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# Cardiac Imaging to Evaluate Left Ventricular Diastolic Function



Frank A. Flachskampf, MD, PhD,\* Tor Biering-Sørensen, MD, PhD,† Scott D. Solomon, MD,†  
Olov Duvernoy, MD, PhD,‡ Tomas Bjerner, MD, PhD,‡ Otto A. Smiseth, MD, PhD§

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**CME Objective for This Article:** At the end of this activity the reader should be able to: 1) review the physiology and pathophysiology of left ventricular diastolic function, including the relation to imaging parameters; 2) understand how different cardiac imaging techniques assess left ventricular diastolic function, and which limitations exist for these approaches; and 3) summarize the published experience with cardiac imaging from clinical trials in which left ventricular diastolic function was important for selection of patients or as an outcome variable.

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From the \*Institutionen för Medicinska Vetenskaper, Uppsala Universitet, Uppsala, Sweden; †Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ‡Institutionen för Kirurgiska Vetenskaper, Enheten för Radiologi, Uppsala Universitet, Uppsala, Sweden; and the §Department of Cardiology and Institute for Surgical Research, Rikshospitalet, Oslo University Hospital, Center for Cardiological Innovation, K.G. Jebsen Cardiac Research Centre, Centre for Heart Failure Research, University of Oslo, Oslo, Norway. Dr. Bjerner has served on advisory boards for Carestream Health. All other authors have reported that they have no relationships relevant to the content of this paper to disclose.

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## Cardiac Imaging to Evaluate Left Ventricular Diastolic Function

### ABSTRACT

Left ventricular diastolic dysfunction in clinical practice is generally diagnosed by imaging. Recognition of heart failure with preserved ejection fraction has increased interest in the detection and evaluation of this condition and prompted an improved understanding of the strengths and weaknesses of different imaging modalities for evaluating diastolic dysfunction. This review briefly provides the pathophysiological background for current clinical and experimental imaging parameters of diastolic dysfunction, discusses the merits of echocardiography relative to other imaging modalities in diagnosing and grading diastolic dysfunction, summarizes lessons from clinical trials that used parameters of diastolic function as an inclusion criterion or endpoint, and indicates current areas of research. (J Am Coll Cardiol Img 2015;8:1071-93) © 2015 by the American College of Cardiology Foundation.

The concept of left ventricular (LV) diastolic function as a characteristic separated from systolic function is not immediately compelling. Classic functional diagrams of LV function, like the pressure-volume loop, show a smooth transition between systolic and diastolic pressure-volume data. Furthermore, the term *function*, although appealing for the pump action of the LV in systole, seems less appropriate for the partially passive ventricular filling phase changes in volume and pressure. Nevertheless, the term *diastolic function* has become firmly rooted in cardiology and denotes the ability of the LV to fill sufficiently to produce the requested stroke volume without exceeding certain pressure limits during filling. LV pressure during diastole is nearly identical to left atrial (LA) and pulmonary capillary pressure because the latter structures have an open communication with the LV during diastole. Increased LA pressure implies pulmonary congestion, which accounts for dyspnea in patients with left heart failure. Clinical interest has been boosted by the realization that about one-half of patients presenting with heart failure symptoms have a “preserved” LV ejection fraction (>50%), although at closer inspection, systolic functional abnormalities such as reduced longitudinal LV shortening are often present. Hence, it has been assumed that a large proportion of the “heart failure epidemic” is primarily caused by diastolic LV dysfunction, and this has been termed heart failure with preserved ejection fraction (HFpEF). However, because symptoms of heart failure, in particular dyspnea, are not always cardiac in origin, direct evidence of such diastolic dysfunction should be sought before

settling on the diagnosis of diastolic dysfunction to explain HFpEF. Alternative diagnoses include noncardiac disorders such as pulmonary disease and obesity. Furthermore, valvular disease, such as mitral stenosis, constrictive pericarditis, congenital heart disease, pulmonary arterial hypertension, and others, may cause HFpEF and should be ruled out. Because exertional dyspnea is a common symptom of coronary artery disease, this disease also needs to be considered. Direct evidence of diastolic LV dysfunction can be provided by invasive measurements (LV pressure tracings or ideally pressure-volume data), natriuretic peptide levels indicating myocardial stretch, or cardiac imaging—first and foremost, echocardiography (1). Imaging techniques, however, lack the capability of directly measuring pressures, although they can measure volumes and blood and tissue velocities; therefore, by nature, they only provide indirect evidence of diastolic pressures or pressure-volume relationships.

Like in any other diagnostic work-up, a clinical question should always be the starting point. Reasons for referring patients for evaluation of diastolic function include: 1) symptoms or signs of heart failure in patients with preserved LV ejection fraction; 2) the need for an estimate of LV filling pressure in patients with known heart disease; and 3) assessment of cardiovascular risk.

In the following, we will review current knowledge on how to assess diastolic LV function by cardiac imaging, how well validated such assessment is, and which prognostic implications these data have. We will also describe the most important current open questions and unmet needs.

## DIASTOLIC LV FUNCTION: A BRIEF SUMMARY OF PHYSIOLOGY AND ITS REFLECTION IN ECHOCARDIOGRAPHIC PARAMETERS

Whereas LV systolic function is routinely quantified by measuring ejection fraction or deformation parameters such as global longitudinal strain, there is no single clinical measure that quantifies LV diastolic function; instead, a large number of indexes based on cardiac imaging have been introduced.

The physiological hallmarks of LV diastolic dysfunction are impaired relaxation, loss of restoring forces, reduced diastolic compliance, and elevated LV filling pressure. The latter is not a primary disturbance of ventricular function but is a compensatory mechanism to maintain LV filling and stroke volume (2). In some patients, elevated filling pressure is observed only during exercise; therefore, normal filling pressure at rest does not exclude clinically significant diastolic dysfunction or HFpEF (3,4). There is no single non-invasive index that provides a direct measure of relaxation, restoring forces, compliance, or LV filling pressure. However, by using a combination of different noninvasive indexes, it is feasible in most patients to determine if diastolic function is normal or impaired (Central Illustration).

In addition, structural changes (e.g., LV hypertrophy) can indicate abnormalities of diastole and should be considered.

### INDEXES OF RELAXATION AND RESTORING FORCES.

Slowing of LV relaxation and loss of restoring forces leads to reductions in velocities of LV lengthening and untwisting and reduces the decay rate of LV pressure during isovolumic relaxation. The latter response can be measured invasively by micromanometer as prolongation of the time constant  $\tau$  of LV pressure fall. LV regional lengthening velocity ( $e'$ ), however, can be measured noninvasively by tissue Doppler imaging and is a key parameter of diastolic function because it reflects relaxation as well as restoring forces (5,6) (Figure 1). It is inversely related to the relaxation constant  $\tau$ . Similar to most other parameters of LV function,  $e'$  is modified by diastolic pressure, but in the failing heart,  $e'$  is less load dependent than transmitral velocities (7). Furthermore, if LV relaxation is slowed,  $e'$  onset and peak, which normally occur close to onset and peak of the transmitral E wave, are delayed, leading to less dependence of  $e'$  on LA pressure (8). Table 1 shows normal reference values for  $e'$ .

LV early diastolic strain rate provides similar diagnostic information as  $e'$  and can technically be derived from speckle tracking-based strain imaging, although

the comparatively low achievable frame rates make substantial information loss likely. Although it is independent of cardiac translational motion, less angle dependent, and less affected by tethering from neighboring segments than velocities by tissue Doppler imaging, it presently must be seen as an experimental parameter of relaxation (9). Similar to  $e'$ , LV untwisting velocity is determined by LV relaxation and restoring forces and has the potential to become an important measure of diastolic function (10,11). Due to methodological challenges, however, assessment of untwisting velocity is not recommended for routine clinical examinations at the present time (9,10).

Because restoring forces are created by systolic contraction, both  $e'$  and untwisting velocity are determined in part by systolic function (12,13), reflecting the tight coupling between systolic and diastolic function.

There is no clinical method that differentiates between myocardial relaxation and restoring forces. In heart failure, both mechanisms are affected and contribute to slowing of LV isovolumic pressure fall and elevation of minimal LV diastolic pressure. Restoring forces may play a unique role by creating negative LV diastolic pressure, which represents the driving force for diastolic suction (13,14). Restoring forces are generated in systole by a complex set of mechanisms (15). A key element is storage of energy due to contraction of myocytes and ventricles below resting length (unstressed dimension), and analogous to a compressed elastic spring, the myocardium recoils in early diastole when the ventricle relaxes. Due to ventricular filling, the negative pressures that result from restoring forces may not be observed clinically when LV pressure is recorded, and there is no easy noninvasive method to measure diastolic suction. Rapid early diastolic mitral-to-apical flow propagation has been proposed as a marker of diastolic suction (16).

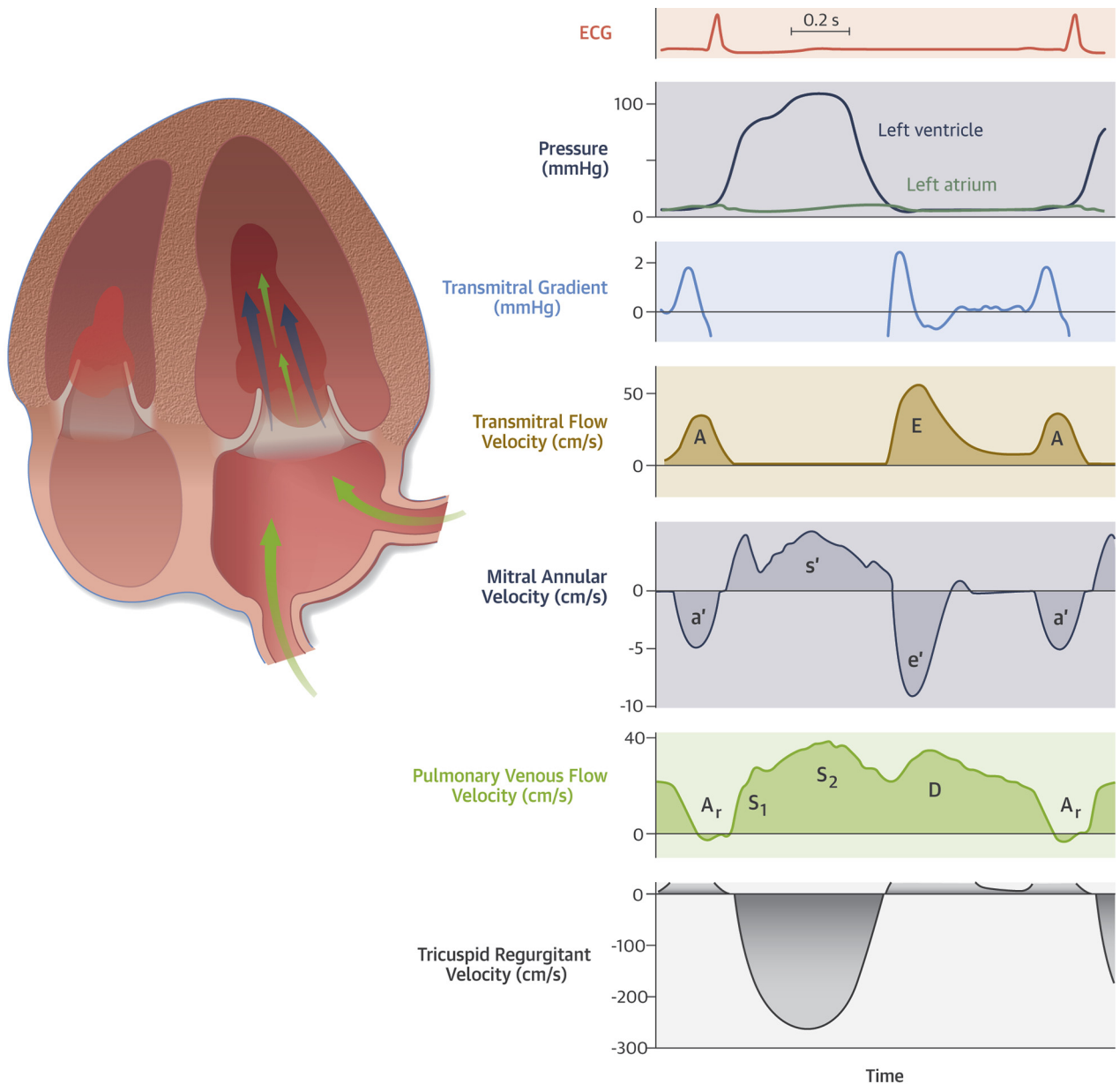
In ventricles with increased end-systolic volumes, restoring forces are attenuated or lost, as indicated by elevation of minimal LV diastolic pressure, and myocardial relaxation becomes an increasingly important determinant of  $e'$ .

