INTRODUCTION

The normal human aorta is not a stiff tube, but is characterized by elastic properties. During systole, the left ventricle ejects a stroke volume into the arterial system. A half of this stroke volume is directly forwarded to the peripheral circulation, but because of peripheral resistance and elastic extension of the aortic wall, the other half of the stroke volume is stored in the aorta ***(Bader, 1983).***

During diastole, when the aortic valve is closed and there is no further blood ejection, aortic pressure falls, the aorta recoils slowly, and the stored volume is pressed into the peripheral circulation. This volume buffering function is known as the Windkessel function ***(Belz, 1995).***

Normally, LV ejection causes a pressure pulse with a relatively slow pulse wave velocity (PWV). When this wave is reflected by the peripheral circulation, it returns to the ascending aorta during early diastole inducing the dicrotic wave. This second increase in pressure is normally dampened by the Windkessel function ***(O'Rourke, 1990).***

Many studies have examined the effect of cardiovascular risk factors on the vessels. It is also recognised that these factors cause structural alteration, which leads to stiffness in large arteries. In particular, arterial stiffness in large arteries has been reported to be the best predictor of cardiovascular morbidity and mortality ***(Arnett et al., 1994).***

Pulse wave velocity, measured either invasively or non invasively, has been used in previous studies that have investigated arterial stiffness ***(Lehman et al., 1993; Asmar et al., 1995).***

Even if the pulse wave can be recorded by the Doppler technique, measuring the distance that the pulse wave travels is a serious problem. The superficial measurement method suggested for measuring this distance has some disadvantages, such as having to correct for age and the effects of fat, breast size, and thoracic or spinal abnormalities ***(Sands, 1925; Hallock, 1934).***

In addition, this method does not give the true distance. To obtain the true distance, invasive and angiographic methods must be used. Thus, the use of pulse wave velocity is difficult in practice. In this respect, it has been suggested that aortic strain and distensibility should be calculated from the aortic diameters measured by echocardiography and blood pressure obtained by sphygmomanometry ***(Della Corte et al., 1979).***

Left ventricular mass increases in normotensive patients with diabetes and diastolic dysfunction occurs ***(Lacombe et al., 1992; Devereux et al., 2000).***

In addition, it is well known that diabetes increases aortic stiffness ***(Poirier et al., 2001).***

Similar results have been reported in hypertensive patients ***(Toutouzas et al., 2000; Isnard et al., 1989).***

From this point of view, it seems that there is a possible relation between aortic stiffness and left ventricular diastolic dysfunction. Also, it has been reported that aortic stiffness influences left ventricular structure and function, independent of arterial blood pressure ***(Dart et al., 1993).***

It has been shown that aortic stiffness increases in patients with coronary artery disease ***(Bouthier et al., 1985).***

In this regard, the present study aimed at determining, by using current methods to evaluate the relation between aortic stiffness and left ventricular diastolic function ***(Devereux et al., 1983; Lartaud-Idjouadiene et al., 1999; Hirai et al., 1989; Stefanadis et al., 1994).***

Aim of the Work

To study the relationship between aortic stiffness and left ventricular diastolic dysfunction by echocardiography.

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Introduction:

Left ventricular diastolic dysfunction is characterized by an elevated diastolic pressure in the left ventricle, despite an essentially normal/physiologic end diastolic volume (EDV) ***(Brutsaert et al., 1993)***.

