Assessment of Left Ventricular Diastolic Function by Echocardiography

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Abstract:

Diastole is an important component of the cardiac cycle, during which time optimum filling of the ventricle determines physiological stroke volume ejected in the succeeding systole. Many factors contribute to optimum ventricular filling including venous return, left atrial filling from the pulmonary circulation, and emptying into the left ventricle. Left ventricular filling is also impacted by the cavity emptying function and also its synchronous function which may suppress early diastolic filling in severe cases of dyssynchrony. Sub-optimum LA emptying increases cavity pressure, causes enlarged left atrium, unstable myocardial function, and hence atrial arrhythmia, even atrial fibrillation. Patients with clear signs of raised left atrial pressure are usually symptomatic with exertional breathlessness. Doppler echocardiography is an ideal noninvasive investigation for diagnosing raised left atrial pressure as well as following treatment for heart failure. Spectral Doppler based increased E/A, shortened E-wave deceleration time, increased E/e', and prolonged atrial flow reversal in the pulmonary veins are all signs of raised left atrial pressure. Left atrial reduced myocardial strain is another correlate of raised cavity pressure (>15 mm Hg). In patients with inconclusive signs of raised left atrial pressure at rest, exercise/stress echocardiography or simply passive leg lifting should identify those with stiff left ventricular which suffers raised filling pressures with increased venous return.

Keywords: Left Ventricule, Diastolic Function, Echocardiography.

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Introduction:

LV diastolic function can be characterized by LV relaxation, LV early diastolic recoil, and chamber stiffness. These 3, in turn, determine LV filling pressures. There are multiple echocardiographic parameters that relate to each of the aspects of LV diastolic function and can be applied for diagnostic and prognostic purposes***(1)***.

Left ventricular (LV) diastolic function is characterized by LV relaxation, chamber stiffness, and early diastolic recoil, all of which determine LV filling pressure. Echocardiographic signals significantly associated with LV relaxation are mitral annulus early diastolic velocity (e′), LV strain rate during isovolumic relaxation (SR_{IVR}), and LV strain rate during early diastole (SR_E). Echocardiographic surrogates of LV chamber stiffness are deceleration time (DT), and A velocity transit time. Inferences about early diastolic recoil can be obtained by LV untwisting rate and e′. Echocardiographic estimation of LV filling pressure in patients with cardiac disease using E/A ratio, average peak early diastolic mitral inflow velocity (E)/e′ ratio, E/SR_{IVR} ratio, E/SR_E ratio, and left atrial (LA) reservoir strain ***(1)***.

LV diastolic dysfunction (LVDD) is typically caused by abnormal LV relaxation, decreased restoring forces, and increased LV chamber stiffness, which results in increased cardiac filling pressures. With impaired LV relaxation, LV filling shifts from early to late diastole, and left atrial (LA) contraction takes over a significant portion of LV diastolic filling and cardiac output. LVDD is asymptomatic in the early stages as long as LA function is preserved and there is an adequate filling period because LV filling pressure (LVFP) remains normal. With further deterioration of diastolic function and loss of diastolic reserve, LVFP rises, causing upstream congestion and symptomatic LVDD, first with exercise and then at rest ***(2)***.

In HF patients with reduced LV ejection fraction (HFrEF), LV diastolic function is virtually always impaired. Thus, when evaluating diastolic function in this setting, the focus is mainly on estimating LVFP, since it can guide therapy, monitor the disease course and improve outcomes. In patients with HFpEF, on the other hand, the focus is on detecting the presence of LVDD which is the likely cause of HF and fundamental to the diagnosis ***(3)***.

A broad spectrum of echocardiographic techniques and parameters may be used to reveal impaired LV relaxation, reduced restoring forces, increased diastolic stiffness, increased LA pressure and LV end-diastolic pressure (LVEDP) in patients presenting with symptoms or signs of HF.

Echocardiographic Diagnosis of LVDD in Patients with HFpEF

By demonstrating relevant structural heart disease and LV diastolic dysfunction in patients with clinical features of HF and preserved LVEF, echocardiography can provide key diagnostic criteria for HFpEF ***(4)***.

Relevant structural alterations are represented by *LV hypertrophy (LVH)* and *LA dilation,* whereas functional abnormalities (e.g. changes in LV relaxation, compliance or stiffness, indices of increased LVFP) are best reflected by *mitral flow velocities, mitral annular e' velocity and E/e' ratio.* Other echocardiographically derived measurements such as *longitudinal strain, or tricuspid regurgitation velocity (TRV)* may provide diagnostic features of LVDD in patients with HFpEF. In case of uncertainty, an echocardiographic diastolic stress test may provide additional information to confirm the diagnosis ***(3)***.