Mitral flow velocities and filling patterns may also be used to evaluate LV relaxation. Reduced decay rate of LV pressure due to slowing of relaxation and loss of restoring forces leads to elevation of minimal LV pressure and therefore a reduction in the early diastolic transmitral pressure gradient and the early transmitral velocity (E) and a compensatory increase in the A wave. The result is a reduction in the E/A ratio

## ABBREVIATIONS AND ACRONYMS

- AV = atrioventricular
- CMR = cardiac magnetic resonance
- CT = computed tomography
- $e'$  = left ventricular regional lengthening velocity, usually the septal or lateral basal LV tissue velocity, also called mitral annular velocity
- $e'sr$  = early diastolic strain rate
- HFpEF = heart failure with preserved ejection fraction
- IVRsr = strain rate during isovolumic relaxation time
- LA = left atrium/atrial
- LV = left ventricle/ventricular
- LVEDP = left ventricular end-diastolic pressure

**CENTRAL ILLUSTRATION Schematic Drawing of Diastolic LV Filling**



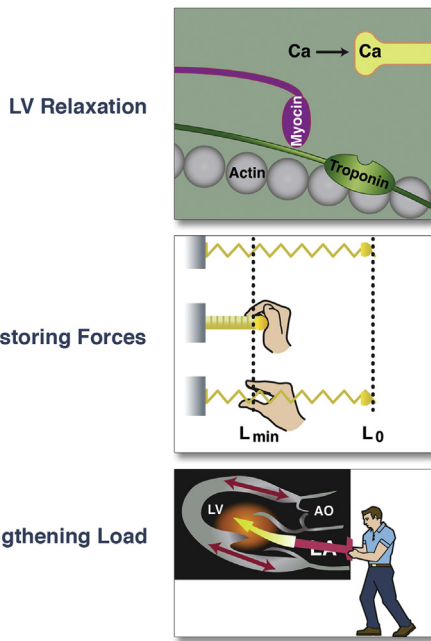
Flachskampf, F.A. et al. *J Am Coll Cardiol Img.* 2015; 8(9):1071-93.

Diastolic left ventricular (LV) filling is shown with simultaneous recordings of left atrial (LA) and LV pressures, the diastolic transmitral pressure gradient, pulmonary venous, transmitral, and transtricuspid flow velocity, and septal tissue (or mitral annular) velocity. Flow velocity and tissue velocity data, together with LA size and systolic pulmonary pressure, are used in echocardiography to infer diastolic LV pressures and hence diastolic LV function.

along with prolongation of the deceleration time of E, and this filling pattern is named impaired relaxation. With further progression of diastolic function, however, this feature may disappear due to compensatory rise in LA pressure, which serves to maintain LV filling,

and result in a pattern named pseudonormal filling with normal transmitral E/A ratio. In contrast to “true” normal filling, there is typically an associated reduction in  $e'$  and often a more marked pulmonary venous reversed velocity during atrial contraction. Such

**FIGURE 1** The 3 Independent Determinants of LV Early Diastolic Lengthening Velocity



**(Top)** Active relaxation, a decay in active fiber force by reduction of actin-myosin interaction as cytosolic calcium is taken up by the sarcoplasmic reticulum. **(Middle)** Restoring forces represent passive elastic recoil, which occurs during left ventricular (LV) relaxation and causes the ventricle to return to its resting position. Restoring forces are the result of systolic contraction to myocardial dimensions less than resting length ( $L_0$ ). The magnitude of restoring forces varies inversely with minimal length ( $L_{min}$ ). In the normal LV, restoring forces result in negative early diastolic pressure, which sucks blood into the ventricle. During heart failure, when the LV does not contract below  $L_0$ , restoring forces are lost and there is a loss of diastolic suction and secondarily reduction in early diastolic lengthening velocity ( $e'$ ). **(Bottom)** Left atrial (LA) pressure at the onset of filling determines the force with which the blood fills the LV and causes it to lengthen. AO = aorta. Modified, with permission from Smiseth et al. (115).

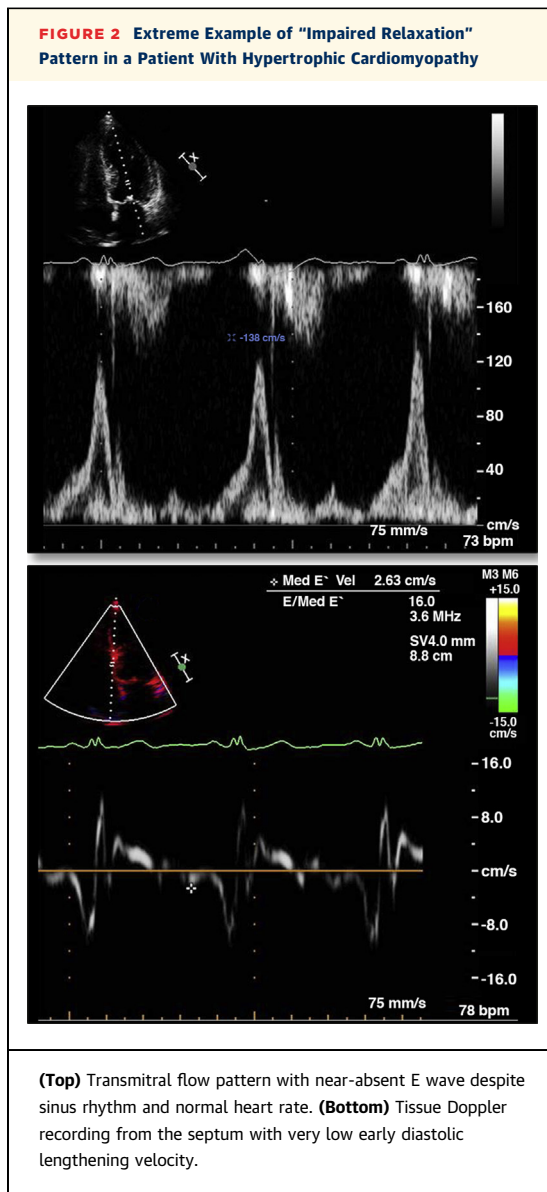
pseudonormalization due to increasing LA pressures generated by advanced disease also occurs with other blood flow-based parameters like isovolumic relaxation time, E-wave deceleration time, and pulmonary venous diastolic flow, and constitutes a fundamental problem in the assessment of diastolic function. In summary, impairment of early diastolic function due to slowing of relaxation and loss of restoring forces can be detected noninvasively in clinical routine practice as reduction in  $e'$  and as a transmitral filling pattern of impaired relaxation (Figure 2). Due to age dependency of both parameters, it is important to use age-adjusted reference values (Table 1).

**TABLE 1** Normal Values for  $e'$  and  $E/e'$

	$e'$ , cm/s	$E/e'$ Ratio
Women, <40 yrs	10.0-19.2	3.0-8.2
Women, 40-59 yrs	6.5-16.1	3.2-10.4
Women, $\geq 60$ yrs	1.8-14.6	3.1-14.3
Women, overall	5.4-18.2	2.5-10.9
Men, <40 yrs	8.7-19.5	2.5-8.5
Men, 40-59 yrs	6.1-15.3	3.0-9.4
Men, $\geq 60$ yrs	4.4-12.0	3.1-12.3
Men, overall	4.8-16.8	2.4-10.4

Normal reference ranges for left ventricular regional lengthening velocity ( $e'$ ; by pulse-wave Doppler) and  $E/e'$  ratio (mean  $\pm$  2 SD) in 1,266 randomly selected healthy individuals. Average values from all 4 left ventricular walls. The findings were similar when  $e'$  was calculated as an average of septal and lateral  $e'$ . Modified from Dalen et al. (114).

**INDEXES OF REDUCED DIASTOLIC COMPLIANCE.** LV diastolic compliance is the relationship between change in LV volume and change in pressure in diastole, or the local slope of the pressure-volume relationship. It is determined by LV myocardial compliance and by elastic properties of extraventricular structures (i.e., pericardium and lungs) and by right ventricular pressure. Because the LV pressure-volume relationship does not reflect myocardial compliance, the term *chamber compliance* is often used. Importantly, because the LV pressure-volume relationship is curvilinear, chamber compliance is a function of the operative LV diastolic pressure and consequently is markedly load dependent. Therefore, a change in LV chamber compliance does not necessarily mean there has been a change in myocardial elastic properties, it may just be a change in loading conditions that moves the pressure-volume coordinate to a part of the curve that has a different slope. There is no noninvasive method that measures diastolic compliance, but there are indexes that are related to LV compliance. There is an association between reduced LV diastolic compliance and short E-wave deceleration time (17-19). Values <150 ms are consistent with reduction in LV diastolic compliance in particular when there is also a mitral filling pattern of restrictive physiology (tall E and high E/A ratio). The relationship between E-wave deceleration time and compliance is consistent with theoretical predictions (18-20) (Figure 3). An additional feature of this filling pattern is abbreviated isovolumic relaxation time due to premature opening of the mitral valve caused by elevated LA pressure (21). Importantly, the relationship between E-wave deceleration time and degree of diastolic dysfunction is nonlinear; therefore, in mild diastolic dysfunction dominated by impaired relaxation, there is prolongation of E-wave deceleration time because of ongoing relaxation during flow deceleration. Furthermore, in



young healthy individuals with a high mitral E, there is often a deceleration time of  $<150$  ms (22). Therefore, a short deceleration time should not be used as a stand-alone index of reduced LV compliance. Reduction in LV chamber compliance is also reflected in attenuation and abbreviation of the transmitral A velocity (23) and is typically combined with accentuation and prolongation of the pulmonary vein reversed A velocity (24,25). When LV compliance is reduced, a small change in volume results in a large change in pressure; therefore, atrial contraction results in a more marked increase in LV pressure. When the atrium contracts against a ventricle with reduced compliance, little blood moves forward across the mitral valve, antegrade mitral flow is interrupted prematurely, and

instead blood regurgitates into the more compliant pulmonary veins. In the early phase of diastolic dysfunction and with a well-functioning LA, there may be a relatively normal LV pre-A-wave pressure and a marked rise in LV pressure during vigorous atrial contraction, particularly when there is reduced LV compliance. Low amplitude and short duration of the transmitral A velocity in combination with a high amplitude and long duration of the reverse pulmonary venous velocity are typical for a ventricle with reduced chamber compliance and elevated end-diastolic pressure (23-26).

