

HEART FAILURE

Echo-Doppler assessment of diastole: flow, function and haemodynamics

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The concepts related to diastolic function were developed by muscle physiologists and by cardiologists with a strong background in physics (cardiac mechanics and fluid dynamics). These scientists described left ventricular (LV) material properties in terms of pressures and volumes, and their mutual relation. When a given volume is added to a ventricle, pressure rises more in a diseased ventricle, which is stiffer or less compliant. These scientists also focused on the dynamics of myocardial relaxation and evaluated the speed of this process by fitting an exponential relation to LV pressure fall, and by calculating the time constant of isovolumetric relaxation tau (τ). A prolonged time constant is associated with a delayed myocardial relaxation, and possibly also with a relaxation that is incomplete and still ongoing at end-diastole. Both decreased compliance and delayed relaxation may induce increased filling pressures, hence heart failure. The measurement of relaxation, compliance and diastolic pressures require the presence of a high fidelity pressure catheter in the LV cavity. This limits the use to clinical situations where an invasive procedure is warranted. Such an invasive procedure, however, remains the golden standard when non-invasive measurements are inconclusive. A less invasive procedure is pulmonary artery catheterisation and measurement of the pulmonary capillary wedge pressure (PCW) as a surrogate for left atrial (LA) or LV filling pressures.

Echocardiography and cardiac Doppler have played an important role in the evaluation of diastolic function since the pioneering work of Liv K Hatle in the mid 1980s.¹ She initiated and supported research, initially in Trondheim (Norway) and later at Stanford (Palo Alto, California, USA) and the Mayo Clinic (Rochester, Minnesota, USA). She was the first to contrast mitral inflow signals to invasively measured filling pressures. With the extraordinary development of cardiac imaging, cardiologists started to look at haemodynamics and at diastolic function, trying to evaluate filling pressures with mitral flow and more recently with tissue Doppler. In addition to evaluating filling pressures, non-invasive imaging has the advantage of giving a comprehensive overview of LV morphology and function, LA size and function, right ventricular pressure and function, and venous congestion. This has led to the surprising evolution that young cardiologists have learned to guide patient management with echo-Doppler indices, and to use them not anymore as surrogates for invasive measurements but as physiological findings in their own right. Echocardiography has become the cornerstone of

the evaluation of diastolic function because of its non-invasive character and because of the possibility to repeat recordings in the same patient, and to compare consecutive findings. The strength of this approach is to use the patient as his or her own control. Data are recorded under optimised therapy and, in order to evaluate changes in haemodynamics, the follow-up Doppler signals are compared to those optimised data.

The present article highlights the clinically most relevant aspects of the recent European Association of Echocardiography/American Society of Echocardiography (EAE/ASE) recommendations for the evaluation of LV diastolic function by echocardiography.² For more detailed information, the reader is directed to these recommendations.

PHYSIOLOGY OF DIASTOLE

Diastole takes over from systolic ejection at aortic valve closure and includes LV pressure fall, rapid filling, diastasis (at slower heart rates), and atrial contraction (figure 1). The ventricle has two alternating functions: systolic ejection and diastolic filling. The optimal performance of the LV depends on its ability to cycle between two states: (1) a compliant chamber in diastole that allows the LV to fill from low LA pressure; and (2) a stiff chamber (rapidly rising pressure) in systole that ejects the stroke volume at arterial pressures. Furthermore, the stroke volume must increase in response to demand, such as exercise, without an increase in LA pressure. The theoretically optimal LV pressure curve is rectangular, with an instantaneous rise to peak and an instantaneous fall to low diastolic pressures, which allows for the maximum time for LV filling. This theoretically optimal situation is approached by the cyclic interaction of myofilaments and assumes competent mitral and aortic valves.³

Elevated filling pressures are the main physiologic consequence of diastolic dysfunction. Diastolic dysfunction may be asymptomatic and can occur with still normal and with elevated filling pressures. Diastolic dysfunction will be observed in heart failure both with reduced (HFREF) and preserved (HFPEF) ejection fraction. Filling pressures are considered elevated when the mean PCW is >12 mm Hg or when the LVEDP is >16 mm Hg. In healthy subjects filling pressures change minimally with exercise. Exercise induced elevation of filling pressures may limit exercise capacity and is indicative of poor diastolic reserve. In these patients, diastolic function is still adequate to maintain low pressures at rest, but diastolic failure occurs when the heart is stressed by increased pressures and heart rate.

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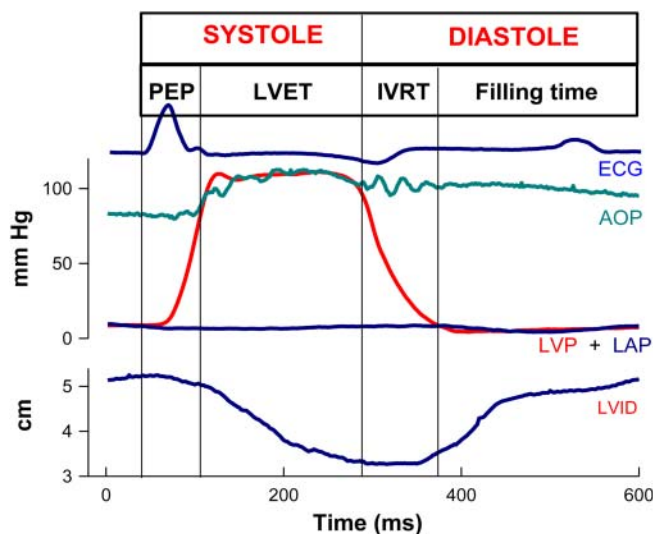


Figure 1 Haemodynamic aspects of the cardiac cycle. Data recorded in anaesthetised open-chest dog. The top panel shows a limb electrocardiogram (ECG). The middle panel displays pressures recorded with a fluid filled manometer in the aortic root (AOP) and with a high fidelity manometer in the left ventricle (LVP) and atrium (LAP). The bottom panel displays the LV internal diameter (LVID), measured with implanted sonomicrometers. This measurement is comparable to an M-mode echocardiographic measurement of the left ventricular cavity at the tip of the mitral valve. The cardiac cycle is commonly subdivided in systole and diastole with diastole starting at aortic valve closure. Diastole comprises isovolumic relaxation, rapid filling, slow filling, and atrial contraction.