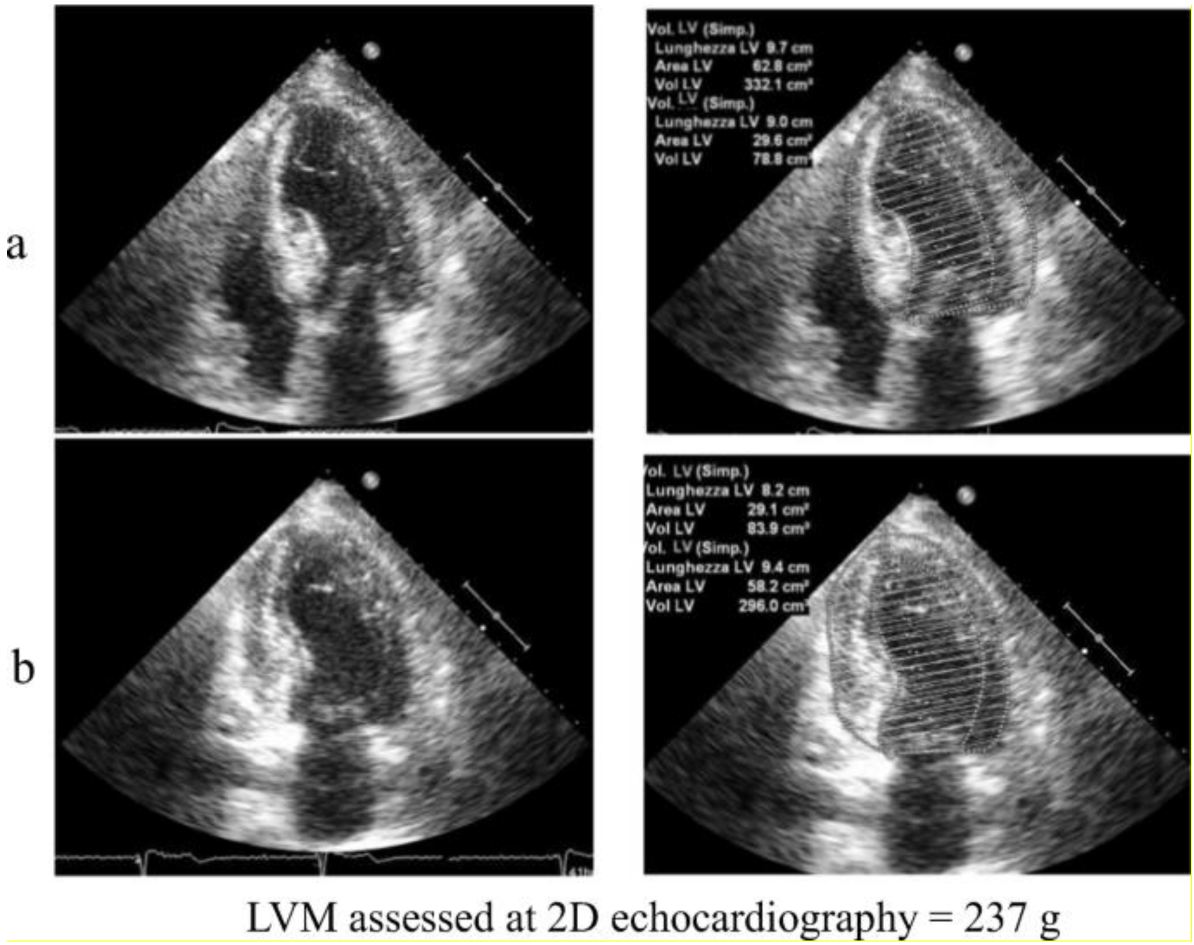
It should be noted that, according to current guidelines, the term ***"preserved"*** LVEF refers to LVEF >50 %. A LVEF between 40 and 50 % in patients with signs and symptoms of HF, along with relevant structural alterations and LVDD has been defined as ***HF with mid-range LVEF*** (HFmrEF). Since LVDD is thought to be the main pathophysiological abnormality in patients with HFpEF and perhaps HFmrEF, LV diastolic function evaluation is of utmost importance in both clinical situations and follows the same diagnostic pathway ***(4)***.

Two-dimensional echocardiography may reveal structural abnormalities of the heart representing either the cause or the consequence of DD and expressing its severity and duration.

LV mass:

Pathological LVH, defined as abnormally ***increased LV mass*** in untrained subjects, is a marker of impaired myocardial relaxation and increased stiffness, which strongly suggest the presence of LV DD. It is the most prevalent structural cardiac abnormality reported in patients with HFpEF, and it was independently associated with an increased risk of morbidity and mortality in this setting ***(5)***.

The currently recommended method for LV mass estimation in patients without significant cardiac geometry distortions relies on M-mode or 2D echocardiographic linear measurements of LV diastolic diameter and wall thickness as most studies relating LV mass to prognosis are based on this method. However, the linear dimension method using the cubed formula (with LV modeled as a prolate ellipse) may be inaccurate in many HF patients exhibiting asymmetric ventricular hypertrophy***(6)***. Two-dimensional methods based on either the area-length or truncated ellipsoid technique are less dependent on geometrical assumptions and more suited for LV mass estimation in patients with regional variations in wall thickness. The main limitations of 2D methods are related to methodology, low reproducibility, and limited prognostic data***(5)***.



Figure(1):2D echocardiography: left ventricular 4 (panel a) and 2 (panel b) LVM = left ventricular mass(7)

Three-dimensional echocardiography provides a more accurate estimation of LV mass in patients with remodeled ventricles, since it is free of geometric assumptions. However, prognostic data with 3D methods are still scarce. 3D LV mass can be determined using the 3D-guided biplane technique or the direct volumetric analysis method. Because 3DE is the only echocardiographic method that can directly measure LV volumes, it is an appropriate approach without geometric assumptions about cavity shape and hypertrophy distribution. 3DE can assist in the diagnosis and avoid over detection of wall thickness, including tendons and right ventricular moderator band ***(8)***.

The upper limits for normal LV mass currently recommended with 2D measurements, indexed to BSA, are 88 g/m^2 in women and 102 g/m^2 in men. Left ventricular DD should be suspected when LV mass by linear measurements is >95 g/m^2 in women and >115 g/m^2 in men ***(4, 5)***. There is insufficient available data in healthy subjects to recommend reference values for LV mass with 3D echocardiography.

Left atrial (LA) dilation

Left atrial (LA) dilation is an important feature for the diagnosis of HFpEF, suggesting the presence of DD with long standing increased LV filling pressure. Moreover, LA size emerged as an independent outcome predictor in patients with HFpEF ***(9)***.Bradycardia, atrial arrhythmias, significant mitral valve disease, high-output states may lead to LA dilation on their own, altering the relationship between LA size and LV filling pressure ***(10)***.

