Left Ventricular Stiffening as Therapeutic Target for Heart Failure With Preserved Ejection Fraction

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The high prevalence of patients with heart failure (HF) with preserved ejection fraction (HFpEF) has highlighted the pivotal role of diastolic function in the development of HF. Abnormalities of diastolic function induce elevated left ventricular (LV) end-diastolic pressure, which leads to pulmonary edema and the symptoms of HF because the LV, left atrium and the pulmonary veins form 1 chamber while the mitral valve is opening. Thus, LV diastolic dysfunction results in the development of HF, in particular, HFpEF. LV stiffness mainly contributes to the transition to HFpEF, but noninvasive assessment and the therapeutic strategy for LV stiffness have not been fully established. This review will focus on the contribution of LV passive stiffness to the development of HFpEF and on the evaluation and treatment of LV stiffening based on insights gained from a hypertensive HFpEF animal model we have developed. (Circ J 2013; 77: 886–892)

Key Words: Diastolic dysfunction; Heart failure; Ventricular function

Heart failure (HF) is a syndrome in which the patient has the following signs and/or symptoms: shortness of breath typically at rest or during exertion; fatigue; fluid retention such as pulmonary congestion or peripheral edema; and objective evidence of an abnormality of the structure or function of the heart. These signs and symptoms are usually secondary to the abnormality of cardiac input (ventricular filling in diastole) and/or cardiac output (ventricular systolic ejection), both of which are dependent on cardiac function. The high prevalence of patients with HF with preserved ejection fraction (HFpEF) has highlighted the important role of diastolic dysfunction in the development of HF. In addition, diastolic dysfunction assessed by changes in the features of ventricular filling is common and associated with exercise tolerance or poor prognosis, particularly in advanced HF with reduced EF (HFrEF).  

Diastolic function is mainly determined by active relaxation and LV passive stiffness. This review will focus on the contribution of LV passive stiffness to the development of HFpEF and on the evaluation and treatment of LV stiffening based on insights gained from a hypertensive HFpEF animal model we have developed.

Role of LV Stiffness in the Development of HFpEF

Abnormalities of diastolic function induce the elevation of LV end-diastolic pressure (LVEDP), which leads to pulmonary edema and the symptoms of HF because the LV, left atrium and the pulmonary veins form 1 chamber while the mitral valve is opening. Thus, LV diastolic dysfunction results in the development of HF, in particular, HFpEF.

Diastole has 4 dynamic phases: isovolumetric relaxation of the contracted ventricle, early ventricular filling phase, diastasis, and atrial contraction. Besides the extrinsic factors such as pulmonary-cardiac contact pressure, pericardial restraint and interaction of both ventricles, 2 intrinsic factors mainly comprise diastolic function: ventricular relaxation and ventricular passive stiffness. Ventricular relaxation is an active, energy-consuming process concerning the calcium homeostasis of cardiac myocytes. Delayed relaxation results in a decrease in the early diastolic atroventricular pressure gradient, leading to impaired early ventricular filling. Ventricular stiffness affects the filling dynamics in the late phase of early filling, diastasis and atrial contraction. LV stiffness is created by a change in LV pressure for a given change in LV volume (dP/dV). There are extrinsic and intrinsic factors that determine LV stiffness. The extrinsic factors are mainly the pulmonary-cardiac contact pressure, pericardial restraint and interaction of both ventricles, and the intrinsic factors include myocardial stiffness, chamber geometry and wall thickness.  

Both delayed relaxation and LV stiffening occur in patients with advanced HFrEF and HFpEF; however, delayed relaxation alone may not be sufficient to increase diastolic filling pressure at rest. This hypothesis is supported by our observations from a hypertensive HFpEF model using Dahl salt-sensitive rats placed on 8% NaCl diet from the age of 6–7 weeks (Figure 1). Compared with rats given a normal diet, the hy-
pertensive HFpEF rats showed higher blood pressure and the development of LV hypertrophy, followed by transition to congestive HF with no reduction in LV fractional shortening. The progression to diastolic dysfunction was examined during this course. LV active relaxation assessed by the time constant of LV isovolumic pressure fall deteriorated even in the compensatory hypertrophic stage and its progression is only a little through transition to HF. On the other hand, the myocardial stiffness constant, which is an important determinant of LV stiffness, remained normal in the compensatory hypertrophic stage, but worsened just before the congestive HF stage. Therefore, LV stiffness is thought to play a key role in the transition to HFpEF.