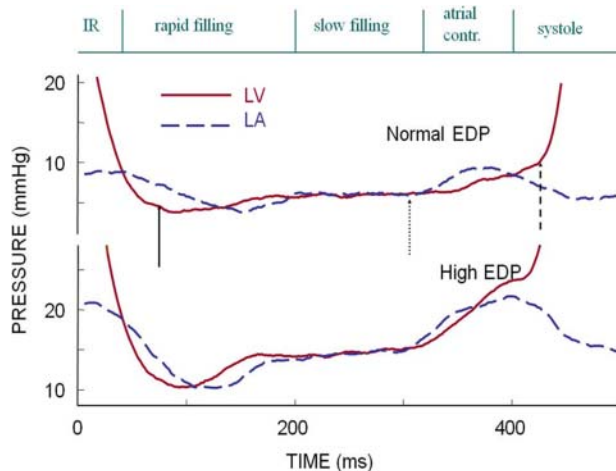


Figure 2 The four phases of diastole. Left ventricle (LV) and left atrium (LA) pressures during diastole. The four phases of diastole are marked in relation to high fidelity pressure recordings from the LA and LV in anaesthetised dogs. The first pressure crossover corresponds to the end of isovolumetric relaxation and mitral valve opening. In the first phase, LA pressure exceeds LV pressure, accelerating mitral flow. Peak mitral E roughly corresponds to the second crossover. Thereafter, LV pressure exceeds LA pressure, decelerating mitral flow. These two phases correspond to rapid filling. This is followed by slow filling, with almost no pressure differences. During atrial contraction, LA pressure again exceeds LV pressure. The solid arrow points to LV minimal pressure, the dotted arrow to LV pre-A pressure, and the dashed arrow to LV end-diastolic pressure. The upper panel was recorded at a normal end-diastolic pressure (EDP) of 8 mm Hg. The lower panel was recorded after volume loading and an EDP of 24 mm Hg. Note the larger pressure differences in both tracings of the lower panel, reflecting decreased operating compliance of the LA and LV. Atrial contraction provokes a sharp rise in LV pressure, and LA pressure hardly exceeds this elevated LV pressure. Reproduced with permission from Leite-Moreira and Gillebert in Nagueh *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165–93.

Relaxation is the process whereby the myocardium returns after contraction to its unstressed length and force. During ejection, energy is stored as the myocytes are compressed and the elastic elements of the myocardial wall are compressed and twisted. This energy is released as elastic elements recoil and causes LV pressure to fall rapidly during isovolumetric relaxation.⁴ The rate of global LV myocardial relaxation is reflected by the exponential course of isovolumetric LV pressure fall. Tau is a widely accepted invasive measure of the rate of LV relaxation, which will be 97% complete at a time corresponding to $3.5 \times \tau$ after dP/dt_{min} (peak rate of pressure fall, occurring shortly after aortic valve closure). In normal hearts, and with normal load, myocardial relaxation is nearly complete at minimal LV pressure. In diseased hearts and under abnormal load, relaxation can be delayed and incomplete, thereby contributing to increased filling pressures.

Contraction and relaxation belong to the same molecular processes of transient activation of the myocyte and are closely intertwined. Similar to contraction, relaxation is subjected to control by load, inactivation, and dyssynchrony.⁵

1. **Load.** A normal heart may tolerate quite elevated blood pressures without diastolic dysfunction. When systolic function is impaired, increased systolic pressures (and correspondingly increased wall stress) will delay myocardial relaxation.⁶ Independently of wall stress levels, increased late systolic wall stress, as induced by reflected arterial waves, will always delay myocardial relaxation and contribute to the diastolic dysfunction of the aged patient.^{7,8}
2. **Inactivation.** Myocardial inactivation relates to the processes underlying calcium extrusion from the cytosol and crossbridge detachment and is affected by a number of proteins that regulate calcium homeostasis, cross-bridge cycling, and energetics. These processes are affected by hypertrophy and ischaemia.⁹
3. **Dyssynchrony.** Minor regional variation of the timing of regional contraction and relaxation is physiological and is inherent to the function of a geometrically and functionally complex pump such as the ventricle. The heart has the capacity to adapt to moderate degrees of dyssynchronous contraction. However, frankly dyssynchronous contraction and relaxation results in a deleterious interaction between early re-extension in some segments and post-systolic shortening of other segments. This contributes to delayed global LV relaxation and elevated filling pressures.^{10,11}

Relaxation is a continuously changing determinant of diastolic function that varies as a function of cardiovascular filling, body position, blood pressure and heart rate. When heart rate increases, diastole shortens and there is less time available for the muscle to relax.

LV filling is determined by the interplay between LV filling pressures and filling properties. Immediately after mitral valve opening (figure 2,

The physiology of diastole: key points

- ▶ Diastolic function is related to myocardial relaxation and passive LV properties.
- ▶ Myocardial relaxation is determined by load, inactivation, and dyssynchrony.
- ▶ Left ventricular stiffness is determined by properties of the myocardial cell, by the extracellular matrix and by the geometry of the ventricle.

upper panel), relaxation of LV wall tension is rapid enough to cause LV pressure to continue to decline despite an increase in LV volume. This fall in pressure produces an early diastolic pressure gradient from the LA that extends to the LV apex and that accelerates blood out of the LA, producing early diastolic flow that quickly propagates to the apex of the LV. This quick propagation is due to ventricular suction. After this initial filling the pressure difference decreases and transiently reverses. This reversed gradient decelerates and stops the flow from the LA to the LV. The initial rapid filling wave corresponds to the E wave of the mitral inflow. During the midportion of filling (diastasis), LA and LV pressures equilibrate and flow is limited to low velocities. Late in diastole, atrial contraction produces a second LA-to-LV pressure gradient that propels blood from the LA to the LV and manifests as the mitral inflow A wave.¹²

