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# Evaluation of Left Ventricular Diastolic Function by Echocardiography

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## 1. Introduction

The normal cardiac cycle consists of two phases, systole and diastole, which are repeated over time to maintain an adequate cardiac output. The systole has been traditionally regarded as the main capital phase, leaving at diastole as a secondary process and almost forgotten. However, today we know that diastole is a crucial stage in the functioning of the heart. Its dysfunction can lead even in cases with preserved systolic function in heart failure. About half of patients with new diagnoses of heart failure have normal or near normal global ejection fractions. These patients are diagnosed with “diastolic heart failure” or “heart failure with preserved ejection fraction” (Zipes et al., 2011).

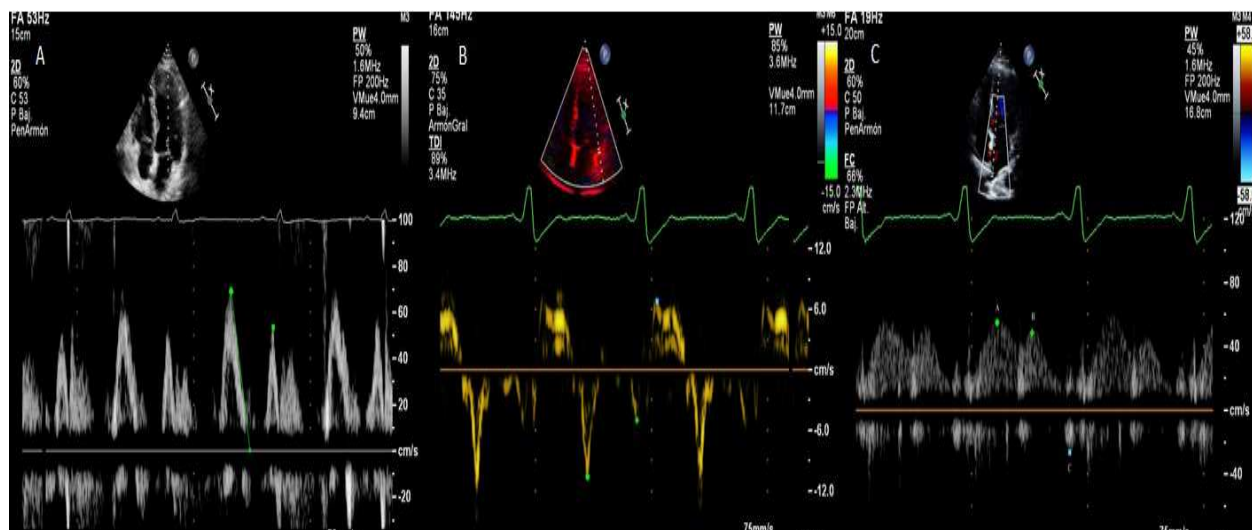


Fig. 1. Normal diastolic Doppler patterns: A) Mitral inflow. B) Mitral annular tissue Doppler. C) Pulmonary venous flow

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Echocardiography has played a central role in the evaluation of left ventricular diastolic function over the past two decades. Alterations in diastolic function may be transient (eg acute ischemia) or persistent (myocardial necrosis, left ventricular hypertrophy or myocardial infiltration). The indices of diastolic function can be organized into three groups: measures of isovolumetric relaxation, indices of passive left ventricular (LV) characteristics derived from the diastolic LV pressure-volume relations, and measurements of the pattern of LV diastolic filling obtained from Doppler echocardiography (figure 1) or radionuclide angiography. Nowadays, echocardiography is the technique of choice for the estimation of diastolic function.

### 1.1 Normal heart cycle

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: first a compliant chamber in diastole that allows the LV to fill from low left atrium pressure and second a stiff chamber (rapidly rising pressure) in systole that ejects the stroke volume at arterial pressures. Diastole can be divided into four phases: isovolumetric diastolic relaxation period, the rapid filling phase, slow filling phase and atrial systole. Ventricular relaxation energy consumed primarily in the first two phases, while in the latter two processes have more influence the ventricular-compliance.

The Valsalva maneuver can be used to decrease preload and unmask the seemingly normal pattern of pseudonormal filling to reveal a pattern characteristic of relaxation abnormality. The pulmonary venous flow pattern, the tissue Doppler mitral annular velocity profile, left atrial (LA) size, and color M-mode, all contribute to the assessment of diastolic function and filling pressures, allowing classification of diastolic function and left ventricular filling pressures.

The first pressure crossover corresponds to the end of isovolumic 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. Slow filling, with almost no pressure differences, follows this. During atrial contraction, LA pressure again exceeds LV pressure.

At baseline, the majority of filling occurs in early diastole ventricular after mitral valve opening, giving rise to the E wave mitral Doppler signal (figure 1). The filling rate is high turn. In meso and diastolic signal originates small and anterograde diastasis, followed by a wave in diastole. The peak velocity ratio E / A is usually greater than 1. There are situations such as tachycardia or arrhythmias such as atrial fibrillation which may affect ventricular filling.

### 1.2 Mechanisms of diastolic dysfunction

Although diastolic dysfunction is not uncommon in patients with normal wall thickness, left ventricular hypertrophy (LVH) is among the important reasons for it. In patients with diastolic heart failure, concentric hypertrophy (increased mass and relative wall thickness), or remodeling (normal mass but increased relative wall thickness), can be observed. In contrast, eccentric LVH is usually present in patients with depressed ejection fractions. Because of the high prevalence of hypertension, especially in the older population, LVH is common, and hypertensive heart disease is the most common abnormality leading to diastolic heart failure. Left ventricular mass may be best measured using 3-dimensional echocardiography. Nevertheless, it is possible to measure it in most patients using 2-

dimensional (2D) echocardiography, with the recently published guidelines of the American Society of Echocardiography (Oh et al., 2006).

The measurement of LA volume is highly feasible and reliable in most echocardiographic studies, with the most accurate measurements obtained using the apical 4-chamber and 2-chamber views, but it is important to consider left atrium volume measurements in conjunction with a patient's clinical status, other chambers' volumes, and Doppler parameters of left ventricular relaxation (Oh et al., 2006).

Symptomatic patients with diastolic dysfunction usually have increased pulmonary artery pressures. Therefore, in the absence of pulmonary disease, increased pulmonary artery pressures may be used to infer the presence of elevated LV filling pressures. Indeed, a significant correlation was noted between pulmonary artery systolic pressure and noninvasively derived LV filling pressures (Rodríguez-Padial et al., 2002).

The assessment of LV diastolic function and filling pressures is of paramount clinical importance to distinguish this syndrome from other diseases such as pulmonary disease resulting in dyspnoea, to assess prognosis, and to identify underlying cardiac disease and its best treatment. The criterion standard for demonstrating LV diastolic dysfunction is cardiac catheterization to obtain pressure-volume curves to measure the rate of pressure decay during isovolumic relaxation (Murphy et al., 2006). However, this measurement is imperfect because of the additional effect of transmural pressure on the LV; routine invasive cardiac catheterization is also not feasible. Noninvasive modalities should thus include routine measurements of diastolic function. Echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades.

## **2. Mitral inflow**

### **2.1 Recording technique**

Doppler mitral inflow velocity-derived variables remain the cornerstone of the evaluation of diastolic function. To evaluate the early and late filling phases, mitral inflow velocities are obtained by placing the pulsed-wave Doppler at the tips of the mitral valve leaflets in the apical 4-chamber view. This is the point at which the mitral inflow velocities are maximal and maximal accuracy and reproducibility of measurement are obtained. Normal mitral inflow consists of biphasic flow from the LA into the LV: rapid filling wave at the beginning of diastole, after mitral valve opening, when the transmitral gradient is higher (E-wave), followed by A-wave corresponding to a further increase in mitral flow velocity after atrial contraction (figure 1 A).

The ultrasound beam needs to be in parallel with the direction of blood flow to obtain an optimal flow signal and can be used to place the color Doppler sample volume in the predominant direction of mitral filling flow. With left ventricular dilatation, as in patients with dilated cardiomyopathy, the heart becomes more spherical, which causes the mitral inflow is directed progressively more lateral and beyond. Therefore, the optimal position of the transducer is approximately 20 degrees lateral to the apex in normal subjects and more lateral in those with growth of the left ventricle. The sample volume should be small (1-2 mm), resulting in a more contrasted flow record (Appleton et al, 1997).

