ORIGINAL ARTICLE

Association between Diastolic Wall Stress in Severe Aortic Stenosis with Preserved Ejection Fraction and Heart Failure

Estrés parietal diastólico en la estenosis aórtica grave con fracción de eyección preservada: Relación con la insuficiencia cardíaca

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ABSTRACT

Background: The pathophysiology of diastolic left ventricular dysfunction includes abnormalities in ventricular relaxation, passive elastic stiffness or a combination of both mechanisms. Doppler echocardiography can evaluate ventricular relaxation but not passive elastic stiffness. Diastolic wall stress evaluates passive elastic stiffness through the reduction of end-diastolic myocardial compression.
Objective: The aim of this study was to evaluate passive elastic stiffness by means of diastolic wall stress in patients with severe aortic stenosis with preserved ejection fraction and its association with class III-IV heart failure.
Methods: A total of 76 patients (mean age 67 ± 11 years) with severe aortic stenosis (aortic valve area < 0.6 cm2/m2) and ejection fraction ≥ 50% were evaluated. Diastolic wall stress was calculated as: (systolic posterior wall thickness - diastolic posterior wall thickness) / systolic posterior wall thickness measured in M-mode echocardiography. E/e' ratio, end-diastolic pressure and end-diastolic pressure/volume ratio were calculated by non-invasive methods. Patients were divided into two groups: Group 1: class III-IV heart failure (n = 5 patients) and Group 2: without heart failure (n = 71 patients).
Results: Passive elastic stiffness was greater in group 1 patients, demonstrated by reduced diastolic wall stress (0.23 ± 0.05 vs. 0.30 ± 0.06 p <0.01), and higher E/e' ratio (20 ± 7 vs. 14 ± 8 p <0.05), end-diastolic pressure and end-diastolic pressure/volume ratio.
Conclusion: Diastolic wall stress could detect abnormalities in passive elastic stiffness in patients with severe aortic stenosis with preserved ejection fraction and heart failure that cannot be evaluated using the traditional parameters of diastolic function.

Key words: Heart Failure - Diastolic/physiopathology - Aortic Valve Stenosis - Vascular Stiffness - Elasticity/physiology

RESUMEN

Introducción: La fisiopatología de la disfunción diastólica del ventrículo izquierdo incluye alteraciones de la relajación ventricular, rigidez elástica pasiva o una combinación de ambos mecanismos. Mediante el eco-Doppler es posible evaluar parámetros relacionados con la relajación ventricular, pero no de la rigidez elástica pasiva. El estrés parietal diastólico evalúa la rigidez elástica pasiva a través de la disminución de la compresión del miocardio al final de la diástole.
Objetivo: Evaluar la rigidez elástica pasiva mediante el estrés parietal diastólico en pacientes con estenosis aórtica grave con fracción de eyección preservada y su relación con la presencia de insuficiencia cardíaca grado III-IV.
Material y métodos: Se estudiaron 76 pacientes (edad promedio 67 ± 11 años) portadores de estenosis aórtica grave (índice de área valvular aórtica <0,6 cm2/m2) y fracción de eyección mayor o igual al 50%. El estrés parietal diastólico fue calculado como: (espesor sistólico de pared posterior – espesor diastólico) / espesor sistólico en modo M. Se calculó por métodos no invasivos la relación E/e´, presión de fin de diástole y presión de fin de diástole / volumen de fin de diástole. Los pacientes fueron ordenados en 2 grupos: Grupo 1: insuficiencia cardíaca grado III - IV (n = 5 pacientes) y Grupo 2: sin insuficiencia cardíaca (n = 71 pacientes).
Resultados: Los pacientes del grupo 1 presentaron mayor alteración de la rigidez elástica pasiva evidenciada por disminución del estrés parietal diastólico (0,23 ± 0,05 vs. 0,30 ± 0,06 p < 0,01), mayor incremento de E/e´ (20 ± 7 vs. 14 ± 8 p < 0,05), presión de fin de diástole y presión de fin de diástole / volumen de fin de diástole.
Conclusión: El estrés parietal diastólico permitiría objetivar alteraciones de la rigidez elástica pasiva en pacientes con estenosis aórtica grave, fracción de eyección preservada e insuficiencia cardíaca que no pueden ser evaluadas mediante los parámetros de función diastólica habituales.

