Arterial Wave Reflections and Ventricular-Vascular Interaction in Patients With Left Ventricular Systolic Dysfunction

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SUMMARY

Central aortic pressure waveform (AoPW) is the summation of a forward-traveling wave generated by the left ventricle and a backward-traveling wave caused by the reflection of the forward wave. The aim of this study was to evaluate the effect of ventricular-vascular coupling on the morphology of AoPW in chronic heart failure patients with different degrees of left ventricular systolic dysfunction (LVSD) using pulse wave analysis (PWA). PWA of AoPW and left ventricular (LV) function were evaluated by applanation tonometry in 26 control subjects, in 12 patients with left ventricular ejection fraction (LVEF) $\leq 30\%$, and in 14 patients with LVEF $> 30\%$. Augmentation pressure, augmentation index, wasted energy, and ejection duration were lower in patients with LVEF $\leq 30\%$ than in those with LVEF $> 30\%$ and in control subjects. Furthermore, augmentation index showed an inverse correlation with Doppler mitral E-wave amplitude ($r = -0.40$; $P = 0.04$) and E/A ratio ($r = -0.42$; $P = 0.03$) and a direct correlation with deceleration time of mitral E-waves ($r = 0.39$; $P = 0.04$). In patients with severe LVSD (LVEF $\leq 30\%$), aortic wave reflections negatively interfere with LV function and induce a shortening of ejection duration. In contrast, AoPW is similar in patients with moderate LVSD (LVEF $> 30\%$) and in control subjects. (Int Heart J 2014; 55: 526-532)

Key words: Arterial stiffness, Heart failure, Ejection fraction, Pulse pressure

High brachial pulse pressure (PP), commonly considered a marker of arterial stiffness, has been shown to predict adverse outcomes in patients with left ventricular (LV) systolic dysfunction.^{1,2} However, in patients with advanced systolic heart failure, the association between PP and outcome is reversed and a low PP is an independent predictor of all cause and cardiovascular death.^{3,4} It is conceivable that different pathophysiological mechanisms may underlie the opposite prognostic significance of PP in patients with LV systolic dysfunction (LVSD) and different severity of cardiac function impairment.

Several sets of data support the greater importance of the central rather than peripheral blood pressure profile in patients with various cardiovascular diseases. A central blood pressure profile offers a more direct measure of LV load and arterial stiffness and provides useful clinical information independently from peripheral PP.⁵⁻⁸ The central aortic pressure wave is composed of a forward-traveling wave generated by LV ejection and a late-arriving reflected wave from the periphery. Normally, wave reflections arrive during diastole, when LV has completed the ejection and contribute to coronary perfusion. As arterial stiffness increases, the velocity of forward and reflected waves increases so that the reflected wave arrives earlier to the heart and boosts pressure in late systole with an extra pulsatile workload on the left ventricle.^{9,10} The availability of

noninvasive methods to accurately measure central blood pressure and flow has increased interest in gaining a further understanding of the role of central hemodynamics in cardiovascular diseases.¹¹

The aim of the present study was to determine the effect of arterial wave reflections and central aortic blood pressure on LV systolic and diastolic function in patients with moderate and severe LVSD using high fidelity tonometry of the radial artery and echocardiographic evaluation.

METHODS

Study population: In this prospective study 26 consecutive patients with ischemic or nonischemic dilated cardiomyopathy (CMP) (left ventricular ejection fraction [LVEF] $< 40\%$) and 26 control subjects (LVEF $> 55\%$) matched for age, gender, and brachial systolic (SBP) and diastolic (DBP) blood pressure were evaluated. Control subjects were recruited in the same period as the subjects referring to our outpatient clinic for cardiovascular examination. All patients underwent coronary angiography for assessment of coronary artery disease (CAD). Exclusion criteria were atrial fibrillation, unstable clinical conditions, valvular heart disease, and cardiac resynchronization therapy. All patients were studied while on regular medications

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and all provided written informed consent for participation in the study. The study was approved by our local ethics committee. Hypertension was defined as repeated measurements ≥ 140 mmHg SBP or ≥ 90 mmHg DBP as recommended by the ESH/ESC Practice Guidelines for the Management of Arterial Hypertension,¹²⁾ or permanent antihypertensive drug treatment. Diabetes mellitus was defined as a fasting blood glucose concentration ≥ 126 mg/dL or anti-hyperglycemic drug treatment. Renal failure was defined as a reduction of the glomerular filtration rate; in our population we detected only mild impairment.