### **2.2 Mitral inflow velocities**

Primary measurements of mitral inflow include the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling

velocity, and the isovolumetric relaxation time (IVRT) (figure 1). Secondary measurements include mitral A-wave duration, diastolic filling time, the A-wave velocity-time integral, and the total mitral inflow velocity-time integral (and thus the atrial filling fraction) with the sample volume at the level of the mitral annulus.

It is well established that the mitral E-wave velocity primarily reflects the LA- LV pressure gradient during early diastole and is therefore affected by preload and alterations in left ventricle relaxation (Appleton et al, 1988). The mitral A-wave velocity reflects the LA- LV ventricle pressure gradient during late diastole, which is affected by LV compliance and LA contractile function. E-wave DT is influenced by left ventricle relaxation, left ventricle diastolic pressures following mitral valve opening, and left ventricle compliance (i.e., the relationship between left ventricle pressure and volume). Patients with conditions associated with increased left ventricle stiffness have more rapid rates of deceleration of early left ventricle filling and shorter deceleration times (Ohno et al, 1994). In summary, mitral deceleration time is an important parameter that should be considered in drawing conclusions about operative left ventricle stiffness, particularly in patients without marked slowing of left ventricle relaxation.

Factors that affect mitral inflow include heart rate, rhythm, PR interval, cardiac output, mitral annular size, left atrium function, left ventricle end-systolic or end-diastolic volumes, and left ventricle elastic recoil.

### **2.3 Diastolic filling patterns**

The initial classification of diastolic filling is based on the measurement of E-wave and A-wave velocities and E/A ratio (figure 2). Mitral valve inflow patterns, which have been attributed in varying degree to diastolic dysfunction, include normal pattern, impaired LV relaxation pattern, restrictive LV filling pattern and pseudonormal LV filling pattern.

#### **2.3.1 Normal pattern**

In healthy, young, disease-free individuals the E-wave exceeds the A-wave, and therefore the E/A ratio is more than 1 (Figure 1-A). In adolescents and young adults, there may be a disproportionate contribution of active ventricular relaxation to ventricular filling, which results in a markedly accentuated E-wave velocity. In this instance, E/A ratio can exceed a value of 2 in a normal, disease-free individual. With advancing age, there is natural stiffening of the ventricle, which results in delayed relaxation and therefore a progressive decrease in E-wave velocity and an increase in A-wave velocity with age so that the E/A ratio in a disease-free individual older than 60 years is often less than 1 (Klein et al, 1994).

#### **2.3.2 Impaired left ventricle relaxation pattern**

In almost every type of heart disease, the initial alteration of diastolic filling is impaired or slowed myocardial relaxation (figure 2 A). When myocardial relaxation is markedly delayed, patients have a mitral filling pattern with prolonged isovolumetric relaxation time (> 200 ms) and deceleration time (> 220 ms), decreased E-wave velocity and increased A-wave, since more of the ventricular filling happens to occur at the beginning of diastole to do at the end of it, with atrial contraction. This produces an E/A ratio <1 (figure 2). In addition, in the presence of bradycardia, a characteristic low meso-diastolic (after early filling) mitral inflow velocity may be seen, due to a progressive fall in LV diastolic pressure related to slow LV relaxation. However, increased filling pressure can mask these changes in



mitral velocities. Therefore, an E/A ratio  $< 1$  and deceleration time  $> 240$  ms have high specificity for abnormal LV relaxation, but can be seen with either normal or increased filling pressures, depending on how delayed LV relaxation is (Oh et al, 1997).

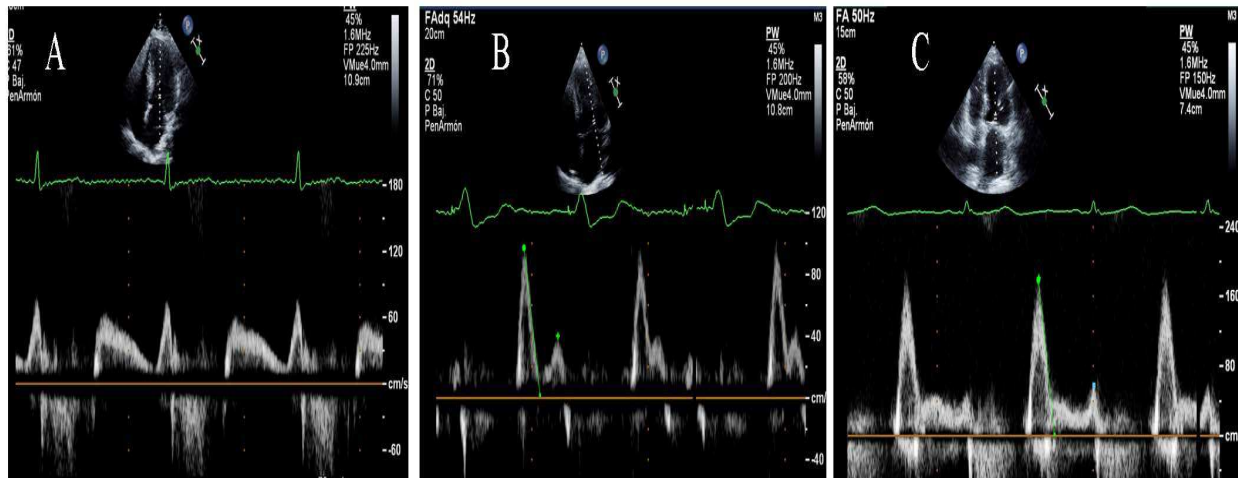


Fig. 2. Pulsed Doppler mitral filling flow showing: A) Impaired relaxation pattern, B) Pseudonormal pattern C) Restrictive pattern

### 2.3.3 Restrictive left ventricle filling pattern

This pattern (figure 2C) represents a combination of a stiff, noncompliant ventricle and elevated LV end-diastolic pressure. Increased left atrial pressure produces an earlier opening of the mitral valve, a shortening of IVRT and increased initial transmitral gradient (high E-wave velocity). Early diastolic filling in a non-distensible ventricle cause a rapid increase in LV early diastolic pressure with a rapid equalization of LV and LA pressures which produce a shortening of the deceleration time. Atrial contraction increases the pressure of the LA, but the speed and duration are shortened because LV pressure is increases even faster. Therefore, the restrictive physiology is characterized by increased E-wave velocity, decreased A-wave velocity, E/A ratio  $> 2$ , shortened deceleration time ( $< 160$  ms) and isovolumetric relaxation time ( $< 70$  ms) (figure 2). A restrictive physiology pattern identifies advanced, usually symptomatic disease, with a poor prognosis (figure 2).

### 2.3.4 Pseudonormal left ventricular filling pattern

Pseudonormalization is a transitional phase between abnormal relaxation and restrictive physiology (figure 2 A). During this transition, the incoming mitral flow pattern is going through a phase that resembles the normal diastolic filling pattern, ie, E / A ratio of 1-1.5 and a normal deceleration time (160-200 ms). This is the result of a moderate increase of filling pressure superimposed on a decreased compliance. This pattern represents a moderate stage of diastolic dysfunction. The determination of pseudonormal filling may be difficult by mitral inflow velocities alone. Monitoring mitral inflow patterns during the Valsalva maneuver, which reduces LV preload, may change the "normal" E/A ratio and unmask evidence of delayed relaxation. Changes of mitral inflow during Valsalva maneuver have a moderate diagnostic value for the differentiation of normal and pseudonormal pattern. Increased duration of atrial phase but not increase in atrial velocity allowed the diagnosis of

pseudonormalization (Wierzbowska-Drabik et al, 2007). Reflex tachycardia during the Valsalva maneuver and subsequent fusion of the E velocity and A velocity waves on the mitral velocity curves is a sign of normal left ventricular filling pressures (Maniu et al, 2004). There are several other techniques for separating the pseudonormal from a truly normal pattern, which are discussed subsequently.

