Left ventricular (LV) diastolic function can be evaluated invasively and noninvasively. Invasive measures of diastolic function include the peak instantaneous rate of LV pressure decline (-dP/dt), the time constant of LV relaxation (tau), and the stiffness modulus(1). Although echocardiography does not directly measure these parameters, echocardiography is the most practical routine clinical approach for evaluating LV diastolic function given clinical and experimental evidence supporting its use as well as its safety, versatility, and portability(1,2). During this lecture we will discuss the following metrics of diastolic function: transmitral pulsed-wave Doppler analysis, pulmonary venous pulsed-wave Doppler analysis, transmitral color m-mode flow propagation velocity (Vp) and tissue Doppler annular early and late diastolic velocities.

Transmitral Pulsed-Wave Doppler Analysis of Diastolic Inflow

The midesophageal 4-chamber view is used for Pulsed-wave (PW) Doppler analysis of mitral inflow velocities to assess left ventricular (LV) filling(1). Color flow imaging may be helpful for optimal alignment of the Doppler beam, particularly in the setting of LV dilation(1). Some authors advocate for initially performing CW Doppler prior to PW Doppler to assess peak E (early diastolic) and A (late diastolic) velocities to ensure that maximal velocities are obtained. Using PW Doppler, from a midesophageal 4-chamber view a 1-mm to 3-mm sample volume is then placed between the ***mitral leaflet tips*** during diastole to record a crisp spectral Doppler velocity profile (fig1). Spectral gain and wall filter settings is important to clearly display the onset and cessation of transmitral inflow. An adequate transmitral spectral Doppler profile may be obtained in most

patients. Velocity recordings should initially be obtained at sweep speeds of 25 to 50 mm/s for the evaluation of respiratory variation of flow velocities, as seen in patients with pulmonary or pericardial disease. If significant variation is not present, the sweep speed is increased to 100 mm/s, and averaged over 3 consecutive cardiac cycles (3).

The following measurements are made (3):

- Peak early filling (E-wave) velocity
- Peak late filling (A-wave) velocity
- E/A ratio
- Deceleration time (DT) of the early filling velocity
- Isovolumetric (Isovolemic) relaxation time (IVRT)

Other less common (secondary measurements) include:

- A-wave duration (A-dur) (sample volume at annulus)
- A-wave velocity time integral (VTI) (sample volume at the annulus)
- Total mitral inflow VTI for calculation of the atrial filling fraction (sample volume at the level of the MV annulus)

The IVRT is obtained from a deep transgastric long axis view by using a CW Doppler beam in the LV outflow tract to simultaneously display the end of aortic ejection and the onset of mitral inflow. Age must be considered when defining normal values of mitral inflow velocities and time intervals. Slightly different normal values may be found in multiple texts and articles, but the most recent guidelines (1,3) represents the best source for these values.

Transmitral inflow patterns are primarily recognized based on IVRT, E/A ratio and DT.

These patterns include (figure 2) (3):

- Normal (Normal IVRT, E/A >1, normal DT)
- Impaired relaxation (Prolonged IVRT, E/A < 1, Prolonged DT)
- Pseudonormal (Normal IVRT, E/A and DT look normal)

- Restrictive (Short IVRT, E/A >>1, Decreased (short) DT)

The distinction between pseudonormal and normal diastolic function requires measuring other parameters of LV diastolic function, as these may not be distinguished by transmitral inflow patterns alone.

There are multiple determinants of LV diastolic function and transmitral inflow. Although this is an oversimplification, two parameters help determine transmitral filling:

1. Active LV relaxation, and
2. LV compliance (which determines LA pressure)

LV relaxation is an active energy dependent process. With the onset of diastolic dysfunction, relaxation is impaired or delayed and an impaired relaxation pattern develops with E/A <1, DT prolonged (Fig 2). As diastolic function worsens LV relaxation is further impaired and there is a progression of filling patterns as follows: Impaired relaxation→ pseudonormal→restrictive. The pseudonormal and restrictive patterns result because the impaired relaxation (which tends to prolong IVRT, and DT and decrease E/A) is overwhelmed by increased left atrial pressures, which tend to shorten IVRT, and DT and increase E/A. With the initial impaired relaxation pattern the LV fails to generate adequate diastolic suction and therefore the IVRT is prolonged (takes a longer time to pop open the MV) and after the MV opens the decreased suction generated causes a low peak E velocity and a prolonged DT (takes a long time for early filling due to decreased suction from impairment of the active energy dependant relaxation). Given the decreased volume of flow during early filling, the LA is relatively full at the time of LA contraction and thus the A wave is larger (larger Peak A wave velocity, A wave VTI, prolonged A wave duration) relative to the E wave (E/A<1). With

continued worsening of diastolic function LV compliance decreases. Active relaxation is still impaired, but the decreased LV compliance results in elevated left atrial pressures. The pseudonormal and restrictive patterns result because the impaired relaxation (which tends to prolong IVRT, and DT and decrease E/A) is overwhelmed by increased left atrial pressures, which tend to shorten IVRT, and DT and increase E/A. (figure 2).