The filling pattern of the LV is determined by both the ongoing relaxation and by the passive properties of the LV. Relaxation is discussed above. The passive properties are described with stiffness ($\Delta P/\Delta V$) or inversely with compliance ($\Delta V/\Delta P$) and commonly refer to end-diastolic properties. End-diastolic evaluation is preferred for minimising the effect of residual relaxation. Several factors extrinsic and intrinsic to the LV determine these passive end-diastolic properties.⁹ Extrinsic factors are mainly pericardial restraint and RV-LV interaction. Intrinsic factors include myocardial stiffness and LV morphology. Myocardial stiffness is related to cellular, sarcomeric properties (such as stiffness of the macromolecule titin) and to extracellular properties (mainly fibrosis of the interstitial space). LV morphology primarily refers to wall thickness, but also to chamber size and shape.

GENERAL MEASUREMENTS

Clinical parameters

A good examination of diastolic function starts with clinical parameters recorded on the echo protocol. These parameters are body weight and height (with computation of body mass index and body surface area (BSA)), blood pressure, heart rate, and heart rhythm. In addition, a clinical examination with central venous pressure, lung and heart auscultation is warranted. The clinical question of the referring physician should always clearly

be noted. A clear and unequivocal answer to this question is and remains the finality of the echo examination.

LV mass

LV dimensions and wall thickness should be measured when trying to arrive at conclusions on diastolic function and filling pressures. The presence of hypertrophy is an indicator of delayed myocardial relaxation and increased myocardial fibrosis, hence LV stiffness. It is also a strong determinant of incident cardiovascular disease.

The measurement of LV mass should optimally be performed with three dimensional echocardiography. An alternative is a computation on two dimensional measurements in accordance with the guidelines of the ASE together with the EAE.¹³ But how should we determine the presence of hypertrophy and what are the cut-offs? At the population level, the main determinants of LV mass are body size, obesity, blood pressure and age. Independently from body size, men have a higher LV mass than women. In the evaluation of hypertension we are interested in the effects of blood pressure and the cardiovascular risk related to blood pressure.¹⁴ The adequate scaling for evaluating hypertrophy in hypertension is to divide LV mass by BSA, so that you largely eliminate the effects on LV mass of body size and obesity. In most other clinical conditions it is advisable to include the effect of both obesity and blood pressure on LV mass. Then the scaling for evaluating hypertrophy and excluding the effects of body size is to divide LV mass by height. The optimal method appears to be to scale allometrically by body height elevated to the exponent 1.7 ($\text{g}/\text{m}^{1.7}$) and using different cut-offs for men and women. The previously used scaling (by height exponent 2.7) merged men and women in computing the optimal allometric exponent. As a consequence, hypertrophy is overestimated in small subjects and underestimated in tall subjects.¹⁴

LA volume

Measurement of LA volume is highly feasible and reliable using the apical four-chamber and two-chamber views or optimally three dimensional echocardiography. Scaling to body size is obtained by dividing LA volume by BSA (m^2). There is a significant relation between LA remodelling and echocardiographic indices of diastolic function. However, while Doppler velocities and time intervals reflect filling pressures at the time of the examination, LA volume often reflects the cumulative effects of filling pressures over time. An LA volume of $\geq 34 \text{ ml}/\text{m}^2$ is an independent predictor of cardiovascular complications.^{2 13} Confounding conditions that are also associated with dilated left atria are prolonged bradycardia, anaemia or high cardiac output states, atrial flutter or fibrillation, and mitral valve disease. Athletes often have dilated atria in the absence of cardiovascular diseases. LA volumes should be considered in conjunction with the volumes of other chambers, clinical status, and parameters of diastolic function.

General measurements relevant for diastolic function: key points

- ▶ LV mass, optimally with three dimensional echocardiography. Scale LV mass for BSA (m^2) or for body height ($g/m^{1.7}$) depending on the clinical question
- ▶ LA volume. Scale LA volume accordingly
- ▶ Pulmonary artery systolic pressure and venous pressures

Pulmonary artery pressures

In the absence of pulmonary artery disease or mitral stenosis, pulmonary artery pressures are a reflection of LV filling pressures. Symptomatic patients with diastolic dysfunction usually have increased pulmonary artery pressures. Low (normal) pulmonary pressures indicate normal LV filling pressures, at least under the conditions of the clinical examination. Low pulmonary pressures may, however, be associated with both normal and abnormal diastolic function.

The easiest and best standardised way of evaluating pulmonary artery pressures is to determine the peak velocity of the tricuspid regurgitation jet by continuous-wave Doppler and to add the calculated pressure difference to the right atrial pressure. The right atrial pressure may be evaluated clinically, but should optimally be confirmed echocardiographically with inferior vena caval diameter, its change with respiration, and the ratio of systolic to diastolic flow signals in the hepatic veins.

