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Impact of global left ventricular afterload on left ventricular function in asymptomatic severe aortic stenosis: a two-dimensional speckle-tracking study

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Aims The present study sought to assess the effect of global left ventricular (LV) afterload on LV myocardial systolic function in patients with aortic stenosis (AS) and preserved LV ejection fraction.

Methods and results We prospectively examined the LV myocardial deformation (i.e. longitudinal, radial, and circumferential) by two-dimensional speckle tracking in 173 patients with asymptomatic severe AS. Thirty-eight patients (22%) had low flow as determined by a low stroke volume index ($\leq$35 mL/m^2). By multivariable analysis, four variables emerged as independently associated with low-flow AS: peak Ea velocity ($P = 0.01$), left atrial area index ($P = 0.017$), global LV afterload ($P = 0.024$), and circumferential myocardial deformation ($P = 0.04$). Forty-nine patients (28%) had an increased global LV afterload ($\geq$5 mmHg mL/m^2). Systemic arterial compliance ($P = 0.001$), circumferential myocardial deformation ($P = 0.024$), and left atrial area index ($P = 0.04$) were independently associated with increased global LV load in multivariable analysis. Of note, LV ejection fraction was not identified as a determinant of low flow or increased afterload.

Conclusion In asymptomatic patients with severe AS, LV ejection fraction markedly underestimates the extent of myocardial systolic impairment. Intrinsic myocardial dysfunction is particularly common in patients with increased global LV afterload, and especially in the subset of patients with low-flow AS.

Keywords Aortic stenosis • Echocardiography • Left ventricular function

Introduction

Valvular aortic stenosis (AS) is now regarded as a growing health problem with sizeable economic impact. Aortic stenosis cannot be viewed as an isolated disease of the valve.[1,2] Indeed, the prevalence of atherosclerosis and hypertension is markedly high in AS. Both conditions may accelerate arterial stiffness and decrease arterial compliance.[3] Reduced systemic arterial compliance additively contributes to the increased systolic load caused by the outflow obstruction; the left ventricular (LV) facing a double load (valvular + arterial).[4] This global LV afterload that may be assessed by valvulo-arterial impedance plays a detrimental effect on LV systolic function.[5] Reduced LV mid-wall shortening—derived from M-mode measurements—is particularly common in patients with paradoxical low-flow AS (reduced stroke despite normal LV ejection fraction).[6] Low-gradient severe AS with preserved LV ejection fraction is a challenging clinical entity that has been recently emphasized. This pattern is observed in approximately one-third of patients with AS and is associated with a dismal prognosis.[7]

In asymptomatic AS, it is well known that LV ejection may remain normal despite impaired LV long-axis function shown by tissue Doppler.[8] Contrary to colour tissue Doppler-derived velocity and strain, two-dimensional (2D) speckle tracking allows

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angle-independent determination of the three components of myocardial deformation (i.e. radial, circumferential, and longitudinal).[9] A recent study has shown that the risk of untoward cardiac events is significantly increased in patients with asymptomatic AS and reduced LV longitudinal deformation.[8] The decrease in LV long-axis function appears before symptoms development and might be more pronounced in the categories of patients with paradoxical low-flow AS.[10] Hitherto no study has quantitatively examined the effects of LV global afterload on the three components of myocardial deformation. This study was thus undertaken (1) to evaluate the impact of global LV load on LV function and (2) to assess the relationship between the quantified LV function and the low-flow state, by using 2D speckle tracking of myocardial deformation in a series of asymptomatic patients with AS and preserved LV ejection fraction.

Methods

Patient population

Asymptomatic patients with severe AS were prospectively screened from our echocardiographic laboratory for inclusion in this study. All patients met the following criteria: severe AS defined by an aortic valve area ≤ 0.6 cm^2/m^2, no symptoms according to a careful history, normal LV ejection fraction ($\geq 55\%$) as calculated by 2D echocardiography, no more than mild associated cardiac valve lesion, sinus rhythm, no renal failure, and optimal quality of speckle-tracking imaging analysis. A total of 173 patients were identified by these criteria. The protocol was approved by the relevant institutional review boards and all patients gave written informed consent.