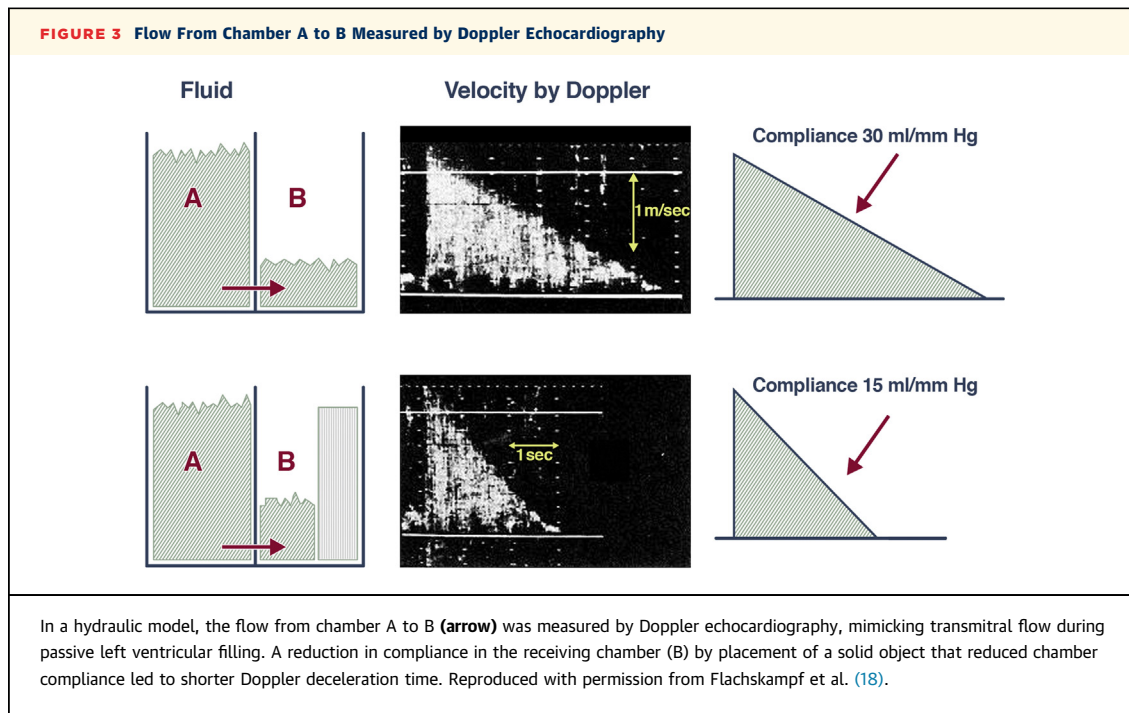
Limitations of the difference in A-wave duration as an index of diastolic compliance include atrial mechanical failure and problems with the quality of the pulmonary venous flow signal. Furthermore, reverse A may be shortened in tachycardia and when the PR interval is prolonged due to atrioventricular (AV) block I or if there is significant antegrade pulmonary venous flow at the time of atrial contraction, reflecting the effect of blood inertia. In these cases, the relation of the difference in A duration between mitral and pulmonary venous flow has less predictive value for an increase in diastolic pressures.

Thus, a short E-wave deceleration time together with a small and abbreviated mitral A and a large reverse A of long duration are consistent with reduced LV compliance.

#### ECHOCARDIOGRAPHIC DETECTION OF ELEVATED LV FILLING PRESSURES IN CLINICAL PRACTICE

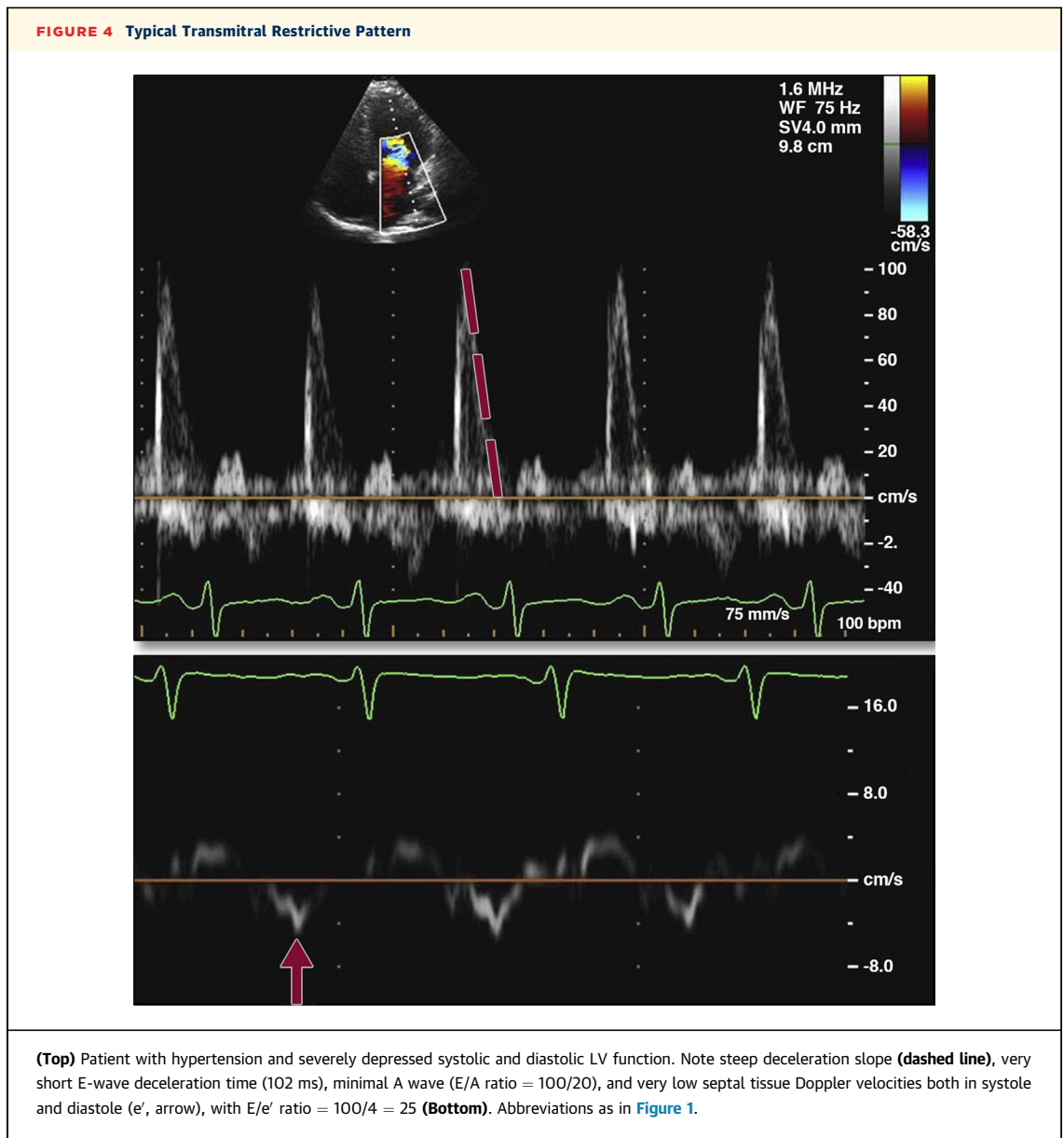
LV filling pressure is invasively measured as left ventricular end-diastolic pressure (LVEDP) or as pulmonary capillary wedge pressure as an indirect measure of mean LA pressure. There is often a slight difference between the 2, but this is rarely of clinical significance as long as there is no mitral stenosis. Filling pressure is considered elevated when the mean pulmonary capillary wedge pressure is  $>12$  mm Hg or when the LVEDP is  $>16$  mm Hg (1).

Like all imaging modalities, echocardiography has no direct way to measure pressures in the LV. Thus, indirect signs of pathological pressure-volume relationships in the LV during diastole must be relied upon. Because mitral flow velocities are determined by the transmitral pressure gradient, peak mitral E is a valuable parameter in the estimation of LA pressure. However, due to a relatively large volume of blood contained within a normal mitral valve, a substantial fraction of the transmitral pressure gradient is needed to overcome inertia. Therefore, mitral velocity cannot be converted to pressure difference using the



simplified Bernoulli equation, like in mitral stenosis, and the real pressure gradient is larger than that predicted by the simplified Bernoulli equation. Nevertheless, peak transmitral filling rate correlates well with the transmitral pressure gradient (27,28). An important limitation of peak mitral E as an index of LA pressure is that it reflects only the AV pressure difference. Because LA pressure is the sum of LV diastolic pressure and the transmitral pressure difference, elevated mitral E velocity alone is not sufficient information to conclude that LA pressure is elevated. Therefore, in normal hearts that have low or even slightly negative early diastolic LV pressures, a tall mitral E obviously does not imply a high LA pressure. However, in ventricles with reduced ejection fraction or when  $e'$  is low, impaired relaxation, and therefore elevated LV early diastolic pressure, can be expected. This is why the combination of a tall E and a low  $e'$  indicates elevated LV diastolic pressure and is expressed as a high E/ $e'$  ratio. Because the normal range of  $e'$  is wide, with values between approximately 5 and 18 cm/s (Table 1), it is obvious that the E/ $e'$  ratio cannot be an accurate index of LA pressure. When used in combination with other indexes, however, it has proven useful. Furthermore, an E/ $e'$  ratio larger than 15 is generally abnormal, regardless of age, and is strong evidence of diastolic dysfunction. Restrictive mitral filling pattern with a tall peak E, short E-wave deceleration time, and small A wave is consistent with

elevated LA pressure if  $e'$  is reduced (Figure 4). As indicated in Table 1, the lower normal limit for  $e'$  is 6 to 6.5 cm/s for individuals under the age of 60 years. In older individuals who are apparently healthy, even lower values of  $e'$  may be found, but this may reflect impaired diastolic reserve with aging or undetected coronary artery disease. Furthermore, if  $e'$  exceeds 8 cm/s, reduced LV relaxation can be excluded and further studies of diastolic function may not be needed. One important exception are patients with constrictive pericarditis, who often have a normal  $e'$ . In addition, patients with significant mitral regurgitation tend to have elevated  $e'$ , and this should be kept in mind when the flow chart proposed in Figure 5 is used to conclude that a patient has normal diastolic function. Because  $e'$  is used as a parameter of global LV diastolic physiology, but is measured locally, local changes may influence  $e'$  in a way not reflecting global LV diastolic function. In particular, septal infarction, ventricular pacing, mitral annular calcification, and left bundle branch block may lead to low septal  $e'$ . In these cases,  $e'$  should be measured at the basal lateral wall. In general, using an average value from septal and lateral  $e'$  measurements (which typically are approximately 10% higher than septal  $e'$  measurements) has been recommended as a surrogate for measuring  $e'$  in all 6 walls; however, in some cases (e.g., very dilated ventricles) it is nearly impossible to correctly measure lateral longitudinal velocity, and



