



The challenge of treating diastolic heart failure

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Editorial

Heart failure is a debilitating disease that has a poor prognosis, and has placed a huge burden on the health care system. However, despite this grim situation, there is cause for optimism, as over the past three decades significant advances have been made in the treatment of heart failure patients presenting with a reduced left ventricular ejection fraction (systolic heart failure). This has helped to improve the outcomes of patients with systolic heart failure significantly. It should be recognized, however, that approximately 50% of heart failure patients present with diastolic heart failure and have a normal left ventricular ejection fraction (sometimes referred to as heart failure with preserved left ventricular ejection fraction). Despite having normal ejection fractions, the morbidity and mortality associated with diastolic heart failure is similar to that of systolic heart failure [1]. Equally disappointing is that while advances have been made in treating systolic heart failure, similar advances have not been made for treating diastolic heart failure. Added to this problem is that patients with diastolic heart failure are less likely to receive the same intensity of primary and specialized care as patients with systolic heart failure [2]. The recognition of this problem has resulted in a recent increased interest in obtaining a better understanding of what causes and contributes to the development of diastolic heart failure, as well as what potential therapeutic strategies could be used specifically to treat diastolic heart failure. In this issue of *Heart and Metabolism* we address the important area of diastolic heart failure.

The Case Report presented by Dr Alda Huqi gives a good example of how a patient with diastolic heart failure presents. In the Main Clinical Article of this issue, Professors Lyons and Ezekowitz nicely highlight what therapeutic options exist for treating diastolic heart failure, and some of the new treatments that are emerging. As we understand better the underlying pathology of diastolic heart failure, the promise of new therapies being developed that target this pathology is emerging. The Basic Article by Professors Jagdip Jaswal and John Ussher addresses what is known about the pathology of diastolic heart failure, and compares the risk factors for both systolic and diastolic heart failure. While many of these are the same, there are important differences between these two forms of heart failure. These include differences in myocardial fibrosis and cardiac energetics that may provide potential therapeutic targets for the management and treatment of diastolic heart failure. As relaxation of the heart muscle is a problem in diastolic heart failure, targeting the processes that control cardiac relaxation may also be an option. The Refresher Corner article by Professors Natasha Fillmore and Gary Lopaschuk reviews how the heart relaxes. This includes the important role of calcium and ATP in this process. Alterations in ATP

supply/use are also evident in diastolic heart failure. This provides an opportunity to optimize energy metabolism as an approach to treat diastolic heart failure. The New Therapeutic Approaches article by Professor Siddiqi and colleagues addresses this issue, and discusses some of the data emerging in the area of fatty acid oxidation inhibition as an approach to treat diastolic heart failure. This includes using the fatty acid oxidation inhibitor trimetazidine as an approach to treat heart failure. The Focus on Vasteral article by Professor Noelia Signoretta and colleagues supports this concept, and reviews recent meta-analyses showing that the use of trimetazidine in heart failure patients may provide significant benefit in lessening the symptoms and severity of heart failure. Finally, the Hot Topic article by Dr Alda Huqi challenges some the existing paradigms as to how we assess coronary artery disease, which is a leading cause of heart failure.

As diastolic heart failure is increasingly being recognized as a distinct and common disease entity, an

increased research effort is needed to understand this disease. The articles in this issue of *Heart and Metabolism* help provide a better understanding of the entity of diastolic heart failure. They also highlight the need to develop new therapeutic approaches to diagnose and treat diastolic heart failure, which hopefully will ultimately lessen the burden of this terrible disease on society. •

Acknowledgements GDL is a scientist of the Alberta Heritage Foundation for Medical Research.

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Differentiating diastolic dysfunction from classic heart failure

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Abstract

Heart failure (HF) is characterized by an impaired ability of the ventricle to fill with and eject blood commensurate with the metabolic demands and requirements of the body, and has emerged as a major cause of morbidity and mortality in the developed world. Approximately 50% of HF patients have preserved ejection fraction, and lack overt signs of systolic failure, but rather have deficits in ventricular relaxation indicative of diastolic dysfunction/HF. Systolic HF and diastolic dysfunction/HF share a number of risk factors including age, myocardial ischemia, hypertension, obesity, and diabetes. As such these risk factors may be of limited utility in discriminating between the two HF phenotypes. However, differences in ventricular remodeling and ventricular function can readily differentiate systolic HF from diastolic dysfunction/HF. To date, a common modality to improve the status of both HF entities remains to be found. As therapeutic interventions that optimize cardiac energy metabolism have proven useful in the management of systolic HF, and because ventricular relaxation is an energy-dependent process, a better understanding of the alterations in energy metabolism in diastolic dysfunction/HF may identify novel treatment strategies for this cardiac pathology.

Keywords: Cardiac energetics; diabetic cardiomyopathy; diastolic dysfunction; heart failure; obesity

■ Heart Metab. (2012) 57:4–7

Introduction

Cardiovascular disease is a major cause of death and disability in the industrialized world. Although the clinical management of patients with cardiovascular disease(s) has greatly improved due to advancements in evidence-based therapy, there has been a concomitant rise in the prevalence of heart failure (HF). HF is a complex clinical syndrome, characterized by an impaired ability of the ventricle to fill with (diastolic dysfunction/HF) and eject blood (systolic HF) commensurate with the metabolic demands and requirements of the body [1]. The etiology of HF is generally attributed to pre-existing ischemic heart disease, or it can be of non-ischemic/idiopathic origin. Epidemiological studies have identified that 50–60% of HF patients have a dilated left ventricular chamber and reduced ejection fraction (systolic HF), whereas the remainder have a normal left ventricular chamber, and preserved ejection fraction (diastolic dysfunction/HF) [2]. As such, systolic HF and diastolic dysfunction/HF encompass two phenotypic classes that contribute to clinically recognized HF. Whether these phenotypes represent two unique clinical entities, or whether the two are different stages along a single HF spectrum

remains unresolved. The aims of this article are to differentiate between systolic HF and diastolic dysfunction/HF with respect to: the risk factors for development; the alterations in ventricular structure (ie, ventricular remodeling); and alterations in ventricular function that accompany these cardiac pathologies. A brief overview of ventricular diastole will also be presented to highlight the potential for therapeutic interventions that target cardiac energy metabolism as a treatment for diastolic dysfunction/HF.

Risk factors for the development of systolic HF versus diastolic dysfunction/HF

Systolic HF and diastolic dysfunction/HF appear to share a number of cardiovascular disease risk factors, including older age, ischemic heart disease, arterial hypertension, obesity, and diabetes [3]. Therefore, the presence of these risk factors before the development of HF does not distinguish between systolic versus diastolic phenotypes. However, key differences emerge when examining risk factor profiles at the time of acute HF diagnosis. The factors increasing the odds of systolic HF include male sex, previous ischemic heart disease/myocardial infarction, and left bundle branch block [4]. Conversely, the factors increasing the odds of diastolic dysfunction/HF include female sex, absence of underlying ischemic heart disease, and atrial fibrillation [4]. These important differences may indicate that systolic HF and diastolic dysfunction/HF are distinct clinical entities. On the contrary, in patients who are obese and have diabetes HF is characterized by early defects in ventricular filling [5], and the eventual development of systolic dysfunction. Therefore, these findings suggest a progression from diastolic dysfunction to overt systolic HF [6, 7], and may indicate that diastolic dysfunction/HF and systolic HF represent different stages along the spectrum of a single clinical syndrome.

Ventricular remodeling in systolic HF versus diastolic dysfunction/HF

The patterns of ventricular remodeling differ considerably, and also influence both end diastolic and end systolic volumes, and therefore can be used to differentiate between systolic HF and diastolic dysfunction/HF. Eccentric ventricular remodeling is observed in systolic HF. As such, ventricular cavity size is increased, and accompanied by increases in both end-diastolic

and end-systolic volumes, decreased or unaltered left ventricular wall thickness, increased wall stress, and depressed left ventricular ejection fraction (LVEF) (<45%) [8–10]. In systolic HF left ventricular mass is increased, while the mass/cavity ratio is unchanged or decreased. In contrast, concentric remodeling is observed in diastolic dysfunction/HF. Ventricular cavity size is unchanged or decreased, end-diastolic and end-systolic volumes remain normal or decrease, left ventricular wall thickness is increased, and LVEF is normal or slightly greater than normal [8–10]. In diastolic HF left ventricular mass and the mass/cavity ratio is increased (ie, the left ventricular cavity is not dilated), and these alterations are associated with increased morbidity and mortality [11].

Myocardial fibrosis represents a hallmark feature in HF. Interestingly, systolic HF patients present with both interstitial and replacement fibrosis, while patients diagnosed with diastolic dysfunction/HF typically present with interstitial fibrosis [3]. Alterations in remodeling at the level of individual cardiac myocytes also differentiate between systolic HF and diastolic dysfunction/HF. Cardiac myocyte diameter is increased, while myofiber density is decreased in diastolic dysfunction/HF relative to systolic HF. Importantly, intrinsic cardiac myocyte stiffness is increased, and may be related to lower levels of compliant titin 2A isoform expression in diastolic dysfunction/HF relative to systolic HF [3].

Ventricular function in systolic HF versus diastolic dysfunction/HF

Systolic HF is characterized by impairments in the ability of the myofibrils to contract against a given ventricular load, thus an impaired ability of the ventricle to eject blood into the aorta leads to deficits in LVEF. Conversely, diastolic dysfunction/HF is characterized by impairments in the ability of myofibrils to return rapidly to a normal resting length, and therefore impairs the ability of the ventricle to accept blood adequately at low pressures, ultimately slowing the rate of ventricular filling (unless there is a compensatory increase in atrial pressure during atrial systole). These differences in underlying pathophysiology can be utilized to discern clearly between systolic HF and diastolic dysfunction/HF through invasive measurement of left ventricular pressure volume relationships via cardiac catheterization (Fig. 1). Systolic HF is characterized by a rightward displacement of the pressure volume relationship

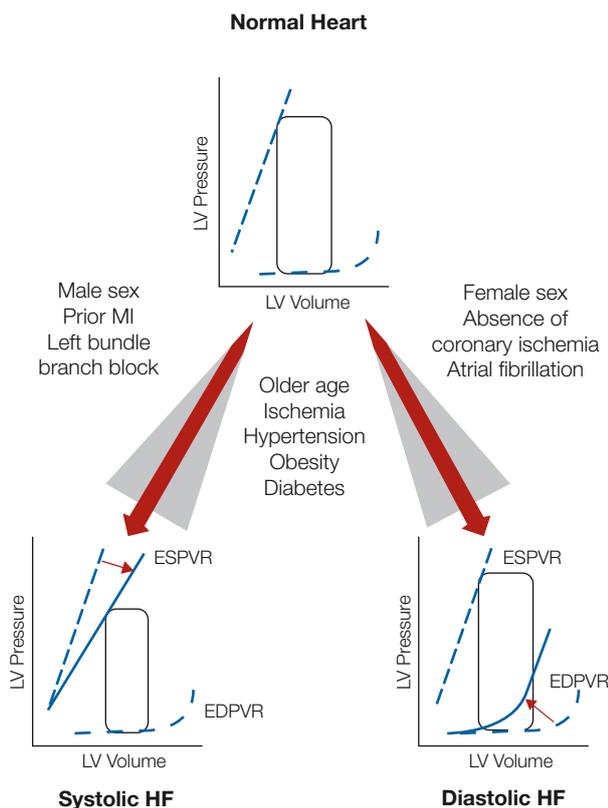


Fig. 1 Separating diastolic dysfunction/heart failure (HF) from systolic HF. Invasive measurement of left ventricular pressure volume relationships via cardiac catheterization reveals a rightward displacement of the pressure volume relationship, reflecting decreased stroke work and depression of the end-systolic pressure volume relation (ESPVR) during systolic HF (decreased slope of ESPVR). In diastolic HF, increased chamber stiffness and a diminished capacity to fill at low diastolic pressures causes the end-diastolic pressure volume relation (EDPVR) to shift upwards and to the left. Common risk factors for both HF entities include older age, ischemia, hypertension, obesity, and diabetes. Factors increasing the odds of systolic HF include male sex, previous myocardial infarction (MI), and left bundle branch block, whereas the factors increasing the odds of diastolic HF include female sex, absence of coronary ischemia, and atrial fibrillation.

(indicative of increased ventricular volumes), decreased stroke work (area inside the pressure volume loop) and a depression of the end-systolic pressure volume relation such that it is shifted to the right and downward (indicative of decreased contractility) [10]. In diastolic dysfunction/HF alterations in the pressure volume relationship reflect increased ventricular stiffness. In particular, systolic function is preserved, and ventricular volumes can remain normal to near-normal; however, the end-diastolic pressure volume relation is shifted to the left and upward [10]. Such displacement causes a disproportionate increase in ventricular pressure for a given increase in volume, indicative of decreased ventricular compliance/increased ventricular stiffness. As

ventricular relaxation is slowed and/or incomplete in diastolic dysfunction/HF, the rate of peak pressure decline ($-dp/dt$) during isovolumic relaxation is also depressed, and the time constant of isovolumic left ventricular pressure decline (τ) is prolonged [10]. A number of non-invasive Doppler echocardiographic variables including measurement of peak early diastolic filling (E-wave), late diastolic filling (ie, atrial contraction) (A-wave), as well as the Doppler-derived peak early diastolic velocity at the mitral annulus (E') can also be utilized to estimate diastolic function, and correlate well with invasive measures obtained by cardiac catheterization [12].

