Differentiating diastolic dysfunction from classic heart failure

Jagdip S. Jaswal1 and John R. Ussher2, 1Cardiovascular Research Centre, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada, 2Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Canada

Correspondence: Dr Jagdip Jaswal, 4–23 HMRC, University of Alberta, Edmonton, Alberta, Canada T6G2S2. Tel: +1 780 2481162, fax: +1 780 4929753 e-mail: jjaswal@ualberta.ca

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

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 (i.e., 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 (i.e., 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...
Indicative of increased ventricular volumes), decreased stroke work (area inside the pressure volume loop) and a 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.

**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...
dysfunctional 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

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

References