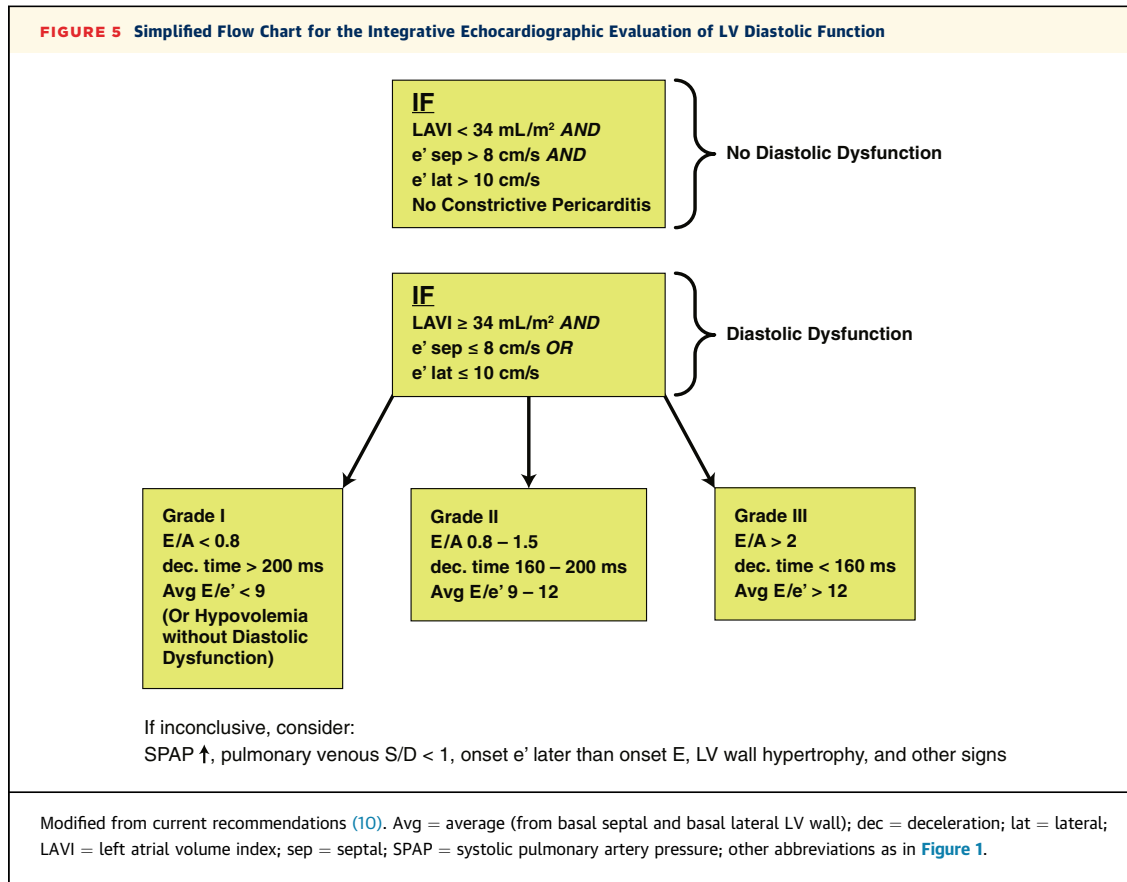
the sample volume records a mix of longitudinal and radial tissue velocities. In these cases, lateral  $e'$  should not be used.

Systolic pulmonary artery pressure calculated as the sum of the estimated right atrial pressure and the systolic tricuspid pressure gradient can be obtained in most patients and is one of the most valuable measures in the evaluation of LV diastolic function. Provided there is no pulmonary arterial disease, an elevated pulmonary artery pressure is strongly suggestive of elevated LA pressure. Mitral regurgitation is another possible cause of elevated pulmonary artery pressure and needs to be considered.

As explained in the section on indexes of diastolic stiffness, the magnitudes and durations of the antegrade mitral A and the reversed pulmonary venous A can be used to roughly estimate LVEDP. A reverse pulmonary venous A wave >30 ms longer in duration than the antegrade A wave is consistent with elevated LVEDP (10).

Another measure from the pulmonary venous flow tracing is the ratio between peak systolic velocity and peak diastolic velocity. A ratio of systolic to diastolic peak velocity of <1 is consistent with, but not specific for, elevated LV filling pressure (10); other conditions associated with such a ratio are atrial fibrillation,



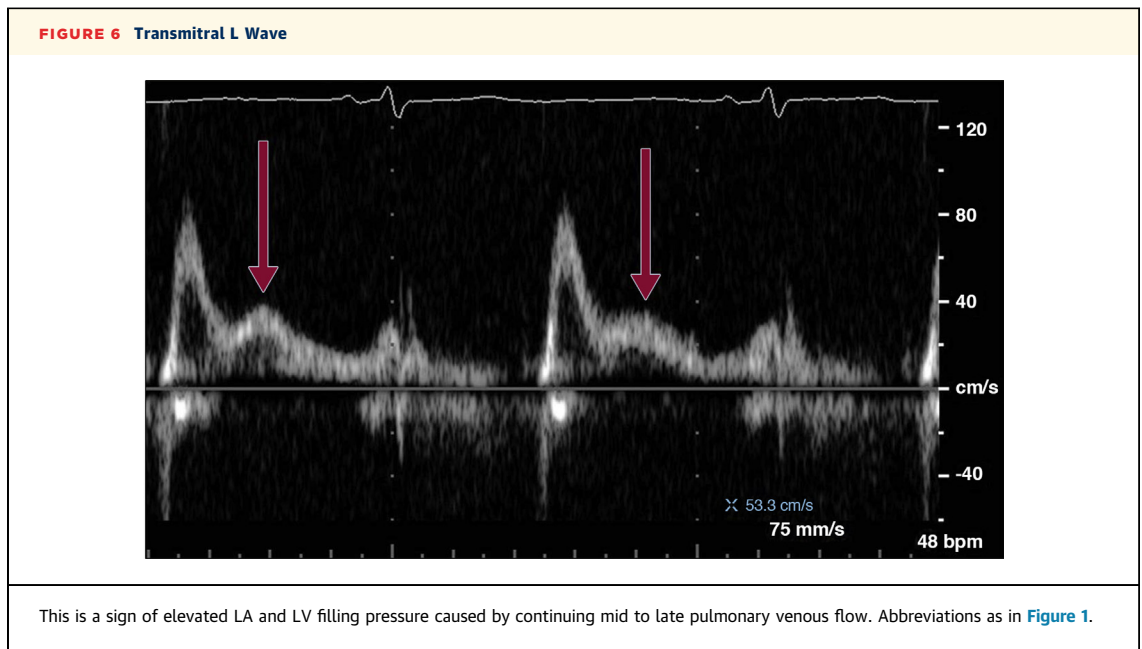


mitral regurgitation, and hypernormal early diastolic relaxation in young patients. Further signs of elevated LA pressure include the occurrence of a transmitral L wave (Figure 6), which is due to continuing antegrade pulmonary venous flow into late diastole in the presence of delayed LV relaxation and a later onset of e' than E wave, indicating that mitral flow volume is “pushed” rather than “pulled” into the LV.

LA volume can be measured by echocardiography and reflects in part the cumulative effects of filling pressures over time. Therefore, an enlarged LA is a marker of elevated LA pressure and a small left atrium suggests normal LA pressure. Importantly, atrial volume is not an index of instantaneous pressure because enlargement of the atrium takes time. Furthermore, an enlarged atrium may persist long after normalization of LA pressures. An upper normal value of 34 ml/m<sup>2</sup> is commonly used; a dilated LA higher than this value may also be seen in young healthy athletes and in patients with bradycardia, anemia, and other high-output states; atrial arrhythmias; and mitral valve disease (10). On the other hand, mild diastolic dysfunction without substantial

pressure elevation at rest may coexist with LA size in the upper range of normal. Thus, LA volume should not be used as a stand-alone parameter to rule in or rule out diastolic dysfunction.

Current recommendations (10) can be summarized as follows. Echocardiographic evaluation of LV filling pressure should include estimation of pulmonary artery systolic pressure, peak mitral E, and E/e' ratio. Duration difference between antegrade and retrograde A wave, LA volume, and E-wave deceleration time are additional useful measures. The only parameter in this list that provides a direct estimate of pressure is the tricuspid regurgitation velocity. An advantage of pulmonary artery systolic pressure and difference in A-wave duration is that they are essentially age independent, and this also applies to the E/e' ratio, which is <15 in healthy individuals. Except for estimated pulmonary artery pressure from tricuspid regurgitation velocity, all other indexes are predictive of LV filling pressure due to associations and therefore need to be interpreted with several limitations in mind. In spite of this, when indexes are consistent, it is possible in most patients to conclude whether the level of filling pressure is normal or elevated (Figure 5). In some



patients, however, there is inconsistency between indexes; therefore, the noninvasive study becomes inconclusive with regard to filling pressure. The diagnosis of diastolic dysfunction by echocardiography has limited reliability in particular in the following circumstances: rapidly changing hemodynamics (29); presence of other local factors influencing  $e'$  (infarction, bundle branch block, pacing); additional substantial valvular heart disease (e.g., mitral regurgitation); mitral annular calcification, which may reduce  $e'$  and augment E; and initial stages of diastolic dysfunction.

#### NEW ECHOCARDIOGRAPHIC TECHNIQUES

**DIASTOLIC STRESS TEST.** In some patients, LV diastolic pressures are normal at rest but become abnormal under exercise; this is opposed to the response of a healthy LV to physical exercise, during which diastolic pressures are maintained within normal ranges, in part due to enhanced myocardial relaxation (shorter tau) (30). Moreover, the invasive finding of elevated pulmonary wedge pressure at rest or at exercise in patients with suspected HFpEF seems to identify sicker patients with higher mortality, as a retrospective study suggested in 355 patients (31), with a 10-year mortality rate of 7% for those with normal pulmonary wedge pressure at rest and with exercise, 28% with elevation of exercise pressures only, and 32% with elevation at rest and with exercise (there was no difference in ejection fraction in these groups). Therefore, acquiring

echocardiographic data under or after physical stress (treadmill or bicycle) is an attractive concept to unmask diastolic dysfunction absent at rest. The typical echocardiographic parameters acquired during exercise or immediately thereafter are the  $E/e'$  ratio and peak tricuspid regurgitant velocity. Because the test is not primarily intended to provoke ischemia, it can be kept to modest degrees of exertion, although the test can also be integrated into a classic stress echocardiographic examination investigating ischemia, with minimal additional time and expense. If there is E-A and  $e'-a'$  fusion under exercise tachycardia, measurement of the  $E/e'$  ratio is performed after the heart rate falls, taking advantage of the delayed normalization of exercise-induced diastolic dysfunction after termination of exercise compared with heart rate.

Published studies of this test have shown the following. Increases in the  $E/e'$  ratio and pulmonary pressure, assessed by peak tricuspid regurgitant velocity, occur in a subset of patients with suspected stress-inducible diastolic LV dysfunction (4,32). The frequency of exercise-inducible diastolic dysfunction obviously depends on the selection of patients undergoing the test; in 1 study of 559 patients undergoing stress echocardiography, it was 20% (32). Interestingly, only 9% of patients with post-exercise  $E/e'$  ratio  $>13$ , which in this study was taken as evidence of inducible diastolic dysfunction, also had evidence of inducible ischemia by wall motion abnormality assessment. An increase in the  $E/e'$  ratio under physical exercise indicates a concomitant

increase in LVEDP (33). Increases in the  $E/e'$  ratio indicate a worse prognosis (34,35).

