may be altered in a way that instigates progression of the disease[1]. Within this framework, testosterone receives vivid research interest.

Many epidemiological studies have found a high incidence of comparably lower testosterone level in men with coronary heart disease, regardless of patient's age[2]. Moreover, population studies have found an association of increased all-cause and cardiovascular mortality with low testosterone levels in general population as well as within a subpopulation of men with coronary heart disease[3-7].

Testosterone deficiency has been implicated in the pathophysiology of HF, contributing to some characteristics of this syndrome such as reduced skeletal muscle mass, oxygen consumption, reduced exercise capacity and cachexia[8]. The association of serum testosterone levels with clinical severity of HF seems to be present only in non-obese HF patients[9]. In obese patients with HF, lower testosterone levels and a lack of correlation with the disease severity may suggest altered hormonal and hemodynamic mechanisms which could contribute to a better prognosis and the obesity paradox[9].

To distinguish and classify various cardiovascular, hormonal, muscular and other mechanisms the terms central, *i.e.*, cardiac and peripheral, *i.e.*, extracardiac effects are used to describe the effects of testosterone on cardiac and extracardiac structures (Figure 1). Those effects are particularly important under the circumstances of nonphysiological testosterone levels (Table 1).

CENTRAL EFFECTS OF TESTOSTERONE

Cardiomyocytes

Testosterone is responsible for protein synthesis and hypertrophy of the cardiac muscle of several investigated species, including humans, through a receptor-specific interaction which results in an increased amino acid incorporation into proteins[10]. In a post-infarction model of HF, testosterone supplementation led to a particular type of myocardial hypertrophy with a significant increase in left ventricular mass, but without increase in hypertrophy markers or collagen accumulation[11]. It appears that testosterone stimulates the expression of α-myosin heavy chain as opposed to β-myosin heavy chain which is usually seen in pathological cardiac hypertrophy, thus indicating a "physiological" type of cardiac hypertrophy with potentially long term improvement in cardiac function[10]. An animal study of ischemia-reperfusion injury showed that testosterone reduced cardiomyocyte injury by upregulating cardiac α1 adrenoceptor and possibly by activating cardiac mitochondrial ATP-sensitive potassium (K^+) channels[12].

It has been also suggested that testosterone has an influence on myocardial contractility. Gonadectomy in male rats changed the transcriptional and translational control of genes encoding the L-type calcium (Ca^{2+}) channel, the Na^+/Ca^{2+} exchanger, β1 adrenoceptors, and myosin heavy chain subunits which reduced cardiomyocyte contractile capacity[13,14].

Ventricular function

Among other clinical parameters, several studies have assessed the left ventricular ejection fraction in HF patients who received testosterone supplementation[15-19]. While some animal studies showed that androgens are important for cardiac contractility, such findings were not reported in humans. Despite improvement in exercise capacity and ventilatory efficiency in patients receiving testosterone supplementation, there was no improvement in left ventricular ejection fraction[15-19].

Higher serum levels of testosterone, most frequently found in athletes using prohibited anabolic androgen steroids, have been shown to cause myocardial hypertrophy[20,21]. However, in a study by Malkin *et al*[4], patients with HF that received testosterone supplementation had no increase in myocardial mass nor in wall thickness, thus suggesting that testosterone supplementation is safe if kept in physiologic doses.

Cardiac electrophysiology

Both endogenous and exogenous sex hormones have been shown to affect cardiac electrophysiology[22,23]. Changes in QT interval are associated with an increased risk of atrial and ventricular tachyarrhythmias, and of sudden cardiac death[24,25]. Several studies have been performed in order to explore the influence of testosterone on QT interval duration. It has been reported that ventricular repolarization was prolonged in castrated men compared with noncastrated men[26]. In addition, women with hyperandrogenism had shorter QT-interval duration than did their respective control[26]. Furthermore a negative linear correlation was found between the duration of QT interval and serum testosterone levels in hypogonadic men after receiving a single intramuscular administration of testosterone[27].

Low testosterone levels have been also associated with the incidence of atrial fibrillation, particularly in men over 80 years of age[28]. Hence, testosterone supplementation could possibly be beneficial for primary prevention of atrial fibrillation. However, an animal study from 2014, showed that testosterone supplementation in aging rabbits increased arrhythmogenesis by

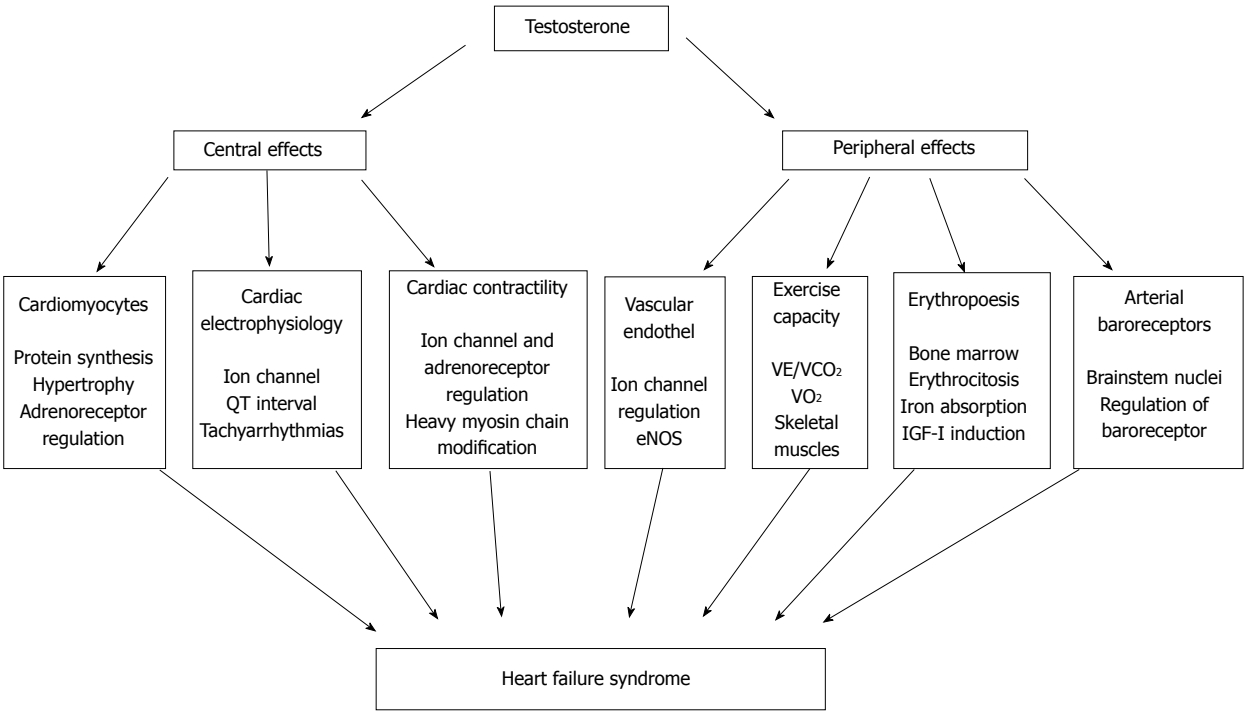

Figure 1 Testosterone effects that may be implicated in the pathogenesis of heart failure syndrome. eNOS: Endothelial nitric oxide synthase; VE/VCO_2: Ventilation to carbon dioxide production ratio; VO_2: Oxygen consumption; IGF-I: Insulin growth factor-I.

enhancing adrenergic activity which brought the previous hypothesis in question[29].

Several mechanisms, through which testosterone acts on cardiac electrophysiology, have been proposed. An animal study from 2005 found that testosterone induced a dose dependent shortening of action potential duration through non-genomic enhancement of slowly activating delayed rectifier K^+ current and suppressing the L-type Ca^{2+} current[30]. In another animal study, dihydrotestosterone, a metabolite of testosterone, induced QT interval shortening through an increased current density of inward repolarizing rectifier K^+ current and by rapidly activating delayed rectifier K^+ current[31]. Finally, in another animal study, repolarization of canine ventricular myocardium was significantly modified by testosterone, most likely due to increased expression of ion channel proteins[32]. However, those mechanisms are still being explored and at the moment there is not enough information about the effects of testosterone on cardiac electrophysiology.

PERIPHERAL EFFECTS OF TESTOSTERONE

Vascular effects

Basic cellular and molecular mechanisms through which testosterone regulates vascular responsiveness are not entirely understood. Animal studies suggest that testosterone affects vascular reactivity by both influencing endothelium-dependent and independent actions in a variety of vascular beds[33]. In HF, peripheral vasodilation produces a reduced cardiac afterload and increased cardiac output[34]. Coronary vasodilation improves myocardial oxygenation thereby achieving a beneficiary effect in HF patients[8,34].

Endothelium-dependent effects of testosterone include long term genomic and rapid non-genomic effects. Nitric oxide (NO) is a powerful vasodilator synthesized by the endothelial NO synthase (eNOS) and released, among other tissues, by the vascular endothelium[35]. Testosterone modulates NO release which in addition way is affecting vasoreactivity[36]. It is not fully understood whether this testosterone effect is genomic or non-genomic. There are several proposed mechanisms through which testosterone may act on NO synthesis and release. A study from 2012 showed that testosterone, *via* non-genomic activation of intracellular signaling pathways and Ca^{2+} influx, increases endothelial NO synthesis and additionally inhibits platelet aggregation[37]. Furthermore, in another study where vascular aging was explored, testosterone increased expression of genes that govern replicative life span which subsequently inhibited endothelial senescence *via* upregulation of eNOS activity[38].

In addition to well explored endothelium-dependent mechanisms, several studies investigated endothelium-independent effects of testosterone. The crucial endothelium-independent mechanism, which may underlie the vasodilatory effect of testosterone, involve ion channel function of the smooth muscle cells influencing K^+ channel opening and/or Ca^{2+} channel inactivation[39]. In an electrophysiological patch-clamp study, testosterone inactivated L-type voltage-operated

Ca^{2+} channels and consequently restricted Ca^{2+} influx and thereby inducing vasodilation[40]. Testosterone also shares the same molecular binding site as nifedipine on the subunit of L-type Ca^{2+} channels which causes channel blockade and may induce vasodilation[41]. Moreover testosterone blocks Ca^{2+} influx *via* store-operated Ca^{2+} channels by blocking their response to prostaglandin F2a[42]. As another option, a study from 2008 showed that testosterone activates voltage-operated K^+ channels and/or large-conductance Ca^{2+} activated K^+ channels, thereby increasing intracellular K^+ efflux and inducing vasodilation[43].

Baroreceptor sensitivity

It has been established that arterial baroreceptor sensitivity is attenuated in HF which is an important adverse prognostic indicator[44]. In light of this, Caminiti *et al*[18], sought out to investigate the effect of testosterone supplementation on baroreceptor sensitivity in patients with HF. Their results showed an increase in baroreceptor sensitivity in the testosterone treated group. Although they weren't able to identify the mechanisms through which testosterone enhances baroreceptor sensitivity, several animal studies have shown that testosterone administration improves arterial baroreceptor control of heart rate through an enhancement of cardiac efferent vagal activity[45-47]. It is possible that this effect takes place at central nervous system sites, because androgen receptors have been identified in brainstem nuclei that are involved in the baroreflex cardiac regulation[48].

Exercise

Patients with HF have poor exercise capacity test results. This is a consequence of poor left ventricular function, a poor ventilatory efficiency and muscle wasting which is enhanced in HF syndrome leading to early fatigue and limited exercise tolerance. Although peak oxygen consumption (VO_2) and ventilation to carbon dioxide production ratio (VE/VCO_2 slope) express different pathophysiologic segments of the cardiorespiratory response to exercise in HF, they both are facets of that response. Ventilatory efficiency, commonly assessed by the minute VE/VCO_2 and VO_2, is a powerful prognostic marker in the HF patients[49].

Another important segment in exercise capacity are skeletal muscles. Several morphological and functional irregularities, relatively independent of reduced blood flow, present in the skeletal muscle of HF patients contribute to early lactic acidosis and fatigue during exercise[50]. These changes are involved in the pathophysiology of HF and have been gathered under the term "the muscle hypothesis"[51]. According to this hypothesis, exaggerated ergoreflex activation occurs in exercising muscles of HF patient which leads, *via* activation of sympathetic system, to fatigue and an excessive ventilatory response in a form of dyspnea.

Recent studies have shown that testosterone supplementation improves exercise capacity, peak VO_2 and VE/VCO_2 slope[16-18]. The mechanism through which testosterone affects cardiorespiratory parameters in HF patients can be in part explained by the association of muscle ergoreflex overactivity with VE/VCO_2 slope[52]. Animal studies have indicated that anabolic androgens attenuate muscle fatigue in response to exercise, though the precise mechanism of this effect has not been identified[53,54]. Combination of exercise training and testosterone supplementation may beneficiary change muscle structure and function[50,55]. This may attenuate muscle ergoreflex activity and ventilatory response to exercise in HF patients and consequently improve exercise test results[50,55].

Erythropoesis

Further mechanism of testosterone that could explain improvement in exercise capacity and ventilatory response is the increase in hemoglobin level and oxygen delivery. A body of evidence suggests an association of lower hemoglobin levels with increased risk of hospitalization, poorer clinical status and death due to HF[56,57].

Testosterone has a strong stimulatory effect on erythropoiesis[58-60]. Suggested mechanisms of this effect are stimulation of intestinal iron absorption, erythrocyte iron incorporation and hemoglobin synthesis[60]. Although testosterone was found not to affect erythropoietin or soluble transferrin receptor levels, it is possible that testosterone has a direct effect on the bone marrow hematopoietic stem cells through the induction of insulin growth factor-I *via* androgen receptor-mediated mechanisms[61-63].

CLINICAL IMPLICATIONS

Testosterone deficiency is an independent risk factor of worse outcome in patients with HF of both sexes[64]. Testosterone supplementation results in positive physiological and biochemical changes in patients with HF and testosterone administration acutely increases cardiac output and reduces peripheral vascular resistance[15,65]. In addition, transdermal testosterone administration induces coronary vasodilation and increases coronary blood flow and improves angina threshold in patients with coronary artery disease[66,67].

An interesting question is whether testosterone may be helpful in women as it prove useful in men? As opposed to men, it seems that testosterone is not a significant factor of sudden cardiac arrest in women[68]. The only testosterone supplementation study that included female patients with HF showed no difference in effect on functional capacity and muscle strength therefore indicating no differences in possible mechanisms of action between male and female HF patients[69].

Another interesting issue is a possibility of the interplay among testosterone therapy and other endogenous anabolic hormones. Growth hormone and insulin growth factor-I levels are important for

preserving both cardiac morphology and performance in adult life[1]. Individuals with low insulin growth factor-I levels undergo cardiovascular alterations that are reminiscent of those observed in HF patients and are corrected by replacement therapy[70,71]. An interaction also exists between testosterone and insulin growth factor-1 through androgen receptor-mediated mechanisms[61-63]. Whether testosterone acts directly on insulin growth factor-I or indirectly by influencing the growth hormone is to be investigated.

FUTURE RESEARCH

Testosterone is currently one of the most investigated hormones in the course and prognosis of HF syndrome. Over the past decade, growing interest has widen research targets that could contribute to symptoms and pathophysiology of HF on all body systems. Studies have been performed in order to establish whether testosterone can be included in the standard therapy for HF patients with a low testosterone level.

Several unanswered questions should be addressed in future studies: (1) are the effects of exogenous testosterone on tissues, organs and body systems the same as the effects of endogenous testosterone? (2) is there a difference between the routs of testosterone administration which could be important for testosterone supplementation? (3) what is the role of testosterone on cardiac fibrosis and remodeling[34,71]? and (4) has testosterone adverse effects in the elderly, particularly in those with an advanced ischemic or other heart disease[34]?

In conclusion, current knowledge about peripheral effects of testosterone may explain much about beneficiary effects in the pathophysiology of HF syndrome. However, many fields of testosterone's central, *i.e.*, cardiac effects are to be further explored.

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REVIEW

Lean heart: Role of leptin in cardiac hypertrophy and metabolism

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Abstract

Leptin is an adipokine that has been linked with the cardiovascular complications resulting from obesity such as hypertension and heart disease. Obese patients have high levels of circulating leptin due to increased fat mass. Clinical and population studies have correlated high levels of circulating leptin with the development of cardiac hypertrophy in obesity. Leptin has also been demonstrated to increase the growth of cultured cardiomyocytes. However, several animal studies of obese leptin deficient mice have not supported a role for leptin in promoting cardiac hypertrophy so the role of leptin in this pathological process remains unclear. Leptin is also an important hormone in the regulation of cardiac metabolism where it supports oxidation of glucose and fatty acids. In addition, leptin plays a critical role in protecting the heart from excess lipid accumulation and the formation of toxic lipids in obesity a condition known as cardiac lipotoxicity. This paper focuses on the data supporting and refuting leptin's role in promoting cardiac hypertrophy as well as its important role in the regulation of cardiac metabolism and protection against cardiac lipotoxicity.

Key words: Leptin; Leptin receptor; Lipotoxicity; Cardiotoxicity; Obesity; Diabetes

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Core tip: Leptin is a hormone derived from adipocytes which regulates food intake and body weight. It is present at high levels in obese individuals where it can impact organs such as the heart. Leptin has been shown to both promote and protect the heart against

obesity induced heart disease. This review examines the controversial role of leptin in the development of cardiac hypertrophy as well as its important role in regulating cardiac metabolism and protecting the heart against obesity induced lipotoxicity.

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INTRODUCTION

Leptin is a hormone most abundantly produced by white adipocytes which then acts in the hypothalamus of the brain to decrease appetite and increase energy expenditure. Leptin was discovered in the early 1990's after genetic mapping of a mutation in the gene found in a specific strain of obese mice, the *ob/ob* mouse, which was originally described in the 1950's[1,2]. These mice are characterized by having no leptin which results in marked hyperphagia, decreased energy expenditure and obesity. Another strain of obese mice called *db/db* mouse was subsequently found to have a mutation in the *ObR* gene encoding the leptin receptor[3]. This strain of mice is characterized by having very high levels of circulating leptin due to lack of functional leptin receptors, marked hyperphagia, decreased energy expenditure and obesity. There are also several rat strains with defective leptin receptor such as the Zucker fatty (*fa/fa*) rat and the Koletsky fatty rat[4,5]. Recently, a zinc-finger approach was utilized to create a rat model of leptin receptor deficiency on a salt-sensitive hypertension background[6]. All of these models as well as development of cell type/tissue-specific knockouts of the *ObR* gene have greatly increased our knowledge about the physiological role of leptin[7].

While leptin is mainly expressed in adipose tissue, it is also expressed in peripheral organs such as the heart[8]. Leptin receptors are also highly expressed in the heart of several species including humans[9,10]. In the rat heart, the long form of the leptin receptor is expressed in addition to other shorter isoforms[11]. Reverse-transcriptase polymerase chain reaction of the mouse heart readily reveals expression of all isoforms of the leptin receptor similar to the expression pattern found in the brain[12] (Figure 1). The long form of the leptin receptor, ObRb, activates signaling through the Janus kinases (JAK)/ signal transducers and activators of transcription (STAT) pathway and other Src Homology 2 domain containing proteins such as suppressor of cytokine signalling and SHP-2 (Src-like homology 2 domain containing protein tyrosine phosphatase) and STAT[13]. Short leptin receptor isoforms (ObRa, ObRc, ObRd) contain a box 1 motif which is able to bind JAK and activate other signal transduction cascades[13]. The ObRe which is also referred to as the soluble leptin receptor can regulate serum leptin concentration and also serves as a carrier protein delivering the hormone to its membrane receptors[14]. Not only are leptin receptors expressed in the heart but they are also regulated by various stimuli. Cardiac ischemia has been reported to have varying effects on expression of leptin receptors, with studies demonstrating that a 30 min ischemic period was associated with a decrease in leptin receptor expression and another study reporting that a 40 min ischemic period increased leptin receptor expression[11,15]. The specific role of leptin in cardiac ischemia was addressed in an elegant study utilizing cardiac-specific deletion of leptin receptors. Cardiac-specific deletion of leptin receptors resulted in a decrease in contractile function and metabolism of glucose and in an increase in mortality and morbidity following cardiac ischemia[16]. These results highlight the important cardio-protective function of leptin in cardiac ischemia due in part to its role in the regulation of cardiac metabolism which will be discussed in greater detail below. Leptin receptors in the heart are also regulated by pressure and stretch. It has been reported that pressure-overload induced cardiac hypertrophy resulted in a significant increase in the long form of the leptin receptor (ObR-B) but not the short form (ObR-A) in the heart[17]. The controversial role of leptin in cardiac hypertrophy will be addressed in the following section below.

THE ROLE OF LEPTIN IN CARDIAC HYPERTROPHY

Leptin has several functions in the heart including stimulation of fatty acid and glucose metabolism, prevention of steatosis, and protection against apoptosis (Figure 2). It also can raise blood pressure and heart rate through central mechanisms and promotes cardiac inflammation (Figure 2). Although obesity is associated with hyperleptinemia, increased cardiac mass and left ventricular (LV) wall thickness, it is unclear if leptin can directly cause cardiac hypertrophy (Figure 2). Epidemiologic studies have demonstrated positive correlations between plasma leptin levels and LV hypertrophy[18]. However, most of these observations are confounded by the fact that increased body mass and plasma leptin levels are highly correlated[19]. Obesity is also usually accompanied by hypertension which is the most common cause of cardiac hypertrophy[20]. In addition to increased blood pressure, obesity may cause cardiac hypertrophy by several other mechanisms including neurohormonal (renin-angiotensin-aldosterone system) and sympathetic nervous system activation, insulin resistance and hyperglycemia, and increased blood volume[21,22]. The exact roles of leptin in regulating cardiac structural changes in obesity such as hypertrophy are not well understood. In fact, differential hypertrophic and antihypertrophic effects of leptin have

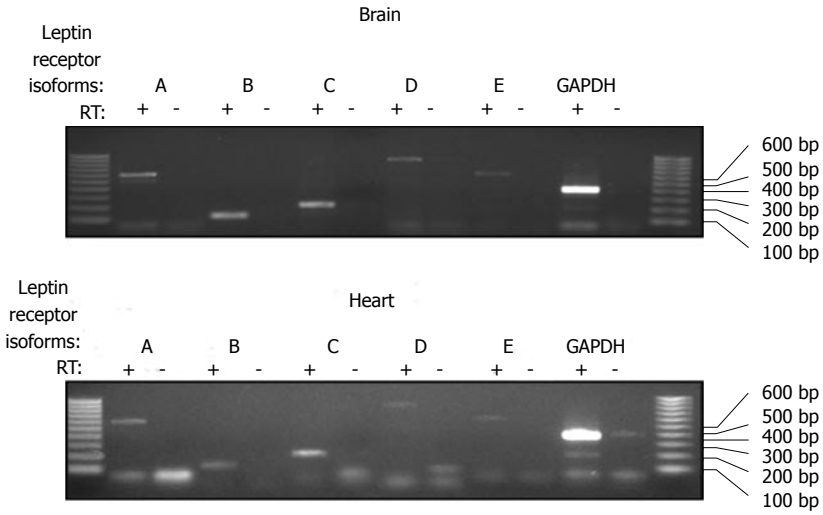

Figure 1 Comparison of leptin receptor isoforms in the mouse brain and heart. RNA was isolated from the brain and heart and reverse transcribed into cDNA. Polymerase chain reaction was then performed using primers specific for each mouse isoform of the leptin receptor as previously described[12]. All 5 of the leptin receptor isoforms were detected in the mouse heart as well as the brain.

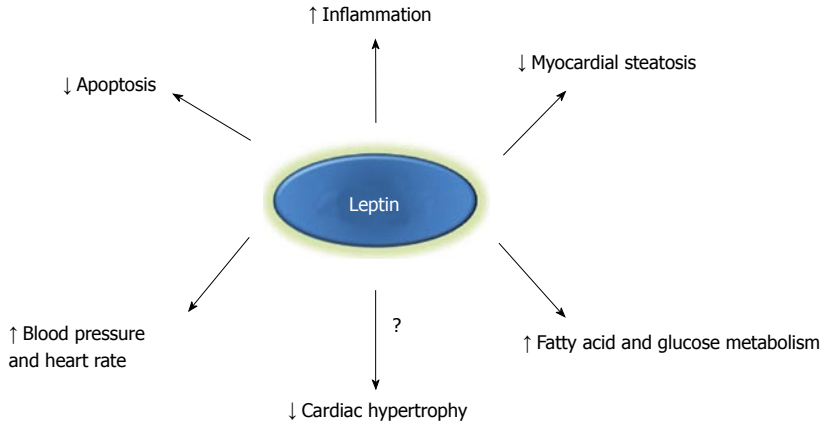

Figure 2 Potential mechanisms by which leptin may mediate cardiac function. Leptin may exert cardioprotective or maladaptive effects through hemodynamic factors such as increased heart rate and blood pressure, metabolic changes including augmented fatty acid or glucose utilization, reduced cardiac apoptosis, or structural cardiac changes such reduced cardiac lipid accumulation and possibly attenuated myocardial hypertrophy. Increased inflammation may be beneficial in some cardiac conditions (*i.e.*, post-myocardial infarction) depending on the timing and extent of the inflammatory response.

been reported and may be related to temporal effects or synergistic interactions with other obesity-associated factors.

Does leptin directly cause cardiac hypertrophy?

One of the earliest studies demonstrating a pro-hypertrophic effect of leptin comes from an experiment by Rajapurohitam *et al*[23] in which cultured neonatal rat ventricular myocytes were treated with varying concentrations of leptin. The authors observed a 42% increase in cell surface area 24 h after administration of 3.1 nmol/L leptin. Exposure to leptin also significantly increased cell size in cultured human and neonatal rat cardiomyocytes[24,25]. Leptin treatment increased matrix metalloproteinase-2 activity and collagen Ⅲ and Ⅳ mRNA expression but resulted in no change in total collagen synthesis. Tajmir *et al*[26] demonstrated hyperplasia of both murine and human cardiomyocytes in response to leptin treatment which appeared to be mediated by activation of extracellular signal-regulated kinase (ERK) 1/2 and phosphatidylinositol-3 kinase. However, studies by Piñieiro *et al*[27] did not observe any effect of Leptn to increase cell size of murine HL-1 cardiomyocytes while these *in vitro* results suggest leptin contributes to adverse cardiac remodeling and hypertrophy, the results from whole animal and human studies are not that clear regarding the direct role of leptin to cause cardiac hypertrophy.

Human patient studies have reported associations of plasma leptin levels with cardiac hypertrophy. In hypertensive insulin-resistant men, fasting plasma leptin levels were positively correlated with myocardial wall thickness, but not with LV mass. This relationship was significant even after controlling for BMI, waist-to-hip ratio and blood pressure suggesting an independent effect of leptin on cardiac structure[28]. In another study, LV mass was found to be positively correlated with leptin levels after controlling for body mass index (BMI)[29]. After gastric bypass surgery and profound weight loss, there were significant reductions in BMI, insulin resistance and leptin levels, but only leptin levels were significantly correlated with the decrease in LV mass on multivariable analyses. These clinical findings suggest that leptin may contribute to the LV hypertrophic process. In a study of 36 hypertensive men, plasma leptin was significantly predictive of echocardiographic wall thickness independent of 24 h ambulatory blood pressure. However, other significant predictors in this model included insulin sensitivity and night-time diastolic blood pressure[18].

The mechanisms by which leptin may contribute to myocardial hypertrophy are poorly understood. In addition to its powerful effects to regulate appetite and body weight, leptin also has a powerful effect to activate

the sympathetic nervous system *via* central nervous system pathways. Chronic leptin infusion increased arterial blood pressure which increases cardiac afterload and which would lead to increased cardiac hypertrophy over the long-term[30]. Leptin is also associated with increased heart rate which would also tend to increase myocardial workload and promote hypertrophy[31]. In addition to these effects, leptin may also contribute to endothelial dysfunction and vascular stiffness which could also contribute to cardiac hypertrophy[32]. It is important to note, however, that many of the reported effects of leptin are based on either short-term animal studies, *in vitro* experiments or epidemiologic data which makes it difficult to determine the direct role of leptin in regulating cardiac hypertrophy.

While it is clear that obesity is associated with cardiac hypertrophy, the role of leptin as a mediator or cause is still under investigation. Evidence strongly supporting an antihypertrophic role of leptin comes from an elegant experiment by Barouch *et al*[33] in which they evaluated LV structure and function, including LV wall thickness and mass, in *ob/ob* and *db/db* mice. To differentiate the direct effects of leptin on cardiac hypertrophy from the effects of obesity, the investigators subjected *ob/ob* mice to intravenous leptin infusion or caloric restriction. Administration of leptin significantly reduced wall thickness and reduced myocyte size by approximately 25%. While both the leptin-treated *ob/ob* mice and the calorie-restricted mice lost a similar amount of body weight, the pair fed group had no significant reduction in LV mass or wall thickness suggesting a leptin dependent effect in the reversal of myocardial hypertrophy. Additionally, the hypertrophic LV changes in the *ob/ob* mouse are not related to changes in blood pressure since these mice are normotensive[34]. Another important observation of this study was that the increase in myocardial wall thickness was not related to fatty infiltration of the heart muscle, as cardiac myocyte size was found to be increased in *ob/ob* mice[33].

Additional evidence for an antihypertrophic effect of leptin comes from experiments performed in our lab[35]. We evaluated the direct effect of leptin on myocardial lipid accumulation and LV hypertrophy in *db/db* mice and transgenic *db/db* "rescue" mice in which the normal rat leptin receptor was overexpressed or "rescued" in a cardiomyocyte-specific manner. After 30 wk of study including serial metabolic parameters and echocardiographic assessments, both the *db/db* and "rescue" mice were morbidly obese, hyperglycemic, and had high plasma triglycerides compared to lean control mice. The *db/db* mice developed significant cardiac hypertrophy and increased LV wall thickness. The "rescue" mice, in which cardiac leptin signaling was restored, had lower heart weights and LV wall thickness compared to *db/db* mice suggesting an antihypertrophic effect of leptin. If leptin had a direct hypertrophic effect, our *db/db* cardiac leptin receptor rescue mice would be primed for an increase in myocardial mass in this setting. *db/db* mice have very elevated circulating leptin levels, and our transgenic "rescue" mice had evidence of increased leptin signaling in the heart as indicated by elevated levels of phosphorylated STAT3. If increased leptin signaling directly leads to cardiac hypertrophy our transgenic "rescue" model would have developed an increase in myocardial mass and wall thickness due to high circulating leptin and augmented leptin receptor responsiveness. One limitation of this study was that we did not specifically evaluate myocyte sizes but instead measured wall thickness and heart weight[35].

In summary, the available data on the effects of leptin on cardiac growth and hypertrophy are conflicting and are summarized in Table 1. Hyperleptinemia is associated with cardiac hypertrophy but the presence of many confounding factors makes it difficult to establish a causal relationship. Furthermore, acute and chronic effects of leptin differentially regulate myocyte growth. Obesity and subsequent leptin resistance may play an important role in this relationship. Animal studies suggest that hyperleptinemia does not directly cause cardiac hypertrophy but may rather play an integral role in cardiac structural alterations that occur in response to obesity and the associated hemodynamic and metabolic changes. Additional, well controlled studies are warranted to better delineate the mechanisms by which leptin may regulate cardiac structural remodeling.

Leptin and cardiac function

In addition to its role in regulating cardiac structural changes, leptin may also be an important factor in regulating cardiac function. Leptin has been associated with pathophysiologic cardiovascular conditions including coronary artery disease and congestive heart failure[36,37]. Leptin has important effects on systemic hemodynamics and myocardial metabolism (as discussed in detail below) which may also have profound effects to regulate cardiac function. Similar to its potential implication in cardiac hypertrophy, the effects of hyperleptinemia on cardiac function have been difficult to assess given the number of confounding factors associated with obesity that all have detrimental effects on the heart. As obesity and its co-morbid conditions such as hypertension and diabetes are increasingly prevalent, understanding the relationships and mechanisms by which each of these conditions impacts the development and progression of congestive heart failure has important clinical implications for its prevention and treatment.

