Evaluation of Left Ventricular Diastolic Function

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DURING the past 20 years, there has been considerable interest in the clinical evaluation of left ventricular diastolic function. Although several conditions produce concomitant alterations in systolic and diastolic function, some drugs and pathologic conditions influence these two processes independently. In most patients, abnormal diastolic function is a consequence of systolic abnormalities. In some patients, symptoms of diastolic dysfunction predominate even though a variable extent of systolic dysfunction is present. This occurs in some patients with acute and chronic coronary artery disease, congestive heart failure, hypertrophic cardiomyopathy, aortic valve disease, and hypertension. In a small group of patients, abnormalities in diastolic function occur in the absence of significant systolic abnormality. Thus, the clinical entity of diastolic dysfunction is a heterogeneous entity. It has been tantalizing to speculate that an abnormal index of diastolic function can be used to identify patients who will subsequently develop systolic abnormalities or left ventricular dysfunction. However, there is little information that prospectively describes the clinical course of patients without overt cardiac disease but with abnormal indexes of diastolic function. It is not clear whether all of these patients will eventually develop symptoms of either diastolic or systolic dysfunction. Thus, the predictive value of abnormal indexes of diastolic function is not known.

How can diastolic dysfunction be diagnosed? Unfortunately, this simple question does not have a simple answer. There are several commonly used indexes of diastolic function, including the peak rate of left ventricular pressure fall (peak \(-dP/dt\)), the time constant of left ventricular pressure fall (\(\tau\)), peak filling rates (measured from cardiac volumes or dimensions), Doppler peak filling velocity during early diastole (E wave) and during atrial systole (A wave), the ratio of E to A wave velocities, left ventricular chamber stiffness (or its inverse, compliance, from diastolic pressure-volume or pressure-dimension data), and myocardial stiffness (from local myocardial stress-strain relations). What is the “best” index of diastolic function? No single index is adequate for separating patients with normal from abnormal diastolic function. Patients may have an isolated abnormality in one index, whereas the other indexes of diastolic function are normal. An intervention may have discordant effects on different indexes (e.g., slow the rate of pressure fall while increasing the rate of peak filling). These apparent discrepancies are possible because the indexes of diastolic function measure a complex set of separate but interrelated processes. As an example, the underlying processes that are important for determining the rate of ventricular relaxation (e.g., the rate of calcium reuptake by the sarcoplasmic reticulum) may not be the most important factor determining the passive stiffness of the left ventricle. Thus, not all indexes of diastolic function are directly comparable, nor can these indexes be used interchangeably. The mechanisms and clinical consequences of diastolic dysfunction may vary depending on which phase of diastole is affected. This heterogeneity of diastolic processes makes it impossible to identify a single “best” index that adequately describes the diastolic properties of the left ventricle.

To understand the usefulness and limitations of the indexes of diastolic function, it is important to first understand the factors that influence diastolic function under normal conditions. The framework for this discussion will use the clinical definition of diastole to examine the events of isovolumic relaxation, early diastolic rapid filling, diastasis, atrial contraction, and end diastole.

Rate of Left Ventricular Pressure Fall

The rate of isovolumic pressure fall is commonly measured with the peak rate of left ventricular pressure fall (peak \(-dP/dt\)), the time constant of left ventricular pressure fall (\(\tau\)), the rate of fall in calculated wall stress, and the duration of the isovolumic relaxation period. Peak \(-dP/dt\) can be
unreliable because it is highly dependent on the ventricular pressure, and the rate of pressure fall is measured only at one time point. The time constant τ is obtained by fitting the rate of left ventricular pressure fall to an exponential equation. Although τ is a useful index, there is some debate as to which portion of the left ventricular pressure curve should be measured and whether a zero pressure asymptote should be assumed.2