Transmitral inflow velocities are influenced by loading conditions, and rhythm disturbances including: sinus tachycardia, conduction system disease, and arrhythmias. Sinus tachycardia and first-degree AV block may cause partial or complete fusion of the E and A waves.

Key Points regarding Transmitral PW Doppler according to EAE/ASE (1)

"(1) PW Doppler is performed in the ME 4-chamber view.

(2) A 1-mm to 3-mm sample volume is then placed between the mitral leaflet tips

(3) Primary measurements include peak E and A velocities, E/A ratio, DT, and IVRT.

(4) Mitral inflow patterns include normal, impaired LV relaxation, Pseudonormal, and restrictive LV filling (fig 2).

(5) In patients with dilated cardiomyopathies, filling patterns correlate better with filling pressures, functional class, and prognosis than LV EF.

(6) In patients with coronary artery disease and those with hypertrophic cardiomyopathy in whom the LV EFs are ≥ 50%, mitral velocities correlate poorly with hemodynamics."

The pulsed-wave Doppler pulmonary venous flow waves are identified as follows:

- ***Systolic wave (S-wave),***
- ***Diastolic wave (D-wave)***
- ***Atrial wave (PV A-wave) = Atrial reversal wave (PV AR-wave)***

Note: A = atrial contraction, S = systole, D = diastole.

If one were to look for the corresponding left atrial pressure (LAP) tracing components you will notice that anything that increases LA pressure will decrease flow through the pulmonary veins to the LA.

Conversely, anything that decreases LAP will increase flow to the LA. Below is a list of the LAP adjacent to its corresponding pulmonary venous flow (PV) wave (figure 4):

LAP A-wave→PV A-wave

LAP X-descent→PV S-wave

LAP V-wave→PV decline in velocity between S and D waves

LAP Y-descent→PV D-wave

Notice as LAP increases, flow into the LA decreases and in some cases reverses (A wave = AR wave = Atrial Reversal wave).

Notice there are two components to the pulmonary venous S wave: S1 and S2.

The following are factors that influence the **maximum velocity and timing** of these two waves:

S1:

1. Atrial relaxation in early systole

S2:

1. Right ventricular stroke volume

2. Left Atrial Compliance

3. Descent of the mitral valve annulus which lowers LA pressure

The following cardiac disorders result in changes to the pulmonary venous flow pulsed-wave Doppler spectral profile:

Elevated left atrial pressure (LAP) from decreased LV compliance as might be seen with pseudonormal or restrictive diastolic dysfunction: S < D, PV A-wave duration > transmitral A-wave duration (AR duration – A duration > 30 ms).

Mitral insufficiency→blunting or reversal of S wave (reversal→severe MR)

Large PV A-wave is seen with: Mitral Stenosis (MS) and complete heart block (CHB). There are no valves in the pulmonary veins, so when the left atrium contracts there will be forward flow into the left ventricle and retrograde flow into the pulmonary veins creating the pulmonary venous A-wave (PV A-wave = Atrial Reversal wave = AR wave). With MS there is obstruction to forward flow through the stenotic mitral valve and therefore a

predominance of retrograde pulmonary venous flow with atrial contraction. CHB can be thought of as the worst MS ever, as the valve is closed when atrial contraction occurs resulting in a large PV A-wave from retrograde pulmonary venous flow. Decreased LV compliance (pseudonormal and restrictive diastolic dysfunction) also may cause a large PV A-wave. With restrictive diastolic dysfunction there is sometimes not a large A-wave and this is thought to be because there is left atrial mechanical failure and the atrium no longer has the ability to generate significant forward or retrograde flow.

Key Points regarding PV PW Doppler according to EAE/ASE (1):

"(1) PW Doppler of pulmonary venous flow is performed in the ME 4-chamber view.
(2) A 2-mm to 3-mm sample volume is placed .0.5 cm into the pulmonary vein for optimal recording of the spectral waveforms.
(3) Measurements include peak S and D velocities, the S/D ratio, systolic filling fraction, and peak Ar velocity in late diastole. Another measurement is the time difference between Ar duration and mitral A-wave duration (Ar - A).
(4) With increased LVEDP, Ar velocity and duration increase, as well as the (Ar – A) duration.
(5) In patients with depressed EFs, reduced systolic filling fractions (< 40%) are related to decreased LA compliance and increased mean LA pressure."

