left ventricular (LV) diastolic dysfunction, as occurs in patients with hypertension, diabetes mellitus, and/or aging, carries a substantial risk of the subsequent development of heart failure and reduced survival, even when it is asymptomatic or “preclinical.”1–4 Diastolic dysfunction is defined as functional failure and reduced survival, even when it is asymptomatic or “preclinical.”1–4 Diastolic dysfunction is defined as functional abnormalities that exist during LV relaxation and filling. When such abnormalities cause or contribute to the clinical syndrome of heart failure with a normal LV ejection fraction, it is appropriate to describe the condition as diastolic heart failure. This diagnosis carries a mortality rate that is similar to that seen in systolic failure, approaching 15% per year in patients older than 65 years.5,6 Over the past 20 years, the survival of patients in systolic failure, approaching 15% per year in patients older than 65 years.5,6 Over the past 20 years, the survival of patients with systolic heart failure has improved, whereas the prognosis of diastolic heart failure has not changed.5 Diagnostic echocardiographic and Doppler techniques have improved,7 and criteria for the diagnosis of diastolic heart failure have been developed,8,9 but the evolution of therapeutic strategies has not kept pace with this growing public health problem. Improved therapy will depend on basic research directed at mechanisms of disease, coupled with clinical investigations directed at diagnosis and therapy.

The article published by Kasner et al10 in this issue of Circulation consists of an exhaustive evaluation of invasive hemodynamic and noninvasive conventional and tissue Doppler echocardiographic parameters to search for the optimal method(s) for the evaluation of LV diastolic function. They studied 43 patients with definite and reliable evidence of diastolic dysfunction obtained during cardiac catheterization. The patients exhibited exercise intolerance, all were in New York Heart Association functional class II or III, and the level of the N-terminal pro B-type natriuretic peptide was elevated. The authors do not mention the physical examination, but presumably, the patients had been treated and signs of congestion were no longer present. In the study by Kasner and colleagues, however, the combination of congestive symptoms, exercise intolerance, an elevated B-type natriuretic peptide, and proven diastolic dysfunction provides clear evidence of diastolic heart failure.

The patients in the study by Kasner et al exhibited normal LV chamber size, increased myocardial mass, and a high ratio of mass to volume. Such chronic structural remodeling was accompanied by normal LV systolic performance, function, and contractility and a high prevalence of abnormal echocardiographic/Doppler indices of diastolic function. This is the expected finding in patients with the LV structural abnormalities seen in such a study group.11 Kasner et al10 found that the ratio of the conventional Doppler measurement of early diastolic peak LV inflow velocity (E) to the tissue Doppler imaging measurement of the early diastolic peak lateral mitral annular velocity (E'), that is, the E/E' ratio, reliably distinguished the patients with diastolic heart failure from normal controls and that this ratio correlated with invasive measures of diastolic function. The study suggests that an elevated E/E' indicates the presence of diastolic dysfunction (in a symptomatic patient), but this ratio was not evaluated as an indicator of asymptomatic diastolic dysfunction. It should also be recognized that the ratio is generally increased in patients with systolic heart failure.

Because the apex of the LV remains nearly fixed during the cardiac cycle, motion of the mitral annulus reflects changes in the long axis. The normal E' is rapid and occurs almost coincident with the LV inflow E velocity, reflecting rapid early diastolic flow propagation to the apex.12 With diastolic dysfunction (slowed relaxation and reduced elastic recoil), flow propagation to the apex is slowed, and E' is reduced and delayed. When the diastolic dysfunction results in an elevated left atrial pressure, the LV inflow velocity (E wave) increases, whereas its deceleration time is reduced. Thus, an increase in the ratio E/E' indicates elevated left atrial pressure and provides a noninvasive indicator of diastolic heart failure. It should be recognized, however, that the E/E' ratio can be normal when diastolic dysfunction has not yet caused an increase in left atrial pressure. For this reason, comprehensive 2D Doppler and tissue Doppler imaging are key to the assessment of LV diastolic function.7