The major factors determining the rate of left ventricular pressure fall include loading conditions, rate of inactivation, and nonuniformity of left ventricular function.3,4 The rate of left ventricular pressure fall slows as peak left ventricular pressures and minimum or end-systolic lengths increase. The rate of pressure fall is also determined by the timing of ventricular ejection and the systolic pressure profile. A late peak in systolic pressure slows the rate of pressure fall more than an early peak.5 In general, positive inotropic stimulation enhances, whereas negative inotropic stimulation slows, the rate of pressure fall. The effects of different inotropic drugs or disease states on the rate of pressure fall may be concordant with (but to a different extent) or discordant with the effects on indexes of systolic function. An increase in ventricular nonuniformity slows the rate of pressure fall,4 which may be important in patients with bundle branch block or ventricular pacing. Some conditions, such as myocardial ischemia and infarction, slow the rate of pressure fall by a combination of mechanisms, that is, by altering nonuniformity, loading conditions, and inactivation.6 Thus, an abnormally slow rate of left ventricular pressure fall may reflect an increase in peak systolic pressure, an increase in end-systolic volume, an alteration in systolic pressure profile, diminished systolic function, negative inotropic effects, or an increase in left ventricular nonuniformity.

Early Diastolic Filling

Early diastolic filling of the ventricle is commonly assessed by the peak filling rate, the peak velocity of early diastolic filling, the velocity–time integral, the percentage of total diastolic filling during rapid (or atrial) filling, and time interval measurements such as the time from end systole to peak filling or to end of rapid filling. Peak filling rates are measured with ventricular volumes (estimated from contrast or radionuclide ventriculograms or echocardiograms) or from cardiac dimensions (e.g., the peak lengthening rate of a ventricular diameter or segment length or the peak rate of wall thinning). The accuracy of these measurements depends on the geometric assumptions used to estimate ventricular volume from a single or multiple cardiac dimension measurements. This is particularly important because peak lengthening rates vary in different regions of the left ventricle.7 In many cases, the sampling rate or frame rate for volume measurements is insufficient to accurately determine the peak filling rate.8 Doppler echocardiography is used to measure the peak filling velocity during early diastole (E wave) and during atrial systole (A wave). The time-velocity integral provides a measurement of cardiac filling volume during these phases. From these measurements, the ratio of E wave to A wave peak velocity or time-velocity integral, and the percentage of total diastolic filling during rapid filling or atrial contraction can be calculated.

The rate and velocity of rapid filling of the left ventricle depends on the early diastolic pressure gradient between the left atrium and left ventricle.9 The early diastolic transmitial gradient increases with an increase in left atrial pressure or a slower rate of left atrial pressure fall after mitral valve opening (e.g., due to decreased left atrial stiffness). The early diastolic transmitial gradient decreases when left ventricular pressures are increased during early diastole, for example, due to a slower rate of left ventricular pressure fall, an increase in left ventricular stiffness, or an increase in viscoelastic effects. Viscoelasticity describes the property of a material to resist stretch when the stretch (strain) rate is rapid. Viscoelastic effects are apparent in the left ventricle during early rapid filling and atrial systole, when the rate of volume change in the ventricle or filling (strain) rate is rapid.10 Viscoelastic effects increase with higher filling or lengthening rates, and they increase with larger ventricular volumes.10 Diastolic suction increases the early diastolic transmitial gradient, particularly at low cardiac volumes. Diastolic suction occurs when elastic recoil forces are released after the ventricle contracts below a critical end-systolic volume.7 Geometric factors such as shape changes and the extent of nonuniformity influence early diastolic filling. Therefore, a decrease in the early diastolic peak filling rate or velocity may indicate a lower left atrial pressure, a slower rate of left ventricular pressure fall, incomplete left ventricular relaxation, increased viscous effects, decreased left atrial stiffness, or increased left ventricular stiffness.

“Passive” Left Ventricular Properties

The passive elastic properties of the left ventricle are determined during diastasis, when the filling or lengthening rates are low (i.e., viscous effects are negligible) and ventricular relaxation is complete. The term “passive” is not entirely correct because there are active processes present throughout diastole. Left ventricular chamber stiffness is defined as the change in pressure for a given change in volume (dP/dV). The inverse relation is termed “compliance” (dV/dP). Cardiac dimensions (e.g., diameter, segment length, or wall thickness) are often used as a surrogate measurement for ventricular volume. Myocardial stiffness describes the material properties of the myocardium itself and can be determined by the local relation between stress and strain. The passive pressure-volume or pressure-dimension relation is curvilinear and can be fit to a variety of nonlinear equations. Left ventricular cham-
ber stiffness constants, calculated from these nonlinear equations, describe the shape of the passive pressure-volume or pressure-dimension curves.

