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Left ventricular regional function and maximal exercise capacity in aortic stenosis

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Aims The objective assessment of maximal exercise capacity (MEC) using peak oxygen consumption (VO_2) measurement may be helpful in the management of asymptomatic aortic stenosis (AS) patients. However, the relationship between left ventricular (LV) function and MEC has been relatively unexplored. We aimed to identify which echocardiographic parameters of LV systolic function can predict MEC in asymptomatic AS.

Methods and results Asymptomatic patients with moderate to severe AS ($n = 44$, aortic valve area <1.5 cm^2, 66 ± 13 years, 75% of men) and preserved LV ejection fraction (LVEF $> 50\%$) were prospectively referred for resting echocardiography and cardiopulmonary exercise test. LV longitudinal strain (LS) of each myocardial segment was measured by speckle tracking echocardiography (STE) from the apical (aLS) 4-, 2-, and 3-chamber views. An average value of the LS of the analysable segments was provided for each myocardial region: basal (bLS), mid (mLS), and aLS. LV circumferential and radial strains were measured from short-axis views. Peak VO_2 was 20.1 ± 5.8 mL/kg/min (median 20.7 mL/kg/min; range 7.2–32.3 mL/kg/min). According to the median of peak VO_2, patients with reduced MEC were significantly older ($P < 0.001$) and more frequently females ($P = 0.05$). There were significant correlations between peak VO_2 and age ($r = -0.44$), LV end-diastolic volume ($r = 0.35$), LV stroke volume ($r = 0.37$), indexed stroke volume ($r = 0.32$), and E/e' ratio ($r = -0.37$, all $P < 0.04$). Parameters of AS severity and LVEF did not correlate with peak VO_2 ($P =$ NS for all). Among LV deformation parameters, bLS and mLS were significantly associated with peakVO_2 ($r = 0.43$, $P = 0.005$, and $r = 0.32$, $P = 0.04$, respectively). With multivariable analysis, female gender ($\beta = 4.9$; $P = 0.008$) and bLS ($\beta = 0.50$; $P = 0.03$) were the only independent determinants ($r^2 = 0.423$) of peak VO_2.

Conclusion In asymptomatic AS, impaired LV myocardial longitudinal function determines reduced MEC. Basal LS was the only parameter of LV regional function independently associated with MEC.

Keywords aortic stenosis • longitudinal strain • cardiopulmonary test • functional capacity

Introduction

Aortic stenosis (AS) is the most frequent type of valvular heart disease in Europe and North America.[1,2] However, there is still ongoing debate regarding the best timing for surgery in asymptomatic patients with preserved left ventricular (LV) ejection fraction.[3,4] An assiduous search for parameters that may identify patients who may benefit from early surgery has begun in recent years. Current guidelines recommend surgery in symptomatic patients with severe AS and in those with LV ejection fraction (LVEF) <50%.[1,2] However, the post-operative outcome of these patients seems worse than in those operated on without symptoms or LV dysfunction.[5] Clinicians are nevertheless reluctant to systematically perform aortic valve replacement in asymptomatic patient with severe AS and preserved LVEF (i.e. >50%), because of the combined risk of aortic valve surgery and late complications of aortic valve prosthesis. Hence, there is a profound need to validate parameters that may help stratify the risk of asymptomatic patients with severe AS (i.e. to select patient who may benefit the most from early surgery) and that may be able to identify subclinical LV dysfunction. There is irrefutable evidence that LVEF is a poor estimator of myocardial contractility in patients with AS.[6–8] LV hypertrophy or concentric remodelling, through a simple geometric effect, can boost LVEF values creating a false impression of normal LV systolic performance.

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Consequently, attention has moved from LVEF measurement to analysis of LV longitudinal systolic function.[6–8] Several studies have shown that global longitudinal strain (GLS), as assessed by speckle tracking echocardiography (STE), is an independent predictor of outcome in AS.[9–11] Cardiopulmonary exercise testing (CPET) with measurement of gas exchange provides quantitative, objective, and more accurate non-invasive evaluation of maximal exercise capacity (MEC).[12] However, very few studies have focused on evaluating MEC in AS.[13,14] In the present study, we sought to examine the relationship between indices of LV function using conventional and STE-derived parameters and MEC in asymptomatic AS.

Methods

Study population

Fifty-five consecutive patients with asymptomatic moderate to severe AS who were able to perform a treadmill CPET were prospectively included in the present study. Exclusion criteria: (i) more than mild aortic or mitral regurgitation at echocardiography, (ii) abnormal cardiac rhythm, (iii) paced rhythm, (iv) dilated or hypertrophic obstructive cardiomyopathy, (v) known ischaemic heart disease, (vi) LVEF $<50\%$, (vii) primary pulmonary hypertension, (viii) evidence of more than mild pulmonary disease, and (ix) inadequate acoustic windows. For the CPET, the absolute exclusion criteria specified by ATS/ACCP Statement on Cardiopulmonary Testing were applied.[12] All patients gave their consent and the local ethics committee approved the protocol.

