Diastolic function assessment by echocardiography: A practical manual for clinical use and future applications

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BACKGROUND

Diastole is an important period in the cardiac cycle when all cardiac chambers and valves integrate to secure optimum ventricular filling which determines the stroke volume, pumped by the ventricle in the succeeding cycle. Three diastolic phases are well recognized; early diastole, diastasis, and late diastole “atrial systole,” all of which can be assessed by cyclic changes in pressure difference between the left atrium (LA) and left ventricle (LV) which result in blood flow between the two chambers (Figure 1). Based on ventricular filling, the three diastolic phases can be named; early filling (E-phase), diastasis (mid diastole or sometimes present as L-wave), and late ventricular filling (or atrial systole A-phase). Absolute intra-cardiac pressure measurements can only be obtained invasively using combined pressure tip...
manometers in the LV and in the pulmonary wedge that reflects the LA pressures, with simultaneous recordings obtained to the closest millisecond. Relative changes in chamber pressures can be studied using LV filling velocities, in different diastolic phases, obtained by spectral Doppler echocardiography, which has now become a well-established integral part of cardiac examination in health and disease. Intra-atrial and intra-ventricular pressure continuously change, in order to maintain optimum cavity circulations; thus, their contribution to the understanding of cardiac function is limited, instead echocardiographers, based on conventional guidelines, rely on LV filling velocities and pulmonary venous flow velocities in assessing different phases of diastolic function. Such approach helps not only assessing intra-cardiac chamber pressure but studying chamber cavity function, compliance, and myocardial function, thus presenting a comprehensive assessment of cardiac physiology in a highly reproducible fashion.

Although very little circulation occurs during the period of diastasis, early LV filling (E-wave) and late LV filling (A-wave) remain the main determinants of cardiac stroke volume. Diastolic events are preceded by an important phase in the cardiac cycle, the isovolumic relaxation time—(IVRT) which is the time interval between aortic valve closure and mitral valve opening, that is, when the two valves are closed and there is no blood entering or exiting the LV.

During IVRT, a number of important events happen which have been shown to predict diastolic patterns; LV pressure declines, and cavity shape change occurs, that is, inward movement of some segments associated with outward movements of others. The latter observations have been shown in normal hearts and get more pronounced with age, therefore, should not always be seen as pathological. Of course, dyssynchrony of cardiac wall motion may worsen in other conditions, for example, hypertension and coronary artery disease and could significantly impact LV filling pattern. IVRT tends to prolong with age, a change that correlates with slow LV relaxation pattern and its effect on cavity filling velocities, become dominantly late diastolic rather than early diastolic. We have previously shown that those changes are closely related to the fall in myocardial early diastolic velocities and increase in late diastolic velocities with age, perhaps due to age-related collagen deposition causing slow relaxation. Similar but rather accelerated changes may happen because of other conditions, for example, pressure overload as systemic hypertension and aortic stenosis, diabetes, and coronary artery disease.

With severe abnormal prolongation of ventricular relaxation, particularly if associated with fast heart rate, early diastolic LV filling might be completely suppressed and the LV becomes A filler or of the summation filling pattern with a single filling component starting before the onset of the P-wave of the ECG. The same filling pattern might be seen in prolongation of PR interval, irrespective of its etiology. These conditions limit the blood volume entering the ventricle and consequently the exiting stroke volume resulting in an overall cardiac output that is maintained by fast heart rate. Those patients, if symptomatic, do not respond well to conventional beta blockers treatment and heart rate slowing medications, since the cardiac output is maintained mainly by heart rate rather than by physiological filling volumes. With further deterioration of myocardial function and ventricular compliance, the cavity becomes stiff and diastolic pressures rise, resulting in a perpetual rise of LA/pulmonary capillary wedge pressure, pulmonary venous hypertension, and eventually pulmonary arterial hypertension. Such changes in LV diastolic function have direct impact on LV filling pattern with IVRT becoming very short <40 ms, could be zero in severe cases, dominant early diastolic filling, and suppressed late diastolic filling velocities. In some cases, with slow heart rate, the raised diastolic pressures might appear as flow reversal during diastasis. In addition to these general features of raised filling pressures, critical assessment of Doppler signals and velocities reveals fast acceleration due to significantly raised LA pressure and fast deceleration due to raised LV diastolic pressures, again with severe cases showing E-wave deceleration faster than its acceleration. This pattern is usually described as restrictive filling pattern. With successful pressure off-loading of the LV and LA, the right ventricular pressures might normalize and stroke volume increases. It is important to note that none of the abovementioned filling patterns
is characteristic or consistent with the clinical diagnosis of heart failure (HF) which is a clinical diagnosis rather than echocardiographic diagnosis. Those patterns of diastolic dysfunction reflect the status of left heart function which should be considered in the context of symptoms, with the restrictive filling pattern, short IVRT, dominant E-wave, and E/A ratio >2.0 as an unstable condition that needs serious pressure relieving medications, in order to avoid the risk of ventricular arrhythmias, which could be life-threatening.