The ejection fraction has become the clinical standard for evaluating systolic function in part because it provides a number that is easily interpreted: the farther below 50% the ejection fraction is, the more abnormal the systolic function. Thus, a reduced ejection fraction has become the diagnostic standard for systolic heart failure and has provided an objective entry criterion for clinical trials. The diagnosis and study of diastolic heart failure has suffered because of the lack of an analogous (easily performed and interpreted) indicator of diastolic function. The study by Kasner et al10 suggests that E/E' may provide this indicator, with a cut point of 8.0. It should be recognized that a limit of 8.0 is less than that used to recognize an elevated left atrial pressure. If the conclusion by Kasner et al10 is confirmed in studies of additional patients, including the elderly, it will be a major advance in the recognition and study of diastolic heart failure.
Kasner et al\textsuperscript{10} also evaluated an extensive panel of other echocardiographic/Doppler indices of diastolic function. These indices did not perform as well as $E/E'$ in discriminating diastolic heart failure from normal function and had lower correlation with invasive measures of diastolic function. Does this mean that these other indices are not valid measures of diastolic function and should be abandoned? We do not think so, for several reasons.

First, the evaluation of a parameter by examination of its correlation with an independent standard is confounded by noise and other limitations that cause errors in the standard. For example, Kasner et al\textsuperscript{10} assessed the rate of relaxation by calculating the exponential time constant of the isovolumic fall in LV pressure between aortic valve closure and mitral valve opening. This is subject to the potential for substantial errors and beat-to-beat variation because of the limited range of measured data, deviation of the data from a monoexponential function,\textsuperscript{13} and its dependency on systolic loads.\textsuperscript{14}

Second, evaluation of the end-diastolic pressure-volume (P-V) relation with a conductance catheter during transient caval occlusion has important technical and theoretical limitations. The caval occlusion alters the LV external constraints and ventricular interaction, which causes shifts in the P-V relation, and it changes the volume offset of the conductance catheter.\textsuperscript{15} Only a limited range of data can be acquired, and these data points can be influenced by reflex changes in autonomic tone. The end-diastolic P-V relation is curvilinear; the slope at any given pressure represents operating stiffness ($dP/dV$), which increases as the pressure rises. Thus, the LV does not have a single stiffness. In an attempt to compensate for this limitation, Kasner et al\textsuperscript{10} used a conventional method of fitting the end-diastolic P-V coordinates by an exponential function, and they report the calculated exponential coefficient as a stiffness constant. It is important to recognize that this constant does not represent operating stiffness but instead indicates the degree that stiffness increases with increasing pressure. The full end-diastolic P-V relation determined in experimental studies is not well represented by a simple exponential function, and the calculated stiffness is very sensitive to where on the P-V curve it is calculated.\textsuperscript{16} Thus, this index is not a load-insensitive measure of diastolic function, as suggested by Kasner et al.\textsuperscript{10}

Finally, there is an additional limitation of the method of evaluating noninvasive diastolic parameters by correlation with invasive measures. Several diastolic parameters, including the transmural E wave, the E/A, and E deceleration time, have a biphasic response to diastolic dysfunction. With mild dysfunction, E and E/A are reduced relative to normal states, and deceleration time is increased. With more severe dysfunction, they progressively change in the opposite direction. Thus, a linear correlation with diastolic dysfunction would not be expected.

Despite these limitations, Kasner et al\textsuperscript{10} found that the filling pattern did not perform as well as $E/E'$ in recognizing patients with diastolic heart failure, because some patients with diastolic heart failure had normal filling patterns. By contrast, there were no false-positives in patients with clearly abnormal filling patterns. Thus, the observations by Kasner et al\textsuperscript{10} indicate that a patient with clinical evidence of heart failure, a normal ejection fraction, and an abnormal filling pattern has diastolic heart failure. Kasner et al\textsuperscript{10} also provide additional important information that helps clarify some areas of uncertainty and controversy.