Assessing LV Stiffness

Because LV stiffness changes at any point in the pressure-volume curve, it is more usual to measure the end-diastolic property of the pressure-volume relationship (EDPVR). The slope of the EDPVR is shallow at relatively low pressure and becomes progressively steeper with increases in LV volume (Figure 2). The curve of the EDPVR is load independent and intrinsically nonlinear. Quantitative analysis of such curves has shown that pressure and volume are interrelated by nonlinear equations; for example, Ped=CoβVed where Ped is the end-diastolic pressure, Ved is the end-diastolic volume, and C is a constant that specifies the curvature of the curve. In applying this equation, chamber stiffness increases linearly with LV volume. Thus, the slope of this relationship (β:U/ml) is defined as the LV chamber stiffness constant and is widely used as a diastolic chamber property.

Conventional Method of Noninvasive Evaluation of LV Stiffness: Doppler Echocardiography

Although the LV chamber stiffness constant is the only standard available in clinical medicine, there are difficulties in adopting it in clinical practice and clinical research because its measurement requires a highly invasive and specialized technique of catheterization. Therefore, an easily applied, noninvasive technique is needed.

Pulse-wave Doppler tracings of mitral inflow are frequently used to study LV filling. As myocardial relaxation becomes abnormal and the LV filling pressure is not elevated, the E velocity of mitral inflow decreases and the deceleration time (DT) is prolonged. The increase in LV stiffness secondarily elevates the LV filling pressure, which increases the E wave and shortens the DT. The velocity of the mitral A wave gradually decreases and its duration becomes shorter. These changes are classified into 4 patterns (ie, normal, abnormal relaxation pattern, pseudonormal filling pattern, and restrictive

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<th>high salt diet</th>
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### Figure 1
Serial course of typical hypertensive heart failure with preserved ejection fraction (HFpEF). In this model of hypertensive HFpEF there was a LV relaxation abnormality followed by LV stiffening. w, weeks.

### Figure 2
Ventricular stiffness. The slope of the end-diastolic pressure-volume relationship (EDPVR) depends on preload because the EDPVR is nonlinear.
EMI = (endocardial movement during diastole – epicardial movement during diastole) / (wall thickness at the beginning of diastole*epicardial movement during diastole) = (LVPWs – LVPWd) / (LVPWs*epicardial movement during diastole)

where LVPWs is the LV posterior wall thickness at end-systole and LVPWd is the LV posterior wall thickness at end-diastole. In the animal study using the hypertensive HFpEF model, we confirmed the significant and inverse correlation of EMI with the myocardial stiffness constant, whereas it did not correlate with LV systolic function, wall thickness at the beginning of diastole, LV chamber size, or indices derived from the transmitral flow velocity curves. To assess the effects of preload alteration on EMI, dextran was continuously infused through the femoral vein. The volume infusion significantly increased the LV end-diastolic pressure and LV end-diastolic dimension, but there was no significant change in EMI. Therefore, EMI has proven to have a relation to the myocardial stiffness constant with load-independency. To use this concept in the clinical setting, a simplified index is necessary because EMI currently needs M-mode echocardiography. We omitted epicardial movement during diastole from the equation of EMI, because this change is very small, and created another equation for diastolic wall strain (DWS): \[ \text{DWS} = \frac{(LVPWs – LVPWd)}{LVPWs}. \]

In our assessment of LV stiffness in animals, the use of DWS produced comparable results to those obtained using EMI and our hypothesis was confirmed. Finally, we conducted a clinical study to compare the usefulness of EMI or DWS in the evaluation of LV stiffness among normal volunteers, asymptomatic patients with LV hypertrophy and patients with a de-

**New Method of Noninvasive Evaluation of LV Stiffness: EMI and DWS**

The Doppler echocardiographic indices are widely used to evaluate diastolic function, but they have several limitations such as load dependence, modest correlation between the LV pressures and other direct measures of mechanical diastolic function, and spread correlation coefficients. Thus, additive information about LV stiffness/distensibility may be helpful in the diagnosis and management of HFpEF patients. We hypothesized that the movement of the outside of the myocardium and the difference between the movement of the surface and the outside of the myocardium would reflect tissue distensibility following the linear elastic theory. As shown in Figure 3, the difference between the movement of the surface and the outside is equal to the difference between the wall thickness before and after the application of the force. If our hypothesis is applied to the LV posterior wall during diastole, the following index (epicardial movement index: EMI) should inversely correlate with wall distensibility:

\[ K = \frac{f}{(D1-D2)} \]

