Left ventricular (LV) diastolic dysfunction induces the increase of LV diastolic pressure and subsequently of left atrial and pulmonary capillary pressures independent of systolic function, resulting in the onset of heart failure. In the early 1990s, several clinical studies demonstrated that diastolic dysfunction is an independent prognostic factor in patients with heart failure with reduced ejection fraction (EF). In the past decade, many clinical studies have clarified that heart failure with preserved EF (HFPEF) accounts for about 40% of heart failure and that its prognosis is as poor as heart failure with reduced EF. With the growing interest in HFPEF, the important role of diastolic dysfunction in the pathogenesis of heart failure has been realized again, because it is plausible that LV diastolic dysfunction is one of the principal causes for this phenotype of heart failure.

Major determinants of LV diastolic function are relaxation and stiffness. Despite the clinical requisite for their evaluation in understanding the pathophysiology of each patient with heart failure, there are no established indices for the noninvasive assessment of these factors. An invasive measure of LV pressure is required for the evaluation of LV relaxation, and the simultaneous recording of LV pressure and geometry is necessary for the assessment of LV stiffness. LV relaxation abnormality is likely to precede LV stiffening or systolic dysfunction during the development of chronic heart failure and has been assigned as a sensitive sign of LV dysfunction.

Quantitative Assessment of LV Relaxation

Peak negative value of the first derivative of LV pressure (peak $-dP/dt$) has been used as a quantitative index for LV relaxation, but it depends on many other hemodynamic and functional factors. Weiss et al. showed that the time course of isovolumic pressure decrease subsequent to peak $-dP/dt$ is exponential and proposed the time constant of LV relaxation ($\tau$) with an assumption of a zero pressure asymptote to characterize this phase of LV pressure tracing and to estimate how fast LV pressure decreases during isovolumic relaxation. Raff and Glantz proposed another calculation of $\tau$ with a monoexponential model of LV pressure tracing assuming a nonzero asymptote. $\tau$ derived from the monoexponential model ($\tau_E$) is less dependent on loading conditions than peak $-dP/dt$ and has been used as a reliable index for LV relaxation in many clinical and experimental studies.

The sequential evaluation of cardiac function is required in the follow-up of patients with heart failure to assess the changes in the severity of heart failure and the effects of therapeutic interventions. Indices derived from invasive measure of LV pressure are not suitable for this purpose, and efforts have been made to establish the noninvasive assessment of LV relaxation. Investigators proposed a calculation of $\tau_E$ through the noninvasive measure of LV pressure tracing by use of continuous wave Doppler mitral or aortic regurgitant velocity curves or developed new noninvasive indices. The changes in LV function and/or clinical status are frequently associated with the hemodynamic alterations in patients with cardiovascular diseases, and $\tau_E$ is believed to be suitable for the evaluation of LV functional characteristics because loading conditions have few effects on it. In those previous studies, a rule to determine the reliability of the noninvasive assessment was the invasively measured $\tau_E$. Recently, the peak velocity of early diastolic mitral annulus movement derived from the tissue Doppler imaging ($E'$) has been widely used as a noninvasive index for LV relaxation in many clinical studies because of its significant correlation with $\tau_E$ and its easiness of the recording.

Limitation of the Quantitative Assessment of LV Relaxation by the Monoexponential Model

In 1995, Matsubara et al demonstrated that the logistic model better fits LV pressure tracing during isovolumic phase than the monoexponential model ex vivo. In a study published in this issue of Circulation: Heart Failure, Szenzaki and Kass expanded the previous experimental study and their own clinical study in the in vivo experimental study. The load sensitivity of $\tau_E$ was minimal at baseline conditions but was enhanced with the development of heart failure. The slope of $\tau_E$-LV end-systolic pressure relation increased by about 10 times in the dogs with heart failure. In contrast, the load sensitivity of the logistic $\tau$ ($\tau_L$) was less even at baseline conditions compared with $\tau_E$ and was not enhanced with the development of heart failure. $\tau_E$ increased by 75% to 85% after the development of heart failure with LV dilatation and reduced EF, but the increase in $\tau_L$ was only 28%. Thus, the...
heart failure–induced change in τE is likely to overestimate the prolongation of τ associated with LV relaxation abnormality because of its load dependence.