Pulse wave analysis: Blood pressure (BP) measurements were performed with a manual manometer at the left brachial artery with the patient in the supine position at rest. Pulse wave analysis (PWA) was performed with the commercially available SphygmoCor system (AtCor Medical, Sydney, Australia) as previously described.¹³⁾ In brief, peripheral pressure waveforms were recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer, and a validated generalized transfer function to generate the corresponding central aortic pressure waveform (AoPW), and calibrating on measured brachial systolic and diastolic pressure. Aortic SBP, DBP, and PP as well as augmentation pressure (AP), augmentation index (Aix), and ejection duration (ED) were derived from this, with the validated technique of PWA.¹⁴⁾ Only high-quality recordings defined as an in-device quality index $\geq 80\%$ (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and shape variation) were included in the analysis. All PWA measurements were taken at rest in the sitting position. Central pulse pressure (PP) was recorded as an estimate of afterload and the augmentation index (Aix) as a measure of the relative contribution of reflected pulse waves to central blood pressure. The merging point of the incident and the reflected wave was identified on the aortic pressure waveform. Augmentation pressure (AP) was calculated as the difference between the second (P2) and first systolic (P1) peaks (P2-P1).⁶⁾ Aix is a measure of wave reflection intensity and is estimated as the ratio of wave reflection amplitude and central PP. In addition, because Aix is influenced by heart rate, an index normalized for heart rate 75/minute (Aix@75) was used. Ejection duration (ED) is a calculated measure of the total systolic period. Time to return of the reflected wave (Tr) to and from the major reflecting site in the lower body, is the time from the beginning upstroke of the synthesized aortic systolic pressure waveform to the upstroke of the reflected wave (inflection point) and is related to arterial stiffness of the entire arterial system. When the reflected wave returns earlier during systole, as a result of increased arterial stiffness, aortic pressure is augmented in late systole and LV must generate an effort to overcome this augmented pressure with a longer systolic duration of the reflected wave. This pressure effort is wasted (Ew) because it does not contribute to blood flow production and can be estimated as the area under the systolic portion of the reflected wave. The systolic pressure time index (SPTI) is estimated as the area under the systolic portion of the aortic pressure wave above zero and is directly related to myocardial oxygen demand.¹⁵⁾ Ew is that portion of the SPTI enclosed by systolic duration of reflected waves (difference between total ejection duration and Tr) and by augmentation pressure.¹⁶⁾ The diastolic pressure time index (DPTI) is a measure of coronary perfusion pressure

and is calculated as the area under the diastolic portion of the pressure wave.¹⁷⁾

Left ventricular function assessment: Left ventricular systolic and diastolic function was evaluated by two-dimensional echocardiography using a Philips digital ultrasound machine (model i-E 33) in all patients and in normal subjects. Left ventricular diastolic and systolic volumes and ejection fraction (LVEF), calculated by Simpson's method, were measured as recommended in the ASE guidelines.¹⁸⁾ According to these guidelines, patients with LVEF $\leq 30\%$ were considered to have severe LVSD.¹⁸⁾ For the assessment of left ventricular diastolic function, we evaluated peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, and the deceleration time (DT) of early filling velocity derived by Pulsed-wave Doppler recordings with the sample volume placed at the tip of the mitral leaflets from the apical 4-chamber view. The mitral annular lateral and septal early diastolic velocities (e') were determined by color-decoded tissue Doppler imaging. E/e' was used as a surrogate of LV end-diastolic pressure.¹⁹⁾ All these measurements were recorded by two operators with the subject at rest.