Elevated leptin levels have been observed in patients with dilated cardiomyopathy and have been suggested to be a marker of heart failure progression[38]. In a prospective study of 4080 older men followed for 9 years, increased BMI and circulating leptin levels were independent predictors of incident heart failure. After adjustment for BMI and other potential mediators, increased leptin levels remained significantly associated with an increased risk for heart failure in men without pre-existing coronary artery disease[39]. Leptin levels were also associated with incident congestive heart failure and cardiovascular disease in an elderly cohort

Table 1 Effects of leptin on cardiac mass and left ventricular hypertrophy

	Ref.	Findings	Effect of leptin on LVH
In vitro experiments	Rajapurohitam *et al*[23]	Exposure of cultured neonatal rat ventricular myocytes to leptin (0.31 to 31.4 nmol/L) increased cell area by 42%	Pro-hypertrophic
	Xu *et al*[25]	Exposure of cultured neonatal rat cardiomyocytes to leptin (1-1000 ng) for 4 h increased cell surface area	Pro-hypertrophic
	Piñieiro *et al*[27]	Exposure of murine HL-1 cells to leptin did not increase cell size of cardiomyocytes	Neutral
	Madani *et al*[24]	Treatment of human pediatric cardiomyocytes with 6 nmol/L leptin increased cell size by 60%	Pro-hypertrophic
	Tajmir *et al*[26]	Treatment of HL-1 cells with 60 nmol/L leptin increased cell numbers 2.3-fold	Pro-hypertrophic
In vivo experiments	Barouch *et al*[33]	6-mo-old leptin deficient *ob/ob* mice had increased myocyte diameters compared with wild-type mice. Leptin (*iv*) treatment in *ob/ob* mice completely reversed LVH and normalized wall thickness as well as reduced cellular hypertrophy by approximately 25%. Pair-feeding did not significantly reduce LV mass despite similar weight loss	Anti-hypertrophic
	Hall *et al*[35]	*db/db* mice developed LVH (increased wall thickness and heart weights). Transgenic *db/db* mice with cardiomyocyte-specific leptin receptor rescue did not cause LVH; in fact the heart weights were reduced	Anti-hypertrophic
Epidemiologic studies	Paolisso *et al*[28]	Plasma leptin level was correlated (n = 55 males) with interventricular wall (r = 0.34) and posterior wall (r = 0.38) thicknesses after adjusting for BMI and waist/hip ratio	Pro-hypertrophic
	Paolisso *et al*[18]	Study of 36 hypertensive patients demonstrating increased LV wall thickness (but not LV mass) measured by echo was associated with plasma leptin independent of BMI or waist/hip ratio (P = 0.001)	Pro-hypertrophic
	Perego *et al*[29]	Study of 31 obese subjects undergoing gastric bypass surgery demonstrated leptin was independently associated with LV mass (β = 10.66, P = 0.001). One year after surgery, decrease in LV mass only correlated with the decrease in leptin levels (P = 0.01)	Pro-hypertrophic
	Lieb *et al*[40]	Cross-sectional analysis of 432 aged (> 70 yr) participants in the Framingham Heart Study demonstrated leptin concentrations were inversely correlated with LV mass (β = -0.134, P = 0.02), left atrial size (β = -0.131, P = 0.04) and LV wall thickness (β = -0.134, P = 0.02) measured by echo	Anti-hypertrophic
	Martin *et al*[41]	In 1464 MESA Study participants who underwent cardiac magnetic resonance imaging, a 1-SD increment in leptin was associated with smaller LV mass (β = -4.66%, P < 0.01), LV volume (β = -5.87, P < 0.01), and reduced odds ratio for presence of LVH (OR = 0.65, P < 0.01) after adjustment for age, gender, race, height, and weight	Anti-hypertrophic

LVH: Left ventricular hypertrophy; BMI: Body mass index.

from the Framingham Heart Study. However, after adjustment for BMI the association with congestive heart failure was negated[40]. More recently, investigators from the Multi-Ethnic Study of Atherosclerosis demonstrated that leptin levels were not associated with incident cardiovascular events after adjustment for cardiovascular risk factors and BMI[41]. Based on these epidemiologic data, it remains unclear whether leptin is associated with development of heart failure, and if so, whether it plays a causal or compensatory role?

Leptin exerts physiologic effects that may be detrimental in states of cardiac dysfunction or heart failure. Leptin's hemodynamic effects generally increase myocardial workload *via* activation of the sympathetic nervous system. These effects include increasing resting heart rate and blood pressure[30]. Leptin may therefore act synergistically with other factors associated with obesity such as hyperglycemia, inflammation, and oxidative stress to accelerate the development of cardiovascular disease. However, it is possible that the chronic effects of leptin may have adverse consequences on myocardial function and the acute effects may provide a compensatory response to cardiac insults such as ischemia or heart failure.

Evidence for an acute beneficial effect of leptin comes from studies in experimentally-induced myocardial infarction and heart failure. McGaffin *et al*[16] induced anterior myocardial infarctions in control mice and in mice with cardiac-specific deletion of the leptin receptor. Mice lacking the leptin receptor specifically in the heart developed more LV dysfunction and had higher mortality after induction of myocardial infarction. The disruption of leptin signaling was associated with more LV dilation, hypertrophy, inflammation and adverse cardiac remodeling post-myocardial infarction. These investigators also demonstrated that many of the beneficial effects of leptin in this setting may be mediated *via* the AMP-activated protein kinase (AMPK) pathway.

We have studied the acute protective effects of leptin in a model of heart failure induced by Cre-recombinase activation[42]. Activation of Cre-recombinase is a widespread molecular tool used to conditionally delete or express genes in a tissue-specific and temporal manner. This technique has been somewhat limited due to observations by our lab and others that induction of Cre-recombinase activity in the heart can lead to transient LV dysfunction and a dramatic drop in ejection fraction[43,44]. Specifically, we reported that conditional deletion of the cardiac leptin receptor resulted in severe cardiogenic shock and death of the animals which was most likely related to impaired myocardial energy metabolism[42].

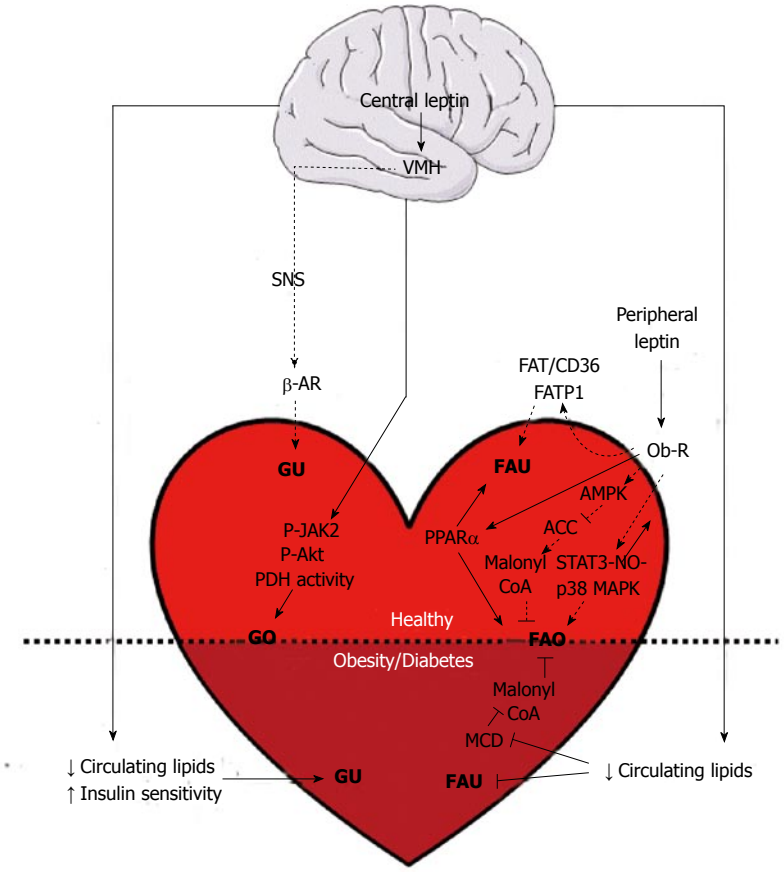

Figure 3 Cardiometabolic effects of leptin in health and obesity. Triangular and flat arrowheads represent stimulatory and inhibitory effects on the designed targets, respectively. Dotted lines indicate acute leptin effects (appearing between less than an hour and several hours of treatment), while plain lines represent chronic leptin effects (reported after several days or weeks of treatment). ACC: Acetyl-CoA carboxylase; AMPK: AMP-activated protein kinase; β-AR: Beta-adrenergic receptor; FAO: Fatty acid oxidation; FAT/CD36: Fatty acid translocase/cluster of differentiation 36; FATP1: Fatty acid transport protein 1; FAU: Fatty acid uptake; GO: Glucose oxidation; GU: Glucose uptake; MAPK: Mitogen-activated protein kinase; MCD: Malonyl-CoA decarboxylase; NO: Nitric oxide; Ob-R: Leptin receptor; P-Akt: Phosphorylated Akt kinase; PDH: Pyruvate dehydrogenase; P-JAK2: Phosphorylated Janus kinase 2; PPARα: Peroxisome proliferator-activated receptor alpha; SNS: Sympathetic nervous system; STAT3: Signal transducer and activator of transcription 3; VMH: Ventromedial hypothalamus. Horizontal black line demarcates differences between the healthy heart and the heart in obesity/diabetes.

These results emphasize the important role that leptin plays in cardiac metabolism which will be discussed in further detail in the next section.

Further evidence for a beneficial effect of leptin on cardiac function comes from experiments showing aged *ob/ob* and *db/db* mice have increased cardiac myocyte apoptosis and decreased survival compared with wild-type controls[45]. Leptin treatment significantly reduced apoptosis in *ob/ob* mice as well as in isolated myocytes. Although *ob/ob* and *db/db* mice generally have normal LV systolic function, they appear to have LV diastolic functional abnormalities[35,46]. These studies suggest that intact cardiac leptin signaling is important for normal cardiac function and may be protective against cardiac insults such as ischemia.

ROLE OF LEPTIN IN THE REGULATION OF CARDIAC METABOLISM

The role of leptin in the control of whole body energy homeostasis in humans is well established[47]. The effects of leptin on myocardial metabolism, and the consequences for cardiac adaptation in disease states, are far less well understood. Our knowledge in that area comes from studies performed on live rodents and isolated heart preparations. These studies have focused on the metabolism of glucose and free fatty acids, the main substrates for energy provision of the heart. Altogether, the investigations have revealed a dichotomy between central and peripheral actions of leptin (Figure 3). However, variations in the age or strain of animals, and in the experimental conditions employed, have made it difficult to identify with certainty the molecular regulatory pathways involved. It should also be noted that most studies used male animals only. Consequently, it is unknown whether the metabolic actions of leptin on the heart are characterized by a sexual dimorphism. This part of the review will focus first on the cardiometabolic effects mediated by leptin signaling in the brain. The metabolic consequence of leptin signaling activation in cardiac muscle will then be reviewed. Lastly, the effects of leptin on cardiac metabolism in disease states, and their impact on contractile function, will be discussed.

Centrally mediated effects of leptin on cardiac metabolism

Pioneering work performed with the leptin-deficient *ob/ob* mice demonstrated that chronic intraperitoneal leptin injection at a sub-active dose for the reduction of body weight gain or hyperinsulinemia was sufficient to normalize blood glucose levels[48]. It was later demonstrated in the same animal model that acute intravenous infusion of leptin increased glucose turnover and stimulated the uptake of glucose in peripheral organs, including the heart. The 6-fold increase in myocardial glucose uptake did not significantly impact heart rate[49]. Both intravenous and intracerebroventricular (*icv*) infusions of leptin were found to similarly increase glucose turnover in C57BL/6J wild-type mice[50]. A single bolus injection of leptin in the ventromedial

hypothalamus of young Sprague Dawley rats also resulted in a 4-fold increase in myocardial glucose uptake[51]. This increase in glucose uptake was shown to be additive to the one induced by an intravenous administration of insulin[42]. Based on these observations it was concluded that this rapid increase in peripheral glucose utilization is governed by a central mechanism, independent from insulin, and involving the activation of sympathetic nerves and the local activation of β-adrenergic receptors on target tissues[52]. A week of daily *icv* leptin administration in C57BL mice on a low-fat diet also resulted in an increase in myocardial glucose oxidation that was associated with increased phosphorylation of JAK2 and Akt kinases, and with increased pyruvate dehydrogenase activity (Figure 3). Rates of palmitate oxidation were not significantly altered, and here again, the switch toward higher glucose utilization did not modify mechanical function of the heart[53]. Thus, in rodents with normal leptin sensitivity, both acute and chronic activation of central leptin signaling favor myocardial glucose utilization through mechanisms stimulating the uptake and the oxidation of this substrate. Although the involvement of other hormonal signals cannot be ruled out, the effect seems to be independent from insulin secretion or from a change in insulin sensitivity.

Peripheral effects of leptin on cardiac metabolism

Unlike the reports on its central actions, there is little evidence to support a stimulatory effect of peripheral leptin on myocardial glucose metabolism: While a small but significant increase in glucose uptake was reported when hearts of Wistar rats were perfused in the Langendorff mode with a low dose of leptin (1 ng/mL), the effect may have been caused by the absence of fatty acids in the perfusate[54]. Indeed, in hearts of male Sprague Dawley rats perfused in the working mode with both glucose and palmitate, rates of glucose oxidation were unaffected by the presence of a pharmacological dose of leptin (60 ng/mL). Conversely, the total oxidation of fatty acids, from both exogenous (palmitate) and endogenous (triacylglycerol stores) origin, increased by 82%[55]. Using similar experimental conditions, Sharma and colleagues confirmed the existence of a leptin-mediated increase in exogenous palmitate oxidation that occurred in absence of changes for the rates of glucose oxidation[56]. Experiments performed with HL-1 cardiomyocytes partly corroborate these results: while a 1 h incubation with leptin failed to modify basal or insulin-stimulated glucose uptake and oxidation, it resulted in increased palmitate uptake and oxidation[57]. The increase in palmitate uptake was linked to the upregulation of the fatty acid transporters FATP1 and CD36. It is noteworthy that the incubation of neonatal rat ventricular myocytes with leptin for 72 h induced the expression of peroxisome proliferator-activated receptor alpha (PPARα), a key activator of fatty acid metabolism in the heart[58]. However, while increased fatty acid oxidation in HL-1 cells was traced to an increase in AMP-activated protein kinase activity and to the subsequent inhibition of malonyl-CoA production (a potent endogenous inhibitor of mitochondrial fatty acid uptake), this mechanism was not induced in the isolated rat heart[55]. Instead, in the intact heart, leptin was found to stimulate fatty acid oxidation by a STAT-3-nitric oxide-p38 MAPK-dependent mechanism (Figure 3)[56]. In conclusion, based on experimental settings where both glucose and fatty acids were present, the activation of myocardial leptin signaling rapidly stimulates fatty acid uptake and oxidation without affecting glucose oxidation. In the long term, leptin may also promote fatty acid oxidation through the upregulation of PPARα.

Metabolic effects of leptin in disease states

Obesity and diabetes are characterized by an increased reliance of the heart on fatty acid oxidation for energy provision. Sustained high rates of fatty acid uptake and oxidation inhibit both basal rates of glucose oxidation and insulin-stimulated glucose utilization, leading to a dramatic reduction in cardiac mechanical efficiency (work performed per unit of oxygen consumed)[59,60]. This metabolic remodeling has been observed in *ob/ob* mice, and persists even when the isolated hearts are perfused under low fatty acid condition[61]. However, this metabolic remodeling is reversible, and glucose intolerant patients undergoing a modest weight loss present with reduced myocardial fatty acid uptake and with improved cardiac mechanical function[62]. Sloan and colleagues elegantly demonstrated the importance of hypothalamic leptin signaling in the regulation of the balance of myocardial substrate selection during weight loss. By combining calorie restriction with leptin treatments in *ob/ob* mice, they showed that the hormone is necessary to normalize basal myocardial palmitate oxidation and to restore the insulin-mediated switch to glucose utilization[63]. The authors attributed their results to the leptin-mediated inhibition of the rise in circulating free fatty acids caused by calorie restriction, thereby leading to the normalization of myocardial fatty acid oxidation gene expression and to the improvement of myocardial insulin sensitivity. In accordance with these results, Keung *et al*[53] observed that chronic central leptin treatment (*via* intracerebroventricular infusion) of C57BL mice inhibited the increase in myocardial fatty acid oxidation caused by high-fat feeding. The effect was also linked to an improvement in insulin sensitivity and to a decrease in circulating lipid levels, with a subsequent reduction in the expression of cardiac malonyl-CoA decarboxylase, the enzyme that degrades malonyl-CoA (Figure 3). Although the absolute rates of myocardial glucose oxidation were unaffected, this resulted in an increased contribution of glucose metabolism to Krebs cycle activity[53]. Lastly, in a rat model of insulin-dependent diabetes, increased glucose uptake in cardiac muscle as well as in several other organs, together with the suppression of hepatic glucose output, is part of the mechanism by which the activation of central leptin signaling normalizes gly-

cemia[64].

Heart failure also elicits disturbances in the balance between fatty acid and glucose oxidation. Severe heart failure has generally been associated with increased glucose oxidation and decreased fatty acid oxidation, a switch in substrate meant to improve mechanical efficiency of the stressed heart[65]. The expression of leptin and of its receptor increases more than 4-fold in the failing human heart, suggesting increased activity of this signaling pathway as the condition progresses[66]. In a murine model with heart failure from ischemic origin, cardiomyocyte-specific deletion of the leptin receptor exacerbated the deterioration of myocardial structure and function. While myocardial metabolism was normal in the unstressed heart, cardiac specific loss of leptin receptors completely inhibited the switch toward increased glycolysis and glucose oxidation post myocardial infarction and enhanced the development of heart failure[16,67]. These results indicate that both central and cardiac leptin signaling play an important role in metabolic adaptation of the heart in heart failure. The beneficial effects of leptin are achieved either by favoring the return to a normal energy balance in dysregulated metabolic states, or by facilitating the transition toward a state of improved mechanical efficiency.

What is lipotoxicity?

Excess fatty acids as occurs in individuals who consume too many calories or expend too few calories are normally stored as triglycerides in white adipose tissue. However, when there is a defect in the amount of adipose tissue as seen in lipodystrophy or an excessive amount of fatty acids are consumed which exceed the ability of white adipose tissue to expand as seen in obesity, fatty acids can start to accumulate in organs such as the heart. With obesity, the substrate preference and utilization of the heart becomes altered such that substrate utilization is shifted towards fatty acids. This switch towards fatty acid metabolism is promoted by the increased expression of proteins involved in fatty acid oxidation such as carnitine palmitoyltransferase-1 (CPT1). These alterations in normal fatty acid oxidation can promote the formation of toxic lipids like ceramide and contribute to cardiac dysfunction observed in obesity[68-71]. Several studies have demonstrated that increases in ceramide production which arises by condensation of unoxidized palmitoyl-CoA and serine causes cells including cardiac myocytes to undergo apoptosis and die[72,73]. Diacylglycerol (DAG) is another lipid that can mediate fatty acid-induced toxicity. DAG acyl transferase (DGAT) is the enzyme responsible for the addition of the final fatty acid onto DAG to convert it to triglyceride. Transgenic mice which overexpress DGAT in the heart have increased lipid accumulation in the form of increased triglyceride levels but they are protected from lipotoxic induced cardiac dysfunction[74]. Thus, the specific role of increased triglyceride accumulation in the development of cardiac lipotoxicity remains controversial.

Role of lipotoxicity in heart disease

Descriptions of fat storage in the heart date all the way back to the 1800's and were thoroughly described by Smith *et al*[75] in the 1930's. Over 10 years ago Sharma and colleagues described intramyocardial lipid accumulation in human heart failure that was identical to that found in the zucker diabetic fatty (ZDF) rat[76]. These studies clearly demonstrated that increased myocardial lipid accumulation was associated with an upregulation of PPARα responsive genes and an increase in the inflammatory marker tumor necrosis factor-α (TNF-α) both of which are thought to contribute to the cardiac contractile dysfunction observed in both ZDF rats and human patients[76]. Recent advances in cardiac imaging techniques has resulted in the measurement of cardiac triglyceride levels in various patient populations with mixed results regarding the significance of increased cardiac triglyceride accumulation on cardiac function. Several studies in overweight and insulin resistant patients have positively correlated increased myocardial triglyceride levels with alterations in cardiac structure and function[77,78]. Myocardial triglyceride accumulation has also been found to contribute to the pathology of severe aortic stenosis[79]. While these studies have implicated cardiac triglyceride accumulation to alterations in cardiac function several studies have not reported such a correlation. McGavock *et al*[80] reported increased myocardial triglyceride accumulation in the absence of any changes in cardiac function in patients with type Ⅱ diabetes. Likewise studies by Nyman correlated increased epicardial and pericardial fats but not intramyocardial triglyceride accumulation with alterations of cardiac function in male patients with metabolic syndrome[81]. Lastly, studies by Liu *et al*[82] reported that although myocardial triglyceride levels correlated with increases in BMI, they failed to correlate with alterations in cardiac function in healthy African-American males. Although increases in cardiac triglyceride levels have been documented in several pathological conditions as well as in the metabolic syndrome and type Ⅱ diabetes, their specific role in altering cardiac function in these conditions is still unresolved.

There are several experimental models of cardiac lipotoxicity in rats and mice. The most studied are the models of leptin signaling deficiency such as the ZDF rat and the *ob/ob* and *db/db* mouse models[83]. Several other models of cardiac lipotoxicity have been developed in which myocardial fatty acid uptake is increased above normal by overexpression of fatty acid transport protein 1 (FATP1) or cardiac specific expression of long chain acyl CoA synthase 1 (ACS1)[84,85]. Models of cardiac lipotoxicity have also been created by overexpression of enzymes CPT1 and the transcription factor PPAR-α stimulating the β-oxidation of fatty acids. Interestingly, both cardiac specific deletion and overexpression of PPAR-α result in cardiac lipid accumulation with the deletion of PPAR-α decreasing expression of critical enzymes involved in β-oxidation

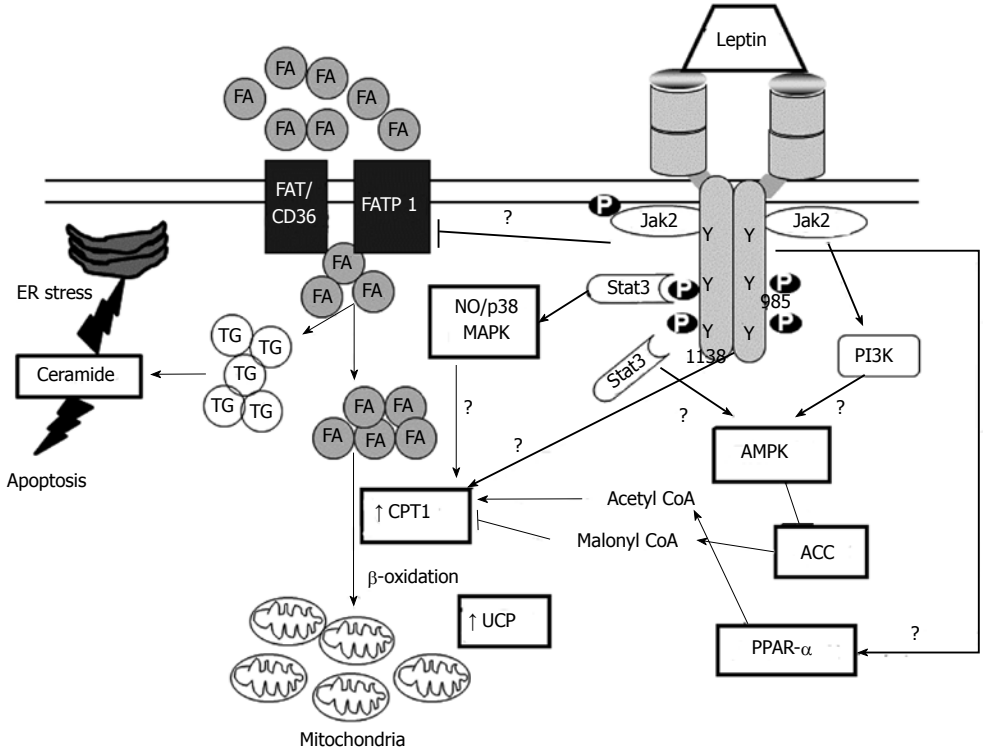

Figure 4 Leptin and cardiac lipotoxicity. Triangular and flat arrowheads represent stimulatory and inhibitory effects on the designed targets, respectively. Heavier lines represent proposed actions of leptin. ACC: Acetyl-CoA carboxylase; AMPK: AMP-activated protein kinase; CPT-1: Carnitine palmityl transferase-1; ER: Endoplasmatic reticulum; FA: Fatty acids; FAT/CD36: Fatty acid translocase/cluster of differentiation 36; FATP1: Fatty acid transport protein 1; NO: Nitric oxide; P-JAK2: Phosphorylated Janus kinase 2; PPARα: Peroxisome proliferator-activated receptor alpha; STAT3: Signal transducer and activator of transcription 3; TG: Triglycerides; UCP: Uncoupling protein.

of fatty acids and overexpression of PPAR-α resulting in increased transport of fatty acids into the heart[86,87].

While the mechanism of cardiac lipid accumulation in these various models may differ, the end result by which lipids cause cardiac dysfunction is similar in these various models. The accumulation of lipids such as ceramide and DAG to toxic levels promotes cardiomyocyte apoptosis *via* increases in reactive oxygen species production which induces non-coding RNAs such as growth arrested DNA-damage inducible gene (*GADD*)[88,89]. Accumulation of these toxic lipids also promotes endoplasmic reticulum stress which induces eukaryotic elongation factor and leads to cell death[90]. Excess lipid accumulation in the heart also interferes with insulin signaling resulting in cardiac insulin resistance and down-regulation of the IRS1/PI3K/Akt pathway which is a protective pathway in the heart[91].

Role of leptin in protection against cardiac lipotoxicity

Plasma leptin levels are elevated in individuals with obesity due to expansion of white adipose tissue mass. In obesity, it is hypothesized that there is central resistance to the effects of leptin on appetite and energy expenditure which results in increased adiposity and an increase in plasma leptin levels[7]. The increase in plasma leptin levels is also believed by some investigators to be an underlying cause for cardiovascular pathology in obesity[92,93]. However, an alternative hypothesis put forth by Unger proposes that increased plasma leptin levels are a protective mechanism preventing steatosis of organs such as the liver, pancreas, and heart in obesity[94].

Much of what is known about the role of leptin in protecting against lipotoxicity is derived from strains of leptin and leptin receptor deficient rodents. For example, leptin receptor deficient rats and mice are characterized by marked steatosis of peripherial organs such as the heart. Previous studies by Sharma *et al*[76] have reported that intracardial lipid accumulation and subsequent alterations in cardiac function and gene expression seen in the ZDF rat are remarkably similar to that observed in human patients with heart failure. Likewise studies in leptin receptor deficient *db/db* mice have also reported increased cardiac triglyceride accumulation that is associated with the development of cardiomyopathy and alteration of cardiac metabolism[95-97]. The leptin deficient *ob/ob* mouse also displays severely increased cardiac triglyceride levels associated with diastolic dysfunction[46]. Interestingly, the alterations in cardiac metabolism and cardiac lipid accumulation characterizing the *ob/ob* mouse appear to be totally dependent on leptin insufficiency as calorie restriction used to normalize body weight does not improve the increase in plasma fatty acid levels, the enhanced uptake of fatty acids by the heart or the increase in cardiac lipid accumulation[63]. Both central and peripheral administration of leptin restored myocardial insulin sensitivity and decreased myocardial fatty acid transport and lipid accumulation

independently of calorie restriction[63].

The important role of leptin to protect against lipotoxicity was first demonstrated in the liver and pancreas where adenoviral restoration of leptin receptor in these tissues in ZDF rats decreased triglyceride accumulation and protected against lipotoxic injury[98,99]. In the heart, increases in plasma leptin levels achieved by adenoviral overexpression of leptin in the liver were able to normalize cardiac triglyceride levels and restore normal cardiac function and histology in cardiac specific acyl CoA synthase transgenic mice which are a model of severe cardiac steatosis[100]. We recently reported that cardiac specific overexpression of leptin receptors normalized cardiac triglyceride levels and diastolic function in *db/db* "rescue" mice despite these mice being severely obese, hyperglycemic, and hyperlipidemic[35]. This effect was associated with enhanced STAT3 phosphorylation in the hearts suggesting that activation of this pathway is involved in the protection against lipid accumulation in the heart[35].

At the molecular level, leptin can protect against cardiac lipotoxicity through several pathways. One mechanism by which leptin protects against cardiac lipotoxicity is through induction of fatty acid oxidation. Fatty acid oxidation is highly regulated by the AMPK pathway. AMPK can phosphorylate acetyl-CoA carboxylase (ACC) and malonyl CoA decarboxylase (MCD). Phosphorylation of these proteins has opposite effects on their activity which results in decreased levels of malonyl CoA which is the first committed step in lipogenesis and a powerful inhibitor of carnitine palmityl transferase-1 (CPT-1)-mediated fatty acid oxidation (Figure 4). Previous studies in skeletal muscle have demonstrated that leptin can increase AMPK phosphorylation to promote fatty acid oxidation[101]. However, acute leptin treatment (60 min) in the isolated working rat heart stimulated fatty acid oxidation without any changes in AMPK phosphorylation state, ACC activity, or malonyl-CoA levels[55]. These results suggest that leptin may stimulate cardiac fatty acid oxidation through a mechanism that does not include AMPK activation; however, the effects of chronic leptin exposure *in vivo* have not been determined. Leptin may also promote fatty acid oxidation in the heart by decreasing the sensitivity of CPT-1 to malonyl CoA *via* an Akt related signaling pathway[102]. Uncoupling proteins are another potential pathway by which leptin may increase fatty acid oxidation. Leptin can act centrally to increase uncoupling protein levels *via* β-adrenergic mediated mechanism,and the hormone may also directly regulate uncoupling protein levels in skeletal muscle and the heart[103]. Leptin can also increase cardiac fatty acid oxidation through a STAT-3–nitric oxide–p38 MAPK-dependent mechanism (Figure 4)[56]. Leptin may also protect against cardiac lipotoxicity by its actions on fatty acid transport into cardiac myocytes. Leptin has been demonstrated to decrease the levels of both the fatty acid transport protein, fatty acid translocase (FAT/CD36), and plasma membrane-associated fatty acid-binding protein (FABPpm) in skeletal muscle; whereas, it has been reported to increase both FAT/CD36 as well as FATP1 in cultured mouse cardiomyocytes[57]. These results from cultured cells are in opposition to studies in leptin deficient *ob/ob* mice in which the levels of expression of genes that stimulate fatty acid uptake were increased in the heart[46]. Although the exact mechanism(s) need to be worked out, it is more than likely that the stimulation of fatty acid oxidation by leptin in the heart reduces the amount of lipid intermediates such as ceramide and DAG below toxic levels[104]. This in turn decreases lipid mediated apoptosis and protects cardiac function in obesity (Figure 4).

CONCLUSION

Leptin is a hormone derived from adipose tissue which undoubtedly plays an essential role in the regulation of body weight and appetite. However, emerging studies have demonstrated that leptin is also a critical hormone for the cardiovascular system which can regulate metabolism and function of the heart. It is clear that leptin exerts diverse functions in the heart (Figure 2). While some of leptin's effects can be deleterious to cardiac function primarily through its central actions on blood pressure and heart rate, its potential growth effects on the heart to promote cardiac hypertrophy are not clear. Leptin does have beneficial actions on myocardial fatty acid and glucose metabolism and the loss of cardiac leptin signaling can adversely affect the heart's response to stresses such as transient ischemia. Leptin may also directly protect the heart against excessive lipid accumulation in obesity. The development of leptin receptor antagonists has resulted in some investigators suggesting that blockade of leptin signaling in the heart may be beneficial in obesity to attenuate cardiac hypertrophy and improve cardiac function[105-107]. However, given leptin's beneficial actions on cardiac metabolism and lipid accumulation, any intervention on leptin's action in the heart must be considered very carefully. Clearly, more animal studies are needed to unravel the biological roles and mechanistic actions of leptin before any interventional studies specifically targeting leptin in the heart are undertaken.

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REVIEW

Coronary physiology assessment in the catheterization laboratory

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Abstract

Physicians cannot rely solely on the angiographic appearance of epicardial coronary artery stenosis when evaluating patients with myocardial ischemia. Instead, sound knowledge of coronary vascular physiology and of the methods currently available for its characterization can improve the diagnostic and prognostic accuracy of invasive assessment of the coronary circulation, and help improve clinical decision-making. In this article we summarize the current methods available for a thorough assessment of coronary physiology.

Key words: Coronary heart disease; Coronary physiology; Endothelial dysfunction; Microvascular dysfunction; Fractional flow reserve; Coronary flow reserve; Index of microcirculatory resistance

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Core tip: Assessment of the coronary circulation in the cathlab cannot be limited to angiography nowadays. The interventional cardiologist needs to be aware of current knowledge on coronary physiology and of the methods and measurements available for its characterization in clinical practice and research. In this article we review the main methods to assess the functional severity of coronary stenosis, myocardial blood flow, microvascular circulation, and endothelial function.