Histological evidence supporting diastolic dysfunction demonstrates ventricular hypertrophy, increased interstitial collagen deposition and infiltration of the myocardium. These influences collectively lead to a downhill in distensibility and elasticity of the myocardium. As a consequence, cardiac output becomes diminished. When the left ventricular diastolic pressure is elevated, venous pressure in lungs becomes elevated too: left ventricular stiffness makes it more difficult for blood to enter it from the left atrium. As a result, pressure rises in the atrium and is transmitted back to the pulmonary venous system, thereby increasing its hydrostatic pressure and promoting pulmonary edema ***(Gary et al., 2011).***

Although the term diastolic heart failure is often used when there are signs and symptoms of heart failure with normal left ventricular systolic function, this is not always appropriate. Diastolic function is determined by the relative end diastolic volume in relation to end diastolic pressure, and is therefore independent of left ventricular systolic function. A leftward shift of

the end-diastolic pressure-volume relationship (i.e. decreased left ventricular distensibility) can occur both in those with normal and those with decreased left ventricular systolic function. Likewise, heart failure may occur in those with dilated left ventricular and normal systolic function. This is often seen in valvular heart disease and high-output heart failure. Neither of these situations constitutes a diastolic heart failure ***(Gary et al., 2011).***

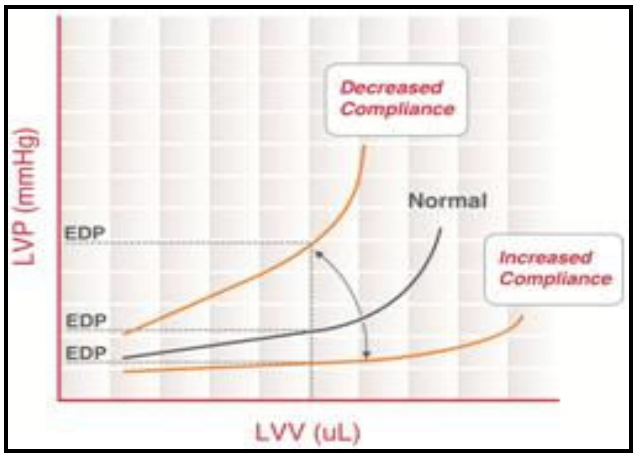


Figure (1): End diastolic pressure–volume relationship. LVP: Left ventricular pressure, LVV: Left ventricular volume, EDP: End diastolic pressure ***(Nishihara et al., 2000).***

Assessment of LV Diastolic Function:

The assessment of left ventricular (LV) diastolic function should be an integral part of a routine examination, particularly in patients presenting with dyspnea or heart failure. About half of patients with new diagnoses of heart failure have normal or near normal global ejection fractions (EFs). These patients are diagnosed with "diastolic heart failure" or "heart failure with preserved EF ***(Paulus et al., 2007).***

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 dyspnea, to assess prognosis, and to identify underlying cardiac disease and its best treatment.

LV filling pressures as measured invasively include mean pulmonary wedge pressure or mean left atrial (LA) pressure (both in the absence of mitral stenosis), LV end-diastolic pressure (LVEDP; the pressure at the onset of the QRS complex or after A-wave pressure),and pre-A LV diastolic pressure **(Figure 2).** Although these pressures are different in absolute terms, they are closely related, and they change in a predictable progression with myocardial disease, such that LVEDP increases prior to the rise in mean LA pressure.

Echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades. The purposes of this document is to provide a comprehensive review of the techniques and the significance of diastolic parameters, as well as recommendations for nomenclature and reporting of diastolic data in adults. The recommendations are based on a critical review of the literature and the consensus of a panel of experts.

The optimal performance of the left ventricle depends on its ability to cycle between two states: (1) a compliant chamber in diastole that allows the left ventricle to fill from low LA pressure and (2) a stiff chamber (rapidly rising pressure) in systole that ejects the stroke volume at arterial pressures. The ventricle has two alternating functions: systolic ejection and diastolic filling. Furthermore, the stroke volume must increase in response to demand, such as exercise, without much increase in LA pressure ***(Brutsaert et al., 1993).***

The theoretically optimal LV pressure curve is rectangular, with an instantaneous rise to peak and an instantaneous fall to low diastolic pressures, which allows for the maximum time for LV filling. This theoretically optimal situation is approached by the cyclic interaction of myofilaments and assumes competent mitral and aortic valves. Diastole starts at aortic valve closure and includes LV pressure fall, rapid filling, diastasis (at slower heart rates), and atrial contraction ***(Paulus et al., 2007).***