Color M-Mode Flow Propagation Velocity (Vp)

In the perioperative setting the Vp slope method(1,4,5) appears to have the least variability(6). Acquisition via transesophageal echocardiography (TEE) is performed with the ME 4-chamber view and with transthoracic echocardiography (TTE) it is performed with the apical 4-chamber view. In both, color flow Doppler with a narrow sector angle and gain adjusted to avoid noise is utilized with an M-mode scan line placed through the center of the LV inflow column from the mitral valve to the LV apex (1,3). The color scale baseline is adjusted so that the central highest velocity jet is blue. Vp is measured as the slope of the first aliasing velocity during early transmitral filling as measured from the mitral valve plane to 4 cm distally into the LV cavity(1,5). Alternatively the slope of the transition from no color to color can be measured(4). Normal Vp is 45-50 cm/sec (1,5,7). Similar to the pulse-wave Doppler transmitral inflow velocities, there is an early wave and a late atrial contraction wave (1). With normal diastolic function, the early filling wave propagates rapidly toward the apex and is driven by the pressure gradient from the LV base to apex(1,8). This suction force results from energy-dependant active LV relaxation. With diastolic dysfunction, from ischemia or heart failure, there is slowing of mitral-to-apical flow propagation consistent with a reduction of apical suction (1,4,9,10). However, in clinical practice evaluation and interpretation of intraventricular filling is complicated by the multitude of variables that determine intraventricular flow(1). Despite the multiple variables affecting flow, the slowing of mitral-to-apical flow propagation by color M-mode Doppler has proved to be a semiquantitative marker of LV diastolic dysfunction(1). In addition, the ratio of the

peak early transmitral inflow velocity (E) to Vp (E/Vp) can be used to predict LV filling pressures (1,5). In patients with decreased systolic function (decreased LVEF) an E/Vp ≥ 2.5 predicts a PCWP ≥ 15 (1,11). However, in patients with normal systolic function (normal LVEF) LV filling pressures can not be predicted by E/Vp (11). Also patients with elevated filling pressures but a normal LVEF, and normal LV volumes can have an erroneously normal Vp (12) (11,13,14). In addition, preload has been shown to have a positive influence on Vp in patients with normal and depressed LVEF(1,13,15).

Key Points regarding Vp according to the EAE/ASE (1)

"1. Acquisition is performed in the 4-chamber view,
using color flow Doppler imaging.
2. The M-mode scan line is placed through the center of the
LV inflow blood column from the mitral valve to the
apex, with baseline shift to the color scale so
the central highest velocity jet is blue.
3. Vp is measured as the slope of the first aliasing velocity
during early filling, measured from the mitral valve
plane to 4 cm distally into the LV cavity, or the slope
of the transition from no color to color.
4. Vp ≥ 45-50 cm/s is considered normal.
5. In most patients with depressed EFs, Vp is reduced, and
should other Doppler indices appear inconclusive, an
E/Vp ratio ≥ 2.5 predicts PCWP ≥15 mm Hg with reasonable
accuracy.
6. Patients with normal LV volumes and EFs but elevated
filling pressures can have misleadingly normal Vp."

Mitral Annular Tissue Doppler Early (Em) and Late (Am) Diastolic Velocities (1,16):

Pulse wave (PW) Doppler tissue imaging (DTI) is performed with TEE in the ME-4-chamber view and with TTE in the apical views, which allow acquisition of mitral annular velocities (1,17). The sample volume should be placed at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5-10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole (1). DTI velocities have higher amplitude and lower peak velocities when compared with transmitral inflow velocities. Spectral gain settings can be manually optimized for DTI, but most current ultraound systems have tissue Doppler presets for the proper velocity scale and Doppler wall filter settings (1). Usually the velocity scale should be set at about 10-20 cm/s above the zero-velocity baseline (1). Given the angle dependance of all Doppler measurements, minimal angulation (< 20 degrees) should be present between the ultrasound beam and the place of cardiac motion (16). Regardless of the 2D image quality, DTI waveforms can be obtained in nearly all patients (>95%). The recommended sweep speed is 50-100 mm/s at end expiration and measurements should reflect the average of ≥ 3 cardiac cycles (1). Primary measurements included systolic (S), early diastolic (e′), and late diastolic velocities (a′) (figure 5) (18). Early diastolic annular tissue velocity has been expressed as Ea, Em, E′ and e', in this syllabus we will use e′ and E′ (1). Peak velocities alone are all that needs to be measured, as E′ deceleration time, acceleration rates and deceleration rates, do not contain incremental information and need not be performed (1,19).