Díez-delhoyo F, Gutiérrez-Ibañes E, Loughlin G, Sanz-Ruiz R, Vázquez-Álvarez ME, Sarnago-Cebada F, Angulo-Llanos R, Casado-Plasencia A, Elízaga J, Fernández-Avilés Díaz F. Coronary physiology assessment in the catheterization laboratory. *World J Cardiol* 2015; 7(9): 525-538 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i9/525.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i9.525

INTRODUCTION

Physicians rely on angiography to assess the coronary vasculature of patients with symptoms of myocardial ischemia. However, angiography has a low interobserver agreement[1], and acknowledged limitations for the assessment of myocardial ischemia in a variety of settings, such as intermediate, eccentric or diffuse coronary stenosis[2]. Notably, intermediate lesions are the most frequently found in coronary angiography[3]. The importance of determining which lesions truly produce ischemia and thus require intervention is underscored by clinical trials showing that revascularization of non-ischemia inducing stable lesions does not improve patient outcomes, and may in fact be deleterious[4-6]. Also, a considerable percentage of patients referred to the catheterization laboratory for angina, or even myocardial infarction, have angiographically normal, or only mildly diseased, coronary arteries[7], which highlights the importance of factors beyond epicardial fixed stenosis in the development of myocardial ischemia. Among these factors, coronary microvascular disease and coronary tone dysregulation due to endothelial dysfunction are frequent causes of myocardial ischemia[8-10]. Furthermore, a normal coronary angiogram does not accurately predict prognosis in all patients, since patients with microvascular or endothelial dysfunction have an increased risk of major adverse cardiac events[11].

This article reviews the most important methods currently available to the invasive cardiologist for a comprehensive physiological assessment of the coronary circulation. After a brief reminder of the coronary structure and the physiology of flow regulation, we will discuss the contemporary methods used to assess coronary flow, flow reserve, epicardial stenosis, microvascular function, and, finally, endothelial function.

CORONARY STRUCTURE AND PHYSIOLOGY

From a physiological perspective, the coronary circulation is structured in three main compartments. The first compartment (R1) is formed by the large epicardial coronary arteries, with a size over 500 μm. These are the conduction vessels, which offer minimal resistance to flow under normal conditions, accounting for less than 10% of the overall resistance of the coronary circulation. Accordingly, blood pressure remains unaltered along these vessels. The second compartment (R2) is formed by extramyocardial prearterioles, 100-500 μm in diameter. The third coronary compartment is formed by arterioles (< 100 μm) and capillary vessels. The second and third compartments, generically known as "microcirculation", are accountable for over 90% of the total coronary resistance, and therefore are the main regulators of flow[3,12].

The microvascular compartments are responsible for coronary autoregulation of flow. Because myocardial extraction of oxygen is very high at rest, an increase in oxygen demands must be met with an increase in coronary blood flow. Intramyocardial arterioles respond to metabolic signals, directly diffused from the myocardium, with vasodilation or vasoconstriction. When arterioles relax to reduce resistance and increase myocardial flow, proximal prearterioles and large epicardial arteries respond with flow-mediated dilation, which happens mainly through the release of nitric oxide by the endothelium[12].

In pathological conditions, when a severe epicardial stenosis develops, epicardial resistance increases causing a pressure drop in the distal circulation. This is registered by the prearterioles, which respond with vasodilation to maintain a normal flow and pressure in the arteriolar compartment. It is through this autoregulation that the coronary circulation manages to maintain myocardial blood flow within a normal range in the face of moderate or even severe coronary atherosclerosis. It is also because of this mechanism that the functional significance of a coronary stenosis may be obscured to the interventional cardiologist at rest, and become evident only under conditions of maximal hyperemia.

CORONARY BLOOD FLOW MEASUREMENT

There are currently two methods available for measuring coronary blood flow in clinical practice: Doppler velocity and thermodilution. Both methods require engaging the coronary artery with a guide catheter, and introducing an intracoronary diagnostic 0.014 wire in the vessel. Heparin must be administered before the procedure, at the same doses as used during percutaneous coronary intervention.

Doppler-velocity coronary flow measurement

Coronary blood flow can be assessed by blood velocity measurement using an intracoronary Doppler wire (Flowire, Volcano Corp, San Diego, CA, United States)[13]. After engaging the coronary artery with a guiding catheter and administering heparin, the Doppler wire is positioned into the artery, usually at a proximal segment. Doppler-derived blood flow velocity is recorded in a dedicated console, and the average peak velocity (APV) is calculated with the use of integrated automatic software. Coronary flow is then estimated from the APV and the crossectional vessel area, 5 mm distal to the tip of the wire. The vessel area can be calculated from the angiographic vessel diameter, or directly measured by intravascular ultrasound or optical coherence tomography. Thus, the formula to calculate the coronary blood flow by Doppler is:

$$CBF = 0.5 \times APV \times (D^2 \pi)/4$$

where CBF is coronary blood flow (cm^3/s); APV is

Table 1 Substances used in the catheterization laboratory for coronary vascular function assessment

Substance	Doses	Site of action	Endothelium response	Effect
Adenosine	Iv: 140 μg/kg per minute Ic: 20-150 μg bolus	Microvascular	Independent	Direct vasodilation
Acetylcholine	Ic: 10^{-6} M/10^{-5} M/ 10^{-4} M	Micro and macrovascular	Dependent	Vasodilation if normal endothelial function; vasoconstriction if endothelial dysfunction
Nitroglycerin	Ic: 200 μg bolus	Macrovascular	Independent	Vasodilation
Nitroprusside	Ic 0.3-0.9 μg/kg bolus	Micro and macrovascular	Independent	Vasodilation
Papaverine	Ic: 8-20 mg bolus	Micro and macrovascular	Independent	Enzyme Phosphodiesterase inhibition Vasodilation
Regadenoson	Iv: 400 μg bolus	Microvascular	Independent	Adenosine receptor agonist vasodilation

average peak velocity (cm/s); and D is coronary diameter (cm).

Thermodilution coronary blood flow measurement

Coronary blood flow can be estimated by the indicator dilution method, using an intracoronary thermodilution wire (PressureWire, St Jude Medical Inc.; St. Paul, MN, United States)[14]. This wire has two temperature sensors, located at its proximal and distal parts. The wire is introduced into the coronary artery, until the more distal sensor is at least 50 mm away from the catheter tip. A bolus of 3 mL of saline injected through the guiding catheter produces a change in temperature that is recorded by both sensors, and a thermodilution curve is recorded. This is repeated 3 times and the results are averaged. Flow is derived from the thermodilution formula:

$$CBF = V/Tmn$$

were *CBF* is coronary blood flow (cm^3/s); *V* is vessel volume (cm^3) between the injection site and measuring site; and *Tmn* is mean transit time (s), which is calculated by the system console from the thermodilution curve.

As can be appreciated, both methods for measuring coronary blood flow require estimation of the vessel crossectional area or the vessel internal volume, which introduces a source of inaccuracy, and limits their actual use in clinical practice. Fortunately, however, both methods are well suited for a simple and reliable estimation of the most important flow-derived measurement: coronary flow reserve.

CORONARY FLOW RESERVE

Coronary flow reserve (CFR) is defined as the ratio between coronary blood flow at maximal hyperemia and at baseline condition[15]. It expresses the capacity of the coronary circulation to respond to a physiological increase in oxygen demands with a corresponding increase in blood flow. In animals and healthy subjects CFR is usually over 3, meaning their coronary circulation can triple the baseline flow when needed. In humans with chest pain and angiographically normal coronary arteries, however, the average CFR is lower, at 2.7 ± 0.6[16]. Therefore, a cutoff value of 2.0 has been widely accepted for CFR in the clinical practice[3]. Because it is a ratio of two flows, CFR is dimensionless.

Two different methods of assessing CFR invasively are available, based on the previously described systems for coronary flow measurement: Doppler and thermodilution. In both cases, flow determination is made at baseline, and then repeated under maximal hyperemia. Hyperemia can be achieved with several drugs, such as papaverine, nitroprusside or adenosine, but most often the latter is used. A complete description of the main substances used in the catheterization laboratory is shown in Table 1.

Adenosine produces a direct, endothelium-independent vasodilation of the coronary microcirculation, while having no appreciable effect on the epicardial vessel. It can be administered intravenously, at a dose of 140 μg/kg per minute[17], which usually achieves maximal stable hyperemia in 2-3 min. A central vein or a large brachial one must be used for the drug to reach sufficient concentration in the coronary circulation. Alternatively, hyperemia can be achieved by a single intracoronary bolus of adenosine administered through the guiding catheter. Doses for intracoronary injection range from 30-60 μg in the left coronary artery, and 20-30 μg in the right[3]. Higher doses, however, have been shown to be safe[18,19].

CFR can be assessed by coronary Doppler, using the method described above for flow measurement[13]. After engaging the artery with a guiding catheter, the wire is advanced and positioned at a segment where a stable Doppler signal is obtained, away from a coronary stenosis and branch ostia. The wire must not move between baseline and hyperemia measurements. Thus, since adenosine does not induce epicardial vasodilation, and the wire position does not change throughout the procedure, the crossectional area of the vessel can be assumed constant and removed from the flow equation, which leaves a simplified formula for CFR estimation:

$$CFR = APVh/APVb$$

where APVh is average peak velocity (cm/s) during maximal hyperemia, and APVb is average peak velocity

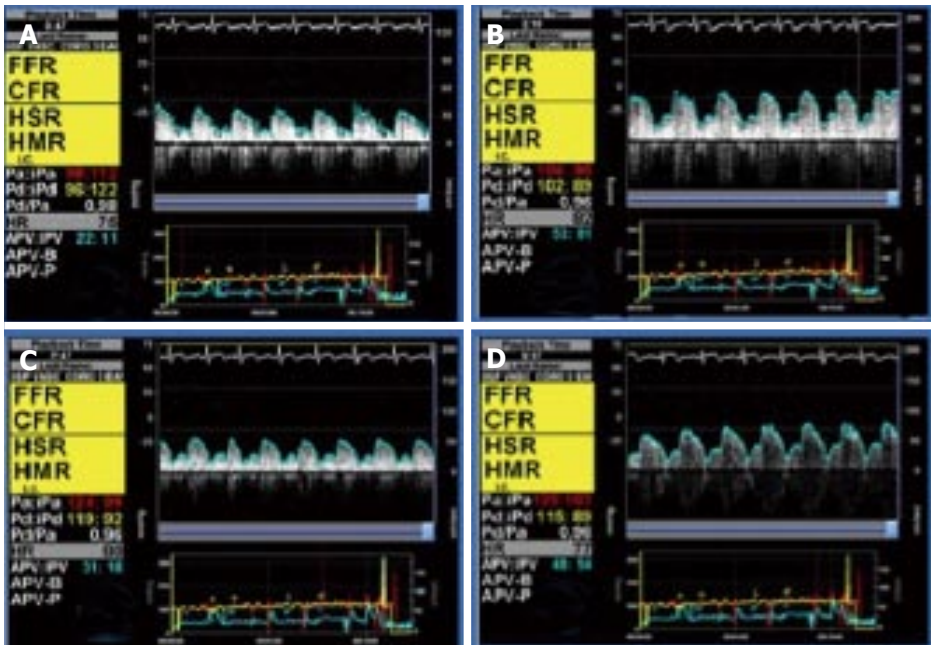

Figure 1 Microvascular function measured by intracoronary Doppler. A shows an intracoronary Doppler tracing at baseline condition, with an APV of 22 cm/s; B shows Doppler at the same position during maximal hyperemia, induced with an adenosine intracoronary bolus of 200 μg, with an APV of 53 cm/s. CFR is therefore 2.4, indicating a normal endothelium-independent microvascular function; in C and D, increasing doses of intracoronary acetylcholine have been administered; the APV is compared with the baseline tracing to determine the degree of microvascular vasodilation induced by acetylcholine, which in this case is normal, suggesting a normal endothelium-dependent microvascular function. CFR: Coronary flow reserve; APV: Average peak velocity.

(cm/s) at baseline condition. Figure 1 shows an example of CFR measurement with intracoronary Doppler.

Similarly, CFR can be calculated with the use of the thermodilution technique, by comparing mean transit time between hyperemia and baseline[17]. The pressure-temperature wire must be advanced distally into the artery, since mean transit time is more reproducible when the distal thermistor is at least 50 mm away from the catheter tip[14]. Care should be taken not to move the wire from the original position where baseline measurements are made. After three baseline thermodilution curves are obtained, hyperemia is achieved by intravenous infusion of adenosine.It is important to use intravenous administration, because the effects of an intracoronary bolus only last a few seconds, and will thus not suffice to obtain the thermodilution curves under stable maximal hyperemia. Finally, CFR is calculated with the equation:

$$CFR = Tmn.b/Tmn.h$$

where Tmn.b is mean transit time at baseline (s), and Tmn.h is mean transit time during hyperemia (s). Note that, because transit time is inversely related to flow, in this equation the hyperemia factor is in the denominator, and the baseline in the numerator, conversely to the Doppler method. An example of this technique can be found in Figure 2.

Pitfalls and contraindications

Since both thermodilution and Doppler techniques require the use of adenosine, the most common side effects associated are those described to this substance: bradycardia, hypotension, flushing, dyspnea and chest discomfort; however, the effects of adenosine disappear in seconds after the infusion is stopped or the bolus is administered, so concerning side effects are exceptional. Probably the only truly serious complication of adenosine administration is persistent bronchospasm, which is why it should be avoided in asthmatic patients[20]. If bronchospasm occurs, adenosine may be antagonized with theophylline[21].

The procedure is safe in experienced hands. However, physicians must be aware of the generic potential complications related to the insertion of guiding catheters and wires in the coronary arteries, such as coronary thrombosis, dissection, and spasm.

CFR has two main limitations. First, when an abnormal CFR value is obtained in a stenotic artery, it does not pinpoint the exact level at which flow is limited - that is, it does not help differentiate between epicardial and microvascular flow limitation. Second, given that CFR arises from the ratio of hyperemic to baseline flow, any disturbances in the baseline condition of the patient (tachycardia, stress, vasoactive drugs, abnormal loading conditions, *etc*.) will alter the ratio, thus possibly rendering a falsely abnormal CFR value.

Since CFR assesses the whole coronary vascular tree (*i.e.*, macrovascular and microvascular compartments), a normal CFR value reflects a basically healthy coronary circulation. The best CFR cutoff value for the detection of inducible ischemia is around 2.0, according to most studies[22-27]. The same cutoff value is useful to decide safe deferral of percutaneous coronary intervention when

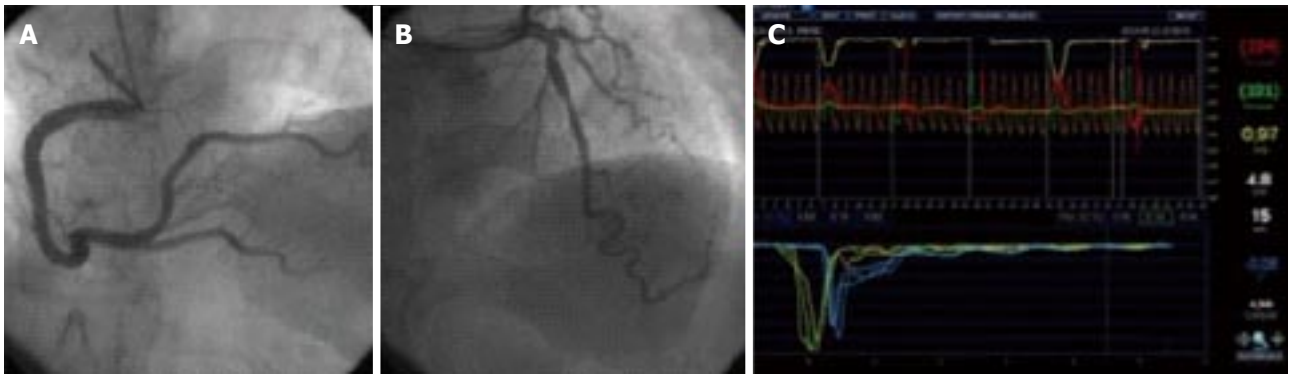

Figure 2 Coronary flow reserve measured by thermodilution. A 60-year-old woman with episodes of atypical chest pain was referred to the catheterization laboratory for coronary angiography. A and B: Show angiographically normal epicardial coronary arteries. A microcirculation study was performed, using a thermodilution PressureWire, and intravenous adenosine for hyperemia; C: Shows the thermodilution curves, with a mean transit time of 0.70 s at baseline and 0.15 s during hyperemia, and a resulting coronary flow reserve of 4.5. Index of Microvascular Resistance was 15, within normal range. We concluded that microvascular function was preserved.

assessing angiographically intermediate lesions[28,29]. A reduced coronary flow reserve, on the other hand, is an independent predictor of poor clinical outcomes in diverse settings, such as angina without severe coronary stenosis[30] and percutaneous coronary intervention[31].

Conclusion

In conclusion, CFR is a simple measurement of flow, which evaluates both the epicardial and microvascular compartments, and usually reflects normal physiology and good prognosis when it is found to be within normal limits. But other measures are needed in order to specifically investigate epicardial and microvascular disease. These measures are described and discussed below.

MEASURES OF EPICARDIAL CORONARY OBSTRUCTION

Fractional flow reserve

As we described earlier in this article, the small vessels of the heart, below 400 μm, are responsible for most of the coronary resistance, and therefore for the regulation of myocardial flow. These vessels autoregulate their resistance with the purpose of maintaining a constant myocardial blood flow independently of blood pressure, across a wide range of pressures. Similarly, when a coronary stenosis appears, the microvascular circulation regulates the resistance to flow to compensate for the stenosis.

In a state of steady maximal hyperemia, as can be achieved with adenosine, coronary autoregulation is abolished, and coronary blood flow is directly proportional to blood pressure. This principle has been used to substitute the measurements of flow by the more simple and reproducible measurements of pressure[32]. Because epicardial stenoses produce a pressure drop due to friction and separation of flow across the obstruction, different pressures can be obtained proximally and distally to a coronary stenosis, and, in a state of hyperemia, these pressures can be considered proportional to flow. Thus fractional flow reserve (FFR) arises from the ratio of the maximal flow achievable by the coronary artery with the epicardial stenosis, compared with the theoretical maximal flow of the same artery without the stenosis. Because in normal conditions the intracoronary pressure does not vary along the epicardial artery, the blood pressure at the tip of the guiding catheter is chosen to represent the theoretical pressure of the non-stenotic artery; this is compared to the pressure detected by a pressure wire distal to the stenosis. Although theoretically venous pressure should be taken into account, in clinical practice it is disregarded, and the simplified equation for FFR is used:

$$FFR = Pd/Pa$$

where Pd is the mean pressure distal to the stenosis (mmHg), recorded by the pressure wire, and Pa is the mean aortic pressure (mmHg), recorded by the tip of the guiding catheter.

To measure FFR, the coronary artery should be engaged with a guiding catheter, as with previous methods. Intracoronary nitroglycerin is administered to abolish epicardial reactivity, and a pressure wire (PressureWire, St Jude Medical Inc., St. Paul, MN, United States; or PrimeWire Prestige, Volcano Corp., San Diego, CA, United States) is advanced into the artery. Pressure is balanced against the fluid filled guiding catheter placing the wire transducer at the tip of the catheter, and then the lesion under investigation is crossed with the wire. Maximal hyperemia is induced, and the simultaneous pressure tracings of the wire and the catheter are recorded. FFR is automatically calculated with integrated software, using the mentioned equation.

Hyperemia is usually achieved with adenosine, either intravenous (140 μg/kg per minute)[33] or by intracoronary bolus. Adenosine bolus doses vary from 40 to 150 μg[33,34], although higher doses have been

proposed and deemed safe[18]. Alternatively, other drugs may be used, such as papaverine, at doses of 8-20 mg[33]; regadenoson, in a single intravenous bolus of 400 μg[35]; or nitroprusside, in intracoronary bolus of 0.3-0.9 μg/kg[36,37]. These three have the advantage of providing a longer hyperaemic plateau than intracoronary adenosine, but have been less extensively tested in the clinical setting.

The theoretical normal value of FFR in a coronary artery without stenosis is 1, since there should be no appreciable pressure drop along the vessel. A cutoff value of 0.75 (expressing a maximal-flow reduction of 25% attributable to the epicardial stenosis) accurately predicts inducible ischemia[38-40]. The most important clinical studies, however, set a cutoff of 0.8 for safe deferral of coronary intervention[41,42], and accordingly, the current European[43] and American[44] guidelines for revascularization recommend intervention in cases of coronary stenosis with FFR $\leqslant$ 0.8. As pointed out by Pijls *et al*[33], less than 10% of lesions fall into this grey area between 0.75 (almost certain ischemia) and 0.8 [safe deferral of percutaneous coronary intervention (PCI)]. In these cases, sound clinical judgement should be applied. It should also be noted that, while great emphasis has been made on cutoff points, the FFR values express a continuous rather than dichotomic function of risk[45], which highlights the importance of keeping a clinical perspective and evaluating the global risk/benefit profile all treatment options[46].

Pitfalls and contraindications

FFR is a feasible and reproducible technique, minimally modified by the baseline characteristics and hemodynamic status of the patient. Despite its reproducibility, some pitfalls and limitations have been reported.

Pharmacological side effects of adenosine are the same as those described in CFR. Accordingly, the patient must be in a stable hemodynamic condition, and adenosine should be avoided in patients with bronchospasm, severe hypotension, bradycardia or conduction disturbances.

In patients with sequential lesions or diffuse coronary disease, FFR does not provide precise information on which specific lesion is responsible for the ischemia. In such patients, the pressure pullback recording during stable hyperemia may allow identification of the culprit lesion. In order to perform this pullback recording, intravenous adenosine should be used, since an intracoronary bolus will not provide stable hyperemia.

Attention should always be paid to careful technique. The pressure wire signal must be carefully balanced at the tip of the catheter, and the balancing checked at the end of the procedure to rule out pressure drift. The tip of the catheter must be correctly positioned, to avoid damping of the pressure signal and obstruction of the coronary ostium. Submaximal hyperemia may occur, especially if a small peripheral vein is used. In this case, a central vein or an intracoronary bolus should be used to obtain maximal hyperemia.

Finally, FFR is not recommended to assess unstable thrombotic coronary lesions, *i.e.*, in acute myocardial infarction, or when thrombus or instability are evident, since pressure drop across the stenosis would provide an incomplete assessment of the risk associated with this kind of lesions.

Conclusion

In conclusion, FFR has become an indispensable tool in the catheterization laboratory to make decisions on revascularization of intermediate lesions. It can be performed in almost all elective clinical situations, providing functional information with relevant clinical implications and limited pitfalls. Figure 3 shows an example of an FFR procedure to decide revascularization in multivessel disease.

INSTANTANEOUS WAVE FREE RATIO

One of the few pitfalls of FFR is the necessity for maximal hyperemia. Without maximal microvascular vasodilation, the linear relation between pressure and flow that supports the use of FFR disappears. Coronary resistance, however, is not constant throughout the cardiac cycle; and we have already mentioned how, in some cases, stable maximal hyperemia is suboptimal or dubious, and in other rare cases adenosine may be contraindicated. To overcome these difficulties, a new physiologic measure of obstruction has been developed: instantaneous wave free ratio (iFR).

Using wave intensity analysis of simultaneous pressure-velocity recordings, Sen *et al*[47] identified a period of the cardiac cycle when there are no compression or expansion waves, and the coronary microvascular resistance at rest is minimal and stable, and very similar to the averaged resistance achieved with adenosine. The wave-free period is calculated beginning 25% of the way into diastole, and ending 5 ms before the end (covering around 75% of diastole).

A pressure wire (Verrata, Volcano Corp, San Diego, United States) is inserted in the coronary artery, following the same steps and precautions as with FFR, except that no hyperemia is induced. The wire is attached to a console with built-in proprietary software, which identifies the diastolic period of interest and automatically calculates iFR. The formula of iFR is identical to FFR, but instead of the averaged pressure of the whole cardiac cycle, it only uses the averaged pressure of the mentioned interval:

$$iFR = Pd/Pa$$

iFR is highly reproducible and has excellent correlation with FFR (r = 0.90; P < 0.001)[47]. A cutoff value of $\leqslant$ 0.90 has been set, which has an overall diagnostic accuracy of 80% to predict an FFR $\leqslant$ 0.80[48]. Because dichotomic agreement is logically lower around the cutoff values, a hybrid strategy has been proposed

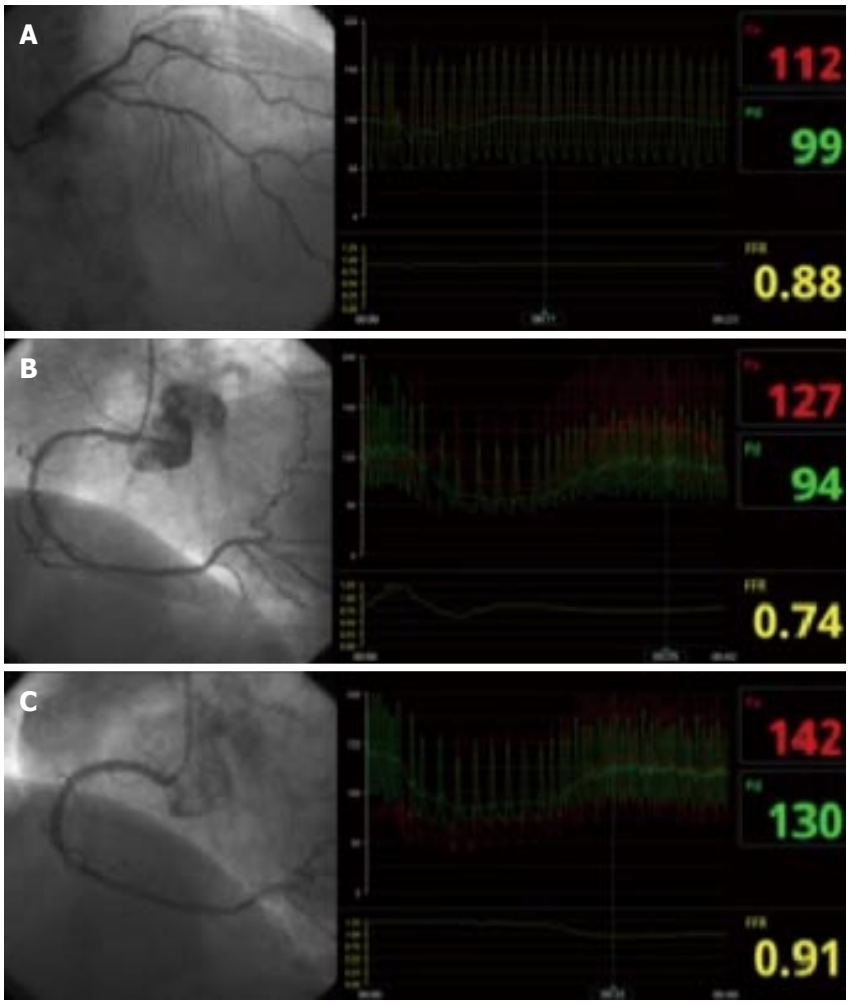

Figure 3 Functional assessment of epicardial stenosis. A 77-year-old woman with exertional angina was referred for coronary angiography. Two intermediate lesions were found in the proximal and distal segments of the left anterior descending artery (LAD) (A), and in the proximal and mid segments of the right coronary artery (RCA) (B). Fractional Flow Reserve was non-significant on the LAD (FFR 0.84) and significant on the RCA (FFR 0.74). Accordingly, percutaneous coronary intervention was performed with a drug-eluting stent on the RCA (C). A post-intervention FFR confirmed that the good angiographic result was also associated with functional improvement (FFR 0.91). Six months after the procedure the patient remains asymptomatic. FFR: Fractional flow reserve.

and tested[49,50], which would involve using an upper cutoff of 0.93, above which the coronary stenosis is considered non-significant, and a lower cutoff of 0.86, below which the stenosis is considered significant and PCI is indicated. When iFR falls between these two values (0.86-0.93, the "adenosine zone"), FFR is indicated, and the clinical decision is made according to the FFR value. This strategy may allow for two thirds of patients to be studied without hyperemia, maintaining a 95% agreement with an FFR-for-all strategy[50]. Benefits of this strategy would include reductions in cost and time, and assessment of patients who are unsuitable candidates for adenosine administration such as those with asthma, bradycardia and hypotension. Upcoming important clinical trials, such as the SYNTAX-II[51] should establish the clinical usefulness of this strategy.

HYPEREMIC STENOSIS RESISTANCE INDEX

Both CFR and FFR show good correlation with non-invasive testing for inducible ischemia. However, when both measurements are made, many patients exhibit a degree of discordance between CFR and FFR determination of ischemia[52,53]. In this context, an index of epicardial resistance that includes information from flow and pressure may have an additional value. The Hyperemic Stenosis Resistance index (HSR) is calculated from simultaneous pressure and Doppler intracoronary tracings, using a pressure-flow guidewire (Combowire, Volcano Corp, San Diego, United States). HSR is defined as the ratio of hyperemic stenosis pressure gradient (Pa-Pd) and hyperemic average peak velocity:

$$HSR = (Pa - Pd)/APV$$

where HSR represents hyperemic stenosis resistance (mmHg × s/cm); Pa represents mean aorta pressure (mmHg); Pd distal pressure (mmHg); and APV average peak velocity (cm/s). In normal epicardial arteries, no pressure gradient is expected, so the HSR should be 0. The best cutoff value has been identified at 0.8, and it

shows better diagnostic accuracy for ischemia than FFR and CFR[52]. The main limitation of HSR is that it requires the use of a Doppler-pressure wire, which increases the cost of the procedure. Also, it is less validated in clinical practice than FFR and CFR. An index of stenosis resistance derived from thermodilution flow calculations has not been validated to date.

MEASURES OF MICROVASCULAR RESISTANCE

As mentioned above, the main determinant of myocardial blood flow in physiological conditions is the microcirculation. FFR, iFR and HSR give specific information on the resistance to flow of epicardial stenoses; on the other hand, CFR provides an estimation of the overall resistance to flow in the coronary circulation. Thus, if a patient has a low CFR with normal FFR, this is usually attributed to microvascular dysfunction. This may not always be correct, however, as diffuse epicardial disease or altered resting conditions may have an impact of CFR independent of the microvascular circulation[53]. For this reason, resistance indices that provide specific information about the microcirculation have been developed.

HYPEREMIC MICROVASCULAR RESISTANCE

Using a Combowire for simultaneous determination of intracoronary pressure and Doppler velocity during adenosine-induced hyperemia, a resistance index called hyperemic microvascular resistance (HMR)[54], can be determined from this equation:

$$HMR = Pd/APV$$

where HMR is hyperemic microvascular resistance (mmHg×s/cm); Pd is the pressure in the distal part of the artery (mmHg); and APV is the average peak velocity at the same point (cm/s). Note that venous pressure is here disregarded to simplify the calculations. There are no clearly set cutoff values for HMR, but Meuwissen *et al*[54,55] have shown that the median HMR of patients with abnormal CFR is 2.4, compared with 1.9 of patients with normal CFR.

INDEX OF MICROCIRCULATORY RESISTANCE

Fearon *et al*[56] first described the index of microcirculatory resistance (IMR) in 2003, representing minimal microcirculatory resistance measured during conditions of hyperemia. IMR is calculated from the average pressure in the distal part of the coronary artery and the coronary blood flow measured by thermodilution, with the use of a specific pressure wire (PressureWire, Radi Medical Systems, St Jude Medical Inc.; St. Paul, Minn). Mean transit time correlates inversely with flow, so its inverse is used to substitute absolute flow. Theoretically, wedge coronary pressure and central venous pressure should be included in the equation to account for collateral flow and loading conditions. However, as this is usually impractical in the clinical setting, it is most common to disregard both measurements and use the simplified equation:

$$IMR = Pd \times Tmn$$

where IMR is index of microcirculatory resistance (mmHg×s); Pd is distal pressure (mmHg); and Tmn is mean transit time (s) - all measured during stable hyperemia. In practice, this simplified equation is usually correct, unless there is severe epicardial disease in the artery, in which case collateral flow may be a confounding factor. In such circumstances, the wedge coronary pressure can be measured during PCI, or alternatively an empirical corrected formula[57] may be used:

$$IMR = Pa \times Tmn \times [1.35 \times (Pa/Pd) - 0.32]$$

An IMR higher than 25 is considered abnormal[58], expressing a damaged coronary microcirculation.