Statistical analysis: Continuous variables are expressed as the mean $\pm$ standard deviation and categorical data as percentages. Baseline characteristics as well as hemodynamic data were compared between LVSD patients and controls, using the unpaired *t*-test (in normally distributed data with equal variances), Welch's test (with unequal variances), and chi-square test, as appropriate. To assess the test-retest reliability of pulse waveform analysis, the study was repeated two days apart by the same investigator in 10 patients and 10 control subjects. The systematic error (the mean of differences of test and retest values) was checked by the paired *t*-test with the significance level set at 0.05, and the Bland-Altman method was employed to calculate the 95% limits of agreement between the paired measures.²⁰⁾ The absolute retest reliability was assessed by the SEM.²¹⁾ The SEM represented the variability between measurements obtained from the 2 sessions and was calculated as the square root of the within subjects error variance. We also evaluated Lin's concordance correlation coefficient (ρ_c) and the intra-class correlation coefficient ($ICC_{2,1}$) using a 2-way random-effects ANOVA model (subject by session) and the absolute agreement definition.²²⁾ ICC values > 0.8 indicated good reliability.

Data were analyzed using STATA 13.1 software packages (StataCorp, College Station, Texas USA). To better assess the relationship between AoPW and systolic function, we compared measures of systolic function in control subjects and in patients with LVEF $\leq 30\%$ and LVEF $> 30\%$ using one-way ANOVA; if a significant F test was found, post-hoc multiple comparisons were performed with the Bonferroni correction. In patients with LVSD the degree of association between systolic function, systolic time intervals, brachial and aortic PP, Aix, Aix@75, AP, Tr, and AoPW was analyzed using Pearson's correlation coefficient. Multivariate regression analysis was used to evaluate the effects of systolic and diastolic function parameters on Aix adjusted for clinical variables such as age, gender, body surface area (BSA), heart rate, CAD, diabetes, creatinine, systolic and diastolic blood pressure, and LVEF.

RESULTS

Patients and normal subjects: Baseline characteristics of patients with LVSD and control subjects are reported in Table I. The two groups were comparable with regards to age, gender, body mass index, and heart rate, while LVSD patients had multiple risk conditions and were on multiple medications. Patients with LVSD had higher values of mean LV volumes than normal subjects with a reduced LVEF; furthermore, two dimensional, pulse wave Doppler, and TDI echocardiographic measures indicate the presence of diastolic abnormalities in these patients.

Radial and central aortic pulse waveform analysis: The test-retest reliability of pulse waveform analysis was good for all the parameters tested (Table II). Brachial SBP, DBP, and PP were comparable between normal subjects and LVSD patients as well as central calculated aortic blood pressure values (Table III).

Patients with LVSD were then divided according to their LVEF values: LVEF was > 30% in 14 patients and ≤ 30% in 12 patients. The results obtained comparing control subjects

with patients stratified into moderate (LVEF > 30%) or severe (LVEF ≤ 30%) LVSD are reported in Table IV. All variables of AoPW were comparable between normal subjects and patients with LVEF > 30%. In contrast, in patients with LVEF ≤ 30%, brachial mean BP, aortic SBP, aortic mean BP, and ED were lower than in control subjects. Furthermore, a significant difference could be also detected in AP, AIx, Ew, and ED between patients with LVEF ≤ 30% and those with LVEF > 30%.

The correlations between AoPW variables and LV measures of systolic and diastolic function in patients with LVSD are shown in Table V. Aortic PP was directly correlated with LVEF ($r = 0.51$; $P = 0.007$) and with mitral DT ($r = 0.46$; $P = 0.02$). AIx was inversely correlated with mitral E-wave amplitude ($r = 0.40$; $P = 0.04$) and with E/A ratio ($r = -0.42$; $P = 0.03$) and directly with mitral DT ($r = 0.39$; $P = 0.04$); AIx@75 showed an inverse correlation with mitral E wave ($r = -0.44$; $P = 0.02$). Wasted energy correlated directly with LVEF ($r = 0.43$; $P = 0.03$). No difference was detectable in AIx between LVSD patients with or without hypertension (23.5 ± 12.3 versus 23.9 ± 8.5 ; $P = 0.92$) or diabetes (24.0 ± 10.9 versus 23.5 ± 9.9 ; $P = 0.89$). In multivariate analysis, E/A ($\beta = -5.61$; 95%