#### **2.4 Variations in mitral inflow patterns**

Not all patterns of mitral flow velocity fit into one of these three patterns (figure 2). The spectrum is broad as a result of different contributions and degree of underlying pathology, abnormal relaxation, and changes in compliance and volume status. The same degree of decreased compliance will result in different curves of mitral flow velocity depending on whether there is impaired relaxation. In the presence of significant LVH, deceleration time can be elongated even with increased pressure in the LA, while a similar increase in pressure in other patients leads to a shortening of the deceleration time. In severe LVH, it can see a pattern of meso-tele-diastolic prominent triphasic mitral flow as a result of markedly prolonged relaxation that continues in the meso-diastole. Even though the initial slope present a short deceleration time, continued filling indicate that the main problem is an abnormal relaxation and not a decrease in distensibility. A counter example is the constrictive pericarditis, in which a normal relaxation and a decrease in compliance may result in a markedly shortened mitral deceleration time without a significant increase in filling pressures (Oh et al, 1994).

In patients with dilated cardiomyopathies, Doppler mitral flow velocity variables and filling patterns correlate better with cardiac filling pressures, functional class, and prognosis than left ventricle ejection fraction (Vanoverschelde et al, 1990). A restrictive filling pattern is associated with a poor prognosis, especially if it persists after preload reduction.

In patients with coronary artery disease (Yamamoto et al, 1997) or hypertrophic cardiomyopathy (Nishimura et al, 1996) in whom left ventricle ejection fractions are  $\geq 50\%$ , mitral variables correlate poorly with hemodynamics. This may be related to the marked variation in the extent of delayed LV relaxation seen in these patients, which may produce variable transmitral pressure gradients for similar LA pressures. A restrictive filling pattern and LA enlargement in a patient with a normal ejection fraction are associated with a poor prognosis similar to that of a restrictive pattern in dilated cardiomyopathy. This is most commonly seen in restrictive cardiomyopathies, especially amyloidosis (Klein, 1990, 1991) and in heart transplant recipients (Valantine et al, 1989).

### **3. Pulmonary Venous Flow**

#### **3.1 Pulmonary flow assessment**

The pulmonary venous flow (PVF) is a very useful tool in the study of LV function (figure 1 C). The arrival of blood to the atrium occurs throughout the cardiac cycle and is highly dependent on the filling conditions. For this reason PVF a useful tool in studying diastolic function and is closely related to the LA pressure and pulmonary capillary pressure (Skagseth et al, 1976). The positive components of pulmonary flow are generated during ventricular systole and early diastole, while the negative cash flow are generated by the contraction of the LA (Rajagopalan et al, 1979). This flow can be obtained by transthoracic

echocardiography, though the records are more accurate by Transesophageal study (Bartzokis et al, 1991).

There are many applications for which the study has found utility of PVF: differentiation between constrictive pericarditis and restrictive cardiomyopathy (Schiavone et al, 1989), the estimation of filling pressures of LV (Kuecherer et al, 1990), the assessment of diastolic function (Klein et al, 1989), the function of the LA and the assessment of mitral insufficiency and stenosis (Castello et al, 1991).

### 3.1.1 Recording technique

The clearest record of flows is achieved by transesophageal study. Generally, from an angle of 45 to 60 degrees and rotating the probe to the left. From this point appears below the right pulmonary veins and superior. To get the left venous flow probe must be rotated 110 degrees. Transthoracic echo also allows in most cases (90%) the obtaining of PVF (Klein et al, 1994). To achieve an adequate flow, must be placed the sample volume or two centimeters into the vein. Usually, achieved in this way flow pattern consistent in: a first positive wave called S1 wave, which coincides with early ventricular systole, a second systolic wave S2 and diastolic wave D. Then, there is a reverse wave corresponding to atrial contraction wave A (figure 3). In relation to the wave pressure in the left atrium records S1 corresponds to the waves a, c and the decrease x. S2 wave is from the peak decrease x to v. (Klein et al, 1991).

### 3.1.2 Factors affecting the pulmonary flow

There are numerous physiological circumstances that may affect the PVF. These include: the age, conditions of preload, left ventricular contractility or conduction disturbances and frequency. All these circumstances should be taken into account when assessing appropriate paths. In any case seems to be a direct relationship between the S2 wave and atrial pressure (Hoit et al, 1992). Changes in LV filling and compliance affect D velocity. Ar velocity, and duration are impacted by LV late diastolic pressures, atrial preload, and LA contractility. The S/D ratio and Ar velocities increase with older age, but Ar velocities higher than 35 cm/s suggest increased LV end-diastolic pressure. (Hoit et al, 1992). Volume overload influence LA pressure and is in the ratio S2/D in the presence of a normal live systolic function of the LA. Therefore there is a relationship between atrial contractile reserve and the ratio S2/D. So that, in the absence of left ventricular dysfunction mean atrial pressure can be estimated by the PVF (Hoit et al, 1992).

### 3.2 Diastolic dysfunction

The PVF is an excellent models proper instrument for differentiating normal filling patterns and pseudo normal (Kuecherer et al, 1990; Appleton et al, 1997) (figure 3). The subjects with diastolic dysfunction slows early ventricular filling while the wave is increased, in these cases increases the ratio S2/D, while extending the deceleration speed of the wave D (Hofmann et al, 1995).

Increased LA pressure normalizes the mitral flow pattern of filling. This phenomenon known as pseudo normalization can be differentiated using the PVF. S2 wave D wave decreases and increases with decreasing the ratio S2/D. At the same time there is an increase in the flow rate back to more than 35 cm /sec (Rakowski et al, 1996). The main difficulty of this method consists in obtaining an adequate record atrial reverse flow.



The restrictive pattern is characterized by increased early filling velocity with rapid deceleration and poor filling late contribution. The PVF in this situation shows a small wave S2 and a D wave, however, very high. Similarly increases atrial reverse flow velocity (Klein et al, 1989).

### 3.3 Estimation of ventricular filling pressure

PVF can be used to estimate LA pressure (Castello et al., 1995). The mean atrial pressure has a negative correlation with S2 systolic wave, in patients with ventricular dysfunction to reduce the displacement of the ring (Hoit et al., 1992). On the other hand the duration of the reverse wave is correlated with increased LV end-diastolic pressure (Dini et al., 2000). A duration of greater than 30 ms has a high sensitivity and specificity for the detection of atrial pressure greater than 20 mm Hg. (Dini et al., 2000).

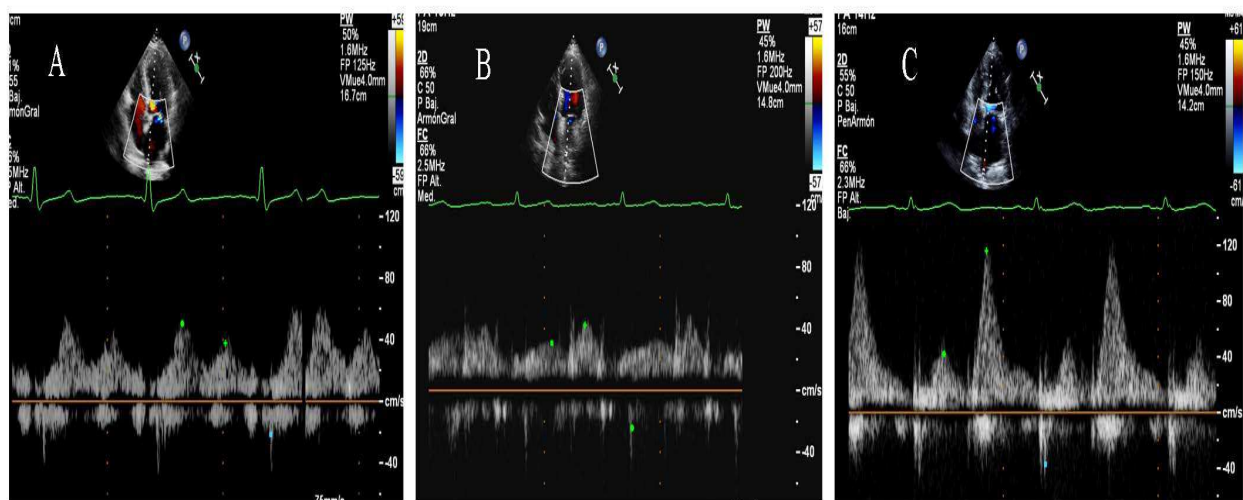


Fig. 3. Pulsed Doppler pulmonary blood flow showing: A) Impaired relaxation pattern, B) Pseudonormal pattern C) Restrictive pattern

## 4. Color M-mode flow propagation velocity

### 4.1 Introduction

One of the most important physiologic parameters that allows LV filling at relatively low pressure is the rate of relaxation. This is best defined by the time constant of isovolumic pressure decay ( $\tau$ , tau). LV relaxation is an important determinant of early transmitral pressure gradients which in turn determine transmitral Doppler filling patterns. The propagation velocity of early flow into the LV cavity measured by color M-mode Doppler was first proposed by Brun (Brun et al., 1992) as an index of LV relaxation (Garcia et al., 1997).