Elevated IMR is related to adverse clinical outcomes in acute myocardial infarction[59], percutaneous intervention[60], and angina with apparently normal epicardial arteries[61].

In conclusion, when simultaneous measurement of pressure and flow indexes is performed, the calculation of a microvascular resistance index (either Doppler or thermodilution derived) adds specific information on the status of the microcirculation, and allows for a better diagnostic and prognostic assessment.

ENDOTHELIAL FUNCTION

The vascular endothelium is a monolayer of cells that covers the internal lumen of all the blood vessels, separating the blood from the vascular wall and organ tissues. The endothelium is a major determinant of coronary resistance and flow. In response to physiological triggers, the vascular endothelium regulates arterial smooth muscle tone through the release of vasodilators - mainly nitric oxide and prostacyclin - and vasoconstrictors, such as endothelin-1. When the vascular endothelium is damaged or dysfunctional, this function of coronary flow regulation is altered, which results in an insufficient vasodilation, or even paradoxical vasoconstriction, in response to a physiological increase in oxygen demands, such as exercise or stress. This flow dysregulation can be the cause of chronic angina or acute coronary syndromes, even in the absence of coronary epicardial stenosis.

The coronary vasomotion can be assessed directly and invasively by coronary angiography, using mainly

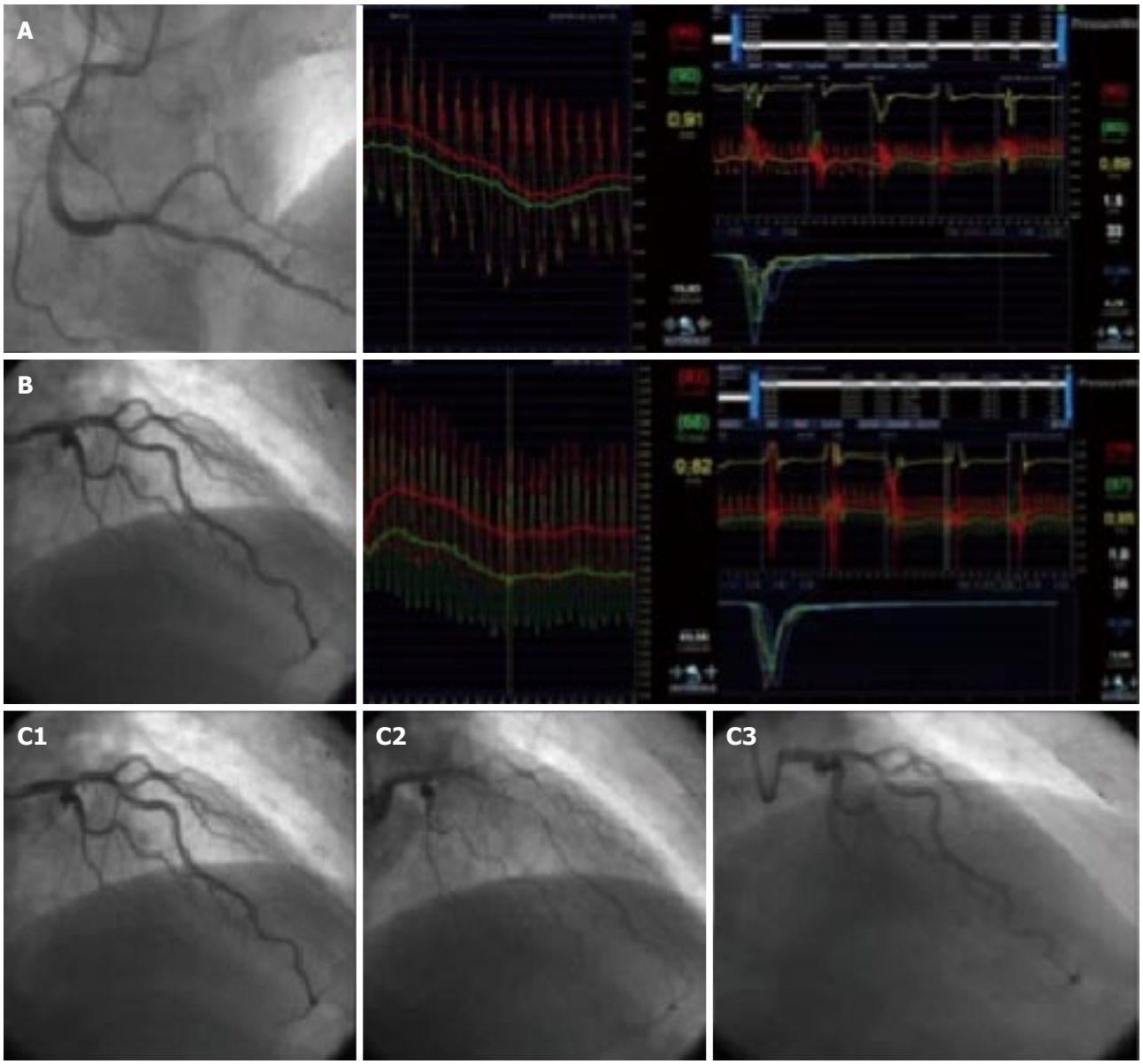

Figure 4 Thorough physiological assessment: Fractional flow reserve, microvascular and endothelial function. A 66-year-old man with typical angina, both resting and exertional, was referred for coronary catheterization. The coronary angiogram showed moderate lesions on the posterior descending artery of the RCA (50%) and on the middle LAD (40%). Panel A depicts the coronary stenosis of the RCA on the left box; FFR of this lesion on the centre box, with a value of 0.91; and microvascular study on the right box, with a CFR of 1.5 (low) and IMR of 33 (elevated); Similarly, Panel B shows the angiogram of the LAD (left), the FFR of 0.82 (centre), and the microvascular study (right), with a CFR 1 (low) and IMR 24 (borderline); Panel C shows the successive angiograms at baseline (C1), after 20 μg of acetylcholine (C2), and after 200 μg of nitroglycerin (C3). As can be appreciated, a severe diffuse spasm of the left coronary artery was induced by acetylcholine. We concluded that both coronary stenosis were non-significant, and decided on optimal medical therapy. The study also revealed microvascular endothelium-independent dysfunction, and macrovascular vasospasm due to endothelial dysfunction. CFR: Coronary flow reserve; FFR: Fractional flow reserve; IMR: Index of microcirculatory resistance; LAD: Left anterior descending artery; RCA: Right coronary artery.

acetylcholine as a trigger of endothelium-dependent vascular reactions[62-64]. In the presence of a healthy endothelium, acetylcholine at the doses used induces NO release, which results in coronary vasodilation, both epicardial and microvascular; conversely, if the endothelium is dysfunctional, NO release will be blunted and the predominant net effect will be vasoconstriction due to muscarinic stimulation of smooth muscle. Macrovascular vasodilation or vasoconstriction is evaluated by successive angiographies; the microvascular compartment, being the major determinant of flow velocity, is evaluated using intracoronary Doppler.

Before the endothelial function test, no nitroglycerin should be administered, to allow for epicardial reactivity. Ideally, the patient should be off vasoactive medication for 48 h, although in clinical practice this is not always feasible. The coronary artery - most often the left - is engaged with a guiding catheter, and a baseline angiography is performed to serve as a reference. A coronary microcatheter is advanced into the proximal part of a main vessel, usually the left anterior descending artery, and a Doppler wire (FloWire

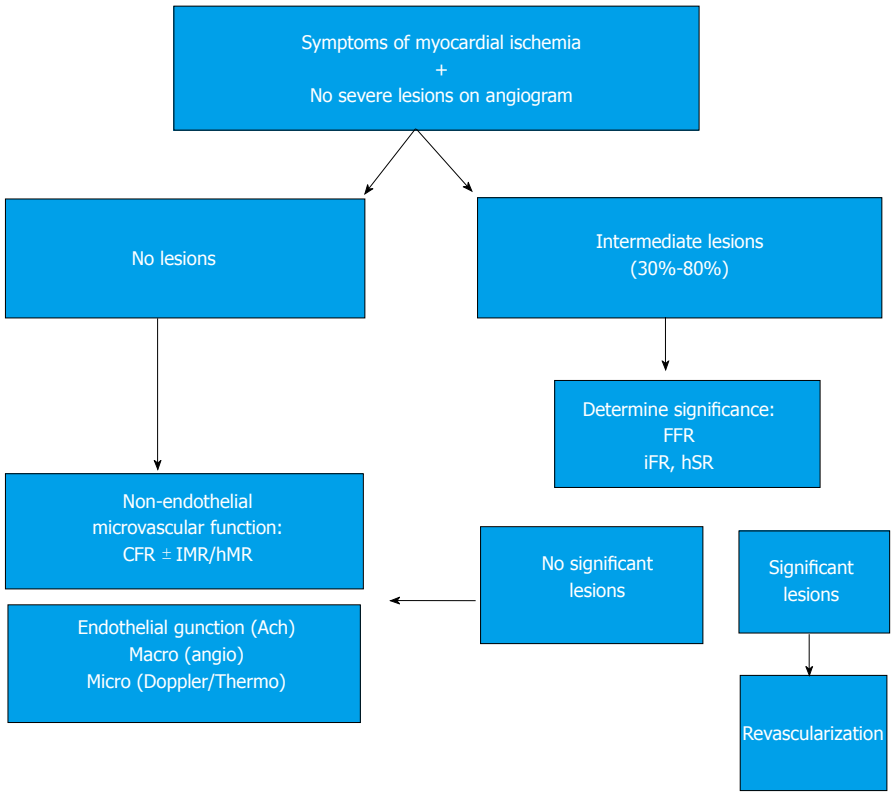

Figure 5 Summary of the proposed evaluation algorithm of patients with symptoms of ischemia without significant coronary lesions. CFR: Coronary flow reserve; IMR: Index of microcirculatory resistance; FFR: Fractional flow reserve; hMR: Hyperemic microvascular resistance; hSR: Hyperemic Stenosis Resistance index.

or ComboWire, Volcano Corp., San Diego, United States) is advanced through the microcatheter into the artery. After checking for signal quality, a baseline tracing of Doppler is recorded. Next, three consecutive infusions of acetylcholine are administered through the microcatheter, at concentrations of 10^{-6} mol/L, 10^{-5} mol/L and 10^{-4} mol/L, at a rate of 1 mL/min, 2-3 min per infusion. After each infusion, the Doppler APV and a coronary angiogram are recorded. Finally, 200 μg of nitroglycerine are administered intracoronary, to evaluate macrovascular endothelium-independent response.

The epicardial endothelial response is considered normal if vasodilation - or at least no vasoconstriction - is observed. The response is considered pathological if a reduction ⩾ 20% in coronary artery diameter occurs. A normal microvascular response to acetylcholine would be a 50% increase in APV. If a lower vasodilation, or even vasoconstriction occurs, the microvascular endothelial response is considered abnormal[64].

Most studies o endothelial function have followed this protocol approximately. It has the advantage of evaluating both the macrovascular and microvascular compartments, and the added safety of injecting the drug directly into the LAD. However, other protocols have been described and found safe. The study of the microvascular response by thermodilution, although seldom used, is feasible and has been validated[65]. Some groups[9,66] inject acetylcholine directly into the left main artery (at increasing doses ranging from 2 to 100 μg, for example 2-20-100 μg; each infusion over 3 min), and perform exclusively macrovascular angiographic assessment. This approach, although admittedly less complete than the first, still frequently offers valuable information.

Pitfalls and contraindications

Acetylcholine should be avoided in patients with severe intestinal and/or urologic obstructive disease, as it may enhance muscular contractions. Special attention should be paid to patients with bradycardia or hypotension. Generally, the coronary spasm related to macrovascular endothelial dysfunction is easily reverted with intracoronary nitroglycerin. In any case, vasospasm may cause serious complications, so the patient must be monitored and the procedure must be conducted with utmost care.

Conclusion

Endothelial dysfunction limits maximal coronary flow, and can be the cause of angina without epicardial stenosis[67,68]. It is an important risk factor for poor outcomes in this setting[11], as well as in stable coronary artery disease[69], acute myocardial infarction[70], heart failure[71], and heart transplant[72]. A more detailed account of the importance of endothelial function in coronary heart disease can be found in our recent review[73]. The finding of severe acetylcholine-induced spasm can also assist the physician in the optimization of the medical therapy.

Table 2 Main parameters available to assess coronary macrovascular and microvascular circulation

Technique	Cutoff value	Implications	Commentary
CFR	< 2	Unspecific macrovascular and microvascular inability to increase flow	Patients with CFR > 2 have favorable outcomes
FFR	≤ 0.8	Functionally significant epicardial stenosis	Extensive clinical validation Requires vasodilation
iFR	≤ 0.9	Functionally significant epicardial stenosis	Functionally significant epicardial stenosis Vasodilation-Independent
HSR	0.8 mmHg × s/cm	Functionally significant epicardial stenosis	Requires doppler-pressure wire Convenient in the presence FFR/CFR discordances
HMR	> 2 mmHg × s/cm	Microvascular dysfunction	Requires doppler-pressure wire
IMR	> 25 mmHg × s	Microvascular dysfunction	Thermodilution method

CFR: Coronary flow reserve; FFR: Fractional flow reserve; iFR: Instantaneous wave free ratio; HSR: Hyperemic stenosis resistance index; HMR: Hyperemic microvascular resistance index; IMR: Index of microcirculatory resistance.

DISCUSSION

Myocardial ischemia should not be considered to happen exclusively in the presence of critical coronary epicardial stenoses. The physiological significance of intermediate lesions cannot be properly assessed by angiography, and in this case a pressure wire should always be used to decide intervention or deferral. In the absence of significant coronary stenoses, a complete evaluation of the microcirculation and the endothelial function can help identify the fundamental problem, or at the very least reassure the patient and the physician.

When studying a patient with stable angina or acute coronary syndrome, the interventional cardiologist should not be content with an angiography showing non-significant epicardial disease. If there are intermediate lesions (30%-70%), FFR should be performed to rule out ischemic lesions; if the arteries are clearly non-stenotic, or if FFR is normal, we propose that microvascular endothelium-independent (CFR and microvascular resistance), and macro and microvascular endothelium-dependent function should be assessed. This thorough protocol can be performed in a matter of minutes, and with a very low risk[10]. Recent studies[9,10] show that, in most patients with angina who are extensively evaluated, an alteration can be found that explains the symptoms. Figure 4 shows an example from our centre following this protocol in a complex patient. Figure 5 summarizes this diagnostic algorithm.

In other clinical settings, such as stenting, myocardial infarction and heart transplant, vascular function affects clinical outcomes, and can serve as a prognostic marker. Also, coronary physiological parameters can be of interest as surrogate markers of safety and efficacy in clinical trials for new devices, such as drug eluting stents[66,74] and bioabsorbable scaffolds[75]. The interventional cardiologist should be acquainted with the methods used to perform these measurements and their interpretation. Table 2 summarizes the main parameters available to date.

CONCLUSION

Coronary physiology assessment in the catheterization laboratory is essential to help decision making in patients with coronary artery disease, providing functional and prognostic information. Physicians, especially interventional cardiologists should implement its use in daily clinical practise.

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MINIREVIEWS

Adrenal G protein-coupled receptor kinase-2 in regulation of sympathetic nervous system activity in heart failure

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Abstract

Heart failure (HF), the number one cause of death in the western world, is caused by the insufficient performance of the heart leading to tissue underperfusion in response to an injury or insult. It comprises complex interactions between important neurohormonal mechanisms that try but ultimately fail to sustain cardiac output. The most prominent such mechanism is the sympathetic (adrenergic) nervous system (SNS), whose activity and outflow are greatly elevated in HF. SNS hyperactivity confers significant toxicity to the failing heart and markedly increases HF morbidity and mortality *via* excessive activation of adrenergic receptors, which are G protein-coupled receptors. Thus, ligand binding induces their coupling to heterotrimeric G proteins that transduce intracellular signals. G protein signaling is turned-off by the agonist-bound receptor phosphorylation courtesy of G protein-coupled receptor kinases (GRKs), followed by βarrestin binding, which prevents the GRK-phosphorylated receptor from further interaction with the G proteins and simultaneously leads it inside the cell (receptor sequestration). Recent evidence indicates that adrenal GRK2 and βarrestins can regulate adrenal catecholamine secretion, thereby modulating SNS activity in HF. The present review gives an account of all these studies on adrenal GRKs and βarrestins in HF and discusses the exciting new therapeutic possibilities for chronic HF offered by targeting these proteins pharmacologically.

Key words: G protein-coupled receptor; G protein-coupled receptor kinase; Heart failure; Sympathetic nervous system; Adrenergic receptor; Adrenal medulla

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Core tip: The present manuscript is a mini-review describing the current knowledge in the field of adrenal GRKs and βarrestins, both of which are protein families that regulate adrenergic receptor function throughout the cardiovascular system. We specifically discuss the roles of these proteins in the adrenal medulla, as they pertain to regulation of catecholamine secretion and of

sympathetic activity in chronic heart failure (HF). We also outline the exciting new possibilities of targeting these molecules in the adrenal glands for HF therapy.

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INTRODUCTION

The sympathetic (adrenergic) nervous system (SNS) induces in the heart positive chronotropy, inotropy, lusitropy, dromotropy, accompanied by a decrease in venous capacitance, and constriction of resistance and cutaneous vessels[1,2]. All of these effects aim to prepare the body for "fight or flight response" and are mediated by the two catecholamines (CAs) norepinephrine (NE) and epinephrine (Epi)[3,4]. These are synthesized and released *via* the following mechanisms: (1) cardiac sympathetic nerve terminals release NE directly into the heart; (2) the adrenal medulla releases Epi and NE into the circulation; and (3) peripheral, local adrenergic nervous systems[5-7].

The actions of NE and Epi are mediated by the ARs, which are all G protein-coupled receptors (GPCRs) and consist of three α_1AR subtypes, three α_2AR subtypes (α_{2A}, α_{2B}, α_{2C}), and three βAR subtypes[8]. The main role of βARs in the heart is positive inotropy and chronotropy in response to CAs[9]. Agonist activation of GPCRs compels the cognate heterotrimeric G protein to dissociate from guanosine triphosphate and instead bind guanosine diphosphate on its Gα subunit; this results in splitting of the heterotrimer into two active functional components, Gα and $G_{\beta\gamma}$ subunits, both of which mediate signaling[9,10]. With specific regards to the α_2ARs, the α_{2B}AR is expressed in vascular smooth muscle causing vasoconstriction, while centrally located α_2ARs lower sympathetic outflow and systemic blood pressure[11,12]. NE release is controlled by presynaptic α_2ARs[13], since genetic deletion of α_2ARs leads to cardiac hypertrophy and HF, thanks to increased cardiac NE release and adrenal CA secretion[14,15].

Most GPCRs are subject to agonist-promoted desensitization and/or downregulation[16-18]. This process occurs courtesy of the GPCR kinases (GRKs) and the βarrestins[19]. The βarrestins uncouple the receptor from the G proteins, subsequently internalizing it[20]. GRK2 and GRK5 are the prominent GRKs in the heart and in most other tissues, including the adrenals[20,21]. Receptor internalization *via* the βarrestins results in either its resensitization or its degradation (downregulation)[20,21]. The receptor-bound βarrestins can also tranduce their own, G protein-independent intracellular signals[20,21]. Herein, we review the current literature regarding the roles of adrenal GRK2 and βarrestins in regulation of SNS activity in HF, with a focus on the therapeutic targeting of adrenal GRK2 as a sympatholytic strategy in chronic heart failure (HF).

ADRENAL GRK2 AND SNS ACTIVITY IN HF

A salient pathophysiological feature of chronic HF is SNS hyperactivity, reflected by increased levels of circulating Epi and NE[3,4,22]. Although it normally serves as a mechanism to re-adjust the heart from underperforming, it ultimately becomes cardiotoxic, contributing to HF progression, morbidity and mortality[3,4,22]. Adrenal CA secretion is stimulated by nicotinic cholinergic receptors and is refined by presynaptic inhibitory α_2ARs[5,23,24]. α_2ARs, similarly to cardiac βARs, also undergo GRK-dependent desensitization[10]. Of note, increased GRK2 expression and activity occur in the adrenal medulla during HF, which critically influence CA secretion from this source[25]. In particular, as we and others have documented, adrenal GRK2 overexpression is responsible for severe adrenal α_2AR dysfunction in chronic HF, leading to a loss of the sympatho-inhibitory function of these receptors in the adrenal medulla (and possibly also in sympathetic neurons); thus, CA secretion is chronically elevated[25-29]. The importance of the role of adrenal GRK2 in HF is evidenced by that its inhibition leads to a significant reduction in CA circulating levels, restoring not only adrenal, but also cardiac function[25]. In fact, HF rats treated with adrenal-specific βARKct (a GRK2 inhibitory mini-gene[30]) gene delivery show improved cardiac function and cardiac βAR number and signaling[25]. Therefore, an important crosstalk at the level of entire organs seems to exist in chronic HF and adrenal GRK2 is a crucial regulator of the circulating CA levels that affect HF progression. Consequently, adrenal GRK2 targeting to restore α_2AR function and reduce CA secretion from the adrenal medulla may provide a novel sympatholytic strategy for chronic HF treatment[25-29].

Another study demonstrating the advantages of therapeutic targeting of adrenal GRK2 is a study performed in transgenic mice having GRK2 genetically deleted only in cells expressing the phenylethanolamine-N-methyl-transferase enzyme. These mice lack GRK2 in their adrenal medullae[26]. These mice exhibit significantly reduced SNS activity during progression to chronic HF secondary to myocardial infarction (MI), as reflected by their circulating CA levels measured at 4 wk post-MI. In addition, their cardiac contractility, structure/morphology (dilatation), and βAR signaling/function, all show marked improvement at the same time-point (4 wk) post-MI[26]. Thus, prevention of the sympathetic "rush" that attacks the myocardium shortly after an MI thanks to adrenal GRK2 inhibition can help the heart work close to normal and limit its tissue damage, which normally occurs in the period directly following a heart attack. Therefore, adrenal GRK2 inhibition applied as early as possible after an MI may provide significant

survival and quality of life benefits in human HF. Of note, this is exactly the same rationale behind start of β-blocker therapy immediately after the heart attack in MI patients.

Adrenal GRK2 regulates CA secretion also under normal conditions, as adrenal βARKct transduction resulted in lowering of circulating CA levels in normal, otherwise healthy rats, and adrenal GRK2 overexpression increased their CA levels[27]. In addition, exercise training, beneficial for the cardiovascular system as it reduces HF-related SNS overactivation, can also normalize adrenal GRK2 expression and α_2AR function in HF rats[28].

It is also very likely that, in chronic HF, GRK2-mediated α_2AR deregulation also occurs in the cardiac adrenergic terminals, thus contributing to excessive NE release. Thus, global GRK2 blockade will decrease systemic circulating CA's, and perhaps a small molecule GRK2 inhibitor is best-suited for that therapeutic purpose. In that vein, it is interesting to point out that the known antidepressant drug (selective serotonin reuptake inhibitor, SSRI) paroxetine was recently shown to inhibit myocardial GRK2, thereby improving experimental HF in post-MI mice[29]. However, the results of this study must be treated with extreme caution, given that paroxetine exerts a variety of pharmacological effects, which may have contributed to its amelioration of cardiac function post-MI. For instance, it can also inhibit the other major cardiac GRK isoform, GRK5 (albeit to a lesser extent than it inhibits GRK2)[30], and it also activates glycogen synthase kinase (GSK)3-beta[31], which is known to have beneficial actions in cardiac fibrosis, hypertrophy and adverse remodeling[32]. In fact, exactly because it activates pancreatic GSK3β, paroxetine can precipitate insulin resistance/diabetes mellitus[31], a significant adverse effect that can potentially limit the drug's usefulness in HF therapy. Nevertheless, paroxetine may aid in the development of more specific (and potent) pharmacological GRK2 inhibitors by serving as a lead drug compound[30].

In summary, GRK2 inhibition is a novel sympatholytic strategy in HF, curbing CA release from SNS nerve terminals and the adrenal glands. In addition, it can be safely combined with β-blockers, as this combination cuts SNS overactivity and blocks adrenal GRK2 in HF[33]. However, while β-blockers improve inotropy of the failing heart indirectly, by protecting it from the catecholaminergic overstimulation[34,35], adrenal GRK2 inhibition can block also the non-cardiac adverse effects of the SNS (activation of endothelin, renin-angiotensin-aldosterone axis, *etc.*). Additionally, β-blockers acutely lower cardiac contractility and thus, are contraindicated in the acute setting of HF[36]. Adrenal GRK2 blockade, by diminishing global SNS activity in a cardiac-independent manner, may thus be much safer than β-blockers, as a sympatholytic approach, for acute HF. Finally, adrenal GRK2 inhibition would allow for reduction of dose and propensity for adverse effects of β-blocker therapy.

ADRENAL βARRESTINS AND SNS ACTIVITY IN HF

Aldosterone is another elevated hormone in HF and produces various detrimental effects on the failing heart, including adverse cardiac remodeling and HF progression post-MI[37-40]. It can also stimulate sympathetic neurons in the central nervous system to enhance NE release[37-40]. Aldosterone is produced by the adrenocortical zona glomerulosa cells in response to AT_1 receptor activation by angiotensin Ⅱ (Ang Ⅱ)[41,42]. A crucial role for βarrestin1 in mediating AT_1 receptor-induced aldosterone synthesis and secretion in the adrenal cortex has been documented[43]. Specifically, βarrestin1 causes upregulation of steroidogenic acute regulatory protein (StAR), the most critical enzyme in its biosynthesis[43]. Moreover, βarrestin1 does so independently of G proteins[43]. *In vivo*, adrenal βarrestin1 appears to be a major regulator of normal circulating aldosterone levels, since its upregulation, specifically in the adrenal gland, can cause hyperaldosteronism in normal healthy animals[43]. Importantly, in chronic HF, which is also characterized by hyperaldosteronism, adrenal βarrestin1 overexpression/overactivity promotes aldosterone elevation, resulting in accelerated cardiac adverse remodeling and deterioration of heart function[44]. Moreover, the cardio-toxic effects of aldosterone in post-MI HF are prevented by adrenal βarrestin1 inhibition *in vivo*[44] and βarrestin1-knockout mice progressing to HF after experimental MI fail to show any elevation in their circulating aldosterone levels, remaining essentially normal even as late as 4 wk post-MI[45]. CA levels are also significantly reduced in post-MI βarrestin1-knockouts, contributing to the overall better survival and cardiac function of these animals in post-MI HF[45]. Thus, adrenal βarrestin1 is a major driving force behind the cardio-toxic hyperaldosteronism and SNS hyperactivity, both of which accompany and aggaravate chronic HF. Thus, adrenal βarrestin1 inhibition might also be of therapeutic value in post-MI HF therapy. In fact, considering that it also participates in the adrenal GRK2-dependent α_2AR desensitization/downregulation, which chronically elevates CA secretion in HF[25,45], it becomes apparent that adrenal βarrestin1 inhibition could be an attractive therapeutic strategy for countering neurohormonal cardiotoxicity in HF.

CONCLUSION

Preclinical studies on cardiac GRK2 inhibition have established it as a promising therapeutic modality for HF. However, recent studies have brought GRK2 targeting in another organ, the adrenal medulla, to the limelight of potential HF therapies. Adrenal GRK2 inhibition appears to directly lower the neurohormonal (*i.e.*, sympathetic) burden of the failing post-MI heart, without affecting the heart muscle *per se*. As better, safer, and more effective vectors for gene therapy and/

or small molecule inhibitors get developed, the potential for GRK2 inhibition, in both the heart and adrenals, to find its place in the HF therapeutic armamentarium will continue to rise exponentially in the years to come.

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MINIREVIEWS

Challenging aspects of treatment strategies in heart failure with preserved ejection fraction: "Why did recent clinical trials fail?"

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Abstract

Heart failure (HF) is the leading cause of hospitalization among older adults and the prevalence is growing with the aging populations in the Western countries. Epidemiologic reports suggest that approximately 50% of patients who have signs or symptoms of HF have preserved left ventricular ejection fraction. This HF type predominantly affects women and the elderly with other co-morbidities, such as diabetes, hypertension, and overt volume status. Most of the current treatment strategies are based on morbidity benefits such as quality of life and reduction of clinical HF symptoms. Treatment of patients with HF with preserved ejection fraction displayed disappointing results from several large randomized controlled trials. The heterogeneity of HF with preserved ejection fraction, understood as complex syndrome, seems to be one of the primary reasons. Here, we present an overview of the current management strategies with available evidence and new therapeutic approach from drugs currently in clinical trials, which target diastolic dysfunction, chronotropic incompetence, and risk factor management. We provide an outline and interpretation of recent clinical trials that failed to improve outcome and survival in patients with HF with preserved ejection fraction.

Key words: Diastolic dysfunction; Preserved ejection fraction; Co-morbidities; Clinical trials

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Core tip: Heart failure (HF) has preserved left ventricular ejection fraction (HFpEF) accounts for approximately 50% of all patients diagnosed with HF, with similary poor outcomes. To date, only the prevention of HFpEF by treating the cardiovascular risk factors (coronary artery disease, atrial fibrillation, hypertension, diabetes, and obesity) has been shown to be efficient. This observation suggests that investigators in future trials should specify the indication of hospitalization for HF and may request to verify the details of patients' admissions. We provide an outline and interpretation

of recent clinical trials that failed to improve outcome and survival in patients with HF with preserved ejection fraction.

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INTRODUCTION

Prevalence of heart failure (HF) has been rising in the recent past[1,2]. Epidemiologic reports suggest that approximately 50% of patients who have signs or symptoms of HF have preserved left ventricular ejection fraction (HFpEF)[3-5]. It has been observed that the morbidity and the mortality rates of HFpEF patients are significantly increased when compared to the reference population[3,6]. Moreover, it appears that the all-cause mortality of patients with HFpEF is comparable to patients with HF with reduced ejection fraction (HFrEF).

Patients with HFpEF are older, more likely women, and more often have hypertension[7,8]. Chronic hypertension is the most common cause in addition to age, with suggestion to 60% of patients suffering from HFpEF being hypertensive[7]. Diabetes and obesity also contribute independently to the development of diastolic and vascular dysfunction[9], both being important in the HFpEF pathophysiology. Most of the common treatment of HFpEF is based on morbidity benefits and reduction of clinical HF symptoms. Several co-morbidities are important drivers of the clinical outcome in the HFpEF population. Excluding patients with co-morbidities from clinical trials to enhance the specificity reduces clinical event rate and entails loss of statistical power to detect differences.

Current guidelines recommend the management of treating hypertension, heart rate reduction, volume status, and prevention of myocardial ischemia[10]. However, current intervention strategies available for HFrEF have not been supported by clinical trials for HFpEF[11,12].

Here, we present an overview of the current recommended therapeutic options with available evidence and new therapeutic approaches from drugs currently in clinical trials, which aim at impaired diastolic function, chronotropic incompetence, and risk factor management. We provide an outline and interpretation of previous clinical trials that failed to improve outcome and survival in the HFpEF population.

BETA-BLOCKERS

Study of effects of Nebivolol Intervention on outcomes and Rehospitalisation in Seniors with HF trial (SENIORS).

The mechanism behind β-blockers' therapeutic potential in enhancement diastolic function in patients with HFpEF is believed to be associated with negative chronotropic and inotropic properties in stabilizing heart rate and optimizing left ventricular (LV) relaxation[13].

The SENIORS trial (Study of effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with HF) enrolled 2128 patients aged greater than 75 years who had either an LVEF less than 35% or a hospitalization for HF in the previous year and randomly assigned them to placebo or nebivolol. In the SENIORS trial 752 patients displayed a preserved LVEF (mean 49.2%).

The SENIORS trial indicated that nebivolol significantly reduced the composite outcome of death and cardiovascular hospitalization. In detail, the SENIORS trial demonstrated a 15% reduction in the relative risk of the composite of all-cause mortality of cardiovascular admission in patients older than 70 years of age with history of congestive HF[14]. The investigators consumed two primary aims distinct from previous trials on β-blockers. First, was to demonstrate the safety and efficacy of nebivolol in elderly HF patients, a group that has been under-represented in previous clinical studies. Secondly, another goal, of this trial was to demonstrate nebivolol's safety and efficiency across a broad range of LVEF, including the HFpEF population.

Conversely, in the SENIORS trial there was no difference in the primary outcome when patients were stratified according to preserved or reduced LVEF using a cut-off of > 35% to define preserved EF[14]. Subsequent analyses suggested no strong interaction between the therapeutic benefit of nebivolol and LVEF above or below 35%, but this does not entirely allay concerns that there might be no benefit in those with an LVEF greater than 45%.