MEASUREMENTS OF DIASTOLIC FUNCTION**The first measurement of diastolic function: annular motion (e')**

In systole the annulus moves toward the LV apex. In diastole it returns to its initial position in two waves, rapid filling and atrial contraction. This manifests on the tissue Doppler signal of the mitral annulus as S' (systolic velocity), e' (early diastolic velocity), and a' (late diastolic velocity) (figure 3, lower left panel). One of the earliest abnormalities of diastolic function is delayed myocardial relaxation. Without delayed myocardial relaxation there is virtually no diastolic dysfunction. The velocity of mitral annulus movement during early filling e' correlates well with the invasively measured time constant τ , but is not solely determined by myocardial relaxation.¹⁵ In healthy and young persons, septal e' is >10 cm/s and lateral e' is >12 cm/s. These velocities increase with exercise and underlie diastolic suction of the LV. There is a gradual decrease of e' with age and correspondingly an increased ratio of E/e' .¹⁶ This is related to the ageing process and implies an age related decrease of myocardial relaxation. In persons with diastolic dysfunction, e' is even more reduced than with age and remains reduced in all grades of diastolic dysfunction.¹⁷ A decreased e'/a' ratio (which was standardised for systolic function by dividing the ratio by S') is an

independent predictor of mortality in the general population.¹⁸

In general, the velocity scale should be set at about 20 cm/s above and below the zero velocity baseline, though lower settings may be needed when there is severe LV dysfunction and annular velocities are markedly reduced (scale set to 10–15 cm/s). Minimal angulation should be present between the ultrasound beam and the plane of cardiac motion. It is recommended that spectral recordings be obtained at a sweep speed of 50–100 mm/s at end-expiration and that measurements should reflect the average of three consecutive cardiac cycles. It is advised to measure both septal and lateral e' with pulsed wave tissue Doppler imaging (rather than with colour coded tissue Doppler imaging) and to average both values.²

It should be taken into consideration that basal regional LV wall motion abnormalities may affect septal or lateral tissue velocities, and that right heart pathology and pulmonary hypertension may affect septal velocities. These conditions may lead to unreliable measurements of e' , as long as the intention is to gather information on global diastolic function.

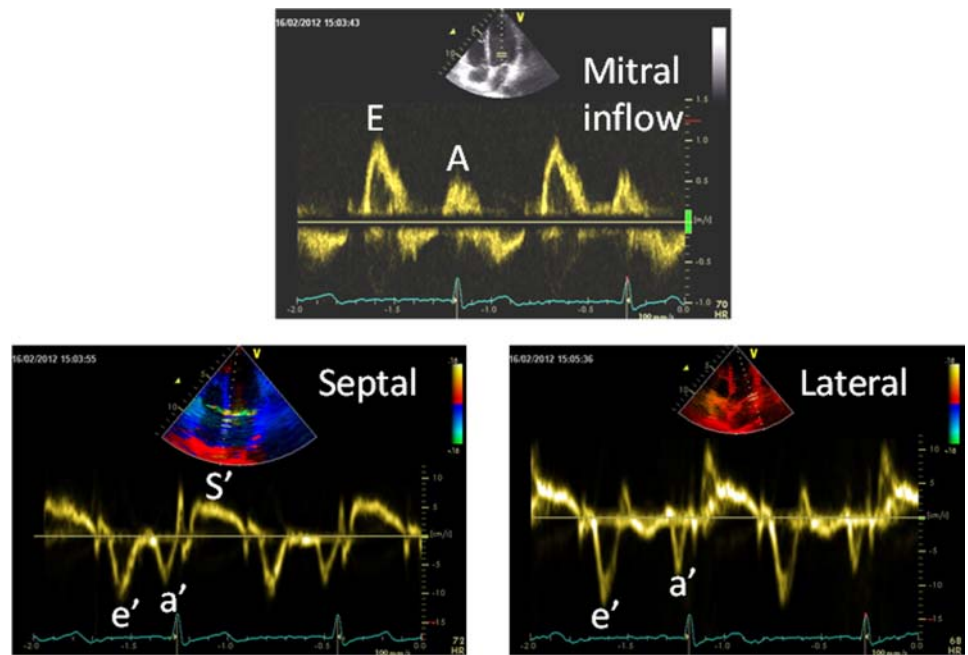
The mitral inflow signal

The recording and the interpretation of the diastolic mitral inflow signal are of paramount importance for the clinical evaluation of a patient with diastolic dysfunction. When comparing the Doppler data of a patient to a previous recording of the same patient under optimised therapy, it is primarily the mitral inflow that varies with altered filling pressures. Changes in mitral E wave are the direct reflection of changes in filling pressures and can be used to evaluate them.

A careful and reliable tracing should be obtained.¹⁹ The colour flow mapping signal is looked at first, and the probe repositioned until the cursor (optimally kept in the middle of the sector) is parallel with the mitral flow direction. In dilated hearts it is sometimes necessary to displace the probe to the axillary region. A CW interrogation for assessing peak E (rapid filling) and peak A (atrial contraction) velocities is then performed. The use of CW Doppler guarantees the registration of maximal velocities. A switch is then made to PW Doppler and a sample volume of 1–3 mm selected. Starting close to the mitral annulus, the sample volume is then displaced toward the apex until a crisp signal with maximal velocities is obtained—ending up between the open leaflets of the mitral valve. Spectral mitral velocity recordings should be initially obtained at a lower speed of 25–50 mm/s for the evaluation of respiratory variation of flow velocities, as seen in patients with pulmonary or pericardial diseases. Then the speed is increased to 100 mm/s and three consecutive cardiac cycles at end-expiration are averaged.

Primary measurements of the mitral inflow signal (figure 3) include peak early filling velocity (E), late diastolic filling velocity (A), the E/A ratio,

Figure 3 Diastolic function in a healthy subject. Data recorded in a healthy 26-year-old woman. The upper panel displays a diastolic mitral inflow. The lower left panel displays the tissue Doppler of the septal mitral annulus and the lower right panel displays the tissue Doppler of the lateral annulus. Measurements were averaged over three cycles at end-expiration. E=105 cm/s, DT 170 ms, A 57 cm/s, E/A is 1.84 and IVRT=78 ms. Septal e' =10.4 cm/s, Septal E/e' =10.0%; Lateral e' =12.6 cm/s, Lateral E/e' =8.3%; Averaged e' =11.5 cm/s, averaged E/e' =9.1% (for explanation of abbreviations see text).



deceleration time (DT) of early filling velocity, and the time interval between aortic closure and mitral opening (IVRT). IVRT is obtained by directing the cursor of the CW Doppler between the mitral and aortic valve in order to record movements of both valves.