Active ventricular relaxation and energy metabolism in diastolic dysfunction/HF

Well-known alterations in metabolic intermediates including ATP, phosphocreatine, and creatine occur in overt systolic HF [13], and correlate with functional status [14]. It should also be noted that a series of energy (ie, ATP) requiring processes including mechanisms regulating cardiac myocyte Ca^{2+} homeostasis (eg, sarcolemmal and sarcoplasmic reticulum Ca^{2+} -ATPase activity), as well as ATP binding that facilitates actin-myosin crossbridge dissociation, contribute to diastole. As such, ventricular relaxation itself is an energy-consuming process, and optimal ATP supply, utilization, and tight regulation of the metabolic pathways that generate ATP are essential in maintaining normal diastolic function [15]. Support for these concepts is provided by observations that diastolic function is impaired in pathologies including pressure overload hypertrophy (secondary to systemic hypertension), obesity, and diabetes, all of which can substantially impact myocardial metabolism [16, 17].

In type 1 diabetic Akita mice diastolic function is selectively impaired, and is associated with elevated rates of myocardial fatty acid oxidation and increased intramyocardial ceramide and diacylglycerol content [18], a metabolic signature that may negatively impact cardiac function and cardiac insulin sensitivity [16]. Of interest, these metabolic abnormalities and diastolic dysfunction/HF are normalized following insulin therapy [18], suggesting that energy metabolism represents a target to attenuate diastolic dysfunction/HF. A similar metabolic profile is observed in humans, as assessment of myocardial metabolism by positron emission tomography in patients with non-ischemic diastolic

dysfunction/HF revealed significant increases in myocardial fatty acid uptake and oxidation, and a decrease in myocardial glucose uptake [19]. However, it should be noted that the metabolic changes that take place in the heart in response to obesity and/or diabetes, which are associated with the development of diastolic dysfunction/HF, can also be associated with reductions in systolic function [17]. Importantly, compounds that shift myocardial metabolism from fatty acid oxidation towards carbohydrate oxidation, including trimetazidine, improve clinical symptoms, cardiac function, and attenuate deleterious ventricular remodeling in patients with chronic HF [20]. It will thus be important to assess whether such metabolic interventions that improve the efficiency of ATP generation and utilization can also improve diastolic function, and attenuate diastolic dysfunction/HF in addition to their benefits against systolic HF.

Conclusions

Although the risk factors contributing to the development of systolic HF and diastolic dysfunction/HF appear to be similar, important differences in ventricular remodeling, myocardial fibrosis, and ventricular function effectively differentiate between the two phenotypes. Furthermore, well-characterized deficits in energetic status accompany overt HF, and interventions that improve the efficiency of both ATP generation and utilization improve cardiac function in the setting of systolic HF. As ventricular relaxation and thus diastolic function is an ATP-requiring process, it will be essential for future studies to discern the underlying mechanisms whereby altered cardiac metabolism may predispose to diastolic dysfunction/HF. A better understanding of the alterations in energy metabolism that occur in diastolic dysfunction/HF may identify novel therapeutic targets that can be utilized in its management. •

Acknowledgments JRJ is a fellow of Alberta Innovates Health Solutions and the Canadian Institutes of Health Research.

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Advances in the treatment of heart failure with preserved systolic function

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Abstract

Heart failure with preserved ejection fraction (HFpEF) comprises 40% of the heart failure (HF) population. The morbidity and mortality of HFpEF is similar to HF with reduced ejection fraction (HFrEF), but unlike this latter population, the prognosis of HFpEF has not changed over the past 30 years. Therapies that are the mainstay of treatment in HFrEF have not been found to be effective in HFpEF, while others have not been fully studied. At present, there are no effective therapies available for the HFpEF population. This paper reviews the current knowledge of HFpEF treatment, as well as the novel therapies that may be coming in the future.

Keywords: Diastolic; drug therapy; heart failure; randomized controlled trials as topic

■ Heart Metab. (2012) 57:8–18

Introduction

Heart failure (HF) is a common cause of morbidity and mortality with a prevalence of 6–10% in those over 65 years of age [1]. It is a leading cause of acute care hospitalizations and more Medicare dollars are spent for this diagnosis than any other [1]. It is well recognized that approximately half of all HF patients have a preserved left ventricular ejection fraction (LVEF). Despite a normal LVEF, they have similar hospital readmission and mortality rates as patients with a reduced LVEF [2]. Over the past three decades, medical advances have improved patient outcomes in those with HF with reduced left ventricular ejection fraction (HFrEF). The same cannot be said for patients with HF with preserved left ventricular ejection fraction (HFpEF) as the prognosis of this population has remained unchanged despite the use of the same advances [2]. Few randomized control trials (RCT) have been performed in HFpEF and most with disappointing results. Past therapies and novel agents are reviewed below.

A definition of heart failure with preserved ejection fraction

HFpEF is defined by the presence of symptoms and/or signs of HF and a preserved LVEF greater than 40–50%, usually measured by echocardiography. There is no agreement on the exact LVEF that corresponds to a preserved LVEF, which varies between guidelines [1, 3–5]. In addition, one guideline recommends demonstration of an increased filling pressure, measured invasively in the coronary catheterization laboratory, by echocardiography using tissue Doppler techniques or by finding elevated brain natriuretic peptide levels on laboratory testing [5].

Regardless of the definition used, HFpEF is of growing interest, an important public health issue and a target for therapy.

Treatment of comorbidities

Hypertension

Hypertension is the most common medical comorbidity in HFpEF and is seen in up to 60% of patients [2]. Hypertension-related left ventricular hypertrophy (LVH) plays an important role in the development of HF potentially due to changes in diastolic filling parameters [6]. Regression of LVH may result in improvements in diastolic function, as demonstrated in a recent meta-analysis evaluating the differential effects of antihypertensive therapies on LVH [7]. This found that angiotensin II receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitors, calcium-channel blockers and diuretics are significantly better than β -blockers at improving LVH. Consistently, RCT of antihypertensive agents reduce the clinical endpoint of HF of which an uncertain percentage of this is related to systolic or diastolic dysfunction [8]. HF guidelines recommend control of systolic and diastolic hypertension in HFpEF and these patients should have their blood pressure managed to targets established by hypertension guidelines [1, 3–5].

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia in HF and has a prevalence of 40% in HFpEF patients [2]. Selby et al [9] illustrated that tachycardia associated with atrial fibrillation can induce diastolic dysfunction associated with increased left ventricular mass, left atrial volumes, and resting tone in patients with normal LVEF. Atrial fibrillation also has prognostic value in HFpEF and was an independent predictor of HF death or hospitalization in HFpEF patients, but not in HFrEF patients [10]. While there is currently no evidence that strict rate control of atrial fibrillation is beneficial in HFpEF, it is strongly recommended by HF guidelines [1, 3–5].

Coronary artery disease

Although coronary artery disease is not as prevalent in HFpEF patients as in those with reduced LVEF, it is present in up to 50% of patients [2]. This high prevalence is probably due to the fact that HFpEF patients often have multiple risk factors for coronary artery disease such as hypertension, diabetes and older age [2].

Furthermore, myocardial ischemia can impair ventricular relaxation inducing diastolic dysfunction. Guidelines recommend consideration of coronary revascularization in HFpEF patients with symptomatic coronary disease or in those with demonstrable myocardial ischemia that is judged to be having an adverse effect on cardiac function [1, 3–5].

Medical therapy

ACE inhibitors and ARB

ACE inhibitor therapy is firmly entrenched in the treatment of HFrEF, but the same cannot be said for HFpEF. In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study, 850 patients aged 70 years or older with evidence of diastolic dysfunction and a LVEF greater than 40% were randomly assigned to either perindopril or placebo [11]. Overall, no conclusion can be drawn with respect to the primary outcome (all-cause mortality and HF hospitalization) as the study was underpowered and had a high treatment withdrawal rate after 1 year. However, a secondary analysis highlights improvements in 6-minute walk time and symptoms as well as a significant reduction in cardiovascular death and HF-related hospitalization at 1 year [11].

Two major RCT have been performed looking at the use of ARB in HFpEF. In the Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (CHARM-P) trial, 3023 patients with New York Heart Association class II–IV symptoms and LVEF greater than 40% were assigned to receive either candesartan or placebo [12]. At a median follow up of 37 months, there was no difference in the primary outcome of cardiovascular death or HF admission, but there was an 18% reduction in the secondary endpoint of HF hospitalizations. The more recently published Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial randomly assigned 4128 patients who were at least 60 years or older with New York Heart Association class II–IV HF and a LVEF of 45% or greater to irbesartan or placebo [13]. At a mean follow-up of 50 months, there was no difference in the primary outcome of death from any cause or hospitalization for cardiovascular causes, or any of the other secondary endpoints [13].

There continues to be no strong RCT data supporting the use of ACE inhibitors/ARB in HFpEF. In the

absence of other indications, guidelines weakly support ACE inhibitor therapy in HFpEF for the reduction of symptoms, and no other large RCT are planned at this time to address this indication better. Similarly, ARB may be considered in HFpEF to reduce hospitalization [4] or symptoms [1, 3], but should not be used in conjunction with ACE inhibitors.

β-Blockers

Much like ACE inhibitors and ARB, β-blockers are important in the treatment of HFrEF, but their use in HFpEF is not established. Small observational studies have shown a morbidity, symptom and mortality benefit with β-blockers in HFpEF [14, 15]. Conversely, larger registry data from OPTIMIZE-HF (4153 patients) with HFpEF showed that discharge use of β-blockers had no association with 1-year mortality or hospitalization rate [16]. In the 752 HF patients with a LVEF greater than 35% in the SENIORS trial (comparing nebivolol versus placebo), there was no statistical difference in the primary outcome of all-cause mortality or cardiovascular admission [17]. At present, there is limited RCT evidence supporting β-blockers for use in HFpEF, and assuming there is not another indication for their use, guidelines give them a weak recommendation.

Diuretics

There are no clinical trial data prospectively evaluating the overall impact of thiazide or loop diuretics on mortality in HF probably because few symptomatic patients can be managed without them. Current guidelines strongly recommend diuretic therapy to control pulmonary congestion and peripheral edema in HFpEF, with caution advised against excessive diuresis as it can lead to volume depletion with subsequent decreased cardiac output and worsening of renal function [1, 3–5].

Aldosterone blockade

Aldosterone is known to promote hypertension, ventricular hypertrophy and progressive myocardial fibrosis – all of which are implicated in the pathogenesis of HFpEF and therefore aldosterone synthesis or receptor blockade may be useful in the treatment of HFpEF. In a small RCT of patients with HFpEF, 6 months of treatment with the aldosterone receptor blocker eplerenone appeared to improve echocardiographic measures of diastolic function, but not 6-minute walk time [18]. HF guidelines do not refer to the use of aldosterone block-

ers in the treatment of HFpEF, but this may change as there are currently two large randomized outcome studies being carried out to explore the use of spironolactone in HFpEF. The Aldosterone Receptor Blockade in Diastolic Heart Failure–ISRCTN94726526 (ALDO-DHF) trial has been completed, but results have yet to be released while the larger Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function–NCT00094302 (TOPCAT) study is expected to have results available in 2013. Their results are highly anticipated and will shed light on the clinical application of aldosterone blockers in HFpEF.

Other agents

Several other agents commonly used in HFrEF have undergone limited study in HFpEF. The DIG trial had similar results in the 988 patients with LVEF greater than 45% as it did for those with an LVEF of 45% or less, with no difference in all-cause or HF-related mortality [19]. Current guidelines either do not or only weakly recommend the use of digoxin in HFpEF, but it can be a useful adjunct for patients with atrial fibrillation.

Calcium channel blockers may improve passive ventricular filling by reducing left ventricular end-diastolic pressure. In a small RCT, verapamil improved exercise capacity and ventricular filling in HF patients with a LVEF greater than 45% [20]; however, this has yet to be corroborated and therefore some guidelines weakly recommend calcium channel blockers for the reduction of symptoms for HFpEF [1, 4] while others recommend it only if there is another indication [3].

Observational data have shown a mortality benefit for the use of statins in HFpEF and HFrEF, but no benefits were found in the GISSI-HF RCT, which included patients with HFpEF [21]. Statins are currently not recommended in HFpEF unless there is another indication.

Exercise therapy

Exercise intolerance is a primary symptom of chronic HF, a predictor of HF mortality and a key therapeutic target [22]. Studies of exercise therapy in HFrEF have shown improvements in exercise performance, and this has recently also been shown in HFpEF. In a single blind study, Kitzman et al [22] randomly assign 53 HFpEF patients to 3 days a week of medically supervised exercise therapy for 16 weeks. Measures of exercise tolerance including peak exercise oxygen uptake and 6-minute walk time increased significantly

in the therapy group compared to the control group. Another small RCT showed similar improvements in peak oxygen uptake with 3 months of exercise therapy, and also demonstrated improvements in measures of left ventricular diastolic function and left atrial size [23]. Exercise therapy that is initially supervised is recommended for all HF patients, and it may exert beneficial effects on myocardial and skeletal muscle function that are yet to be fully understood.

Novel agents

A rational approach to the treatment of HFpEF is to target regression of LVH. Animal and human studies have revealed that inhibition of phosphodiesterase-5 leads to cardiac antihypertrophic and antifibrotic effects resulting in improved cardiomyocyte relaxation and increased left ventricular distensibility [24]. In a RCT, Guazzi et al [24] assigned 44 patients with HFpEF and pulmonary hypertension (pulmonary artery systolic pressure >40 mmHg) to placebo or sildenafil. At 6 months and 1 year, the sildenafil group had improvements in mean pulmonary artery pressure and right ventricular function, and a reduction in wedge pressure and isovolumetric relaxation time. There was, however, no difference in quality of life measures or symptoms between the two groups. The ongoing Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure–NCT00763867 (RELAX) trial, expected to be complete in January 2013, will offer further enlightenment on the clinical use of phosphodiesterase-5 inhibitors in HFpEF.