Flow propagation velocity evaluation and interpretation of LV filling in clinical practice is complicated by the multitude of variables that determine intraventricular flow: preload, stroke volume, cardiac output, driving pressure, inertial forces, and viscous friction, but geometry, systolic function, and contractile dyssynchrony play major roles (Nagueh et al., 2009). Taking advantage of this property, color M-mode Doppler indexes have been used for solving the problem of differentiating normal from pseudonormal pulsed Doppler patterns.

#### 4.2 Recording technique

Doppler recordings are obtained in apical four chambers view. We must display the color Doppler sector map of the mitral inflow and make some adjustments to obtain the longest column of color flow from the mitral annulus to the apex. The M-mode scan line is placed through the center of the left ventricular inflow blood column, aligning the cursor in the same direction, from the mitral valve to the left ventricular to the apex. Then the color flow baseline is shifted to lower the Nyquist limit so that the central highest velocity jet is blue. Flow propagation velocity is determined by the slope of the first aliasing line during early filling, from the mitral plane to 4 cm distally into the left ventricle cavity (figure 4). The velocity of the M-mode spectra must be 100 mm/s. Flow propagation velocity ( $V_p$ ) > 50 cm/s is considered normal (Garcia et al., 1997 ; Nagueh et al., 2009).

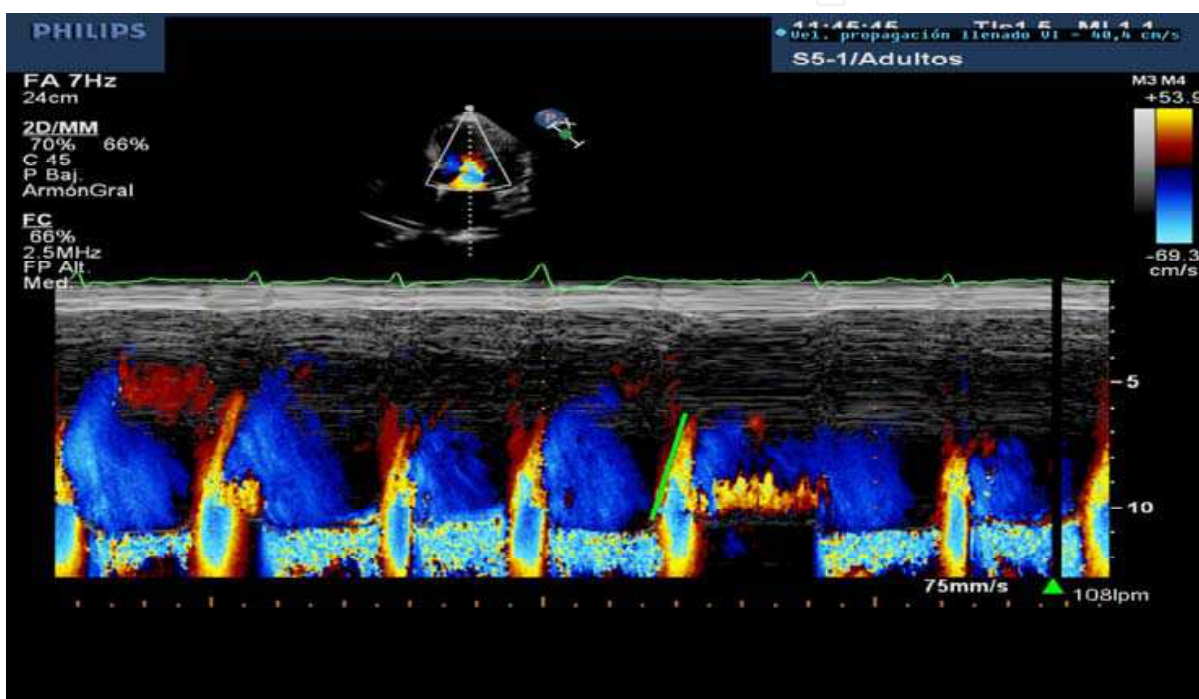


Fig. 4. Color M-mode flow propagation velocity from a patient with depressed ejection fraction and impaired LV relaxation

#### 4.3 Clinical settings

Noninvasive estimation of LV filling pressures is currently utilized using Doppler echocardiography. Flow propagation velocity has been used to solve the problem of differentiating normal from pseudonormal pulsed Doppler patterns and to determine mean pulsed capillary wedge pressure.

It's known that flow propagation velocity, as assessed by color M-mode Doppler, has a good correlation with the time constant of isovolumic relaxation ( $\tau$ , tau) and, along with isovolumetric relaxation time, is a key parameter for the prediction of pulmonary wedge pressure and such methods are useful for the estimation of left ventricular filling pressure, both in patients with depressed and preserved systolic function (Gonzalez-Vilchez et al., 1999). In the same way, García (Garcia et al., 1997), based on the relation among peak E wave velocity, tau and LA pressure, have reported a strong correlation between dimensionless, have been confirmed too in patients with atrial fibrillation (Nagueh et al., 1997).

Flow propagation velocity correlates with the rate of myocardial relaxation. However, caution should be with patients with high filling pressures and normal ejection fraction because flow propagation velocity can be increased in these patients, despite impaired relaxation. Flow propagation velocity is inversely related to end systolic volume but directly to ejection fraction, stroke volume, and cardiac output (Rivas-Gotz et al., 2003). Accordingly, it is possible for the flow propagation velocity to fall in the normal range in patients with normal ejection fraction despite the presence of impaired relaxation. In most of patients with depressed ejection fractions exists a lot of signs of impaired diastolic function and measure flow propagation velocity it could be redundant. However, if other Doppler indices appear inconclusive, flow propagation velocity can provide useful information for the prediction of LV filling pressures. Thus  $E/V_p \geq 2,5$  predicts pulsed capillary wedge pressure  $>15$  mm Hg, with reasonable accuracy in patients with low ejection fraction (Rivas-Gotz et al., 2003). Then, flow propagation velocity is most reliable as an index of LV relaxation in patients with depressed ejection fractions and dilated left ventricles. In the other patient groups, it is preferable to use other indices.

## 5. Tissue Doppler annular early and late diastolic velocities

### 5.1 Introduction

Tissue Doppler imaging (TDI) is a ultrasound modality which has become an essential part of the echocardiography evaluation of diastolic function. This technique allows the assessment of the movement and the velocities within the myocardium and the mitral annulus. The velocity of annular motion reflects shortening and lengthening of the myocardial fibers along the longitudinal plane and provides information about segmental and global cardiac function. These data, when coupled with more traditional mitral inflow velocity data can be used to predict diastolic function and LV filling pressures. Normally, three different annular velocities can be recognized as a mirror image of the transmitral inflow pattern: the systolic (S), early diastolic ( $e'$ ) and late diastolic ( $a'$ ) velocities (figure 1 B).