Table I. Baseline Characteristics of Controls and LVSD Patients

Clinical characteristics	Controls ($n = 26$)	LVSD patients ($n = 26$)	<i>P</i>
Age (years) (mean $\pm$ SD)	61 $\pm$ 11	63 $\pm$ 11	0.604
Gender (M/F)	22/4	22/4	1.000
BSA (mean $\pm$ SD)	1.9 $\pm$ 0.2	1.9 $\pm$ 0.2	0.631
	0 = 26	0 = 0	0.000
	I = 0	I = 3	0.000
NYHA class, <i>n</i>	II = 0	II = 15	0.000
	III = 0	III = 8	0.000
CAD, <i>n</i>	0	20	0.000
Hypertension, <i>n</i>	2	14	0.001
Diabetes, <i>n</i>	1	13	0.000
Renal failure, <i>n</i>	0	7	0.010
Total cholesterol (mg/dL) (mean $\pm$ SD)	154 $\pm$ 9	161 $\pm$ 39	0.000
Creatinine (mg/dL) (mean $\pm$ SD)	0.9 $\pm$ 0.2	1.3 $\pm$ 0.5	0.000
Hemoglobin (g/dL) (mean $\pm$ SD)	13.9 $\pm$ 1.2	13.4 $\pm$ 1.9	0.216
Device, <i>n</i>	0	11	0.001
Therapy			
Beta-blockers, <i>n</i>	0	24	0.000
ACEI, <i>n</i>	1	22	0.000
Calcium antagonists, <i>n</i>	1	2	1.000
Nitrates, <i>n</i>	0	5	0.051
Aldosterone blockers, <i>n</i>	0	13	0.000
Furosemide dosage (mg/day) (mean $\pm$ SD)	0	33.2 $\pm$ 57.9	0.000
Echocardiographic Measures			
LVEF (%) (mean $\pm$ SD)	58 $\pm$ 3	33 $\pm$ 5	0.001
LVEDV (mL) (mean $\pm$ SD)	100 $\pm$ 8.5	178 $\pm$ 63.2	0.000
LVESV (mL) (mean $\pm$ SD)	42 $\pm$ 5	120 $\pm$ 47	0.000
Mitral E-wave (cm/s) (mean $\pm$ SD)	76.1 $\pm$ 13.6	72.9 $\pm$ 26.1	0.022
Mitral A-wave (cm/s) (mean $\pm$ SD)	65.7 $\pm$ 15.3	75.5 $\pm$ 25.5	0.002
Mitral DT (ms) (mean $\pm$ SD)	203.2 $\pm$ 17.7	206.7 $\pm$ 57.6	0.000
E/A (mean $\pm$ SD)	1.2 $\pm$ 0.2	1.1 $\pm$ 0.7	0.003
Lateral e' DTI (cm/s) (mean $\pm$ SD)	13.1 $\pm$ 1.5	6.6 $\pm$ 2.5	0.016
Septal e' DTI (cm/s) (mean $\pm$ SD)	10.1 $\pm$ 1.5	4.9 $\pm$ 2.3	0.793
E/e' (mean $\pm$ SD)	5.8 $\pm$ 0.8	11.9 $\pm$ 4.4	0.000

ACE-I indicates angiotensin converting enzyme-inhibitors; BSA, body surface area; CAD, coronary artery disease; DT, deceleration time; E/A, mitral E-wave, mitral A-wave ratio; E/e', mitral E-wave and early diastolic velocity by Doppler tissue imaging ratio; Lateral e' DTI, early diastolic velocity by Doppler tissue imaging at the lateral mitral annulus; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVSD, left ventricular systolic dysfunction; Mitral A wave, atrial diastolic transmitral flow velocity; Mitral E wave, early diastolic transmitral flow velocity; NYHA, New York Heart Association; SD, standard deviation; and Septal e' DTI, early diastolic velocity by Doppler tissue imaging at the septal mitral annulus.