1.1 Factors influencing diastole

1.1.1 Age

With age, significant changes occur in diastolic function, over and above those affecting systolic function. In the young, up to the fourth decade of life, LV filling is dominant in early diastole followed by a smaller late diastolic filling component. The pronounced early diastolic phase is caused by the low (negative) LV apical pressures compared to that at the base, maintained by an apical untwist (Figures 1A and 2) and its suction effect.

With progressive collagen deposition in the myocardium, 5th decade of life, cavity relaxation becomes slower and delayed. This results in prolongation of IVRT and delayed opening of the mitral valve. These changes incur on the overall diastolic period but mainly the early diastolic phase (Figure 1B) and results in compromised early filling component (or volume) with a compensatory increase in the late diastolic filling and more pronounced apical untwist that results in the E/A ratio to be consistently <1.0. Reversal of E/A ratio to become >1.5 in individuals above 60 years of age should be taken as an indication for diastolic dysfunction with increased LV and LA diastolic pressures, Figure 3.

The above age-related changes worsen and become faster if there is additional pathology affecting the LV, for example, coronary artery disease, valvular disease, cardiomyopathy, or systemic hypertension. In some patients, the early diastolic filling could be completely truncated and the LV fills with an isolated late diastolic component, commonly seen with LV dyssynchrony, as mentioned above. If such patients develop atrial fibrillation, the isolated late diastolic filling component will be shifted to early diastole but on the expense of raising the LA pressure, postcapillary pulmonary hypertension, and reduced stroke volume.

FIGURE 2 Apical untwist and mitral inflow in young (left) and elderly (right) healthy subjects. Note the time difference of onset of untwist (end systole, blue line) and onset of E-wave (after T-wave, green line) in both subjects. This might be part of mechanism behind suction effect.
1.1.2 | Electrical disease

Diastolic phases are also influenced by the electrical pattern of LV activation (depolarization) and repolarization. QRS broadening, irrespective of bundle branch block (BBB), is associated with delayed activation and delayed septal inward motion, which consequently is reflected in delayed segmental outward motion with post-ejection shortening, the combination of the two results in delayed onset and shortened early diastolic LV filling. The same pattern is seen in individuals with absent septal Q-wave and patients with coronary artery disease, particularly those with Q-wave infarction. LV filling pattern could also be affected by other arrhythmia and conduction abnormalities, an absent P-wave, for example, atrial fibrillation results in absent late diastolic filling component, which compromises overall LV filling and stroke volume. Patients with severe LV disease and broad QRS may also develop prolonged PR interval. The combination of the two electrical disturbances may result in long mitral regurgitation with pre-systolic component which shortens filling and reduces stroke volume, particularly with fast heart rate. If these patients do not respond to heart rate slowing medications, they should benefit from DDD pacing with short A-V delay.