### 5.2 Recording technique

These velocities are obtained from the apical four-chamber view by placing a 2 to 5-mm pulsed Doppler sample volume at the lateral and medial (septal) borders of the mitral annulus, ensuring the coverage of the longitudinal excursion of the mitral annulus in both systole and diastole (Waggoner et al., 2001 ). For a correct acquisition, angulation between the ultrasound beam and the annular plane of motion should be minimized, and gain and filter settings must be optimized to allow for a clear tissue signal with minimal background noise. Although annular velocities can also be obtained by color-coded tissue Doppler image (TDI), this method is not recommended, because there is a paucity of studies and the validation studies were performed using pulsed wave Doppler.

Occasionally, an additional mid-diastolic flow velocity can be recorded by tissue Doppler imaging demonstrating a mid-diastolic component ( $L'$ ), resulting in triphasic mitral inflow filling pattern, it suggests advanced diastolic dysfunction (Jong-Won Ha et al., 2006).

For the assessment of global LV diastolic function, it is recommended to acquire and measure tissue Doppler signals at the septal and lateral sides of the mitral annulus and their average, given the influence of regional function on these velocities and time intervals (Rivas-Gotz et al., 2003).

### 5.3 Clinical settings

Several studies in animals and humans have demonstrated significant correlation between  $e'$  and the LV relaxation so its value is a good indicator of the cardiac function. Usually,  $e'$  from the lateral annulus is higher than  $a'$  so different cut off values, should be applied. A value  $\geq 10$  cm/s (septal) or  $\geq 15$  cm/s (lateral) are consistent with normal function. The  $e'$  velocity is determined by LV relaxation, preload, systolic function and LV pressure whereas the main hemodynamic determinants of the  $a'$  velocity are left atrial systolic function and LV end-diastolic pressure. The early diastolic velocity ( $e'$ ) decreases progressively with age and also is reduced in patients with other conditions leading to an impaired relaxation such as LVH or restrictive cardiomyopathy, where  $e'$  decreases as LV filling pressure increases (Ommen et al., 2000). This velocity is essential for classifying the diastolic filling pattern (Figure 5) and estimating filling pressures and furthermore, it is useful to distinguish between constrictive pericarditis and other forms of diastolic dysfunction. In constrictive pericarditis, the impairment in ventricular filling occurs as a result of an external constriction, whereas in restrictive cardiomyopathy there is an inherent abnormality in ventricular relaxation. Therefore,  $e'$  will be normal or even above normal in patients with pure constrictive pericarditis as compared to those with restriction where  $e'$  will be lower.

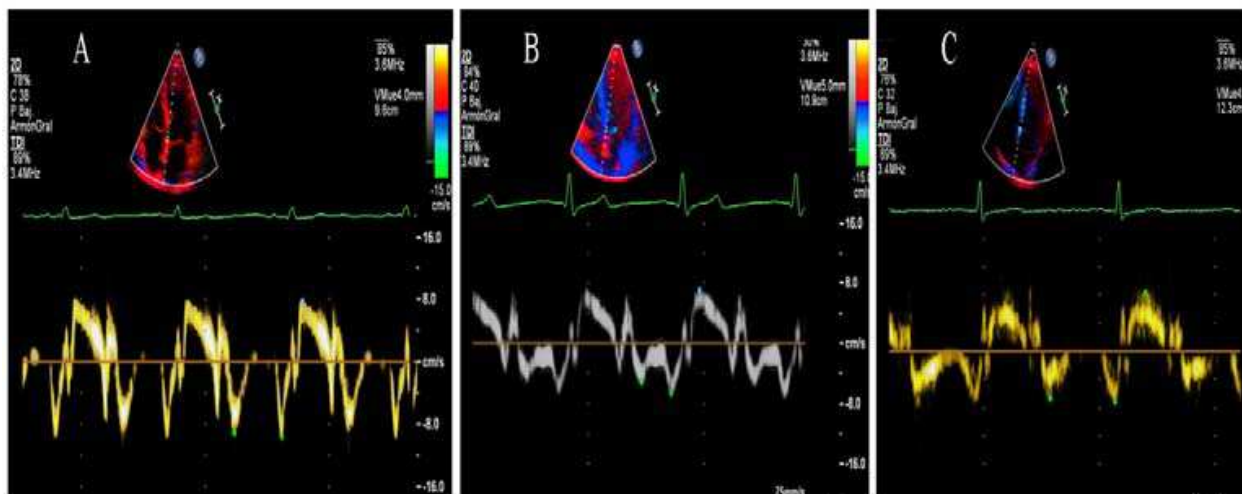


Fig. 5. Doppler tissue imaging of mitral annular motion: A) Impaired relaxation pattern, B) Pseudonormal pattern C) Restrictive pattern

In addition and interestingly, it should be noted that TDI mitral annular velocities are considered less load-dependent than other conventional Doppler parameters (Dae-Won Sohn et al., 1997). For this reason, its assessment appears to be useful to correct the effect of LV relaxation on mitral inflow E velocity in patients with cardiac disease, especially in the detecting a pseudonormalization pattern of mitral inflow. In these cases, the annular  $e'/a'$  ratio and the mitral E velocity to TDI Doppler  $e'$  ( $E/e'$  ratio) can predict LV filling pressures and correlates well with pulmonary capillary wedge pressure (Rivas-Gotzet et al., 2003; Ommen et al., 2000) (figure 5 B). For the diagnosis of diastolic dysfunction, the  $E/e'$  ratio has been identified as the best parameter for diagnosis when compared to other Doppler measures (Nagueh et al., 2009; Kasner et al., 2007). This ratio is also clinically very useful in patients with atrial fibrillation where  $a'$  is not present.



An  $E/e'$  ratio  $< 8$  is associated with normal filling pressures and a ratio  $> 15$  is associated with increased filling pressures (Ommen et al., 2000). When values are between 8 and 15, other echocardiography indices should be used and it is recommended that  $e'$  and the  $E/e'$  ratio should not be used as the sole data in drawing conclusions about LV diastolic function. TDI derived velocities also have some limitations. There are some conditions where this  $E/e'$  ratio is not accurate to estimate the LV filling pressures: in normal patients  $e'$  is directly related to preload (Firstenberg et al., 2000), so this index may not provide a reliable information, patients with localized disease process, such as lateral myocardial infarction or patients with mitral valve disease and heavy lateral annular calcification can result in mitral annulus velocities being lower at the lateral annulus than at the septal annulus, patients with constrictive pericarditis have an inverse relationship between  $E/e'$  and with pulmonary capillary wedge pressure (Garcia et al., 1997) additionally,  $e'$  velocity can be increased in patients with moderate to severe mitral regurgitation due to increased flow. To summarize, Tissue Doppler imaging provides accurate and valuable information and should be included as part of an echocardiography study when studying myocardial diastolic function.

## 6. Deformation measurements

### 6.1 Deformation measurements assessment

Doppler tissue (DT) and speckle tracking echocardiography (STE) has been introduced as quantitative method for measuring systolic and diastolic function. DT can measure myocardial functional parameters such as speed, acceleration, displacement, velocity of myocardial deformation and deformation. The STE can measure the twist of the LV.

Strain means deformation and can be calculated using different formulas. In clinical cardiology, strain is most often expressed as a percentage or fractional strain (Lagrangian strain). Systolic strain represents percentage shortening when measurements are done in the long axis and percentage radial thickening in the short axis. Systolic strain rate (SR) represents the rate or speed of myocardial shortening or thickening, respectively. Myocardial strain and SR are excellent parameters for the quantification of regional and global contractility and may also provide important information in the evaluation of diastolic function. Until recently, the only clinical method to measure myocardial strain has been magnetic resonance imaging with tissue tagging, but complexity and cost limit this methodology to research protocols.