Table II. Test-Retest Reliability of Pulse Waveform Analysis

	Mean $\pm$ SD Test	Mean $\pm$ SD Retest	Mean differences $\pm$ SD	P	95% Limits of agreement	SEM	ρ_c	ICC (95%CI)
PP aortic (mmHg)	34 $\pm$ 7	35 $\pm$ 6.6	-0.3 $\pm$ 1.6	0.4	-3.4 to 2.8	1.1	0.97	0.97 (0.94-0.99)
AIx (%)	24 $\pm$ 9.6	24 $\pm$ 10.4	-0.05 $\pm$ 1.4	0.9	-2.9 to 2.8	0.1	0.99	0.99 (0.98-0.99)
ED (ms)	293 $\pm$ 26	292 $\pm$ 2	1.4 $\pm$ 6.2	0.3	-10.7 to 13.6	4.4	0.96	0.96 (0.94-0.99)
Ew (dyne s/cm ²)	2.8 $\pm$ 1.4	2.8 $\pm$ 1.4	-0.03 $\pm$ 0.3	0.6	-0.6 to 0.5	0.2	0.98	0.98 (0.96-0.99)

AIx indicates augmentation index; CI, confidence interval; ED, ejection duration; Ew, wasted effort; ICC, intraclass correlation; PP, pulse pressure; ρ_c , Lin's concordance correlation coefficient; SD, standard deviation; SEM, standard error of the measurement.

Table III. Peripheral Blood Pressures and Central Pulse Waveform Measures of Controls and LVSD Patients

	Controls (n = 26) Mean $\pm$ SD	LVSD patients (n = 26) Mean $\pm$ SD	P
SBP brachial (mmHg)	121 $\pm$ 9	118 $\pm$ 13	0.17
DBP brachial (mmHg)	75 $\pm$ 9	71 $\pm$ 9	0.78
PP brachial (mmHg)	46 $\pm$ 7	47 $\pm$ 9	0.10
Mean BP brachial (mmHg)	91 $\pm$ 8	86 $\pm$ 10	0.54
SBP aortic (mmHg)	111 $\pm$ 9	107 $\pm$ 13	0.20
DBP aortic (mmHg)	76 $\pm$ 9	72 $\pm$ 9	0.88
PP aortic (mmHg)	35 $\pm$ 6	35 $\pm$ 7	0.19
Mean BP aortic (mmHg)	91 $\pm$ 8	86 $\pm$ 9.7	0.54
AP (mmHg)	8.2 $\pm$ 3.6	8.4 $\pm$ 4	0.70
AIx (%)	22.9 $\pm$ 8	23.7 $\pm$ 10.2	0.16
AIx@75 (%)	18.9 $\pm$ 6.8	20.2 $\pm$ 8.5	0.55
Tr (ms)	142.6 $\pm$ 10.7	138.3 $\pm$ 11.2	0.44
ED (ms)	306 $\pm$ 24.3	292.1 $\pm$ 26.5	0.93
SPTI (mmHg s/min)	2046.9 $\pm$ 270.1	1902.1 $\pm$ 332.9	0.18
DPTI (mmHg s/min)	3401 $\pm$ 383.8	3229.6 $\pm$ 408.9	0.86
Ew (dyne s/cm ²)	2.9 $\pm$ 1.5	2.9 $\pm$ 1.7	0.80
HR (bpm)	66 $\pm$ 7.5	73 $\pm$ 9	0.26

AIx indicates augmentation index; AIx@75, augmentation index normalized for heart rate 75/min; AP, augmentation pressure; BP, blood pressure; DBP, diastolic blood pressure; DPTI, Diastolic Pressure Time Index; ED, ejection duration; Ew, wasted effort; HR, heart rate; LVSD, left ventricular systolic dysfunction; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; SPTI, systolic Pressure Time Index; and Tr, Time to return of reflected wave.

confidence interval - 9.57 to -1.65; $P = 0.008$) and heart rate ($\beta = -0.42$; 95% confidence interval -0.77 to -0.07; $P = 0.02$) were the only significant predictors of AIx after adjustment for the other systolic and diastolic function parameters and for clinical variables (model $r^2 = 0.50$).