The interpretation of the mitral inflow signal may appear complex until some basic determinants are understood. With age and with disease IVRT increases, E/A decreases, and DT increases. These changes reveal a slower process of myocardial relaxation. This compromised rapid filling is compensated by a forceful atrial contraction and increased A. Increased filling pressures and the shift toward a steeper portion of the diastolic pressure-volume relation will have opposite effects (see figure 2 lower panel for pressure tracings). IVRT will decrease, E will increase, DT will decrease, and A and A duration will decrease. In this situation the patient is more diseased and has higher filling pressures, but his mitral inflow appears less abnormal, even normal. We therefore call such a signal a pseudo-normal filling. When disease progresses and filling pressures are markedly elevated, an elevated E, a short DT, and a small and narrow A will be observed. This is a restrictive inflow pattern. A mid-diastolic flow ≥ 20 cm/s may also be observed. The analysis of the mitral inflow signal therefore leads to a classification as normal, impaired LV relaxation ($E/A < 0.8$), pseudo-normal ($E/A 0.8-1.5$) and restrictive ($E/A \geq 1.5-2$). Figures 3 and 4 (upper panels) show a normal and a pseudo-normal mitral inflow pattern. In the pseudo-normal and restrictive pattern, increased filling pressures (and increased operational stiffness) are superposed on delayed relaxation. In these cases the pattern of delayed relaxation may be revealed by the Valsalva manoeuvre, thereby decreasing venous return and filling pressure (figure 5). Nowadays this

classification is no longer based solely on the mitral inflow signal but rather on tissue Doppler velocities, LA size, mitral inflow, and other measurements as discussed below.

Other useful approaches for evaluating diastolic function

Other signals may give very useful and additional information in individual patients, but should not be routinely recorded in all. These signals are the pulmonary vein signal and the flow propagation velocity (Vp). In the pulmonary vein signal, the peak velocity of S, D, and A is measured and the duration of A carefully recorded.²⁰ The flow propagation exceeds 50 mm/s in normal individuals and is mainly used as the ratio E/Vp. The measurement of Vp is subjected to more inter-observer variability than other common measurements of diastolic function.

Newer indices are based on speckle tracking imaging and include global diastolic strain rate, regional diastolic strain rate, and LA strain.¹² The quantification of LV torsion is another measurement related to diastolic function, which is increasingly used. Measurements may be repeated after altering loading conditions such as during the Valsalva manoeuvre or leg lifting, and most importantly during exercise. The latter is known as the diastolic stress test. The diastolic stress test reveals cases where diastolic function is not visible or limited (grade 1) at rest with normal filling pressures, but where filling pressures increase during left lifting and even more during exercise.²¹ These patients may compensate their diastolic dysfunction and keep low filling pressures at rest, but decompress during exercise due to decreased diastolic reserve and increase their filling pressures. The diastolic reserve is challenged by increased pressures mainly when systolic function is reduced,⁶ by

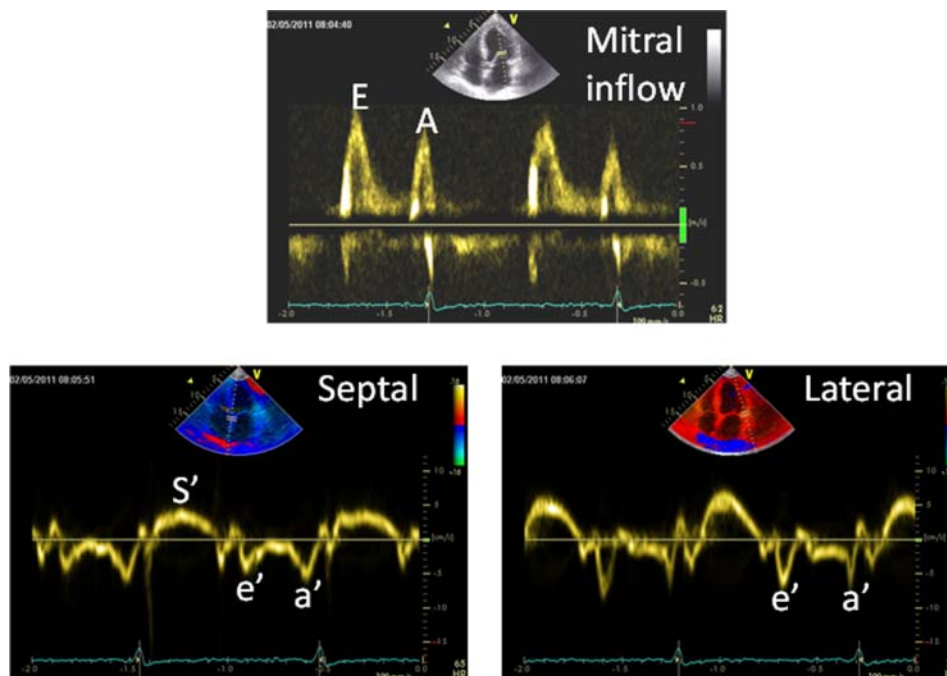


Figure 4 Diastolic function in a diseased subject. Data recorded in a 78-year-old diabetic patient with coronary artery bypass graft more than 10 years ago who presently complains of exercise induced dyspnoea. Ejection fraction is 56% (not shown). The upper panel displays a diastolic mitral inflow. The lower left panel displays the tissue Doppler of the septal mitral annulus and the lower right panel displays the tissue Doppler of the lateral annulus. Measurements were averaged over three cycles at end-expiration. $E=101$ cm/s, DT 150 ms, A 78 cm/s, E/A is 1.30 and $IVRT=84$ ms. Septal $e'=5.2$ cm/s, Septal $E/e'=19.4\%$; Lateral $e'=7.1$ cm/s, Lateral $E/e'=14.2\%$; Averaged $e'=6.2$ cm/s, averaged $E/e'=16.3\%$ (for explanation of abbreviations see text). The measurements of the mitral inflow are comparable to those of the normal subject. Analysis of the TDI data of the mitral annulus leads to diastolic dysfunction stage 2, pseudo-normal inflow signal with elevated filling pressures. On the basis of the clinical history and the echo-Doppler data, the diagnosis of heart failure with preserved ejection fraction is made.