Echocardiographic measurements

Doppler echocardiographic examinations were performed with the use of a VIVID 7 ultrasound machine (General Electric Healthcare). M-mode, 2D, colour Doppler, pulsed-wave, and continuous-wave Doppler data were stored on a dedicated workstation for off-line analysis. For each measurement, at least two cardiac cycles were averaged. Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the continuity equation. Stroke volume was calculated using the Doppler method as follows: $0.785 \times$ (LV outflow tract diameter)$^2 \times$ LV outflow tract velocity time integral.[11–13] Left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured by the bi-apical Simpson disk method. Left atrial area was obtained by planimetry of an end-systolic frame from the apical four-chamber view. To complete the analysis of the LV systolic function, both the long- and short-axis myocardial deformations were evaluated from standard 2D images (frame rates $\geq 70\ s^{-1}$). Two-dimensional strain is a non-Doppler-based method.[14–16] In brief, the endocardial borders were traced manually at the end-systolic frame and an automated tracking algorithm outlined the myocardium in successive frames throughout the cardiac cycle. After the tracking quality was verified for each segment (with subsequent manual adjustment of the region of interest in case of tracking score of 3), myocardial motion was analysed by speckle tracking within the region of interest bound by endocardial and epicardial borders. Inadequate tracked segments were automatically excluded from analysis ($<10\%$ of segments analysed). Numerical and graphical displays of strain parameters were then generated. The peak systolic local strain in each segment was measured with systole manually defined by aortic valve closure. The global longitudinal deformation—strain—was the average of the segment strains from the apical four-chamber and two-chamber views.[9] The short-axis function—radial and circumferential deformation—was obtained from a short-axis image at the papillary muscle level. The reproducibility of the quantification of myocardial deformation in our laboratory has been reported previously.[9] The peak velocities of the E-wave (early diastole) and the A-wave (late diastole) were measured and the ratio of these velocities was calculated. By using pulsed-wave tissue Doppler, peak velocities during early (Ea) and late (Aa) diastole obtained at the level of septal and lateral mitral annulus were measured separately and then averaged. The E/Ea ratio was then calculated.[17]

Systemic arterial haemodynamics and global left ventricular afterload

Systemic arterial pressure was measured with the use of an arm-cuff sphygmomanometer at the time of the Doppler echocardiographic examination. The ratio of the stroke volume index to the brachial pulse pressure (the difference between the systolic and the diastolic blood pressure) was used as an indirect measure of the total systemic arterial compliance. To estimate the global LV afterload, we calculated the valvulo-arterial impedance as the sum of the systolic arterial pressure and the mean transvalvular pressure gradient divided by the stroke volume index, as appropriate.[7]

Plasma brain natriuretic peptide

Venous blood samples for brain natriuretic peptide (BNP) were drawn before echocardiography, after 10 min of supine rest. Chilled EDTA tubes were centrifuged immediately at 4000 *g* (4°C) for 15 min. Separated plasma samples were processed by immuno-fluorescence assay (Beckman-Coulter, Biosite®). The inter- and intra-assay variations were 5 and 4%, respectively. The assay detection limit was 1 pg/mL.

Statistical analysis

Data are expressed as mean $\pm$ SD or percentages unless otherwise specified. Group comparisons were obtained for categorical variables with χ^2 test and for continuous variables with one-way analysis of variance (Statistica Software, version 7). Variables with a *P*-value <0.1 on univariable analysis were incorporated into the logistic regression model to identify determinants of low-flow AS or with an increased global afterload. A *P*-value <0.05 was considered to indicate statistical significance. Receiver–operator characteristic curves were generated to determine the cut-off values that best distinguished patients with low-flow AS or increased LV global afterload. To determine cofactors associated with global afterload, a stepwise multiple linear regression was performed.