DISCUSSION

Interactions between the LV and peripheral arterial system are key determinants of cardiovascular function (ventricular/vascular coupling).²³⁾ Aortic reflection waves arising in peripheral arteries and returning to the proximal aorta during mid to late systole are an important determinant of LV afterload and interfere significantly with LV mechanics.²⁴⁻²⁶⁾

Aortic pressure waves and left ventricular systolic and diastolic function: Our study demonstrates that reflection waves induce a deleterious effect on the ventricular-vascular interaction in the subgroup of patients with severe LV impairment (LVEF $\leq 30\%$) whereas this influence is negligible in those with less severe LV impairment (LVEF $> 30\%$). In the subgroup of patients with LVEF $\leq 30\%$, central PP, AIx, Ew, and ED values were clearly lower than in controls and in patients with less compromised LV function, whereas in these two latter groups these values are comparable. It is likely that in patients with severe LV impairment, myocardial compensation is lost and

the LV cannot generate the extra force necessary to overcome the late systolic augmented pressure with a decrease in ED and Ew. Therefore, in these patients arterial wave reflections induce a negative influence on flow rather than a positive influence on pressure.²⁷⁾ This deleterious effect of wave reflections has been described in patients with LVSD by Denardo, *et al.*²⁸⁾ They reported a decrease in all components of central and peripheral blood pressure compared with normal subjects with a reduction in ED, in reflected wave amplitude, and in Ew of LV effort. It must be pointed out that these authors considered patients with severe LV impairment (mean LVEF = 24%) to be comparable to our LVSD patient subgroup of 12 patients with more compromised LV function (mean LVEF = 29%).

In patients with moderate LVSD the effects of reflection waves on ventricular vascular coupling have been studied and increases in aortic stiffness, pulse wave velocity, and PP have been observed.²⁹⁻³²⁾ However, these studies had some limitations with respect to their small sample sizes, the combination of patients with LV systolic and diastolic dysfunction, and the methods utilized. Weber, *et al* studied 63 patients with ischemic or nonischemic cardiomyopathy and LVEF less than 45% (mean = 29.9%).³³⁾ In contrast to us, in LVSD patients central PP was lower and the ejection duration was shorter as compared with controls. It must be mentioned that 62% of "controls" were hypertensive, 18% diabetic, 6% suffered a myocardial infarction, and 50% had a history of coronary artery

Table IV. Echocardiographic and Central Pulse Waveform Measures of Controls and LVSD Patients Divided According to LVEF Values

