

# Impact of aortic stenosis on longitudinal myocardial deformation during exercise

Erwan Donal<sup>1\*</sup>, Christophe Thebault<sup>1</sup>, Kim O'Connor<sup>2</sup>, David Veillard<sup>1</sup>,  
Monica Rosca<sup>2</sup>, Luc Pierard<sup>2</sup>, and Patrizio Lancellotti<sup>2</sup>

<sup>1</sup>Service de Cardiologie et de Maladies Vasculaires et CIC-IT 804, LTSI INSERM U 642, Centre Cardio Pneumologique, CHU Pontchaillou 2 rue Henri Le Guilloux, 35033 Rennes Cedex 9, France; and <sup>2</sup>Department of Cardiology, Valvular Heart Disease Clinic, University of Liège, CHU Sart Tilman, Liège, Belgium

Received 1 November 2010; accepted after revision 13 December 2010; online publish-ahead-of-print 17 January 2011

In aortic stenosis (AS), left ventricular (LV) adaptation to exercise has poorly been examined. Changes in LV ejection fraction may lack accuracy in identifying the presence of intrinsic myocardial impairment.

## Aims

We sought to determine the impact of aortic stenosis (AS) on left ventricular (LV) longitudinal function at exercise in a series of asymptomatic patients with AS and preserved LV ejection fraction.

## Methods and results

Long-axis function was assessed at rest and at exercise by using 2D speckle tracking of myocardial deformation in 207 AS patients (aortic valve area  $0.87 \pm 0.19$  cm<sup>2</sup>) and 43 aged-matched control subjects. When compared with control subjects, patients with AS have reduced longitudinal myocardial function at rest ( $-20.2 \pm 2.7$  vs.  $-15.4 \pm 4.0\%$ ) and at peak exercise ( $-25.0 \pm 3.7$  vs.  $-16.5 \pm 4.9\%$ ) ( $P < 0.0001$  for both). Exercise changes in global longitudinal strain were correlated with changes in LV ejection in controls but not in patients with AS. Changes in LV global longitudinal strain during test were lower in AS patients with an abnormal response to exercise ( $-0.5 \pm 2.7$  vs.  $-1.5 \pm 2.8\%$ ,  $P = 0.001$ ). In multivariate analysis, a lower global longitudinal strain at rest ( $P = 0.04$ ), a higher increase in mean trans-valvular pressure gradient ( $P < 0.001$ ) at exercise, and smaller exercise-induced changes in global longitudinal strain ( $P < 0.001$ ) were associated with an abnormal exercise test.

## Conclusion

In AS, subnormal LV function can be reliably identified by 2D strain imaging at rest and during a sub-maximal exercise. That sensitive measure of LV systolic function is depressed in AS and even more in patients having the most severe AS.

## Keywords

Aortic valve stenosis • Exercise echocardiography • Strain • Left ventricle

## Introduction

The management of asymptomatic patients with severe aortic stenosis (AS) remains controversial.<sup>1–3</sup> Currently, surgery is indicated when the left ventricular (LV) ejection fraction (<50%) is reduced or when symptoms (class I for ESC, IIb for AHA:ACC) are unmasked during an exercise test.<sup>4–6</sup> However, it is well known that the LV ejection fraction is a crude estimate of LV function.<sup>7,8</sup> In asymptomatic AS, the LV ejection fraction may remain normal for years despite the occurrence of deep structural (i.e. LV remodelling) and functional (i.e. reduced long-axis function) changes that may affect the clinical outcome.<sup>9,10</sup> Understanding the pathways of progression from compensatory

hypertrophy to heart failure may bring important information for better decision-making.<sup>11–16</sup>

Long-axis function which is governed by the subendocardial myocardial fibres can be reliably quantified by the measurement of myocardial deformation using the 2D-speckle tracking imaging.<sup>13</sup> In AS, subendocardial blood flow misdistribution related to LV hypertrophy and increased wall stress and the changes in myocyte's architecture contribute to subendocardial dysfunction.<sup>14–16</sup>

Decline in long-axis function may limit the adaptive response of the LV to exercise and contribute to limited exercise tolerance.<sup>17</sup> Recently, it has been shown that small exercise changes in the LV ejection fraction may identify a subset of patients with AS who are at

\* Corresponding author. Tel: +33 2 99 28 25 25; fax: +33 2 99 28 25 11, Email: erwan.donal@chu-rennes.fr

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increased risk of events.<sup>18,19</sup> Moreover, the acute exercise changes in LV load—depending on the residual valve and vascular compliance—and the limited coronary flow reserve may create or aggravate the subendocardial dysfunction resulting in afterload mismatch. The limited contractile recruitment at exercise could thus identify a subset of patients with asymptomatic AS who have a subclinical haemodynamically significant valvular obstruction.<sup>20</sup> The consequence of AS on exercise-induced changes in LV long-axis function has, however, never been examined. This study was thus undertaken to evaluate the impact of AS on LV long-axis function by using 2D speckle tracking of myocardial deformation in a series of asymptomatic patients with AS and preserved LV ejection fraction.