Results

Characteristics of the patients

The population was predominantly of male gender ($n = 111$, 64%). By definition, the LV ejection fraction was preserved in all patients ($66.5 \pm 7.3\%$; range 55–83.5%). Among the 173 patients examined, 38 (22%) had a low stroke volume index (≤ 35 mL/m^2) and 49 (28%) an increased global LV afterload (≥ 5 mmHg mL/m^2). *Table 1* provides both the comparisons between patients with normal vs. low-flow AS, and between increase vs. non-increase low global LV afterload.

Table 1 Demographic, clinical, and echocardiographic characteristics of patients with low-flow and increased global left ventricular afterload

Variables	Global LV afterload <5 mmHg mL/m^2 (n = 124, 72%)	Global LV afterload ≥5 mmHg mL/m^2 (n = 49, 28%)	Normal flow (n = 135, 78%)	Low flow (n = 38, 22%)
Clinical variables				
Age, years	69.5 ± 9.7	69.7 ± 10.5	69.8 ± 9.5	68.3 ± 11.3
Male gender, n (%)	82 (66)	29 (59)	93 (69)	18 (47)*
Hypertension, n (%)	60 (48)	25 (51)	66 (49)	19 (50)
Diabetes mellitus, n (%)	17 (14)	11 (22)	21 (16)	7 (18)
Hypercholesterolemia, n (%)	61 (49)	16 (33)	65 (48)	12 (32)
Current smoking, n (%)	35 (28)	15 (31)	38 (28)	12 (32)
Serum creatinine, mg/L	8.5 ± 1.9	9.2 ± 1.9**	8.6 ± 1.9	8.9 ± 2.02
Systemic arterial haemodynamics				
Systolic arterial pressure, mmHg	138 ± 18	147 ± 19*	142 ± 18	139 ± 18
Diastolic arterial pressure, mmHg	76 ± 10	76 ± 11	76 ± 10	74 ± 10
Systemic arterial compliance, mL/mmHg/m^2	0.83 ± 0.28	0.49 ± 0.16**	0.80 ± 0.29	0.50 ± 0.13**
Aortic stenosis severity				
Indexed aortic valve area, cm^2/m^2	0.48 ± 0.09	0.41 ± 0.09	0.47 ± 0.09	0.43 ± 0.10*
Peak aortic velocity, m/s	4.29 ± 0.64	4.2 ± 0.58	4.3 ± 0.6	3.9 ± 0.57*
Mean pressure gradient, mmHg	46 ± 14	44 ± 13	47 ± 14	38 ± 12**
LV global afterload				
Valvulo-arterial impedance, mmHg mL/m^2	3.8 ± 0.65	6.01 ± 1.12**	3.9 ± 0.81	6.1 ± 1.3**
LV mass, g/m^2	93 ± 47	89 ± 37	91 ± 47	93 ± 38
Relative wall thickness, %	50 ± 12	52 ± 11	49 ± 12	54 ± 11*
LV systolic function				
LV end-diastolic volume, mL	98 ± 32	102 ± 34	100 ± 32	94 ± 33
LV end-systolic volume, mL	35 ± 19	36 ± 16	35 ± 18	35 ± 19
LV ejection fraction, %	66 ± 9	66 ± 7	66 ± 8.5	65 ± 8.7
Mid-wall fractional shortening, %	21 ± 5	19 ± 4**	22 ± 5	18 ± 3**
LV stroke volume index, mL/m^2	50 ± 11	33 ± 6**	49.6 ± 10.3	30.3 ± 4.3**
LV longitudinal strain, %	16 ± 3	14.8 ± 3.2**	16.2 ± 2.9	14.6 ± 3.3**
LV radial strain, %	38 ± 14	28 ± 10**	37.9 ± 13.9	26.3 ± 9.3**
LV circumferential strain, %	18 ± 5	15 ± 3**	18.4 ± 4.9	14.4 ± 3.04**
LV diastolic function				
LA area index, cm^2/m^2	11.7 ± 3.4	14.3 ± 3.09**	12.02 ± 3.34	14.01 ± 3.7*
Mitral E-wave, m/s	0.84 ± 0.27	0.80 ± 0.27	0.84 ± 0.28	0.79 ± 0.26
Mitral A-wave, m/s	0.94 ± 0.28	0.86 ± 0.29	0.94 ± 0.29	0.86 ± 0.28
Mitral E/A ratio	0.96 ± 0.53	1.02 ± 0.52	0.97 ± 0.54	0.98 ± 0.46
Peak Ea velocity, cm/s	8.5 ± 2.3	7.6 ± 2.14*	8.4 ± 2.4	7.6 ± 1.6*
Peak Aa velocity, cm/s	9.4 ± 1.97	7.95 ± 1.98**	9.1 ± 1.97	8.2 ± 2.2*
E/Ea, average annuli	11.3 ± 4.25	12.2 ± 5.7	11 ± 4.2	12.3 ± 6.2