Elevated filling pressures are the main physiologic consequence of diastolic dysfunction. Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure (PCWP) is more than 12 mmHg or when the LVEDP is more than 16 mm Hg ***(Paulus et al., 2007).***

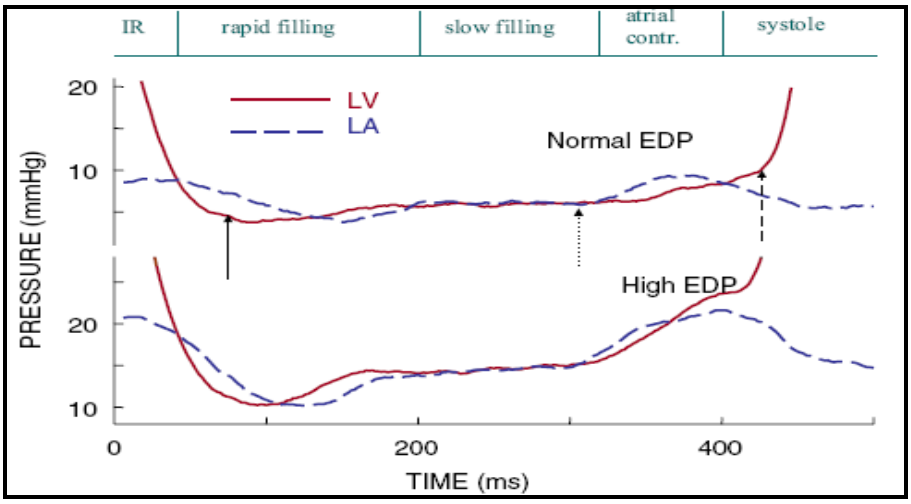


Figure (2): The 4 phases of diastole are marked in relation to high-fidelity pressure recordings from the left atrium (LA) and left ventricle (LV) in anesthetized dogs. The first pressure crossover corresponds to the end of isovolumic relaxation and mitral valve opening. In the first phase, left atrial pressure exceeds left ventricular pressure, accelerating mitral flow. Peak mitral E roughly corresponds to the second crossover. Thereafter, left ventricular pressure exceeds left atrial pressure, decelerating mitral flow. These two phases correspond to rapid filling. This is followed by slow filling, with almost no pressure differences. During atrial contraction, left atrial pressure again exceeds left ventricular pressure. The solid arrow points to left ventricular minimal pressure, the dotted arrow to left ventricular pre-A pressure, and the dashed arrow to left ventricular end-diastolic pressure. The upper panel was recorded at a normal end-diastolic pressure of 8 mmHg. The lower panel was recorded after volume loading and an end-diastolic pressure of 24 mm Hg. Note the larger pressure differences in both tracings of the lower panel, reflecting decreased operating compliance of the LA and LV. Atrial contraction provokes a sharp rise in left ventricular pressure, and left atrial pressure hardly exceeds this elevated left ventricular pressure ***(Courtesy of TC, Gillebert and AF, 1989; Leite-Moreira, 2006).***

At the molecular level, the cyclic interaction of myofilaments leads to a muscular contraction and relaxation cycle. Relaxation is the process whereby the myocardium returns after contraction to its unstressed length and force. In normal hearts, and with normal load, myocardial relaxation is nearly complete at minimal LV pressure. Contraction and relaxation belong to the same molecular processes of transient activation of the myocyte and are closely intertwined ***(Yip et al., 2002).***

Relaxation is subjected to control by load, inactivation, and asynchrony. Increased after load or late systolic load will delay myocardial relaxation, especially when combined with elevated preload, thereby contributing to elevating filling pressures. Myocardial inactivation relates to the processes underlying calcium extrusion from the cytosol and cross-bridge detachment and is affected by a number of proteins that regulate calcium homeostasis, cross-bridge cycling, and energetics ***(Leite-Moreira et al., 1999).***