Besides, patients with atrial fibrillation, a common co-morbidity of both HFrEF and HFpEF, do not appear to benefit whether or not LVEF is reduced[15]. In addition, it has to be mentioned that more than half of the patients, included in the SENIORS trial, had LVEF values ranging between 35%-50% and therefore would not be considered to have HFpEF.

However, in a separate analysis of patients with an LVEF cut-off greater than 40%, there was no statistical interaction, suggesting that nebivolol was of comparable benefit in reduced LVEF and preserved LVEF patients. The definition of HFpEF used a low cut-off LVEF of greater than 35% therefore making it difficult to extrapolate these findings to most patients with HFpEF who have a higher LVEF.

Furthermore, the SENIORS echocardiography substudy randomized 112 patients in 29 european centres, of whom 104 were evaluable for the study; 43 with LVEF ⩽ 35% and 61 with an LVEF > 35%[16]. LV end-systolic volume (ESV), LVEF, mitral valve E/A ratio, and E-wave deceleration time were assessed at baseline and after 12 mo.

In the group with LVEF ⩽ 35%, nebivolol reduced

ESV and improved EF; no changes were observed in the E/A ratio or E-wave deceleration time. In LVEF > 35% group, no significant changes in either systolic or diastolic parameters were observed. This absence of detectable differences with standard echocardiography in patients with predominant diastolic dysfunction questions the mechanism of benefit on morbidity and/or mortality in this HF population. In the separate analysis of patients with an EF cut-off greater than 40%, there was no noted statistical interaction, suggesting that nebivolol was of comparable benefit in reduced EF and preserved EF patients.

Swedish HF registry

Lund *et al*[17] from the Karolinska Institute, Stockholm in Sweden, conducted a study to examine whether β-blocker therapy is associated with reduced mortality in patients with HFpEF.

The investigators used data from the Swedish HF Registry, which includes 67 hospitals with inpatient and outpatient units and 95 outpatient primary care clinics in Sweden. The analysis included 41976 patients, 19083 patients with HFpEF[17]. Of these, 8244 were matched 2:1 based on age and β-blocker use, yielding 5496 treated and 2748 untreated patients with HFpEF. Another analysis involved 22893 patients with HFrEF, of whom 6081 were matched, yielding 4054 treated with β-blockers and 2027 untreated patients.

In patients with HFpEF, use of β-blocker therapy was associated with lower all-cause mortality but not with lower combined all-cause mortality or HF hospitalization. In detail, in the matched HFrEF cohort, β-blockers were associated with reduced mortality (HR = 0.89; 95%CI: 0.82-0.97; *P* = 0.005) and also with reduced combined mortality or HF hospitalization (HR = 0.89; 95%CI: 0.84-0.95; *P* = 0.001).

This study provides a rationale for performing large-scale randomized trials with this inexpensive category of drugs.

However, because myocardial ischemia can drive the development of HFpEF, its presence should be detected and treated with anti-ischemic therapies, which still include β-blockers. Patients with evidence of myocardial ischemia could also be considered for revascularization with percutaneous coronary intervention or coronary artery bypass surgery.

However, current guidelines do not recommend the use of β-blockers solely for HFpEF, unless it is used to optimize treatment of comorbidity, such as controlling ventricular rate in atrial fibrillation or tachyarrhythmia, or hypertension.

Since cardiac output is the product of heart rate and stroke volume, patients with HFpEF are often dependent on augmentation of heart rate in order to increase cardiac output.

Negative chronotropic medications are recommended in HFpEF to increase the diastolic filling period, but slowing the heart rate in the absent of tachycardia tends to only prolong diastasis, where transmitral flow is minimal or absence[18]. More importantly, recent studies have repeatedly shown that chronotropic incompetence is highly prevalent and associated with exercise disability in HFpEF[19-21]. Indeed, in the setting of reduced systolic and diastolic reserve, chronotropic reserve may represent the only mechanism to augment cardiac output during exercise, although there is concern that inadequate ability to enhance relaxation with tachycardia may limit stroke volume responses. β-blockers, especially at high doses may aggravate rather than alleviate exercise intolerance.

However, slowing elevated heart rate can prolong LV filling time in abnormally stiff LV and also prolong coronary perfusion. As a result, we recommend the careful use of β-blockade to optimize chronotropic incompetence (induced by atrial fibrillation or tachyarrhythmia) by stabilizing heart rate and optimizing LV relaxation with regard to heart rate profile under basal and exercise conditions in patients with HFpEF. Moreover, additional benefical effects of β-blockers have to be reconsidered. In detail, nebivolol itself would possible confer additional effects due to the NO enhancing action of the drug. This action of nebivolol is exerted *via* a signaling pathway starting from the activation of β3-adrenergic receptors and leading to overexpression of inducible NO synthase. Cardiac NO production by nebivolol could participate in the cardiovascular effects of nebivolol treatment in patients affected by hypertension and HF.

Adequate prospective trial data regarding the effects of β-blockers in HFpEF are not currently available. In this regard it is interesting to know that Pieske *et al* (Charité - Berlin, Germany) are planning an additional large multicenter trial with about 2300 participants with preserved LVEF in order to investigate the effects of β-blockers treatment starting in 2015.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Perindopril in elderly people with chronic HF trial

The theoretical benefits of Angiotensin-converting enzyme inhibitors (ACEi) in HFpEF rest on pathophysiological basis that angiotensin II contributes to myocardial hypertrophy and adverse cardiac fibrosis. To date, only one substantial trial of ACEi has been conducted in the HFpEF population, the perindopril in elderly people with chronic HF (PEP-CHF). The PEP-CHF Trial included 850 patients, older than 70 years of age with HFpEF (LVEF > 45%) with echocardiographic evidence of diastolic dysfunction[22]. The primary endpoint of the trial was a composite of all-cause mortality or unplanned HF related hospitalization. A significant reduction in HF hospitalization rate was observed in posthoc analysis of the results at 1 year, when cross over rates to open label ACEi were used. However, early beneficial effects of perindopril treatment

were lost by the end of the trial.

A major limitation of the trial was the high rate of discontinuation at 18 mo (62%), the majority of whom went on open-label ACEi (about 90%). In addition, the event rate in the trial was lower than expected, further reducing the power of the trial. Perindopril appeared favorable at 1-year follow-up when the large majority of patients were on study drug, although these data should not be considered definitive given the post-hoc nature of the analysis. Although the PEP-CHF trial also does not provide conclusive evidence that perindopril is of benefit in this population, the observed favourable trends on hospitalization and days in hospital for HF (early seen beneficial effects), combined with improvements in symptoms and functional capacity provide arguments for its use.

Effects of candesartan in patients with chronic HF and preserved left-ventricular ejection fraction: The CHARM-Preserved trial

In the effects of candesartan in patients with chronic HF and preserved left-ventricular ejection fraction: The CHARM-Preserved trial (CHARM-Preserved) trial, 3023 (mean age 67 years, 40% women) patients were randomly assigned to the angiotensin receptor blocker (ARB) candesartan or placebo and followed 37 mo[23]. Adequate patients were aged greater than 18 years, suffering from HF for more than 4 wk, were in NYHA class II-IV, had a history of hospital admission and had a greater LVEF than 40%. The primary outcome (cardiovascular death or HF admission) was neutral (P = 0.051), but only slightly short of the primary outcome. A possible explanation of this finding could be the rates of study-drug discontinuation due to adverse events or laboratory abnormalities, which were significantly higher in the candesartan group (17.8% *vs* 13.5%, P = 0.001). In detail, candesartan was discontinued in more patients due to hyperkalemia, worsening creatinine levels or hypotension. In an echocardiography substudy of CHARM-Preserved, only 44% had moderate or severe diastolic dysfunction, which conferred a 3-fold increased risk but it is not clear whether these patients obtained a greater benefit from candesartan. Overall, CHARM-Preserved results were related with reduced hospitalization with candesartan[23]. However, the LVEF cut-off value of 40% and a non-defined diastolic function identified the study population as not a true HFpEF population.

Irbesartan in patients with HF and preserved ejection fraction trial

The Irbesartan in patients with HF and preserved ejection fraction trial (I-Preserve), the largest trial in the HFpEF population so far, randomly assigned 4128 patients (mean age 72 years, 60% female) to irbesartan or placebo[24]. The observation period was about 49.5 mo (mean). All included patients were aged greater than 60 years, had symptoms of HF and had a greater LVEF than 40%. The primary outcome (death from any cause or hospitalization for cardiovascular cause) occurred 36% of patients in the irbesartan group and 37% in the placebo treated group[24]. There were no significant differences in the primary endpoints between the two groups. This trial also found no treatment benefit in any group and no significant difference in secondary endpoints such as CV death, HF death, exercise testing, NT-proBNP levels, and quality of life (Table 1).

However, it is essential to mention that in this study a high percentage of patients were already receiving ACEi and spironolactone. The investigators speculated that the treatment of a large proportion of patients with multiple inhibitors of the RAS might have left reduced opportunity for further benefit from the addition of an angiotensin-receptor blocker. Furthermore, it seems to be possible that HFpEF does not appear to involve neurohormonal activation as a critical pathophysiologic mechanism in the same way that HFrEF does.

The rationale for using ACEi and ARBs in patients with HFpEF is blocking the neurohumoral signaling leading to HF progression and poor clinical outcomes. First, the CHARM-Preserved trial showed a significant reduction in hospitalization rate caused by HF, but failed to display a significant reduction in cardiovascular mortality. Moreover, in an echocardiography substudy of CHARM preserved, only 44% had moderate or severe diastolic dysfunction. Second, the I-Preserved trial failed to show a reduction in risk of the composite outcome, cardiovascular hospitalization and all-cause mortality. However, the not insignificant co-medication in this trial could be one reason for the neutral endpoints. Third, the PEP-CHF trial also failed to demonstrate a reduction in composite all-cause mortality and hospitalization caused by HF.

Also because of the neutral results of these three main outcome trials the current guidelines do not recommend the use of ACEi and ARBs for HFpEF. Nevertheless, when hypertension and other co-morbidities like LV hypertrophy and atherosclerotic vascular disease are involved ACEi and ARBs are first-line therapy and should also be given to patients with HFpEF. A possible mechanism for potential benefit of ACEi and ARBs could be afterload reduction and reduced and reduced wall tension, leading to improved diastolic function.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Randomized controlled aldosterone receptor blockade in diastolic HF trial

Series of RCTs[25,26] have shown that treatment with mineralocorticoid-receptor antagonists (MRAs) improved some properties of cardiac performance in patients suffering from HFpEF. The randomized controlled aldosterone receptor blockade in diastolic HF (ALDO-HF) trial displayed an improvement in ejection fraction,

Table 1 Clinical trials in heart failure with preserved ejection fraction

Acronym (yr)	Drug	Number of patients	Age (mean)	Percentage female (mean, %)	LVEF (mean, %)	Primary outcome	Follow up period
Swedish heart failure registry[17]	Beta-Blocker	8244	78	45	40-49; > 50	ACM, HFH	24 mo
TOPCAT[33]	Aldactone	3445	68.6	52	60.1	CVD-HFH: NS	27 mo
PARAMOUNT[51]	LCZ696	292	70.6	56	57.7	Reductions in NT-proBNP levels	36 wk
RELAX[43]	Sildenafil	216	69	48	60	EC-CS: NS	24 wk
ALDO-DHF[27]	Spironolactone	422	67	52	67	Reduced E/É	12 mo
I-Preserve[24]	Irbesartan	4128	72	60	59.5	D-CVH: NS	49.5 mo
PEP-CHF[22]	Perindopril	850	75	55.5	65	D-HFH: NS	26.2 mo
DIG[26]	Digoxin	6800	63.8	22.7	28.6	ACM: NS; improvements in DFWHF, HFWHF	37 mo
SENIORS[14]	Nebivolol	2128	76.1	38.4	36	Improvements CVD, HFH	21 mo
CHARM-Preserved[23]	Candesartan	3023	67.1	40	54	CVD-HFH: NS	36.6 mo

ALDO-DHF: Aldosterone Receptor Blockade in Diastolic Heart failure; CHARM-Preserved: Effects of candesartan in patients with chronic HF and preserved left-ventricular ejection fraction trial; DIG: The Effect of Digoxin on Mortality and Morbidity in Patients with HF trial; I-Preserve: The irbesartan in HF with preserved systolic function trial; PARADIGM: Angiotensin–Neprilysin Inhibition *vs* Enalapril in HF trial; PARAMOUNT: The angiotensin receptor neprilysin inhibitor LCZ696 in HF with preserved ejection fraction: a phase 2 double-blind randomised controlled trial; PEP-CHF: The perindopril in elderly people with chronic HF trial; RELAX: Phosphodiesterase-5 Inhibition in Diastolic HF: The RELAX Trial Rationale and Design; SENIORS: Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with HF trial; TOPCAT: Spironolactone for HF with Preserved Ejection Fraction trial; ACM: All-cause mortality; CS: Clinical status; CVA: Cardiovascular admission; CVD: Cardiovascular death; CVH: Cardiovascular hospilization; DFWHF: Death from worsening HF; EC: Exercise capacity; FHCVE: First hospitalization for a cardiovascular event; HF: Heart failure; HFAR: Hospitalization for any reason; HFH: Heart failure hospitalization; HFWHF: Hospitalization for worsening HF; NS: Not significant.

E/É relation, LV mass and LV end-diastolic volume[27]. However, these findings were not related with an enhancement in exercise capacity.

In the ALDO-HF trial, treatment with MRAs decreases renal function. Therefore, MRAs cannot be recommended based on the mentioned results. Physicians treating patients with MRAs should carefully monitor renal function and potassium levels. Whether the improved left ventricular function observed in the ALDO-HF trial is of clinical significance requires further investigation in larger HFpEF populations.

Treatment of preserved cardiac function HF with an aldosterone antagonist trial

The rationale to use MRAs for HFpEF therapy has been initially generated in experimental studies. These studies suggested that a blockade of the aldosterone-induced signaling may lead to anti-hypertrophic and anti-fibrotic effects[28]. Moreover, clinical trials EPHESUS and EMPHASIS-HF demonstrated significant reductions in risk of death from cardiovascular causes or first hospitalization for HF in patients after myocardial infarction and mild HF symptoms. However, in these trials solely patients with reduced LVEF were included.

MRAs such as spironolactone are highly effective in patients with HF accompanied with reduced LVEF[29-32].

In the treatment of preserved cardiac function HF with an aldosterone antagonist (TOPCAT) trial, patients with at least one symptom of HF were included if those patients had an ejection fraction greater than or equal to 45%[33].

Moreover, increased natriuretic peptide levels in the foregoing 60 d or a hospital admission in the previous year (with management of HF a major component of the care provided) were required, and these eligibility criteria were used for stratification of patients at randomization of this study[33]. Three thousand four hundred and forty-five patients undertook randomization in 6 different countries (United States, Argentina, Brazil, Canada, Russia and Georgia) to spironolactone or placebo.

Regarding a mean follow-up of 3.3 years (mean), the incidence rate of the primary composite outcome of death from cardiovascular causes, cardiac arrest, or hospitalization for HF was 5.9 events per 100 person-years in the spironolactone group and 6.6 events per 100 person-years in the placebo group.

Overall, the TOPCAT trial showed neutral results. There was a significant reduction in the secondary outcome of hospitalization for HF with spironolactone treatment.

Patients randomized to treatment with spironolactone had a fewer admission rate for HF, but an increased risk for renal dysfunction and hyperkalemia[34].

The majority of patients from Russia and Georgia were included in the hospitalization stratum (therefore no increased NT-proBNP was present) and thus were at lower cardiovascular risk, whereas patients from the United States were further balanced between the two mentioned strata. However, a post hoc analysis showed, that spironolactone treatment seemed to benefit patients in the United States but not those patients in Russia or Georgia. In detail, a total of 3445 subjects were recruited over a period of 4 years from 270 clinical centers in the United States (1151), Russia (1066), Georgia (612), Canada (326), Brazil (167) and Argentina (123), and were randomized on 1:1 basis

to either spironolactone (target dose of 30 mg daily) or placebo. Patients with uncontrolled hypertension, those with infiltrative or hypertrophic cardiomyopathy and patients with elevated baseline serum potassium levels (> 5.0 mmol/L) were excluded. The overall event rate was low, with 3-year mortality being 10.2%. This is in sharp contrast with the previously reported annual mortality rates of 22%-29% in large community-based studies[35]. This concern is further intensified by a primary event rate (in the placebo group) of 8.4% in Russia and the Republic of Georgia: A rate which not only is unheard of in HF studies, but also one that is remarkably less than that observed in the "American" arm of the same study (31.8%).

It is remarkable that geographic differences in outcome have been a significant relevance in previous trials involving patients with HF. Possible factors in such geographic variation include differences in the clinical characteristics of the patient population, standards of care and methodological knowledge of clinical trials[34].

To conclude, TOPCAT was a neutral study. Spironolactone failed to reduce the primary outcome compared to placebo in patients with HFpEF. However, it did reduce the rate of HF hospitalizations. A signal of benefit was also seen in patients with elevated natriuretic peptides and in a geographical subset of patients. Based upon these findings, a mixed response from the medical community is expected: Some clinicians will not prescribe spironolactone for HFpEF patients, while others will continue using it especially in patients with elevated natriuretic peptides and/or in those with objective evidence of diastolic dysfunction. Finally, we prescribe spironolactone for HFpEF patients during carefully monitoring of renal function and serum potassium levels given the overall positive data from the Americas in TOPCAT.

DIGITALIS THERAPY

Digitalis investigation group ancillary trial

It has been shown that treatment with digoxin has beneficial effects on hospitalization in patients with HFrEF. Treatment with digoxin reduced the total number of hospitalizations. In the digitalis investigation group ancillary trial 988 patients suffering from chronic HF and ejection fraction greater than 45% were randomized to treatment with digoxin or placebo[36].

After 37 mo (mean follow-up), patients treated with digoxin or placebo had similar rates of the primary composite of hospitalization of HF or cardiovascular death[36]. However, an early benefit in patients with digoxin treatment was lost by the end of follow-up of the trial.

In ambulatory patients with chronic mild to moderate diastolic HF and normal sinus rhythm receiving angiotensin-converting enzyme inhibitor and diuretics, digoxin had no effect on natural history end points such as mortality and all-cause or cardiovascular hospitalizations[36].

To conclude, there is fragile evidence of digoxin in patients with HFpEF. Similar to β-blockers, guidelines do not recommend the use of digoxin solely for HFpEF, unless for treatment of co-morbidities, such as atrial fibrillation or tachyarrhythmia. However, common use of digoxin in the elderly HFpEF population with increased renal dysfunction seems not to be advisable.

INHIBITION OF THE LATE CURRENT OF THE CARDIAC ACTION POTENTIAL (LATE INA)

RAnoLazIne for the treatment of diastolic HF in patients with preserved ejection fraction: the RALI-DHF proof-of-concept study

In a small, randomized (phase Ⅱ) trial 18 patients were included who received ranolazine infusion followed by 2 wk of oral application[37]. It was shown by the investigators that left ventricular end-diastolic pressure and pulmonary capillary wedge pressure were reduced in patient with ranolazine treatment whereas in patients with placebo treatment there were no significant effects seen (clinicaltrails.gov NCT01163734). However, at the end of the trial no significant differences were observed by echocardiography and exercise capacity. In addition, a planned multi-center trial has been abandoned due to low recruitment. Finally, results of two ongoing studies are earliest expected in 2016.

PHOSPHODIESTERASE-5 INHIBITION

Sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor is currently approved for treatment of pulmonary arterial hypertension (PAH)[38-40]. A small clinical trial observed improvements in pulmonary pressure, right ventricular (RV) function and LV relaxation after treatment with sildenafil in patients suffering from HFpEF. In a phase Ⅲ ongoing trial the effect of sildenafil on patients suffering from HFpEF and PAH will be studied[41]. Moreover, sildenafil treatment led to an enhancement of systolic and diastolic LV function in a one-year randomized double-blind study placebo controlled study in patients suffering from stable HF and reduced ejection fraction[42].

PhosphdiesteRasE-5 inhibition to improve clinical status and exercise capacity in diastolic HF trial

Controversial findings have been oberserved from the PhosphdiesteRasE-5 inhibition to improve clinical status and EXercise Capacity in Diastolic Heart Failure (RELAX) trial[43] with HFpEF patients. Here, no significant improvement in diastolic function, exercise capacity and quality of life was observed.

In addition, in a multi-center study 216 patients with HFpEF and increased pulmonary artery pressures did not affect exercise capacity or clinical constitution over a time period of 24 wk[44]. Furthermore, longterm analyses of NT-proBNP and endothelin-1 displayed no significant changes between sildenafil and placebo

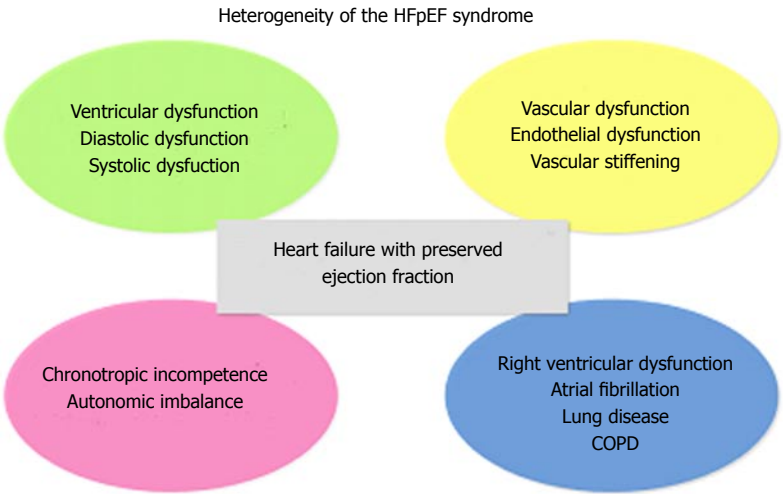

Figure 1 Overview of multiple effectors for the heterogeneity of the heart failure has preserved left ventricular ejection fraction syndrome. COPD: Chronic obstructive pulmonary disease; HFpEF: Heart failure has preserved left ventricular ejection fraction.

treated groups. However, in a one-year single center trial of sildenafil in patients with HFpEF described significant improvements in with sildenafil treated patients when compared to placebo treated patients[41].

The lack of benefit of sildenafil treatment could be because the inclusion and exclusion criteria. In this trial, the included patients did not have pulmonary hypertension and suggested by highly increased NT-proBNP levels had advanced HF; this could explain the less-responding to sildenafil-treatment.

Furthermore, in a small clinical trial including 44 patients suffering from HFpEF (LVEF > 50%) and PAH inhibition by PDE-5 displayed a significant improvement in diastolic dysfunction, pulmonary pressures and right ventricular performance over an oberservation period of 12 mo[41]. Given the results, PDE-5 inhibition for HFpEF without proven increased PAP should not be used.

DEVICE THERAPY

No substantial clinical trials of implantable cardiac defibrillators or cardiac resynchronization therapy exist in the HFpEF population.

A large trial of cardiac resynchronization therapy (CRT) in patients suffering from an LVEF between 36% to 50% has been stopped due to poor outcome[45].

CRT is currently limited to those patients with LVEF < 35%, sinus rhythm, QRS > 150 ms, and left bundle branch block (LBBB) pattern. A retrospective analysis of the predictors of response to CRT has shown that CRT may offer a valuable option for these patients[46,47]. However, this finding has to be proven in a prospective, randomized multicenter trial. To date, CRT should not be used as matter of routine in patients with HFpEF. Furthermore, a current small clinical trial used a cardiovascular simulation to provide insights into the potential effects of an inter-atrial shunt on rest and exercise hemodynamics in patients suffering from HFpEF[48]. The principal finding of this study is that the inter-atrial shunt lowers left atrial (LA) pressure and that this effect is particularly pronounced during the marked increase in LA pressure and increased left-to-right atrial pressure gradient during exercise in this patient population.

However, the marked reduction in LA pressure (and pulmonary capillary pressure) could allow patients to exercise longer, potentially resulting in higher heart rates and higher values of cardiac output.

There exist currently two different devices in clinical development to create a device to make a precisely sized interatrial septal defect that will maintain patency for this purpose. Whether the findings of this theoretical simulation provide insights into patient selection criteria and the expected magnitude of hemodynamic improvement has to be proven in further clinical trials.

Possible optimizations of clinical trials for HFpEF in the future

For future clinical trials in HFpEF better matching of treatments for the precise type of HFpEF seems to be necessary (Figure 1).

However, in retrospect it has been elucidated that the type of therapy tested in previous clinical trials may not be the correct match for the type of HF population included. This line of argument incorporates the ALDO-DHF trial, which included patients with early-stage HFpEF and not manifest volume overload.

Moreover, in the RELAX trial, which enrolled symptomatic HF patients with volume overload but not necessarily those with overt PAH and RV dysfunction. However, the inclusion and exclusion criteria should focus on patients with early HFpEF, in whom exercise intolerance is one of the main indicators and in whom there is objective evidence of exercise-induced increase in LV filling pressures. Excluding patients with co-morbidity to try to increase the specifity of HFpEF may purely make matters worse by excluding those patients at high risk. If co-morbidities drive the clinical course of the patient, then treatment directed only at cardiac function may be ineffective. In addition, diagnosis of HFpEF should not be based solely on clinical criteria and the absence of HFrEF (Figure 2).

Natiuretic peptides provide considerable confidence for improved clinical trial design. HFpEF is a

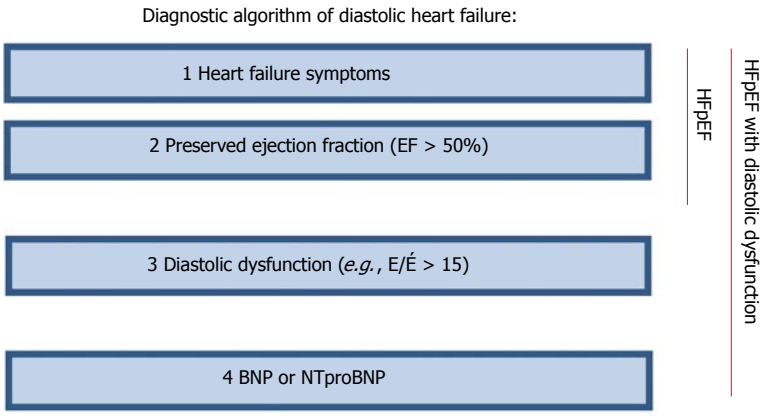

Figure 2 Diagnostic algorithm of diastolic heart failure. BNP: B-type natriuretic peptide; NT-proBNP: N-terminal of the B-type natriuretic peptide; E/É: Pulsed-wave Doppler E wave velocity divided by tissue Doppler E wave velocity; HFpEF: Heart failure has preserved left ventricular ejection fraction.

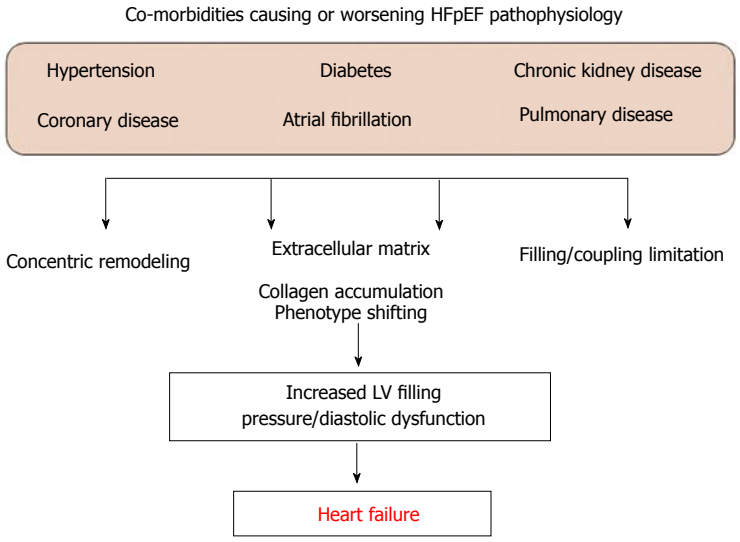

Figure 3 Scheme of co-morbidities causing or worsening heart failure has preserved left ventricular ejection fraction pathophysiology. LV: Left ventricular; HFpEF: Heart failure has preserved left ventricular ejection fraction.

heterogeneous and a complex syndrome and only specific phenotypes may respond to a particular therapeutic intervention (Figure 1).

Sufficient diagnosis and phenotyping seems to be essential. The disappointment in the last clinical trials that have proven so effective in treating HFrEF supports an urgent need for novel drug approaches to HFpEF (Figure 3). Underpowered clinical trials should be avoided and study designs need a focus on more consistent patient populations to control the impact cardiovascular co-morbidities. To conclude, ethnicity, cultural differences, co-medication, cut-off values and local clinical practice might influence results of clinical trials. Additional endpoints that include for example, quality of life evaluation and correct timing for effective therapeutic intervention must be kept in mind when planning expensive multicenter RCTs.

PROMISING NEW THERAPY STRATEGIES

Soluble guanylate cyclase inhibitors

Solid evidence supports augmentation of (cGMP) signaling as a potential therapeutic strategy for HFpEF[49]. Direct soluble guanylate cyclase stimulators target reduced cGMP generation due to insufficient sGC stimulation and represent a promising method for cGMP enhancement.

In the SOCRATES-Preserved trial (soluble guanylate cyclase stimulator in HF patients with PRESERVED EF; clinicaltrial.org NCT01951638) stimulation of the soluble guanylate cyclase by the oral soluble guanylate cyclase stimulator BAY1021189 is currently being investigated over 12 wk in patients with worsening HFpEF.

I_f channel inhibition

The SHIFT trial demonstrated that significant heart rate reduction *via* ivabradine, inhibitor of the I_f channel of the sinoatrial node, led to a significant reduction in hospitalization caused by HF and cardiovascular mortality in the HFrEF population[50]. Interestingly, the effects of ivabradine in HFpEF have been studied in a small recent trial of 61 patients, randomized to placebo or ivabradine (5 mg twice a day). Treatment with ivabradine showed an enhancement in exercise capacity and an improvement in LV filling pressures. In addition, a larger multi-center study enrolling about 400 patients is going to evaluate the properties of ivabradine concerning diastolic function, NT-proBNP levels and exercice capacity (www.clinicaltrialsregister.eu-EUCTR2012-002742-20-DE).

Dual angiotensin receptor blocker-neutral endopeptidase inhibitors

Although studies conducted with ARBs or ACEi alone did not display enhancements in HFpEF patients, pathophysiological evidence support the rationale for targeting the renin angiotensin system (RAS) in this population of patients.

The Prospective comparison of ARNI with ARB on Management of HF with preserved ejectionN fraction (PARAMOUNT) study[51], a phase Ⅱ trial conducted in 308 patients in 13 countries, compared the effects of LCZ696 and the ARB valsartan on the concentrations of natriuretic peptides. The natriuretic peptide investigated in this study, NT-proBNP, is a marker of cardiac wall stress, and levels are increased in patients with HF[51].

The agent LCZ696 in the PARAMOUNT study is the first compound to show both reductions in NT-proBNP and left atrial size (LA) in HFpEF patients, powerful predictors of outcome in HF. The favorable effects of LCZ696 seen in patients with HFpEF in the PARAMOUNT trial are encouraging, and further testing of this agent in this patient population is warranted.

LCZ696 acts by inhibiting both the angiotensin receptor and the enzyme responsible for the breakdown of the natriuretic peptides (neprilysin). LCZ696's dual mechanism of action thus acts to restore the altered neurohormonal balance in HFpEF[52]. These dual effects may be important in the treatment of HFpEF. Moreover, the large outcome trial PARAGON-HF will test the efficacy and safety in HFpEF patients (clinicaltrials.gov NCT01920711).

CONCLUSION

HFpEF accounts for approximately 50% of all patients diagnosed with HF, with similary poor outcomes. To date, only the prevention of HFpEF by treating the cardiovascular risk factors (coronary artery disease, atrial fibrillation, hypertension, diabetes, and obesity) has been shown to be efficient. This observation suggests that investigators in future trials should specify the indication of hospitalization for HF and may request to verify the details of patients' admissions.

However, dual inhibition of the RAS and neprilysin by the agent LCZ696 represents a novel promising therapeutic target for treating patients with HF. LCZ696 in the PARAMOUNT trial is the first agent to show both reductions in NT-proBNP levels and LA size in HFpEF patients, each strong predictors of outcome in HF. The favorable effects of LCZ696 seen in patients with HFpEF in the PARAMOUNT trial are encouraging. Further testing of dual of RAS and neprilysin inhibition in the HFpEF population is warranted.