## Methods

### Population

From October 2005 to July 2006, a total of 207 consecutive patients with significant AS were enrolled in this study. No patient reported any symptom despite a careful questioning. All patients met the following specific criteria: moderate (1.2–1 cm<sup>2</sup>) to severe (<1 cm<sup>2</sup> or 0.6 cm<sup>2</sup>/m<sup>2</sup>) AS defined by the aortic valve area ( $\leq 1.2$  cm<sup>2</sup>), normal LV ejection fraction ( $\geq 50\%$ ) as calculated by two-dimensional echocardiography, no more than mild associated cardiac valve lesion, sinus rhythm, capability to perform an exercise test, and good images quality. No patient had a history of coronary artery disease (prior to the study or in the immediate follow-up) and suboptimal quality of speckle tracking or tissue Doppler reconstruction. Eleven patients were excluded for insufficient image quality at rest and over the exercise (of the 2D strain especially). For them, it was not possible to perform the speckle tracking analysis in apical views.

During the same period, 43 patients matched for age and sex who were examined using the same exercise protocol and with a negative test served as the control group. The images and the measurements were identical to the AS group of patients except that the aortic valve area was not calculated as no trans-valvular pressure gradient was present by definition in these control subjects. These controls were having one or less cardiovascular risk factor and were proposed

to participate to the study. None of them had any history of any heart disease and were just pleased to get a stress test to insure that their heart function was normal. All patients gave informed consent and the study was approved by the hospital ethics committee. None of these controls had any cardiovascular disease and none of them had more than one cardiovascular risk factor.

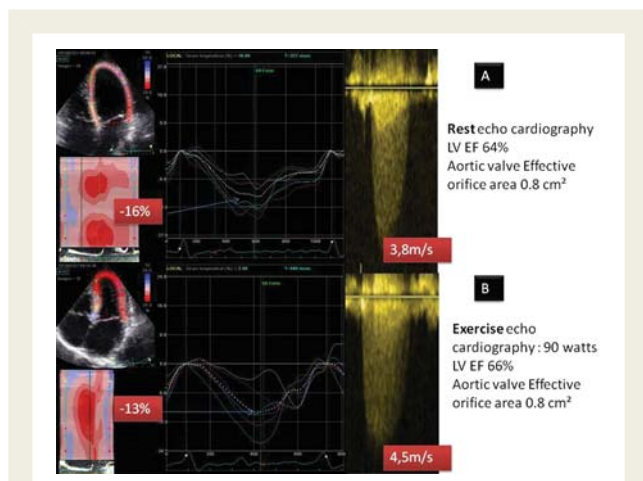
### Exercise testing

Following clinical examination, arterial blood pressure measurement (Dinamap Procure Auscultatory 100), 12-lead electrocardiogram and resting transthoracic echocardiography (Vivid 7, General Electric Healthcare, Horten, Norway), the patients underwent a standard exercise echocardiography on a tilting table with electromagnetic cycle ergometer (Ergometrics). Exercise testing was started at an initial workload of 30 W, the workload being increased by increments of 20 W every 2 min, depending on physical training. The pedalling rate was  $\geq 60$  r.p.m., the electrocardiogram was recorded continuously and blood pressure was measured every 2 min both on exercise and during recovery from exercise. Exercise test was interrupted promptly when age-related maximum heart rate was reached or in case of typical chest pain, limiting breathlessness, dizziness, muscular exhaustion, severe hypertension (systolic blood pressure  $\geq 250$  mmHg), or significant ventricular arrhythmia. The test was considered abnormal if the patient presented  $\geq 1$  of the following criteria: angina, evidence of shortness of breath at low workload level (<50 W), dizziness, syncope, or near-syncope,  $\geq 2$  mm ST segment depression in comparison with baseline levels, rise in systolic blood during exercise <20 mm Hg or a fall in blood pressure and complex ventricular arrhythmias.