Values are expressed as mean ± SD or n (%). Low flow: SVi ≤ 35 mL/m^2; Normal flow SVi > 35 mL/m^2.
BNP, brain natriuretic peptide; LV, left ventricular; LA, left atrial.
*$P < 0.05$ between groups.
**$P < 0.001$ between groups.

Factors associated with increased global left ventricular afterload

Patients with increased LV afterload had higher systolic blood pressure and left atrial area index and lower systemic arterial compliance, peak Ea velocity, and peak Aa velocity but similar LV ejection fraction (*Table 1*). The longitudinal, radial, and circumferential myocardial deformations were also markedly impaired in these patients (*Figures 1* and *2*). By multivariable logistic analysis (*Table 2*), the systemic arterial compliance ($P = 0.001$), the circumferential myocardial deformation ($P = 0.024$), and the left atrial area index ($P = 0.04$) were independently associated with increased global LV afterload. Using receiver–operator characteristic curve analysis, a systemic arterial compliance ≤0.61 mL/mmHg/m^2

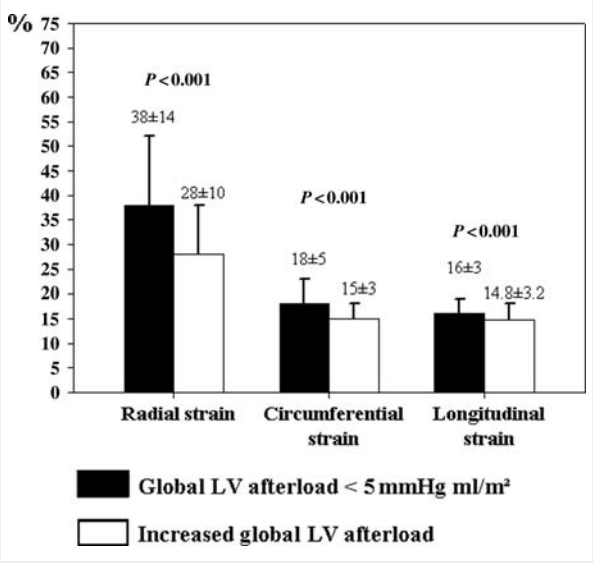

Figure 1 Bar graphs representing left ventricular (LV) strains (mean ± SD) according to the global LV afterload.

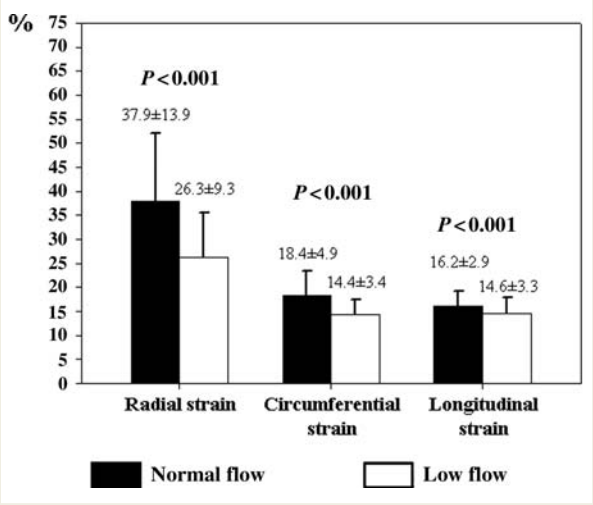

Figure 2 Bar graphs representing left ventricular (LV) strains (mean ± SD) according to the flow state.