The longitudinal motion of the heart shows a descent of the base toward the apex during systole, with a reverse movement during the phases of early filling (E) and atrial systole (A), whereas the apex remains virtually stationary throughout the heart cycle. Both longitudinal M-mode and Doppler tissue imaging (DTI) of the mitral annulus have demonstrated this. (Rodriguez et al., 1996). Thus the velocities increase from zero at the apex to a maximum at the base of the ventricle for all phases, with a longitudinal velocity gradient. It can be shown that the longitudinal velocity gradient is a measure of the rate of longitudinal deformation, or SR. (Støylen et al., 1999). The unit of SR is centimeters per second per centimeter, or  $s^{-1}$ , and the values of SR can be displayed in the same manner as velocities: as color mapping or digital curves, as shown in figure 6. This method is termed strain rate imaging (SRI). In SRI, velocities are converted to regional velocity differences, showing regional systolic and diastolic dysfunction in coronary disease and also temporal distribution of deformation in normal ventricles. The velocities caused by contraction of more apical segments or by



translation of the whole heart are subtracted. SRI provides quantitative measurement of local deformation rates, whereas color mapping provides semiquantitative data and information about the spatial-temporal relations between events in the ventricle during the heart cycle.

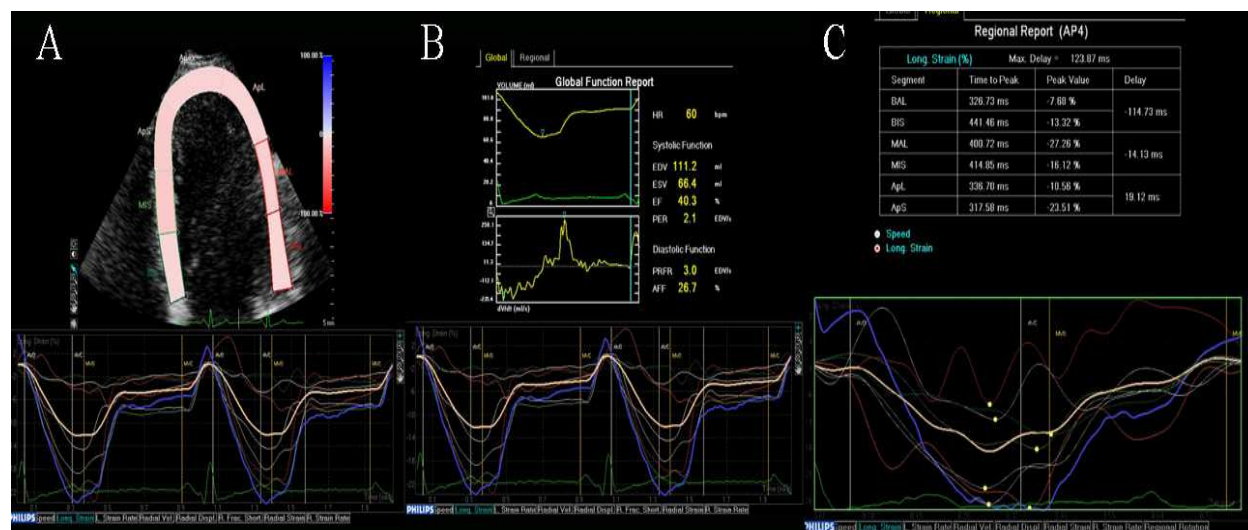


Fig. 6. Digital curves of strain rate (A), global function (B), regional function (C)

Lengthening during isovolumic relaxation generally is seen first in the midwall, and at the same time, reciprocal shortening is seen in neighboring segments, whereas stretching starts later in the apex. M mode or DTI of the mitral ring can demonstrate a slight lengthening of the whole ventricle during this phase, mainly in the basal parts. In addition, SRI is subject to misinterpretation as a result of angle deviation (Støylen et al., 2000) and this effect is especially pronounced in the apex.

The peak velocity of the mitral annulus is determined not only by the rate of deformation (the local strain rate), but also by the propagation of the stretch wave. DTI and tissue Doppler-derived measurements are sensitive measures of diastolic function. Strain rate imaging shows a complex pattern of deformation during diastole because of its high sampling frequency, compared with all other methods, including MR. The main deformations during early and late filling phases are the result of both local relaxation rate and the propagation of the stretching wave from base to apex. This provides new physiologic and pathophysiologic information. The present application, however, seems to overestimate true peak strain rate. In contrast to regional systolic function, the DTI measurements are quicker and may be more practical for clinical work, whereas the level of detail in SRI data enables deeper insight into diastolic physiology. (Courtois et al., 1990).

SRI shows the ventricular deformation during early filling to be a dynamic event that is slowed in subjects with delayed relaxation. The strain rate propagation is the main determinant of the filling rate, and is consistent with filling time.

## 6.2 Recording technique

Tissue Doppler-based myocardial strain has been introduced as a bedside clinical method and has undergone comprehensive evaluation for the assessment of regional systolic function (Heimdal et al., 1998). Myocardial motion in DT (Figure 7) is shown as color-coded speeds along a series of ultrasound scan lines within a 2D sector. The frequency of pictures

for DT must be 80 to 200 frames per second, depending on the width of the ultrasound sector, and is usually set higher than for the simultaneous images in grayscale. Myocardial velocities are decoded into numerical values that can be stored digitally for "off-line" analysis. By convention, since the flat apical long-axis motion is dominated by red-coded velocities during systole and diastole in blue. Dysfunctional myocardium, however, may show abnormal movements with reversed velocities during systole. Myocardial function is rarely assessed 2D color but postprocessing can be done with mode M, but the usual method is the analysis of rates from multiple regions within a 2D image. Tissue velocities can be assessed, integrated tissue displacement or velocity, SR and myocardial SR integrated. Limitations are noise signal, angle dependence and the reverberations.

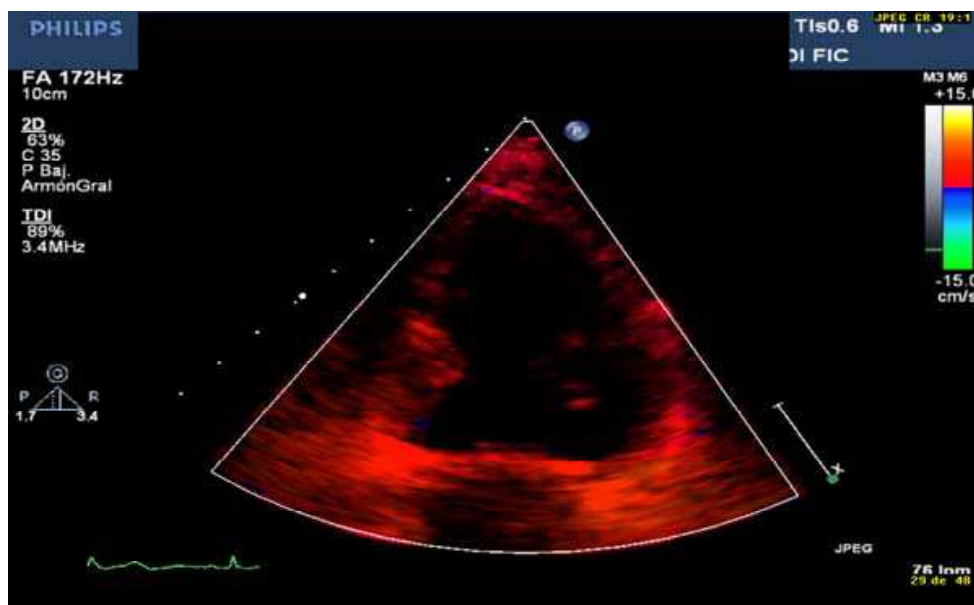


Fig. 7. Myocardial motion in DT shown as color-coded speeds of ultrasound scan lines within a 2D sector

Strain may also be measured by 2D STE, an emerging technology that measures strain by tracking speckles in grayscale echocardiography images of the LV, obtained in the apical 2-, 3- and 4-chamber views and short-axis basal, mid, apical-ventricular views. The LV radial and circumferential functions must be determined in the short-axis views (figure 8) and longitudinal function in the 3 apical views (figure 6) using grey-scale acquisition at a frame rate over  $80 \text{ s}^{-1}$  (Amundsen et al., 2006). The glare is created by interference of ultrasound beams in the myocardium and are observed in B-mode images in gray scale, functioning as natural acoustic markers can be tracked in their motion frame by frame, measuring the distance automatically between shine on a piece defined myocardial deformation, independently of myocardial insonation angle and translational heart. In contrast with strain DT-based, STE can measure the deformation of the LV short-axis circumferential, radial and longitudinal multiple segments in areas near the apex. Another promising feature is the ability to measure the rotation and twisting of the LV. This is in contrast to tissue Doppler-based strain, which is very sensitive to misalignment between the cardiac axis and the ultrasound beam. Problems with tissue Doppler-based strain include significant signal noise and signal drifting. STE is limited by relatively lower frame rates.