Diastolic filling and myocardial relaxation is impaired in HFpEF and therefore heart rate slowing may improve diastolic parameters in these patients. While β -blockers and calcium channel blockers do not appear particularly useful in this population, use of the “funny” current (I_f)-channel blocking agent ivabradine may be of benefit [25]. Because there are no I_f channels in the myocardium, it selectively reduces heart rate without a negative effect on myocardial contractility or cardiac output. Trials investigating the use of this agent are ongoing in patients with HFpEF both on (NCT01373619) and off (NCT00757055) dialysis.

The increased left ventricular stiffness often seen in elderly people with HFpEF is partly due to non-enzymatic crosslinks that develop between advanced glycation end products on collagen and elastin [26].

Alagebrium chloride (ALT-711) is a novel compound that breaks these crosslinks and was associated with reduced left ventricular mass and improved diastolic filling in an open label trial of elderly HFpEF patients [27]. This compound has not been shown to be of benefit in a RCT enrolling HFrEF patients [26], but has yet to be adequately tested in patients with HFpEF.

See table « Prior, current and future trials in heart failure with preserved ejection fraction » in online-only data supplement [28-40]

Conclusion

Significant advances in understanding HFpEF have occurred in the past decade, and it is likely that there will be a treatment that reduces morbidity and mortality for these patients by the end of this decade. The heterogeneity of causal diseases, complexity of cardiac and skeletal muscle derangements, chronic metabolic and fibrosis changes and vascular dysfunction that occurs in HFpEF make this a very complex puzzle to solve. Which cellular pathway or combination of therapies will correct the underlying pathophysiology remains to be seen. •

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Diastolic dysfunction: improved understanding using emerging imaging techniques

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Abstract

New echo-Doppler imaging techniques enable detailed evaluation of left ventricular (LV) diastolic function and an estimate of LV filling pressure, since they are less load sensitive than traditional mitral flow variables. In recent years, tissue Doppler imaging (TDI) has emerged as a reliable tool to assess LV diastolic function noninvasively. An averaged mitral-to-TDI early velocities (E/e') ratio ≥ 13 is considered the stand alone evidence of LV diastolic dysfunction. In the presence of an E/e' ratio between 8 and 13, the so called "grey zone", additional investigations are deemed necessary to diagnose diastolic dysfunction. A multiparametric approach, including measurements of left atrial volume, pulmonary venous flow, colour M-mode flow propagation velocity showed to have a superior sensitivity and specificity compared with standard approach in identifying an increased LV filling pressure in patients with a wide range of LV ejection fractions. Strain analysis has been used to evaluate myocardial relaxation in a variety of cardiac diseases associated with diastolic dysfunction. Since myocardial mechanical events precede LV filling, these ultrasound modalities may be less dependent on extrinsic variables and therefore more accurate in characterizing intrinsic myocardial properties. The ratio of mitral E to 2D global longitudinal diastolic strain has been found to be a better predictor of LV filling pressure than E/e'.

Keywords: Diastolic function; left ventricular filling pressure; tissue Doppler imaging; strain analysis

■ Heart Metab. (2012) 57:13–17

Introduction

Diastole allows left ventricular (LV) filling to ensure the forward movement of blood while maintaining a normal LV filling pressure at rest, during exercise, and through a wide range of heart rates. LV filling is determined by the active relaxation of the myocardium, the LV compliance, left atrial (LA) contraction, and the return of blood from the pulmonary circulation (Table 1). Patients with diastolic dysfunction have concomitant alterations in LV relaxation, filling, and compliance [1]. Diagnostic evidence of LV diastolic dysfunction can be obtained invasively by left or right cardiac catheterization: LV end-diastolic pressure greater than 16 mmHg or mean pulmonary capillary wedge pressure (PCWP) greater than 12 mmHg, or noninvasively by Doppler echocardiography [2].

- LA pressure
- LV relaxation
- LV compliance
- LV suction
- Diastolic restoring forces
- Ventricular interaction
- LA systolic function
- Pericardial restraint
- Coronary artery turgor
- Viscoelastic properties
- Loading conditions
- Nonuniformity
- Heart rate
- Age

LA = left atrial, LV = left ventricular.

Table 1 Determinants of LV filling.

The interpretation of Doppler echocardiographic information has increased our understanding of LV diastolic function. Spectral Doppler ultrasound is ideally suited to the evaluation of the instantaneous velocities of blood flow. The importance of Doppler echocardiography for non-invasive assessment of LV filling pressure is mainly dependent on the close relationship between LV flow velocities and LA–LV diastolic pressure differences. The Doppler patterns of mitral flow velocity curves are determined by changes in the LA–LV driving pressures throughout the diastolic filling period. The early flow velocity (E) is related to rapid filling, while the latter (A) is due to atrial contraction.

When a compromised relaxation is the dominant LV diastolic alteration, the reduction in the initial LA–LV pressure gradient and the accompanying compensatory flow at atrial contraction are considered responsible for low E velocity, prolonged deceleration time (EDT) and high A velocity with an E/A ratio less than 1. This type of abnormality has usually been considered to be associated with normal or nearly normal LV filling pressure. In patients with an abnormal relaxation filling pattern, increased loading conditions – especially in the presence of decreased LV compliance – may be responsible for an elevation in LA pressure or PCWP, that is necessary to maintain the early LA–LV driving pressure, and this is followed by changes in LV filling dynamics. This accounts for increased mitral E velocity, E/A ratio of 1.0 to 1.5 and normalized EDT. As diastolic dysfunction progresses,

there is a further reduction in LV compliance and this results in early cessation of filling due to rapid equalization of LA and LV pressures. Therefore, faster and more pronounced increases in LA pressure are necessary to maintain the driving pressure to a degree that allows LV filling to accommodate in a stiffer ventricle. The resulting mitral flow velocity profile – characterized by marked elevation of E velocity, shortened EDT with an increased E/A ratio – is referred to as restrictive pattern, i.e., similar to that associated with restrictive cardiomyopathy [3–6].

Analyzing the Doppler mitral velocity curve and PCWP recorded at catheterization, a strong correlation was found between EDT and LV filling pressure [7, 8], but only in patients with reduced LV ejection fraction [9]. Additional diagnostic flow information – beyond that contained in mitral flow velocity recordings – may be attained from the study of pulmonary venous flow velocities and combined analysis of mitral and pulmonary venous flow tracings [10–12].

Tissue Doppler imaging

In recent years, tissue Doppler imaging (TDI) has emerged as a reliable tool to assess LV diastolic function noninvasively (Fig. 1). TDI is obtained in the apical view by placing the sample volume at the junction between the LV wall and the mitral annulus. Lateral annulus velocity is usually higher than the velocity from the medial annulus. Values can be averaged for medial and lateral walls. In patients with normal diastolic function, the early diastolic TDI velocity (e') is higher than the late TDI (a') velocity. Although e' has been suggested as being less load sensitive than mitral flow variables, this issue remains controversial [13].

Similar to mitral flow, with mild diastolic dysfunction the early TDI diastolic velocity decreases below the late diastolic velocity (ie, e'/a' became less than 1.0). However, in contrast to mitral flow, with worsening diastolic dysfunction e' continues to decrease. As mitral flow E velocity is determined equally by both LA pressure and LV relaxation, whereas e' is related primarily to LV relaxation, when LV filling pressure rises, e' remains decreased (ie, persistent underlying relaxation abnormality), while E velocity increases.

The ratio E/e' may be used to predict LV filling pressure [14,15]. In individuals with normal LV relaxation and normal LV filling pressure, both E and e' are elevated. In patients with impaired relaxation and normal

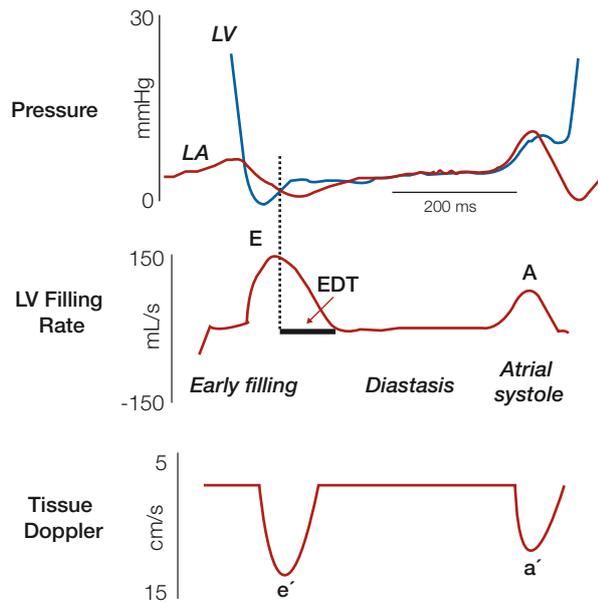


Fig. 1 Doppler-derived mitral flow and tissue Doppler pattern changes during diastole. A = mitral atrial velocity, a' = atrial tissue Doppler velocity, E = mitral velocity, e' = early tissue Doppler velocity, EDT = E velocity deceleration time, LA = left atrial, LV = left ventricular.

LV pressure, both E and e' are decreased. In patients with impaired relaxation and elevated LV filling pressure, E is elevated but e' is reduced.

An averaged E/e' ratio of 13 or greater is considered the stand-alone evidence of LV diastolic dysfunction. In the presence of an E/e' ratio between 8 and 13, the so called "grey zone", additional investigations are deemed necessary to diagnose diastolic dysfunction. These consist of mitral flow E/A ratio, its reduction with the Valsalva maneuver, EDT less than 150ms, LA volume index of 34 mL/m² or greater, pulmonary venous reversal flow duration greater than mitral A duration plus 30ms, E/color M-mode velocity of propagation greater than 1.5 [16–18]. The noninvasive identification of elevated LV filling pressure may be particularly challenging in patients with heart failure and preserved LV ejection fraction, hypertrophic and restrictive cardiomyopathy. In these cases, different methods, including specific diagnostic flow charts, have been proposed for the prediction of LV filling pressure [19, 20]. A multi-parametric approach, including measurements of LA volume, pulmonary venous flow, color M-mode flow propagation velocity, with a sequential testing based on the classification and regression tree analysis (Fig. 2) was shown to have a superior sensitivity and specificity compared with the standard approach in

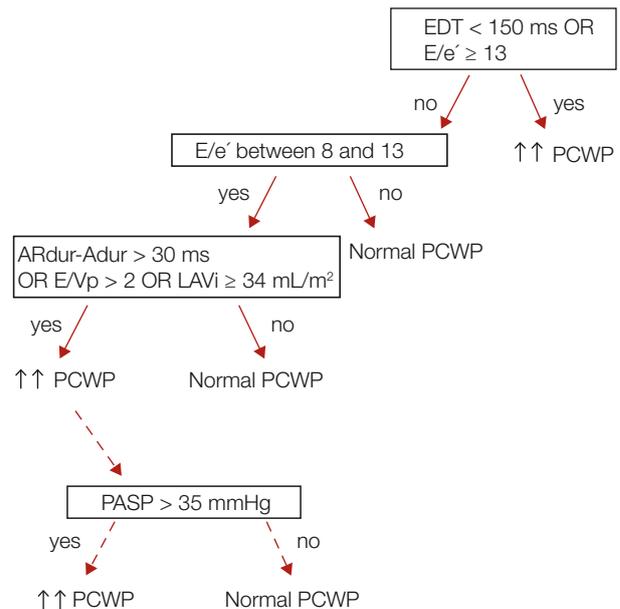


Fig. 2 Classification and regression tree-based predictive model of elevated pulmonary capillary wedge pressure constructed with Doppler and echocardiographic variables. Variables are connected by OR Boolean operators, so that the whole box response is positive if at least one criterion is satisfied, and negative if all criteria are not satisfied. ARdur-Adur = difference in duration of pulmonary venous and mitral flow at atrial contraction, EDT = E-wave deceleration time, E/e' = ratio of mitral to myocardial early velocities, E/Vp = ratio of mitral E-wave and color M-mode flow propagation velocity, LAVi = left atrial volume index, PASP = pulmonary artery systolic pressure, PCWP = pulmonary capillary wedge pressure.

identifying an increased LV filling pressure in patients with a wide range of LV ejection fractions [21].

Early echo-Doppler indexes of LV diastolic function have proved to be useful in patients with diastolic dysfunction or mixed systolic and diastolic dysfunction. A reduced e' has been associated with decreased survival in patients with cardiac disease [22]. An increased E/e' ratio velocity exhibited an additional predictive power with respect to demographic, clinical and echocardiographic variables both in myocardial infarction and heart failure [23, 24]. However, TDI parameters have limited accuracy in predicting intrinsic parameters of diastolic function due to the confounding effects of extrinsic loading conditions and therefore are less reliable in patients with preserved LV ejection fraction.

Myocardial strain imaging

Myocardial strain imaging may be applied to study LV myocardial mechanics [25]. Myocardial strain is a measure of regional deformation defined as the percentage change in length of a segment of the

myocardium in comparison to its original length (end-diastolic length minus end-systolic length/end-diastolic length). Strain rate (Sr) can be defined as the speed at which deformation occurs [26]. According to the direction of different myocardial strain vectors, myocardial strain can be divided into longitudinal, radial and circumferential strain (Fig. 3). Myocardial strain may be quantified using TDI or high-frame rate two-dimensional echocardiography with Speckle tracking. TDI-derived strain quantifies tissue deformation based on Doppler velocity shifts, but it is considerably affected by tissue tethering and translational motion. Speckle tracking echocardiography (STE) is a novel non-Doppler-based method for the objective quantification of myocardial deformation. In contrast to Doppler flow-derived indexes, STE has the advantage of being angle independent, and to be less affected by reverberations, and dropout artefacts.

Strain analysis has been used to evaluate myocardial relaxation in a variety of cardiac diseases associated with diastolic dysfunction. As myocardial mechanical events precede LV filling, these ultrasound modalities may be less dependent on extrinsic variables and therefore more accurate in characterizing intrinsic myocardial properties.