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DWS can be measured by 2D echocardiography. In our assessment of LV stiffness in animals, the use of DWS produced comparable results to those obtained using EMI and our hypothesis was confirmed. Finally, we conducted a clinical study to compare the usefulness of EMI or DWS in the evaluation of LV stiffness among normal volunteers, asymptomatic patients with LV hypertrophy and patients with a de-
Excessive collagen deposition is attributed to not only exaggerated synthesis of collagen but also depressed collagen degradation. Collagen degradation involves matrix metalloproteinases (MMP) in the tissue. In our hypertensive HFpEF model, the hypertrophied cardiac tissue was rich in MMPs, but in the transition to overt HFpEF, tissue inhibitors of MMP were also upregulated, resulting in reduced collagen degradation. This phenomenon is observed in patients with HFpEF, and our study failed to show a reduction in clinical events with mineralocorticoid-receptor blockade, or angiotensin-converting enzyme inhibitor (ACEI) or angiotensin type 1 receptor blockers (ARB). Prevented LV myocardial stiffening through attenuation of the development of LV fibrosis in our hypertensive HFpEF model. This effect is widely observed in other animal models and human studies. Despite the beneficial effect of blockade of the RAS on LV stiffening through LV geometry and LV myocardial stiffness in animal and human studies, large prospective clinical trials have failed to clearly show efficacy of ACEI or ARB treatment in patients with HFpEF. Those results suggest that monotherapy for RAS blockade may not be enough in patients with HFpEF and new therapeutic regimens are awaited.

Future Therapeutic Strategies for Regulation of LV Stiffness

There are some candidates for regulation of LV stiffening. First is pursuing the possibilities of drugs that have proven effective in patients with HFrEF. Mineralocorticoid-receptor blockers improve the prognosis of HFrEF patients, and our study also showed beneficial effects of such treatment in our animal model of HFpEF. Although a recent observational study failed to show a reduction in clinical events with mineralocorticoid-receptor blockade, a large randomized trial, TOPCAT (Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart) is ongoing. The beneficial effects of β-blockers on the prognosis of patients with HFrEF has been fully established. Ours and other experimental studies have shown that β-blocker therapy improves the survival rate in the animal model of HFpEF through inhibition of oxidative stress, inflammatory changes,
LV hypertrophy and fibrosis. Although a randomized trial, the J-DHF trial, did not show carvedilol-induced improvement in the prognosis of the overall patient population with HFpEF, it gives us an important suggestion that high-dose prescription might be effective. Further investigation is still needed. The next target is another determinant of myocardial stiffness, cardiomyocytes. In 12 patients with HFpEF, one-third of their myocardial tissue specimens showed a normal level of collagen accumulation compared with controls, although the resting force of the myocytes was higher in all HFpEF patients than in the controls, meaning that in addition to collagen deposition, intrinsic cardiomyocyte stiffening also contributes to diastolic LV dysfunction in HFpEF patients. The elevation of the resting force of cardiomyocytes is also observed in patients with diabetic cardiomyopathy and congenital heart disease. The cause of “cardiomyocyte stiffening” is not fully clarified, but an important determinant is thought to be the cytoskeletal protein, titin. Titin acts as a spring responsible for late diastolic resistance to stretch. A switch toward the stiffer isoform and/or alteration in its phosphorylation status are observed in patients with HFpEF or HFrEF. Therefore, modulation of the titin-related passive force via phosphorylation (eg, cGMP-activating therapies) represents a novel therapeutic target for improving LV diastolic stiffness and is currently under development.

Finally, we still need a systematic survey of the factors that are closely related to pathophysiology of HFpEF. We used the recently established metabolomics with capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) for that purpose in our hypertensive HFpEF model. Analysis with CE-TOFMS revealed that plasma free-carnitine levels were decreased by more than 20% at any stage of the HFpEF rats compared with the control rat. Using an enzymatic cycling method, we confirmed the decreased plasma free-carnitine levels, and found decreased left ventricular (LV) free-carnitine levels and increased urinary excretion of free-carnitine in this model. L-carnitine treatment restored the LV free-carnitine levels, attenuated LV fibrosis and stiffening, prevented pulmonary congestion, and improved survival in the HFpEF model independent of the antihypertensive effect. These beneficial effects were likely provided through enhanced provision of arachidonic acid with upregulation of fatty acid desaturase (FADS) and subsequent promotion of the production of prostacyclin. L-carnitine administration may become a new therapeutic strategy for HFpEF, and should be investigated in future clinical studies.

**Figure 5.** Therapeutic targets of left ventricular (LV) stiffening. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; cGMP, cyclic guanosine monophosphate; RAS, renin-angiotensin system.

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**Conclusion**

LV stiffening plays a pivotal role in the development of HFpEF, but noninvasive method for assessment of LV stiffness and treatment for LV stiffening have not been established yet. We raise challenging proposals for these issues (Figure 5) and future studies are awaited to clarify their relevance.

**Disclosures**

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