(AUC = 0.92), a circumferential myocardial deformation ≤17% (AUC = 0.74), and a left atrial area index ≥13.6 cm^2/m^2 (AUC = 0.75) were the best cut-off values to identify patients with increased global afterload.

Impact of global left ventricular afterload on left ventricular function

Global LV afterload had a negative relationship with radial myocardial deformation ($r = -0.36$, $P < 0.001$), peak Ea ($r = -0.22$, $P = 0.0038$), and Aa ($r = -0.35$, $P < 0.001$) velocities, while it was positively correlated with longitudinal ($r = 0.26$, $P = 0.004$) and circumferential ($r = 0.37$, $P < 0.001$) myocardial deformations, left atrial area index ($r = 0.28$, $P < 0.001$), and E/Ea ($r = 0.22$, $P = 0.005$). By multiple linear regression analysis, after adjustment for cofactors, global LV afterload remained only associated with circumferential myocardial deformation ($P = 0.004$) and peak Ea velocity ($P = 0.027$) ($R^2 = 0.58$).

Determinants of low-flow aortic stenosis

Patients with low-flow AS were more frequently women, presented excessive global LV load and had lower systemic arterial compliance, peak aortic velocity, and mean transaortic pressure gradient. The valve area was more severely reduced in these patients. Both LV systolic and diastolic function were impaired in this subgroup of patients despite similar LV ejection fraction (*Figure 3*). The longitudinal, radial, and circumferential myocardial deformations were markedly reduced in the low-flow AS group. Finally, in these patients, the left atrial area was increased, whereas the early and late diastolic annular velocities were significantly reduced. By multivariable logistic analysis (*Table 2*), four variables emerged as independently associated with low-flow AS: peak Ea velocity ($P = 0.01$), left atrial area index ($P = 0.017$), global LV afterload ($P = 0.024$), and circumferential myocardial deformation ($P = 0.04$). Using receiver–operator characteristic curve analysis, a peak Ea velocity ≤7.8 (AUC = 0.60), a left atrial area index ≥13.9 cm^2/m^2 (AUC = 0.71), a global LV afterload ≥4.8 mmHg/mL/m^2 (AUC = 0.93), and a circumferential myocardial deformation ≤18% (AUC = 0.78) were identified as the best cut-off values to identify patients with a low-flow AS. To note, when the circumferential myocardial deformation was not included in the multivariable model, the radial deformation emerged as independently associated with a low-flow state.

Brain natriuretic peptide, low flow, and global afterload

Patients with increased global LV afterload (184 ± 273 vs. 55.7 ± 56 pg/mL, $P < 0.001$) and/or low-flow state (181 ± 295 vs. 69 ± 85 pg/mL, $P < 0.001$) had higher BNP release ($P < 0.001$) as compared with those with a global LV afterload <5 mmHg mL/m^2 or a normal flow. Using receiver–operator characteristic curve analysis, a BNP release ≥61 pg/mL was identified as the best cut-off value to identify patients with an increased global LV afterload (AUC = 0.80) or a low-flow AS (AUC = 0.72). Patients with both a low-flow state and an increased global LV afterload had higher BNP release than the others (209 ± 318 vs. 68 ± 83 pg/mL, $P < 0.001$).

Discussion

The results of the present study can be summarized as follows: (1) 28% of asymptomatic patients with severe AS have a significant increase in global LV afterload; (2) increased global LV afterload negatively affects the LV myocardial function, predominantly the short-axis myocardial deformation, in spite of preserved LV ejection fraction; (3) high global LV afterload is prevalent in patients with low-flow AS particularly when the systemic arterial compliance is reduced; and (4) the low-flow state relates predominantly