However, many patients in whom such a dysfunction would be suspected (e.g., patients with LV hypertrophy or multiple risk factors but no clear-cut echocardiographic signs of diastolic dysfunction at rest) have a normal diastolic stress test; although a positive test does seem to identify diastolic dysfunction and impaired prognosis with high specificity (4,34), the sensitivity and negative predictive value of the diastolic stress test are less clear, largely due to the difficulty in obtaining an independent standard (i.e., pressure measurements) during exercise. In a study with invasive hemodynamic validation, an exercise  $E/e'$  ratio  $>13$  had a sensitivity of 73% and a specificity of 96% for an exercise LVEDP  $>15$  mm Hg (33). In 498 Korean patients with preserved ejection fraction (34) who were specifically referred for a diastolic stress test, mainly to evaluate unexplained dyspnea on exertion or "LV functional reserve," 171 (34%) developed exercise-induced pulmonary hypertension, of whom only 49 (29%) developed an  $E/e'$  ratio  $>15$  under exercise; this again confirms the apparent low sensitivity of the diastolic stress test for inducible diastolic dysfunction. Exercise-induced pulmonary hypertension had a distinctly worse outcome if associated with  $E/e'$  ratio  $>15$ , whereas the outcome of patients with pulmonary hypertension without  $E/e'$  ratio elevation was similar to that of patients without inducible pulmonary hypertension. By study criteria, none of these patients had an exercise-inducible ischemic wall motion response. In an Australian study of 493 patients with an indication for exercise stress echocardiography and preserved ejection fraction, 436 patients had a normal  $E/e'$  ratio at rest, but only 41 (9%) developed an  $E/e'$  ratio  $>13$  with exercise (35), and there was no relationship between  $E/e'$  ratio and the development of ischemia, which occurred in more than one-half of the patients. Follow-up over 1 year showed no cardiovascular deaths, but there were more hospitalizations in the group with exercise-inducible increases in  $E/e'$  ratio than in patients without such increases. Published studies of the diastolic stress test have examined differently selected groups of patients, which is evident from the widely differing (between none and one-half of patients) rates of exercise tests positive for ischemic wall motion abnormalities. This adds to the uncertainty regarding the diagnostic accuracy of the test.

**STRAIN IMAGING.** Longitudinal LV function has been found to be reduced in patients with HFpEF. This has been assessed both by tissue Doppler and speckle-tracking strain imaging. A recent study comparing

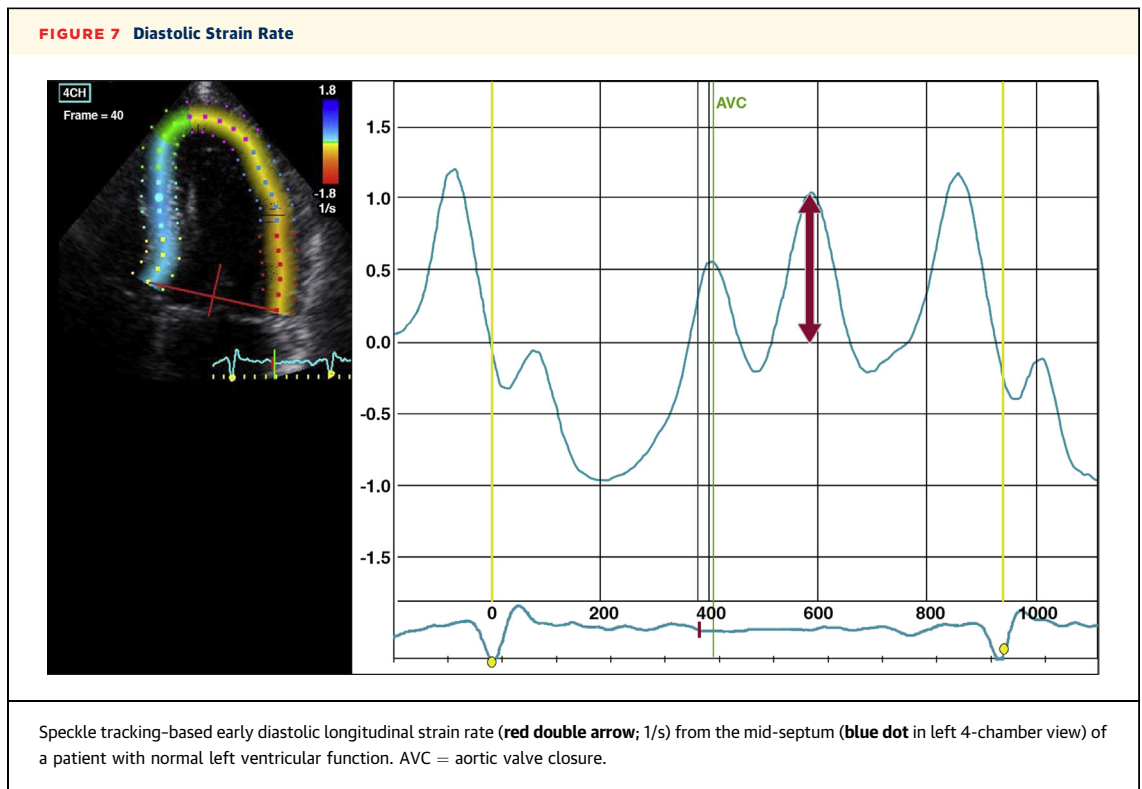
longitudinal and circumferential global strain in patients with manifest HFpEF, patients with hypertension without heart failure, and control patients found lower longitudinal and circumferential peak strain in patients with HFpEF (36).

Strain rate during the isovolumic relaxation time (IVRsr) or early diastolic strain rate ( $e'sr$ ) (Figure 7), derived from global longitudinal speckle-tracking strain, recently were proposed as a better substitute for  $e'$  to estimate LV filling pressures (37). Although  $E/IVRsr$  correlated better with filling pressures than  $E/e'sr$ , both parameters are noisy and IVRsr is especially challenging to measure and thus is experimental at best. Nevertheless, the parameter  $E/e'sr$  was shown to contain independent prognostic information in a large longitudinal study of 1,048 survivors of myocardial infarction (38).

#### **ECHOCARDIOGRAPHIC ASSESSMENT OF DIASTOLIC FUNCTION DURING OR IMMEDIATELY AFTER ACUTE ISCHEMIA.**

Echocardiographic signs of diastolic dysfunction typically do not imply acute myocardial ischemia. However, during acute supply ischemia (e.g., balloon inflation during coronary angioplasty), an abrupt reduction in the transmitral flow velocity integral (affecting both E and A waves) is observed (39,40). Further, diastolic tissue velocities decrease or are even reversed in the ischemic region, and  $e'sr$  decreases drastically. These diastolic changes in deformation during acute ischemia have been proposed as markers of acute ischemia and have been shown to last longer than wall motion abnormalities after reperfusion. Ishii et al. (41) showed that delayed relaxation could be detected using a radial myocardial strain index during and up to 10 min after induction of ischemia by treadmill stress echocardiography. In more recent work (42), a modification of this index, now based on global longitudinal strain, was correlated with simultaneous LV pre-A-wave pressure in patients assessed for coronary disease; these patients, however, did not have acute ischemia.

**TORSION.** The clinical evaluation of the twisting motion of the LV has become feasible as a by-product of speckle tracking-based circumferential strain measurements. Being largely still a research tool, there is little standardization of measurements and even of terminology. Recommendations from international echocardiographic societies (9) define *rotation* as rotational displacement around the long axis of the LV (in degrees); *twist* as the net difference between (small) rotation of the LV base and the larger rotation of the apical portion of the LV (in degrees)—in systole, the apex rotates counterclockwise (looking from apex toward base) and the base clockwise; *torsion* as



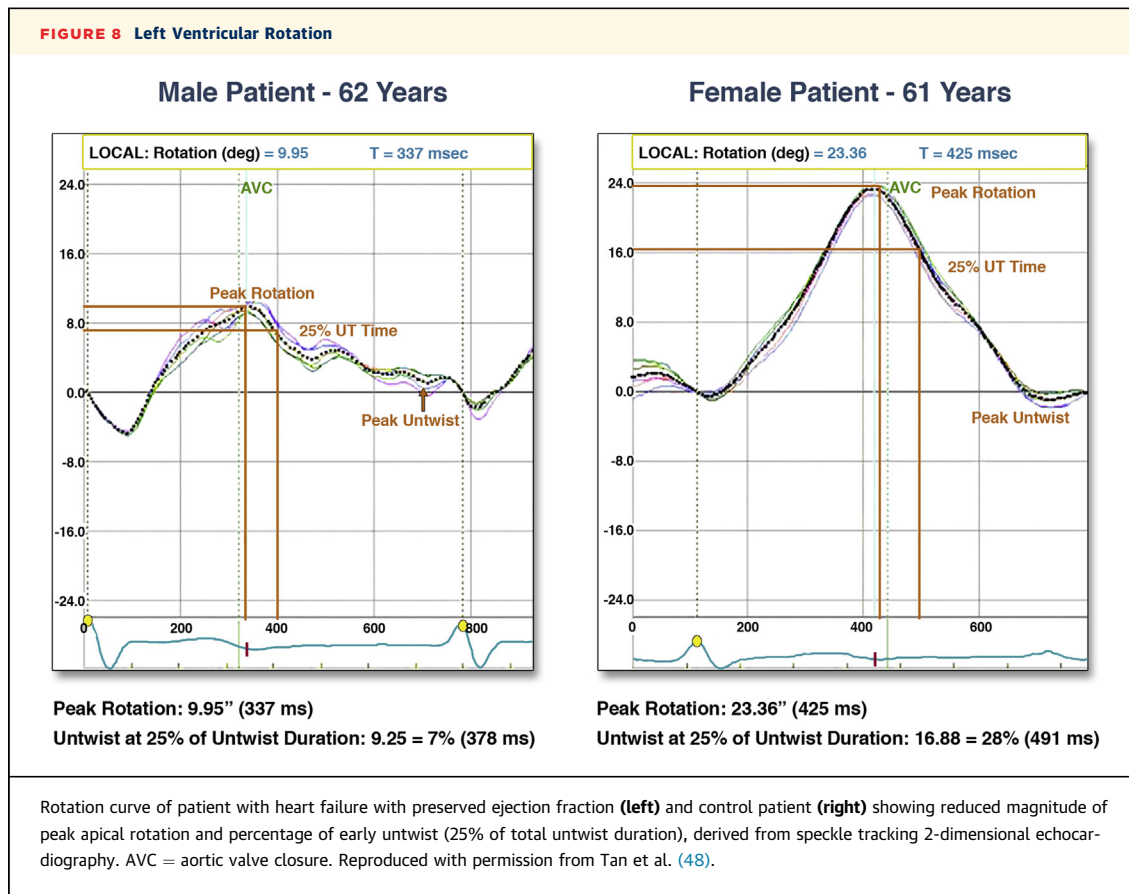
the ratio (or gradient) of twist and long-axis length (in degrees/cm).