Left ventricular chamber stiffness is determined by the passive elastic properties of the myocardium, the extent of myocardial relaxation, viscoelastic forces, coronary turgor, geometric factors such as left ventricular shape and wall thickness, and external or extracardiac factors. External factors affecting left ventricular chamber stiffness include the pericardium, the influence of the right ventricle (and to a lesser extent, the atria) through ventricular interaction effects, the surrounding thoracic structures, and the intrathoracic pressure. To determine the passive elastic properties of the left ventricle, pressure-volume or pressure-dimension measurements are made during the period of diastasis or at end diastole when viscous and diastolic suction effects are minimal and when left ventricular relaxation is largely complete. During early diastolic rapid filling and during atrial systole, there are significant deviations in the pressure-dimension relation from the passive curve. Ventricular relaxation is normally complete by end diastole unless the rate of left ventricular pressure fall is very slow or the heart rate is very rapid or both. At end diastole, the ventricular volume is maximal so that ventricular interaction and pericardial restraining effects become potentially more important. The transmural left ventricular pressure provides a more accurate measurement of distending forces. Alterations in left ventricular chamber stiffness can cause a change in shape or a shift in the entire diastolic pressure-volume or pressure-dimension curve (e.g., an upward shift with ischemia). To measure a stiffness constant that accurately describes the shape and position of the entire passive pressure-volume curve, it is important to obtain data throughout a wide range of passive diastolic pressures and volumes (or dimensions) and to take into account the transmural pressure. An increase in left ventricular chamber stiffness may indicate a change in the operating position on the passive pressure-volume curve, a change in the passive elastic properties of the myocardium (e.g., increased stiffness with scar formation after infarction), incomplete relaxation, increased viscous effects, increased pericardial or extracardiac restraint, ventricular interaction effects, or altered geometry.

Clinical Evaluation of Diastolic Function

In this issue of Circulation, Stoddard and coworkers examined the influence of preload on indexes of diastolic function. Left ventricular end-diastolic pressures were decreased with nitroglycerin and increased with contrast medium injections. A decrease in preload decreased the peak filling velocity and time-velocity integral during early diastole (E wave) but not during atrial systole (A wave), resulting in a lower E wave to A wave ratio and a greater atrial contribution to total diastolic filling.

An increase in preload increased both Doppler E and A wave peak velocities, but it did not change the E wave to A wave ratio or the percentage of atrial contribution to filling. Left ventricular chamber stiffness constants did not change with either an increase or decrease in preload. The investigators concluded that a decrease in preload alters the Doppler filling pattern to mimic diastolic dysfunction, whereas an increase in preload may alter the Doppler filling pattern to mask diastolic dysfunction.

This study underscores the current difficulties in the clinical evaluation of diastolic function. Many of the indexes of diastolic function show considerable intrasubject variability making it difficult to separate normal from abnormal patients. In this study for example, τ and the Doppler indexes of diastolic function do not separate normal patients from patients with coronary artery disease or aortic stenosis. In fact, patients with coronary artery disease actually had higher peak Doppler E wave and A wave velocities and a higher E wave to A wave ratio than the normal patients. The problem of intrasubject variability can be overcome by designing a protocol in which each patient serves as his own control. This method permits the detection of a small, but statistically significant, alteration in an index of diastolic function after an intervention.

The results of Stoddard et al can be analyzed with the framework developed above, that is, by separately analyzing the effects of an intervention on each phase of diastole. There was a slight decrease in τ (faster rate of left ventricular pressure fall) with nitroglycerin but not with contrast. τ is related directly to peak systolic pressure and is considered independent of preload. This is consistent with the results because both interventions altered preload, but only nitroglycerin altered peak systolic pressure and τ (both decreased). Contrast injections did not alter either peak systolic pressure or τ. Systolic shortening also influences τ but did not change with either intervention.