In order to assess the usefulness of STE parameters for the evaluation of diastolic dysfunction in patients with cardiac disease and preserved LV systolic function, a study was carried out in 50 patients with a mean LV ejection fraction of $49 \pm 18\%$ [27]. Two-dimensional global longitudinal diastolic strain (ϵ) and

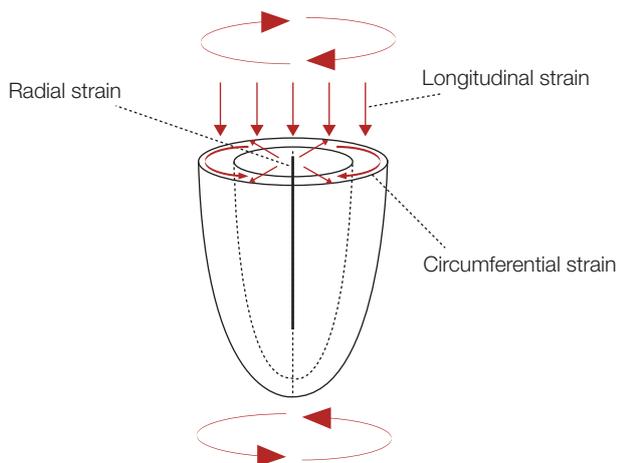


Fig. 3 The diagram indicates the direction of different myocardial strain vectors. The basal clockwise twist and the apical counter-clockwise twist are also indicated; torsion is the sum of both components.

Sr were measured during peak mitral filling, and combined with E (E/ϵ and $E/10DSr$). These indexes were compared with simultaneously invasively measured LV pre-atrial (pre-A) contraction pressure and E/e' . The correlations between E/ϵ and $E/10DSr$ with LV pre-A pressure were closer ($R = 0.81$; $P < 0.001$ and $R = 0.80$; $P < 0.001$) compared with that of E/e' with LV pre-A pressure ($R = 0.63$; $P < 0.001$). Therefore, both E/ϵ and $E/10DSr$ were better predictors of LV filling pressure than E/e' .

STE has recently evolved enabling the quantification of longitudinal myocardial LA deformation dynamics [28]. LA deformation analysis by STE was recently proposed as an alternative approach to estimate LV filling pressure. A close negative correlation between global peak atrial longitudinal strain and PCWP was found. The potential mechanism of this inverse correlation could be explained by the principle that PCWP is the afterload of LA function; if PCWP is high, the left atrium should be chronically stressed, resulting in a decrease of LA reservoir function and finally in remodeling with LA chamber dilation, as demonstrated in patients with heart failure. In a recent study performed in 54 patients with normal LV ejection fraction, the assessment of LA strain indexes was useful at identifying the presence of LA dysfunction among patients with preserved LV systolic function and an E/e' ratio between 8 and 13 [29].

In addition to myocardial strain, there is torsional deformation of the left ventricle during the cardiac cycle due to the helical orientation of the myocardial fibers [30]. LV torsion, defined as the instantaneous net difference of the basal and apical rotation, and subsequent untwisting, plays an important role in diastolic filling [31]. There is, however, limited information about how LV torsion and untwisting are related to the severity of diastolic dysfunction. The results of this study showed that systolic torsion and diastolic untwisting were significantly increased in patients with mild diastolic dysfunction. In patients with advanced diastolic dysfunction with increased filling pressure, they were normalized or reduced. •

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Metabolic therapy for heart failure including diastolic heart failure

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Abstract

Cardiac energetic impairment is a feature of systolic heart failure irrespective of the underlying etiology, and the magnitude of this impairment is predictive of subsequent mortality. It is also a feature of other forms of heart muscle diseases including hypertrophic cardiomyopathy and heart failure with normal ejection fraction. While the adult heart normally uses predominantly free fatty acids to generate energy, this consumes more oxygen than the use of carbohydrate to generate energy. In the context of heart muscle disease the reduction in efficiency of fatty acid versus carbohydrate utilization may be substantial. This provides the rationale for the use of drugs that inhibit fatty acid utilization and increase carbohydrate utilization. These agents either prevent the uptake of long chain fatty acids into the mitochondria (eg, perhexiline) or inhibit fatty acid β -oxidation (eg, trimetazidine). Studies in patients with systolic heart failure have shown encouraging results with increased cardiac performance and exercise capacity with these agents.

Keywords: Cardiac energetics; cardiac metabolism; cardiomyopathy; heart failure; metabolic therapy

■ Heart Metab. (2012) 57:18–24

Introduction

The heart cycles approximately 6 kg of ATP each day [1] required to drive the actin–myosin interaction in myofibrils, and for other vital functions including the activity of ion channels. It is perhaps not surprising that cardiac pathology is associated with an impairment of cardiac energy production and/or utilization, as originally described by Herrman and Decherd [2]. Studies in animal models of systolic heart failure have confirmed this initial observation, and in the rapid pacing model of heart failure, cardiac energetic impairment begins before the appearance of overt left ventricular systolic dysfunction or heart failure [3]. In patients with systolic heart failure ^{31}P cardiac magnetic resonance spectroscopy shows a reduced ratio of phosphocreatine (PCr)/ATP, the magnitude of which predicts mortality [4]. These observations support the concept that energy impairment is both a consequence of the cardiomyopathic process and a contributor to its progression.

Cardiac substrate use and energy production in health and disease

The heart is a metabolic omnivore, able to use different substrates (fatty acids, carbohydrates, lactate, ketones, amino acids) in varying amounts in different circumstances. In fetal life

carbohydrates form the primary substrate, but soon after birth there is a metabolic shift and in the adult in the fasting state fatty acid utilization accounts for approximately 70% of ATP generation and even more during conditions of increased work [5]. With adequate oxygen availability and normal underlying cardiac biochemical function, fatty acid oxidation provides an extremely efficient source of energy, generating more ATP per gram of substrate than carbohydrate oxidation. However, it costs more oxygen per unit of ATP generated than carbohydrate oxidation, theoretically approximately 12%, but when plasma free fatty acids (FFA) are markedly raised there is a substantial “oxygen wasting” effect (approximately 40–50%) [6]. The mechanism responsible has not been proved but is likely to be related to increased mitochondrial “uncoupling”, and to futile metabolic cycles. Fatty acids increase the expression of uncoupling proteins (by peroxisome proliferator activated receptor alpha activation), and lipid peroxides derived from oxidative conversion of lipids in the mitochondrial matrix increase uncoupling protein activity. They dissipate the electrochemical gradient across the inner mitochondrial membrane that drives the phosphorylation of ADP to ATP. Plasma FFA are increased by high plasma catecholamines (by activation of lipoprotein lipase), and consequently high FFA levels are typically observed in acute myocardial infarction and in heart failure; thus uncoupling protein expression was increased in the hearts of patients with left ventricular systolic dysfunction and expression was correlated with plasma FFA [7]. Furthermore, the accumulation of acetyl coenzyme A (CoA) and NADH from high levels of fatty acid oxidation inhibits the enzyme pyruvate dehydrogenase (PDH) that catalyses the conversion of pyruvate to acetyl CoA. This results in pyruvate accumulation and its conversion to lactate leading to harmful proton accumulation particularly in the context of myocardial ischaemia, which can be lessened using partial inhibitors of fatty acid β -oxidation, reducing ischaemic left ventricular dysfunction [8].

In animal models of systolic heart failure developing in the context of left ventricular hypertrophy, the expression of fatty acid β -oxidation enzymes is consistently downregulated. There is a shift towards increased glucose uptake but because of the reduced activity of PDH, there is reduced carbohydrate oxidation only partly compensated by anaerobic reactions. Accord-

ingly, the heart is unable to utilize fully either major substrate and this contributes importantly to its energy starvation [9]. Furthermore, the combination of increased plasma FFA together with a reduced capacity to oxidize them sets the scene for increased expression and activity of the uncoupling proteins, probably further reducing the efficiency of energy generation. In other animal models of heart failure different findings have been reported. For example, in the canine rapid pacing model substrate utilization was relatively normal in the early stages but in advanced heart failure fatty acid utilization was markedly reduced [10].

Studies in patients with systolic heart failure have been conflicting, potentially explained by factors including etiology, stage of heart failure and technique employed (for example positron emission tomography (PET) with [18 F]fluorodeoxyglucose gives information about glucose uptake but does not provide information about pyruvate oxidation, which is likely to be impaired as noted above even if glucose uptake is preserved or increased). In explanted hearts from patients with advanced heart failure there is downregulation of the expression of fatty acid oxidation enzymes compared to donor hearts [11]. Funada and colleagues [12] demonstrated preserved FFA uptake in compensated heart failure using an assessment of cross-heart uptake of stable isotopes. Using cross-heart indirect calorimetry and stable isotope infusion, fasting glucose uptake was shown to be impaired and fatty acid utilization increased in patients with heart failure of moderate severity [13]. Using PET-based assessment Taylor and colleagues [14] reported increased fatty acid uptake and lower glucose uptake in the hearts of patients with severe left ventricular systolic dysfunction and stable heart failure symptoms, whereas Davila-Roman et al [15] reported reduced fatty acid uptake and increased glucose uptake.

“Metabolic modulation” as a therapy for heart failure

The observation that FFA are increased in heart failure and that high FFA levels reduce the efficiency of energy generation has led to the concept that reducing FFA utilization and increasing carbohydrate utilization may increase the efficiency of energy generation in heart failure, improving cardiac function and functional status.

The concept that increased carbohydrate oxidation may be beneficial is underscored by a study in which

dichloroacetate was infused in patients with severe heart failure. Dichloroacetate is an activator of PDH that is used in the treatment of lactic acidosis. A 30-minute infusion increased left ventricular stroke work at a lower oxygen cost [16]. However, its short half-life necessitates continuous infusion, and as a sodium salt this involves a high sodium load making its long-term use in heart failure impractical. However, as fatty acid utilization generates NADH and acetyl CoA, which are both potent inhibitors of PDH, inhibition of fatty acid oxidation should theoretically increase PDH activity and therefore simultaneously reduce fatty acid utilization and increase carbohydrate oxidation. Three major strategies could potentially facilitate this (Fig. 1):

1. Reduction in plasma FFA by the inhibition of lipoprotein lipase activity using nicotinic acid derivatives. Acute treatment with acipimox in patients with heart failure due to dilated cardiomyopathy reduced plasma FFA, reduced myocardial fatty acid oxidation and increased glucose uptake (assessed by PET) but left ventricular stroke work and cardiac efficiency fell [17]. The reason for this could be that the increase in glucose uptake was insufficient to compensate for the loss of the fatty acid substrate, or more likely that despite increased glucose uptake the reduced PDH activity was not acutely reversed so that the loss of fatty acid oxidation was not matched by an increase in carbohydrate oxidation. However, a 28-day placebo controlled trial of acipimox in patients with ischemic left ventricular dysfunction did not demonstrate any improvement in left ventricular performance despite reducing plasma FFA [18].
2. Blockade of the uptake of long chain fatty acids into the mitochondria. Long chain FFA are first converted to long chain acyl CoA (by fatty acid acyl CoA synthase), which can only cross the mitochondrial membrane as a result of the addition of a carnitine molecule by the enzyme carnitine palmitoyl transferase (CPT) 1. On the other side of the mitochondrial membrane the carnitine is cleaved off by the enzyme CPT2 and the long chain acyl CoA then undergoes β -oxidation. This is the rate-limiting step in fatty acid metabolism, and the activity of the CPT enzymes is potently regulated by malonyl CoA, formed by acetyl CoA carboxylase and degraded by malonyl CoA decarboxylase. A number of malonyl CoA decarboxylase inhibitors are available. In a

pig cardiac ischemia model one of these inhibitors reduced fatty acid utilization and increased carbohydrate oxidation [19].