Palabras claves: Insuficiencia Cardíaca Diastólica/fisiopatología - Estenosis de la Válvula Aórtica - Rigidez Vascular

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Abbreviations

LA	Left atrium	**NYHA**	New York Heart Association
AS	Aortic stenosis	**PCWP**	Pulmonary capillary wedge pressure
DWS	Diastolic wall stress	**EDP**	End-diastolic pressure
eFS	Endocardial fractional shortening	**ESP**	End-systolic pressure
mFS	Midwall fractional shortening	**PES**	Passive elastic stiffness
HR	Heart rate	**EDV**	End-diastolic volume
EF	Ejection fraction	**LV**	Left ventricular
HF	Heart failure	**Zva**	Valvulo-arterial impedance
LVMI	Left ventricular mass index		

INTRODUCTION

Severe aortic stenosis (AS) with preserved ejection fraction (EF) (>50%) and New York Heart Association (NYHA) class III-IV heart failure (HF) is one of the clinical presentations of HF with preserved EF. Diastolic dysfunction has been mentioned as one of the main determinants of increased left ventricular (LV) diastolic pressure. The mechanisms involved include abnormalities in ventricular relaxation, passive elastic stiffness (PES) or a combination of both mechanisms. (1) Ventricular relaxation is an active process that depends on ATP availability which occurs mainly at the beginning of diastole, but under abnormal conditions (as hypertrophy or ischemia) it can be extended until the end of the diastole. Passive ES is observed during mid and late diastole and is illustrated with the exponential pressure-volume relationship, represented as a curve (Figure 1) whose slope is determined by the passive elastic stiffness constant k. An upward and to the left shift of the curve indicates that the ventricle is less distensible, since a higher diastolic pressure will be required to distend the LV to a similar volume, and can be expressed by the end-diastolic pressure (EDP)- end-diastolic volume (EDV) ratio. Cardiac catheterization can be used to evaluate left ventricular function, assessing ventricular relaxation through the time constant of LV isovolumic relaxation (tau) and negative dP/dt, and PES with the elastic stiffness constant k and chamber stiffness (dP/dV). Doppler echocardiograhy is used to evaluate ventricular relaxation by the analysis of mitral inflow, e' wave of tissue Doppler imaging and flow propagation velocity obtained by color M-mode echocardiography. However, PES is only indirectly evaluated by echo-phonocardiography, (2) deceleration time, elevated diastolic pressures reflected by the E/e' ratio, prolongation of the pulmonary venous atrial reversal flow wave and the estimation of EDP. Diastolic wall stress (DWS) is a new method to evaluate PES using simple echocardiographic measurements, based on the linear elastic theory which states that the epicardial motion of the myocardial wall is directly related to wall stiffness. (3, 4) Figure 2 shows that when pressure is applied to a distensible tissue (for example, at end-diastole), the