Two-dimensional echocardiography LA size is measured with M-mode and two-dimensional transthoracic echocardiography (2DE) by evaluating the anteroposterior diameter. However, this has proven inaccurate, as the LA does not dilate uniformly. The maximal left atrial volume indexed to the body surface area (LAVi) is the method of choice as it is considered the most accurate. In fact, it is strongly associated with cardiac outcomes and enables risk stratification. The predictive power of LAVi has been enhanced by the advent of three-dimensional echocardiography (3DE), which allows a more precise evaluation of the left atrial volume (LAV) without geometric assumptions and foreshortening ***(10)***.

Three-dimensional echocardiography (3DE) allows a better assessment of LA size due to lack of geometric assumptions, higher accuracy than 2D echo in determining LA volume when compared to CMR, and better prognostic value ***(11)***. Scaling LA volume to body size by dividing it to body surface area is recommended. The cut-off value for normal LA volume is 34 ml/m^2 which is also the reference value for the diagnosis of LVDD and for LVFP assessment. However, a LA volume index <34 ml/m^2 does not rule out the LVDD when other relevant parameters are strongly suggesting it. A normal LA volume has been reported in patients with early stages of diastolic dysfunction or with acute elevations of LVFP ***(5)***.

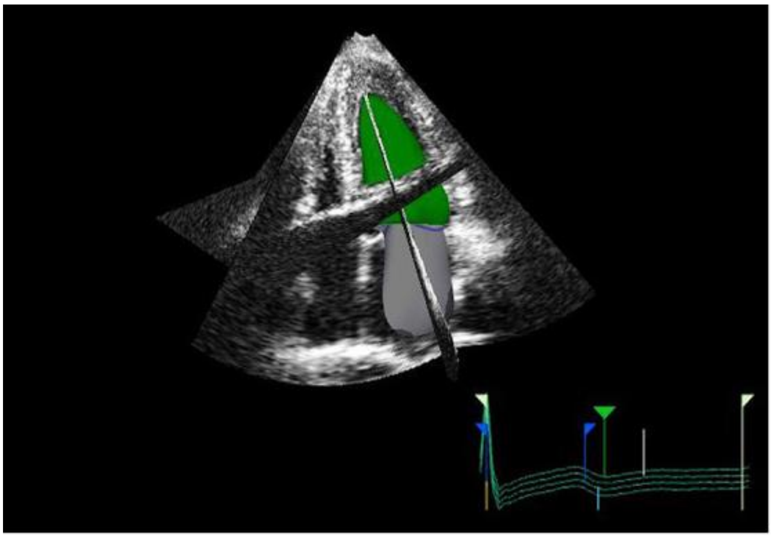


Figure (2):3D echo reconstruction of the left atrium (LA) and left ventricle (LV). LA is shown at its end-diastolic phase in order to appreciate left maximal atrial volume.(10)

Conventional Doppler echocardiography is critical to reaching correct conclusions regarding LV diastolic function in patients with HFpEF.

Transmitral flow profile parameters (peak early transmitral filling velocity E, peak atrial contraction velocity A, the E/A ratio, E velocity deceleration time, and isovolumic relaxation time IVRT), continue to play a significant role in the workup of HFpEF patients However, the age and load dependency of these parameters limit their use as first-line tools in this process***(3)***.

Slowing of LV relaxation and LV pressure decay, in the absence of elevated left atrial pressure, leading to "***impaired LV relaxation"*** pattern, may be encountered in the early stages of LVDD, but also with increasing age, higher heart rate, right ventricular overload, and other conditions. On the other hand, several studies reported cases of patients presenting with acute or chronic HFpEF and „impaired relaxation pattern" and increased LVFP probably due to markedly delayed LV relaxation ***(12)***.

Moreover, a ***"pseudonormal"*** filling pattern in patients with progressive LV diastolic dysfunction and increased left atrial pressure which restores the early diastolic gradient between the LA and the LV (E/A ratio>1) may be difficult to differentiate from normal transmitral filling. Further information supporting the presence of LVDD in this setting may be obtained from response to *Valsalva maneuver and pulmonary venous flow analysis*. Thus, a decrease in E/A ratio with Valsalva Maneuver with more than 0.5 in patients with baseline E/A>1 is highly accurate for ***"pseudonormal filling"*** due to increased LV filling pressures and supports the presence of LVDD. Likewise, an increase in pulmonary vein atrial reversal wave Ar, with a difference between Ar duration and mitral A in duration >30 ms has a good accuracy in predicting elevated LVEDP in patients with abnormal LV relaxation ***(3)***.

Echocardiographic assessment of *pulmonary artery systolic pressure* (PASP) based on Doppler assessment of tricuspid regurgitation jet peak velocity and inferior vena cava evaluation by 2D, should not be overlooked when assessing LV diastolic function in patients with suspected HFpEF***(13)***. In previous studies, PASP estimated by echocardiography emerged as a better predictor of HFpEF when compared to other echocardiographic parameters associated with DD (E/e' ratio, LA volume, and LV wall thickness). Elevated PASP values can identify patients with increased LV filling pressures due to LVDD provided pulmonary vascular disease or other potential causes of PH such as valvular heart disease, lung disease, chronic thromboembolic disease, and obstructive sleep apnea have been excluded*(14)*.