Echocardiographic measures	Group 0 (n = 26)	Group 1 (n = 14)	Group 2 (n = 12)
	Controls Mean $\pm$ SD	LVSD patients LVEF > 30% Mean $\pm$ SD	LVSD patients LVEF $\leq$ 30% Mean $\pm$ SD
LVEDV (mL)	100.2 $\pm$ 8.5 ^{****}	157.3 $\pm$ 44.3 [§]	201.5 $\pm$ 74.9
LVESV (mL)	41.7 $\pm$ 5.4 ^{****}	101.6 $\pm$ 31.0 [§]	142.6 $\pm$ 53.8
Mitral E-wave (cm/s)	76.1 $\pm$ 13.6	69.8 $\pm$ 22.6	76.7 $\pm$ 30.3
Mitral A-wave (cm/s)	65.7 $\pm$ 15.2	81.5 $\pm$ 24.4	68.6 $\pm$ 25.7
E/A	1.2 $\pm$ 0.2	0.9 $\pm$ 0.3	1.4 $\pm$ 0.9
Mitral DT (ms)	203.2 $\pm$ 17.7	217.4 $\pm$ 54.0	194.2 $\pm$ 61.2
Septal e' DTI (cm/s)	10.1 $\pm$ 1.5 ^{****}	4.6 $\pm$ 1.4	5.4 $\pm$ 3.1
E/e'septal DTI	5.8 $\pm$ 0.8 ^{****}	12.4 $\pm$ 3.9	11.5 $\pm$ 5.0
Central Pulse Waveform Measures			
Brachial SBP (mmHg)	121.1 $\pm$ 9.3	120.7 $\pm$ 15.8	114.6 $\pm$ 8.4
Brachial DPB (mmHg)	74.8 $\pm$ 8.5	73.6 $\pm$ 9.9	68.3 $\pm$ 7.5
Brachial mean BP (mmHg)	90.7 $\pm$ 8.3 ⁺	88.6 $\pm$ 11.0	82.2 $\pm$ 6.9
Brachial PP (mmHg)	46.4 $\pm$ 6.6	47.1 $\pm$ 8.9	46.3 $\pm$ 10.0
Aortic SBP (mmHg)	110.7 $\pm$ 9.3 ⁺	111.2 $\pm$ 14.2	101.6 $\pm$ 8.0
Aortic DPB (mmHg)	76.0 $\pm$ 8.4	74.3 $\pm$ 9.7	69.0 $\pm$ 7.6
Aortic mean BP (mmHg)	90.7 $\pm$ 8.3 ⁺	88.6 $\pm$ 11.0	82.2 $\pm$ 6.9
Aortic PP (mmHg)	34.5 $\pm$ 6.0	37.0 $\pm$ 6.3	32.5 $\pm$ 7.3
AP (mmHg)	8.2 $\pm$ 3.6	10.4 $\pm$ 3.6 [§]	6.0 $\pm$ 3.0
Aix	22.9 $\pm$ 8.0	28.1 $\pm$ 8.9 [§]	18.7 $\pm$ 9.6
Aix@75 (%)	18.9 $\pm$ 6.8	22.9 $\pm$ 7.8	17.1 $\pm$ 8.6
SPTI (mmHg)	2046.9 $\pm$ 270.1	1958.1 $\pm$ 392	1836.8 $\pm$ 247.2
DPTI (mmHg)	3401 $\pm$ 383.8	3347.9 $\pm$ 445.2	3091.7 $\pm$ 327.5
Ew (dyne s/cm ²)	2.9 $\pm$ 1.5	3.7 $\pm$ 1.6 [§]	1.8 $\pm$ 1.0
Tr (ms)	142.6 $\pm$ 10.7	138.1 $\pm$ 11.1	138.6 $\pm$ 11.8
ED (ms)	306.0 $\pm$ 24.3 ⁺	304.6 $\pm$ 26.2 [§]	277.0 $\pm$ 18.6

Aix indicates augmentation index; Aix@75, Augmentation Index normalized for heart rate 75/minute; AP, augmentation pressure; BP, blood pressure; DBP, diastolic blood pressure; DPTI, Diastolic Pressure Time Index; DT, deceleration time; E/A, mitral E-wave and mitral A-wave ratio; ED, ejection duration; Ew, wasted effort; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVSD, left ventricular systolic dysfunction; Mitral A wave, atrial transmitral flow velocity; Mitral E wave, early diastolic transmitral flow velocity; PP, pulse pressure; Tr, Time to return of reflected wave; E/e'septal, mitral E-wave and early diastolic velocity by Doppler tissue imaging at the septal mitral annulus ratio; SBP, systolic blood pressure; SD, standard deviation; Septal e' DTI, early diastolic velocity by Doppler tissue imaging at the septal mitral annulus; and SPTI, Systolic Pressure Time Index. ⁺P < 0.05 group 0 versus group 1; ⁺⁺P < 0.001 group 0 versus group 1; ⁺P < 0.05 group 0 versus group 2; ⁺⁺P < 0.001 group 0 versus group 2; [§]P < 0.05 group 1 versus group 2; ^{§§}P < 0.001 group 1 versus group 2.