E′ has been shown to have a significant association with LV relaxation in human

and animal studies (1,20-24). E′ is related to LV diastolic properties, such as elastic recoil and relaxation, regardless of filling pressures or systolic function but E′ is also influenced by systolic function, preload, and LV minimal pressure (1,16,25). E′ changes in the same direction as preload in patients with normal diastolic function(16). This effect is less pronounced in ventricles with impaired relaxation where E′ remains decreased regardless of changes in preload (16,21,26,27). Thus E′ is relatively preload independent in sick patients, (those with significant diastolic dysfunction) including most of the patients presenting for cardiac surgery.

The time interval between the QRS complex and the E′ onset is prolonged with impaired LV relaxation and can provide incremental information in special patient populations (1). Given the influence of regional function on tissue velocities and intervals, it is recommended to acquire and measure tissue Doppler signals at least at the septal and lateral sides of the mitral annulus and calculate their average, for assessment of global LV diastolic function (1,2,11,28).

Once transmitral inflow PW flow, annular velocities and time intervals are acquired, it is possible to compute additional time intervals and ratios (1,16). Important ratios include: E/e′, E′/A′ and IVRT/$T_{E\text{-}e'}$. The ratio E/e′, has been shown to help estimate LV filling pressures in patients with LV diastolic dysfunction (18). An E/e′ > 12-15 is consistent with elevated LV filling pressures (2,18). In addition, E/e′ has been shown to be a marker of severe cardiac disease. In a recent study of 205 patients an E/e′ ratio ≥8 was shown to be associated with increased intensive care unit length of stay (ICU-LOS) P = 0.037) and need for inotropic support (P = 0.002) (29). These results were seen after making adjustments to account for other predictors (female gender,

hypotension, diabetes, history of myocardial infarction, emergency surgery, renal failure, procedure type, and length of aortic cross-clamp time) thereby implicating E/e′ as a serious prognostic indicator (29,30). The $T_{E\text{-}e'}$ interval is the time interval between the QRS complex and the onset of the mitral E velocity subtracted from the time interval between the QRS complex and the e′ onset (1). The $T_{E\text{-}e'}$ interval is prolonged with diastolic dysfunction, and animal and human studies have shown it to be strongly dependent on the time constant of LV relaxation (tau) and minimal LV pressure (1,31,32). Technically, it is essential to match the RR intervals for measuring both time intervals (time to E and time to e′) and to optimize the Doppler gain and filter settings, because higher gain and filter settings interfere with correct identification of the onset of e′(1).

The main hemodynamic determinants of a′ include: LA systolic function and LVEDP. An increase in LA contractility leads to an increase in a′, and an increase in LVEDP leads to a decrease in a′(1,19). Normal values for DTI-derived velocities are influenced by age, similar to other indices of LV diastolic function, but an but an e′ <8 cm/sec is generally considered low(1,2). With age e′ decreases, a′ increases and E/e′ increases(1,33).

Clinical Application of DTI(1,16):

DTI mitral annular velocities assist in the evaluation of LV relaxation, and E/e′ can be used to estimate LV filling pressures (1,2). Reliable conclusions require consideration of multiple factors such as patient age, coexisting cardiovascular disease and other echocardiographic abnormalities. Thus e′ and E/e′ should not be used in isolation. It is

also important to use the average of e′ obtained from the septal and lateral sides of the mitral annulus over several cardiac cycles. Skubas et al. (16) suggest utilizing the lateral mitral annulus e′ in the E/e′ ratio for estimating filling pressures because the lateral mitral annulus is rarely involved in ischemic disease and e′ measurements at this location will usually reflect LV relaxation. An E/e′ < 8 indicates normal filling pressures and E/e′ > 12-15 indicates elevated filling pressures. The mean pulmonary capillary wedge pressure can be estimated by the following formula: mean PCWP = (1.3 x E/e′) + 2 (1,16).

Technical limitations to DTI include factors such as angle dependence, proper sample size, gain, and Doppler filter settings. In addition, there are a number of clinical settings in which e′ and E/e′ are misleading. In normal subjects e′ velocity is positively related to preload and E/e′ can not be used to estimate filling pressures (1). E′ is also significantly reduced in patients with significant mitral annular calcification, surgical rings, mitral stenosis and prosthetic mitral valves(1). E′ is increased in patients with moderate to severe MR and normal LV relaxation due to increased flow across the MV. E/e′ should not be used in these patients, but the isovolumetric relaxation time to $T_{E\text{-}e'}$ ratio (IVRT/$T_{E\text{-}e'}$) can be applied (an IVRT/ $T_{E\text{-}e'}$ <2 is consistent with increased filling pressures) (1,31,34). Patients with constrictive pericarditis usually have elevated e′ due to preserved LV longitudinal expansion compensating for limited lateral and anteroposterior diastolic excursion. Lateral e′ may be less than septal e′ in theis condtion and the E/e′ should not be used to estimate filling pressures(1). However, a normal e′ in the setting of restrictive transmitral inflow velocities can help distinguish constrictive pericarditis from restrictive diastolic dysfunction due to an infiltrative restrictive

cardiomyopathy (35).