1.1.3 | Coronary artery disease

The most sensitive myocardial layer to coronary artery disease and ischemia is the subendocardium, even in patients with no obstructive lesions in the epicardial vessels. Early subendocardial dysfunction has been shown to be predominantly diastolic, and as it worsens, it becomes systolic. Disturbances are similar to those described above, but the delayed segmental shortening and lengthening is more profound and reverse after revascularization, particularly in patients with no additional electric disease. In those with a prior infarction, the scarred myocardial segment might be dysynchronous and hence adds to the extent of filling abnormalities. In severe cases and with more than one dysynchronous segment, the LV cavity might fill with an isolated late diastolic component. Specific patterns of myocardial incoordination have been described, with inferior infarcts causing global LV segmental dyssynchrony because of the papillary muscle blood supply being from the right coronary artery and even more aggressive form of global incoordination that contributes to subendocardial ischemia at rest in patients with unstable angina.

1.2 | Heart failure and diastolic function

1.2.1 | Heart failure symptoms

The main symptom of HF is breathlessness and fatigue. If cardiac dysfunction is the prime cause of symptoms, it is likely to be caused by either impaired emptying of the LA due to early diastolic dysfunction (relaxation disturbances, Figure 1B) or due to raised LA pressure (restrictive filling pattern, Figure 1C) as a complication to raised LV end-diastolic pressure. The latter has clear characteristics: dominant early diastolic component, short IVRT, reduced and delayed apical early diastolic untwist and increased time duration of flow reversal in the pulmonary veins in late diastole. The two conditions result in LA enlargement, reduced compliance, and unstable function, hence potential development of atrial arrhythmia, even fibrillation. Development of these complications is helped by the

FIGURE 3 E/A and age in males (green dots) and females (blue dots). Data taken from 260 healthy subjects, 20–90 years.
significantly thin LA myocardial wall which cannot support raised cavity pressures.

1.2.2 | Heart failure signs

A third heart sound, heard in a HF patient, is consistent with restrictive LV filling (Figure 1C) and is caused because of rapid turn of early diastolic filling acceleration into deceleration. This condition reflects unstable cardiac function that needs LA pressure off-loading therapy with vasodilators. The fall in LV pre- and afterload results in consequent drop in LA pressure and normalization of LV filling pattern which unmasks the original underlying diastolic function abnormalities, in most cases dyssynchronous patterns become apparent and influence LV filling (Figure 1B,C), as described above.

Such change in LV filling should be a treatment objective, while increasing the vasodilators doses, in order to stabilize LA function and avoid arrhythmias. A fourth heart sound, in most cases, reflects isolated late diastolic filling due to severe early diastolic dysynchrony. Signs of pulmonary edema reflect raised LA pressure, which is again, secondary to stiff LV and raised end-diastolic pressure. Most patients with HF present with some degree of mitral regurgitation, which further accentuates LA pressure and post-capillary pulmonary hypertension. Systemic fluid retention is a sign of either stiff right ventricle or significant tricuspid regurgitation, secondary to left heart disturbances and post-capillary PH or due to primary right heart problems with/without pulmonary hypertension.11,12

1.3 | Guidelines based assessment of diastolic function

Guidelines recommend grading diastolic function into four categories; normal, slow relaxation, pseudo-normalized, and restrictive filling pattern.13 While the first two categories suggest normal filling pressures, the third and fourth patterns are consistent with raised filling pressures, although to different severities. Invasive assessment of filling pressures itself could be clinically confusing, with some studies using LV end-diastolic pressure,14 others using pre-A-wave pressure from LV pressures and some pulmonary capillary wedge pressures (PCWP).15,16 Add to this inconsistency in defining filling pressures, the respiratory cycle also impact the filling pressures. Furthermore, discrepancies due to different ways of assessing LV filling pressures exist with respect to the use of a cutoff value >12 or >15 mm Hg in determining abnormally raised pressures.17

For non-invasive estimation of filling pressures, a number of echocardiographic measures have been suggested in recent recommendations.12 Trans-mitral flow, pulmonary venous flow, myocardial velocities, and estimated pulmonary pressures, either by right ventricular–right atrial retrograde pressure drop from tricuspid regurgitation or pulmonary–right ventricular early or late diastolic pressure drop from pulmonary regurgitation, are the most useful measures in this algorithm. These markers of raised LV filling pressures remain applicable in patients with HF, irrespective of ejection fraction, LVEF <50% or >50%, despite varying specificity in different studies.18