Measurements of diastolic function: key points

- ▶ Annular motion during rapid filling (e') at the septal and lateral annulus.
 - Septal and lateral e' values are averaged
 - In selected cases septal or lateral e' is not a reliable marker of diastolic function
 - E' is reduced in all degrees of diastolic dysfunction
- ▶ The mitral inflow signal
The mitral inflow signal varies with varying filling pressures and is the best parameter of filling pressures when consecutive examinations are considered in a given patient
Mitral inflow patterns include normal, impaired relaxation, pseudo-normal and restrictive signal

increased heart rate and reduced filling time, and by the inability of these hearts to enhance relaxation during stress and exercise.

GRADING OF DIASTOLIC FUNCTION

The proposed grading of diastolic function corresponds to the recommendations for the evaluation of LV diastolic function.² There are three grades of diastolic dysfunction: grade 1 or mild diastolic dysfunction, with the impaired relaxation pattern of

mitral inflow; grade 2 or moderate diastolic dysfunction, with the pseudo-normal filling of the mitral inflow; grade 3 or severe diastolic dysfunction, with the restrictive filling of the mitral inflow (figure 6). Such a grading yielded an important predictive value for all-cause mortality in the Olmsted community.²²

The grading of diastolic dysfunction starts with the volume of the LA and the analysis of both septal and lateral early diastolic velocities. The diastolic function is considered normal if the LA is small and if the diastolic velocities e' are high (table 1). Figure 3 shows data from a healthy subject.

Some confounders of LA volume should be taken into account and were discussed under the corresponding section. For example, athletes may have enlarged left atria in the absence of diastolic abnormalities.

In all grades of diastolic dysfunction early diastolic velocities (e') are reduced and LA volume is increased. The grade is then determined by looking at the mitral inflow signal, in particular at the E/A ratio and the deceleration time DT. Figure 4 shows data from a patient with diastolic dysfunction grade 2, and a pseudo-normal filling pattern. In addition, filling pressures, evaluated with the ratio E/e' (see later), are taken into account.

When the above mentioned measures give uncertain or conflicting results, the clinician may be helped by comparing the duration of the reversed atrial contraction wave of the pulmonary vein

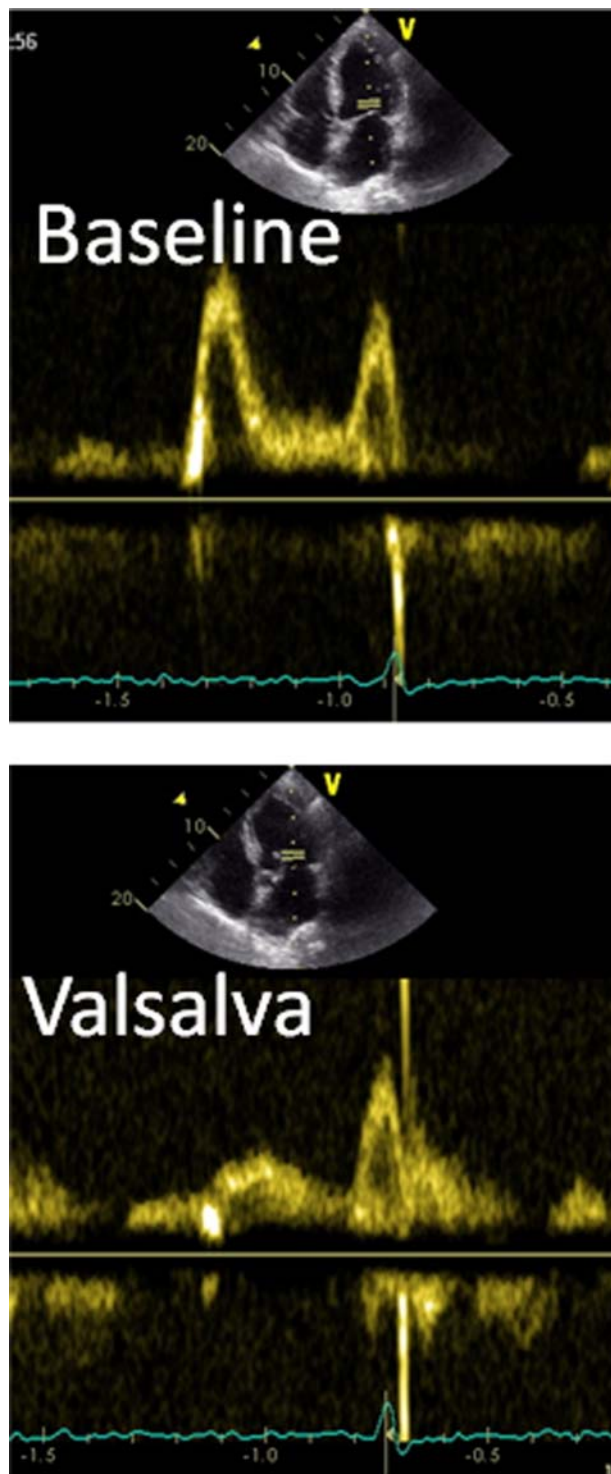


Figure 5 Valsalva manoeuvre in the same patient as figure 4. Combining annular tissue Doppler imaging (TDI) with the mitral inflow signal is the first approach to differentiating normal from pseudo-normal signals. The second approach is to decrease venous return, hence filling pressure with the Valsalva manoeuvre. The upper panel is baseline end-expiration, the lower panel is during Valsalva. In this 78-year-old diabetic patient, E/A drops from 1.3 until 0.55 (>0.5). The lower panel reveals the extent to which myocardial relaxation and initial filling are impaired. This severe diastolic dysfunction was 'hidden' in the baseline mitral inflow signal, due to elevated filling pressures.

signal and the forward atrial contraction wave at the level of the mitral annulus.²⁰ If the pulmonary A wave is longer than the mitral annulus A wave,