Direct pharmacological inhibitors of the CPT enzymes are available. Oxfenicine slowed the development of heart failure in the rapid pacing canine model [20], but is not available for human use. Etomoxir is a potent irreversible inhibitor of the CPT enzymes. It did not reverse the development of heart failure in the rat aortic banding model [21]. An initial open label (uncontrolled) study in 10 patients with heart failure reported an increase in left ventricular ejection fraction (LVEF), and an improvement in exercise hemodynamics [22], but a subsequent randomized controlled trial was abandoned at an early stage of recruitment because four patients in the etomoxir group had unacceptably elevated liver transaminase levels [23]. Perhexiline is a drug that was used in the 1970s and 1980s to treat angina, for which it was highly effective. At the time it was not clear exactly how it worked. A small proportion of patients developed liver toxicity and neuropathy that were found to be caused by phospholipid accumulation, and the drug was voluntarily withdrawn by the manufacturers. Subsequent work in isolated mitochondria showed that perhexiline reversibly inhibits cardiac (and hepatic) CPT1 and CPT2 [24]. Furthermore, the toxicity was shown to be caused by long-term exposure to high plasma concentrations of the drug that is predominantly metabolised by P450 2D6, which is subject to substantial genetic variations in activity. Dose titration according to plasma levels avoids long-term toxicity [25], and this has led to a resurgence in the use of the drug in some parts of the world – particularly Australia and New Zealand. We evaluated the effects of perhexiline in a randomized double blind placebo controlled trial of 56 patients with stable chronic heart failure who were on optimally tolerated conventional medical therapy and who were treated for 2 months. There was a substantial improvement in peak oxygen consumption (the primary endpoint) and also in the predefined secondary endpoints of LVEF, and quality of life assessment [26]. These encouraging data have yet to be evaluated further in a large multicenter study with “hard” endpoints. Perhexiline has pleotropic effects potentially relevant to its beneficial effects in heart

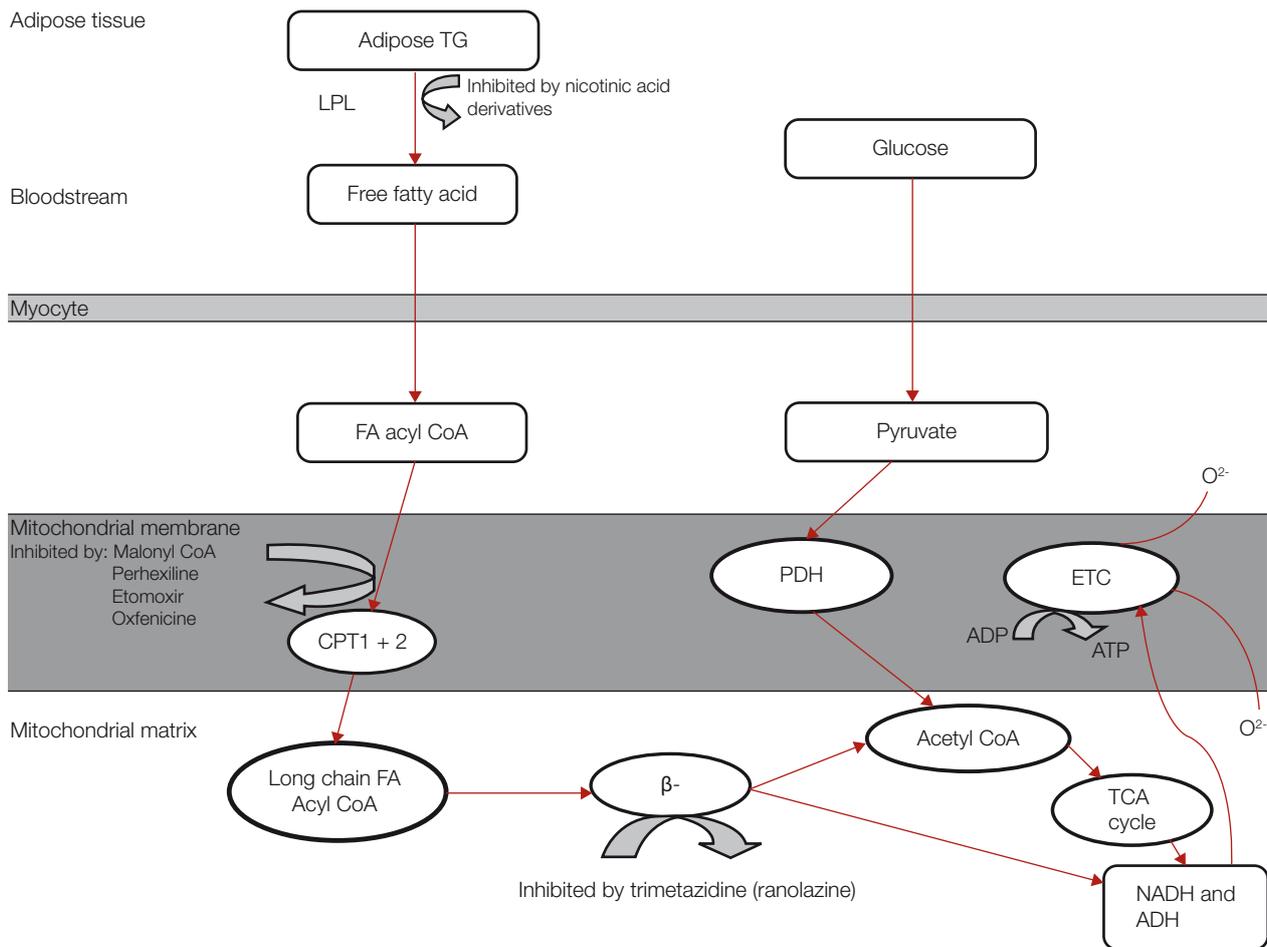


Fig. 1 CoA = coenzyme A, CPT = carnitine palmitoyl transferase, ETC = electron transport chain, FA = fatty acid, LPL = lipoprotein lipase, PDH = pyruvate dehydrogenase, TCA = tricarboxylic acid, TG = triglyceride.

muscle diseases. Indeed, a study in the working rat heart model raises the possibility that at least some of the beneficial effects on cardiac performance are not mediated by CPT1 inhibition. While 48 hour pretreatment was associated with an increase in cardiac mechanical efficiency and reduced palmitate uptake, increased efficiency was also seen with 24 hour pretreatment without any change in palmitate uptake [27]. These pleotropic mechanisms include:

- i) Altered redox status – perhexiline reduces superoxide generation by the phagocytic form of NADPH oxidase 2 [28], and was recently shown to reduce cardiac expression of thioredoxin interacting protein (a potent inhibitor of thioredoxin) in patients pretreated with perhexiline versus placebo before coronary artery bypass grafting [29].
- ii) Altered cell survival mechanisms. Perhexiline reversibly inhibits the mammalian target of complex 1 (mTORC1) and therefore stimulates cell

autophagy, which may be an important cell survival mechanism [30].

Interestingly, β -blockers that have been shown to improve outcome markedly in patients with heart failure may also work in part by a similar mechanism. Metoprolol reduced CPT1 activity in a micro-embolization canine model [31], and using PET, Wallhaus et al [32] showed that carvedilol treatment reduced fatty acid uptake and increased glucose uptake in patients with heart failure.

3. Partial inhibition of fatty acid β -oxidation enzymes. Trimetazidine inhibited fatty acid oxidation in isolated cardiac myocytes, conferring protection from hypoxia [33], and in the working rat heart model clinically relevant concentrations of trimetazidine reduced fatty acid oxidation, increased glucose oxidation, and inhibited long chain 3 ketoacyl CoA thiolase, a key fatty acid β -oxidation enzyme [34]. It is noteworthy that the study also demonstrated that in hearts

subjected to low-flow ischemia, trimetazidine resulted in a 210% increase in glucose oxidation rates.

Trimetazidine is an effective anti-anginal agent. It has also been evaluated in a series of studies in patients with heart failure. Cardiac and systemic metabolism was evaluated using PET in a randomized placebo controlled trial of 19 patients with dilated cardiomyopathy. Trimetazidine significantly increased LVEF, modestly decreased cardiac FFA oxidation, and did not change the myocardial oxidative rate, implying increased oxidation of glucose and increased insulin sensitivity [35]. In a recent study in obese humans trimetazidine inhibited oxidation of endogenous intramyocardial lipids and increased cardiac mechanical efficiency [36]. In another study, improvements in symptomatic status and LVEF were accompanied by a 33% increase in the cardiac PCr/ATP ratio, indicating an improvement in the myocardial high-energy phosphate levels [37]. Two recent meta-analyses have assessed the benefits of trimetazidine as add-on therapy in patients with congestive heart failure [38, 39]. The last one, published in 2012 in the *Journal of the American College of Cardiology* [39], showed that the addition of trimetazidine significantly increases LVEF by 6.46%, which is consistent with the improvement of LVEF by 7.5% obtained in the other meta-analysis reporting data on nearly 1000 patients with heart failure and published in the journal *Heart* in 2011 [38].

Moreover, these meta-analyses showed significant improvements in New York Heart Association status and exercise time, a reduction in hospitalization due to heart failure and a trend towards reduced mortality. Aside from its primarily metabolic effects, trimetazidine has been shown to lower plasma C-reactive protein [40]. Generally well tolerated, it rarely induces a Parkinsonian syndrome [41].

Ranolazine is a widely used anti-anginal agent. In the Langendorff perfused normoxic rat heart it reduced fatty acid oxidation and increased PDH activity [42]. It appears to be a partial inhibitor of fatty acid β -oxidation but the concentrations achieved clinically are considerably lower than those that substantially inhibit fatty acid β -oxidation, and more recently its therapeutic action has been attributed primarily to blockade of the slow inward sodium current [43]. Ranolazine increased left ventricular power and mechanical efficiency in the canine rapid pacing heart failure model [44], and

in a recent placebo controlled study in patients with diastolic heart failure, acute intravenous ranolazine reduced left ventricular end-diastolic pressure, and 14 days of oral therapy reduced the minute ventilation/carbon dioxide production slope on exercise [45].

“Metabolic therapy” for other heart muscle diseases including HCM and heart failure with preserved LVEF?

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disease usually caused by mutations of one of several genes encoding sarcomere proteins. Cardiac energetic impairment is an almost universal finding, irrespective of the gene responsible, precedes the development of left ventricular hypertrophy [46], and is caused by an energy wasting effect from increased crossbridge turnover associated with increased sarcomeric calcium sensitivity [47]. We recently conducted a double blind placebo controlled trial in 46 patients with symptomatic non obstructive HCM of (mean) 4.6 months duration [48]. Perhexiline significantly improved exercise capacity – measured as peak oxygen consumption – the primary endpoint, and improved the quality of life score. The cardiac PCr/ATP ratio was substantially increased by perhexiline. We also measured the effect of therapy on cardiac diastolic function at rest and during exercise using radionuclide ventriculography. The time to peak filling (TTPF), measured from the time activity curve is an indirect marker of the rate of left ventricular active relaxation. Sympathetic activation causes an increase in the rate of left ventricular active relaxation during exercise by protein kinase A (PKA)-mediated phosphorylation of key proteins including troponin I, SERCA and titin, which are highly energy dependent processes. Even after correcting the TTPF for the RR interval (to produce a normalized TTPF) there was a slight shortening of this from rest to peak exercise in an age-matched control group permitting adequate left ventricular filling during the shortened diastolic filling period occurring at high heart rates on exercise. In contrast, normalized TTPF became markedly longer on exercise in the patients with HCM. Perhexiline nearly normalized the response of corrected TTPF during exercise, almost certainly due to the marked associated improvement in cardiac energetic status. While systolic heart failure is typically associated with elevated plasma FFA, providing a rationale for the beneficial effect of metabolic modulators, this is not usually so in HCM. One

study reported PET evaluation of eight patients with HCM due to alpha tropomyosin gene mutations. There was increased FFA metabolism in those patients with mild hypertrophy, but not in those with severe hypertrophy [49]. It is not known whether increased fatty acid metabolism is common in HCM, and/or whether the beneficial effects of perhexiline on energetics in HCM might be due to an alternative pleotropic effect.

Up to 50% of patients with the clinical features of heart failure have normal LVEF and are usually said to have heart failure with normal ejection fraction (HF_nEF). While many patients have impairment of left ventricular active relaxation and/or increased passive left ventricular stiffness at rest, this is not universal. Increased passive stiffness is attributable to myocyte hypertrophy and interstitial fibrosis, a consequence of the hypertension that commonly predisposes to the disorder, and to a shift of expression of the giant sarcomere protein titin to the shorter stiffer form, and/or impairment of titin phosphorylation [50]. We recently demonstrated that the exercise pathophysiology of HF_nEF may share some features in common with that of HCM. The cardiac PCr/ATP ratio was substantially lower than in a group of age-matched controls. These patients typically have stiff large arteries, and accordingly have increased arterial elastance (a measure of left ventricular afterload) at rest, and this tended to increase more during exercise in patients versus controls. As in HCM patients there was an acute dynamic lengthening of normalized TTPF in patients during exercise and a failure to increase left ventricular contractile function appropriately, attributable to the cardiac energetic impairment and to the increased left ventricular afterload [51]. The mechanisms responsible for this cardiac energetic impairment in HF_nEF are uncertain. Many patients with the disorder have insulin resistance and elevated plasma FFA similar to that seen in systolic heart failure, and this almost certainly contributes [52]. Currently, there are no effective therapies for HF_nEF, and the above pathophysiological observations provide a rationale for the evaluation of metabolic therapies in the disorder. We currently have a double blind placebo controlled trial of perhexiline in HF_nEF underway (clinicaltrials.gov NCT00839228).

Conclusions

Cardiac energetic impairment plays an important pathophysiological role in systolic heart failure irrespec-

tive of etiology and in other diseases of heart muscle including HCM and HF_nEF. Promising results have been obtained with metabolic modulators thought to increase cardiac energetic status by shifting cardiac substrate use away from fatty acids and towards carbohydrates, in systolic heart failure and in HCM. •

Acknowledgments Professor Frenneaux is the inventor of method of use patents for perhexiline in heart muscle diseases.

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New pharmacological targets in the treatment of heart failure: inhibition of free fatty oxidation by trimetazidine

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Abstract

Heart failure may promote alterations of cardiac metabolism, resulting in the depletion of myocardial ATP, phosphocreatine and creatine kinase with decreased efficiency of mechanical work. A direct approach to manipulate cardiac energy metabolism consists in modifying substrate utilization by the failing heart. To date, the most effective metabolic treatments include pharmacological agents that directly inhibit fatty acid oxidation. Trimetazidine (Vastarel® MR) appears to be the most investigated agent in this setting. The results of current research support the concept that shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism could be an effective adjunctive treatment in patients with heart failure. More specifically, very recent meta-analyses have confirmed that the additional use of trimetazidine in heart failure patients may yield a significant protective effect for all-cause mortality, cardiovascular events and hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously ameliorate left ventricular remodeling. Certainly, in order to clarify the exact therapeutic role of metabolic therapy in heart failure, a large multi-center randomized controlled trial should be performed.