Relaxation abnormalities can also impact LV filling, in the presence of normal filling pressures. This condition is characterized by reduced E-wave velocity, increased A-wave velocity, E/A <0.8, prolonged E-wave deceleration time (>200 ms), and IVRT >100 ms Such pattern is commonly seen in the healthy elderly above 60 years and therefore has low sensitivity in detecting heart failure (Figure 1B). However, if associated with an enlarged LA (volume > 34 mL/m²), it raises strong suspicion of unstable LA pressures and an exercise provocation such as exercise echo or passive leg lifting can be useful in order to confirm raised LA pressure as shown by increase in E/A, E/e’, and TR velocity and unchanged stroke volume Table 1.19

Resting Doppler echocardiographic measures of diastolic function and their existing discrepancies create significant limitation, mainly because of heart rate impact on time relations and the commonly seen arrhythmias. Such limitation highlights the need for using more than one parameter before drawing a clinical conclusion. A short IVRT as the interval between the end of the aortic Doppler velocity signal and the onset of the E-wave is also a good reflection of raised LA pressure. A short transmitral E-wave deceleration time is a good marker of raised LV end-diastolic pressure but not always that reproducible, particularly in patients with atrial fibrillation. A

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**TABLE 1** | Useful clinical echocardiography measures of raised LV filling pressures taken from recent guidelines

| Method | Cutoff | Major pros | Major cons | Estimating LVFP |
|--------|--------|------------|------------|-----------------|
| E/A    | >2     | Feasible and reproducible | Not feasible and reproducible in arrhythmias and fast HR | Using age as factor in the interpretation very useful to exclude high LVFP |
| E/e’ mean | >14 | Feasible and reproducible | Regional differences in e’ values, age dependent, not accurate in mitral valve disease and annulus calcification | Not useful in modestly elevated LVFP |
| TR velocity | >2.8 | Commonly indirect measure of PCWP | Not always feasible and reproducible. Increased TR velocity not specific for postcapillary pulmonary hypertension. | Accurate indirect measure of LVFP |
| LA volume indexed for BSA | >34 mL/m² | Feasible and reproducible | Sometimes limited image quality in bi-chamber views. Overlapped with healthy athletes. Difficult to interpretate in atrial fibrillation | Not direct measure of LVFP rather information of unstable pressure overloaded |
simple observation of E/A ratio could give a rough impression on diastolic function and LV filling pressures. In a patient over 50 years of age, a normal filling pattern is expected to show an E/A <=1.0, in the presence of normal LA size (<28 mL/m²), normal LV configuration (no LV shape changes or increased wall thickness), and normal LV intrinsic relaxation velocity (e' mean >8 cm/s). The combination of E/A >1, enlarged LA, abnormal LV function and configuration and abnormal LV intrinsic relaxation (reduced e') strongly suggests raised LA pressures.20,21

A wide range of diastolic patterns can be seen between the abnormal relaxation and restrictive filling patterns, but all could be described in one category based on the following measurements: LA volume, E/A, IVRT, and DT.22

In those patients, additional methods can be used for accurate evaluation, for example, e’ from tissue Doppler echocardiography and calculating E/e’, time difference between the duration of the transmitral A-wave and respective retrograde pulmonary venous Ar (Ar-A). In addition, the ratio of systolic (S) and diastolic (D) flow velocities from pulmonary venous flow (PVF). An E/e’ (mean LV septal and lateral e’) >13, PVF S/D <1, and Ar-A >30 ms are highly suspicious of elevated LA pressure.19

Irrespective of LV size and function, the development of myocardial stiffness and the rise in LV diastolic pressures cause LA enlargement, which with time may become unstable, hence atrial fibrillation (AF). In patients with AF, there is a single component of LV filling, the E-wave, with absent A-wave on the trans-mitral and pulmonary venous flow, hence E/A ratio and A-wave duration difference are not applicable. However, E/e’ remains of diagnostic value for raised LA pressure in addition to the short E-wave deceleration and the increased LA volume.23 However, the assessment of filling pressures using Doppler echocardiography is difficult, especially shortly after cardioversion of AF to sinus rhythm.