Echocardiographic measurements

Echocardiographic examination was performed using a Vivid ultrasound (7 or E9) System (GE Healthcare, Little Chalfont, UK). All data were stored in a digital format, which enabled subsequent off-line analysis using dedicated software (EchoPAC, GE Vingmed Ultrasound AS, Horten, Norway). Eleven patients were excluded from the analysis because of poor acoustic windows that made comprehensive LV function assessment by STE impossible. The final cohort was composed of the remaining 44 patients.

Evaluation of AS severity

Continuous wave Doppler was used to measure trans-aortic velocities. Peak and mean trans-aortic pressure gradients were calculated using the simplified Bernoulli equation ($\Delta P = 4v^2$, where v is maximal aortic velocity in m/s). Aortic valve area (AVA) was calculated using the continuity equation. AS was considered severe if the valve area was <1 cm^2. Indexed AVA was obtained by dividing the AVA by the body surface area.

Evaluation of LV geometry, LV systolic, and diastolic function using conventional resting echocardiography

The LV mass was calculated from the parasternal long-axis 2D greyscale images using the formula of the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[15] The LVEF, end-systolic, and end-diastolic volumes were measured by Simpson's biplane method. The LV stroke volume was calculated by multiplying the LV outflow tract area to LV outflow tract velocity time integral measured by pulse wave Doppler. Stroke volume was indexed to body surface area. The LV cardiac output was calculated as the product of heart rate and stroke volume. Peak mitral E- and A-wave velocities were measured using pulsed-wave Doppler. Peak early diastolic mitral annular velocities both at medial and lateral mitral annulus sites were measured using tissue Doppler imaging in apical 4-chamber view and their values were averaged (e'). The E/e' ratio was then calculated.

Assessment of LV deformation parameters

LV longitudinal strain (LS), radial strain (RS), and circumferential strain (CS) quantifications were performed using commercially available software (EchoPAC version 112; GE Healthcare, Norway). Standard 2D greyscale images, focused on the LV, were acquired in conventional apical 4-chamber, 2-chamber, and long-axis views, and in parasternal short-axis view at the level of the papillary muscles. Care was taken to obtain good endocardial border delineation, avoid artefacts and LV chamber foreshortening and acquire loops with at least 60 frames per second. With off-line analysis, the regions of interest were manually defined by marking endocardial border at end-systole by the point-and-click approach. The automatic tracking of the endocardial contour was verified carefully, and the region of interest was manually corrected to ensure optimal tracking of each myocardial segment throughout systole and diastole. Any segment with inadequate tracking was excluded from the final analysis. Peak segmental LS, CS, and RS analysis was performed by dividing the LV into six segments in each of the obtained views. An average value for each myocardial region (basal, mid, and apical) was provided for LV LS (bLS, mLS, and aLS, respectively). CS and RS were also obtained after averaging peak segmental strain values. If more than two segments in the short-axis view were not adequately tracked, the average values of RS and CS were not reported, as more than half of the myocardial segments were not available for analysis. Reproducibility, as well as both inter-observer and intra-observer variability of the LV strain analysis by speckle tracking in our laboratory were already reported elsewhere.[16] In our study, 75% (590/792) of the myocardial segments for LS were adequately tracked. For CS and RS strain, only 55% (145/264) were analysable.

Cardiopulmonary exercise testing

All patients underwent a multistage symptom-limited treadmill CPET. A modified Bruce protocol was used with three distinct stages: a warm up stage, an exercise stage with a progressive increase in workload, and a recovery stage. Patients were encouraged to exercise until exhaustion, and discouraged from grasping and leaning on the handrails. Blood pressure values were carefully monitored at the end of each stage of the protocol using a calibrated sphygmomanometer, and continuous 12-lead electrocardiogram monitoring was recorded. Patient's medications were not stopped for the test. A cardiologist monitored closely the patient during the test and carefully searched for symptom development or signs of abnormal test: angina, dizziness, sustained ventricular arrhythmias, drop or inadequate rise (<20 mmHg) in systolic blood pressure, or ≥ 2 mm ST segment depression 80 ms after the J point. The test was promptly stopped in case of symptom occurrence. Peak oxygen consumption (peak VO_2) was measured. Device calibration was performed before each test. Each CPET was performed within 1 month following echocardiographic examination.