Keywords: Carnitine palmitoyl transferase I; free fatty acid inhibitors; heart failure; left ventricular function; metabolic therapy; myocardial metabolism; trimetazidine

■ Heart Metab. (2012) 57:25–30

Introduction

Recent studies in patients with heart failure have investigated the possibility of increasing cardiac performance without affecting oxygen consumption and hemodynamics by agents aimed at enhancing myocardial energy efficiency. Most investigators have focused their efforts on agents that shift energy substrate utilization away from fatty acid metabolism and towards glucose metabolism, which is more efficient in terms of ATP production per mole of oxygen utilized. Of the latter pharmacological class, trimetazidine (Vastarel® MR) is the most investigated drug in the context of heart failure. Trimetazidine has been shown to affect myocardial substrate utilization by inhibiting fatty acid oxidation and by shifting energy production from free fatty acids (FFA) to glucose oxidation [1] (Fig. 1). By increasing utilization of glucose and lactate,

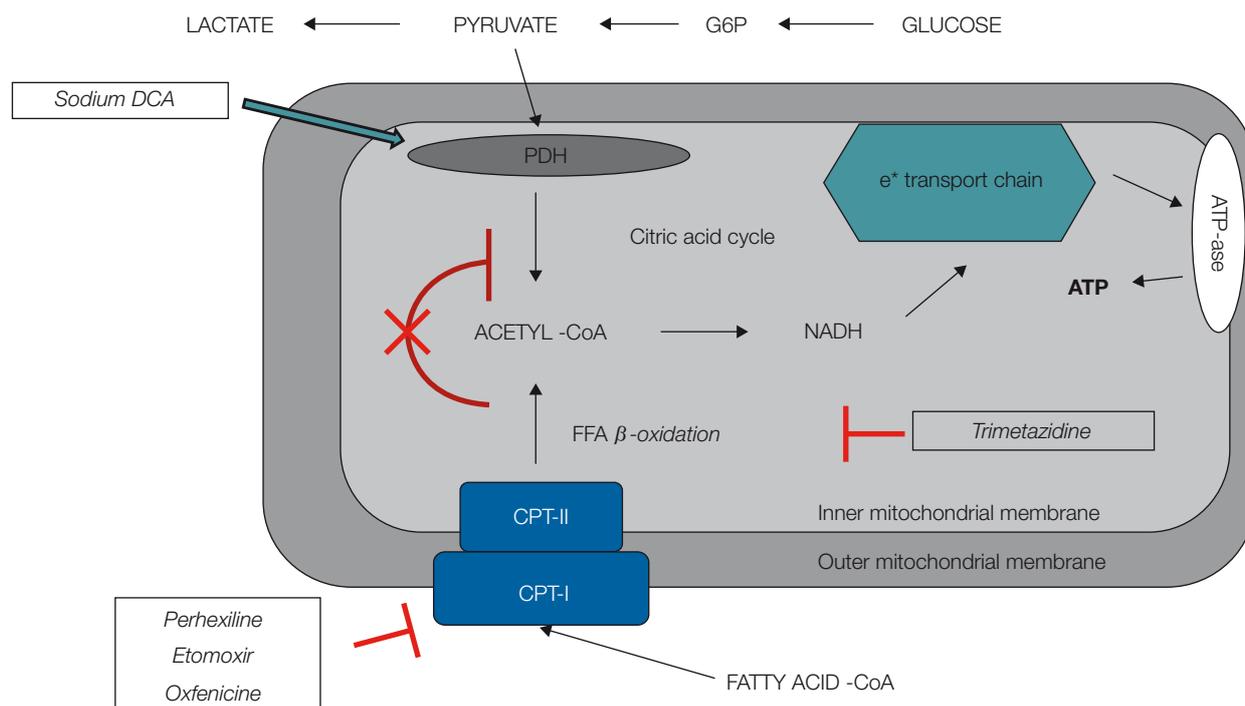


Fig. 1 The effects of metabolic agents on myocardial metabolism. Carbohydrate metabolism may be directly increased by agents such as sodium dichloroacetate, which stimulates pyruvate dehydrogenase (PDH) activity by inhibiting pyruvate dehydrogenase kinase. Stimulation of PDH activity leads to enhanced glycolysis of glucose and utilization of lactate by the myocardium for aerobic respiration. Myocardial consumption of free fatty acids (FFA) is simultaneously inhibited, with the overall effect of a change of substrate utilization from predominantly FFA to glucose and lactate. Perhexilline, oxfenicine, and etomoxir prevent the uptake of FFA by inhibiting carnitine palmitoyltransferase I, which is a key mitochondrial enzyme involved in this process. Trimetazidine inhibits β-oxidation of FFA. These actions shift myocardial substrate use from FFA to glucose, which is more efficient in terms of energy production, leading to an oxygen-sparing effect. CoA = coenzyme A, CPT = carnitine palmitoyltransferase, DCA = dichloroacetate, FA = fatty acid, G6P = glucose-6-phosphate.

which are more efficient fuels for aerobic respiration, the oxygen consumption efficiency of the myocardium can be improved by 16–26% [2].

The aim of this paper is to review the reported evidence on the protective effects of metabolic therapy, and its potential clinical application, in patients with heart failure.

Effects of metabolic modulation on left ventricular dysfunction

Based on the hypothesis that FFA inhibitors could act as metabolic modulators in the protection of ischemic myocardium, Brottier and colleagues [3] assessed the value of long-term treatment with trimetazidine in patients with severe ischemic cardiomyopathy. Twenty patients were randomly assigned to receive either placebo or trimetazidine. All patients on trimetazidine, at 6 months follow-up, reported a clinically considerable improvement in symptoms and showed a higher ejection fraction compared to patients on placebo. The authors concluded that their study recom-

mended the use of trimetazidine as a complementary therapeutic tool in patients with severe ischemic cardiomyopathy.

On this basis, the effects of trimetazidine on dobutamine-induced left ventricular dysfunction in patients with coronary artery disease were assessed [4]. Patients were randomly assigned to a 15-day treatment period with either placebo or trimetazidine. They were then crossed over to the other regimen for another 15 days. At the end of each treatment period, a stress echo with dobutamine was performed. Both in resting condition and at peak dobutamine infusion, the wall motion score index was significantly lower on trimetazidine therapy than on placebo. Furthermore, trimetazidine induced an increase in dobutamine infusion time and dose before the development of ischemia. These results indicated that trimetazidine may not only protect from dobutamine-induced ischemic dysfunction, but could also improve resting regional left ventricular function, as shown by the significantly decreased peak and resting wall motion score index during the active

treatment period. A subsequent study confirmed these preliminary results [5].

Modulation of myocardial metabolism in post-ischemic heart failure

By keeping in mind the concept that 3-ketoacyl coenzyme A thiolase inhibitors should, therefore, be able to promote the utilization of glucose and non fatty substrates by the mitochondria, attention was focused on heart failure, in which the maintenance of metabolic efficiency is a crucial issue.

The effects of the addition of trimetazidine to standard treatment of patients with diabetes, with ischemic dilated cardiomyopathy on symptoms, exercise tolerance and left ventricular function, were assessed [6]. Thirteen such patients on conventional therapy were randomly allocated to either placebo or trimetazidine, each arm lasting 15 days, and then again with placebo or trimetazidine for two additional 6-month periods. Both in the short and long terms, trimetazidine showed a significant beneficial effect on left ventricular function and control of symptoms, compared to placebo. The observed short-term trimetazidine benefit was maintained in the long term and contrasts with the natural history of the disease, as shown by the mild but consistent decrease in the ejection fraction when on placebo. These results paved the way to additional studies, which have invariably confirmed the positive effects of trimetazidine in patients with post-ischemic left ventricular dysfunction [7–11].

Modulation of myocardial metabolism in heart failure of different etiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to the preservation of phosphocreatine (PCr) and ATP intracellular levels [12]. The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on an imbalance of myocardial oxygen supply and demand [13], and a reduction of the total creatine pool, a phenomenon known to occur in heart failure [14]. In a recent study performed in patients with heart failure of different etiologies on full standard medical therapy, trimetazidine improved functional class and left ventricular function in association with an improvement of the PCr/ATP ratio, supporting the hypothesis that trimetazidine probably preserves myocardial high energy phosphate intracellular levels [15]. These results appear particu-

larly relevant, especially in view of previous evidence indicating that the PCr/ATP ratio is a significant predictor of mortality [16].

Based on the results of this pilot study, it has also been tested whether trimetazidine could also be beneficial in a more consistent group of patients with systolic dysfunction heart failure of different etiologies [17]. Compared to patients on conventional therapy alone, those on trimetazidine improved functional class, exercise tolerance, quality of life, left ventricular function and plasma B-type natriuretic peptide levels. These beneficial effects on left ventricular function could explain the subsequent observation of a potential anti-arrhythmic effect of trimetazidine in patients with post-ischemic heart failure [18].

Effects of metabolic therapy on whole-body energy metabolism of patients with heart failure

A higher resting metabolic rate has been observed in patients with heart failure [19–21], and this factor probably contributes to progressive worsening of the disease. The rate of energy expenditure is related to increased serum FFA oxidation, and both energy expenditure and serum FFA oxidation are inversely correlated with left ventricular ejection fraction and positively correlated with growth hormone (epinephrine and norepinephrine) concentrations [22]. Norepinephrine increases whole-body oxygen consumption, circulating FFA concentrations, and FFA oxidation [23]. These changes have been attributed to stimulation of hormone-sensitive lipase in adipose tissue, and to stimulation of oxygen consumption independent of lipolysis by norepinephrine [24]. These data, together with close correlations between plasma norepinephrine concentrations, energy expenditure at rest and FFA oxidation, make increased sympathetic activity the most likely explanation for alterations in fuel homeostasis in patients with heart failure [24]. Therefore, intervention strategies aimed at optimizing global and cardiac metabolism could be useful for interrupting the vicious circle of reduced function at greater metabolic expenses in different cardiac conditions [25]. In a very recent study, it has been shown that 3 months' treatment with trimetazidine added to usual treatment consistently reduces whole-body resting energy expenditure along with improved functional class, quality of life and left ventricular function in patients with systolic heart failure, regardless of its etiology and diabetic

status [26] (Fig. 2). The observation that the beneficial effect of trimetazidine on left ventricular function is also paralleled by a reduction in the whole-body rate of energy expenditure when compared to patients on conventional treatment underlies the possibility that the effect of trimetazidine may be mediated through a reduction of metabolic demand at the level of the peripheral tissues and, in turn, in some sort of central (cardiac) relief. Therefore, a reduction of whole-body energy demand could be one of the mechanisms by which trimetazidine could improve symptoms and left ventricular function in patients with heart failure.

Systematic literature search on the beneficial effect of trimetazidine in heart failure

A systematic literature search was recently conducted by Gao and colleagues [27] to identify randomised controlled trials of trimetazidine for heart failure. The results of the search identified 17 trials with data for 955 patients. Trimetazidine therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic and non-ischemic heart failure. With trimetazidine therapy, the New York Heart Association classification was also improved, as was exercise duration. More importantly, trimetazidine had a significant protective effect for all-

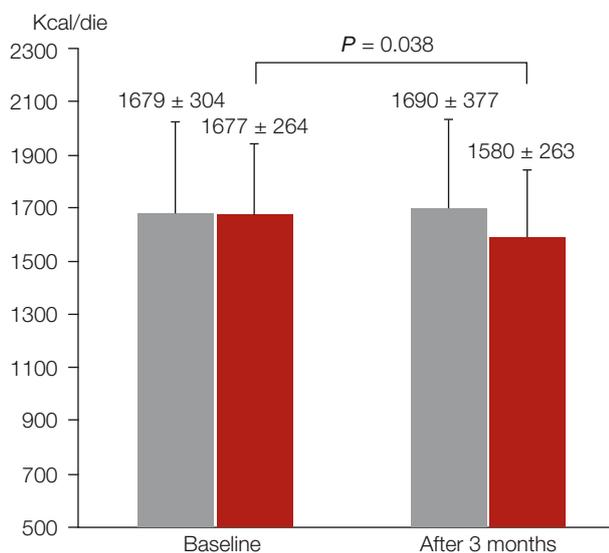


Fig. 2 The rate of energy expenditure in patients with heart failure at baseline and 3 months after receiving either conventional therapy alone (grey histograms) or conventional therapy and trimetazidine (red histograms). Adding trimetazidine to conventional heart failure therapy reduced the rate of energy expenditure of the whole organism (*P* = 0.038). Adapted with permission from Fragasso et al [26]. HF = heart failure, TMZ = trimetazidine.

cause mortality (RR 0.29, 95% CI 0.17 to 0.49; *P* < 0.00001) and cardiovascular events and hospitalization (RR 0.42, 95% CI 0.30 to 0.58; *P* < 0.00001).

Finally, a very recent meta-analysis has confirmed that additional use of trimetazidine in heart failure patients may decrease hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously ameliorate left ventricular remodeling [28].

Effects of metabolic modulation on left ventricular diastolic dysfunction

Both animal models of left ventricular pressure overload and clinical studies in humans with hypertension implicate abnormal myocardial metabolism in the development of left ventricular diastolic dysfunction. Myocardial fatty acid metabolism is also a key modulator of diastolic dysfunction [29–31]. It has recently been shown that in symptomatic hypertrophic cardiomyopathy, perhexiline, a modulator of substrate metabolism, ameliorates cardiac energetic impairment, corrects diastolic dysfunction, and increases exercise capacity [32]. Animal studies have shown that trimetazidine could also improve the function of pressure overload hypertrophied left [33] and right [34] hearts. These studies support the hypothesis that energy deficiency contributes to the pathophysiology and provides a rationale for further consideration of metabolic therapies in hypertrophic cardiomyopathy.

Another cardiac condition characterized by early diastolic involvement is the so-called diabetic cardiomyopathy. This is a condition characterized functionally by myocyte hypertrophy, prominent interstitial fibrosis and initially preserved systolic function in the presence of diastolic dysfunction. After a long latent phase, systolic dysfunction, left ventricular dilation and symptomatic heart failure usually ensue. Therefore, an optimal control of diabetes and frequently occurring comorbidities, such as hypertension, is advocated. On these grounds, it has recently been hypothesized that the early administration of a metabolic modulator such as trimetazidine may prevent or ameliorate diabetic cardiomyopathy [35]. This hypothesis is substantiated by the previous observation that trimetazidine may increase both insulin-induced forearm glucose oxidation and forearm cyclic-guanosine monophosphate release, with a decrease in forearm endothelin-1 release [36]. These ancillary effects of

trimetazidine could be particularly effective in preventing or ameliorating the cardiovascular complications of diabetes. Certainly, further studies aimed at evaluating the role of cardiac metabolic modulation in patients with diabetes are necessary.