Table 2 Multivariable analysis

Variables	Increased global LV afterload		Low flow	
	P-value	OR (95% CI)	*P*-value	OR (95% CI)
Male gender	–	–	0.72	0.42 (0.01–45)
Serum creatinine	0.78	1.06 (0.65–1.74)	–	–
Systolic arterial pressure	0.18	1.03 (0.99–1.05)	–	–
Systemic arterial compliance	0.001	0.2 (0.1–0.4)	0.21	0.022 (0.05–9.25)
Indexed aortic valve area	0.18	2.4 (1.01–5.5)	0.87	6.2 (0.08–38)
Peak aortic velocity	–	–	0.54	5.8 (0.02–51.2)
Mean pressure gradient	–	–	0.80	1.03 (0.79–1.34)
Valvulo-arterial impedance	–	–	0.024	2.2 (1.3–3.5)
Relative wall thickness	–	–	0.94	1.2 (0.02–34)
Mid-wall fractional shortening	0.15	0.92 (0.82–1.03)	0.27	1.07 (0.95–1.2)
LV longitudinal strain	0.27	1.15 (0.89–1.49)	0.62	1.15 (0.65–2.03)
LV radial strain	0.69	1.01 (0.95–1.09)	0.69	1.03 (0.87–1.2)
LV circumferential strain	0.024	1.22 (1.01–1.48)	0.04	1.88 (1.01–3.5)
LA area index	0.04	1.11 (1.01–1.25)	0.017	1.74 (1.1–2.7)
Mitral A-wave	0.10	0.37 (0.035–3.86)	0.99	1.03 (0.01–326)
Peak Ea velocity	0.69	0.94 (0.68–1.3)	0.01	0.14 (0.03–0.62)
Peak Aa velocity	0.50	0.89 (0.64–1.25)	0.93	1.04 (0.4–2.62)

LV, left ventricular; OR, odds ratio, CI, confidence interval.
Increased global LV load $\geq$5 mmHg mL/m^2. Low flow: SVi $\leq$ 35 mL/m^2.

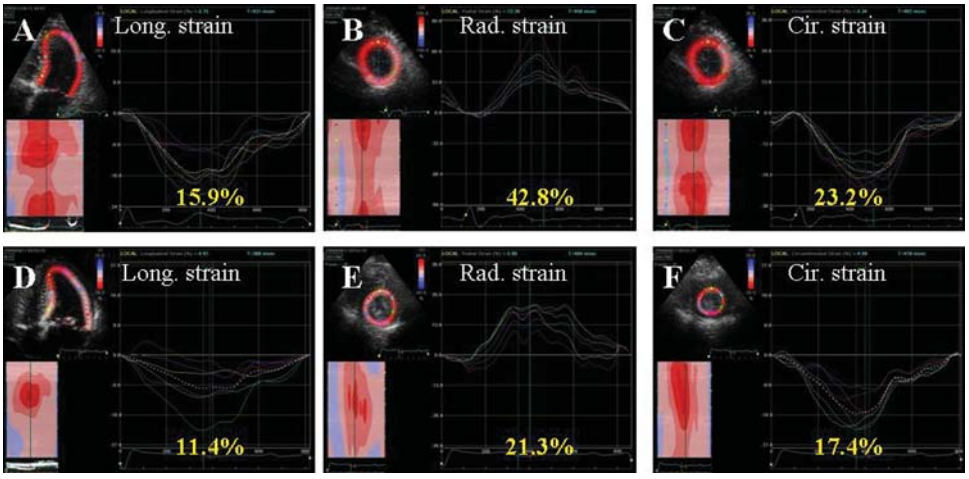

Figure 3 (*A*–*C*) myocardial strains in a patient with a global left ventricular afterload <5 mmHg mL/m^2; (*D*–*E*): myocardial strains in a patient with increased global left ventricular afterload. Long, longitudinal; Rad, radial; Cir, circumferential.

to both an impaired LV diastolic function and a reduced short-axis function.