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Electrical storm: A clinical and electrophysiological overview

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Abstract

Electrical storm (ES) is a clinical condition characterized by three or more ventricular arrhythmia episodes leading to appropriate implantable cardioverter-defibrillator (ICD) therapies in a 24 h period. Mostly, arrhythmias responsible of ES are multiple morphologies of monomorphic ventricular tachycardia (VT), but polymorphic VT and ventricular fibrillation can also result in ES. Clinical presentation is very dramatic in most cases, strictly related to the cardiac disease that may worsen electrical and hemodynamic decompensation. Therefore ES management is challenging in the majority of cases and a high mortality is the rule both in the acute and in the long-term phases. Different underlying cardiomyopathies provide significant clues into the mechanism of ES, which can arise in the setting of structural arrhythmogenic cardiomyopathies or rarely in patients with inherited arrhythmic syndrome, impacting on pharmacological treatment, on ICD programming, and on the opportunity to apply strategies of catheter ablation. This latter has become a pivotal form of treatment due to its high efficacy in modifying the arrhythmogenic substrate and in achieving rhythm stability, aiming at reducing recurrences of ventricular arrhythmia and at improving overall survival. In this review, the most relevant epidemiological and clinical aspects of ES, with regard to the acute and long-term follow-up implications, were evaluated, focusing on these novel therapeutic strategies of treatment.

Key words: Electrical storm; Ventricular tachycardia/fibrillation; Structural heart disease; Antiarrhythmic therapy; Implantable-cardioverter defibrillator; Shock; Catheter ablation

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Core tip: Electrical storm is an increasingly common and life-threatening syndrome. The proper management of this arrhythmic emergency is related to a comprehensive assessment of each case. In this review we report all the essential aspects regarding the clinical and

diagnostic evaluation, pharmacological treatment and, with special emphasis, catheter ablation approaches.

Conti S, Pala S, Biagioli V, Del Giorno G, Zucchetti M, Russo E, Marino V, Dello Russo A, Casella M, Pizzamiglio F, Catto V, Tondo C, Carbucicchio C. Electrical storm: A clinical and electrophysiological overview. *World J Cardiol* 2015; 7(9): 555-561 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i9/555.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i9.555

INTRODUCTION

Electrical storm (ES), also referred as arrhythmic storm, refers to a clinical condition characterized by 3 or more arrhythmia episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) leading to implantable cardioverter-defibrillator (ICD) therapies (Antitachycardia Pacing, ATP, or Direct Current shock, DC-shock), occurring over a single 24 h period[1]. ES represents an arrhythmic emergency that often affects patients at high risk of sudden cardiac death who previously underwent ICD implantation. In this setting ICD correctly interrupts VT/VF episodes; however ventricular arrhythmias, in terms of arrhythmogenic substrate, represent the gradual evolution of the underlying structural heart disease. In this review, we assess the most relevant epidemiological and clinical aspects of ES, with regard to the acute and long-term follow-up implications, focusing on novel therapeutic strategies of treatment.

CLINICAL CHARACTERIZATION

The term ES was introduced in the 1990s to describe an instability condition, highly malignant, characterized by repetitive episodes of ventricular arrhythmias[2]. Nowadays, ES implies several appropriate ICD interventions aimed at terminating the arrhythmic episodes.

ES has been reported in 10%-40% of patients in secondary prevention whereas the incidence of ES is lower (3.5%-4%) in primary prevention[3-16]. However, the correct incidence of ES is uncertain due to several confounding factors such as population considered, type of cardiomyopathy, pharmacological therapy undertaken and other variables. In addition, most of the studies concerning ES incidence were retrospective thus including only the patients who survived the arrhythmic event.

ES mainly affects patients with advanced dilated cardiomyopathy, both ischemic and non-ischemic, representing the gradual evolution of the underlying arrhythmic substrate; however, ES may affect patients with different types of structural heart disease, such as valvular or congenital heart disease, as well as patients without structural heart disease (*i.e.*, Brugada syndrome)[17].

The most significant predictors of ES are severe reduction of left ventricle (LV) function, advanced age and previous VT/VF episodes[8,10,11,13,18,19]. Monomorphic ventricular tachycardia is the most common arrhythmia documented in ES patients. VT episodes, hemodynamically unstable and interrupted with ATP or DC-shock, are the rule, with evidence of multiple VT morphologies[20]. Anyway, clinical presentation of ES is variable[9].

Less commonly, ES has been recorded in patients in whom premature ventricular complexes are the trigger of VT/VF both in acute myocardial infarction and in absence of structural heart disease[16,21]. The latter are often patients with "primitive ventricular fibrillation", in whom the trigger of the arrhythmia has not been documented, presenting with multiple VF episodes after ICD implantation, mostly refractory to pharmacological therapy. Therefore, in this setting, the identification of ES triggers may be of interest in preventing VT/VF episodes, particularly in case of electrolyte disorder[9,14]. The role of adrenergic system in maintaining ES is of special interest as well; in terms of acute event treatment[7,16]. Adrenergic activation seems to play a key role in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia due to the well known arrhythmic sensitivity to adrenergic stimulation; although in the majority of these patients the trigger is unkown[22].

ACUTE PRESENTATION, PROGNOSTIC RELEVANCE

ES is an arrhythmic emergency related to recurrent consecutive episodes of ventricular arrhythmia, with low likelihood of spontaneous termination.

The clinical scenario of ES is the result of a combination of various factors: in patients with structural heart disease affected by chronic heart failure, ES causes worsening of heart failure with high risk of pulmonary edema/cardiogenic shock. These events are much more frequent and severe, less stable the arrhythmic condition and the functional status are. ICD therapies even if allow arrhythmic episodes termination and prevent sudden cardiac death, do not play any role in stabilizing the clinical scenario. Moreover, the continuous intervention of ICD, implies unfavorable hemodynamic effects[3], also resulting in psychological distress, adrenergic hyperactivity, and patient discomfort[22,23].

No reproducible data on acute mortality in ES are available. It should be reminded that acute mortality represents a common cause of death in patients with severe structural heart disease, in most of cases as cardiogenic shock or electromechanical dissociation in the setting of unmanageable arrhythmias[3]. Literature data show that patients with ES present an increased risk of sudden arrhythmic or cardiac death in the mid-term follow up[8-10,16,24]; furthermore, these findings were not confirmed just in few papers[7,13]. The MADIT Ⅱ trial showed that patients with VT episodes interrupted by ICD have a significantly higher risk of sudden and non-sudden cardiac death. Moreover, patients who have survived ventricular arrhythmias have an increased risk

of worsening heart failure and of mortality related to it[25]. Specifically, in the MADIT Ⅱ trial, Sesselberg *et al*[11] have shown that ES is the most important independent predictor of mid-term cardiac death (increased risk of 7-fold), resulting particularly significant in the first 3 mo after ES (increasing risk of 18-fold). The results of SCD-HeFT trial are comparable, in addition, Poole *et al*[26] observed that not only appropriate shocks - directly related with arrhythmic events - but also inappropriate shocks impact on an increased mortality. More specifically the authors reported a significant increase of death in patients with appropriate (HR = 5.68; $P < 0.001$) and inappropriate shocks (HR = 1.98; $P = 0.002$). In particular, multiple shocks were associated with a 8-fold risk of death (HR = 8.23; $P < 0.001$).

These findings support the hypothesis that the recurrence of frequent arrhythmic events (and even more ES) strongly impacts on the evolution of patients' clinical history, particularly by worsening the cardiac function. In this setting multiple shocks could have their own etiopathogenetic role related to repeated myocardial injury.

DIAGNOSIS AND CLINICAL MANAGEMENT

Patients with ES require a diagnostic evaluation of their structural heart disease, the type of arrhythmia and the presence of clinical triggers. The most common triggering factors are acute myocardial ischemia, electrolytic disorders and adverse drug effects. Identification of triggers is a key point: sometimes it allows the suppression of arrhythmias through simple therapeutic interventions, such as in case of hypokalaemia. Acute myocardial ischemia must be accurately identified and excluded through clinical and non-invasive diagnostic parameters. However, in most patients with coronary artery disease and previous history of myocardial infarction presenting with ES, myocardial ischemia is just a secondary effect of the arrhythmias. Myocardial ischemia should therefore be interpreted and consequently treated with the aid of pharmacological and/or interventional therapies in the presence of acute coronary syndrome. In the majority of cases, however, ES represents the evolution of an arrhythmogenic substrate in patients with previous VT/VF episodes.

Therapeutic interventions first depend on the arrhythmic pattern and on the hemodynamic stability of patients. ICD interrogation is the preliminary diagnostic step to evaluate the appropriateness of shock delivery and arrhythmic parameters (heart rate, electrogram analysis, trigger). ICD reprogramming is mandatory in order to both limit ICD shock delivery and attempt VT/VF interruption with antitachycardia pacing[27,28]. The accuracy of the diagnosis of ventricular arrhythmia may only occasionally show interpretative troubles in single-chamber ICD recipients in whom the comparison between basal and arrhythmic electrograms should be carried out carefully privileging reading from multiple recording channels.

ES patients require hospitalization. A continuous ECG and vital signs monitoring must be performed in the Coronary Intensive Care Unit or in a dedicated Emergency Arrhythmia Unit. During the evaluation phase, the possibility to document and characterize different morphologies of VT responsible for the clinical scenario is relevant, also with regard to a possible ablative treatment[20].

Hemodynamic and metabolic evaluations are needed in order to perform urgent interventions through intravenous therapies, such as inotropic agents or hydroelectrolytic infusion.

In the acute setting, prevention of arrhythmic recurrence should be as efficient as possible, by means of: (1) amiodarone is the first choice drug, unless contraindicated (presence of hyperthyroidism, long QT interval)[29]; (2) beta-blocker administration plays an important role because of its antiarrhythmic and antiadrenergic effect. Beta-blockers administration should be limited in patients with labile hemodynamic compensation or severe reduction of LV function; (3) lidocaina and azimilide are second choice drugs, useful in case of contraindications to previous medications[14,30]; (4) verapamile should be used as drug of choice in case of premature ventricular beats originating from His-Purkinje system; and (5) finally, atrial or sequential atrio-(bi)ventricular pacing are useful to avoid bradycardia[31,32].

Sedation is pivotal to stabilize patients with ES, but hemodynamic and/or respiratory instability can limit the use of sedation drugs, such as benzodiazepine. In these cases mechanical ventilation with oro-tracheal intubation are absolutely required in refractory forms of ES. In some cases mechanical ventilation allows safer drugs administration otherwise not tolerated.

ROLE OF CATHETER ABLATION

The role of catheter ablation (CA) in patients with VT is becoming more and more relevant, as a definite treatment of multiple forms of arrhythmias and a complementary intervention in cases of high electrical instability, thus improving prognosis and quality of life in patients with advanced forms of heart disease. This observation creates the rationale to investigate the possibility to apply CA in patients with frequently recurring ventricular arrhythmias and ES[33].

Preliminary reports regarding the role of CA in the treatment of ES are limited to patients with specific clinical characteristics and/or small case series. Silva *et al*[34] reported a success rate of 80% in an ES population with recurrent hemodynamic stable VT; Schreieck *et al*[35] reported acute success in most of cases of a selected population undergoing CA of hemodynamic unstable arrhythmias guided by substrate mapping. Also Bänsch *et al*[16] described CA in patients with acute

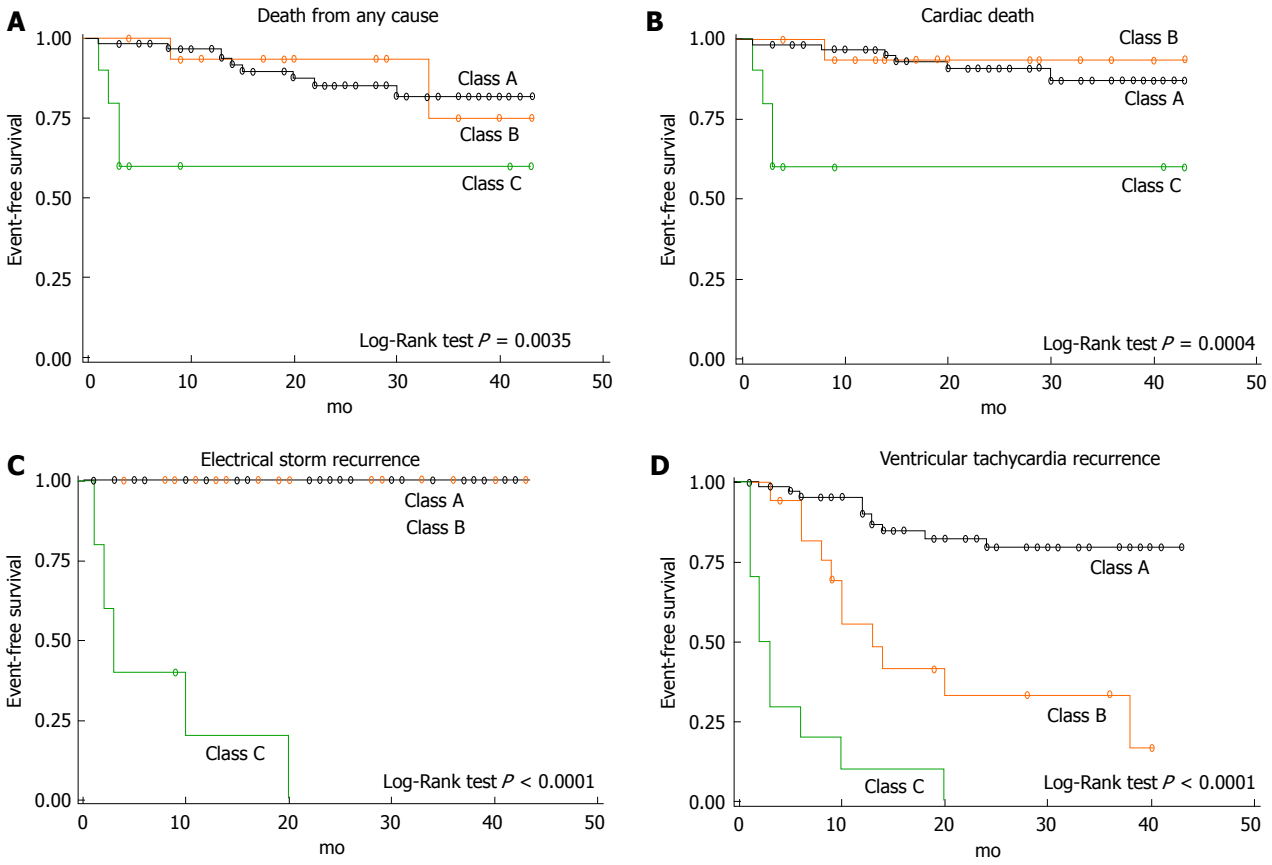

Figure 1 Kaplan-Meier survival analysis after catheter ablation of electrical storm. Class A indicates catheter ablation success, defined as suppression of each ventricular tachycardia (VT) morphology; Class B indicates partial success, defined as suppression of each clinical VT; Class C indicates failure, defined as persistence of one or more clinical VT (reprinted from Carbucicchio *et al*[20]).

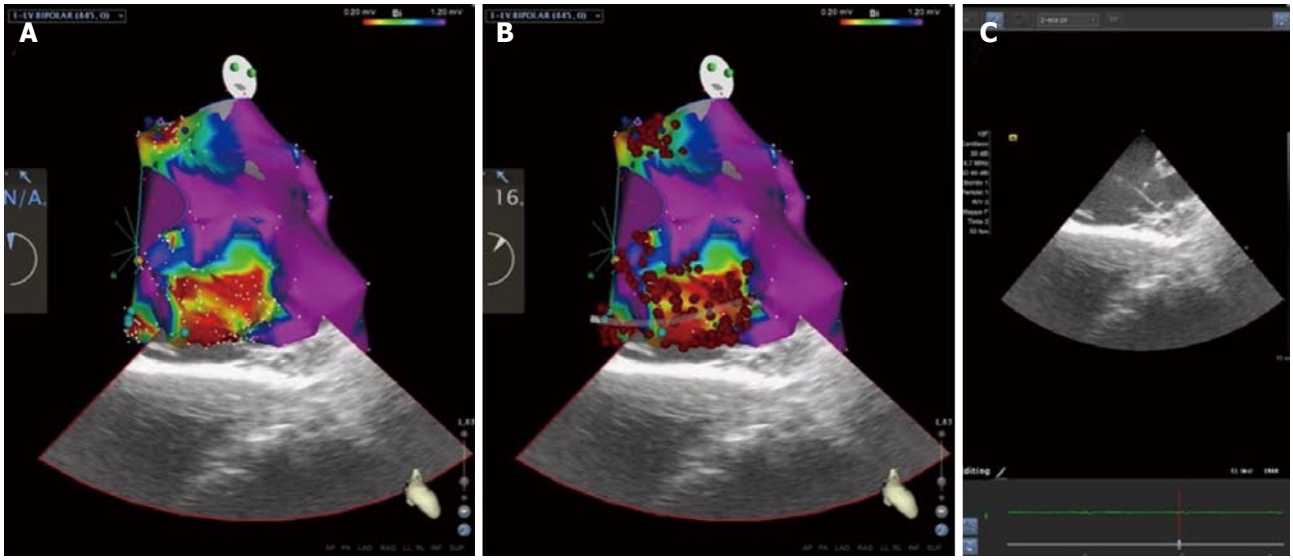

Figure 2 Modern approach of mapping and ablation for the treatment of electrical storm: High-density electroanatomical mapping of the left ventricle using CARTOSOUND contact-force technology (Biosense Webster, Diamond Bar, CA, United States). A: Two distinct peri-valvular scars, in the mitro-aortic continuity and below the mitral annulus, in the setting of idiopathic cardiomyopathy are visualized. Scars are characterized by dense scar (abnormal bipolar electrograms < 0.20 mV), surrounded by a border zone (0.20-1.20 mV) in which late potentials, are tagged (dark and light blue dots); B: Radiofrequency ablation lines are dragged for dechanneling and isolation of all proarhythmic sites; C: Intracardiac echocardiography imaging is aiming at substrate characterization and correct positioning of the catheter during mapping and ablation.

myocardial infarction and ES in whom VF was triggered by premature ventricular contractions, targeted by CA.

The ability to assess the feasibility and effectiveness of CA in a wider ES population arises from more

recent experiences, which better represent the profile of patients with complex, hemodynamically non-tolerated, drug-refractory ventricular arrhythmias, mostly in the setting of structural heart disease with severe impairment of left ventricular function. In this population, Carbucicchio *et al*[20] have described for the first time VT suppression in 90% of patient undergoing one or more CA procedures with or without the use of haemodynamic mechanical support. Moreover, the authors have shown that non-inducibility of VT at the end of the procedure was predictive of no recurrence of ES or VT at 2 years follow-up; accordingly, CA survival was improved in arrhythmia-free patients (Figure 1). This experience once again shows that ES represents a turning point in the natural history of patients with dilated cardiomyopathy and ventricular arrhythmias and that the treatment of arrhythmic burden plays a favourable effect on the clinical history of these patients both in terms of arrhythmic death and acute heart failure. More recent studies have confirmed that CA of ES is effective in reducing mortality in the middle-term follow up[18,36].

Regarding management of patients with ES or with recurrent VT following points must be taken in account: (1) clinical management in this setting is highly demanding. It requires an experienced Intensive Care Unit staff and a multidisciplinary approach that includes anesthesiological and psychological support; (2) advanced CA strategies in these patients are particularly complex (Figure 2). Obviously, the use of electroanatomical mapping (EAM) to guide CA is mandatory, and a substrate-guided approach is commonly more efficient, limiting activation mapping manoeuvres[37]. An epicardial approach should be preferred in all patients with non-ischemic cardiomyopathy to minimize recurrences. In patients with unstable VT or very depressed cardiac function, or in those presenting with cardiogenic shock, hemodynamic mechanical support allows patients stabilization and enhances efficacy and safety of CA, and can be used both during intraprocedurally as in the post-procedural period[38]; and (3) in selected patients, requiring concomitant surgical indications or in whom a percutaneous approach is not feasible, surgical ablation guided by EAM (endo- and/or epicardial) may be taken into account, in an experienced and multidisciplinary setting.

CONCLUSION

ES is an "extreme" ventricular arrhythmia affecting ICD patients with structural heart disease and is a major predictor of cardiac death in the short-term follow-up. Problems related to the treatment of ES patients are complex, depending on the type of patient as well as on the treatment of cardiac emergency, and require high standard facilities and specialized skills.

CA for the treatment of ES is particularly promising and should be considered the elective form of treatment to achieve long-term rhythm stabilization and to prevent heart failure. The possibility to modify the arrhythmic substrate by CA in an early phase, thus preventing critical situations deriving from repetitive ICD interventions, looks promising, but necessitates further corroborations.

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ORIGINAL ARTICLE

Basic Study

Initial clinical experience using the EchoNavigator®-system during structural heart disease interventions

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Author contributions: Balzer J and Zeus T designed the concept of the study, prepared the manuscript and figures, performed the interventional procedures and drafted the manuscript; Hellhammer K and Veulemans V performed the clinical and echocardiographic data assessment before and during the intervention; Eschenhagen S and Kehmeier E made critical revisions related to the quality of the acquired data and participated in the creation of figures and images; Meyer C, Rassaf T and Kelm M participated in the performance of the interventional procedures, and in the design and review of the manuscript; all authors read and approved the final manuscript.

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Institutional review board statement: No ethical approval by the local institutional review board was necessary for the additional application of this novel fusion imaging technology. The data analysis was conducted retrospectively without the necessity of providing an ethics committee approval.

Institutional animal care and use committee statement: Animal experiments were not performed for the conduction of this study.

Conflict-of-interest statement: Jan Balzer has received fees for serving as a speaker from Philips Healthcare. Other authors have none conflict of interest to declare.

Data sharing statement: Technical appendix, statistical code, and datasets are available from the corresponding author. Participants gave written informed consent for the performance of each interventional procedure. Written informed consent was not obtained for the additional application of the fusion imaging software. The presented data are anonymized and the risk of identification is low.

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Abstract

AIM: To present our initial clinical experience using this innovative software solution for guidance of percutaneous structural heart disease interventions.

METHODS: Left atrial appendage, atrial septal defect and paravalvular leak closure, transaortic valve repair and MitraClip® procedures were performed in the catheter laboratory under fluoroscopic and echocardiographic guidance. The two-dimensional and three-dimensional images generated by the transesophageal echocardiography probe were interfaced with the fluoroscopic images in real-time using the EchoNavigator®-system.

RESULTS: The application of the novel image fusion technology was safe and led to a better appreciation of multimodality imaging guidance due to improved visualization of the complex relationship between catheter devices and anatomical structures.

CONCLUSION: The EchoNavigator®-system is a feasible and safe tool for guidance of interventional procedures in structural heart disease. This innovative technology may improve confidence of interventional cardiologists in targeting and positioning interventional devices in order to increase safety, accuracy, and efficacy of percutaneous interventions in the catheter laboratory.

Key words: Fusion imaging; Interventional guidance; Percutaneous interventions; Structural heart disease; Echocardiography

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Core tip: Interventions in structural heart disease require adequate echocardiographic and fluoroscopic imaging for safe accomplishment of the procedure. Recently, a novel fusion imaging technology has been introduced, allowing for the first time to merge echocardiographic and fluoroscopic images in the catheter laboratory in real time. As one of the first centers worldwide, we used this innovative technology for guidance of interventions in structural heart disease, demonstrating its potential benefits for guiding complex interventions in structural heart disease.

Balzer J, Zeus T, Hellhammer K, Veulemans V, Eschenhagen S, Kehmeier E, Meyer C, Rassaf T, Kelm M. Initial clinical experience using the EchoNavigator®-system during structural heart disease interventions. *World J Cardiol* 2015; 7(9): 562-570 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i9/562.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i9.562

INTRODUCTION

Adequate peri-procedural image guidance is indispensable for safe accomplishment of cardiovascular interventions[1]. In contrast to coronary interventions where fluoroscopy remains the dominant imaging modality, the evaluation and treatment of structural heart disease requires continuous soft-tissue information that cannot be provided by fluoroscopy alone. Therefore, percutaneous interventions in the catheter laboratory are usually monitored additionally by two-dimensional (2D) and especially three-dimensional (3D) transesophageal echocardiography (TEE)[2]. Both techniques are presented side by side on different screens, necessitating the interventionalist to mentally reconstruct and fuse the presented information. Recently, the EchoNavigator®-system (Philips Healthcare, Best, The Netherlands) has been introduced as a novel software solution, allowing to merge echocardiographic and fluoroscopic images on the same display in real time[3,4]. In this study we aim to present our initial clinical experience with this innovative technology and describe its potential benefits during percutaneous interventions in structural heart disease.

MATERIALS AND METHODS

From January 2014 until July 2014 we used the EchoNavigator® software for guidance of 127 interventions in structural heart disease [3 paravalvular leaks, 11 atrial septal defects (ASDs), 31 transapical transcatheter aortic valve repair (TAVR) procedures, 35 left atrial appendage (LAA) occlusions, and 47 MitraClip® procedures]. Conscious sedation with continuous hemodynamic monitoring was applied in all cases, with the exception of the 31 transapical TAVR procedures, where general anesthesia was applied. After insertion of the procedure specific sheath, patients were sedated, and the TEE probe was inserted by an experienced echocardiographer before initiating the procedure by the interventionalist. For the additional application of this fusion imaging technology no ethical approval was necessary. All patients gave written informed consent for the performance of each interventional procedure.

EchoNavigator®

The technology of the EchoNavigator®-system relies on a real-time co-registration and visualization of 2D/3D TEE and fluoroscopy. The method consists of an image-based TEE probe localization and calibration algorithm. This algorithm automatically finds and tracks the position and the direction of the TEE probe within the fluoroscopic image[5]. After synchronization of TEE and fluoroscopy images, the system automatically tracks and follows the rotation of the C-Arm, based on the angulation of the gantry[6]. The results of this co-registration process are visualized to the interventional cardiologist on a large specific display that can be divided and arranged in up to 4 sections at discretion of the interventionalist. The 4 sections are assigned to different functions, depicting different views and are labeled as follows: (1) Echo: The Echo-view demonstrates online the images from the echo machine that can only be manipulated by the echocardiographer; (2) X-ray: The X-ray-view displays the actual fluoroscopic view depending on the angulation of the gantry. For a precise co-registration of the TEE probe, the probe has to be central in this view, the correctness of the co-registration being illustrated by a green edging of the probe. In case that the co-registration is not correct, *e.g.*, after movement of the TEE probe, the edging of the probe will turn into red; (3) C-Arm: The beam flow of the matrix array transducer is marked as a purple 3D sector in the X-ray-view, presenting the 3D Echo information of this sector in the C-Arm-view. Changes in angulation, rotation or position of the TEE probe are immediately registered

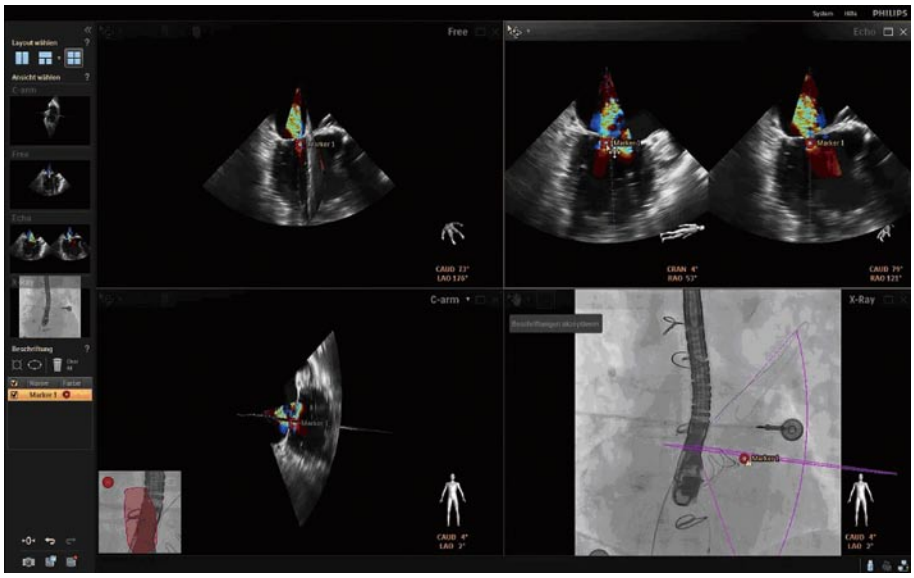

Figure 1 Specific points of interest can be marked in the ultrasound image by the interventionalist that will automatically appear on the fluoroscopic image. In this case of a MitraClip® procedure, the echocardiographer displays the mitral valve with Color Doppler in the X-plane mode in order to define the most regurgitant jet (right upper panel). The interventionalist can then steer particular markers using the table-side control mouse, and place them to define the region of interest for the MitraClip® procedure. After adjusting the marker, it will appear on the fluoroscopic image, representing the exact region of interest, where the MitraClip® should be implanted (right lower panel).

and updated on the fluoroscopic image; and (4) Free: The Free-view also displays 2D and 3D TEE information that can be manipulated by the interventionalist with a sterile covered mouse on the catheter table. The interventionalist can rotate and crop into 3D data sets in any direction.

Specific points of interest can be marked in the ultrasound image by the interventionalist that will automatically appear on the fluoroscopic image (Figure 1). There is also the opportunity to switch between different TEE modalities (2D, 3D, 2D and 3D Color Doppler), and different view settings (2D, X-Plane, 3D Zoom and 3D Full Volume).

RESULTS

Feasibility of the EchoNavigator® during interventions in structural heart disease

All 127 procedures were performed using the EchoNavigator®-system for peri-interventional guidance. The application led to safe accomplishment of all performed procedures without any complications related to the peri-procedural imaging guidance.