Animal studies (11) have shown that the peak LV untwisting rate in early diastole is a marker of diastolic function; the rate depends on LA pressure, active myocardial relaxation, and elastic “restoring forces” stored during the buildup of systolic twist. Twist and torsion increase with LV hypertrophy (43), volume loading (44), physical endurance training (45), and age (43). However, the untwisting rate during isovolumic relaxation reflects active relaxation and passive restoring forces only, thus being largely load independent, although not independent of systolic function because this feeds the passive restoring forces of the LV (46). Peak untwisting rate, which occurs in early diastole, has been calculated in healthy volunteers at  $115 \pm 40^\circ/\text{s}$ , more than doubling during physical exercise (45,47) and increasing after volume loading (44), perhaps due to higher restoring forces built up by higher previous systolic twist. Although hypertrophy, due to hypertension or cardiomyopathy, leads to higher twist, patients with hypertrophic cardiomyopathy (46) and patients with HFpEF have been reported to have lower diastolic untwisting velocity (48) (Figure 8). Thus, the loss of rapid untwisting, due to decreased LV restoring forces, deprives the LV of its early diastolic suction mechanism, leads to an increase

in LV diastolic pressures, and is a crucial event in the evolution to heart failure symptoms. Published reports are not entirely consistent, however, and increased systolic twisting and diastolic untwisting rates were observed in a group of patients with mild diastolic dysfunction compared with healthy control patients, potentially related to LV hypertrophy and smaller end-systolic volumes in these patients (49).

In spite of their theoretical attractiveness, however, these rotational events have very small amplitudes—in healthy humans, peak LV twist has been estimated at just  $11 \pm 4^\circ$  (47). Thus, the robustness of such measures in clinical practice remains to be determined.

**DIASTOLIC FUNCTION ASSESSED BY ECHOCARDIOGRAPHY IN LARGE CLINICAL INTERVENTION TRIALS.** Echocardiographic measures in clinical trials can be used to either select the eligible participants or evaluate the treatment effect. Echocardiographic parameters of LV diastolic function have not been used as vigorously as systolic function measures for inclusion into clinical trials or as surrogate endpoints in clinical therapeutic interventional trials. Several smaller phase II clinical trials have used diastolic measures for participant selection and/or assessment of treatment effect. These trials have primarily focused on 2 disease categories, hypertension and HFpEF, in which diastolic dysfunction is frequently present.



**USING DIASTOLIC ECHOCARDIOGRAPHIC PARAMETERS IN PARTICIPANT SELECTION.** Parameters of diastolic function are strong predictors of future cardiovascular morbidity and mortality (50-54). Because diastolic function is not evaluated by a single measure, but through the interpretation of several echocardiographic parameters, using diastolic function as an entry criterion for trials generally requires sophisticated interpretation of data and is best suited for a core laboratory. The use of diastolic function as a measure for entry has been minimal in trials of HFpEF, despite HFpEF initially being called “diastolic heart failure” (55-59). Diastolic echocardiographic measures have been used in patient selection only in smaller clinical trials (54,55). In the SIDAMI (Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction) trial, the investigators hypothesized that sildenafil would reduce filling pressure during exercise in patients with diastolic dysfunction after myocardial infarction (60). The investigators used only 2 measures of diastolic function as inclusion criteria: E/e' ratio and LA volume index. Even so, they had to screen approximately 1,300 patients by echocardiography to identify approximately 300 patients with an

E/e' ratio  $\geq 8$  and an LA volume index  $\geq 34$  ml/m<sup>2</sup>. This illustrates that the complexity of diastolic function grading can make it challenging to identify appropriate candidates to include in trials.

In the Use of Exercise and Medical Therapies to Improve Cardiac Function Among Patients With Exertional Shortness of Breath Due to Lung Congestion trial (59), the investigators were aware of the low specificity of exertional shortness of breath to diagnose diastolic dysfunction. They sought to overcome this problem by performing the evaluation of diastolic dysfunction during exercise. The investigators therefore identified patients who had exertional shortness of breath and a coherent increase in the E/e' ratio to  $>13$ . Again, however, due to the difficulties cited in identifying patients with congruent symptoms and echocardiographic parameters, the researchers only randomized 61 patients in this trial.

**USING DIASTOLIC ECHOCARDIOGRAPHIC MEASURES TO ASSESS TREATMENT EFFECT.** Evaluation of a possible treatment effect with diastolic echocardiographic parameters has important limitations. Doppler velocity curves, especially obtained from blood flow, show

substantial interindividual and day-to-day variability with changes in afterload, pre-load, and sympathetic tone. Additionally, they are highly susceptible to spectral broadening of the time-velocity curve, making it difficult to accurately assess true peak velocities and to identify small changes in diastolic function with treatment. Further, there is considerable interobserver and test-retest variability in diastolic echocardiographic parameters, necessitating relatively large sample sizes to detect a treatment effect. Thus, echocardiographic core laboratories are crucial to assess diastolic echocardiographic parameters in multicenter trials (61-63). Furthermore, even if a therapeutic intervention leads to an improved diastolic function, in the absence of clear-cut symptomatic or prognostic clinical benefit, the improvement in echocardiographic parameters alone would not be sufficient evidence for drug or device approval. Moreover, some measures are very age dependent (10,64,65). Hence, for example, in the VALIDD (Valsartan in Diastolic Dysfunction) trial, patients with diastolic dysfunction based on lateral mitral  $e'$  were enrolled—the exact cutoff that allowed entry was dependent on patient age (66). Furthermore, the U-shaped nature of the E/A ratio, isovolumic relaxation time, and deceleration time in the progression through the diastolic function grades, with similar values seen in healthy individuals and patients with cardiac disease, make it impossible to assess the point in the progress of diastolic dysfunction a specific participant is, if other diastolic measures are not included in the assessment. Lastly, sinus tachycardia and first-degree AV block can result in partial or complete fusion of the mitral E and A waves, making it difficult to assess the E/A ratio and the deceleration time. These limitations make blood flow Doppler measures especially poor as surrogate endpoints. On the other hand,  $e'$ , E/ $e'$  ratio, and LA volume incrementally change with worsening diastolic function, making them easier to use as surrogate diastolic endpoints in interventional trials.

Whereas Doppler velocities and time intervals reflect filling pressures and diastolic relaxation at the time of measurement, the LA volume reflects the cumulative effects of diastolic dysfunction and increased filling pressures over time and has been called the hemoglobin A1c of diastolic function. Trials using this marker as a surrogate endpoint should therefore be planned for a sufficient amount of time for the LA to undergo remodeling to a smaller volume. This is probably one of the reasons why most trials testing a treatment of diastolic function have mainly focused on  $e'$  and/or the E/ $e'$  ratio (59,66-68). In the PARAMOUNT (Prospective Comparison of the Angiotensin Receptor Nephilysin Inhibitor With Angiotensin

Receptor Blocker on Management of Heart Failure With Preserved Ejection Fraction) trial (69), the investigators assessed the effect of LCZ696 on echocardiographic measures as secondary endpoints; the primary endpoint was the change in the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). The investigators found that the only echocardiographic measure that improved, coherent with an improvement in the levels of NT-proBNP, was LA size (both defined by the diameter and the volume). In comparison, the authors found no change in  $e'$  or the E/ $e'$  ratio. This emphasizes that LA size, which reflects sustained increase in LV filling pressure, may be a more robust metric of diastolic function than Doppler-derived measures, which are subject to greater variability and are more sensitive to changes in afterload, pre-load, and sympathetic tone.

Recent studies have focused on assessing LA function instead of maximal size as a sensitive marker of diastolic dysfunction and morbidity (70-72). Because the LA is a thin-walled structure, continuously exposed to LV pressure and function, it may provide information on pre-clinical and early impairment of the LV. Measures of LA function have been demonstrated to identify minuscule impairment of LV function even when ejection fraction is normal (72) and to identify patients with hidden paroxysmal atrial fibrillation following a cryptogenic ischemic stroke as the only echocardiographic parameter (70). However, investigators using LA measures of structure and function have to bear in mind that the pathophysiological factors that affect function and maximal size are different. Parameters of LA function (e.g., longitudinal shortening, minimal size, emptying fraction) are determined by LA contractility and the instantaneous loading conditions, which strongly depend in turn on LV properties and pulmonary vein compliance, whereas the maximal LA size is a marker of chronic pressure overload caused mainly by severe LV diastolic dysfunction.

#### **LARGE INTERVENTION TRIALS ASSESSING THE EFFECT OF TREATMENT ON DIASTOLIC FUNCTION.**

Only a few large interventional phase II trials have assessed the treatment effect on diastolic dysfunction as a surrogate primary endpoint. They generally fall into the category of diastolic dysfunction due to hypertension (66,67) or diastolic function in HFpEF (59,68). The aim of the VALIDD trial was to determine whether lowering blood pressure with an angiotensin receptor blocker would improve diastolic function to a greater extent than would pharmacological approaches not based on inhibition of the renin-angiotensin-aldosterone axis. The investigators found that lowering blood pressure

improved diastolic function, defined by an increase in  $e'$  at follow-up, irrespective of the type of antihypertensive agent used (66). They also found that the participants in the valsartan group improved the isovolumic relaxation time and longitudinal systolic peak tissue velocity. Whether the improvement in early relaxation was due to an actual improvement in the diastolic function of the heart or due to decreased afterload, which is well known to improve the rate of early relaxation (73,74), remains unknown.

In the EXCEED (Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction) trial, the aim was to test whether intensive blood pressure control among patients with uncontrolled hypertension and diastolic dysfunction would be more effective in improving diastolic function than standard blood pressure control (70). The investigators found that the degree of blood pressure reduction observed was the most important determinant of the degree of improvement in diastolic function, determined by  $e'$ . However, they found no difference in the improvement in  $e'$  between the intensive blood pressure treatment group and the standard blood pressure treatment group. Isovolumic relaxation time was the only diastolic measure that showed a statistically significant improvement in the intensive treatment group compared with the standard treatment group, which is comparable to the results of the VALIDD trial (66). Again, whether these improvements in the diastolic function actually represent improved diastolic function or rather changes in the diastolic measures accompanying decreased afterload is unclear.

The aim of the Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial was to evaluate the effect of spironolactone on diastolic function and exercise capacity in patients with HFpEF (68). The investigators found that spironolactone improved diastolic function, as determined by the  $E/e'$  ratio (and natriuretic peptide levels). This improvement in function (including  $e'$ ,  $E$ , LV ejection fraction and mass index, and LV end-diastolic diameter) was not associated with improvement in the maximal exercise capacity, patient symptoms, or quality of life. Again, as in the VALIDD and EXCEED trials, the improvement in the  $E/e'$  ratio was accompanied by a highly significant reduction in blood pressure. However, the investigators demonstrated that after adjustment for baseline and follow-up blood pressure values, the effects of spironolactone on diastolic function ( $E/e'$  ratio) remained statistically significant, suggesting that the reverse remodeling effects of spironolactone were independent of blood pressure reduction. Nevertheless, blood pressure is only an indirect measure of LV afterload, and correction for blood pressure reduction

in the statistical model may not be adequate to refute a primary effect of changes in loading conditions to explain the differences seen between the 2 groups. Additionally, even though spironolactone improved an echocardiographic measure of diastolic function, the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial recently demonstrated no benefit of spironolactone in preventing adverse outcomes in HFpEF (75). In this trial, the  $E/e'$  ratio was among the strongest prognosticators in patients with HFpEF, re-emphasizing the importance of diastolic impairment in the progression of the disease.