Impact of global afterload on left ventricular function

In AS, the increase in LV afterload does not only result from outflow obstruction but also from reduced systemic arterial compliance.[18] When the prolonged high LV global afterload exceeds the limit of LV compensatory mechanisms, an intrinsic impairment of myocardial function can occur and the patient outcome can be compromised.[14] However, despite the presence of significant myocardial dysfunction, the LV ejection fraction is commonly normal in patients with AS. The LV ejection fraction relates to the relative contribution of the short- and long-axis contraction which can be reliably quantitated by the measurement of myocardial deformation using the speckle-tracking analysis. The longitudinal function is governed by the subendocardial myocardial fibres (aligned longitudinally), whereas the short-axis function depends on

mid-wall myocardial fibres (aligned circumferentially). As the subendocardial fibres are more sensitive to microvascular ischaemia (subendocardial blood flow maldistribution related to LV hypertrophy and increased wall stress) and fibrosis, the longitudinal function is the first to be altered in AS.[8,19] The reduced subendocardial function is initially compounded by the preserved short-axis function. In these patients, abnormalities in LV long-axis function have been shown to be associated with impaired exercise tolerance, changes in symptomatic status, and poor prognosis.[8,12,20] In the advanced stage, as the LV becomes more hypertrophied and remodelled, the LV ejection fraction still remains in the normal range despite the progressive decrease in short-axis function.[21] The data of the present study are in line with these considerations. For the first time, we have demonstrated that the three components of myocardial deformation—longitudinal, radial, and circumferential—are significantly impaired in patients with high global LV afterload. However, the longstanding increased in global LV afterload particularly affects the short-axis function related to the contraction of circumferential myocardial fibres and is associated with significant BNP release. Furthermore, the decrease in circumferential function translates to an advanced disease process and could identify patients at higher risk, particularly when it is associated with a low-flow state. In these patients, it should be mentioned that the increased apical rotation and LV twist probably compensates the decreased short-axis function to maintain normal LV ejection fraction.[22] The prognostic impact of short-axis dysfunction needs to be addressed. To note, at the end of the disease process, the global LV systolic performance may decrease and symptoms can occur. By histology, myocardial cell death and fibrosis can be observed in this stage and may continue even after successful aortic valve replacement.[23]

Low-flow aortic stenosis

Low-flow AS with preserved LV ejection fraction is a challenging clinical entity that has been recently highlighted by the group of Pibarot and Dumesnil.[18] This 'paradoxical' low-flow AS is associated with more pronounced LV concentric remodelling, smaller LV cavity, increased global LV afterload, and reduced mid-wall shortening.[6,7] The present study confirms and extends these previous results by showing that this low-flow state relates predominantly to both an impaired LV relaxation—decrease in peak Ea velocity—and a reduced LV short-axis myocardial deformation as assessed by 2D speckle-tracking echocardiography. In these patients, the ability of the LV to adequately fill under normal pressures is thus altered and the LV diastolic pressure increases producing increased left atrial wall tension and myocyte stretch inducing myolysis, fibrosis, apoptosis, and in turn atrial enlargement.[24] In patients with low-flow AS, the increase in left atrial size reflects thus the chronicity of the diastolic burden. In the advanced stage of the disease, the decrease in short-axis function contributes to the progressive reduction in forward stroke volume and finally triggers BNP release. These structural and functional changes may precede symptoms development and predict the outcome.[16,25]

Limitations

This study has some limitations. Our results pertain only to patients with asymptomatic AS and preserved LV ejection fraction. The presence of coronary risk factors could affect our data. However, their incidences were similar in patients with and without low-flow state or high global LV afterload. Although mid-wall shortening can be used to unmask intrinsic myocardial dysfunction in patients with AS, this index is affected by its moderate accuracy. On the contrary, 2D strain imaging overcomes such limitations. However, despite its advantages, the success of 2D speckle tracking depends on the quality of grey-scale images and frame rate which were both high.

Conclusions

In asymptomatic patients with severe AS, LV ejection fraction markedly underestimates the extent of myocardial systolic impairment in presence of LV hypertrophy. Intrinsic myocardial dysfunction is particularly common in patients with increased global LV afterload, and especially in the subset of patients with low-flow AS. The low-flow state results mostly from a reduced circumferential function. Assessing regional LV myocardial function in patients with preserved LV ejection fraction may help identifying patients who might benefit from early elective aortic valve surgery.

Conflict of interest: none declared.

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