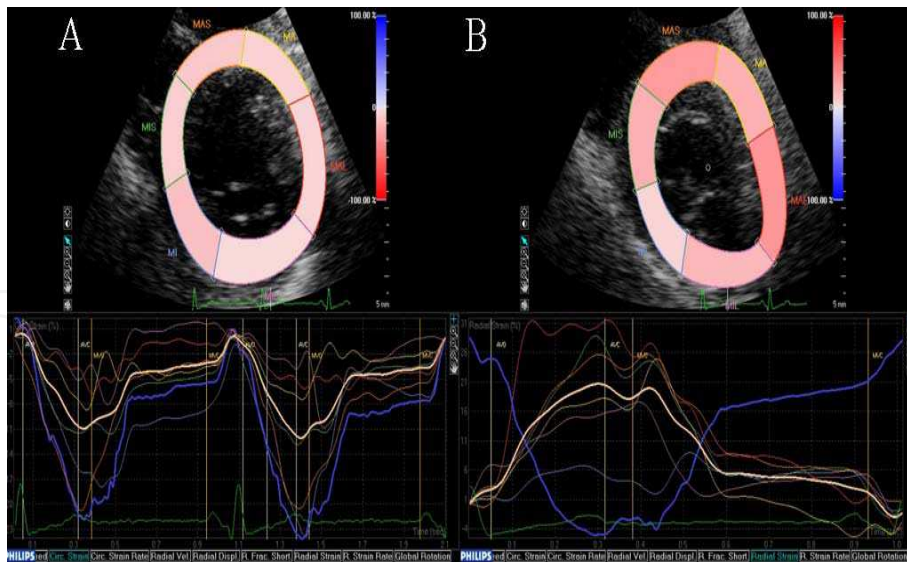


Fig. 8. Strain measured by 2D speckle-tracking echocardiography. The LV circumferential (A) and radial (B) functions shown as digital curves in the short-axis views

Similarly, regional Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography differences in the timing of transition from myocardial contraction to relaxation, with SRI can identify ischemic segments. (McMahon et al., 2004). Currently, Doppler flow velocity and myocardial velocity imaging are the preferred initial echocardiography methodologies for assessing LV diastolic function.

### 6.3 Clinical settings

Analysis of diastolic function for assessment of myocardial viability has been evaluated (Hoffmann et al., 2005). SR analysis allows quantitative segmental analysis of myocardial function and has been used during dobutamine stimulation for assessment of systolic functional reserve and related to F18-fluorodeoxyglucose positron emission tomography. Early and late diastolic function during dobutamine stimulation is impaired for nonviable segments compared with viable segments. Diastolic SR analysis during dobutamine stimulation may be added to systolic function analysis in the assessment of myocardial viability.

STE may be helpful for the detection of early changes in LV diastolic function in patients with essential hypertension. Hypertensive patients had a lower mean relaxation based on SRE and SRE/A at the basal, mid, and apical regions, with the basal parts appearing more compromised and with higher segmental diastolic dysfunction compared with controls. Abnormal segmental relaxation might also be present in individuals with 'normal' mitral annular early diastolic velocities (Pavlopoulos & Nihoyannopoulos, 2009).

Myocardial shortening after aortic valve closure, i.e. PSS (Post-systolic shortening), has been suggested as a sensitive marker of regional myocardial dysfunction (Voigt et al., 2003). However, PSS may also occur in healthy subjects. To discriminate between pathological and physiological PSS, Voigt et al. (Voigt et al., 2003) described that the timing and the magnitude are different between these two situations. In this study PSS was significantly larger and reduced in diabetic patients compared with control subjects. The precise mechanism is unknown, but not related to myocardial ischemia induced by epicardial coronary artery stenosis, thus they described the first signs of systolic dysfunction following

established diastolic dysfunction in diabetic patients. This study reinforces that LVEF is not a sensitive indicator for the detection of subclinical systolic dysfunction. 2D STE has the potential for detecting subclinical LV systolic dysfunction, and it might provide useful information for the risk stratification of an asymptomatic diabetic population.

Diastolic dysfunction in diabetic patients can be also assessed with more novel echocardiography techniques such as STE. Despite a normal LV mass, LV volume, and LVEF, the diabetic population show impairment of LV longitudinal strain and SR but preserve circumferential and radial strain and SR. Using 2D STE to assess all myocardial segments it has been demonstrated a reduced longitudinal strain and SR (predominantly derived from epicardial/endocardial fiber contraction) but preserved circumferential and radial strain and SR (predominantly derived from mid-wall circumferential fibers contraction) in diabetic patients. This finding suggests that myocardial dysfunction in early diabetic cardiomyopathy might start in the subendocardium (Arnold et al., 2009). The novel aspect of the present study was the multidirectional strain and SR analysis using 2D STE in patients with uncomplicated type 2 diabetes mellitus.

In other study Shanks M and cols. examined the prognostic value of novel diastolic indexes in ST-elevation acute myocardial infarction (AMI), derived from strain and SR analysis using 2-dimensional STE and only mean SRIVR was an independent predictor of outcome in patients with AMI. This could be in part because SR measured during the isovolumic relaxation period (before mitral valve opens) reflects the rate of myocardial expansion that is least influenced by LV loading conditions (Shanks et al., 2010).

## 7. Left ventricular untwisting

### 7.1 Introduction

2-D STE has been successfully applied to the relatively simple and accurate measurement of LV torsion during systole and untwisting at early diastole. In addition, LV untwisting is commonly seen at the LA contraction, whereas its determinants and clinical significance have not been clarified. Both parameters may provide an additional noninvasive insight into LV systolic and diastolic function (Buchalter et al., 1990). Given the angle independence of speckle tracking and its higher reproducibility, this technique is preferred for measuring rotation. LV twist is calculated as the difference between basal and apical rotation.

LV twisting motion (torsion) is due to contraction of obliquely oriented fibers in the subepicardium, which course toward the apex in a counterclockwise spiral. The moments of the subepicardial fibers dominate over the subendocardial fibers, which form a spiral in opposite direction. Therefore, when viewed from apex toward the base, the LV apex shows systolic counterclockwise rotation and the LV base shows a net clockwise rotation. Untwisting starts in late systole but mostly occurs during the isovolumetric relaxation period and is largely finished at the time of mitral valve opening. Diastolic untwist represents elastic recoil due to the release of restoring forces that have been generated during the preceding systole. LV twist appears to play an important role for normal systolic function, and diastolic untwisting contributes to LV filling through suction generation. It has been assumed that the reduction in LV untwisting with attenuation or loss of diastolic suction contributes to diastolic dysfunction in diseased hearts. (Bell et al., 2000). Diastolic dysfunction associated with normal aging, however, does not appear to be due to a reduction in diastolic untwist. (Hees et al., 2004).



## 7.2 Recording technique

With the recent introduction of STE, it is feasible to quantify LV rotation, twist, untwist clinically. Wang et al (Wang et al., 2007) demonstrated that, in patients with diastolic dysfunction, the LV torsion and peak untwisting rate are preserved, as opposed to patients with systolic dysfunction in which the measurements are reduced. Thus, the assessment of torsional recoil, or untwisting, should provide an accurate estimate of LV relaxation. Stuber et al (Stuber et al., 1999) found that early diastolic untwisting and untwisting rates were significantly reduced in parallel to the degree of LVH in hypertensive patients.

## 7.3 Clinical settings

In the present study (Appleton et al., 1988), was identified that the late diastolic LV untwisting rate is related to peak A velocity of the transmitral flow,  $E/e$ , and LA volume index in patients with cardiovascular risk factors and mild to moderate LV diastolic dysfunction ( $E/A < 1$ ). In addition, multivariate equation for predicting late diastolic untwisting was highest for LA volume index. This provide the correlation between LV untwisting during LA contraction and LA size, suggesting “disease history” in patients with LV diastolic dysfunction.