Grading of diastolic dysfunction: key points

- ▶ The presence or absence of diastolic dysfunction relies on the annular velocity e' and the size of the left atrium.
- ▶ Once diastolic dysfunction is deemed present, the mitral inflow and the ratio E/e' allow the distinction between grade 1 (impaired relaxation), 2 (pseudo-normal filling) and 3 (restrictive filling).
- ▶ In case of uncertainty, the pulmonary vein signal or the mitral inflow signal during the Valsalva manoeuvre may help to classify.

this intuitively indicates increased end-diastolic pressures and/or poor LV compliance. As the ventricle can no longer fill, the blood is expelled backwards from the atrium toward the pulmonary veins. Another very helpful measure is to repeat the mitral inflow registration during a carefully performed Valsalva manoeuvre. In normal subjects, both E and A decrease so that the ratio remains essentially unchanged. When faced with the combination of delayed myocardial relaxation and increased filling pressures (grade 2 or grade 3 diastolic dysfunction), Valsalva will decrease venous return and filling pressures. This manoeuvre will reveal the diastolic dysfunction that was masked by increased filling pressures: E will decrease and A will be maintained or increase so that E/A will be markedly reduced (figure 5).

EVALUATION OF FILLING PRESSURES

Several studies have documented the possibility of diagnosing elevated LV filling pressures with Doppler echocardiography. These data were elegantly summarised by Bill Little and Jae Oh.⁴ E/e' has been found to correlate with PCW in a wide range of patients across multiple laboratories. The measurements are similar to the measurements used for the grading of diastolic function. The scope and the experimental evidence, however, are distinct. The grading is validated for the prognostic stratification of patients. The evaluation of filling pressures is validated for predicting invasively measured capillary wedge pressures or LV filling pressures. The evidence is different in patients with heart failure and reduced EF (HFREF) and in patients with heart failure and preserved ejection fraction (HFPEF) and different algorithms were proposed.²

In HFREF, the evaluation starts with the mitral inflow pattern. The filling pressures are elevated in grade 3 (restrictive) and often but not always normal in grade 1 (impaired relaxation). If the pattern is grade 2 (pseudo-normal) or grade 1 with an $E > 50$ cm/s, additional measurements are required to differentiate between normal and elevated filling pressures. The validated additional measurements are E/e' , E/Vp , pulmonary venous flow, Valsalva manoeuvre, and pulmonary artery pressure. A careful study by Nagueh and Smiseth

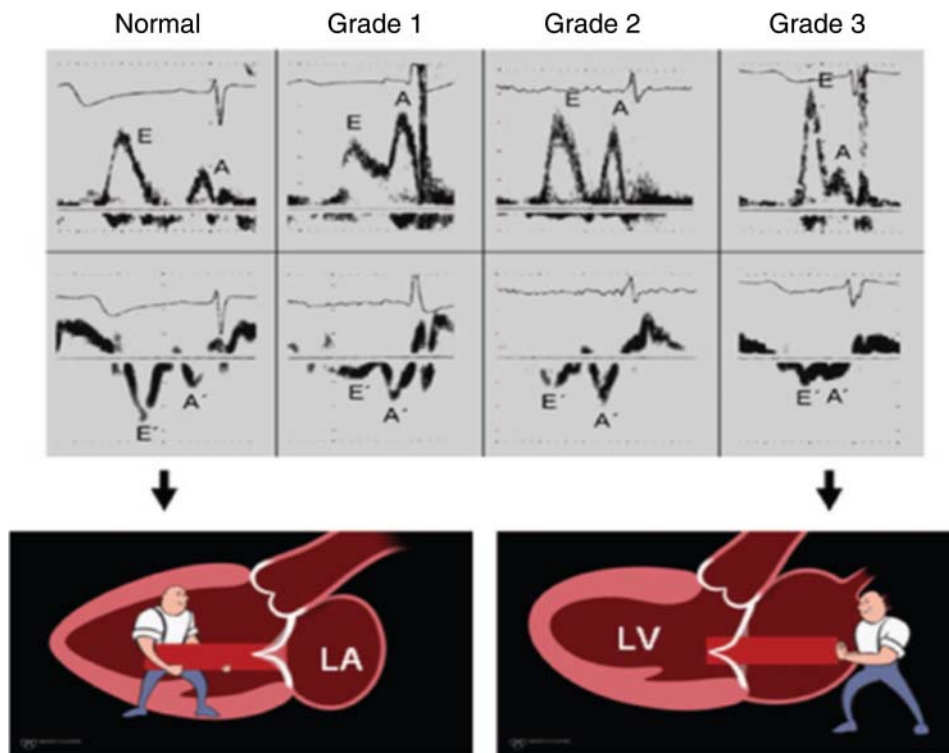


Figure 6 Grades of diastolic dysfunction. If we look from left to right we see tracings of a normal and healthy subject, a patient with mild (grade 1), moderate (grade 2) and severe (grade 3) diastolic dysfunction. The early diastolic velocity e' decreases from left to right. The mitral inflow shows a biphasic evolution. On the left, early diastolic ventricular suction underlies an elevated E wave. This is illustrated as a man pulling blood into the left ventricle. This diastolic ventricular suction decreases due to relaxation disturbances in grade 1, 2 and 3 as indicated by the low value of e' . This manifests as a lower amplitude of E in grade 1. Nevertheless we see an elevated mitral E wave in grade 2 and even more in grade 3. This elevated mitral E wave in grade 2 and 3 is due to elevated filling pressures, as illustrated by the man pushing blood from the left atrium into the already overfilled left ventricle. Elevated filling pressures mask the delayed myocardial relaxation in these patients, which can be revealed, for example, by the Valsalva manoeuvre. Reproduced with permission from Oh *et al.* Established and novel clinical applications of diastolic function assessment by echocardiography. *Circ Cardiovasc Imaging* 2011;4:444-55.

recently confirmed that in advanced, decompensated heart failure, the proposed paradigm works equally well.²³

In HFPEF the analysis starts with E/e' . A septal $E/e' \geq 15$ (or lateral ≥ 12 , or average ≥ 13) has been found to clearly indicate elevated PCW, whereas an $E/e' < 8$ (septal, lateral or average) is associated with normal

LA pressures. In the intermediary range (E/e' 9–14), an assessment of filling pressures should include LA size, mitral inflow pattern, DT, isovolumetric relaxation time, and the pulmonary artery pressures. We have to be aware as well that the hearts of patients become older, and that values and cut-offs should take into account the age related changes of E/e' .¹⁶ Figure 3 shows a subject with normal filling pressures and low E/e' values (normal) and figure 4 shows a patient with elevated filling pressures and high E/e' values (pseudo-normal).