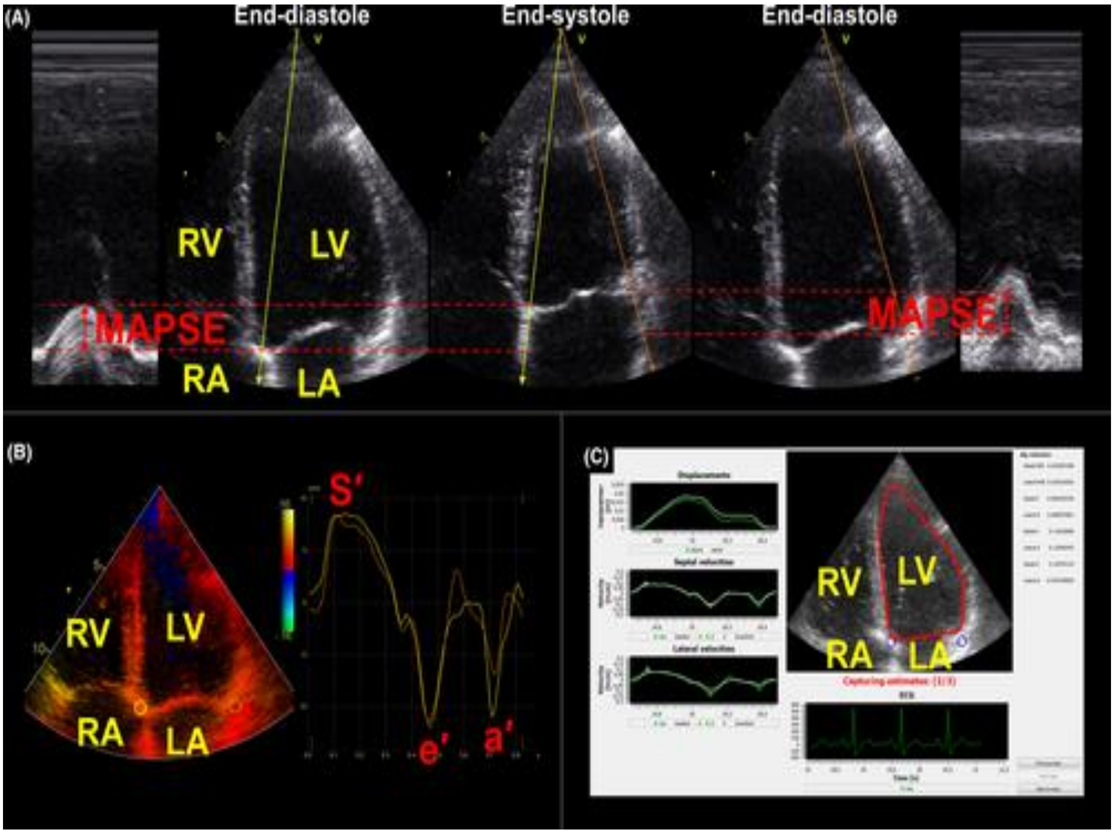
Tissue Doppler measurements of mitral annular velocities are now considered key echocardiographic measurements in assessing diastolic dysfunction. In patients with myocardial disease, the mitral annulus early diastolic velocity e' is of primary interest for assessing LV diastolic function because it decreases with impaired LV relaxation and is less preload dependent than the mitral E wave *(3, 14)*.

Whereas the E/A ratio of the mitral inflow exhibits a U-shaped relationship with progressive LVDD, the e' velocity decreases in a continuous manner being less affected by the gradual increase in LVFP. It was suggested that the decrease in e' velocity precedes the reduction in E/A ratio with 10–15 years. Therefore, normal e' velocity is unusual in patients with LVDD related to a myocardial abnormality or disease, which is the main reason that the joint Diastology Working Group recommends that an evaluation of diastolic function begins with e' in patients with normal LV ejection fraction. The E/e' ratio is thought to be a reflection of LVFP and can be used as a marker of LVDD. The correlation between E/e' and LVFP has been confirmed in patients with both HFrEF and HFpEF. To date, reduced e' and elevated E/e' are incorporated in guidelines as evidence of LVDD *(1, 3)*.

The recently updated recommendations for the evaluation of LV diastolic function by echocardiography proposed four variables to be evaluated when searching for the presence of LV DD in patients with normal LVEF. Three out of the four recommended variables are Doppler-derived indices: *annular e' velocity* (septal e' <7 cm/s, lateral e' <10 cm/s), *average E/e' ratio* >14 (E/e'lat > 13 or E/e'sep > 15), and *peak TR velocity* >2.8 m/s. Left atrial maximum volume index >34 mL/m^2 is the fourth parameter required for the diagnosis of LVDD *(3)*.

More than half of the available parameters should meet these cutoff values to make the diagnosis of LVDD. If more than two (or 50 %) of the available parameters do not satisfy these cutoff values, LV diastolic function will be considered normal. Between these two situations the study is considered inconclusive *(3)*.

In patients with suspected HFpEF and inconclusive diastolic function parameters, evaluation of LV longitudinal systolic function may aid the diagnosis, providing evidence of myocardial dysfunction. Parameters such as mitral annular plane systolic excursion using M-mode (MAPSE), tissue Doppler–derived mitral annulus systolic velocity (S), and LV global longitudinal strain (GLS) by speckle-tracking may provide further insight when assessing LV diastolic function, since previous studies have demonstrated a close relationship between systole and diastole and a high prevalence of systolic longitudinal dysfunction in HFpEF population *(15)*



Figure(3):Measurement acquisition. A, Manual MAPSE measurements from the septal (yellow line) and lateral (orange line) side by reconstructed M-mode. B, Manual measurements of S′, e′, and a′ from the septal (yellow curve) and lateral (orange curve) side by color tissue Doppler imaging. C, Graphical user interface for automatic measurements of MAPSE, S′, e′, and a′ by color tissue Doppler imaging. Only a grayscale frame is shown. a′ = peak late diastolic mitral annular velocity; e′ = peak early diastolic mitral annular velocity; LA = left atrium; LV = left ventricle; MAPSE = mitral annular plane systolic excursion; RA = right atrium; RV = right ventricle; S′ = peak systolic mitral annular velocity(16)

a) Grading Diastolic Function

The American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) have published guidelines for the integrated grading of diastolic dysfunction ***(17)*** The original guidelines from 2009 incorporated many of the same measures in their classification scheme,***(17)*** while a recent update in 2016 aimed to simplify the approach to evaluation of diastolic function and increase the utility of these guidelines in daily clinical practice.***(3)***