To overcome the above limitations of resting Doppler echocardiography in demonstrating evidence for raised LA pressure as a cause for exertional breathlessness in patients with HF, particularly those with normal ejection fraction, additional techniques might be of significant clinical relevance.

Stress echocardiography, physical or pharmacological, has been shown of pivotal value in managing such patients, what appears like normal resting Doppler echocardiographic findings.24,25 The increase in heart rate with exercise stress accentuates venous return which raises LV and LA pressures in patients with stiff and noncompliant LV. Such increase in LV and LA pressures has its consequences in the form of pulmonary venous hypertension, pulmonary hypertension, and clinical symptoms of shortness of breath. Similar pathophysiological findings have been shown by simple leg lifting at rest.26,27

Stress echocardiography has also been shown to play an important prognostic role in such patients and in showing better clinical outcome in patients with restrictive filling pattern who convert into nonrestrictive filling pattern at fast heart rate which is consistent the presence of significant myocardial diastolic reserve,28,29 compared with those who remain with restrictive filling.30

1.3.1 | Diastolic function measurements in HFpEF

Heart failure with preserved ejection fraction (HFpEF) has no specific characteristic pattern of diastolic function. All patterns described above apply to HFpEF, in particular LA enlargement. In addition, an E/A >1.5 in an elderly patient (>60 years)31 is highly suggestive of elevated filling pressures.

The only difference might be the disproportionate small volume of the LA with respect to the poor LV myocardial function might be in patients with ATTR amyloid heart disease, in whom the LA could be just slightly enlarged, due to atrial myocardial infiltration, Figure 4.25 However, others have not found the same pattern of left atrial morphology in cardiac amyloidosis.33

1.3.2 | Diastolic function in fast heart rate

It is very important not to apply the absolute values of diastolic function parameters in patients with HF when presenting with tachycardia. Since heart rate affects diastole before it affects systole and all diastolic intervals become shorter, this behavior is the opposite of what treatment with beta blockers does in optimizing diastolic function and increasing stroke volume. With fast heart rate, diastasis becomes minimal making the two filling components close until they eventually merge and become one summation filling component. Therefore, correcting all time intervals to heart rate is strongly advisable. An example of such approach is the assessment of total isovolumic time, which is the product of subtracting the sum of the filling time and ejection times from RR interval and correcting it for heart rate. This gives a value in s/m. It is simple and highly reproducible. It has also been shown to be very accurate in assessing the presence and severity of LV dyssynchrony in HF.31 Furthermore, LV filling time can be measured and indexed to RR, a simple measure which normally should not reduce by more than 40% at peak exercise.

1.3.3 | Diastolic function and ventricular interaction

Ventricular interactions are known as a hemodynamic phenomenon since Bernheim.34 However, in primary RV disease such as pressure overload (pre-capillary PH) or RV volume overload, the overload creates a septal shift as well as suppressed LV filling volume. Commonly in both conditions, a reduced LV E/A is expected, a finding that indeed has a significant prognostic value.35

1.4 | Left atrial myocardial function in assessing raised cavity pressure

The recently developed speckle tracking based assessment of LV myocardial deformation technique has been implemented also for the LA. Studies have shown that LA myocardial strain and strain rate play important role in estimating cavity pressure and
in predicting response to myocardial arrhythmia. Figure 5.\textsuperscript{36,37} Indeed, a recently published meta-analysis showed that LA systolic strain <19\% is a very accurate marker for estimating raised pulmonary capillary wedge pressure of >15 mm Hg.\textsuperscript{38} Interestingly, the same value has been shown in another meta-analysis to predict successful response to atrial fibrillation ablation.\textsuperscript{39} Such measurements are easy to obtain although may slightly differ between vendors.