#### ASSESSMENT OF DIASTOLIC FUNCTION: NUCLEAR IMAGING

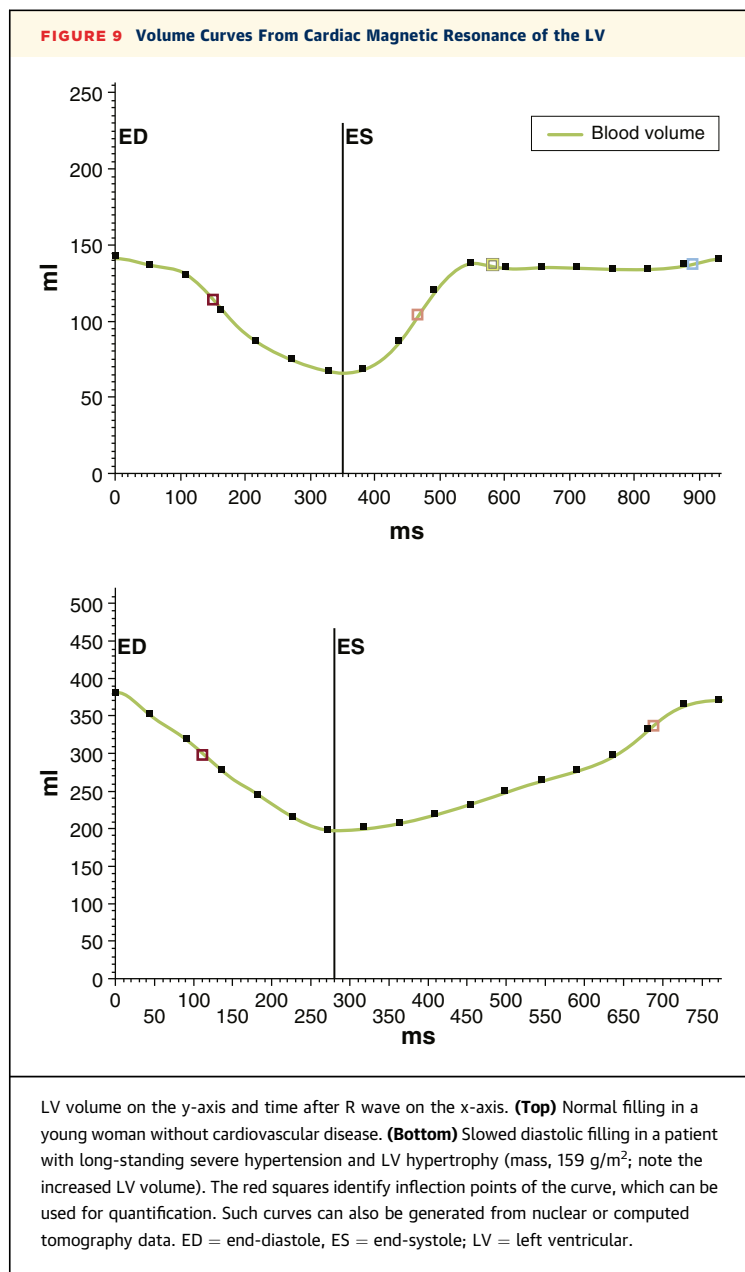
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From gated radionuclide ventriculography data, LV filling rates can be calculated by comparing sequential LV volumes during diastole, which can be calculated with frame rates of approximately 20/s. From these, time-volume filling curves, peak filling rates, and time to peak filling rates can be determined (Figure 9), which decrease with slowed LV relaxation. Low time resolution and pre-load dependence of filling rates affect their interpretation; thus, nuclear imaging is rarely used to assess diastolic function.

#### ASSESSMENT OF DIASTOLIC FUNCTION: CARDIAC MAGNETIC RESONANCE

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Cardiac magnetic resonance (CMR) is generally regarded as the gold standard for assessing the volume of cardiac chambers and, as such, is well suited to provide LV volume changes over time, which can be converted to filling curves routinely by analysis packages (Figure 9). Similar to the less accurate and temporally coarser nuclear ventriculography data, peak filling rates and time to peak filling are the fundamental parameters. However, in a study examining the use of early and late LV peak filling rates in assessing iron load in thalassemia, which can be directly estimated by  $T2^*$  CMR (76), these parameters were not found to be useful. Blood flow velocity can be measured directly (i.e., not via volumetric filling rates) by velocity encoding or “phase-contrast” CMR. Hence, transmitral and pulmonary vein flow can be measured and used in a manner analogous to echocardiographic Doppler values (77). In addition, tissue velocity (e.g., of the ventricular walls) can be measured, although only small validation studies exist (78). Of course, CMR is also an established technique to measure LA volume (79); however, systematically and substantially higher LA volume values by CMR than by echocardiography have to be taken into



account. Newer reports also have looked at the predictive value of CMR parameters of LA function (e.g., minimal volume or LA strain by CMR feature tracking) and found predictive value of such measures for the development of heart failure (80).

Strain, strain rate, and torsion can be extracted from CMR data by 3 entirely different approaches: 1) tagging, in which material points in the myocardium are marked by “nulling” the signal from these points at baseline (e.g., in a grid pattern) and then following these points in the myocardium over time (Figure 10); 2) feature tracking, which is akin to speckle tracking

by echocardiography—this is a post-processing technique applied to CMR or computed tomography (CT) images that primarily depends on the characteristics of the images (e.g., contrast, noise), not the underlying imaging technique; and 3) velocity encoding (or phase-contrast) CMR; this technique, which is standard in CMR for blood flow velocity measurement, can be applied to tissue as well, analogous to tissue Doppler imaging in echocardiography, and the data can be processed to estimate strain (81).

Higher torsion by CMR has been found in women and older individuals, which is ascribed to the concomitant increase in concentric remodeling and relative wall thickness (43). These researchers also saw lower circumferential strain in older individuals.

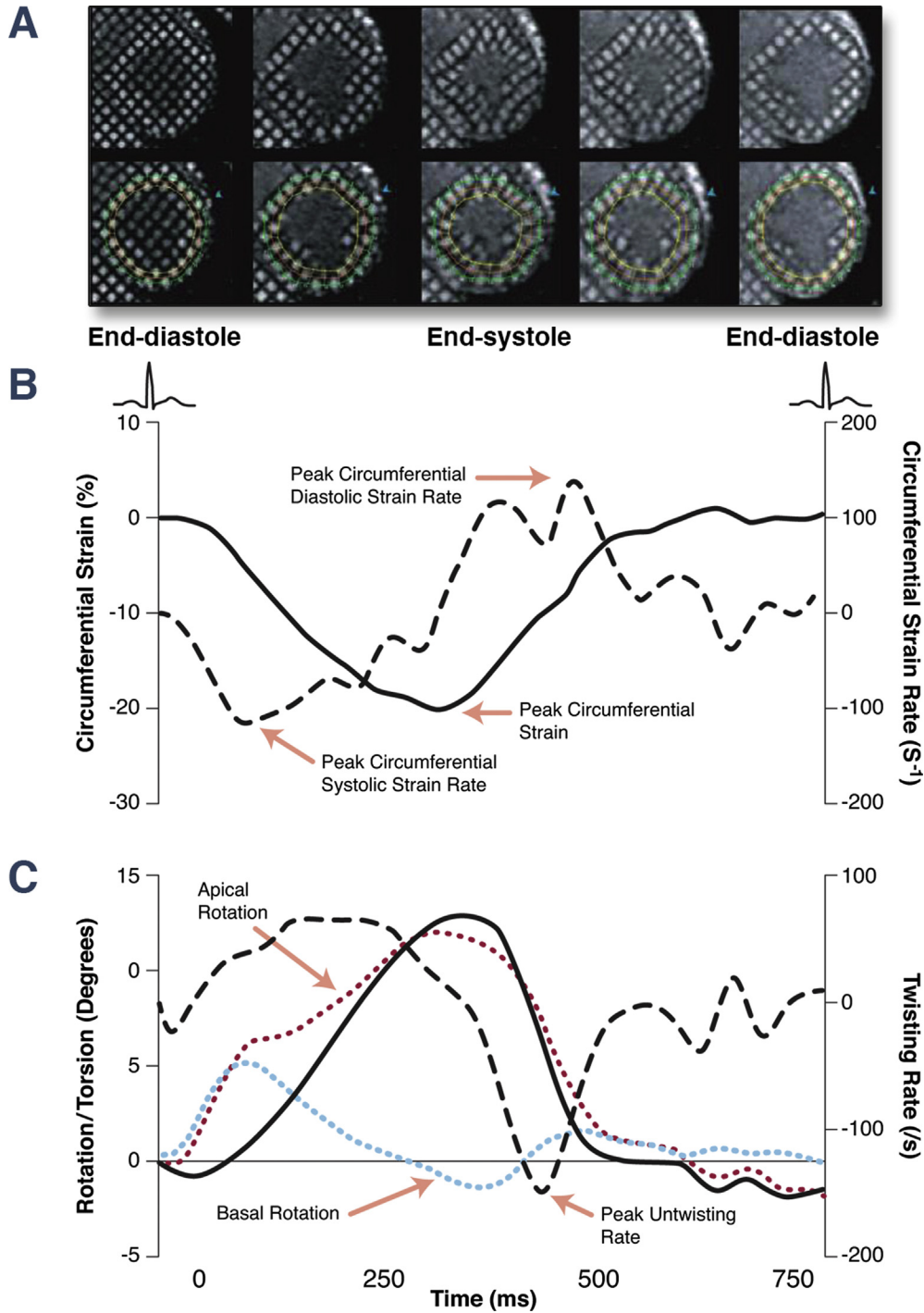
The prognostic utility of CMR indexes of diastolic strain was evaluated in a substudy from the MESA (Multi-Ethnic Study of Atherosclerosis) project, a large-scale prospective, population-based observational study (82). From CMR tagging, circumferential LV strain and strain rate were calculated; in addition to peak torsion rate and early diastolic circumferential strain rate, a new index of relaxation analogous to the isovolumic relaxation time was computed from these curves in 1,544 patients. Although torsion rate and e’sr were of no or little value, the new index predicted (independently from clinical variables, ejection fraction, and natriuretic peptide levels) the occurrence of heart failure and/or atrial fibrillation over a mean follow-up of 8 years. Similar findings were reported more than a decade ago with simple echocardiographic measurements of LV systolic and diastolic function, particularly peak E velocity (83). Similarly, a baseline echocardiographic pattern of impaired relaxation, combined with LA enlargement, was found to be predictive of heart failure or atrial fibrillation during follow-up (84).

Recently, in a small study of women with “signs and symptoms” of ischemia but no epicardial coronary stenosis, CMR was used to evaluate both systolic and diastolic LV function by strain and torsion (Figure 10). Although no differences in systolic strain were found, peak (early) diastolic strain rate and peak untwisting rate seemed to differentiate these “syndrome X” patients from healthy individuals (85).