This is certainly confusing for the clinical cardiologist, but is the way careful science proceeds. We therefore attempted to reconcile the previously published decision trees for both HFREF and HFPEF in one single decision tree (table 2). The E/e' ratio and the mitral inflow pattern constitute the base for the evaluation of filling pressures. When E/e' is in the intermediary range or if the mitral inflow is (pseudo)-normal, additional measurements are required as indicated.

Annular measurements of e' are not reliable for the prediction of filling pressures in specific patient populations. When the ventricle is pumping an elevated stroke volume (ie, a hyperdynamic ventricle), annular motion is enhanced. This is typically the case in severe mitral regurgitation. When the

Table 1 Grades of diastolic dysfunction

Normal subjects	Normal/athletes/constriction	Grade 1 Impaired relaxation	Grade 2 Pseudonormal filling	Grade 3 Restrictive filling
Septal $e' \geq 8$	Septal $e' \geq 8$	Septal $e' < 8$	Septal $e' < 8$	Septal $e' < 8$
Lateral $e' \geq 10$	Lateral $e' \geq 10$	Lateral $e' < 10$	Lateral $e' < 10$	Lateral $e' < 10$
LA < 34 ml/m ²	LA ≥ 34 ml/m ²	LA ≥ 34 ml/m ²	LA ≥ 34 ml/m ²	LA ≥ 34 ml/m ²
		E/A < 0.8	E/A 0.8–1.5	E/A ≥ 1.5
		DT > 200 ms	DT 160–200 ms	DT < 160 ms
		Average $E/e' \leq 8$	Average E/e' 9–12	Average $E/e' \geq 13$
		Ar-A < 0 ms	Ar-A ≥ 30 ms	Ar-A ≥ 30 ms
		Valsalva $\Delta E/A < 0.5$	Valsalva $\Delta E/A \geq 0.5$	Valsalva $\Delta E/A \geq 0.5$

Modified after Nagueh *et al.*² with permission.

DT, deceleration time; LA, left atrium; see text for explanation of other abbreviations.

Table 2 Evaluation of filling pressures in patients

Normal LA pressures	Elevated if...	Elevated LA pressures
Septal E/e' ≤8	Septal E/e' 9–14	Septal E/e' ≥15
Lateral E/e' ≤8	Lateral E/e' 9–11	Lateral E/e' ≥12
Average E/e' ≤8	Average E/e' 9–12	Average E/e' ≥13
Mitral E/A <1 E ≤50 cm/s	Mitral E/A 1–2 Mitral E/A <1 and E >50 cm/s	Mitral E/A >2

Elevated if LA volume ≥34 ml/m², E/Vp ≥2.5, pulmonary vein flow S/D <1, pulmonary Ar-A ≥30 ms, Valsalva Δ E/A ≥0.5, pulmonary artery pressure >35 mm Hg. Please note that this table is not applicable to normal subjects, as defined in table 1. Modified after Nagueh *et al.*,² with permission. LA, left atrium; see text for explanation of other abbreviations.

Evaluation of filling pressures with echocardiography and cardiac Doppler: key points

- ▶ Is feasible in most patient populations including severe systolic heart failure
- ▶ Is mainly based on the E/e' ratio and the mitral inflow signal
- ▶ Requires additional measurements when values of E/e' are in the intermediary range or when the mitral inflow is (pseudo)-normal
- ▶ In selected disease states E/e' is not reliable as a predictor of filling pressures

patient has a left bundle branch block and mechanical dyssynchrony, there might be a delayed hyperfunction of the lateral wall. This manifests as an increased lateral e'. Another particular situation is constrictive pericarditis.¹² In this condition with major filling abnormalities and elevated filling pressures, enhanced mainly septal longitudinal motion (hence septal e') is a compensation for the inability of the heart to expand in the radial direction.

CONCLUSIONS

Diastolic function is a complex combination of events allowing the healthy and young ventricle to fill in an almost explosive way, 3–4 times faster than to eject. This capacity to suck the blood toward the LV apex and to briskly fill at low pressures is even more pronounced during exercise and tachycardia, where the atrial contraction can be superimposed on early diastolic filling, which still enhances rapid filling flow without elevation of filling pressures. These properties decrease with age and can be severely reduced by various disease processes. Modern cardiology has evolved from invasive haemodynamics, and has developed the tools to carefully describe diastolic filling in a non-invasive and repetitive way using echocardiography and cardiac Doppler. The tools are powerful and fairly reliable, but will never be simple to use and will in some particular cases not work as predicted.

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In every single case we therefore should attempt to record a full examination and to understand the pathophysiology behind the diastolic dysfunction of each particular patient. We may certainly not assimilate diastolic dysfunction to one single pattern or a single number. The binary approach has never worked and will never work. Only with a comprehensive echo we will be able to understand more complex pathologies such as dyssynchrony, constriction, cardiomyopathies or diastolic function in valvular heart diseases. The cardiologist's brain or the sonographer's brain should form an integrated tool with the ultrasound machine. The ultrasound machines are good. The cardiologist and the sonographer become good with training and clinical experience. Such an integrated tool will always be hard to beat.

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Echo-Doppler assessment of diastole: flow, function and haemodynamics

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