Minor regional variation of the timing of regional contraction and relaxation is physiological. However, dyssynchronous relaxation results in a deleterious interaction between early reextension in some segments and postsystolic shortening of other segments and contributes to delayed global LV relaxation and elevated filling pressures ***(Gillebert, 1989).***

LV filling is determined by the interplay between LV filling pressures and filling properties. These filling properties are described with stiffness ($\Delta P/\Delta V$) or inversely with compliance

($\Delta V/\Delta P$) and commonly refer to end-diastolic properties. Several factors extrinsic and intrinsic to the left ventricle determine these end-diastolic properties. Extrinsic factors are mainly pericardial restraint and ventricular interaction. Intrinsic factors include myocardial stiffness (cardiomyocytes and extracellular matrix), myocardial tone, chamber geometry, and wall thickness ***(Westermann et al., 2008).***

Causes of Diastolic Dysfunction:

1. Long standing hypertension
2. Aortic stenosis of any cause
3. Diabetes
4. Age - elderly patients mainly if they have hypertension.
5. Constrictive pericarditis
6. Restrictive cardiomyopathy, which includes Amyloidosis (most common), Sarcoidosis and fibrosis ***(Garcia et al., 1997).***

Echocardiographic Patterns of LV Diastolic Dysfunction:

No one single echocardiographic parameter can confirm a diagnosis of diastolic heart failure. Multiple echocardiographic parameters have been proposed as sufficiently sensitive and specific, including mitral inflow velocity patterns, pulmonary vein flow patterns, E:A reversal, tissue Doppler measurements and M-mode echo measurements (i.e. of left atrial size). Algorithms have also been developed which combine multiple echocardiographic parameters to diagnose diastolic heart failure. There are four basic Echocardiographic patterns of diastolic dysfunction, which are graded as follows ***(Nagueh et al., 2009):***

- The mildest form is called an "abnormal relaxation pattern", or grade I diastolic dysfunction. On the mitral inflow Doppler echocardiogram, there is reversal of the normal E/A ratio and normal E/E' ratio. This pattern may develop normally with age in some patients, and many grade I patients will not have any clinical signs or symptoms of heart failure.
- Grade Ia diastolic dysfunction (Impaired myocardial relaxation with elevated filling pressures) The pattern is similar to Grade 1, with the exception of the E/E' ratio (septal) which is > 8, suggestive of a high LA pressure.
- Grade II diastolic dysfunction is called "pseudonormal filling dynamics". This is considered moderate diastolic dysfunction and is associated with elevated left atrial filling pressures. These patients more commonly have symptoms of heart

failure, and many have left atrial enlargement due to the elevated pressures in the left heart.

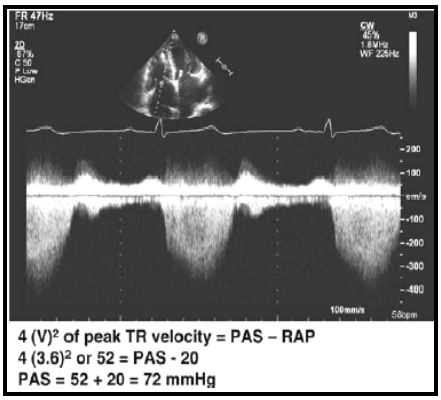
- Grade III&IV diastolic dysfunction patients will demonstrate restrictive filling dynamics and usually present with heart failure symptoms.