Key Points regarding DTI according to the EAE/ASE (1)

"(1) PW DTI is performed in the ME-4 Chamber view

(2) The sample volume should be positioned at or 1 cm

within the septal and lateral insertion sites of the

mitral leaflets.

(3) It is recommended that spectral recordings be obtained

at a sweep speed of 50 to 100 mm/s at end-expiration

and that measurements should reflect the average of

≥3 consecutive cardiac cycles.

(4) Primary measurements include the systolic and early (e´)

and late (a´) diastolic velocities.

(5) For the assessment of global LV diastolic function, it is

recommended to acquire and measure tissue Doppler

signals at least at the septal and lateral sides of the

mitral annulus and their average.

(6) In patients with cardiac disease, e´ can be used to correct

for the effect of LV relaxation on mitral E velocity, and

the E/e´ ratio can be applied for the prediction of LV

filling pressures.

(7) The E/e´ ratio is not accurate as an index of filling pressures

in normal subjects or in patients with heavy annular

calcification, mitral valve disease, and constrictive pericarditis. "

Addendum regarding perioperative TEE and diastolic function(36). Recently Swaminathan M, et. al. found that a simplified perioperative approach using the lateral mitral annular tissue Doppler e´ measurement and the ratio of the transmitral pulsed-wave Doppler E peak velocity to the lateral mitral annular tissue Doppler peak early velocity ratio (E and E/ e´) can be used to predict survival. In summary: an e´<10 cm/sec + E/ e´> 13 predicted a significantly lower survival vs patients with an e´ > 10 cm/sec in 905 patients undergoing CABG.