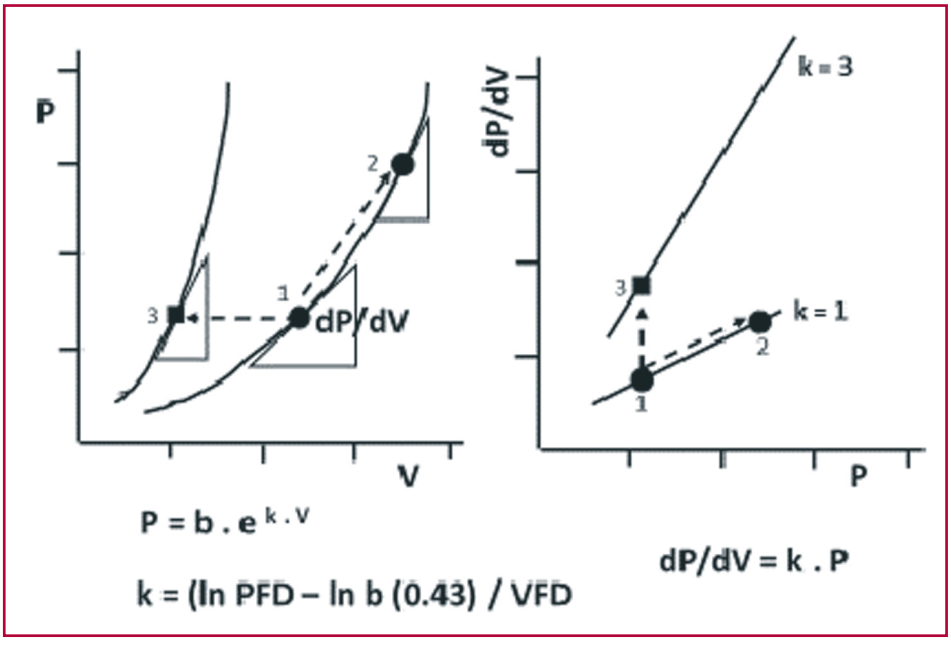

Fig. 1. Left: Pressure (P) - volume (V) diagram, representing the exponential curve of passive elastic stiffness and the P value estimated for each V value with the equation: P = b. e k. V, where the slope of a tangent to the curve is determined by the constant k. A leftward shift of the curve (from k = 1 to k = 3) represents higher passive elastic stiffness. Chamber stiffness (dP/dV) can also be determined and depends on the operational point along the same curve and on k for a similar P value. In this way, chamber stiffness is greater in points 2 and 3 than in point 1. Right: dP/dV can be represented as a function of P. In this case, the relationship is linear and can estimate dP/dV by multiplying k . P.

effect on epicardial motion is small. When the same pressure is applied to a stiffer tissue, there is more resistance to compression and the epicardial motion will be greater. Thus, epicardial motion has a direct correlation with tissue stiffness or PES if we consider the myocardial wall. Epicardial motion can be evaluated by measuring the LV posterior wall with M-mode echocardiography, and mathematically demonstrated (3) as the difference between LV end-systolic posterior wall thickness (PWTs) and end-diastolic posterior wall thickness (PWTd) divided by PWTs:

DWS = (PWTs - PWTd) / PWTs

The aim of this study was to evaluate PES using DWS in patients with severe AS with preserved EF (>50%) and its possible association with NYHA class III-IV HF.

METHODS

A total of 76 patients (48 men and 28 women; mean age: 67 ± 11 years) with severe AS, defined as aortic valve area (AVA) < 0.6 cm2/m2 and EF ≥50%, who underwent Doppler echocardiography, were included in the study. Patients were excluded if they had moderate to severe aortic or mitral regurgitation and history of ischemic heart disease based on the presence of one or more of the following criteria: history of myocardial infarction, percutaneous coronary intervention or myocardial revascularization surgery, coronary artery stenosis >50% documented by angiography (28 symptomatic patients) and akinetic segments documented by echocardiography. All the patients underwent anamnesis to detect the presence of coronary risk factors and symptoms, cardiovascular physical examination and blood pressure measurement before complete Doppler echocardiography.

Echocardiogram and Doppler echocardiography

The study was performed with an ESAOTE Mylab 50 ultrasound machine and 2.5 to 3 MHz transducer with the patient in left lateral decubitus position, using simultaneous recording of lead II electrocardiogram as reference. M-mode echocardiography was used to calculate PWTs, PWTd, LV endocardial fractional shortening (eFS), LV midwall fractional shortening (mFS), relative wall thickness (RWT), EDV (estimated by the biplane Simpson method), end-systolic volume (ESV), EF, stroke volume index (SVI) and left atrial volume index (LAVI) according to the American Society of Echocardiography (ASE) criteria. (5) Two-dimensional echocardiography (2DE)–guided M-mode was used to measure PWTs and PWTd, trying to align the M-mode cursor perpendicular to the long axis of the left ventricle. This approach was preferred due to the higher temporal resolution compared with 2DE. Left ventricular mass was calculated using the Devereux equation (6) and the LV mass index (LVMI) as left ventricular mass indexed by body surface area. Peak gradient (PG) and mean gradient (MG) across the aortic valve and the time velocity integral (TVI) were recorded with continuous Doppler echocardiography from apical, right parasternal, subcostal and suprasternal views. Effective AVA was calculated with the continuity equation (7) and was divided by body surface area to obtain the AVA index. The estimation of the energy loss index (ELI) and valvulo-arterial impedance (Zva) are detailed in the Appendix.