Conclusions

Metabolic therapy could play an important role in the therapeutic strategy of patients with heart failure. At present trimetazidine, a partial FFA oxidation inhibitor, appears to be the most promising agent for the metabolic approach to heart failure. Although highly suggestive, whether the observed benefits would translate into improved survival should be ascertained by multicenter trials. The time has come to test this potentially huge therapeutic advance in heart failure syndromes, which still have very high morbidity and mortality rates. •

Acknowledgments The authors would like to thank Associazione per la Ricerca e la Terapia dello Scompenso Cardiaco (ARTS) for continuous financial support of their research projects.

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Acute shortness of breath and chest tightness in an elderly patient: clinical history tells it best!

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Abstract

Almost 50% of patients presenting with heart failure have no systolic left ventricular dysfunction and thus are diagnosed with diastolic heart failure (HF). Diastolic HF reflects an increased sensitivity to volume status and vasoreactivity of patients with underlying diastolic dysfunction, a condition commonly observed in elderly patients with numerous comorbidities. In this case report, an example of the diagnostic and therapeutic challenges in a patient with diastolic HF is illustrated. Indeed, while defined international guidelines are available for patients with systolic HF, the management of diastolic HF patients is less well defined and largely dependent on patients' characteristics.

Keywords: Comorbidities; comprehensive evaluation; diastolic dysfunction; diastolic heart failure; non invasive assessment.

■ Heart Metab. (2012) 57:31–33

Case report

A 78-year-old woman was admitted to our clinic for evaluation of acute shortness of breath and chest tightness. She had a history of hypertension, diabetes and mild chronic renal insufficiency, with no previous ischemic heart disease or pulmonary disease. In the last few months before admission the patient reported a history of accidental trauma resulting in chronic lumbosacral pain that she had been managing with non steroidal anti-inflammatory drugs. Her medical history was unremarkable for other pathological conditions.

On physical examination she presented with increased jugular venous pressure, peripheral edema (1+) and blood pressure levels of 195/110 mmHg. Arterial oxygen saturation was 88% on a 100% non rebreather mask. The heart rate was regular at 93 beats/min. On lung auscultation there were rales at the bases, and cardiac examination revealed a normal S1 and S2 with an early peaking systolic ejection murmur (2/6 L), but no S3. The abdomen was tender and there were no bruits or palpable masses. The 12-lead electrocardiogram showed normal sinus rhythm and diffuse non specific ST-T segment changes. On chest X-ray there were signs of pulmonary congestion, with no signs of cardiomegaly (Fig. 1). An echocardiogram revealed mild left ventricular hypertrophy with preserved dimensions and ejection fraction (63%), increased left atrium dimensions with only mild mitral insufficiency and no other valve



Fig. 1 The chest X-ray shows pulmonary venous congestion with normal cardiac profile.

dysfunction. There was an abnormal ventricular Doppler filling pattern with elevated peak E-velocity, short E-deceleration time and a markedly increased E/A ratio, reduced E' velocity of tissue Doppler images, increased E/E' ratio (>16) and reverse S/D ratio, all findings consistent with elevated pulmonary-capillary wedge pressure. Blood tests documented increased brain natriuretic peptide (960 pg/mL) and creatinine levels (2.4 mg/dL), with almost normal troponin I, creatine phosphokinase and myoglobin levels.

Discussion

According to major international guidelines, heart failure (HF) is a syndrome in which patients have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest [1, 3].

Although there was no direct evidence of structural abnormalities of the heart, the described is clearly a case of HF (symptoms and objective findings of HF). In addition, there was indirect evidence (left atrium enlargement, altered Doppler indices) of increased pulmonary-capillary wedge pressure, which could justify the clinical presentation.

Diastolic dysfunction refers to an abnormal distensibility and/or relaxation of the left ventricle that can

take place regardless of the overall left ventricular systolic function. The condition is now recognized as a common cause of HF, perhaps representing up to 50% of all HF patients, with a similar dire prognosis [3]. Diastolic dysfunction can be diagnosed through the identification of abnormalities in diastolic filling pattern, commonly assessed with non invasive Doppler techniques. Diastolic HF (or HF with preserved systolic function) reflects an increased sensitivity to volume status and vasoreactivity [4]. Therefore, hypertensive episodes due to labile hypertension, medical and dietary non compliance, non steroidal anti-inflammatory drugs, atrial fibrillation, ischemia, or iatrogenic volume overload are all conditions known to precipitate acute HF in this patient population. In addition, there is a remarkable female predominance [5], and as compared to systolic HF, a relative increase in the hospitalization rate [6].

The diagnostic flowchart of patients with diastolic HF is similar to that of patients with systolic HF, and includes a complete blood count, urinalysis, serum electrolytes, glycohemoglobin and blood lipids, as well as tests of both renal and hepatic function, a chest radiograph, a 12-lead electrocardiogram and echocardiographic evaluation; elevated levels of natriuretic peptides lend additional support to the diagnosis [7]. However, the diagnosis of diastolic HF is basically based on the exclusion of a systolic abnormality of left ventricular function. The presence of high left ventricular filling pressures is accurately assessed by invasive hemodynamic evaluation, which represents the gold standard method. However, in clinical practice, invasive assessment is difficult to apply, and filling pressures are commonly extrapolated from combined echocardiographic parameters and natriuretic peptides levels.

Our patient did not have systolic dysfunction, whereas Doppler indices and blood tests suggested a diagnosis of acute HF with preserved ejection fraction, probably secondary to acute renal injury.

Implementation of the therapeutic strategy represents another challenge in diastolic HF. Indeed, despite its clinical and epidemiological significance, treatment of diastolic HF remains largely empirical and not evidence based. The few available clinical trials only evaluated the effectiveness of renin-angiotensin system inhibitors, with none showing survival benefit [8-10]. Even less is known about the therapeutic

benefits of β -blockers and diuretics, and the lack of evidence appears secondary to the numerous associated comorbidities that are major contributors to clinical outcomes in this patient population [11,12].

Following the identification of a worsening renal function with fluid retention as a possible precipitation factor, our patient was treated with intravenous diuretics and fluids, as well as continuous oxygen support through a non rebreather mask, obtaining rapid improvement of the clinical status. On day 2 after admission, brain natriuretic peptide and creatinine levels were 195 pg/mL and 1.5 mg/dL, respectively, and blood pressure levels were normal. Furthermore, care was taken to optimize the discharge therapy allowing for an optimal 24 hours blood pressure control and renal protection by adjusting angiotensin converting enzyme inhibitor and diuretic dosages. The patient was also advised to limit non steroidal anti-inflammatory drugs and encouraged to perform regular exercise training, a measurement that appears to confer benefit in terms of enhancements in exercise capacity and health-related quality of life [13].

Conclusion

As previously mentioned, no specific treatment regimens have been shown to benefit diastolic HF patients, and treatment will often be multifactorial and individualized to each patient. Currently, many studies (in vitro and animal) are assessing the effects of several growth factors, cytokines and signaling molecules that have been shown to reverse myocardial fibrosis, a determinant factor for increased ventricular stiffness and diastolic dysfunction [14]. However, we are still far from adopting these new therapeutic agents. Until more progress is made in this area, treatment of precipitating factors (ie, aggressive blood pressure control by restricting salt intake and administration of diuretics, thus enhancing renal function; maintenance of sinus rhythm to preserve atrial contraction and heart rate control to improve diastolic function; and treatment of underlying comorbidities, using an integrated and multidisciplinary approach) appears the most effective strategy to reduce morbidity and hospitalization in this patient population. •

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How the heart relaxes

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Abstract

Normal functioning of the heart is dependent on its ability both to contract and relax. Heart contraction is a complex process that is initiated by an increase in intracellular calcium, which results in myosin binding to actin and myosin movement of the actin filament. Relaxation is reliant on removal of calcium from the contractile filaments, which in turn is dependent on the availability of ATP. If the heart does not relax properly, it cannot fill with blood during diastole, which subsequently compromises its ability to pump sufficient quantities of blood to the body. The inability of the heart to relax properly can cause heart failure. Therefore, reduced ATP levels such as are observed in heart failure may contribute to impairments in heart diastolic function. This paper reviews the mechanism of cardiac muscle contraction and relaxation as well as the role of relaxation in heart disease.

Keywords: Calcium; diastole; sarcomere; sarcoplasmic reticulum

■ Heart Metab. (2012) 57:34–37

Introduction

The heart's ability to contract and relax appropriately is essential. Contraction of the heart, termed systole, is responsible for pushing the blood out of the chambers of the heart. Diastole, relaxation of the heart, allows the chambers of the heart to fill with blood. Therefore, both diastole and systole are equally necessary for the heart to function properly.

Contraction and relaxation of cardiac muscle is a complex process. At the subcellular level it involves binding of myosin to actin followed by movement of the myosin head, which moves actin causing the cell to contract (Fig. 1). Initial contraction of the heart muscle is stimulated by a rise in intracellular calcium (Fig. 2) [1]. Alterations in the regulation of calcium release and uptake, or alterations in the response of the contractile proteins to calcium, can lead to arrhythmias and contractile dysfunction [1, 2]. Initiation of calcium uptake by the cardiomyocyte is triggered by action potentials that cause calcium channels on the cell membrane to open. The influx of calcium activates the ryanodine receptor allowing calcium in the sarcoplasmic reticulum (SR) to be released, a process referred to as calcium-induced calcium release [1]. Calcium then binds to troponin causing it to move, which then exposes the myosin binding site on actin. The myosin head can now bind to its site on actin. Upon binding, the myosin head cocks back, pulling the contractile filament inward. Relaxation is reliant on intracellular calcium levels returning to normal [1] and the availability of ATP, which is necessary for myosin to release from actin [3].

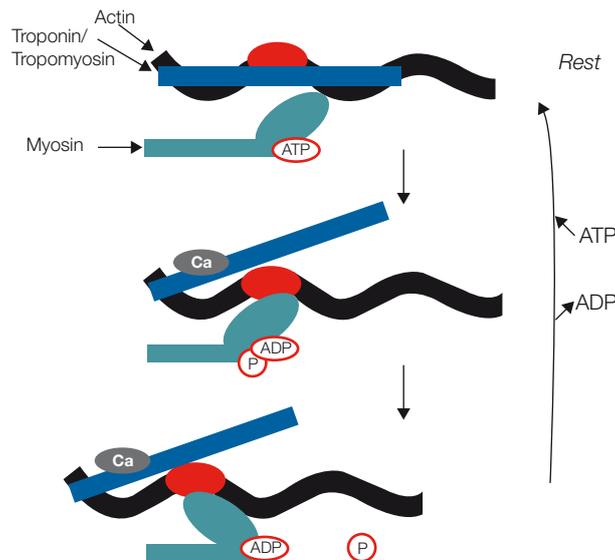


Fig. 1 Myosin and actin involvement in cardiac muscle contraction and relaxation: As a result of the rise in calcium caused by an action potential, calcium binds to troponin C, which in turn moves the troponin/tropomyosin complex from blocking the myosin binding site on actin. Myosin then interacts with actin. Release of the phosphate from hydrolysis of the ATP on myosin produces the energy required for the cocking of the myosin head, which moves actin, a process referred to as contraction. In order for myosin to release from actin, resulting in relaxation, the ADP bound to myosin must be replaced with ATP. When the intracellular calcium levels return to normal the troponin C is no longer bound by calcium and the troponin/tropomyosin complex can once again block the myosin binding site on actin.

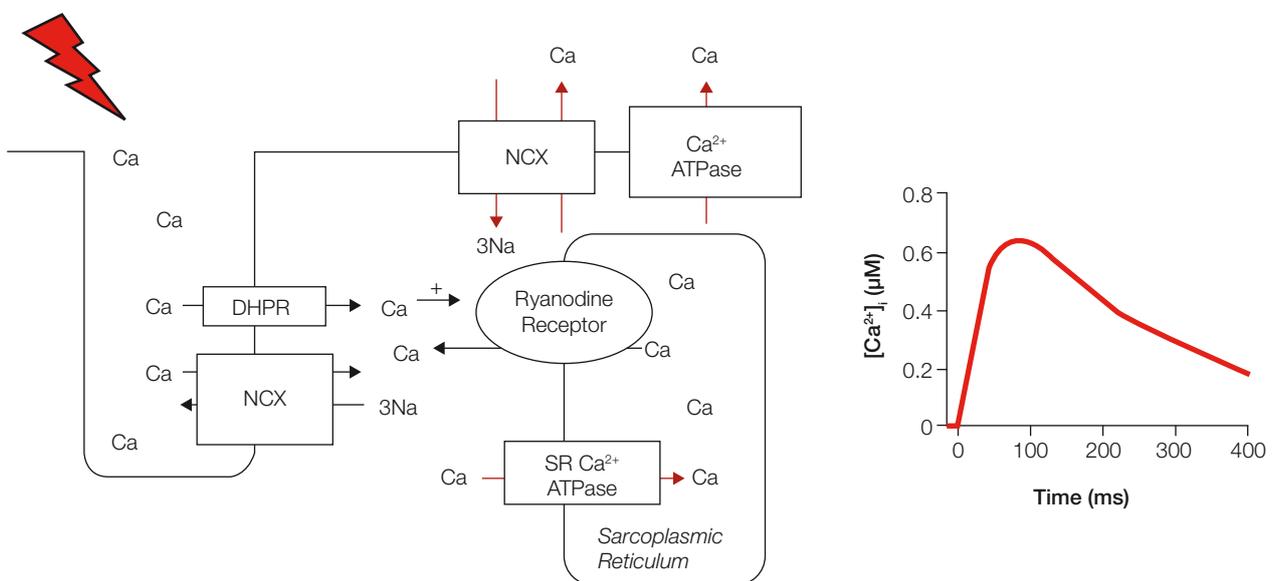


Fig. 2 Calcium handling in cardiac muscle contraction and relaxation +. In cardiac muscle, an action potential activates the dihydropyridine receptors (DHPR) and sodium/calcium exchanger (NCX), which causes the initial rise in intracellular calcium. This small increase in calcium stimulates the ryanodine receptor, which transports calcium from the sarcoplasmic reticulum (SR) into the cytosol. Once the calcium reaches a certain level, calcium transporters including SR Ca²⁺-ATPase, sarcoplasmic Ca²⁺-ATPase, and NCX start pumping calcium either back into the SR or out of the cell. Cytoplasmic calcium level must drop in order for the cell to relax and for subsequent action potentials to stimulate cardiomyocyte contraction appropriately. The graph represents the change in intracellular Ca²⁺ ([Ca²⁺]_i) during the process of contraction and relaxation.