### Echocardiography

Echocardiographic examinations were performed using a Vivid 7 imaging device (GE Healthcare, Horten, Norway) and stored on a workstation for off-line analysis (EchoPAC, GE Healthcare, Horten, Norway). All echocardiographic measurements were obtained at rest and during exercise. The exercise data were all recorded during the exercise at a submaximal stage (heart rate stable between 100 and 120 bpm; imperatively <125/min). The exercise echocardiographic data were recorded using exactly the same protocol in controls and patients. Patients were stable during this submaximal exercise; it was thus feasible to get good images in every patient at that stage. For each measurement, at least two cardiac cycles were averaged. Left ventricular diameters and parietal thicknesses were assessed by time-motion analysis; aortic valve area was calculated using the continuity equation; mean and maximum transaortic gradients were obtained with continuous wave Doppler. Left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured by the bi-apical Simpson disk method. Peak E-wave and A-wave velocities of the mitral inflow were measured using pulsed wave Doppler. By using pulsed wave tissue Doppler, peak velocities during systole, early (e') diastole obtained at the level of septal and lateral mitral annulus were measured separately and then averaged. The  $E/e'$  ratio was also calculated.

Strain measurement was based on the speckle tracking approach: To complete the analysis of the LV systolic function, the global longitudinal myocardial deformation was evaluated from standard two-dimensional images (frame rates  $\geq 70$  s<sup>-1</sup>) using the 2D strain software.<sup>10</sup> In brief, by tracing the endocardial borders on an end-systolic frame, the software automatically tracked the contour on the subsequent frames. Adequate tracking was verified in real-time and was manually corrected, if necessary. For every patients, the image quality was good enough for the borders tracking for each segment at rest and during the exercise



**Figure 1** Two examples of changes in left ventricular function during exercise in a patient with an aortic stenosis. (A) At rest, the global longitudinal strain is—16%. (B) During an exercise, the global longitudinal strain is—13%.

(never obtained at a heart rate >125 bpm). The global longitudinal deformation—strain—was the average of the segment strains from the apical views (apical 4, 3, and 2 chambers) (Figure 1). The image acquisition frame rate was (60–90 Hz) (mean value 75 Hz). We used the same data acquisition and treatment as in Lancellotti et al.<sup>21</sup>

The readers of the echocardiographies were obviously able to recognize patients with and without any AS. But, they were blinded to the result of the exercise stress test. They did not have any clinical, ECG, or blood pressure data when reading the echocardiographic files.

## Statistical analysis

Data are expressed as mean  $\pm$  SD or percentages unless otherwise specified. Data were analysed with parametric statistics after mathematical confirmation of normal distribution with Shapiro-Wilk tests. Group comparisons for categorical variables were obtained with  $\chi^2$  test and for continuous variables with one-way analysis of variance completed by a Bonferroni test when necessary. To detect independent predictors of a positive exercise test, a logistic multivariate analysis was performed. Significant variables were included in the statistical model. A value of  $P < 0.05$  was considered significant. Linear regression analysis and the Pearson correlation coefficient were applied to study the correlations between changes in longitudinal myocardial deformation ( $\Delta$  global longitudinal strain during – global longitudinal strain at rest) and other echo data. Receiver-operator characteristic curve analysis was performed to determine the cut-off values that best distinguished the issue. The statistical analysis was performed on SAS® version 9.1 (SAS Institute, Inc., Cary, NC, USA).

## Results

### Baseline and exercise characteristics in the study population

The AS patients were  $67 \pm 11$  years old and the body surface area was  $1.8 \pm 0.2$  m<sup>2</sup>. It was not significantly different in the control group aged  $68 \pm 11$  and having a body surface area  $1.8 \pm 0.1$  cm<sup>2</sup>.

The sex ratio was also comparable between groups: 66% (patients) and 71% (controls) were male. By definition, the prevalence of cardiovascular risk factors was different between groups. Controls had one or less ongoing risk factor. In the AS population, the prevalence of hypertension was 54%, obesity 32%; hypercholesterolaemia 47%; diabetes 18%; left bundle branch block 17%. The LV mass was  $167 \pm 78$  g/m<sup>2</sup> ( $304 \pm 147$  g) and the QRS-duration  $101 \pm 18$  ms.