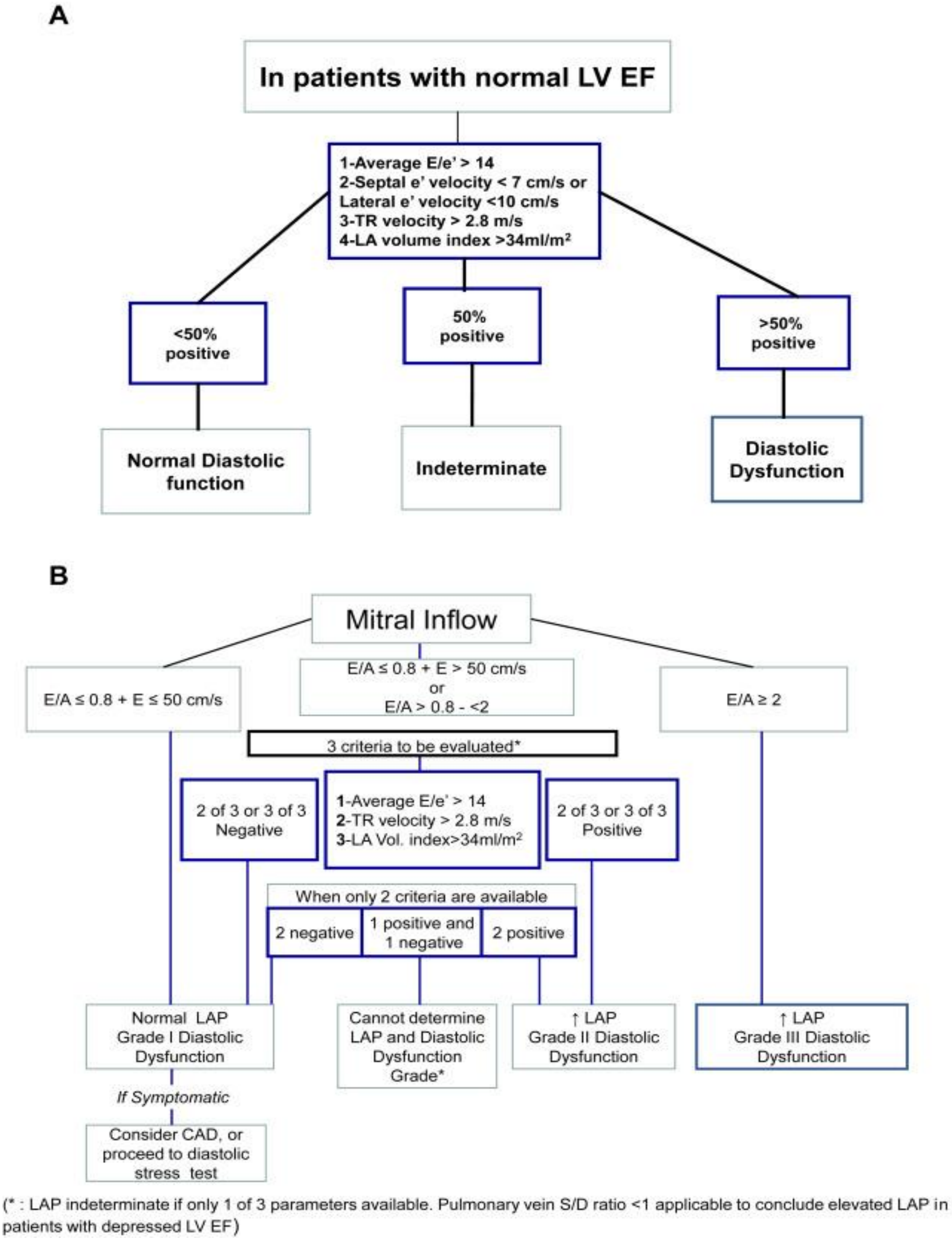


Figure (4): (A) Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF. (B) Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEFs and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data(3)

b) Assessing Left Ventricle Filling Pressures and Diastolic Dysfunction Grade in Abnormal Systolic Function

In patients with reduced LVEF, diastolic function will be abnormal. The main reason for evaluating diastolic measures in these patients is to estimate LV filling pressure. Since mean left atrial pressure (LAP) correlates better with PAWP as compared to LV end-diastolic pressure (LVEDP), algorithms to estimate LV filling pressures assumes the estimation of mean LAP. ASE/EACVI guidelines recommend using mitral inflow velocities, mitral e′ velocity, mitral E/e′ ratio, LA volume index, and peak TR velocity. In most cases, ***mitral inflow pattern*** including E/A ratio and peak E wave velocity should be sufficient to estimate LV filling pressure in patients with reduced LVEF. In patients with intermediate values for E/A ratio and E wave velocity, evaluation of additional measures of filling pressure, E/e′ ratio, LAVi, and TR velocity is recommended. Notable situations in which this approach to estimating filling pressures is problematic include atrial fibrillation, moderate or greater mitral valve calcification, moderate or greater mitral stenosis or regurgitation, prior mitral valve repair or replacement, LV assist devices, left bundle-branch block, and paced rhythms.*(3)*

TABLE (1): Classification of Diastolic Dysfunction (18).

	Normal	**Mild (Grade I)**	**Moderate (Grade II)**	**Severe* (Grade III)**
Pathophysiology		(-)Relaxation and normal LVEDP	(-)Relaxation and (-)LVEDP	(-)Compliance and (+)LVEDP
E/A ratio	≥0.8	<0.8	>0.8 to <2.0	≥2.0
Valsalva _*E/A*		<0.5	≥0.5	≥0.5
DT (ms)	150–200	>200	150-200	<150
*E_* velocity (cm/s)	≥10	<8	<8	<5
*E/E_* ratio	≤10	≤10	10–14	>14
IVRT (ms)	50–100	≥100	60–100	≤60
PV S/D	=1	S > D	S < D	S ≤ D
PVa (m/s)	<0.35	<0.35§	≥0.35	≥0.35
adur-*A*dur (ms)	<20	<20§	≥30	≥30
LA volume index	*<34 mL/m2*	*Mildly enlarged*	*Moderately enlarged*	*Severely enlarged*

*An additional grade of irreversible severe dysfunction is characterized by the absence of a decrease in E velocity with the strain phase of

the Valsalva maneuver.

