Murine Models of Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Left ventricular diastolic dysfunction leads to heart failure with preserved ejection fraction, an increasingly prevalent condition largely driven by modern day lifestyle risk factors. As heart failure with preserved ejection fraction accounts for almost one-half of all patients with heart failure, appropriate nonhuman animal models are required to improve our understanding of the pathophysiology of this syndrome and to provide a platform for preclinical investigation of potential therapies. Hypertension, obesity, and diabetes are major risk factors for diastolic dysfunction and heart failure with preserved ejection fraction. This review focuses on murine models reflecting this disease continuum driven by the aforementioned common risk factors. We describe various models of diastolic dysfunction and highlight models of heart failure with preserved ejection fraction reported in the literature. Strengths and weaknesses of the different models are discussed to provide an aid to translational scientists when selecting an appropriate model. We also bring attention to the fact that heart failure with preserved ejection fraction is difficult to diagnose in animal models and that, therefore, there is a paucity of well described animal models of this increasingly important condition. (*J Cardiac Fail 2014;20:984–995*)

Key Words: Animal models, diastolic dysfunction, heart failure with preserved ejection fraction (HFpEF), hypertension, diabetes and obesity.

The prevalence of left ventricular (LV) diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) is rising. More and more, physicians are confronted by this spectrum of disease largely because of aging populations, the obesity epidemic in conjunction with a rise in the incidence of diabetes, and poorly controlled hypertension.[1–3] The heart failure (HF) guidelines of both the American College of Cardiology Foundation/American Heart Association and the European Society of Cardiology indicate that no treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF.[4,5] Recent large clinical trials using standard therapies for HF with reduced ejection fraction have failed to demonstrate improvement, emphasizing differences in the underlying pathophysiology of diastolic dysfunction.[6–9] Almost one-half of all patients with HF have HFpEF, underscoring the requirement for appropriate nonhuman animal models that reflect the pathophysiology of this increasingly important condition.[10]

Although there is still no criterion-standard definition for HFpEF, recent guidelines indicate that 4 conditions are required to diagnose this disease: [1] symptoms typical of HF, [2] signs typical of HF, [3] normal or only mildly reduced EF (>40%) with no LV dilation, and [4] relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction.[4,5] Normal diastolic function is characterized by adequate filling of the ventricles during rest and exercise without an abnormal increase in diastolic pressures.[11] The initial lusitropic event is myocardial relaxation, an energy-dependent event that causes a rapid decrease in LV pressure after the end of contraction (systole). This is also known as isovolumetric relaxation (Fig. 1). When LV pressure falls below left atrial pressure, the mitral valve opens and the next phase of diastole begins: early diastolic filling. The majority (~80%) of LV filling occurs during this phase. The final phase of diastole is accounted for by atrial contraction, which represents late diastolic filling. Diastolic dysfunction

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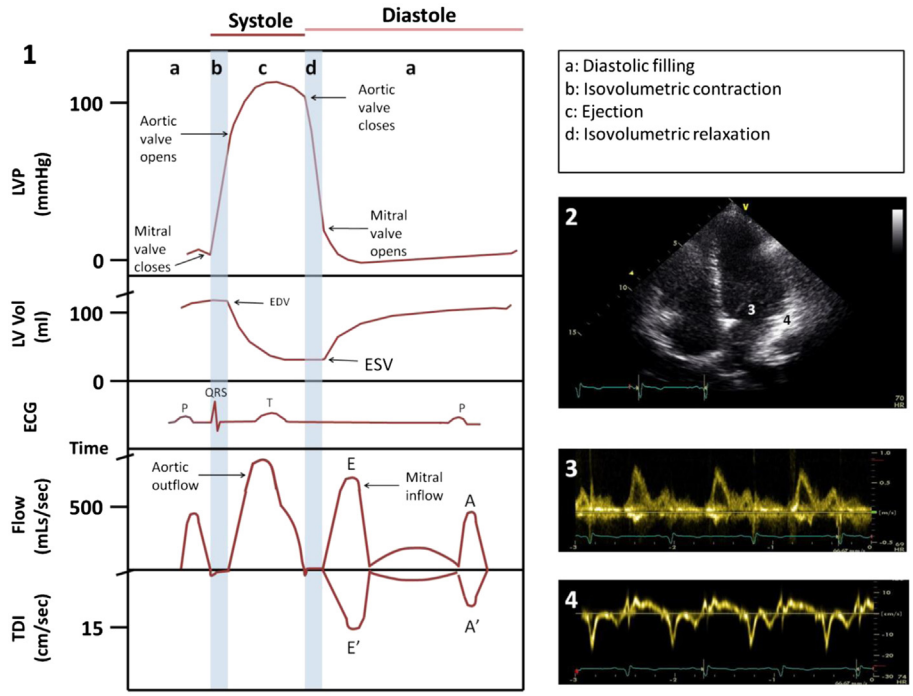