By definition, aortic valve area was reduced in AS patients (Table 1). Although the LV ejection fraction was similar to controls ( $65.5 \pm 9$  vs.  $64 \pm 6\%$ ,  $P = 0.24$ ), the LV volumes were greater in patients with AS. Moreover, the LV long-axis function—both systolic (peak systolic velocity, global strain) and diastolic ( $e'$ )—was significantly reduced in AS when compared with controls ( $P < 0.0001$ ). Higher  $E/e'$  was also found in AS. At baseline, the systolic blood pressure was lower in controls. During test, although significant, the increase in heart rate ( $62 \pm 16$  vs.  $46 \pm 18$  bpm) and systolic blood pressure ( $48 \pm 20$  vs.  $25 \pm 17$  mmHg) were lower in AS ( $P < 0.0001$ , respectively). Overall, the long-axis function improved during exercise in both groups. However, the increment in peak systolic velocity ( $8 \pm 2.6$  vs.  $11.6 \pm 1.4$  cm/s) and in global longitudinal strain ( $-16.5 \pm 4.9$  vs.  $-25 \pm 3.7\%$ ) was weaker in AS even more when the exercise stress test was judged positive

( $P < 0.0001$ , respectively) (Figure 2). At peak test, the  $e'$  was lower, whereas the  $E/e'$  was higher in AS ( $P < 0.0001$ ).

### Abnormal response to exercise and left ventricular function in aortic stenosis

Exercise testing was abnormal (dyspnoea, angina, fall or rise in systolic blood during exercise  $< 20$  mmHg,  $\geq 2$  mm ST segment depression) in 69 (34%) AS-patients (Table 1). At rest, although the LV ejection fraction was similar between groups, the global longitudinal strain but not the peak systolic velocity was significantly reduced in patients with an abnormal test ( $P < 0.01$ ). In these patients, the  $e'$  was reduced, the  $E/e'$  and the aortic pressure gradients were increased. At peak exercise, the increase in heart rate and in systolic blood pressure tended to be lower in patients with a positive test ( $P = \text{NS}$ ). Although the duration of the test was similar, the maximal workload was weaker in these patients. The LV ejection fraction and volumes at peak test did not differ between groups. Conversely, the increase in long-axis function (global longitudinal strain:  $-0.5 \pm 2.7$  vs.  $-1.5 \pm 2.8\%$ ,  $P = 0.001$ ) was greater in patients with a normal test. At peak test, the impairment in LV diastolic function observed at rest was maintained. The  $E/e'$  increased as a result of a higher increase in mitral E wave than in  $e'$ . The aortic valve area was lower in this group whereas the aortic pressure gradients were higher ( $P < 0.0001$ ). In multivariate analysis, parameters associated with an abnormal response to exercise were: a lower global longitudinal strain at rest ( $P = 0.04$ , OR 0.91), a higher increase in mean transvalvular pressure gradient ( $P < 0.001$ , OR 1.09) at exercise, and smaller exercise-induced changes in global longitudinal strain ( $P < 0.001$ , OR 0.54). Using receiver-operator characteristic curve analysis, a global longitudinal strain at rest  $< 15.5\%$  (AUC 0.58) and its change by less than  $-1.4\%$  at exercise (AUC 0.77, sensitivity 89.8%, specificity 85.7%), an increase in mean transvalvular pressure gradient  $\geq 14$  mmHg (AUC 0.72) were identified as the best cut-off values associated with an abnormal response to exercise. According to changes in global longitudinal strain and in mean aortic pressure gradient, four categories of patients can be identified (Figure 3).

### Correlations with exercise-induced changes in left ventricular longitudinal function

Exercise changes in global longitudinal strain ( $\Delta$  between global longitudinal strain during exercise and at rest) were correlated with changes in the LV ejection fraction in controls ( $R = 0.45$ ,  $P = 0.009$ ). That was not observed in AS patients. Longitudinal strain and especially its modification during exercise did not correlate with LV EF in the AS patients as opposed to the correlation observed in controls (Table 2). The aortic pressure gradients, at rest and during an exercise, were not correlated with changes in long-axis function during exercise. The LV mass did not correlate with the long-axis function as assessed by global longitudinal strain.