**LV Size**

LV end-diastolic volume has traditionally been said to be normal or near-normal in patients with diastolic heart failure.\textsuperscript{18,19} This conventional wisdom has been questioned, and it has been suggested that LV chamber size is increased and that chronic volume overload contributes to the pathophysiology of heart failure in some patients with a normal ejection fraction.\textsuperscript{20} Indeed, a modest increase in LV end-diastolic volume is seen in some patients, but it appears that end-diastolic volume remains in the normal range in the majority of patients with diastolic heart failure.\textsuperscript{21} Kasner et al\textsuperscript{10} report normal LV end-diastolic diameter (echocardiography) and normal end-diastolic volume (conductance catheter) in patients with diastolic heart failure. These results are consonant with other small invasive and noninvasive studies,\textsuperscript{22,23} large noninvasive epidemiological surveys,\textsuperscript{24} and published consensus statements.\textsuperscript{25}

**Systolic Function**

The published criteria for the diagnosis of diastolic heart failure require an LV ejection fraction $>50\%$,\textsuperscript{8,9} but some randomized clinical trials use a near-normal limit of 40% or 45%. The presence of a normal or near-normal ejection fraction virtually dictates that other indices of global ventricular performance are normal, and it excludes systolic pump dysfunction as a cause of the heart failure. Indeed, Kasner et al\textsuperscript{10} found a normal stroke volume and stroke work, normal shortening, and normal maximum (+)dP/dt and systolic elastance. These results are consonant with other studies,\textsuperscript{24,26} and they are not inconsistent with the observation that some patients with diastolic heart failure exhibit abnormalities in regional function in the presence of normal global function.\textsuperscript{27} The data provided by Kasner et al\textsuperscript{10} support the concept that the systolic properties and pump performance of the whole ventricle are normal in patients with diastolic heart failure.

It should be recognized that these indices of systolic performance, function, and contractility are sensitive to short-term alterations in the inotropic state and/or loading conditions, as well as to chronic ventricle remodeling. For example, systolic elastance (Es), an index of ventricular contractility, is sensitive to short-term alterations in the inotropic state, but because it is determined by altering end-diastolic volume or systolic pressure, it is considered to be independent of the effects of loading conditions. This does not mean that Es is independent of the chronic LV remodeling that is present in patients with heart disease.\textsuperscript{28,29} As a result, it may be difficult to interpret Es values in patients with diastolic heart failure. Kasner et al\textsuperscript{10} describe a small increase in Es (which was of borderline statistical significance) in their patients with diastolic heart failure. Others also
have found an increase in Es in patients with diastolic heart failure.\textsuperscript{24,26} However, when Es is normalized for the ratio of LV mass to volume (thereby correcting for the effects of chronic remodeling), the values for Es/(mass/volume) are nearly equal to those seen in the control groups, which indicates that contractility is not increased in patients with diastolic heart failure.

**Arterial Elastance**

Effective arterial elastance (Ea) tends to be increased in patients with diastolic heart failure, and it has been suggested that such vascular stiffening might contribute to the pathophysiology of diastolic heart failure.\textsuperscript{20} The data reported by Kasner et al\textsuperscript{11} and those of others do indicate high values for Ea, but the arterial-ventricular coupling ratio (Ea/Es) is similar to that seen in control subjects and in those with hypertension without diastolic heart failure.\textsuperscript{24,26} This pattern is distinctly different from that seen in patients with systolic heart failure, in which Ea is increased, Es is low, and the coupling ratio (Ea/Es) is high, which indicates adverse coupling. Thus, diastolic heart failure is characterized by increased arterial stiffness (arterial load) and increased ventricular stiffness (nominal contractility), but the normal coupling ratio indicates that abnormal ventricular-vascular coupling is not a feature of diastolic heart failure.

The findings of Kasner et al,\textsuperscript{10} especially when examined in concert with other published data, indicate that diastolic heart failure can be diagnosed reliably with noninvasive echocardiographic and tissue Doppler imaging techniques and that the global performance of the LV is normal in patients with diastolic heart failure. The next challenge will be to demonstrate the utility of the E/E\textsuperscript{1} ratio in the management of patients with heart disease. Can it be used to reliably diagnose diastolic dysfunction and thereby avoid the cardiac catheterization that some authors believe is necessary to make the diagnosis of diastolic heart failure? Does E/E\textsuperscript{1} have better prognostic value than other indices of diastolic function? Can it be used as a reliable surrogate for clinical outcome in therapeutic trials?

**Disclosures**

None.

**References**


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Assessment of Left Ventricular Diastolic Function and Recognition of Diastolic Heart Failure
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