†Only the yellow rows are included in the American Society of Echocardiography guidelines

plus consideration of tricuspid regurgitant jet

velocity. In the absence of other causes for elevated pulmonary pressures, a tricuspid regurgitant velocity greater than 2.8 m/s is

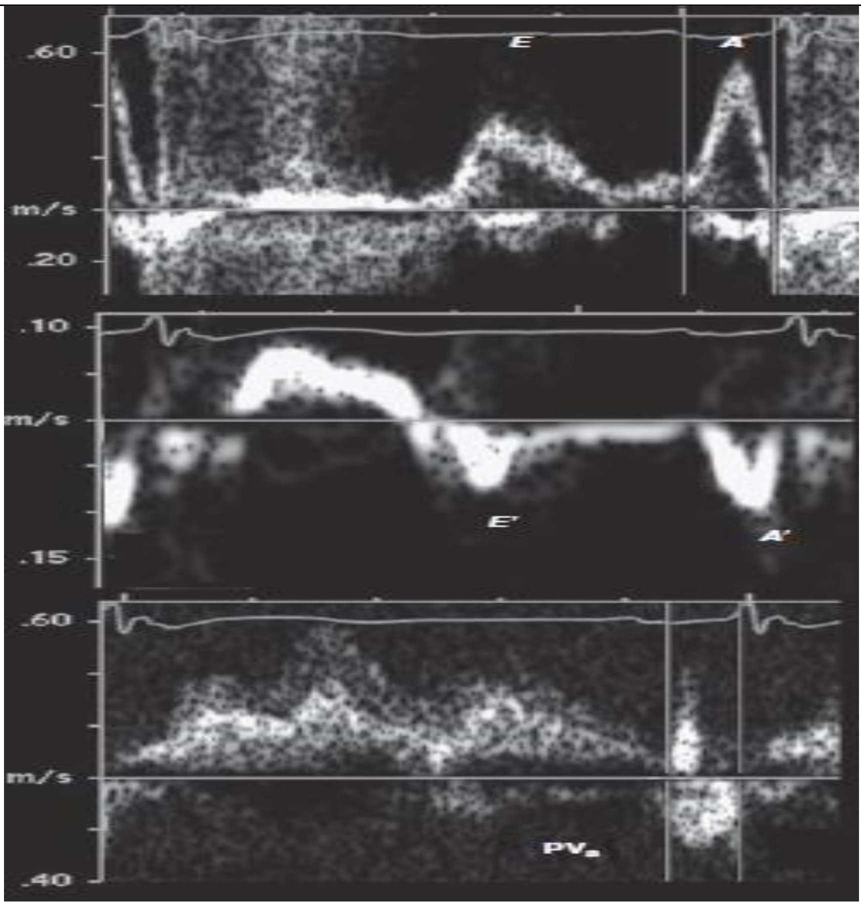
consistent with moderate to severe LV diastolic dysfunction.

‡E/A with the Valsalva maneuver is <1.

§Pulmonary vein a duration and velocity may be increased if filling pressures are elevated.

A, Late diastolic ventricular filling velocity with atrial contraction; DT, deceleration time; E, early diastolic peak velocity; E′, early diastolic

tissue Doppler velocity; IVRT, isovolumic relaxation time; LVEDP, LV end-diastolic pressure; PV, pulmonary vei



Figure(5):Mild diastolic dysfunction. In this patient with LV hypertrophy and decreased relaxation, the mitral inflow at the leaflet tips (top) shows an E/A <1 and a prolonged deceleration time. The myocardial tissue Doppler (center) confirms impaired relaxation with an E′A′ <1, indicating the mitral flow pattern is not related to loading conditions. The pulmonary venous inflow (bottom) shows relatively slightly greater systolic flow compared with diastolic flow and a normal atrial reversal velocity and duration (PVa), consistent with normal LV filling pressures. In addition, the E/E′ ratio is only 4(18).