Figure 1: Transmitral Pulsed-Waved Doppler Spectral Profile

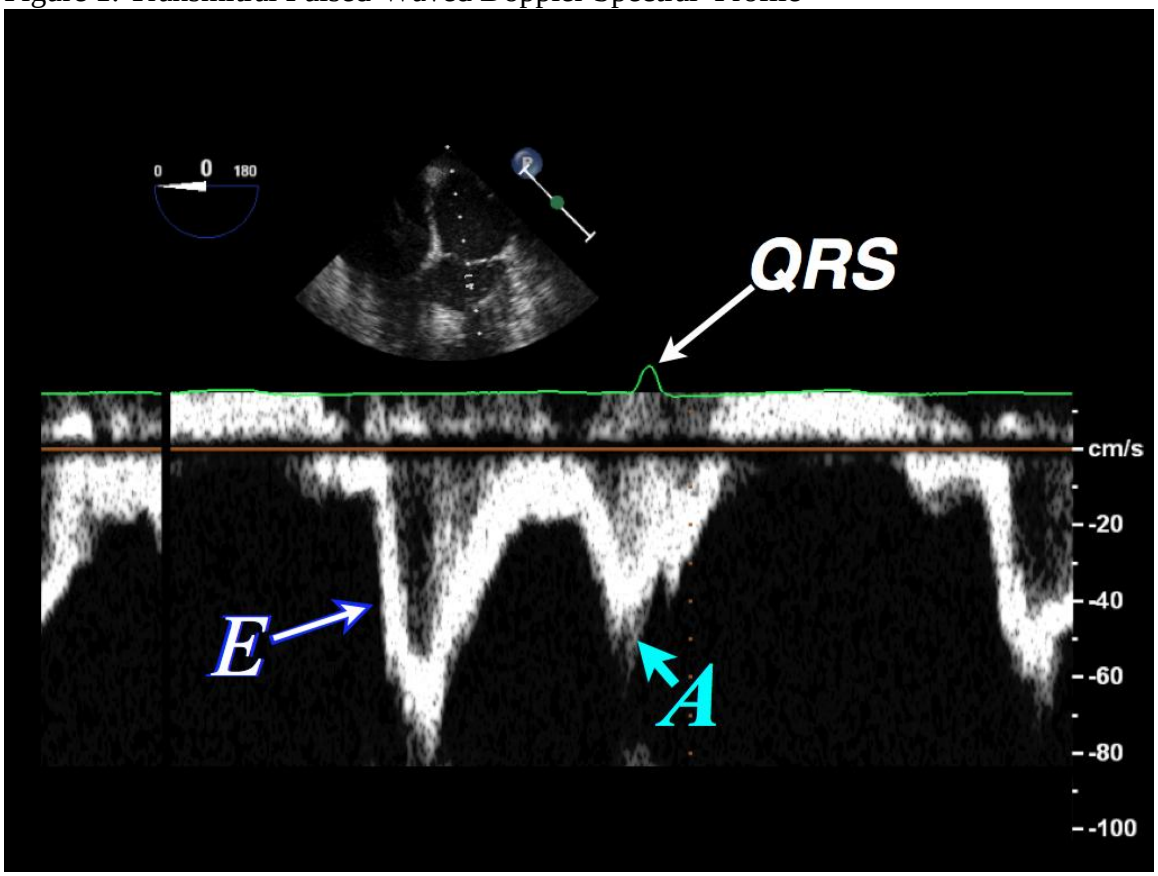


Figure 2: Transmitral Pulsed Wave Doppler Profiles

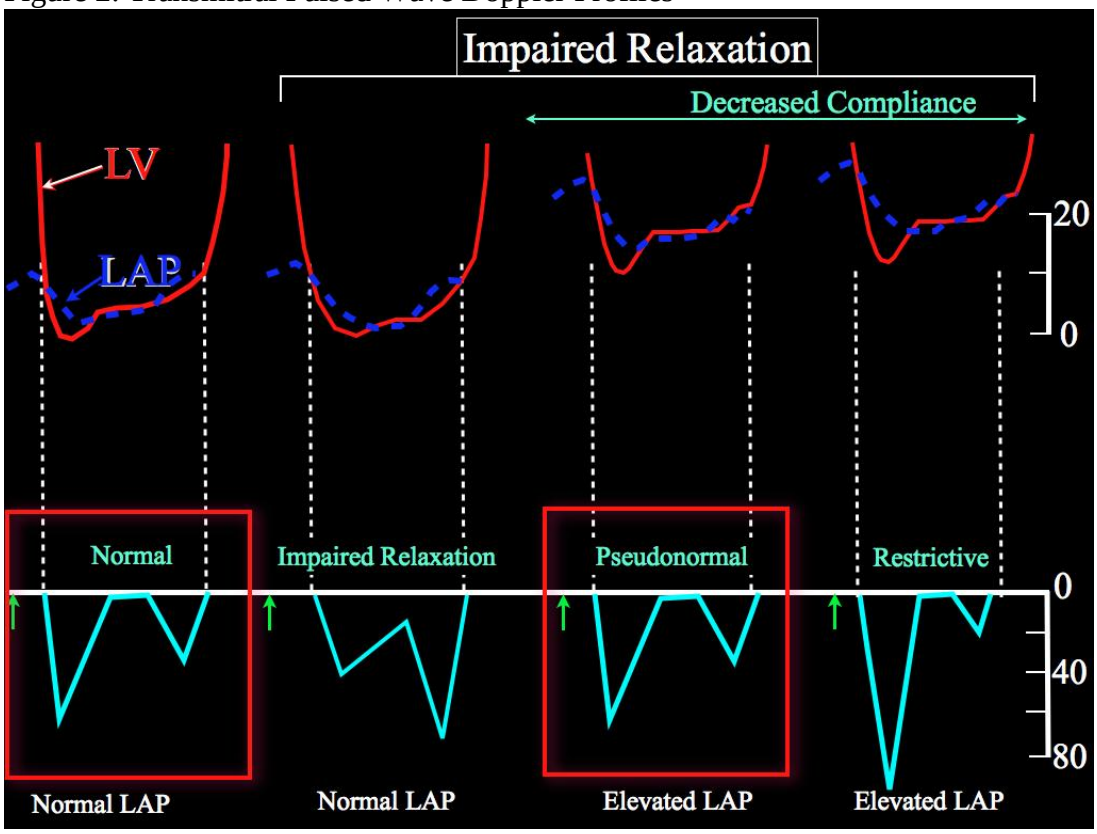