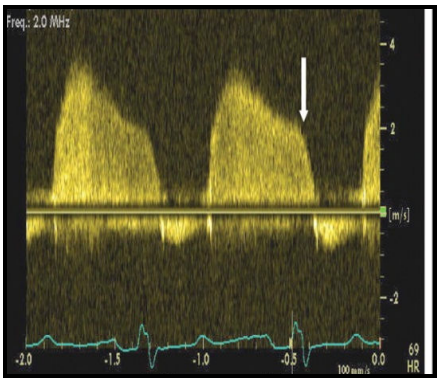
Echocardiographic Parameters in Assessment of Diastolic Dysfunction:

A. *Pulmonary artery systolic and diastolic pressures:*

Symptomatic patients with diastolic dysfunction usually have increased pulmonary artery (PA) pressures. Therefore, in the absence of pulmonary disease, increased PA pressures may be used to infer the presence of elevated LV filling pressures. Indeed, a significant correlation was noted between PA systolic pressure and noninvasively derived LV filling pressures ***(Bouchard et al., 2008).***

The peak velocity of the tricuspid regurgitation (TR) jet by continuous-wave (CW) Doppler **(Figure 3)**, together with systolic right atrial (RA) pressure, are used to derive PA systolic pressure. In patients with severe TR and low systolic RV–RA pressure gradients, the accuracy of the PA systolic pressure calculation is dependent on the reliable estimation of systolic RA pressure. Likewise, the end-diastolic velocity of the pulmonary regurgitation (PR) jet can be applied to derive PA diastolic pressure ***(Quinones et al., 2002).***





End diastolic PR velocity=2m/s

PAD= 4(2x2)+ 15=31mmHg

Figure (3): Left: Calculation of PA systolic pressure using the TR jet. In this patient, the peak velocity was 3.6 m/s, and RA pressure was estimated at 20 mm Hg. Right: Calculation of PA diastolic pressure using PR jet, end diastolic PR velocity was 2m/s. PA= pulmonary artery, PR=pulmonary regurgitation, TR=tricuspid regurgitation, PAS= pulmonary artery systolic pressure, PAD= pulmonary artery diastolic pressure ***(Nagueh et al., 2009).***

B. Pulmonary Venous Flow:

A significant correlation was noted in several studies between PA systolic pressure and noninvasively derived LV filling pressures ***(Quinones et al., 2002).***

Pulsed wave (PW) Doppler of pulmonary venous flow (PVF) is performed in the apical 4-chamber view. Color flow imaging is useful for the proper location of the sample volume in the right upper pulmonary vein. A 2-mm to 3-mm sample volume is placed 0.5 cm into the pulmonary vein for optimal recording of the spectral waveforms **(Figure 5).**

The normal PVF usually shows a tri- or quadriphasic pattern consisting of a pulmonary venous first systolic wave (S1), pulmonary venous second systolic wave (S2), pulmonary venous early diastolic wave (D), and pulmonary venous atrial reversed flow wave (AR). The S1 occurs during LA pressure "a" to "c" and "c" to "x" descent, and the S2 occurs during LA pressure increase between the "x" pressure nadir and the "v" pressure peak. There is a direct correlation between the mitral inflow E-wave velocity and the D wave velocity ***(Appleton et al., 1997).***

Averaged normal values for PVF waves are: Peak S= 57cm/s, Peak D= 49cm/s, Peak A= 20cm/s, D deceleration time =150ms, S:D ratio=1.29 ***(De Marchi et al., 2001)***.

The correlation between LV diastolic dysfunction and PVF is as follows **(Figure 4).**

In patients with impaired LV relaxation, the S2/D ratio increases and the deceleration time of the D wave prolongs so that the LA reservoir volume during ventricular systole could compensate for the impaired early LV filling.

To differentiate "pseudonormalization" from a normal mitral inflow pattern, the classic way is by observing a normal or decreased S2 ("blunted" systolic pattern) and increased D velocities resulting in decreased systolic fraction and S2/D ratio and with a large atrial reversal >35 cm/s.

In patients with a restrictive mitral inflow pattern (a deceleration time <150 ms), the PVF shows a lower S2 and higher D velocities (severely blunted systolic flow) and increased atrial reversals (unless atrial systolic failure), suggesting decreased LV operating compliance ***(Yamamato et al., 1997).***