Table V. Univariate Correlations Between Echocardiographic and Central Pulse Waveform Measures in Patients With LVSD

	LVEF (%)		Mitral E wave (cm/s)		Mitral A wave (cm/s)		E/A		Mitral DT (ms)		E/e'septal	
	Pearson's r	P	Pearson's r	P	Pearson's r	P	Pearson's r	P	Pearson's r	P	Pearson's r	P
PP aortic (mmHg)	0.51	0.007 [*]	-0.04	0.86	0.24	0.23	-0.15	0.48	0.46	0.02 [*]	0.14	0.50
PP brachial (mmHg)	0.33	0.09	0.09	0.64	0.09	0.66	0.07	0.74	0.24	0.24	0.06	0.98
Aix (%)	0.30	0.14	-0.40	0.04 [*]	0.15	0.45	-0.42	0.03 [†]	0.39	0.04 [*]	-0.04	0.82
Aix@75 (%)	0.33	0.10	-0.44	0.02 [*]	0.007	0.97	-0.36	0.07	0.23	0.25	-0.17	0.41
Ew (dyne s/cm ²)	0.43	0.03 [†]	-0.18	0.38	0.26	0.19	-0.32	0.11	0.36	0.07	0.12	0.58
Tr (ms)	-0.005	0.97	0.13	0.52	-0.09	0.65	0.12	0.56	-0.14	0.49	0.25	0.22
ED (ms)	0.35	0.08	-0.03	0.87	0.22	0.27	-0.18	0.37	0.11	0.59	0.15	0.46

Aix indicates augmentation index; Aix@75, Augmentation Index normalized for heart rate 75/minute; DT, deceleration time; E/e'septal, mitral E-wave and early diastolic velocity by Doppler tissue imaging at the septal mitral annulus ratio; ED, ejection duration; Ew, wasted effort; Mitral A wave, atrial transmitral flow velocity; Mitral E wave, early diastolic transmitral flow velocity; LVEF, left ventricular ejection fraction; PP, pulse pressure; and Tr, Time to return of reflected wave. ^{*}P < 0.05.

disease. Therefore, altered values of AoPW measured in subjects considered as "controls" could reflect the presence of increased stiffness, commonly described in patients with those pathologies. We found no difference in Aix between LVSD patients with or without hypertension or diabetes; it is conceivable that LVSD may overcome the negative influence of these clinical variables on arterial stiffness. The difference in AoPW measures that we observed between patients with more or less severe LV impairment suggests LVEF values should be taken

into account when AoPW analysis is performed in patients with LVSD.

Interestingly, we found a direct correlation between aortic PP and LVEF, whereas no correlation was detectable between brachial PP and LVEF. Therefore, our data confirm that brachial PP is only a poor predictor of aortic blood pressure values and it is the latter that influences cardiac function.³³⁾ Blood pressure in central arteries, such as the ascending aorta and common carotid arteries, is directly related to the loads im-

posed on the heart, influencing also coronary blood flow.^{5,6} Thus, the superiority of central PP over peripheral PP in the prediction of LVEF impairment is not surprising.

It is well known that the elevation in afterload directly impairs myocardial relaxation properties and increases LV end-diastolic pressure.^{34,35} Commonly, in patients with more compromised LV function, LV end-diastolic pressure is increased, isovolumic relaxation is reduced, early filling is increased, and late filling is reduced.^{36,37} In our patients, AIx showed an inverse correlation with E-waves and a direct correlation with DT. These data indicate that in patients with a severe reduction of LVEF, the reflected wave interferes negatively with diastolic function, and consequently, early diastolic filling is increased and DT decreased contributing to the restrictive pattern commonly observed in these patients. The results of multivariate analysis confirm this finding. In fact, the E/A ratio was a significant negative predictor of AIx after adjustment for other systolic and diastolic parameters and for clinical variables.

Conclusion: In patients with severe LVSD (LVEF $\leq$ 30%), AoPW negatively influences both LV systolic and diastolic function, and in contrast to patients with moderate LVSD (LVEF > 30%), this negative effect is negligible. It is conceivable that when LV is only moderately impaired, it is able to counteract the extra pulsatile workload imposed by the reflected waves, whereas when it is severely impaired, the compensation is lost. Therefore, our data suggest that LVEF values must be taken into account when AoPW measures are considered in patients with LVSD.

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