### Reproducibility of measurements

The reproducibility of measurements was tested by random selection of 10 patients (Table 3). There was good intra observer agreement for global longitudinal strain at rest ( $r = 0.91$ ) and at peak

**Table 1** Patients and controls characteristics at rest and at exercise

Variables	Controls <i>n</i> = 43	AS: normal test <i>n</i> = 136	AS: abnormal test <i>n</i> = 69	ANNOVA <i>P</i> -value
Rest				
Heart rate (bpm)	73 ± 12	71 ± 12	72 ± 11	0.54
Systolic arterial pressure (mmHg)	133 ± 14	142 ± 20*	151 ± 24**	0.001
LV mass (g/m <sup>2</sup> )	—	101 ± 45	106 ± 50	0.16
LV end-diastolic volume (mL)	75 ± 27	103 ± 34*	102 ± 36**	<0.0001
LV end-systolic volume (mL)	27 ± 12	37.5 ± 20.4*	36.9 ± 21.3**	0.027
LV ejection fraction (%)	64 ± 6	65.5 ± 8.5	65.9 ± 10	0.17
Peak systolic velocity (cm/s)	7.7 ± 1.2	6.2 ± 2.4*	6.1 ± 2.1**	0.008
Global longitudinal strain (%)	-20.2 ± 2.7	-15.9 ± 2.9*	-14.9 ± 3.6*****	<0.0001
Mitral E velocity (m/s)	0.8 ± 0.2	0.8 ± 0.25	0.88 ± 0.29***	0.1
Mitral e' velocity	9.3 ± 2.6	8.2 ± 2.5*	7.3 ± 2.2*****	<0.0001
E/e' ratio	8.9 ± 2.8	10 ± 3.5	13 ± 6*****	0.002
Aortic valve area (cm <sup>2</sup> )	—	0.89 ± 0.20	0.81 ± 0.17***	0.005
Aortic peak pressure gradient (mmHg)	—	69 ± 22	81 ± 26***	0.002
Aortic mean pressure gradient (mmHg)	—	42 ± 15	49 ± 16***	0.002
Exercise				
Duration of the test (min)	9.3 ± 1.9	8.9 ± 2.8	8.7 ± 3.0	0.57
Maximal workload (W)	92 ± 22	96 ± 26	86 ± 30***	0.03
Heart rate (bpm)	131 ± 11	119 ± 16*	116 ± 18**	<0.0001
Systolic arterial pressure (mmHg)	180 ± 18	175 ± 22	169 ± 26**	0.11
LV end-diastolic volume (mL)	74 ± 27	104 ± 38*	99 ± 35**	<0.0001
LV end-systolic volume (mL)	20 ± 14	36 ± 19*	37 ± 22**	0.03
LV ejection fraction (%)	74 ± 8	67 ± 9*	64 ± 11**	<0.0001
Peak systolic velocity (cm/s)	7.7 ± 1.2	7.9 ± 2.8*	6.8 ± 1.9*****	<0.0001
Global longitudinal strain (%)	-25 ± 3.7	-17.4 ± 3.9*	-14.9 ± 6.2*****	<0.0001
Mitral E velocity (m/s)	1.25 ± 0.3	1.25 ± 0.36	1.4 ± 0.4***	0.028
Mitral e' velocity	12.7 ± 2.5	11.5 ± 4.5	9.8 ± 3.6*****	0.0065
E/e' ratio	10.1 ± 2.3	12.1 ± 5.4	16.3 ± 7.9*****	<0.0001
Aortic valve area (cm <sup>2</sup> )	—	0.99 ± 0.29	0.86 ± 0.23***	0.0005
Aortic peak pressure gradient (mmHg)	—	69 ± 22	90 ± 26***	0.0017
Aortic mean pressure gradient (mmHg)	—	43 ± 15	61 ± 17***	0.003

AS, aortic stenosis; LV, left ventricular.

\**P* < 0.05 normal test vs. controls.

\*\**P* < 0.05 abnormal test vs. controls.

\*\*\**P* < 0.05 abnormal test vs. normal test.

exercise ( $r = 0.86$ ). The inter observer regression coefficient was 0.88 for global longitudinal strain at rest and 0.87 when exercising (submaximal test). Low coefficients of variation were found for global strain at rest (8%) and at peak exercise (11%). No difference between walls was observed according to the robustness of the measurements. The inter- and intra- observer regression coefficients for peak systolic velocity obtained by tissue Doppler reconstruction have been reported as good by our group.<sup>21,22</sup>