1.5 | Diastolic function and passive leg lifting

Vasalva maneuver has been proposed to test the ability of LV to reduce filling pressures through decreasing preload, i.e. reduced E/A with Vasalva indicates reversible restrictive LV. However, accuracy in having the pulsed Doppler sample volume placed at the same region is very difficult as the LV geometry changes while reducing preload and image quality reduces too. Therefore, and inverse Valsalva manoeuvre with preload increase might be beneficial in providing such information. Along with the concept of increasing venous return with stress/exercise as means for assessing pathological rise of LA pressure as an explanation of exertional breathlessness, simple passive leg lifting (Figure 4) has been recently proposed to achieve similar objective. We have found PLL together with NT-pro-BNP useful in identifying HF patients with increased PCWP >25 mm Hg during supine exercise.\textsuperscript{26} We tested PLL and echocardiography in 29 patients with HF symptoms but normal resting PCWP based on invasive pressure recording. Resting measures of LA volume and strain rate during atrial contraction predicted unstable PCWP (>15 mm Hg during PLL). Furthermore, the latter measured during PLL correlated well with PCWP during PLL.\textsuperscript{27} Such simple procedure should be easily used in open access HF clinics for fast and accurate stratification of patients for optimum management (Figure 6). Example of the use of echocardiography in indicating raised LV filling pressures during PLL is shown in Figure 7.
1.6 | Diastole and exercise test

Resting echocardiographic findings may not always succeed in explaining symptoms/signs of patients presenting to HF clinics, for various reasons, one of which is that those symptoms are usually exertional, therefore, likely reflecting a different physiological status to that existed at the time of the resting Doppler echocardiographic examination. BNP has been proposed by all guidelines to suggest a potential explanation but yet, in some it does not. For this reason, stress echocardiography has been suggested as the test of choice in assessing patients with exertional symptoms. Most patients requiring stress echocardiography present with E/A <1, enlarged LA and have undetermined peak tricuspid retrograde pressure drop. In a stiff LV, the increase in stroke volume cannot be maintained without significant rise in filling pressures which leads to pulmonary hypertension. Despite the compensatory increase in LV filling pressures in HF patients, the respective increase in stroke volume remains limited. So the ratio cardiac output/PCWP at rest and during exercise can be taken as a marker for abnormal exercise response due to diastolic dysfunction. In practical terms, PCWP can be measured from peak TR velocity. E/e’ has also been used to estimate LV filling pressures, but the relationship proved to be only modest in a wide range of patients. Thus, Doppler echocardiographic parameters cannot be used to reflect slight dynamic changes in filling pressures; however, a combination of an increase in trans-mitral E-wave velocity, unchanged e’, (thus raised E/e’), increase in TR peak velocity (>3.3 m/s), and none or only small increase in cardiac output during exercise could together with abnormal BNP and clinical signs of HF give an indication for raised LV filling pressures. Example of the use of echocardiography in methods indicating elevated LV filling pressures during supine exercise is shown in Figure 8.

Despite that, a number of technical limitations in using exercise/stress echo still remain, especially with fast heart rate and breathing disturbances. To avoid such limitations, a moderate exercise test at

**FIGURE 6** Passive leg lifting

**FIGURE 7** Upper resting measures of E/A, e’ TR peak velocity, and LV VTI. Lower same measures during passive leg lifting
a heart rate of 100-120 beat per minute could suffice the development of disturbances enough to support the diagnosis of raised LV filling pressures that is responsible for symptoms. A diagnostic algorithm for identifying patients with elevated left ventricular filling pressures in rest and during cardiac stress is shown in Figure 9.

**FIGURE 8** Upper resting measures of E/A, e’ TR peak velocity, and LV VTI. Lower same measures during submaximal exercise.

**FIGURE 9** Diagnostic algorithm for identifying patients with elevated left ventricular filling pressures in rest and during cardiac stress.

**CONCLUSION**

While ejection fraction is the most commonly used marker of left ventricular systolic function, it does not reflect well aging, symptoms, or signs of cardiac diseases. Diastolic function assessment, in
contrast, provides wealth of knowledge on global, segmental, and compliance function of the cardiac pump. Furthermore, Doppler echocardiographic measurements of diastolic function guide toward clearer interpretation of patient’s symptoms and signs, particularly those related to exertion. Recently developed modalities, stress/exercise echocardiography, and passive leg lifting represent simple, fast, and radiation free means for assessing left ventricular filling pressures, a cardinal explanation of breathlessness in all cardiac diseases.

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