The method to calculate τ amplifies the inaccuracy of τE. LV relaxation should be analyzed using LV pressure tracing between aortic valve closure and mitral valve opening (isovolumic phase). Peak−dP/dt occurs shortly after the time of aortic valve closure, and its point can be easily determined with LV pressure recording. Thus, LV pressure tracing after peak−dP/dt is used for the calculation of τ. In contrast, to exactly determine the time of mitral valve opening, left atrial pressure or LV filling has to be recorded simultaneously with LV pressure. To simplify the calculation of τ, the crossover pressure of left atrial and LV pressure tracings is assumed to be LV end-diastolic pressure plus the constant value. Senzaki et al showed that the assumption of this constant value significantly affects the value of τE in heart failure.14,15 The nonzero asymptote τE is determined by the calculated pressure decay asymptote, which is load dependent. In addition, the deviation of the isovolumic LV pressure tracing from the monoexponential model is influenced by β-adrenergic activity, indicating that the discrepancy is directly related to the condition of cardiac dysfunction and the pathophysiology of the patients. These points have clarified the critical limitations of τE, and τL does not have these limitations.

How Great Is the Contribution of LV Relaxation Abnormality to the Pathophysiology of Heart Failure?

Here is an important issue. How great is the contribution of LV relaxation abnormality to the development of heart failure, in particular, of HFPEF? Senzaki et al16,17 proved the enhanced load dependence of both zero and nonzero asymptote τEs in heart failure with LV dilatation and reduced EF (although Raff and Glantz7 pointed out the load dependence of τE 30 years ago, many studies have used τE as an index for LV relaxation with only minimal effects of loading condition) and raised a suspicion that the changes in τE during the development of heart failure or therapeutic interventions in the previous studies were attributed to the changes in not only LV relaxation but also loading condition. Kawaguchi et al16 showed that nonzero asymptote τE of HFPEF patients without LV dilatation or reduction of EF was not different from that of controls despite high systolic blood pressure that would prolong τE even without the exacerbation of LV relaxation.14 They also demonstrated that a ratio of peak early to late diastolic pulsed Doppler transmitral filling velocity (E/A) was decreased in HFPEF patients without the prolongation of τE.16 The decrease in E/A in patients with cardiovascular diseases has been explained by LV relaxation abnormality and has been used as a proof of the contribution of LV relaxation abnormality to the pathophysiology of the patients. We may have overestimated the contribution of the slow rate of LV relaxation to the pathophysiology of cardiovascular diseases and heart failure.

A rate of relaxation as assessed by τ determines LV pressure tracing during early diastolic phase, and a extent of relaxation is considered to affect LV diastolic pressure at late diastolic phase; incomplete relaxation increases LV diastolic pressure at late diastolic phase. Weisfeldt et al17 demonstrated in normal hearts that relaxation was complete by 3.5 zero asymptote τE after peak−dP/dt. This rule has been also applied to failing hearts, and the study by Senzaki and Kassi14 suggests that the effects of incomplete relaxation on failing hearts have been overestimated by use of τE.

To investigate the correlation between the noninvasive indices and τE, the subjects with a widespread of τE were included as study subjects in previous studies. Among such subjects, loading conditions might well be widely distributed. The significant correlation of the noninvasive indices to the load-dependent τE suggests the load dependence of the indices. Previous studies have shown that τE, one of the most used indices for the noninvasive assessment of LV relaxation, is load dependent and affected by other LV functional parameters.18,19

Although the study by Senzaki et al does not necessarily deny the reliability of the conclusions of previous experimental and clinical studies, we should be cautious about the interpretation of τE or noninvasive indices for LV relaxation and reconsider how to assess LV relaxation. A fundamental question, “how important a role does LV relaxation abnormality play in the pathogenesis of heart failure?,” remains to be resolved with an accurate estimation of LV relaxation.

Disclosure

None.

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The Time Constant of Left Ventricular Relaxation: Extrication From Load Dependence and Overestimation of Functional Abnormality
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