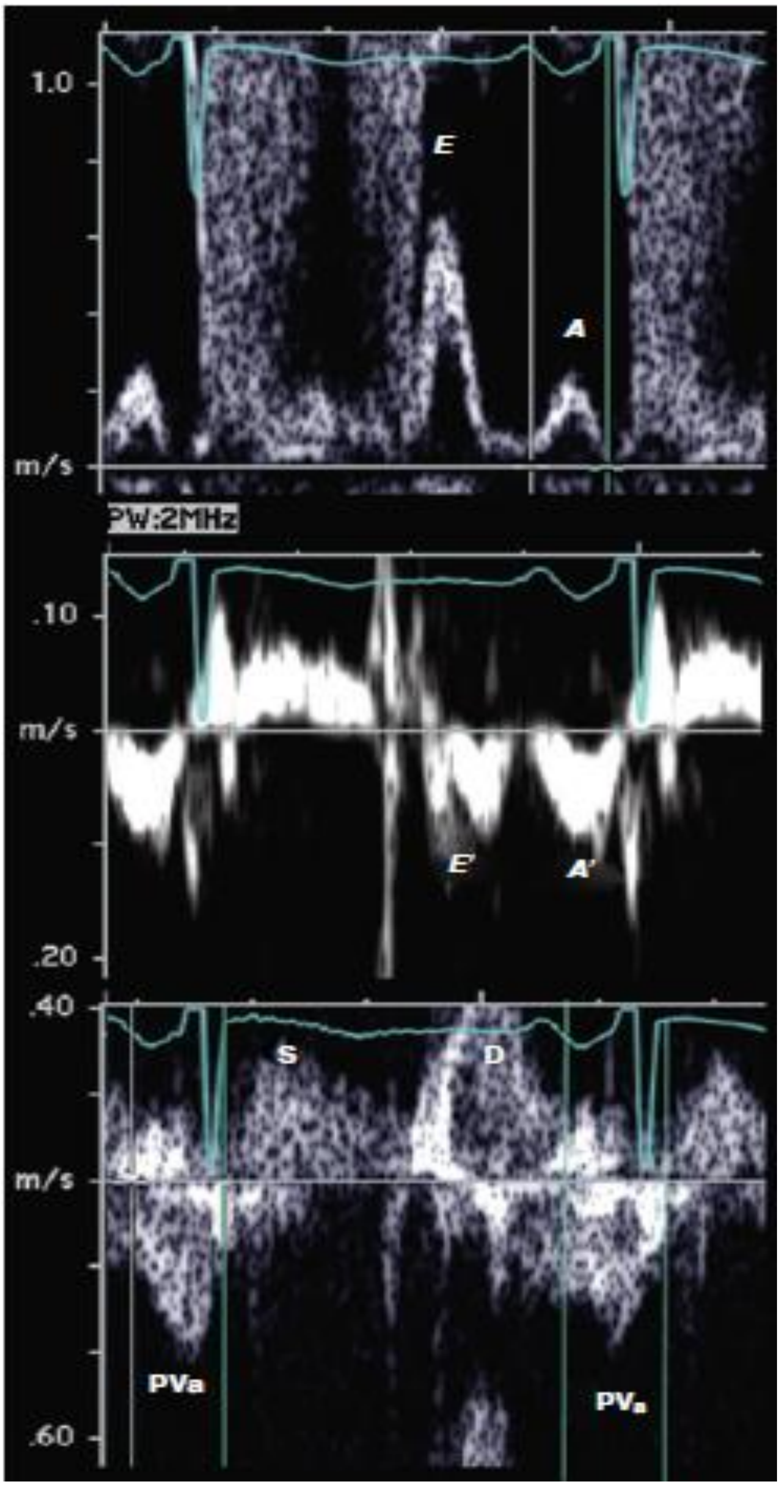
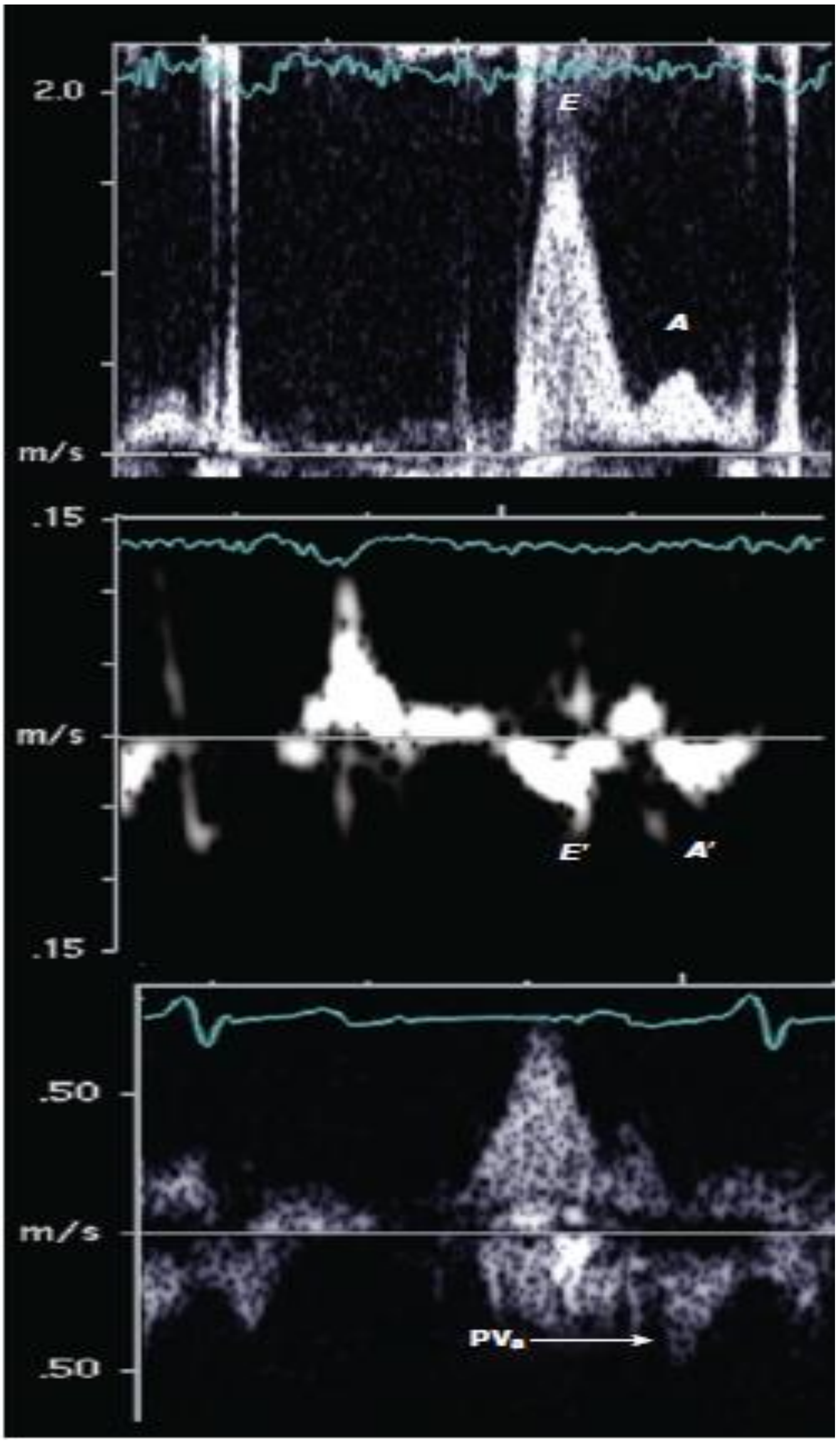
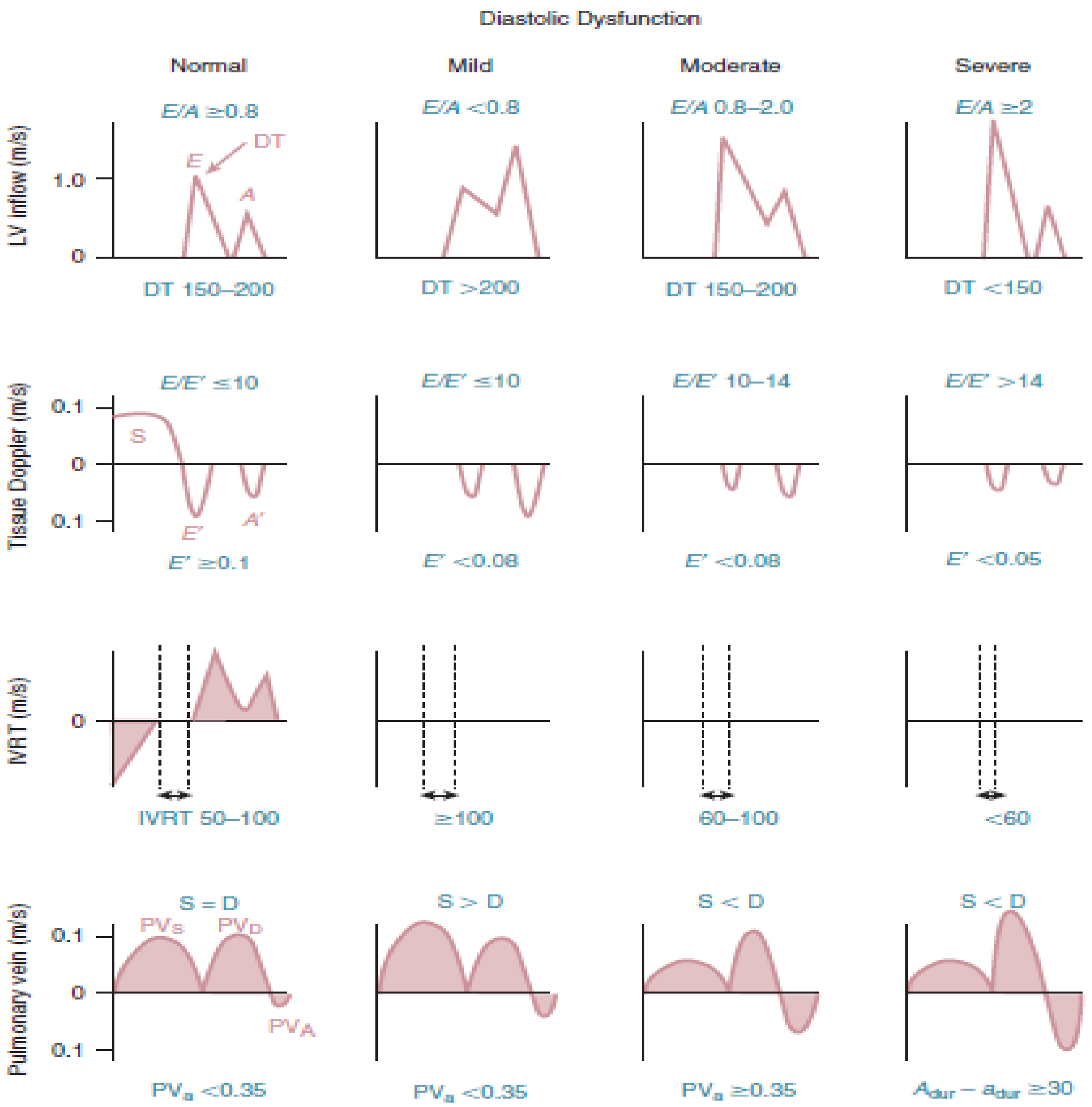