Mechanism of cardiac muscle contraction and relaxation

Myosin and actin

The binding of myosin to actin, cocking of the myosin head, and release of the myosin head from its binding site on actin (relaxation) is dependent on both calcium and ATP. The first step involves calcium binding to troponin C causing exposure of the myosin binding site on actin by troponin C moving the troponin I/tropomyosin complex off the myosin binding site (Fig. 1) [3, 4]. The energy necessary for the myosin head to cock comes from the ATP bound to myosin being dephosphorylated to ADP and the phosphate group being released [3]. The cocked myosin head releases from actin once the ADP is replaced by ATP [3]. This process repeats itself once ATP is hydrolyzed again to ADP (assuming the calcium is still bound to troponin C), thereby relieving inhibition by troponin/tropomyosin [3]. If ATP is not available to replace the hydrolyzed ADP on myosin the heart does not relax and would stay in the contracted state despite intracellular calcium levels returning to normal.

In order for the heart to relax cytoplasmic calcium levels must drop down to very low levels. This is achieved by a number of processes, including the SR calcium ATPase (which pumps the calcium back into the SR), the sodium/calcium exchanger (which normally exchanges intracellular calcium for extracellular sodium), and the sarcolemmal calcium ATPase pump (which pumps calcium out of the cell) [1]. The return of cytoplasmic calcium levels back to low levels results in calcium releasing from its troponin binding site, resulting in a conformational change in troponin/tropomyosin, such that it blocks the myosin binding site on actin, resulting in subsequent relaxation of the heart.

Calcium handling during contraction and relaxation

Alterations in cytoplasmic calcium levels is not only required for cardiac muscle contraction but also for muscle relaxation. Action potentials cause activation of the depolarization activated calcium channels including dihydropyridine receptors (DHPR) on the cardiomyocyte cell membrane, causing an influx of calcium into the cell (Fig. 2) [1]. This increase in calcium activates ryanodine receptors causing a much larger release of calcium from the SR [1]. Once the calcium reaches a high enough intracellular level, calcium binds to troponin C [1]. Calcium binding to troponin C

relieves troponin C inhibition of myosin binding to actin [1]. Half maximal cardiac contraction requires an intracellular calcium concentration of 600 nM [1]. There are a few types of calcium channels involved in the process of cardiomyocyte contraction. These include voltage-dependent calcium channels, which are activated by the action potential and are responsible for the initial influx of calcium, and either transient (T-type) or long acting (L-type) calcium channel, also called DHPR [1]. The rise in calcium due to release of calcium from the SR calcium inactivates DHPR and the ryanodine receptors, contributing to the initiation of cardiomyocyte relaxation [1, 5].

Relaxation of the heart also involves the regulation of intracellular calcium levels. In the rabbit ventricular cardiomyocyte 70% of the calcium is pumped out by the SR Ca^{2+} -ATPase, 28% is pumped out by the sodium/calcium exchanger, 1% by the mitochondrial uniporter, and 1% by the sarcolemmal calcium ATPase [1]. The SR Ca^{2+} -ATPase is negatively regulated by SR phospholamban. Phospholamban inhibition is reduced by phospholamban being phosphorylated by protein kinase A or calmodulin-dependent protein kinase II resulting in decreased time to relaxation [1, 6]. In order for the cell to relax, the calcium levels must drop low enough so that troponin C is no longer bound by calcium. Once the ADP on myosin is replaced by ATP, it allows myosin to dissociate from actin, the troponin/tropomyosin complex can again block the myosin binding site on actin.

Heart failure and energy metabolism

Impairment in the ability of the heart to produce ATP can lead to impaired heart function. ATP content in the failing heart can decrease to 60–70% of levels seen under normal conditions [7–10]. As heart failure progresses, cardiac mitochondrial oxidative capacity tends to decrease along with elevation in glycolysis and glucose uptake [7–11]. Not only is there a shift towards metabolic pathways that produce less ATP, but there is an increase in glycolysis uncoupled from glucose oxidation, which results in the consumption of ATP to maintain sodium and calcium at normal levels (ions that rise as the protons produced as a result of uncoupled glycolysis are transported out of the cell) [11–13]. As mentioned earlier, ATP is required for heart relaxation both for returning calcium levels to normal and for myosin to release from actin. Therefore,

lower ATP levels could impair the ability of contraction to end and contribute to cardiac dysfunction.

Changes in energy metabolism observed in heart failure can be caused by an increase in circulating fatty acids [11]. Fatty acids reduce both the efficiency with which ATP is produced and utilized in the cardiomyocyte. For example, fatty acid oxidation inhibits glucose oxidation (Randle cycle), switching the source of ATP from glucose towards a less efficient source of ATP production (ie, fatty acid oxidation) [11]. For example, the oxidation of palmitate requires 23 O₂ to produce 104 ATP, while 6 O₂ are used in glucose oxidation to generate 31 ATP [4]. In addition, fatty acids cause ATP to be used less efficiently. Many of these mechanisms involve the uncoupling proteins (UCP) 2 and 3 and are related to the finding that UCP2 and UCP3 protein expression is elevated in the failing heart [14]. For example, increased expression of UCP3, which can transport fatty acid anions out of the mitochondrial matrix, would elevate the amount of ATP wasted in transporting fatty acids into the mitochondria [13, 15].

ATP is also necessary for the function of certain ATP-dependent co-transporters and calcium channels necessary for heart relaxation. One such transporter is the Na⁺/K⁺-ATPase, which by pumping three sodium molecules out and two potassium molecules into the cell prevents a rise in intracellular sodium caused by the Na⁺/Ca²⁺ exchanger contributing to relaxation of the cardiomyocyte [11, 16]. In addition, if the activity of the SR Ca²⁺-ATPase is impaired calcium overload occurs, which would impair heart relaxation [11].

Conclusion

The ability of the heart to relax and fill with blood is vital to its ability to function properly as a pump. Alterations in relaxation can lead to an inability to pump enough blood to the body, which can potentially lead to heart failure. Causes of impaired heart relaxation can include insufficient supply of ATP and/or failure to remove calcium appropriately from the cytoplasm following the initiation of contraction. In the future, metabolic modulation may be used to increase ATP levels in diastolic heart failure resulting in an improvement of diastolic function. •

Acknowledgments GDL is a scientist of the Alberta Heritage Foundation for Medical Research. NF holds a Motyl student-ship award

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The undisputed principles of myocardial ischemia!

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Advances in research have allowed for the construction of algorithms that assist physicians in the management of patients with suspected heart disease. Among heart problems, ischemic heart disease (IHD) represents the most frequent clinical presentation, and algorithms for patients presenting with chest pain are consequently those that have gained major attention [1]. Such algorithms are based on the pathophysiological principles that cardiac pain is an expression of myocardial ischemia, which becomes clinically manifest when the lumen of the coronary arteries is reduced beyond a critical level, a phenomenon mainly secondary to coronary atherosclerotic obstructions. Therefore, it is not surprising that ruling out obstructive coronary artery disease (CAD), the ultimate culprit element derived from this chain cause-effective relationship, is a fundamental step in the stepwise evaluation of patients with chest pain.

Identification of patients with obstructive CAD has encountered progressive evolution. The likelihood of obstructive CAD in the individual patient was initially estimated through the construction of models composed of a number of clinical risk factors [2]. More recently CAD has been non-invasively assessed by numerous methods, in this way promoting a new era in cardiovascular medicine.

However, contrary to expectations, the predictive ability for obstructive CAD still remains low [3]. Moreover, a mismatch between coronary physiology and anatomy has also been demonstrated. Nonetheless, the later phenomenon appears not to bother researchers, who continue undisturbed their search for the “best” technique. In line with these considerations, four recently published studies independently sought to demonstrate the ability of their tested methodology to identify mechanism(s) or prediction model(s) of CAD.

The study by Reszko et al [4], involving 14 048 consecutive patients with suspected CAD who underwent computed tomographic angiography (CTA), found that the traditional approach (age, sex and angina typicality based) greatly overestimates the prevalence of disease (coronary atherosclerosis). However, a significant number of patients with CAD had no symptoms of angina and, on the other hand, nearly as many patients with angina had no detectable CAD.

The discrepancy between anatomical severity and clinical findings has been related to the physiological effects that the individual CAD obstruction exerts on the myocardial perfusion territory. Naya et al [5] sought to determine the effects that the morphology and extent of coronary atherosclerosis (assessed by CTA) exert on myocardial flow reserve (MFR) (evaluated by positron emission tomography). The authors found that the description of atherosclerosis by CTA had only a modest effect on downstream MFR. Indeed, the severity of stenosis did not

reliably predict physiological myocardial blood flow effects. More specifically, while patients with 0% stenosis diameter or a zero summed stenosis score by CTA may have a MFR ranging from 1 to 5, on the other hand those patients with 70% or greater stenosis diameter or a higher summed stenosis score may present with normal MFR. Given that CTA has a very high negative predictive value for CAD, what is the cause of reduced MFR in patients with no documentable CAD? Moreover, in light of these findings, is there any reason to believe that the exclusion of visible CAD is a fundamental step in the stepwise evaluation of patients with suspected heart disease? On the other hand, does the documentation of obstructive CAD automatically authorize us to assume that this is the underlying cause of the symptoms?

To shed further light on this topic, Kang et al [6] assessed the value of intravascular ultrasound (IVUS) in predicting the functional significance of intermediate coronary lesions. In that study, 201 patients with 236 coronary lesions underwent IVUS and invasive physiological assessment with fractional flow reserve (FFR) before intervention. The authors identified an IVUS minimal lumen area (MLA) of 2.4 mm² or greater as a cutoff with a high predictive value for an FFR of 0.80 or greater. However, 63% of lesions with an MLA less than 2.4 mm² had an FFR of 0.80 or greater, and the results were similar when other IVUS measured parameters were related to FFR, in this way once again questioning the reliability of atherosclerotic obstructions as a cause of myocardial ischemia.

Similar results were also obtained in acute settings. Reynolds et al [7] studied the mechanism(s) of myocardial infarction (MI) in 50 women with no angiographically demonstrable obstructive CAD by using IVUS and cardiac magnetic resonance (CMR). Plaque disruption (rupture or ulceration) by IVUS was demonstrated in 38%, and abnormal CMR findings were documented in 59%. The authors concluded that plaque rupture and ulceration with CMR abnormalities are common in women with MI without angiographically demonstra-

ble obstructive CAD. Both IVUS and CMR play a significant role in the evaluation of this patient subset providing complementary mechanistic insights. However, if the results of that study are analyzed critically, the message emerging from adopting these high quality imaging modalities is that, currently, we are not able to detect the mechanism of MI in the vast majority of patients with no obstructive CAD (ie, 62% of patients). Moreover, plaque distribution was not related to the presence of left ventricular wall motion abnormalities or ECG changes. Given these observations, is there any evidence to suggest that a similar pattern does not affect vessels with angiographically significant obstructions?

The incremental value of the single technique tested is indubitable. However, at the moment, while the disease (ie, MI) can be diagnosed reliably, the underlying mechanism(s), the ones we thought we already knew, remain(s) unknown in the vast majority of patients.

Has the time for questioning fundamental pathophysiological postulations arrived yet? •

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Hypoxia

Hypoxia is a pathophysiological state characterized by decreased oxygen content in inspired air and/or blood that ultimately decreases oxygen delivery to metabolising tissues of the body despite adequate perfusion/blood flow.

Inflammation

Inflammation is the normal response to stimuli including physical (e.g. physical injury) and chemical stresses (e.g. foreign substances in the body) that elicit cellular damage. The inflammatory process is characterized by distinct phases including initiation, the recruitment of cellular mediators, and the release of inflammatory mediators, and contributes to tissue repair following injury. An inappropriate and/or prolonged inflammatory response that is not self-limiting can contribute to cellular damage.

Viability

Viability, at the tissue level, is the ability of parenchymal cells to withstand a pathological insult, and subsequently survive and maintain normal-to-near normal function.

Edema

Edema is the excess extravasation into, and hence accumulation of fluid in the interstitial/extracellular space.

Chemokines

Chemokines are small protein cytokines secreted by cells that induce chemotaxis (migration towards chemicals in the nearby environment) of neighbouring responsive cells.

Adhesion molecules

Adhesion molecules are cell surface proteins that bind other cells or the extracellular matrix during the process of cellular adhesion.

Growth factors

Growth factors are primarily proteins or steroid hormones that can stimulate cellular proliferation, growth, and/or differentiation. They are usually essential signalling molecules involved in the differentiation and maturation of cells (ie. preadipocyte to adipocyte). •