Evaluation of LV diastolic function

Passive elastic stiffness was evaluated by means of DWS obtained with the M-mode left parasternal view measurement of posterior wall thickness. Diastolic function parameters were assessed using the mitral inflow signal obtained by pulsed and continuous Doppler echocardiography (isovolumic relaxation time) and recorded following the recommen-

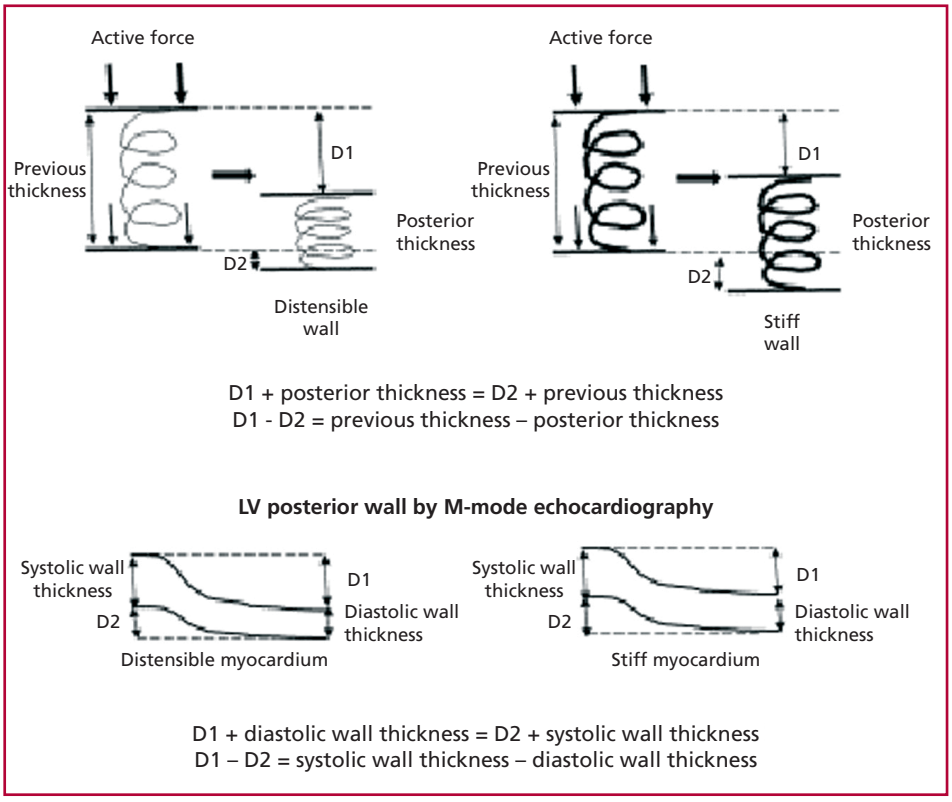

Fig. 2. See text for explanation.

dations of the ASE. Passive elastic stiffness was estimated through the EDP/EDV ratio, where EDV was obtained by 2D echocardiography (biplane Simpson method) and EDP was calculated with a previously described method, (8) based on stroke volume and transmitral flow deceleration time. The elastic stiffness constant k was calculated by using Gaasch's equation (9) (see Appendix) and chamber stiffness (dP/dV) as k multiplied by EDP (Figure 1).