Percutaneous edge to edge repair of mitral regurgitation using the MitraClip® system: The unique visualization of the mitral valve apparatus using 3D TEE for planning and performing the procedure allows improved understanding of the morphological and functional changes induced by the MitraClip® system. In this context, a recent study demonstrated that the procedural effects of the MitraClip® system upon the mitral valve apparatus can best be detected using 3D TEE with various offline reconstruction techniques[7]. The peri-interventional evaluation of the mitral valve, including the leaflets, the annulus, and the subvalvular apparatus using 3D TEE is therefore of major importance. On the other hand, the orientation of the guiding system and the dedicated structures of the Clip with its grippers can be much better delineated using fluoroscopy. Therefore, a multimodality approach for guidance of MitraClip® implantations using 2D/3D TEE and fluoroscopy is of essential importance. Our results demonstrate that the translation of specific echocardiographic markers into the X-ray-view can improve the visualization of the complex relationship between catheter devices and anatomical structures during MitraClip® procedures (Figure 2). In this context, the EchoNavigator®-system was especially usefull for the transseptal puncture, that can be performed using fluoroscopy and 2D TEE imaging alone. In special situations, the 3D images improve the visualization of the transseptal puncture side for better definition of the correct height above the mitral valve, necessary for sufficient movement of the delivery guide and the device[8]. The fact, that the designated point of puncture can be marked in either the 2D or the 3D echocardiographic view, is very helpful for placement of the needle in the fluoroscopic image. Severe complications can arise when the Clip perforates the thin wall of the atrial septum, leading to cardiac tamponade[9]. The designation of three echocardiographic orientation points (interatrial septum at puncture site, crista terminalis between pulmonary vein and the LAA, and the center of the mitral valve) into the fuoroscopic image can prevent injury of the left atrium, even when the Clip movements are monitored with X-ray within this virtual triangle. When more than

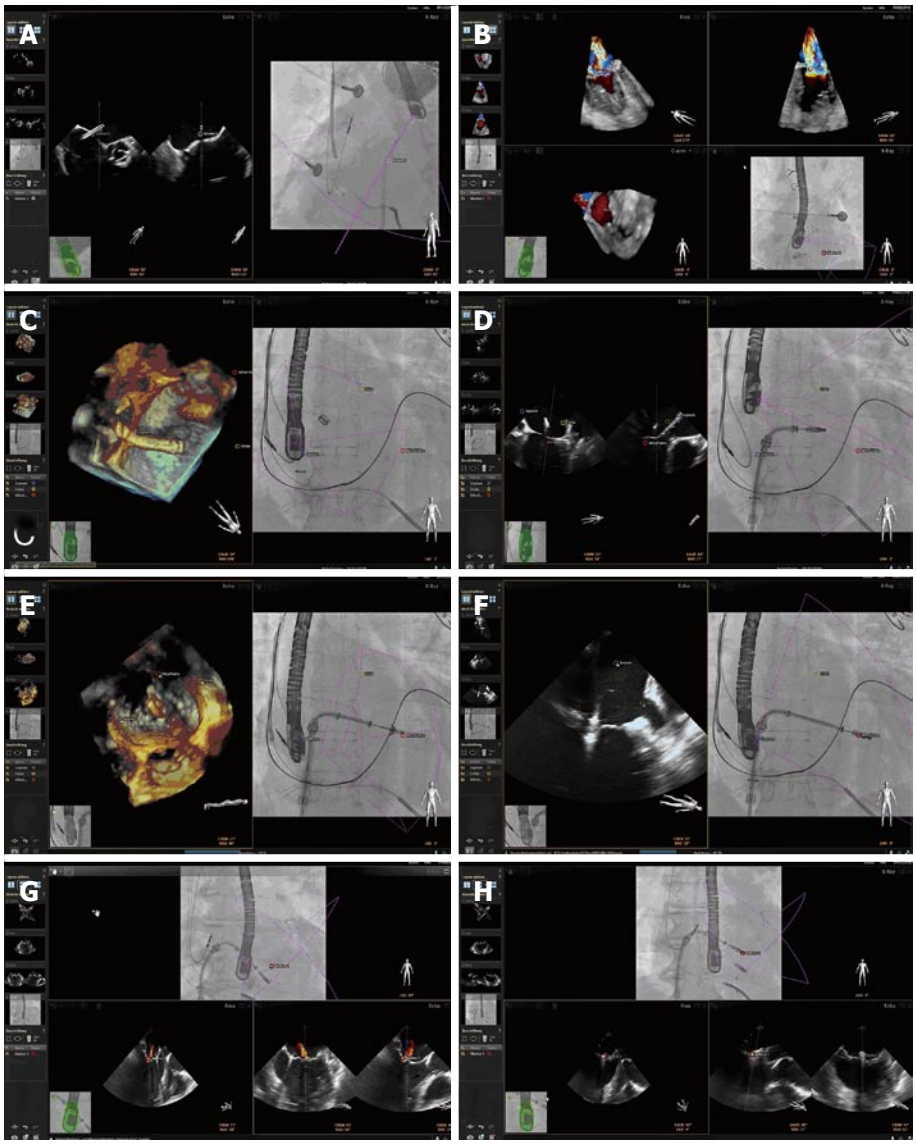

Figure 2 EchoNavigator® during MitraClip® procedures. A demonstrates the Echo-view on the left, depicting an X-plane-view of the interatrial septum. The interventionalist can set markers in this view for exact delineation of the optimal puncture site that will automatically appear in the X-ray-view on the right. A 3D full volume color doppler image is shown in the right upper panel of B. After cropping into this data set, the maximum regurgitant jet was depicted and marked within this image. On the left side of C, a 3D view of the septum with the delivery system and especially the three points of interest (Septum, Crista, and Mitral valve) is demonstrated. The connection between these three points creates a virtual triangle in the X-ray-view on the right side of C, outlining the area at risk outside this triangle in the X-ray-view in D, where contact of the MitraClip® device with its surrounding structures potentially can lead to complications, such as perforation with cardiac tamponade. E demonstrate the process of Clip orientation orthogonally towards the commissure in the 3D view, and the grasping of leaflets in the 2D intercommisural view in F. The X-ray-view in both figures on the right display demonstrates the correct position of the Clip right on top of the red marker, corresponding with the echo images. G demonstrates the residual regurgitant jet on the lateral side of the first Clip. This jet was marked in the echo image and was then used for orientating a second Clip in the X-Ray image, as demonstrated in H. 2D: Two-dimensional; 3D: Three-dimensional.

one Clip needs to be implanted, the exact relation of the Clips to each other can be misjudged due to blooming artefacts of the echocardiographic image[10]. In this situation, fluoroscopy is very helpful to illustrate the spatial relation of both Clips. The EchoNavigator®-system enables the translation of the residual jet from the echocardiographic image into the X-ray image for exact implantation of the second Clip.

LAA occlusion: In non-valvular atrial fibrillation the interventional closure of the LAA has shown to be a successful alternative to oral anticoagulation[11]. The main steps of the procedure are the transseptal crossing of the guiding catheter into the left atrium and the placement of the occluder into the LAA. Basically, the intervention can be performed using fluoroscopy alone, but the advantages of 3D TEE for peri-interventional guidance during the procedure could be clearly demonstrated in recent studies[12]. 2D TEE allows the interventionalist to measure the orifice of the appendage in different 2D cut planes, but 3D TEE additionally allows 3D measurement of the perimeter for exact definition of the landing zone and correct device selection[13]. The EchoNavigator®-system revealed to be very useful for the performance of the transseptal puncture (Figure 3). Furthermore, the exact delineation of the landing zone

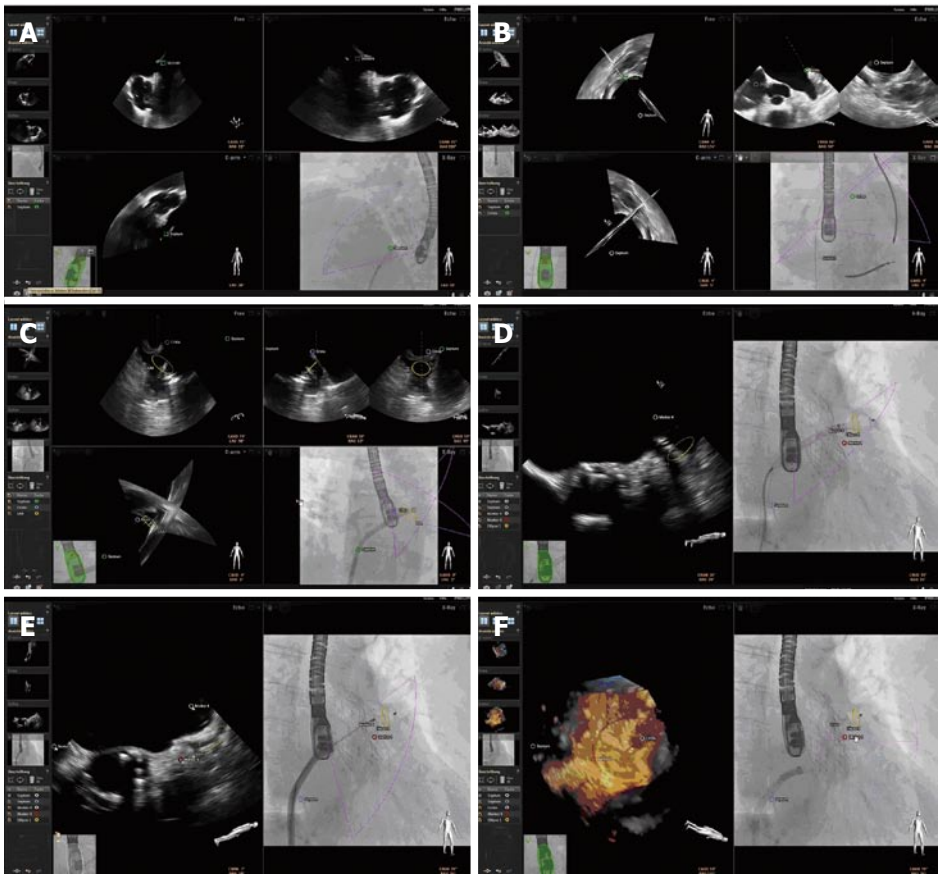

Figure 3 Echonavigator® during left atrial appendage occlusion. A demonstrates how the point of interest for potential transseptal crossing along the interatrial septum is marked in the Echo image. B demonstrates in the X-ray-view, that the wire is located cranial of the Crista terminalis, that initially was assigned in the Echo image. C depicts an ellipsoid ring, representing the landing zone for the occluder device marked yellow in the X-plane view of the 2D Echo image. D displays the deployment of the lobe of the left atrial appendage occluder, detecting that correct device size was chosen. E shows this ellipsoid marker right in between the lobe and the disc of the occluder after deployment of the disc. The red marker represents the location of the circumflex coronary artery. F shows the final result after disconnecting the guiding system from the occcluder. The left panel gives a nice 3D overview of the site of implantation, displaying the difference of the landing zone (yellow circle) and the orifice area of the left atrial appendage.

derived from the echocardiographic images allowed for secure implantation of the device, therewith preventing mismatch and dislocation of the occluder.

ASD occlusion: Interventional techniques for the closure of interatrial communications can be performed using echocardiography as the only imaging modality. In a recent study the feasibility of interventional closure of ASDs without fluoroscopy was demonstrated[14]. TEE provides an imaging technique to guide ASD closures, providing fast and complete information about the underlying pathomorphology, improving spatial orientation, and additionally monitoring online the appropriate position of the device without loss of image quality. Furthermore, the additional information supplied by the 3D images helps to better understand the anatomy and the pathomorphology of the defect during guidance of the intervention, leading to shorter procedure times and less radiation exposure to the patient[15]. Our initial experience with the EchoNavigator®-system in such procedures indicates safe implantation of devices in ASDs. After placement of the echocardiographic marker delineating the ASD into the X-ray-view, the guide wire passage orientated towards this point enormously facilitated the procedure (Figure 4).

TAVR: For safe and precise performance of TAVI procedures, knowledge about the exact anatomy of the aortic root an its surrounding structures obtained by different imaging modalities is indispensable[16]. The use of TEE for peri-interventional guidance is limited, as it often requires general anesthesia and the probe may also partially obstruct the optimal fluoroscopic view. Particularly in patients treated over the transapical approach where general anesthesia is needed anyway, TEE has its place during and after valve implantation. For secure valve implantation, the exact knowledge about the alignment of the hinge points of the three leaflets is crucial[17]. With fluoroscopic imaging alone it is difficult to place the gantry in a position, where the hinge points are in the exact same cut plane. 3D TEE has proven to be very useful for aortic annular sizing and exact delineation of the hinge points during valve sizing and implantation[18]. The EchoNavigator®-system allows transfer of specific 2D and 3D echocardiographic

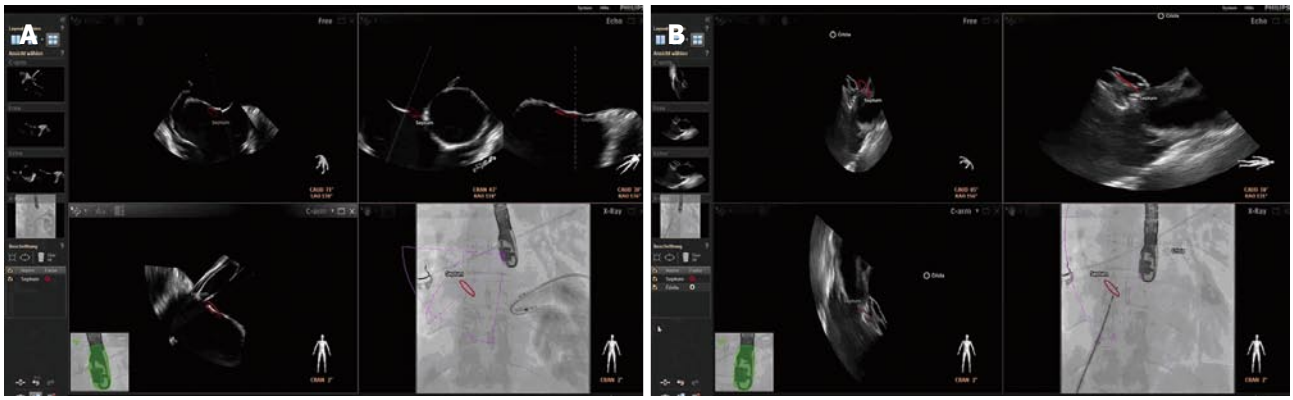

Figure 4 EchoNavigator® during atrial septal defect closure. A: Shows in the Echo-view in the right upper panel an X-plane view of the interatrial septum with a bicaval and a short axis view. The defect is clearly illustrated and marked with a red circle, appearing also in the X-ray-view as the target lesion; B: Demonstrates the occluder device after deployment of both the left and the right atrial disc. Note in the right upper panel that the two discs embrace the red target marker, where the defect was previously located.

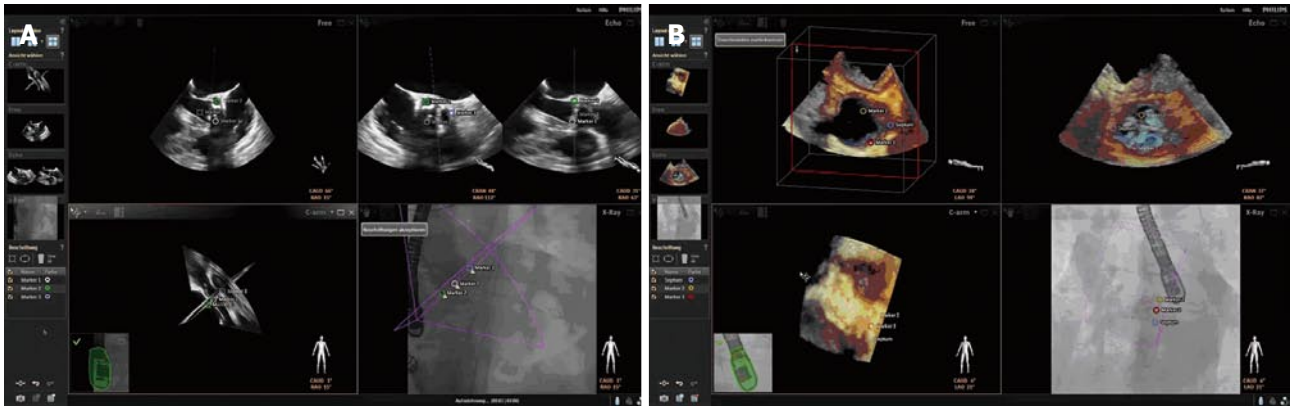

Figure 5 EchoNavigator® during transcatheter aortic valve repair. For precise delineation of the aortic annulus, the hinge points of the three leaflets of the aortic valve were marked in the Echo image, as illustrated in the right upper panel in A. These markers then appeared in the fluoroscopic X-ray-image in the right lower panel. Afterwards, the gantry was moved in order to transfer the three markers in one orthogonal image plane. This was also performed using 3D TEE for a better spatial orientation along the annulus plane of the aortic valve (B).

markers into the fluoroscopic image (Figure 5). This allows the interventionalist to correct the position of the gantry to the point where all three hinge point markers derived from echocardiography create one orthogonal plane.

Percutaneous closure of prosthetic paravalvular leaks: Different multimodality imaging techniques have been proposed for peri-interventional guidance of these procedures, including a combination of fluoroscopy and TEE[19]. The advantage of 3D TEE is the improved spatial resolution of the defect, especially during placement of the guide wire through the defect after transseptal puncture[20]. The interaction between the prosthetic leaflets and the occluder system leading to possible obstruction and malfunction of the prosthetic valve can better be illustrated by 3D TEE. The application of the EchoNavigator®-system is very helpful for percutaneous closure of paravalvular leaks (Figure 6). It allows the interventionalist to focus more upon the fluoroscopic image as it better delineates the catheter and the devices. Especially the precise steering of the guide wire through the defect is facilitated using this innovative technology.

DISCUSSION

The major findings of the present study are: (1) the application of the EchoNavigator®-system is feasible and safe during interventions in structural heart disease; (2) the EchoNavigator®-system allows merged display of echocardiographic (2D, 3D, Color-Doppler, X-Plane Imaging) and fluoroscopic images in real-time, allowing the interventionalist to interact with both imaging modalities simultaneously.

The benefits of fusion imaging technologies have already been described in the recent past, especially for the combination of CT-angiography and fluoroscopy images during transapical TAVR procedures for exact assignment of the correct site for the transapical access[21]. The integration of echocardiographic images into the X-ray image in real-time during percutaneous interventions were hampered so far by the complex nature of the echocardiographic data. The EchoNavigator®-system

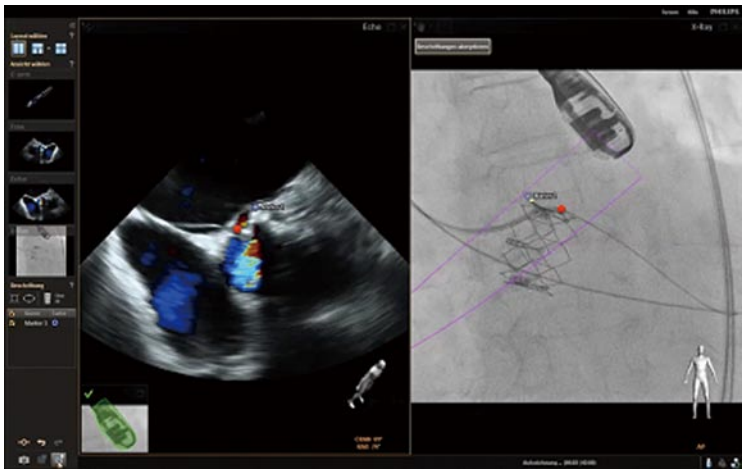

Figure 6 A case of a prosthetic paravalvular leak presenting aortic regurgitation after transcatheter aortic valve repair. The left panel demonstrates the Echo image in a short axis view, presenting the aortic annulus and depicting the regurgitant jet with Color Doppler. Here the marker was placed incorrectly, consequently transfering the marker next to the destination in the fluoroscopic image in the right panel. The red marker demonstrates where the region of interest should have been defined, reflecting the correct position in the fluoroscopic image.

is the first integrative solution to merge the two major important imaging modalities echocardiography and fluoroscopy in real time during interventions in structural heart disease. This technology facilitates the procedures, as echocardiographic soft tissue information is copied into the fluoroscopic image in real-time without time-consuming offline reconstruction. Traditionally, the interventional cardiologist is more familiar with the standard fluoroscopy projections compared with the classical TEE orientations. This new technology therewith fulfills the needs of the traditional interventionalist, who is not always used to the different 2D and 3D image orientation from TEE, by delineating the information from echocardiography into the more familiar fluoroscopic image. Only few studies have described the application of the EchoNavigator® during structural heart disease interventions so far. Sündermann *et al*[4] were the first to document an influence of radiation dose and procedure time under guidance of MitraClip procedures using the EchoNavigator®. They discovered a reduction in radiation and procedure time especially in complex procedures were more than one clip was implanted. This underlines the strength of this technology, simplifying the exact detection of the target point for the implantation of more than one clip next to the already implanted clip. The more complex the intervention becomes during the procedure, the more beneficial is the gain of the additional information given by the supporting software. Recently, González Gómez *et al*[22] described the advantage of the technique for transseptal punctures, according to our own results. Especially in MitraClip procedures the exact height of the puncture is essential for the success of the intervention. Using the EchoNavigator® the puncture site can even be defined before pullback of the needle from the superior caval vein into the right atrium. The precision of this fusion imaging technology is remarkable. Our own experience indicates that the applied markers depicting the target structures correlate very well with the definite location of the catheter devices. Moreover, in cases where the matching of echocardiographic and fluoroscopic data was unsatisfactory, we switched back to the conventional image guidance without the overlay. This approach always warrants an exit strategy in cases where the confidence into the fusion technology is somehow affected, anticipating possible misguidance by the EchoNavigator®-system. Next to the advantages of the EchoNavigator®, there also are some limitations. The technology described in this paper is based on a co-registration process of the TEE probe into the fluoroscopic image, simultaneously transferring the data into the virtual coordinate system of the X-ray display. The specific points of interest that can be marked with the software do not follow the acute movements of the echocardiographic speckles, making the combined image with the marked reference points quite static. The newest release of the EchoNavigator® allows a translation of the entire echocardiographic dataset into the X-ray-image, making the fusion of both modalities even more impressive, as recently published by our group[23].

Limitations

Our manuscript is supposed to give "tips and tricks" while working with the EchoNavigator® technology according to our initial experience in 127 patients. Our study lacks information about the benefit of the technology in the context of reducing the procedure length or the radiation dose. Data demonstrating these effects are currently only available for MitraClip procedures[4]. Prospective randomized multi-center studies with a larger sample size are necessary to demonstrate potential benefits of this promising technology for the patient. At this time, the main benefit of the EchoNavigator®-system is the facilitation of procedures by online fusion of two important imaging modalities, leading to better confidence of the interventionalist into the procedure and producing a better communication between the echocardiographer and the operator.

In conclusion, the EchoNavigator®-system is a feasible and safe tool for guidance of interventional procedures in structural heart disease. This innovative technology may accelerate the learning curve of interventional cardiologists in order to increase safety, accuracy, and efficacy of percutaneous interventions in the catheter laboratory. Further research is necessary

to evaluate the clinical value of this promising new tool, but it is likely that such a visualization technology might have a significant impact on the success and the safety of cardiovascular procedures in the catheter laboratory.

COMMENTS

Background

The number of percutaneous interventional procedures for the treatment of structural heart disease in patients that are ineligible for conventional open heart surgery is increasing permanently. Less invasive techniques allow for save accomplishment of these highly complex interventions in the catheter laboratory. Still, complications can arise during the procedure due to inadequate imaging of the target structures, often with fatal outcome for the patient.

Research frontiers

Side by side imaging of cardiac soft tissue anatomy and catheter devices using echocardiography and fluoroscopy is essential for safe performance of interventional procedures in structural heart disease, though assuming mental fusion and reconstruction of each imaging modality by the interventionalist. Online fusion imaging technologies can determine a faster and better understanding of the complex relationship between anatomical landmarks and catheter devices and have the potential to facilitate the procedure.

Innovations and breakthroughs

In the current study the authors demonstrate for the first time the application of a novel image fusion technology (EchoNavigator®) to guide different types of complex interventions in structural heart disease. To our knowledge, no similar studies presenting such a broad applicability of this hybrid imaging technique have been published so far.

Applications

The study results of the present study suggest that online fusion of echocardiographic soft tissue anatomy and fluoroscopic catheter devices is a breakthrough for precise monitoring of interventions in structural heart disease. The impressive images in this article implicate the value of this innovative technology for upcoming interventional procedures that afford even more an exact delineation of cardiac anatomy for safe performance of complex procedures. Furthermore, the technique does not exclude the standard operating procedure using solely echocardiography and fluoroscopy side-by-side. The generated overlay images rather must be considered accessory with in fact tremendous additional value.

Terminology

The name of the new software "EchoNavigator®" implicates the way it is used for monitoring of interventions in the catheter laboratory. 2D and 3D echo information can be translated into the fluoroscopic image for best navigation of the procedure using a combination of both imaging modalities.

Peer-review

This is an excellent manuscript about the clinical experience using the EchoNavigator®-system. The authors have suggested that the EchoNavigator®-system is a feasible and safe tool for guidance of interventional procedures, such as left atrial appendage, atrial septal defect and paravalvular leak closure, transaortic valve repair and MitraClip® in structural heart disease. This manuscript is nicely structured and very well written.

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ORIGINAL ARTICLE

Observational Study

Single *vs* double antiplatelet therapy in acute coronary syndrome: Predictors of bleeding after coronary artery bypass grafting

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Abstract

AIM: To investigate the contribution of anti-platelet therapy and derangements of pre-operative classical coagulation and thromboelastometry parameters to major bleeding post-coronary artery bypass grafting (CABG).

METHODS: Two groups of CABG patients were studied: Group A, treated with aspirin alone (n = 50), and Group B treated with aspirin and clopidogrel (n = 50). Both had similar preoperative, clinical, biologic characteristics and operative management. Classic coagulation parameters and rotational thromboelastometry (ROTEM) profiles were determined preoperatively for both groups and the same heparin treatment was administered. ROTEM profiles (INTEM and EXTEM assays) were analyzed, both for traditional parameters, and thrombin generation potential, expressed by area-under-curve (AUC).

RESULTS: There was no significant difference between

rates of major bleeding between patients treated with aspirin alone, compared with those treated with aspirin and clopidogrel (12% *vs* 16%, $P = 0.77$). In the 14 cases of major bleeding, pre-operative classic coagulation and traditional ROTEM parameters were comparable. Conversely we observed that the AUC in the EXTEM test was significantly lower in bleeders (5030 ± 1115 Ohm*min) than non-bleeders (6568 ± 548 Ohm*min) ($P < 0.0001$).

CONCLUSION: We observed that patients with a low AUC value were at a significantly higher risk of bleeding compared to patients with higher AUC, regardless of antiplatelet treatment. This suggests that thrombin generation potential, irrespective of the degree of platelet inhibition, correlates with surgical bleeding.

Key words: Platelet inhibitors; Thromboelastometry; Bleeding; Acute coronary syndrome; Coronary artery bypass grafting

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Core tip: To establish the timing of discontinuation of double antiplatelet therapy before coronary artery bypass grafting (CABG), it is crucial to identify predictors of bleeding. We analysed preoperatively classic parameters and thromboelastometry on 100 patients operated for CABG after presenting with acute coronary syndrome, to investigate the contribution of anti-platelet therapy and derangements of pre-operative coagulation status to major bleeding post-CABG. We observed that patients with a low area-under-curve (AUC) value in EXTEM were at a significantly higher risk of bleeding compared to patients with higher AUC, regardless of anti-platelet treatment. This suggests that thrombin generation potential, irrespective of the degree of platelet inhibition, correlates with surgical bleeding.

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INTRODUCTION

Post-operative bleeding is a major complication following coronary artery bypass grafting (CABG), with excessive bleeding occurring in 10% of patients, causing increased requirements of blood products, re-intervention and mortality[1-3]. Guidelines recommend ceasing clopidogrel therapy 5 d prior to CABG in order to minimise the risk of post-operative haemorrhage[4,5]. However, patients presenting for urgent and emergent CABG are often treated with double antiplatelet therapy, as recommended in major guidelines for the emergency management of acute coronary syndrome (ACS), prior to performing the diagnostic angiogram[6]. Ceasing clopidogrel and waiting the recommended 5 d prior to performing CABG would put these patients at higher risk of adverse coronary events[7]. Furthermore, as newer more potent platelet inhibitors such as ticagrelor and prasugrel become more widely used, patients presenting for CABG will increasingly be treated with these drugs[8-10]. As a result, it would be important to be able to detect patients at risk of excessive bleeding post-CABG, especially among those treated with double anti-platelet therapy. We devised the following study to determine whether bleeding risk could be predicted from the presence of double antiplatelet therapy, classical coagulation parameters or by rotational thrombo-elastometry performed prior to surgery.

MATERIALS AND METHODS

Patient selection

Among 905 patients operated for CABG between January 2006 and December 2008, we selected those presenting with ACS, and prospectively enrolled 50 consecutive patients without pre-operative clopidogrel exposure (Group A = 50 pts) and 50 consecutive patients with preoperative clopidogrel exposure within two days prior to intervention (Group B = 50 pts), who fulfilled inclusion criteria. The decision to stop double-antiplatelet therapy was at the discretion of the treating cardiologist. All patients signed informed consent for this observational study on prospectively collected data.

All patients who, within 2 d of surgery, were either on a daily oral regimen of 75 mg of clopidogrel or received a 300 mg oral loading dose prior to percutaneous coronary intervention (PCI), made up the clopidogrel study group. They were compared with a control-group of patients who had no clopidogrel exposure. Both patient groups received aspirin (100 mg) and low-molecular-weight-heparin (nadroparin calcium) prior to surgery. Patients with a history of previous cardiac surgery, concomitant valvular surgery or preoperative exposure to either warfarin or platelet glycoprotein IIb/IIIa inhibitors were excluded.

Recognized risk factors for perioperative bleeding in cardiac surgery were assessed including advanced age, female gender, low weight and renal insufficiency (Table 1).

Clotting profiles

Baseline haematocrit, platelet counts, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were assessed because of their influence on blood product transfusions.

Thromboelastometry was performed on fresh blood within 2 h of being drawn from patients prior to induction of anaesthesia, with a ROTEM® (Tem International GmbH, München, Germany) coagulation analyzer, according to the standard protocols supplied by the

Table 1 Patient demographic, pre-operative characteristics, operative data

	Group A ASA	Group B ASA + Clopidogrel	*P*
Age	67 ± 9.4	66.3 ± 10.1	0.71 (*T-t*)
Gender (M/F)	42/8	45/5	0.46 (P-χ^2-*t*)
Weight (kg)	75.2 ± 13	76.4 ± 10.3	0.60 (*T-t*)
Hypertension	46/50 (92%)	50/50 (100%)	0.11 (*F-t*)
Dyslipidaemia	45/50 (90%)	45/50 (90%)	1 (*F-t*)
Diabetes	14/50 (28%)	18/50 (36%)	0.39 (P-χ^2-*t*)
COPD	12/50 (24%)	8/50 (16%)	0.45 (*F-t*)
Renal failure	7/50 (14%)	4/50 (8%)	0.33 (P-χ^2-*t*)
History of MI	28/50 (56%)	29/50 (58%)	0.5 (*F-t*)
History of CVA	4/50 (8%)	1/50 (2%)	0.36 (*F-t*)
Urgent surgery	22/50 (44%)	25/50 (50%)	0.34 (*F-t*)
EF%	56 ± 8.5	50 ± 9.5	0.04 (KW)/0.03 (LR)
LVEDV mL/m^2	60.8 ± 10.4	62.6 ± 12.5	0.54 (KW)
No. of anastomoses	2.5 ± 0.8	2.5 ± 0.7	0.99 (P-χ^2-*t*)
No. of grafts	2.5 ± 0.8	2.4 ± 0.7	0.99 (P-χ^2-*t*)

T-t: *T* test; *F-t*: Fisher's exact test; P-χ^2-*t*: Pearson's chi-square test; KW: Kruskal Wallis-test; ASA: Acetylsalycilic acid; COPD: Chronic obstructive pulmonary disease; CVA: Cardio-vascular accident; EF: Ejection fraction; LVEDV: Left ventricular end-diastolic volume.

manufacturer[11].

Prior to analysis, the samples were stored at room temperature. The sample tubes were gently inverted five times to re-suspend any sedimentation before pipetting the blood. Two standard ROTEM® assays named INTEM® and EXTEM® were performed. INTE® and EXTEM® (ellagic acid and tissue factor activation, respectively) represent assays in which the intrinsic and the extrinsic coagulation pathways are triggered, respectively. The ROTEM® method defines various parameters: Clotting time (CT, s) the time from the beginning of the coagulation analysis until an increase in amplitude of 2 mm, which reflects the initiation phase of the clotting process. Clot formation time (CFT, s) the time between an increase in amplitude of the thrombelastogram from 2 to 20 mm. Alpha-angle (°), the tangent to the clotting curve through the 2 mm point. The CFT and alpha-angle reflect measures of the propagation phase of WB clot formation. Maximum clot firmness (MCF, mm) is the maximum amplitude reached in thromboelastogram and correlates with the platelet count and function as well as the concentration of fibrinogen[12]. Area-under-curve (AUC), defined as the area under 1st derivative (*i.e.,* velocity) curve ending at a time point that corresponds to MCF, reflects thrombin generation potential[13].

Intraoperative management

All surgical procedures were performed through a median sternotomy and with cardiopulmonary-bypass (CPB), in a standard fashion. A comparable intraoperative heparin anticoagulation regimen was utilized in all patients; initial heparin dose was calculated using a minimum standard of 400 units/kg with additional dosing administered during the procedure, in order to maintain a target activated-clotting-time (ACT) value greater than 480 s.

Management of bleeding

Post-operative bleeding was carefully managed according to our institution's diagnostic - therapeutic algorithm[14]. PT, aPTT, platelet count, antithrombin III and ROTEM paramaters (INTEM, EXTEM and HEPTEM) are assessed and any abnormalities are corrected with relevant blood products (platelets, fresh frozen plasma, cryoprecipitate), protamine sulphate, fibrinogen or recombinant factor VIIa according to the underlying cause of bleeding.

Ongoing bleeding at a rate of 500 mL/h in the first hour, 400 mL/h in the first 2 h, 300 mL/h in the first 3 h, 200 mL/h in the first 4 h, despite optimisation of coagulation paramaters or the presence of cardiac tamponade are considered indications for re-intervention for bleeding. The amount of post-operative blood loss and the rate and amount of transfused blood products used both intra- and post-operatively were recorded.

Clinical outcomes

Major bleeding was considered to have occurred when $\geqslant$ 3 units of blood, fresh frozen plasma, platelets or surgical revision were required. Chest tube outputs assessed at 12 h were the primary measure of postoperative bleeding. Transfusion quantity was recorded for the three main blood product types (red blood cells, platelets and fresh frozen plasma) during operation and ICU stay. Clinical outcomes specific to CABG recovery included reoperation for bleeding, mortality, acute myocardial infarction, stroke and postoperative atrial fibrillation until discharge. General post-surgical outcomes evaluated were duration of intubation and postoperative length of ICU stay.