Measurements of LV twist and untwisting rate, although not currently recommended for routine clinical use and although additional studies are needed to define their potential clinical application, may become an important element of diastolic function evaluation in the future.

## 8. Future directions

### Diastolic strain rate

Myocardial strain and SR are excellent parameters for the quantification of regional contractility and may also provide important information in the evaluation of diastolic function (Nagueh et al., 2009). Signal noise, signal drifting and angle dependency are included in the potential problems of tissue Doppler derived strain and SRI.

The speckles function as natural acoustic markers that can be obtained simultaneously from multiple regions within an image plane (Nagueh et al., 2009). It has a number of advantages over established methods. It is acquired directly from LV myocardium, as opposed to indirect data of annulus and blood flow velocities. It is not affected by mitral annulus or valvular disease. It occurs during IVRT when valves are closed and therefore is not exposed to transmitral pressure gradient. It is derived from all myocardial segments and thus is a true global index. It is not affected by translation and tethering and takes into consideration the initial resting length (Wang & Nagueh, 2009). It is demonstrated that in patients with diastolic dysfunction, the LV torsion and peak untwisting rate are preserved, as opposed to patients with systolic dysfunction in which the measurements are reduced (Wang et al., 2007). STE also allows for appreciation of accentuated regional myocardial rotation, torsion and twist during positive inotropic stimulation with dobutamine or during ischemia (Helle-Valle et al., 2005). Assessment of post-systolic strain and early diastolic untwist by echocardiography provides important insights into mechanisms of diastolic function.

Limitation of this technique include the dependence on 2D image quality and frame rates, difficulty of selection of image plane, and the reproducibility and variability of measurements from ventricles with different geometries. It also includes the longer time



needed for analysis and the lower frame rate (80 per second) which can lead to an underestimation of peak SR, although the concept itself is not affected by this limitation. The development of 3D speckle tracking may assist with these limitations. The newly developed 3D-STE imaging used with real-time 3D echocardiography data sets has the potential to avoid the limitations of 2D-STE imaging in the assessment of LV wall motion, because it tracks the motion of speckles within the scan volume, regardless of the direction of motion (Maffessanti et al., 2009). 3D-STE shows more homogenous color distribution in normal ventricles, consistent with the expected normal patterns of LV wall motion, compared to 2D-STE in the same subject. The regional time curves allow better quantitative discrimination between normal and abnormal segments. In segments with normal wall motion, 3D-STE demonstrates a larger magnitude of displacement, likely reflecting the ability to register all 3 components of the motion vector compared to the 2D-STE single-plane analysis. The relatively smaller normal variability of measurements using 3D-STE compared with those using 2D-STE provide additional support to the superiority of 3D-STE in imaging the complexity of 3D wall motion. The limitations of the 3D-STE technique are the relatively low temporal and spatial resolution, both affecting the accuracy of endocardial tracking in a considerable proportion of the segments.

#### **Left ventricular twisting and untwisting**

The clinical value of assessing LV untwisting rate is not defined. When LV twist and untwisting rate were assessed in patients with diastolic dysfunction or diastolic heart failure, both twist and untwisting rate were preserved, and no significant relation was noted with the time constant of LV relaxation. The complex interplay between preload, afterload and contractility determines twist values in diastolic heart failure (DHF).

In patients with LVH, Takeuchi et al (Takeuchi et al., 2007) showed a normal LV torsion, without intergroup differences based on its extent. In another study (Park et al., 2008), observed that LV twist was increase in patients with early diastolic dysfunction and normal in patients with advanced grades. The independent predictors of LVEF in DHF patients were circumferential strain and LV twist, and it is possible that normal twist is a compensatory mechanism in DHF that can help maintain a normal LVEF (Wang et al., 2008). The limitation of this technique is the selection of the image plane, and further clinical testing of STE in patients is needed to determine whether reproducible measurements can be obtained from ventricles with different geometries. STE can be suboptimal at the LV base, showed in the significant variability in the measurements.

#### **Left atrial volume measurements**

LA volume index is a more robust marker than LA area or LA diameter, in patients with suspected heart failure and normal LVEF. For these reasons, in a recent consensus document LA volume index  $>40$  ml/m<sup>2</sup> is considered to provide sufficient evidence of diastolic LV dysfunction when the E/e' ratio is non-conclusive or when plasma levels of natriuretic peptides are elevated (Paulus et al., 2007); and a LA volume index  $<29$  ml/m<sup>2</sup> is proposed as a prerequisite to exclude heart failure with normal LVEF.

In another study (Park et al., 2011) evaluated the LA volume index (LAVi) over late diastolic mitral annulus velocity (A') ratio (LAVi/A') as a useful parameter to identify advance diastolic dysfunction and predict clinical outcomes in patients with dyspnea. They showed that LAVi/A' is a useful new echo index to discriminate advanced diastolic dysfunction in dyspneic patients with a wide range of LVEF. They also added that this ratio has the

additional benefit in the assessment of the gray zone diastolic dysfunction with  $8 \leq E/e' \leq 15$ , concluding that a  $LAVi/A' \geq 4.0$  was an independent predictor of clinical outcomes.

### Diastolic stress test

During exercise, to maintain adequate LV filling and stroke volume, the filling pressures raise provoking symptoms to patients with diastolic dysfunction. Therefore, it is useful to evaluate LV filling pressure with exercise. The  $E/e'$  ratio has been applied for that objective.  $E$  and  $e'$  velocities increase proportionally in subjects with normal myocardial relaxation, and the  $E/e'$  ratio remains unchanged or is reduced (Ha et al., 2003). In patients with impaired myocardial relaxation, however, the increase in  $e'$  with exercise is lower than that of mitral  $E$  velocity, such that the  $E/e'$  ratio increases (Ha et al., 2005). Furthermore, mitral DT decreases slightly in normal individuals with exercise, but shortens  $>50$  ms in patients with a marked elevation of filling pressures. Mitral  $E$  velocity increases with exertion and, after the termination of exercise, stays increased for a few minutes, in cardiac patients. In these patients, at baseline, exercise, and recovery,  $e'$  velocity remains reduced. Therefore,  $E$  and  $e'$  velocities can be recorded after exercise. Exercise is usually performed using a supine bicycle protocol or with dobutamine infusion (Duncan et al., 2005).

This test is most useful in patients with unexplained exertional dyspnea who have mild diastolic dysfunction and normal filling pressures at rest. However, the potential limitations in patients with mitral valve disease, atrial fibrillation and regional LV dysfunction, and the lack of clinical data, diminish recommendations for its routine clinical use.

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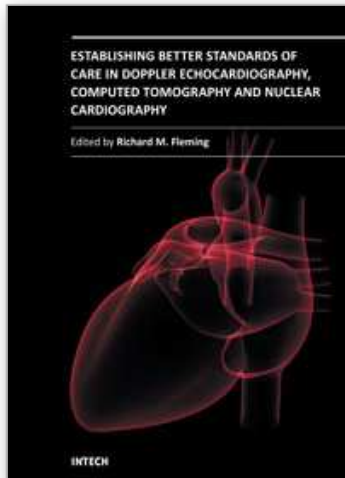
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Edited by Dr. Richard M. Fleming

ISBN 978-953-307-366-8

Hard cover, 260 pages

**Publisher** InTech

**Published online** 13, July, 2011

**Published in print edition** July, 2011

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Juan Lacalzada, Amelia Duque, Alejandro de la Rosa, Antonio Barragan, María Manuela Izquierdo, Eduardo Arroyo, Ana Laynez and Ignacio Laynez (2011). Evaluation of Left Ventricular Diastolic Function by Echocardiography, Establishing Better Standards of Care in Doppler Echocardiography, Computed Tomography and Nuclear Cardiology, Dr. Richard M. Fleming (Ed.), ISBN: 978-953-307-366-8, InTech, Available from: <http://www.intechopen.com/books/establishing-better-standards-of-care-in-doppler-echocardiography-computed-tomography-and-nuclear-cardiology/evaluation-of-left-ventricular-diastolic-function-by-echocardiography>

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