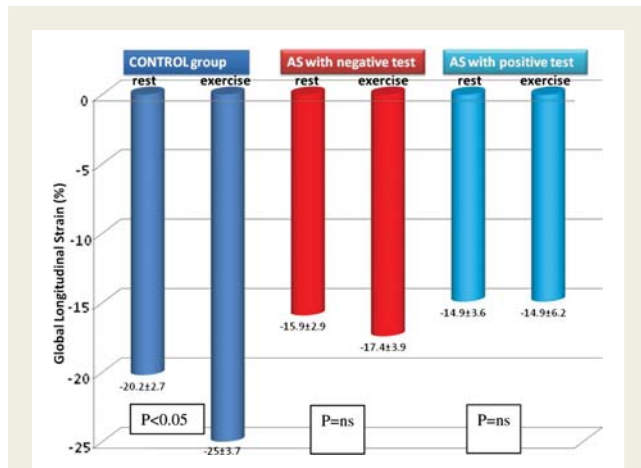
## Discussion

The present study shows that in patients with moderate to severe AS, long-axis contraction of the LV can be reliably examined at rest and during exercise by 2D strain imaging. When compared with normal subjects, patients with AS have reduced longitudinal myocardial function and limited contractile reserve during exercise, in

spite of preserved LV ejection fraction at rest. The LV contractile reserve during exercise was predominantly altered in patients with AS and abnormal exercise test.

## Myocardial function and pressure overload

In AS, when the chronically increased 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. However, despite the presence of significant myocardial dysfunction, the LV ejection fraction is commonly normal in patients with AS. The LV ejection fraction is influenced by both intrinsic myocardial function and LV cavity geometry.<sup>7,8</sup> In AS, the greater contribution of wall thickening, a result of LV hypertrophy, to the LV ejection fraction can thus mask subtle degrees of LV dysfunction.<sup>23,24</sup>



**Figure 2** Global longitudinal strain obtained at rest and at exercise in aortic stenosis and controls.

<p><b>Low <math>\Delta</math>MPG + No CR</b></p> <p><math>\Delta</math>MPG &lt; 14 mmHg  <math>\Delta</math>GLS &lt; -1.4%                      LV EF 66±12%  <math>\Delta</math>LV EF -0.5±11%                      AVA 0.88±0.20 cm<sup>2</sup>  <math>\Delta</math>AVA 0.10±0.19 cm<sup>2</sup>                      GLS -15±3.3%                      N=50 (24%)</p> <p>Abnormal Ex test = 18 (36%)</p>	<p><b>Low <math>\Delta</math>MPG + CR</b></p> <p><math>\Delta</math>MPG &lt; 14 mmHg  <math>\Delta</math>GLS &gt; -1.4%                      LV EF 64±7%  <math>\Delta</math>LV EF 2.1±9.3%                      AVA 0.89±0.20 cm<sup>2</sup>  <math>\Delta</math>AVA 0.11±0.19 cm<sup>2</sup>                      GLS -15.6±2.9%                      N=58 (28%)</p> <p>Abnormal Ex test = 8 (14%)</p>
<p><b>High <math>\Delta</math>MPG + CR</b></p> <p><math>\Delta</math>MPG &gt; 14 mmHg  <math>\Delta</math>GLS &gt; -1.4%                      LV EF 66±8.8%  <math>\Delta</math>LV EF 0.2±9.1%                      AVA 0.87±0.18 cm<sup>2</sup>  <math>\Delta</math>AVA 0.02±0.14 cm<sup>2</sup>                      GLS -16.1±2.8%                      N=49 (23.6%)</p> <p>Abnormal Ex test = 15 (31%)</p>	<p><b>High <math>\Delta</math>MPG + No CR</b></p> <p><math>\Delta</math>MPG &gt; 14 mmHg  <math>\Delta</math>GLS &lt; -1.4%                      LV EF 67±8%  <math>\Delta</math>LV EF -0.8±8.8%                      AVA 0.82±0.21 cm<sup>2</sup>  <math>\Delta</math>AVA 0.06±0.11 cm<sup>2</sup>                      GLS -15.2±3.8%                      N=50 (24%)</p> <p>Abnormal Ex test = 27 (54%)</p>

**Figure 3** According to changes in global longitudinal strain and in mean transaortic pressure gradient, four categories of patients can be identified. MPG, mean trans aortique pressure gradient (mmHg); CR, contractile reserve; GLS, global longitudinal strain; AVA, aortic valve area; LV EF, left ventricular ejection fraction.