Figure 3 Pulmonary Venous Flow

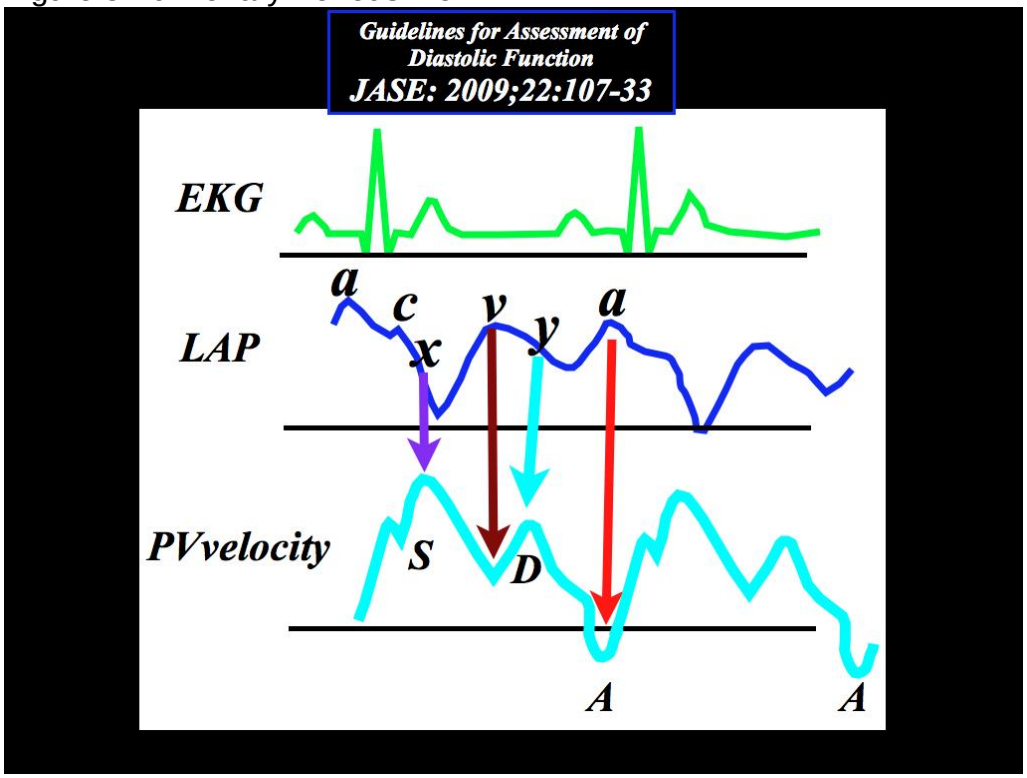


Figure 4: Pulmonary Venous Pulsed Wave Doppler

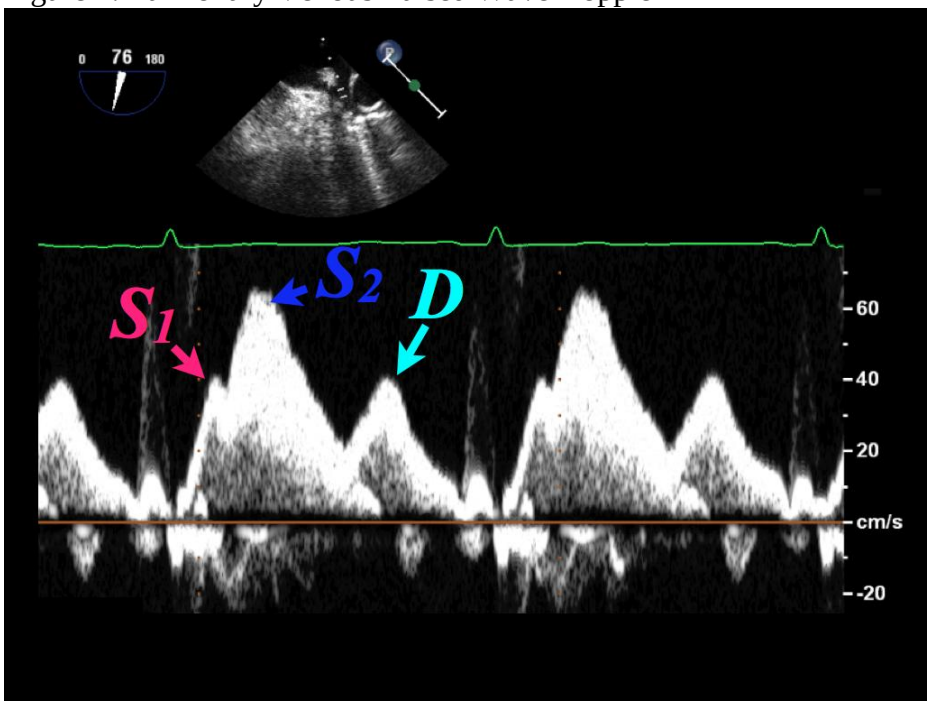


Figure 5: Mitral Annular Tissue Doppler(1)