Figure (6):Moderate diastolic dysfunction. In a patient with impaired compliance and an elevated LV end-diastolic pressure, the mitral inflow at the leaflet tips (top) shows an E/A >1 and a short deceleration time. The myocardial tissue Doppler (center) shows about equal E′ and A′ velocities, with an E′ <0.8 m/s, consistent with decreased compliance. The E/E ′ ratio is slightly higher than 8. The pulmonary venous inflow (bottom) shows a relatively larger diastolic component than systolic component and an increased atrial reversal velocity (PVa) (approximately 0.40 m/s) and duration, consistent with elevated LV filling pressures(18).



Figure(7): Severe diastolic dysfunction. In this patient with heart failure and a low ejection fraction, the transmitral inflow shows a very high E/A ratio of 4 and a steep deceleration time (top). The myocardial tissue Doppler (center) shows a very low E′ velocity of 0.5 m/s and a very high E/E ′ ratio of 32. The pulmonary venous inflow pattern (bottom) is suboptimal, but diastolic flow is seen with no systolic component and the atrial reversal velocity (PVa) is at the upper limits of normal (approximately 0.35 m/s) (arrow), with a duration slightly longer than the mitral A duration, also supporting the diagnosis of elevated LV filling pressures(18).

Despite the numerous potential shortcomings of Doppler echocardiographic evaluation of diastolic filling, it has proven to be a repeatable, noninvasive, widely available method for the evaluation of diastolic function ***(18)***..



Figure(8): Doppler findings in patients with normal diastolic function and with mild, moderate, and severe diastolic dysfunction. The top row shows LV inflow with early (E) and atrial (A) phases of diastolic filling, the second row from the top shows tissue Doppler imaging recorded at the septal side of the mitral annulus with the myocardial early (E′) and atrial (A′) velocities and the expected ratio of (E/E′), the third row from the top shows the isovolumic relaxation time (IVRT), and the bottom row shows the pulmonary venous inflow pattern with systolic (S) and diastolic (D) antegrade flow and the pulmonary vein atrial (PVa) reversal of flow(18).

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