Subclinical LV dysfunction is classically detected by a decrease in longitudinal myocardial function which can be reliably quantified by the measurement of myocardial deformation using the 2D-speckle tracking analysis.<sup>10,25</sup> The present study confirms that long-axis function was significantly impaired in patients with AS, although the LV ejection fraction was within normal ranges. The reduction in longitudinal myocardial function was even more pronounced in patients with an abnormal response to exercise. But no relationship between the increase in pressure gradient across the aortic valve and the global longitudinal function was found. Very probably, in asymptomatic AS patients at rest and during exercise, these two parameters are highlighting different things that we might have to take together for the decision-making in regard to the treatment.

Also, no correlation was observed between the degree of LV hypertrophy and the global longitudinal strain (as a measurement of the longitudinal LV function). That is different to Cramariuc *et al.* results. It has also been proposed that increased LV mass index reflect in abnormal longitudinal strain.<sup>26</sup> We believe that that relationship between mass and longitudinal function is more complex and more impact by the composition of the tissue than by the mass as a whole.

The longitudinal function is governed by the subendocardial myocardial fibres which are aligned longitudinally and more sensitive to microvascular ischaemia.<sup>16,27</sup> In AS, the selective impairment in long-axis function is related to the increase in subendocardial stress and associated reduction in coronary flow reserve (subendocardial ischaemia). Both phenomena lead to progressive myocardial fibrosis that complementary participates to reduce long-axis function. In asymptomatic patients with AS, reduced subendocardial function has been shown to be associated with impaired exercise tolerance, changes in symptomatic status during follow-up and adverse outcomes.<sup>10</sup> For the first time, we showed that AS patients with an abnormal response to exercise had higher degree of subendocardial dysfunction when exercising. This could reflect the presence of severely impaired coronary flow reserve and extensive myocardial fibrosis. In some patients, subendocardial function may recover after aortic valve surgery.<sup>27,28</sup> However, when the reactive subendocardial fibrosis to pressure overload and ischaemia becomes severely disproportionate, irreversible myocardial damage may occur. Detection of intrinsic myocardial dysfunction in AS patients with preserved LV ejection fraction could thus be of help for risk assessment.

### Impact of aortic stenosis on left ventricular functional reserve during exercise

In AS, exercise testing could be performed safely and is of prognostic value.<sup>29,30</sup> However, current AHA/ACC and ESC guidelines are discrepant regarding the level of evidence for referring asymptomatic patients with severe AS to surgery according to exercise test results.<sup>4,6</sup> Indeed, shortness of breath when exercising is not rare in non-trained elderly subjects. We and others have previously reported that both limited valve compliance and the absence of contractile reserve characterized asymptomatic AS patients with an abnormal exercise test.<sup>18,29,31</sup> Monitoring the LV response during exercise by echocardiography can thus offer valuable objective and additional information to that provided by conventional exercise testing.<sup>31</sup>

The present observation confirms that the acute changes in LV load may alter the LV adaptation during exercise and promote symptoms onset. However, changes in pressure gradients and in LV function are not uniform. Indeed, the heart may adapt successfully, by recruiting LV contractile reserve, to the increased afterload. Both inotropic contractile reserve and rise in transaortic pressure gradients are thus concomitant. Conversely, when the aortic valve is no longer compliant or in case of profound myocardial damage (fibrosis, ischaemia), a mismatch between afterload and contractility may occur. Gradients might still increase despite the absence of contractile recruitment. In more advanced stage,

**Table 2** Correlations with exercise-induced changes in left ventricular longitudinal function

Variables	Controls		AS: normal test		AS: abnormal test	
	r	P	r	P	r	P
Rest						
LV end-diastolic volume	0.13	0.46	0.11	0.20	0.072	0.54
LV end-systolic volume	0.03	0.83	0.009	0.90	0.086	0.47
LV ejection fraction	0.22	0.23	0.11	0.21	0.09	0.41
Peak systolic velocity	0.07	0.67	0.22	0.07	0.21	0.09
Global longitudinal strain	0.08	0.66	0.18	0.11	0.037	0.76
Aortic valve area	—	—	0.009	0.91	0.03	0.80
Aortic mean pressure gradient	—	—	0.13	0.13	0.22	0.06
Exercise						
LV end-systolic volume	0.13	0.46	0.03	0.68	0.1	0.40
LV ejection fraction	0.16	0.37	0.014	0.86	0.087	0.47
Peak systolic velocity	0.45	0.009	0.12	0.17	0.10	0.40
Global longitudinal strain	0.43	0.015	0.58	0.0001	0.48	0.0002
Aortic valve area	—	—	0.026	0.76	0.27	0.054
Aortic mean pressure gradient	—	—	0.11	0.19	0.05	0.67
Exercise-rest						
LV end-systolic volume	0.09	0.62	0.06	0.46	0.09	0.45
LV ejection fraction	0.45	0.0093	0.08	0.33	0.085	0.48
Peak systolic velocity	0.34	0.05	0.14	0.09	0.24	0.043
Aortic valve area	—	—	0.029	0.73	0.09	0.45
Aortic peak pressure gradient	—	—	0.04	0.61	0.078	0.52
Aortic mean pressure gradient	—	—	0.0028	0.91	0.017	0.88