Stoddard et al found a decrease in the Doppler peak E wave (but not A wave) velocity and a decrease in the ratio of E wave to A wave velocities with a decrease in preload. An increase in preload increased both E wave and A wave peak velocities without altering the E wave to A wave ratio. These results confirm several prior studies. The peak filling rate or peak early filling velocity (peak Doppler E wave velocity) is linearly related to the left atrial pressure and the peak early diastolic transmural gradient. Recently, a direct relation between the left atrial pressure and the peak atrial filling velocity (A wave) has also been described. The peak filling rate is inversely related to τ. An increase in τ (i.e., a slower rate of pressure fall) is associated with a slower peak filling rate. However, this relation between pressure fall and peak filling may be dissociated. In this regard, some interventions that slow the rate of pressure fall can result in a higher peak filling rate, and some inter-
ventions that accelerate the rate of pressure fall can be associated with a slower peak early filling velocity. Stoddard et al.\textsuperscript{11} produced alterations in Doppler filling velocities without changing $\tau$. This underscores the fact that an index such as peak filling rate or velocity cannot be used interchangeably with an isovolumic relaxation index such as $\tau$.

Stoddard et al.\textsuperscript{11} concluded that altering preload with nitroglycerin and contrast did not alter the chamber stiffness. Although their conclusions are likely correct, their methods for measuring chamber stiffness should be scrutinized. Cardiac diameter measurements from M-mode echocardiograms were used to calculate ventricular volumes. Pressure-volume data were fit to an exponential equation from the time of minimum diastolic pressure to the peak of the "$a$" wave to derive a stiffness constant. This method poses several problems. First, ventricular volume calculations based on a single echocardiographic diameter measurement are not reliable, particularly in the presence of regional inhomogeneities that occur in coronary artery disease patients. Second, chamber stiffness measurements are most meaningful when pressure-volume data are obtained during passive filling (diastasis). The stiffness constant calculated by Stoddard et al.\textsuperscript{11} included pressure-volume data from early rapid filling and atrial systole. During early rapid filling, the pressure-volume relation deviates significantly from the passive pressure-volume curve\textsuperscript{10} because ventricular relaxation is not complete, viscous effects are most prominent, and diastolic suction effects may be present. Third, stiffness constants were calculated from data throughout a narrow range of pressures. These stiffness constants may not accurately reflect the entire passive pressure-volume or pressure-volume relation. These methodologic problems decrease the likelihood that a significant change in chamber stiffness could be detected.

Stoddard et al.\textsuperscript{11} varied preload with nitroglycerin and contrast in injections. Prior studies have shown that nitroglycerin reduces right ventricular pressures and produces a downward shift in the left ventricular diastolic pressure-volume relation.\textsuperscript{16} This effect is largely related to ventricular interaction effects secondary to lower right heart pressures and volumes and reduced pericardial restraining effects.\textsuperscript{17}

In this situation, left ventricular transmural pressure provides a more reliable estimate of left ventricular preload. To estimate transmural pressures clinically, right atrial pressures can be used to estimate pericardial pressures.\textsuperscript{18} Nitroglycerin may decrease viscous effects due to lower filling rates, may increase diastolic suction due to the decrease in ventricular volume, and may increase myocardial stiffness due to coronary turgor effects. These are probably relatively minor effects. Contrast injections depress myocardial contractility, which may slow the rate of pressure fall. The increase in ventricular volumes with an increase in preload will make the effects of ventricular interaction and peri-

cardial constraint more prominent. Thus, nitroglycerin and contrast may alter diastolic properties of the ventricle through several complex mechanisms other than a simple alteration in preload. A more accurate assessment of the diastolic alterations induced with nitroglycerin and contrast should take into account the influence of the right heart and pericardium on the left ventricle.

In summary, the clinical entity of diastolic dysfunction is heterogeneous and difficult to define numerically. Diastole itself is a complex set of separate but interrelated processes. Because several indexes of diastolic function describe different aspects of the diastolic processes, these indexes should be considered complementary, not interchangeable, measurements. Many clinicians are undoubtedly frustrated by the ever-expanding number of indexes of diastolic function. The initial enthusiasm for new indexes of diastolic function invariably yields to a concern about their limited usefulness to diagnose diastolic dysfunction. Although all indexes of diastolic function have limitations, these indexes serve as a useful reflection of the underlying physiologic and pathophysiologic diastolic properties of the heart. A thorough understanding of the physiologic determinants of the indexes of diastolic function serves as a useful framework for evaluating the benefits of therapy and the clinical course of patients with diastolic dysfunction. The index of diastolic function or the pattern of diastolic dysfunction should receive less emphasis than the functional and pathophysiologic information derived from such measurements.

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