An entirely different CMR-specific, albeit indirect, way to assess diastolic function is based on the concept of “T1 mapping,” which calculates T1 (or longitudinal) proton relaxation times (in ms) after an electromagnetic pulse and depicts them as pixel intensity (86,87). Pathological changes of T1 times in myocardial space may be due to excess water, iron, or protein deposition. T1 mapping can be carried out with or without gadolinium contrast (“native” T1



**FIGURE 10** LV Circumferential and Torsional Strain Derived From CMR Tagging



(A) Representative cardiac magnetic resonance (CMR) image obtained at the level of the papillary muscles, with a tissue tagging sequence (Top). Analysis was performed using commercially available software (HARP, Diagnosoft, Durham, North Carolina), which constructs a mesh tracking tissue deformation over a single cardiac cycle, using the harmonic phase. (B) Representative tracing of circumferential strain (solid line) and circumferential strain rate (dashed line) over a single cardiac cycle. (C) Representative data tracing of apical (red line) and basal (blue line) rotation, net torsion (solid black line), and the rate of ventricular twisting (dashed line) over a single cardiac cycle. Reproduced with permission from Nelson et al. (85).

mapping vs. extracellular volume imaging). Whereas native T1 mapping encompasses both intracellular and extracellular changes, the so-called extracellular volume technique, which requires gadolinium-based contrast application, allows quantification of the extracellular volume fraction of myocardium, which is a surrogate for myocardial fibrosis, interstitial edema, and others (Figure 11). Different than late enhancement after gadolinium contrast injection, which visualizes localized increases in extracellular volume and has become commonplace for myocardial scar imaging, T1 mapping does not require focal differences and thus allows quantification of diffuse myocardial changes such as nonfocal edema or fibrosis. T1 mapping of extracellular volume gives no specific information why the extracellular space is increased and what kind of material fills it—it only measures the fraction of the total myocardial volume that is extracellular. In a small series of post-heart transplant

patients, a modest correlation of T1 times with the constant of chamber stiffness was found. Importantly, in this small group of patients, there was no significant relation of T1 relaxation times to invasively measured LV diastolic pressure, the relaxation constant  $\tau$ , or near simultaneous echocardiographic E/e' ratio, thus cautioning against a too simplistic equation between T1 times and diastolic function (88). In another study comparing patients with heart failure with reduced or preserved ejection fraction with control patients, patients with HFpEF had larger extracellular volume fractions (29%) than control patients (27%) but smaller than patients with reduced ejection fraction (31%); however, the differences were very small (89). Another study found a weak correlation of the E/e' ratio with myocardial T1 times after contrast application and in a small subgroup with myocardial biopsy, a good inverse correlation between T1 time after contrast application and extracellular volume fraction (90). Thus, there are conflicting results for T1-related techniques, fibrosis, and diastolic function. The technique still has to be considered experimental, with a clear need for more validation and establishment of procedural and analytical standards. Thus, although CMR techniques at present allow the characterization of tissue to a degree and thus allow for unique diagnostic information, their utility for diagnosing and following diastolic LV function remains limited and impractical.

Finally, CMR is a well-established modality for the difficult diagnosis of constrictive pericarditis, for which it not only can directly assess pericardial thickening but also help diagnose the amount of respiratory variation in left and right ventricular filling (91).

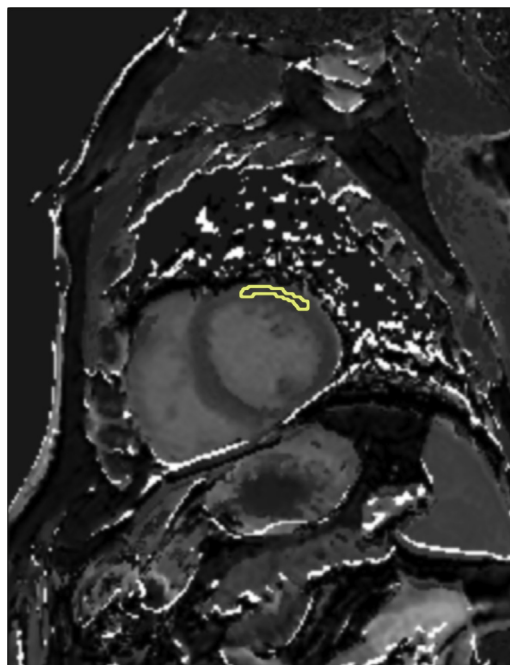
#### ASSESSMENT OF DIASTOLIC FUNCTION: CARDIAC CT

Because of radiation exposure and the availability of other techniques for this purpose, CT has only sporadically been used to assess diastolic function. Similar to nuclear imaging and CMR, it provides LV volume data, albeit at a modest temporal resolution. An important application of CT is the detailed morphological diagnosis of constrictive pericarditis.

#### ROLE OF AGE AND PHYSICAL EXERCISE FOR THE LIMITS OF NORMALCY

A vexing question is the extent to which age-related changes in diastolic function, and their correlates on imaging, are truly related to aging and thus unavoidable and which changes are due to modifiable factors. The relaxation constant  $\tau$  has been found by some (92), but not all (93), investigators to increase with age.

**FIGURE 11** Determination of ECV Fraction by T1 Imaging With Contrast Cardiac Magnetic Resonance



T1-based extracellular volume map in which signal intensity is proportional to extracellular volume fraction (the percentage of total tissue volume that is extracellular). The map was calculated from T1 times before and after contrast application, and extracellular volume fraction was calibrated by measuring extracellular volume (ECV) in a blood sample as  $(1 - \text{hematocrit})$  (86). In the sample region of interest in the myocardium, the average ECV fraction was 22%.

LV chamber stiffness, the inverse of LV compliance, increases with age in sedentary, but not in highly endurance-trained, individuals (94). Therefore, it is not clear how much of the changes observed in diastolic imaging parameters in older adults (e.g., decreased transmitral E/A ratio) are due to aging alone and how much is caused by either diseases, such as hypertension, or physical deconditioning (“sedentary lifestyle”). It may well be that aging plays a relatively modest role in the changes observed in elderly individuals. For example, higher transmitral peak E/A ratios have been found in athletes than in sedentary individuals of the same age, particularly in older adults (95-98). A study of nearly 3,000 middle-aged individuals participating in a fitness program (98) found these effects not only in high-level athletes but also in less trained individuals. Individuals with higher exercise capacity had less concentric LV remodeling (but higher LV mass in men), smaller relative wall thickness, lower E/e' ratios, and higher E/A ratios than less fit individuals. Interestingly, LA and LV size increased with exercise capacity, indicating that it is not unambiguously related to diastolic function. Ejection fraction, on the other hand, was not related to exercise capacity. Several trials have shown positive effects of exercise training on patients with HFpEF and indirectly demonstrated improved diastolic function (99-101).

An important question is what significance imaging signs of diastolic dysfunction have in patients without clear-cut symptoms. This situation has been termed *pre-clinical diastolic dysfunction*, a suggestive name in need of objective evidence from longitudinal studies. Several large studies have suggested that even mild diastolic abnormalities in the presence of preserved LV ejection fraction imply an impaired prognosis independently from age and baseline symptoms (102-104). On the other hand, population-based studies have shown a high prevalence of asymptomatic diastolic dysfunction based on echocardiographic parameters. Abhayaratna et al. (105) showed that in an Australian population aged  $\geq 60$  years with preserved ejection fraction, 23.5% had mild and 5.6% had moderate or severe diastolic dysfunction by echocardiography; even of the latter group, 36% were asymptomatic. In contrast, only 0.5% of the group with reduced ejection fraction was asymptomatic. Similar numbers have been reported from the Framingham Heart Study in the United States (106), with 36% of elderly participants having asymptomatic diastolic dysfunction and 5% asymptomatic systolic dysfunction. From Italy, similar values for silent diastolic dysfunction (35% of a population 65 to 84 years old), again far more than

for systolic dysfunction, have been documented (107). A retrospective study following patients who at baseline had moderate or severe diastolic dysfunction on echocardiography, but no heart failure symptoms, showed that only 12% went on to develop overt heart failure over the next 3 years (108). However, in patients with diabetes, asymptomatic diastolic dysfunction and, in particular, E/e' ratio  $>15$  (septal e') have been shown to predict more than a doubling of the rate of overt heart failure over the next 5 years (109,110).

### OPEN QUESTIONS AND UNMET NEEDS

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There continue to be large gaps in our understanding of diastolic heart failure, and delayed relaxation, reduced compliance, and atrial dysfunction may have very separate causes and yet all produce the clinical syndrome of diastolic dysfunction. Further, whether this condition is due to a specific myocardial disease or results from a myocardial response to unfavorable working conditions, in particular arterial stiffening, remains unclear.

The issue of diastolic function grading remains hotly debated. A large observational study reported that patients frequently (17% of patients examined at a clinical echocardiography laboratory) had intermediate features between grades 1 and 2 (E/A ratio  $\leq 0.75$ , deceleration time  $>140$  ms, and E/e' ratio  $\geq 10$ ) and had a distinctly worse prognosis than those with classic grade 1 dysfunction (differing in that E/e' ratio  $\leq 8$ ), which was similar to the prognosis of grade 2 dysfunction (111). This classification purports to reflect different severities and advancement of diastolic dysfunction, and for some diseases, like amyloidosis, this has been convincingly shown (112). However, it is based on echocardiographic patterns and thus indirect signs of elevated diastolic LV pressures, not any specific disease pathology. It is also unclear whether the existing stages are optimal for clinical use. An additional subdivision of stage 1 (defined by E/A ratio  $\leq 0.75$ , deceleration time  $>140$  ms, and E/e' ratio  $<10$ ) has been suggested, with the same limits for E/A ratio and deceleration time but E/e' ratio  $\geq 10$  (111). Others have proposed to add reversibility of stage 3 after therapy as a stratifying criterion. More epidemiological data are needed to better understand the clinical and prognostic value and perhaps to modify this classification.

Mitral regurgitation considerably complicates the interpretation of imaging data with regard to LV diastolic function: it elevates diastolic pressures in the LA and LV, causes chronic dilation of the LA, increases pulmonary capillary pressure and pulmonary

pressures, and leads to the clinical picture of heart failure. Most of the routinely evaluated parameters of diastolic function, such as transmitral and pulmonary venous flow patterns,  $E/e'$  ratio, systolic pulmonary pressure, LA size, and others, are affected by mitral regurgitation indistinguishably from primarily LV myocardial dysfunction. In the presence of gross morphological abnormalities of the mitral valve (e.g., a flail leaflet), the differential diagnosis is relatively easy; however, this is not the case in functional mitral regurgitation, and separation of valvular and myocardial etiology is particularly difficult in patients with atrial fibrillation and degenerative valvular changes like annular calcification, among other conditions.

No established drug or other therapy for HFpEF exists, perhaps with the exception of physical exercise training. Given the heterogeneity of HFpEF populations, it may well be that only targeted therapies (113), addressing specific subgroups of such patients, will be successful. This underscores the need of “deep phenotyping” these patients, a task for which cardiac imaging with its ever more differentiated, multi-pronged armamentarium appears well suited.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Frank A. Flachskampf, Uppsala Universitet, Institutionen för Medicinska Vetenskaper, Akademiska Sjukhuset, Ingång 40, Plan 5, 751 85 Uppsala, Sweden. E-mail: frank.flachskampf@medsci.uu.se.

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**KEY WORDS** cardiac magnetic resonance, computed tomography, diastolic dysfunction, echocardiography, heart failure with preserved ejection fraction (HFpEF), left ventricular function

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