AS, aortic stenosis; r, Pearson correlation coefficient.

**Table 3** Intra- and inter-observer variability in longitudinal strain measurements

Global longitudinal strain	Intra-observer variability		Inter-observer variability	
	Absolute difference (%)	Relative difference (%)	Absolute difference (%)	Relative difference (%)
Rest	-0.87 ± 1.03	5.7	1.2 ± 1.4	8
Exercise	1.1 ± 0.93	6.2	1.7 ± 1.9	11

the absence of contractile reserve might be accompanied by a low-flow state with no change or even a decrease in transaortic pressure gradients during exercise. Hence, limited contractile recruitment during exercise probably reflects a more advanced disease process with more extensive myocardial fibrosis, myocytes degeneration, and exhausted coronary flow reserve (ability of coronary circulation to increase flow to match myocardial demand).

In the present study, we have shown, for the first time, that the magnitude of exercise-induced changes in the LV ejection fraction was not correlated to changes in global longitudinal strain (as a measurement of LV long-axis function) in AS patients; the correlation being however present in controls. This emphasises that, in AS, the assessment of myocardial contractile function by 2D-speckle tracking is more appropriate than by changes in the LV ejection fraction in the setting of pressure overload. Moreover, this probably explains why changes in the LV ejection fraction did

not emerge any more as a predictive factor in the study of Maréchaux *et al.*<sup>19</sup> To note, changes in mitral annulus pulse tissue Doppler during exercise seemed to be less accurate to distinguish patients with limited contractile reserve.<sup>15</sup> Despite the great sensitivity of the 2D-speckle tracking approach, overlap exist between normal and severe AS' responses. But, the identification of subclinical LV dysfunction in AS is challenging and of clinical importance. So far no studies have examined how the AS by itself may affect the contractile recruitment at exercise, especially by using quantitative method instead of volume-based parameters as the LV fraction ejection. Two-dimensional strain allows accurate assessment of regional LV function. The present paper is the first to assess the LV contractile response at exercise using 2D strain in a large cohort of patients with significant AS. The changes in longitudinal function during exercise are not homogeneous. Different categories of patients can be identified according to the changes in

longitudinal function, the changes in mean aortic pressure gradient and the clinical response to exercise. It is emphasizing the interest of exercise echo and of the assessment of longitudinal component of LV deformation, in AS patients. The longitudinal dysfunction is severe AS patients might be weak at rest and emphasized during exercise. It remains, of course, to be demonstrated that observation can adequately impact on the patient's management.

## Limitations

The absence of coronary artery disease was based on history taking rather on invasive imaging, which could limit the interpretation of our results. However, no patient developed regional wall motion abnormalities during exercise. Although less demanding than recording Doppler echocardiographic data shortly after exercise, a learning curve is required to obtain reliable measures during exercise. Recordings during test might be affected by noise artefacts. Although 2D strain imaging has a lot of advantages, the success of 2D speckle tracking depends on the quality of gray-scale images and frame rate which were both high. In the present study, inadequate tracked segments were automatically excluded from the analysis (<10% of segments analysed). We did not succeed in measuring radial and circumferential component of LV-strain in every patient at rest and during the exercise, we thus report only on the most sensitive component of LV systolic deformation. This is also probably the most useful in current routine clinical practice: the longitudinal strain.

To note, prognosis was not the scope of the present study. But, the current paper is the first to deal exercise test and 2D strain myocardial deformation.

## Conclusions

In AS, subnormal LV function can be reliably identified by 2D strain imaging at rest and during a submaximal exercise. That sensitive measure of LV systolic function is depressed in AS and even more in patients having the most severe AS.

**Conflict of interest:** none declared.

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