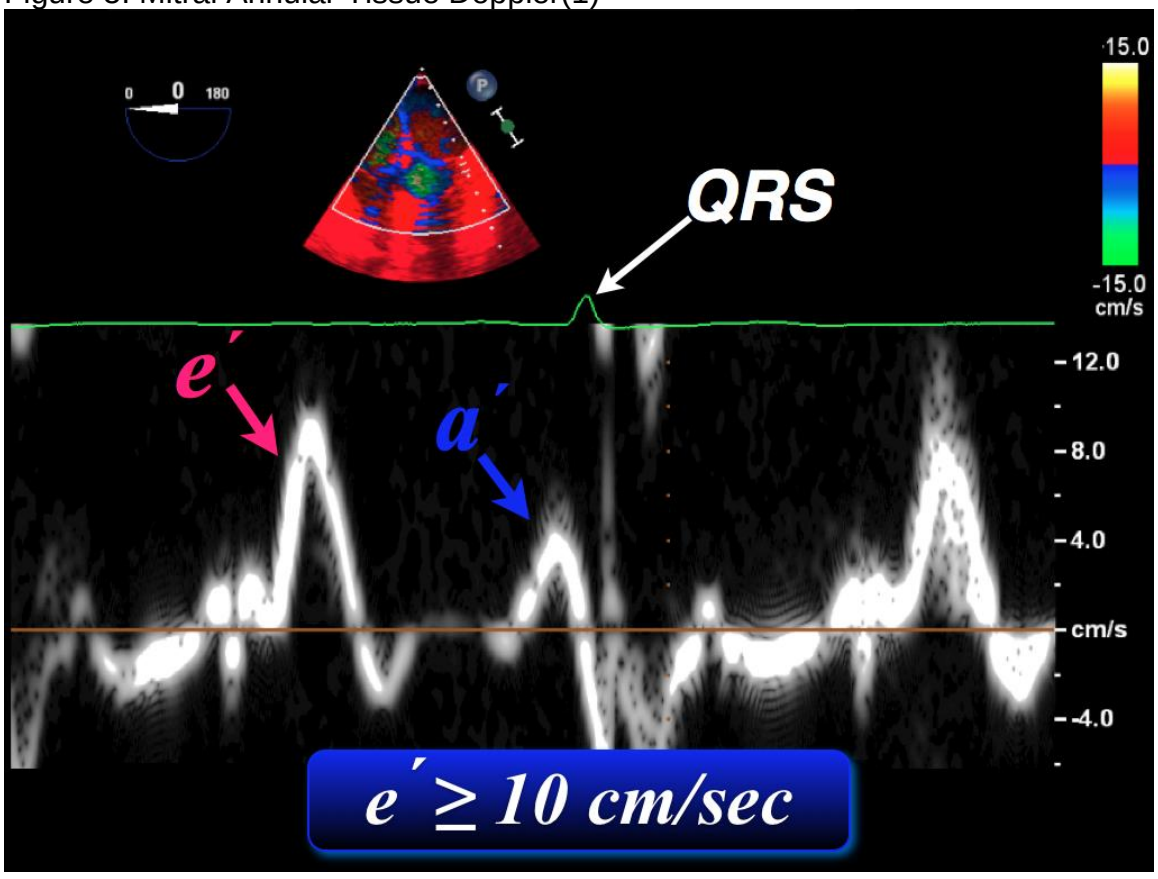
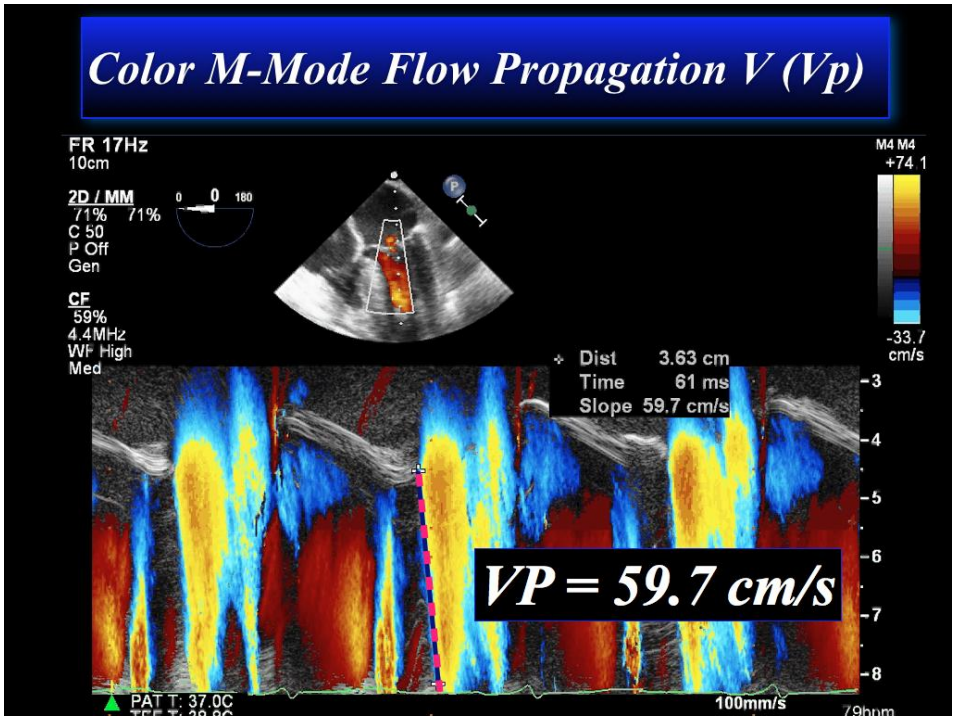


Figure 6: Color M-Mode Flow Propagation Velocity (Vp)



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