Fig. 1. Hemodynamic and echocardiographic measurements of left ventricular diastolic function. (1) Diagram demonstrating the hemodynamic events during the cardiac cycle. Intracardiac pressures, volumetric changes, aortic outflow, and mitral inflow are illustrated. The invasive measures dP/dt and −dP/dt correspond to isovolumetric contraction (b) and isovolumetric relaxation (d), respectively. LVP, left ventricular pressure; LV Vol, left ventricular volume; ECG, electrocardiogram; TDI, tissue Doppler imaging; EDV, end-diastolic volume; ESV, end-systolic volume. (2−4) Transthoracic echocardiographic images showing the apical 4-chamber view and the positions for sample placement when measuring (3) mitral inflow with the use of pulsed-wave Doppler and (4) mitral annulus velocity with the use of tissue Doppler. E, early passive filling; A, atrial contraction measured with pulsed-wave Doppler; E′, early passive filling; A′, atrial contraction measured with tissue Doppler.

describes an abnormal mechanical property of the LV that results in functional abnormalities during LV relaxation and filling. Diastolic dysfunction can occur in the presence or absence of a clinical syndrome of HF and with normal or abnormal LV systolic properties. Excessive fibrosis in the cardiac interstitium and hypertrophy leads to reduced compliance, or increased stiffness, of the LV and consequently diastolic dysfunction.[12−14] The basic pathophysiologic abnormality in HFpEF is impaired ventricular relaxation and compliance which leads to an alteration in the pressure-volume relationship within the ventricle, predisposing to high filling pressures, which results in the signs and symptoms of HFpEF.[15] Pathologic hypertrophy with diastolic dysfunction is the hallmark feature of HFpEF, in which the fundamental problem is the inability of the LV to relax and accommodate blood volume during diastole at low filling pressures.

Diastolic function can be assessed by invasive and noninvasive techniques. Invasive methods typically involve pressure and conductance catheters placed retrogradely in the LV via arterial access. Chamber relaxation is measured with the use of a pressure or micromanometer catheter, whereas for chamber compliance (or its inverse stiffness) this is best achieved by combining this pressure catheter with a measurement of instantaneous volume from a conductance catheter, with the use of data from multiple cycles.[16] Measurements generally acquired from pressure-volume curves include LV end-diastolic pressure (LVEDP) dP/dt, −dP/dt, and tau (Table 1; Fig. 1). Echocardiographic Doppler modalities provide a means to noninvasively evaluate diastolic dysfunction by assessing mitral inflow velocities, tissue Doppler, and pulmonary venous velocities (Table 1; Fig. 1).

The purpose of the present review is to describe murine models that reflect conditions resulting in diastolic dysfunction and/or HFpEF and to provide an aid to the basic or translational scientist when choosing such an animal model.

Models

Nonhuman animal models of HFpEF are scarce, leading to the utilization of diastolic dysfunction models, that are more widely published and similar regarding the basic pathophysiologic mechanisms.[17] Representative murine models can be divided into groups according to HFpEF risk factors, including hypertension, diabetes/obesity, and age. Although transgenic models are also described, there is little in the literature exploring ischemic diastolic dysfunction/HFpEF models. Table 2 outlines the various models in each group described in this review. Unless otherwise stated, LV hypertrophy and/or mass were determined with the use of echocardiographic measurements and myocardial fibrosis was