Pulmonary capillary wedge pressure (PCWP) was estimated from the relationship between peak velocity of the transmitral E wave and peak velocity of the e' wave measured by mean tissue Doppler of the lateral and septal mitral annulus (E/e' ratio) according to the following equation:

$$PCWP = 1.91 + 1.24 \times (E/e'). \quad (10)$$

The time constant of LV isovolumic relaxation (tau) was calculated as the reference method for ventricular relaxation (11) using the isovolumic relaxation time, ESP and PCWP (see Appendix). The average of three consecutive measurements was considered for each parameter. Patients were divided into two groups: Group 1: class III-IV heart failure (NYHA) (n = 5 patients) and Group 2: without heart failure (n = 71 patients, 48 without symptoms, 13 with class I-II dyspnea, 8 with angina and 2 with syncope).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Student's t test was used to compare between groups. All the calculations were performed with the Statistix 7.0 software package. A p value < 0.05 was considered statistically significant. Interobserver and intraobserver variability (M. E. A. and M. B.) of PWTs and PWTd was analyzed in 20 randomly selected patients measured within 15 days of the first determination.

Ethical considerations

The study was approved by the institutional Ethics Committee.

RESULTS

There were no significant differences in age, body surface area, and systolic and diastolic blood pressure between both groups (Table I). In addition, no differences were observed in LV geometry assessed by systolic and diastolic dimensions, wall thickness, relative wall thickness and LV mass index. The parameters of systolic function were similar in both groups (eFS, mFS and EF) except for stroke volume that was decreased in group 1 (27 ± 7 ml/m2 vs. 39 ± 10 ml/m2, p <0.02). Aortic stenosis was more severe in group 1 according to the aortic valve area, aortic valve area index, loss of energy index, addimentional index and valvulo-arterial impedance, but no significant differences were found in peak gradient and mean gradient.

Diastolic function

The E/A ratio was higher and isovolumic relaxation time and deceleration time were shorter in group 1 compared with group 2 patients, with predominance of pseudonormal and restrictive patterns. However, the degree of impaired ventricular relaxation was similar in both groups, with no significant differences in the value of the e' wave (tissue-Doppler echocardiography) and tau constant.

Elastic stiffness was significantly higher in group 1 due to the increased k constant, chamber stiffness (dP/dV) and EDP/EDV ratio. Associated with this impaired diastolic function, ventricular pressures were also significantly higher due to the increased E/e' ratio and EDP. According to these findings, the abnormal diastolic pattern in group 1 is due to increased diastolic pressures secondary to abnormal PES and not to impaired relaxation which is similarly altered in both groups.

Diastolic wall stress

Diastolic wall stress was significantly reduced in group 1, indicating higher ventricular stiffness in patients with class III-IV HF with increased PES indexes. In group 2 patients with class I-II dyspnea, mean DWS was 0.31 ± 0.07, similar to the mean DWS of the entire group (0.30 ± 0.06), with no significant differences in tau, E/e' ratio, EDP and dP/dV. However, the value of the elastic stiffness constant k in patients with class I-II dyspnea was similar to that of group 1 patients with class III-IV dyspnea, suggesting that the mechanism of impaired PES is the same (an upward and leftward shift of the P-V curve) (Figure 3), but as diastolic pressures are lower than in group 1, chamber stiffness (dP/dV) and EDP/EDV are similar to those of group 2. These findings would indicate that DWS would be more influenced by dP/dV and EDP/EDV than by the elastic stiffness constant k. Intraobserver variability was 4.9 ± 5% (M. E. A.) and 5.2 ± 5.8 % (M. B.) with a correlation coefficient r of 0.98 for both and a mean difference of 0.11 ± 0.6 mm and 0.15 ± 0.7 mm, respectively. Interobserver variability was 6.4 ± 7% with a correlation coefficient r of 0.96 and a mean difference of 0.12 ± 0.87 mm.