Statistical analysis

The prevalence of bleeding-related haematologic, laboratory and clinical risk factors in the two groups was compared by means of contingency tables of categorical variables and the two-sided Fisher exact test. Two sample *t* tests with equal or unequal variances were used to compare continuous variables with reasonably normal distribution of the original or transformed units, otherwise Kruskal-Wallis equality-of-populations rank test was used. Distributional differences were further analyzed with Graphic Box plot comparisons between groups. Multivariable stepwise forward and backward logistic regression of the bleeding event *vs* risk factors was made, with 0.05 significance limits to enter or retain. Confounding factors (age, weight and sex), bleeding related clinical risk factors (hypertension, renal failure, cerebrovascular events and treatment) and the variables enumerated above in the clotting profile paragraph were included. The event probability predicted from the logistic result was compared to the observed empiric probability, calculated on patients' deciles. A correlation analysis of laboratory ROTEM tests

Table 2 Preoperative hematologic and coagulation profile

	Group A ASA	Group B ASA + Clopidogrel	*P* (KW)
Hb (g/dL)	13.44 ± 0.2	13.42 ± 0.2	0.95
Hematocrit (%)	39.9 ± 0.6	39.3 ± 0.5	0.67
Platelet count (10^3/mm^3)	247 ± 8.6	245 ± 0.2	0.83
PT (%)	80.3 ± 1.6	80.5 ± 1.7	0.95
PTT (%)	32.2 ± 0.7	31.8 ± 0.8	0.67
CT-INTEM	153 ± 16	179 ± 15	0.87
CFT-INTEM	57 ± 4	63 ± 7	0.28
Alpha angle-INTEM	81 ± 10	75 ± 8	0.49
MCF-INTEM	65 ± 4	63 ± 5	0.51
AUC-INTEM	6543 ± 520	6320 ± 731	0.65
CT-EXTEM	55 ± 6	58 ± 7	0.52
CFT-EXTEM	96 ± 8	102 ± 9	0.51
Alpha angle-INTEM	71 ± 6	66 ± 5	0.33
MCF-EXTEM	65 ± 6	61 ± 9	0.057
AUC-EXTEM	6529 ± 643	6177 ± 978	0.056

ASA: Acetylsalycilic acid; PT: Prothrombin time; PTT: Partial thromboplastin time; CFT: Clot formation time; MCF: Maximum clot firmness; AUC: Area-under-curve; KW: Kruskal Wallis-test.

Table 3 Postoperative measures of bleeding and blood product transfusions

	Group A ASA	Group B ASA + Clopidogrel	*P*
Major bleeding	6 (12%)	8 (16%)	0.77 (*F-t*)
Re-intervention	1 (2%)	0 (0%)	1.0 (*F-t*)
Chest tube output (12 h)	509 ± 234	539 ± 239	0.41 (KW)
PRBCs (U)	1 ± 1	0.9 ± 0.9	0.87 (KW)
FFP (U)	0.5 ± 2	0.5 ± 1.9	0.99 (KW)
PLTs (U)	0.7 ± 2.7	1 ± 2.5	0.35 (KW)

ASA: Acetylsalycilic acid; FFP: Fresh frozen plasma; PRBCs: Packed red blood cells; PLT: Platelets.

was further performed to identify parameters closely related to the logistic result. All data were manipulated and analyzed using STATA (StataCorp LP, Texas, United States). The statistical review of the study was performed by a biomedical statistician.

RESULTS

Patient characteristics

The baseline characteristics of those with and without preoperative clopidogrel exposure were comparable in age, gender, weight and renal failure (Table 1). There was a significantly higher incidence of ventricular dysfunction (P = 0.02) in the clopidogrel group. The baseline classic coagulation parameters (hematocrit, platelet count, PT, aPTT) and ROTEM parameters (CT, CFT, MCF, alpha angle and AUC of INTEM and EXTEM) were also comparable between the groups (Table 2).

Surgical and clinical outcomes by anti-platelet therapy exposure

No statistically significant differences between the two groups in term of postoperative bleeding, blood product transfusions (Table 3) and clinical outcomes (Table 4) were observed.

Patients on double treatment showed a greater frequency of major bleeding (8 *vs* 6 episodes), greater mean chest tube output at 12 h (539 ± 239 mL *vs* 509 ± 234 mL), and mean number of blood products transfusions, although these differences were not statistically significant. One patient in the single treatment group required surgical re-intervention due to bleeding.

The length of stay in the ICU (days) and of mechanical ventilation (hours) were comparable between the groups. There was 1 death in group A and 0 in group B, 1 myocardial-infarction in group A and 0 in group B, 1 stroke in group A and 0 in group B. Therefore there was a greater number of major adverse events in the group treated with aspirin alone (3 events, 6%; OR = 0.75; P = 0.24) compared with the double treatment group (0 events, 0%).

Table 4 Clinical outcomes

	Group A ASA	Group B ASA + Clopidogrel	*P*
AMI	1 (2%)	0%	0.5 (*F-t*)
IABP	3 (6%)	2 (4%)	0.5 (*F-t*)
Stroke	1 (2%)	0 (0%)	0.5 (*F-t*)
Renal failure	1 (2%)	1 (2%)	1.0 (*F-t*)
AF	12 (24%)	7 (14%)	0.15 (*F-t*)
MV (h)	8 ± 11	6 ± 2	0.22 (KW)
ICU stay (d)	1.8 ± 3.3 (Med 1)	1.4 ± 0.9 (Med 1)	0.77 (KW)
Mortality	1 (2%)	0 (0%)	0.5 (*F-t*)
MACE (death, stroke. AMI)	3 (6%)	0 (0%)	0.24 (*F-t*)

F-t: Fisher's exact test; KW: Kruskal Wallis-test; ASA: Acetylsalycilic acid; AMI: Acute myocardial infarction; AF: Atrial fibrillation; MV: Mechanical ventilation; MACE: Major adverse cardiac events.

Table 5 Logistic multivariate analysis of factors related to bleeding risk

	Coefficient	OR	95%CI	*P*
Age	-0.14	0.87	0.73-1.03	0.11
Weight	-0.35	0.71	0.52-0.97	0.03
Gender (female)	-10.54	0.00003	0.06-3.9	0.04
EF	-0.02	0.98	0.83-1.16	0.81
AUC EXTEM	-0.0099	0.99	0.98-0.99	0.008
Aspirin only	-1.18	0.31	0.02-4.58	0.39

Odds ratios are adjusted for concomitant variables. EF: Ejection fraction; AUC: Area-under-curve.

Preoperative predictors of bleeding risk

From the comparison of the risk-factors for perioperative bleeding (advanced age, female gender, low weight and renal insufficiency), and preoperative haemocoagulatory status between all patients who bled (n = 14) and those who did not, no significant difference was noted.

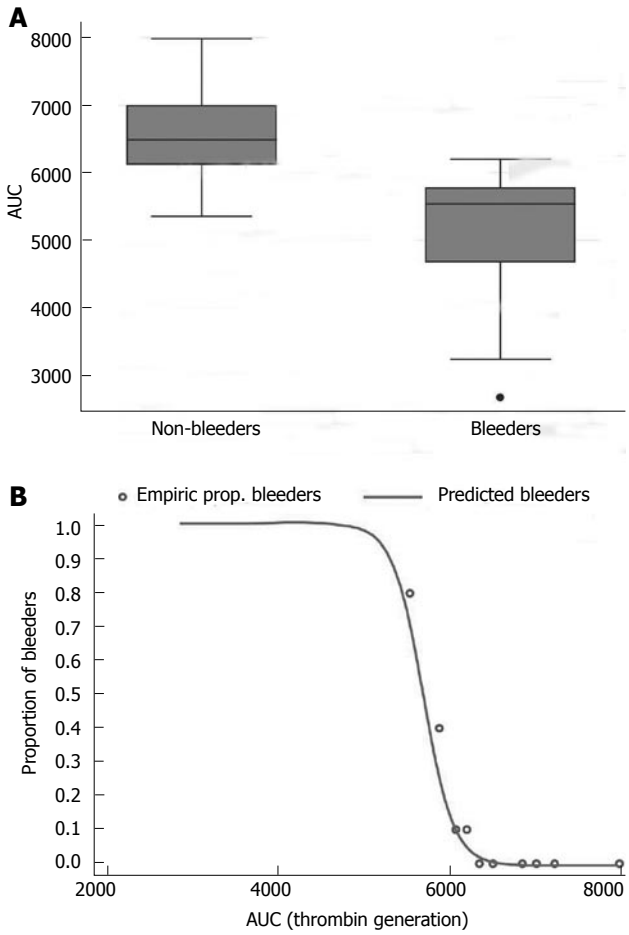

Figure 1 Predictors of bleeding risk. A: AUC-EXTEM in non-bleeders and in bleeders (patients with major bleeding) (P = 0.0001); B: Bleeding risk prediction and AUC-EXTEM: Each circle represents one decile of the patient population, showing the proportion of patients who bled compared with their mean AUC. The curve is a line of best fit, clearly showing a threshold at an AUC of 6000, below which the bleeding risk increases markedly. AUC: Area-under-curve.

After performing a logistic multivariate analysis (details in Table 5), the backward stepwise variable selection showed a significant independent relationship of bleeding risk only with AUC activity (coefficient –0.0099; OR = 0.99; 95%CI: 0.98-0.99; P < 0.001). In fact, patients who bled had lower AUC-value (Thrombin-generation-potential) in the EXTEM test (5030 ± 1115 Ohm*min) than those who did not bleed (6568 ± 548 Ohm*min) (P < 0.0001) (Figure 1A). We observed a good correlation (r = 0.96) between AUC and MCF, a clot quality indicator, that similarly was increased in patients who did not bleed (65.7 ± 5.6 mm) than those who did (51.9 ± 12.5 mm) (P < 0.0001), although these values were still within the normal range (50-72 mm). At this point we identified a threshold value for AUC and MCF which predicted bleeding in our patients, that is 6000 for AUC and 60 for MCF (Figure 1B). In fact, all patients with an AUC and MCF below these cut off values were at increased risk of major bleeding, and the lower these values the greater the risk. Furthermore patients with higher AUC and MCF values were at a lower risk of significant haemorrhagic events.

DISCUSSION

Post-CABG bleeding is a major issue in cardiac surgery and remains difficult to predict. Concerns about bleeding risk have resulted in the recommendation to cease double antiplatelet therapy prior to elective CABG[5]. There are still many patients who present for urgent CABG with double antiplatelet therapy, and increasingly patients will have been exposed to more potent antiplatelet agents such as prasugrel and ticagrelor[8-10]. Hence, we set out to determine if it was possible to predict post-operative bleeding with pre-operative clotting characteristics via analysis of classical coagulation assays (aPTT, PT) as well as a suite of ROTEM analyses. We also compared haemorrhagic and thrombotic complications between single and double treated patients.

Main findings

Our data showed a higher frequency of major bleeding in the double antiplatelet therapy group (16% *vs* 12%), but this was not statistically significant (P = 0.77). However, assuming that it represents a true difference, to attain a P value of 0.05 with a test power of 70% the sample size required is 978 patients on each arm. On the contrary the major adverse events (MACE: Death, stroke and myocardial infarct) were limited to group A (6%) (Table 4), but this difference was not statistically significant (P = 0.24).

Comparison of classic and ROTEM parameters between the 14 "bleeder" patients and the "non-bleeders", showed that differences were limited to AUC and MCF, in the EXTEM test. Patients with lower AUC and MCF values were at a higher risk of suffering major bleeding, regardless of whether they were treated with clopidogrel or not. MCF reveals the quality of the clot and is linked to thrombin generation and the change in AUC observed here is a reflection of the increase in MCF.

Clot generation is a composite process involving both primary and secondary haemostasis, as well as intrinsic and extrinsic pathways. Yet bleeding risk after CABG, the tendency has been to focus on the platelet, probably because of its major role in athero-thrombosis[15,16]. And the extensive experience with the use of antiplatelet agents in minimising further ischemic events. Nevertheless, despite receiving the same standard ACS medical treatment some patients bleed while others do not, and although this may be attributed to the recognized response variability (so called "resistance") observed with clopidogrel or aspirin[15], our results indicate that differences in patients' thrombin generation potential may be an important determinant of bleeding.

We believe that a broader perspective may be necessary: Platelets and platelet-inhibition play very important roles but their complicate interplay with other pieces of the haemostatic process should be taken into account. ROTEM is appropriate for providing such analyses, and unique in allowing evaluation of

every element of thrombosis and clot lysis[17], especially fibrinogen and factor XIII.

Indeed, we found that clot quality is a predictor of post-operative bleeding. We believe that association of MCF and AUC with haemorrhagic risk derives from the role of thrombin, which is fundamental as it affects every step of clot formation: It has a role in activation of fibrinogen to fibrin as the final common pathway from both intrinsic and extrinsic pathways, it activates factor XIII which promotes clot stability by cross linking fibrin polymers within the clot[18] and contributes to platelet activation, acting on at least three diverse platelet receptors[19]. We propose that in post surgical patients a high clot quality prior to surgery, as indicated by higher MCF and AUC values in the EXTEM test, can effectively clot despite the inhibition of platelet activation by aspirin and clopidogrel.

The mechanism by which patients with greater thrombin generation potential are able to form effective clots in the face of double antiplatelet therapy are probably twofold: (1) platelet activation is multifactorial, in addition to adenosine diphosphate (ADP) and thromboxane A2, thrombin also plays a critical role and is the most potent of the platelet activators[15], and patients who are better able to generate thrombin may thus sufficiently activate their platelets despite inhibition of the first two pathways by clopidogrel and aspirin respectively; and (2) patients with a higher MCF and hence higher thrombin generation may be able to affect greater thrombin deposition and stabilisation by factor XIII and hence form a stable clot despite decreased platelet activation and aggregation. In such circumstance the metaphor would be to a brick wall: Despite the presence of fewer effective bricks (platelets) in the presence of clopidogrel therapy, patients with a higher MCF can counterbalance by applying more higher-quality mortar (thrombin), thus producing a stable wall (clot).

Clinical implications

Besides characterizing MCF and AUC as factors influencing post-surgical bleeding, we identified a threshold at which the risk becomes significant: an AUC < 6000, corresponding to an MCF of < 60. This is important in two ways: (1) these values are within the normal range and yet the patients are at high risk of post-operative bleeding; and (2) identification of patients at risk may allow improved management in these patients.

While rotational thromboelastometry has been previously studied in relation to post CPB haemorrhage it has demonstrated mixed results. Published studies generally show that ROTEM parameters obtained intra-operatively or-post operative can predict post-operative excessive blood loss, but not those obtained prior to commencing bypass[20-23]. Our results differ from these as we have seen that ROTEM analysis performed prior to the institution of CPB can predict post-operative bleeding. This difference is difficult to explain, but may be related to the use of different ROTEM parameters, the high proportion of patients treated with clopidogrel in our cohort and differing definitions of major post-operative bleeding amongst these studies.

The capacity to recognize patients at high risk of post-operative bleeding may influence the decision to perform CABG in the first instance and further permit adjustment of surgical procedure and post-operative management to reduce the risk of haemorrhage in patients who are treated with CABG. As an example, patients at a high risk of bleeding may be treated with off pump CABG, avoiding CPB and hence lowering the risk of haemorrhagic events[24]. This is extremely important as CPB results in coagulopathy due to activation and consumption of platelets and coagulation factors, such as thrombin, which results in an increased risk of post-operative bleeding[25]. Other management options would include a more targeted use of blood product derived coagulation factor infusions, as well as the potential development of new pharmacological interventions involving replacement of individual clotting factors, such as recombinant activated factor VII, and factor XIII, prothrombin complexes and fibrinogen.

On the other hand, patients with higher thrombin generation potential may represent a subgroup more prone to develop ischemic rather than hemorrhagic complications (myocardial infarction, recurrent angina, stroke), thus deserving double antiplatelet therapy[26].

Study limitations

While these results are promising for the determination of risk of post-operative bleeding in CABG patients, the study does have several limitations. While AUC and MCF were seen to correlate well with bleeding risk in EXTEM analysis, INTEM analysis did not demonstrate such a relationship. This may result from the use of LWMH in all patients, a factor which affects the intrinsic pathway and hence INTEM analyses. Furthermore, ROTEM, while giving a good overall impression of a patient's haemostatic function, is not the ideal tool for the assessment of platelets, rather a platelet function analyzer would be the gold standard for such analyses[13], which would have allowed better determination of the contribution of antiplatelet response variability to bleeding risk in our cohort[27]. Additionally the sample size in this study was small and the patients were not randomised to the two treatment arms, thus limiting our ability to comment on the differential effect of single and double antiplatelet on postoperative haemorrhage risk. Further studies in groups not treated with LMWH, the use of platelet function analyser and greater sample size and randomization would allow greater understanding of the factors relating to bleeding risk identified in our study. Finally, we cannot generalize our results to newer antiplatelet agents such as prasugrel and ticagrelor.

In conclusion, we have seen that patients with a low AUC value (thrombin-generation-potential) are at a significantly higher risk of bleeding as compared to patients with higher AUC, regardless of whether they were treated with clopidogrel. Hence this study provides

a promising insight into the potential role of ROTEM analyses in the prediction of post-CABG bleeding risk; future research on this topic may contribute to a more effective intra- and post- operative management.

COMMENTS

Background

Post-operative bleeding is a major complication following coronary artery bypass grafting (CABG). Guidelines recommend ceasing clopidogrel therapy 5 d prior to CABG in order to minimise the risk of post-operative haemorrhage. However, patients presenting for urgent and emergent CABG are often treated with double antiplatelet therapy, as recommended in major guidelines for the emergency management of acute coronary syndrome, prior to performing the diagnostic angiogram. Ceasing clopidogrel and waiting the recommended 5 d prior to performing CABG would put these patients at higher risk of adverse coronary events.

Research frontiers

As yet there is no effective way to predict which patients will have significant bleeding after CABG. In fact, it would be important to be able to detect patients at risk of excessive bleeding, especially among those treated with double anti-platelet therapy.

Innovations and breakthroughs

While rotational thromboelastometry has been previously studied in relation to post cardiopulmonary-bypass haemorrhage it has demonstrated mixed results. Published studies generally show that rotational thromboelastometry (ROTEM) parameters obtained intra-operatively or-post operative can predict post-operative excessive blood loss, but not those obtained prior to commencing bypass. The authors devised the following study to determine whether bleeding risk could be predicted from the presence of double antiplatelet therapy, classical coagulation parameters or by rotational thrombo-elastometry performed prior to surgery. The authors found that there was no significant difference between rates of major bleeding between patients treated with aspirin alone, compared with those treated with aspirin and clopidogrel. In the cases of major bleeding, pre-operative classic coagulation and traditional ROTEM parameters were comparable. Conversely the authors observed that the area-under-curve in the EXTEM test was significantly lower in bleeders than non-bleeders, regardless of antiplatelet treatment. This suggests that thrombin generation potential, irrespective of the degree of platelet inhibition, correlates with surgical bleeding. Moreover, the authors were able to define a threshold at which bleeding risk becomes significant.

Applications

The ability to identify patients at high risk of post-operative bleeding is important as it may influence the decision to perform CABG in the first instance and further allow tailoring of surgical technique and post-operative management to reduce the risk of haemorrhage, and achieve a more targeted use of blood products. On the other hand, patients with higher thrombin generation potential may represent a subgroup more prone to develop ischemic rather than hemorrhagic complications, thus deserving double antiplatelet therapy.

Terminology

ROTEM consists in a viscoelastic method for hemostasis testing in whole blood, which can be used to detect clotting disorders and drug effects. Moreover, through appropriate assays, it can provide differential diagnostic information to support decisions in therapy.

Peer-review

This is an interesting manuscript about the predictive factors of bleeding after CABG in patients with previous acute coronary syndrome.

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CASE REPORT

Eggshell calcification of the heart in constrictive pericarditis

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Author contributions: All authors were actively involved in management of the index case.

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Informed consent statement: It is not required as the manuscript is about a case report. There is no personal information about the patient in the figures enclosed.

Conflict-of-interest statement: On the behalf of all the authors of the manuscript, I the first and corresponding author of the manuscript make the statement that there is no conflict of interest of any of the authors for the present manuscript.

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Abstract

Constrictive pericarditis (CP) is an inflammatory disease of pericardium. Pericardial calcification in X-ray provides a clue for the diagnosis of CP. An extensive "eggshell" type of calcification is rarely seen in CP. We hereby report a case of CP with eggshell calcification of pericardium, encircling whole of the heart. A need for multimodality imaging and hemodynamic assessment followed by surgical pericardiectomy is discussed.

Key words: Contrictive pericarditis; Calcification; Pericardiectomy; Right heart failure

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Core tip: Idiopathic contrictive pericarditis (CP) with extensive pericardial calcification is rarely seen. We hereby report a case of CP with extensive "eggshell" calcification of heart, who presented with right heart failure. A need for multimodality imaging and hemodynamic assessment is discussed in the article.

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INTRODUCTION

Constrictive pericarditis (CP) is an inflammatory disease of pericardium. Its etiology includes infection,

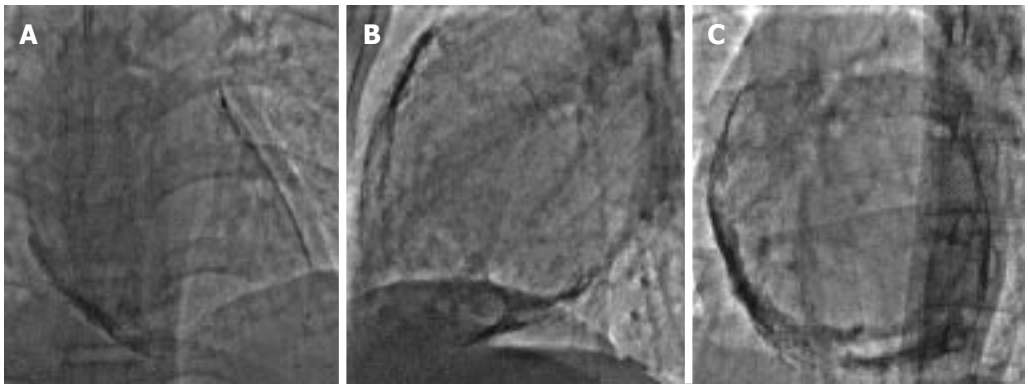

Figure 1 Fluoroscopy images in antero-posterior (A), lateral (B) and left anterior oblique 30º (C) views show circumferential pericardial calcification around the heart.

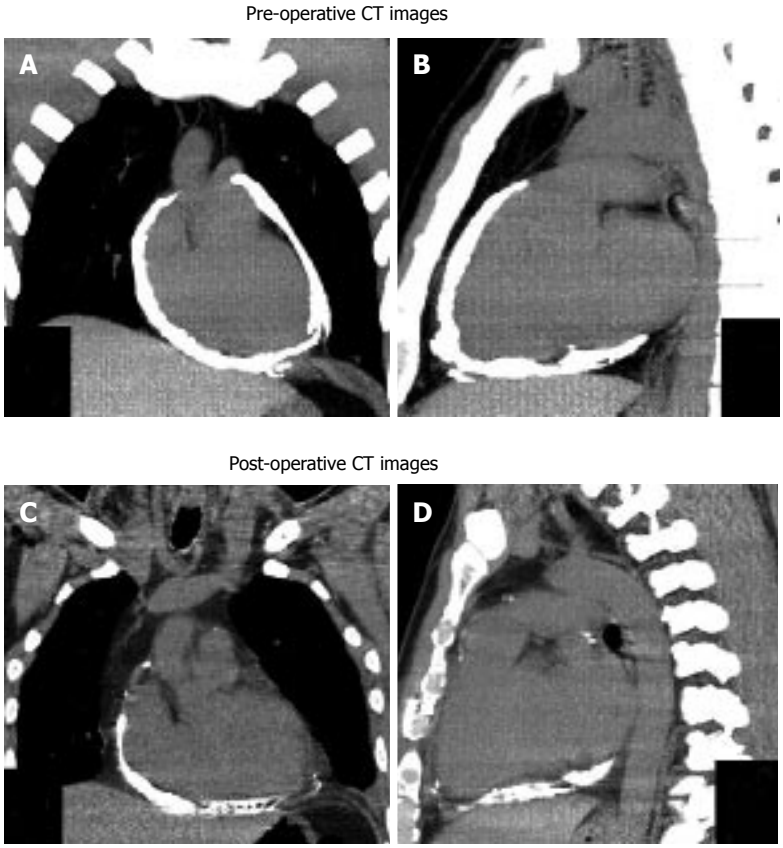

Figure 2 Computed tomography. Non-contrast computed tomography reconstructed images in coronal (A) and sagittal (B) planes show thick, calcified pericardium around the heart. A repeat CT following partial pericardiectomy in coronal (C) and sagittal (D) planes show residual calcified pericardium at right atrial and posterior surface of the heart. Calcified pericardium is absent along the antero-lateral surface of the heart. CT: Computed tomography.

connective tissue disorders, chest trauma, irradiation, post-cardiac surgery and idiopathic-type[1]. Extensive pericardial calcification is rarely seen in CP. We hereby report a case of CP presented with extensive "eggshell" like calcification of whole of pericardium.

CASE REPORT

A 43-year-old male presented with shortness of breath, NYHA class-Ⅲ of 6-mo duration. There was no history of fever, productive cough, joint pain, orthopnea and pedal edema. Clinical examination revealed a jugular venous pulse of 18 cm, prominent X and Y descents. Cardiac auscultation revealed a pericardial knock. Two-dimensional echocardiogram showed 10-mm thick, calcified pericardium; about 25%-variation in mitral diastolic flow velocities with respiration and a dilated inferior vena cava of 24-mm dimension. Fluoroscopy revealed dense circumferential calcification all around the heart (Figure 1). A computed tomography (CT) scan confirmed the circumferential thick pericardial calcification like an eggshell, encircling the heart (Figures 2 and 3). Angiography revealed normal epicardial coronaries without any external compression.

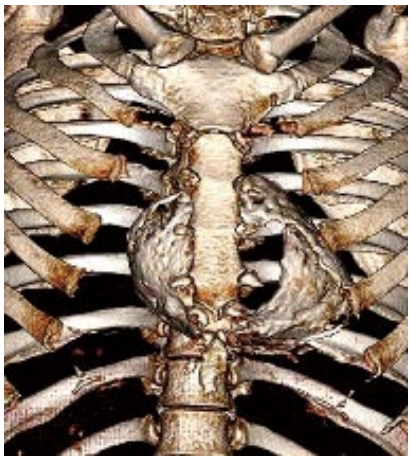

Figure 3 Pre-operative non-contrast computed tomography reconstructed volume rendered image shows pericardial "eggshell" calcification around the heart.

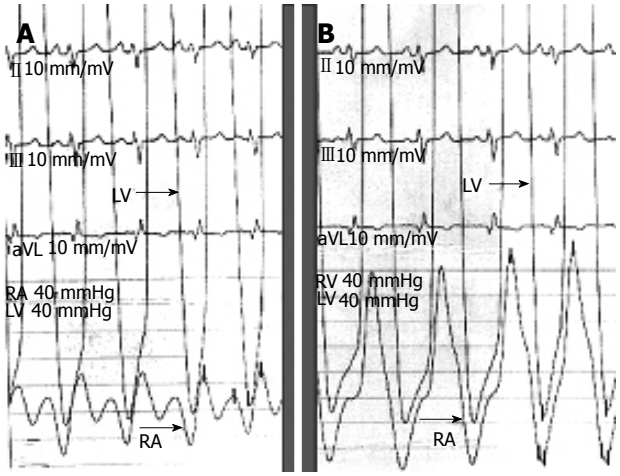

Figure 4 Hemodynamic tracing during catheterization. A: Right atrial (RA) pressure tracing shows prominent X and Y descent; B: Ventricular pressure tracing shows typical "dip-and-plateau configuration" during diastole. RV: Right ventricle; LV: Left ventricle.

Hemodynamic data revealed elevated mean right atrial (RA) pressure of 20 mmHg. Right ventricle (RV) and left ventricle (LV) end-diastolic pressure was 23 and 28 mmHg, respectively. Pulmonary artery systolic and mean pulmonary capillary wedge pressures were 44 and 24 mmHg, respectively. There was near equalization of elevated RA, RV and LV end-diastolic pressures. Right atrial pressure tracing showed prominent X and Y descent (Figure 4A), and ventricular pressure tracing showed typical "dip-and-plateau configuration" (Figure 4B) suggestive of CP. He had surgical pericardiectomy for densely calcified CP. Following median thoracotomy, thickened, calcified, firmly adherent pericardium was resected and excised from anterior and left lateral aspect of the heart (Figure 5). The densely adherent pericardium from surface of right atrium and posterior wall was not resected. Histopathology of pericardium revealed dystrophic calcification without any evidence of granulomatous or giant cell inflammation. Mycobacterial

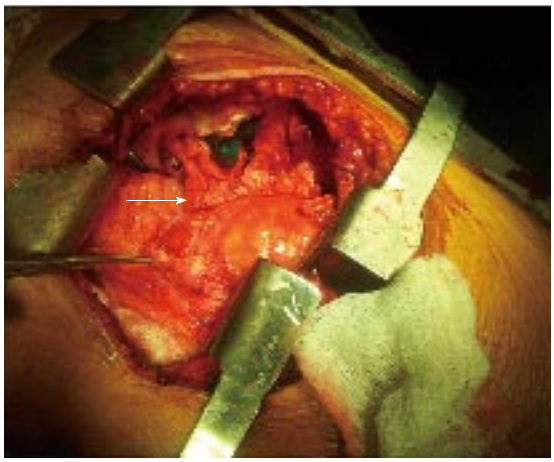

Figure 5 Surgical image shows resected thick and calcified pericardium (white arrow) from anterior surface of heart.

and fungal cultures of the excised pericardium were negative. He had uneventful recovery and was discharged on 7th post-operative day. A post–operative CT scan showed absence of calcified pericardium along antero-lateral surface of the heart (Figures 2C and D). He remained asymptomatic during 1-year follow-up.

DISCUSSION

Constrictive pericarditis is a sequale of chronic inflammation of pericardium. Among the various etiologies, idiopathic type is a common cause for CP[1,2], which was present in index case. The clinical presentation is mostly of right heart failure. Any patient presented with dyspnea, raised jugular venous pulse, hepatic and systemic venous congestion should be evaluated for CP. Pericardial calcification in chest X-ray can suggest CP, however it is present in only 5%-27% of cases[3]. Extensive "eggshell" like calcification is rarely seen in CP[4], as was present in index case. Echocardiography is an initial imaging test for diagnosis of CP[5]. In patients with equivocal echocardiography findings, CT or Cardiac Magnetic Resonance can confirm the diagnosis[5]. The extent of severe calcification and involvement of adjacent structures is clearly defined by CT, as demonstrated in index case. Cardiac catheterization is required for hemodynamic assessment and to rule out coronary compression by calcified thickened pericardium[6]. A multi-modality imaging and hemodynamic assessment is essential for proper evaluation of CP[5]. Surgical pericardiectomy is the definite treatment for CP. Those with calcified and firmly adherent pericardium, median thoracotomy is preferred over antero-lateral thoracotomy[7]. Calcified CP also has higher surgical risk, incomplete pericardial resection and poor hemodynamic outcomes following surgery[7]. However, index case had a successful outcome following partial antero-lateral pericardiectomy *via* median sternotomy approach. In conclusion, we present a case of idiopathic CP with extensive eggshell calcification of

the heart, who had successful surgical pericardiectomy, and had a favourable long term outcome.

COMMENTS

Case characteristics

A 43-years-old male presented with shortness of breath, New York Heart Association class-III of 6-mo duration.

Clinical diagnosis

Clinical examination revealed a raised jugular venous pulse with prominent X and Y descents.

Differential diagnosis

Cardiac auscultation revealed a pericardial knock. Two-dimensional echocardiogram showed 10-mm thick, calcified pericardium with significant trans-mitral diastolic flow velocities variation.

Imaging diagnosis

Fluoroscopy revealed dense circumferential calcification all around the heart. A computed tomography scan confirmed the circumferential thick pericardial calcification like an eggshell, encircling the heart. Cardiac catheterization revealed near equalization of elevated right atrial, right ventricle, and left ventricle end-diastolic pressures and ventricular pressure tracing showed typical "dip-and-plateau" pattern suggestive of constrictive pericarditis.

Pathological diagnosis

He had surgical pericardiectomy for densely calcified CP. Histopathology of pericardium revealed dystrophic calcification without any evidence of granulomatous or giant cell inflammation. An importance of multi-modality imaging with hemodynamic assessment is discussed in management of constrictive pericarditis.

Peer-review

This is an interesting article on calcified constrictive pericarditis. The paper is nicely documented.

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