DISCUSSION

The main finding of this study is that patients with severe aortic stenosis with preserved systolic function (EF >50%) and class III-IV HF have impaired PES compared with patients without HF and that they can be evaluated by a simple parameter as DWS. Many non-invasive methods have been attempted to quantify ventricular relaxation and PES, but only Doppler echocardiography is used nowadays. Doppler echocardiography can supply information about ventricular relaxation (isovolumic relaxation time, slope measured by color M-mode echocardiography and mitral inflow pattern). However, it can only indirectly provide PES through shortened deceleration time and the estimation of diastolic pressures (E/e' ratio, prolongation of the pulmonary venous atrial reversal flow wave, etc.) which are assumed to be elevated when PES is impaired. Over the past years, DWS has been described as a parameter based on the linear elastic theory, which states that if the ventricular wall is stiff at the end of diastole, its "compression" will

Table 1. Clinical and echocardiographic parameters of group 1 (AS with HF) and group 2 (AS without HF)

	Group 1 (n = 5)	Group 2 (n = 71)	p
Age (years)	75 ± 8	67 ± 11	0.11
Body surface area (m2)	1.73 ± 0.19	1.82 ± 0.19	0.31
Systolic blood pressure (mm Hg)	129 ± 19	133 ± 22	0.28
Diastolic blood pressure (mm Hg)	68 ± 11	77 ± 12	0.13
Left ventricular diastolic dimension (mm)	47 ± 1.7	48 ± 6.4	0.56
Left ventricular systolic dimension (mm)	30 ± 2.8	29 ± 5.7	0.63
LV posterior wall thickness at end-diastole (mm)	13 ± 1.9	13 ± 1.8	0.34
Interventricular septum thickness at end- diastole (mm)	15 ± 2.7	14 ± 1.9	0.07
Relative wall thickness	0.58 ± 0.09	0.54 ± 0.10	0.33
Body mass index (gr/m2)	162 ± 35	144 ± 42	0.34
eFS (%)	34 ± 4	39 ± 7	0.16
mFS (%)	16 ± 4	19 ± 4	0.12
EF (%)	64 ± 2	67 ± 8	0.24
Stroke volume index (ml/m2)	27 ± 7	39 ± 10	< 0.02
Peak gradient (mm Hg)	77 ± 25	72 ± 28	0.64
Mean gradient (mm Hg)	46 ± 18	42 ± 18	0.55
Aortic valve area (cm2)	0.49 ± 0.14	0.73 ± 0.19	< 0.007
Aortic valve area index (cm2/m2)	0.28 ± 0.05	0.40 ± 0.11	< 0.01
Energy loss index (cm2/m2)	0.31 ± 0.08	0.46 ± 0.14	< 0.02
Addimentional index	0.17 ± 0.03	0.22 ± 0.06	< 0.05
Zva (mm Hg/ml/m2)	5.85 ± 1	4.42 ± 1.2	< 0.01
E/A ratio	1.57 ± 1.38	0.91 ± 0.44	< 0.01
Isovolumic relaxation time (ms)	62 ± 12	91 ± 23	< 0.007
Decelaration time (ms)	147 ± 43	244 ± 87	< 0.01
Left atrial volume index (ml/m2)	58 ± 22	49 ± 15	0.11
e' wave (cm/seg)	6 ± 3	6 ± 4	0.84
Tau (mseg)	50 ± 15	57 ± 21	0.49
E/e' ratio	20 ±7	14 ± 8	< 0.05
End-diastolic pressure (mm Hg)	19 ± 5	10 ± 9	< 0.05
EDP/EDV ratio (mm Hg/ml)	0.22 ± 0.06	0.12 ± 0.08	< 0.01
Passive elastic stiffness constant (k)	0.045 ± 0.008	0.033 ± 0.011	< 0.05
dP/dV (mm Hg/ml)	9.2 ± 6.2	2.5 ± 4.8	<0.01
Diastolic wall stress	0.23 ± 0.05	0.30 ± 0.06	< 0.01

eFS: Endocardial fractional shortening. mFS: Midwall fractional shortening. LV: Left ventricular. Zva: Valvulo-arterial impedance. e': Peak e wave velocity obtained by pulsed tissue- Doppler imaging. EDP: Left ventricular end-diastolic pressure. EDV: Left ventricular end-diastolic volume. dP/dV: Left ventricular chamber stiffness.

be lower; therefore, the epicardium will have greater outward excursion and the decrease in diastolic thickness will be smaller compared with systolic thickness (3, 12) (Figure 2). Diastolic wall stress can be recorded from the M-mode left parasternal view measurement of the posterior wall, which is reproducible, easy to obtain, and does not require subsequent analysis as with other technologies. (13-15) We tried to quantify ventricular relaxation and PES using traditional reference parameters obtained by non-invasive methods. To assess ventricular relaxation we used the time constant of ventricular relaxation (tau), calculated from the isovolumic relaxation time, the end-systolic pressure obtained with the calibrated carotid pulse tracing and the pulmonary capillary wedge pressure estimated with the E/e' ratio. (11) Passive elastic stiffness was calculated using reference parameters as the elastic stiffness constant k, chamber stiffness (dP/dV) and the EDP/EDV ratio, evaluated with a method developed by us to calculate EDP (which correlates with cardiac catheterization) (8) and EDV obtained by 2D echocardiography. The time constant of ventricular relaxation (tau) was similar in both groups of patients, while PES was significantly impaired in group 1 when the constant k, dP/dV and the EDP/EDV ratio were considered. The e' wave in pulsed tissue Doppler imaging, which evaluates ventricular relaxation, was similar in both groups and consistent with the tau observed. Diastolic wall stress was significantly reduced in group 1, indicating higher PES in patients with

	Class I-II dyspnea (n = 13)	Group 2 (n = 71)
eFS (%)	38 ± 9	39 ± 7
mFS (%)	19 ± 4	19 ± 4
EF (%)	68 ± 6	67 ± 8
Stroke volume index (ml/m2)	43 ± 17	39 ± 10
Peak gradient (mm Hg)	71 ± 27	72 ± 28
Mean gradient (mm Hg)	41 ± 18	42 ± 18
Aortic valve area (cm2)	0.78 ± 0.23	0.73 ± 0.19
Aortic valve area index (cm2/m2)	0.45 ± 0.14	0.40 ± 0.11
Energy loss index (cm2/m2)	0.52 ± 0.19	0.46 ± 0.14
Addimentional index	0.24 ± 0.06	0.22 ± 0.06
Zva (mm Hg/ml/m2)	4.22 ± 1.62	4.42 ± 1.2
E/A ratio	1.15 ± 0.7	0.91 ± 0.44
Isovolumic relaxation time (ms)	78 ± 21	91 ± 23
Decelaration time (ms)	247 ± 109	244 ± 87
Left atrial volume index (ml/m2)	48 ± 13	49 ± 15
e' wave (cm/s)	6 ± 3	6 ± 4
tau (ms)	53 ± 19	57 ± 21
E/e' ratio	15 ± 9	14 ± 8
End-diastolic pressure (mm Hg)	11 ± 9	10 ± 9
EDP/EDV ratio (mm Hg/ml)	0.13 ± 0.09	0.12 ± 0.08
Passive elastic stiffness constant (k)	0.045 ± 0.012 *	0.033 ± 0.011
dP/dV (mm Hg/ml)	2.7 ± 3	2.5 ± 4.8
Diastolic wall stress	0.31 ± 0.07	0.30 ± 0.06

*p < 0.05
Abbreviations as in Table 1.

Table 2. Comparison of echocardiographic parameters between patients with class I-II dyspnea and group 2

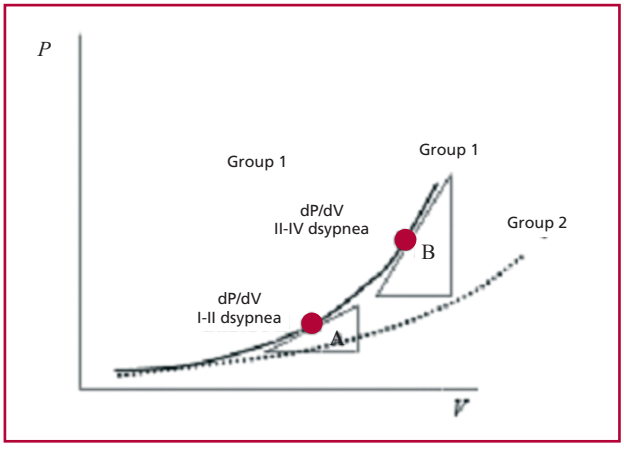

Fig. 3. See text for explanation.

class III-IV HF. One explanation for this finding could be that although both groups had severe AS, valve involvement was greater in group 1 patients, since aortic valve area, energy loss rate and arterial-valvulo impedance were significantly lower. Thus, despite systolic function was not impaired, myocardial fibrosis can develop increasing PES. In addition, in group 2 patients with class I-II dyspnea, PES presented intermediate impairment with increased constant k, but with dP/dV and EDP/EDV ratio that was similar to the rest of the group (Figure 3) suggesting that in this group the upward and leftward shift in the P-V curve precedes the increase in dP/dV and EDP/EDV. In these patients, DWS was similar to that of group 2, indicating that DWS is more influenced by dP/dV and EDP/EDV ratio, which correlate with the ventricular operational point along the P-V curve, than by its slope (k constant).

Limitations

The estimation of LV PWTs and PWTd by M-mode echocardiography may be affected by the angulation of the transducer compared with 2D echocardiography. However, the M-mode was preferred due to its higher temporal resolution that is especially important for LV PWTs and because it can also record epicardial motion. Although magnetic resonance imaging is the gold standard to calculate ventricular volumes, this method was not available in the present study.

CONCLUSION

Diastolic wall stress could detect abnormalities in PES in patients with severe AS with preserved EF and HF that cannot be evaluated using the traditional parameters of diastolic function.

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APPENDIX

Midwall fractional shortening (mFS) was estimated using the Koide formula (16) from the dimensions obtained with M-mode echocardiography:

$$mFS = \frac{(LVDD + h) - (LVSD + 2a')}{(LVDD + h)} \times 100$$

where
h: combined diastolic wall thickness (PWTd + IVSd / 2)
hfs: combined systolic wall thickness (PWTs + IVSs / 2), and
a': systolic midwall point calculated by the following formula:

$$a' = 1/2\ [\sqrt{}\ (hfs\ (2\ LVDD + h)\ (VVSD + hfs) / (LVDD + h) + LVSD2) - LVSD]$$

Calibrated carotid pulse tracing: After echocardiography, carotid pulse tracing was recorded with a TOSHIBA SSH140A system and TPW – 01 A pulse transducer, and blood pressure was measured in the right arm by means of a cuff sphygmomanometer with the patient in left lateral decubitus position. Carotid pulse tracing calibration was performed according to the method used in our laboratory, (8) which considers that systolic blood pressure corresponds with the highest wave of the carotid pulse tracing (phase 5) and diastolic blood pressure with the lowest portion. The distance between the peak and through is measured and is considered as equivalent to differential blood pressure or pulse pressure. Then, the distance between the end-systolic point and the base is measured, converted to mm Hg by simple rule of three and then added to diastolic blood pressure. In this way, end-systolic pressure (ESP) is non-invasively estimated.

Energy loss index: The energy loss index considers pressure recovery in the ascending aorta and provides a more accurate transvalvular pressure gradient, avoiding the overestimation derived by the continuity equation. We used the formula proposed by García: (17, 18)

ELI (cm2 /m2) = [(AVA . AA) / (AA – AVA)] / BSA

where AA(cm2) is aortic cross-sectional area measured at the sino-tubular junction and BSA (cm2) is body surface area.

Valvulo-arterial impedance (Zva): in AS, total afterload includes both the valve obstruction and systemic circulation afterload. Zva was then calculated as:

Zva (mm Hg/ml/m2) = (SBP (mm Hg) + MPG (mm Hg)) /SVi (ml/m2)

where SBP is systolic blood pressure, MPG is mean transvalvular pressure gradient corrected for recovery pressure according to the Baumgartner formula (19) and SVi is stroke volume index.

Passive elastic stiffness constant (k):

k = (Ln EDP – Ln 0.43) / EDV

Left ventricular relaxation constant (tau):

tau = IRT/ (Ln ESP – Ln PCWP)

Where IRT is isovolumic relaxation time.