Statistical analysis

Patients were divided into two groups according to the median value of the peak VO_2 distribution. The results were expressed as mean $\pm$ standard deviation or percentages unless otherwise specified. The statistical differences between groups were assessed using a Student's t-test, χ^2 test, or Fisher's exact test, as appropriate. The relationship between echocardiographic data and peak VO_2 was evaluated using a linear regression model. To identify the independent predictors of exercise capacity, we used multiple linear regression analysis. Only variables associated with peak VO_2 in univariable analysis were included in the model and were carefully chosen in order to avoid colinearity. Receiver operating characteristic (ROC) analysis was used to estimate cut-off values of strain parameters able to predict reduced MEC. Values of

$P < 0.05$ were considered significant. All the statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the population

Among the 44 patients included in the study (age 66 ± 13 years, 75% men), 29 (66%) had severe AS. None of the patients had known peripheral artery disease or intermittent claudication during treadmill exercise. Patients' clinical and demographic characteristics and main CPET data are summarized in *Table 1*. The echocardiographic characteristics of the studied population are depicted in *Table 2*.

Functional capacity in AS

Absolute peak VO_2 was 20.1 ± 5.8 mL/kg/min (median 20.7 mL/kg/min; range 7.2–32.3 mL/kg/min, *Figure 1*). Twelve patients (27%) had peak VO_2 < 84% of predicted values for age and sex. Of note, none of them developed symptoms during the test. Patients with reduced MEC (peak VO_2 < median) were significantly older, more frequently females (*Table 1*) and had lower LV end-diastolic and end-systolic volumes, LV stroke volume and cardiac output, and higher *E*/*e*′ ratio (*Table 2*). There were no other significant differences between the two groups regarding clinical, demographic, and conventional echocardiographic data (*Tables 1* and *2*).

There was a significant correlation between absolute peak VO_2 and age ($r = -0.44$), LV end-diastolic volume ($r = 0.35$), LV stroke volume ($r = 0.37$), indexed stroke volume ($r = 0.32$), and *E*/*e*′ ratio ($r = -0.37$) (*Table 4*). In contrast, there was no significant correlation between peak VO_2 and LVEF or any parameters of AS severity (*Table 4*).

Relationship between LV myocardial deformation parameters and functional capacity

Among LV myocardial deformation parameters, bLS and mLS were significantly associated with peakVO_2 ($r = 0.43$, $P = 0.005$, and $r = 0.32$, $P = 0.04$, respectively, *Figure 2A* and *B*). Patients with reduced MEC had also lower bLS values compared with those with preserved MEC (−13.53 ± 3.84 vs. −16.62 ± 3.68%, $P = 0.01$, *Table 3*). However, aLS, CS, and RS were statistically similar between patients with low and high MEC groups (all P = NS, *Table 3*, *Figure 2C* and *Figure 3*). There was a trend for lower mLS in patients with reduced MEC ($P = 0.09$, *Table 3*). Among all regional LV systolic function parameters derived by speckle tracking, the strongest univariable determinant of peak VO_2 was bLS (*Table 4*). In multivariable analysis, in the model including age, LV stroke volume, *E*/*e*′ ratio, and mLS, the main determinants of peak VO_2 ($r^2 = 0.39$) were female gender ($\beta = 5.09$, SE = 1.9, $P = 0.01$) and bLS ($\beta = 0.86$, SE = 0.42, $P = 0.046$, *Table 5*).

Taken separately, when only one of the regional LV systolic function parameters derived by speckle tracking was included in the model (i.e. either bLS or mLS), only bLS was identified as a determinant of peak VO_2 ($r^2 = 0.42$, *Table 6*). In a similar model, mLS failed to predict peak VO_2 ($\beta = 0.24$, SE = 0.23, $P = 0.30$) and only female gender remained a predictor of peak VO_2 ($\beta = 4.59$, SE = 1.99, $P = 0.03$, total $r^2 = 0.39$).

Using ROC curve analysis, the best cut-off values of bLS to predict reduced MEC were −15.3%, with a sensitivity and specificity of 70 and 68%, respectively [area under the curve (AUC) = 0.71, $P = 0.02$]. Of note, mLS was not accurate to discriminate between patients with preserved MEC and reduced MEC (AUC = 0.61, $P = 0.09$).

Discussion

The major findings of the present study are (i) MEC varies widely in asymptomatic patients with moderate to severe AS and is often lower than expected; about one-third of the study population had peak VO_2 lower than age, gender, and level of training-predicted values, (ii) classical parameters of AS severity do not influence MEC, (iii) MEC is modestly related to the degree of LV diastolic dysfunction and to LV end-diastolic volume, (iv) the only classical echocardiographic parameter of LV systolic function related to MEC is LV stroke volume, (v) LVEF does not affect MEC in AS patients with apparently preserved LV systolic function, and (vi) LV longitudinal function of the basal myocardial segments is an important determinant of MEC; a cut-off value of −15.3% could be used to predict reduced MEC in asymptomatic patient with moderate to severe AS.

Functional capacity in AS

Several small studies have shown that exercise capacity is frequently altered in patients with AS.[13,17,18] In a study by Clyne *et al.*,[13] asymptomatic patients with AS had a reduced exercise tolerance when compared with controls. Moreover, Rajani *et al.*[18] showed that peak indexed LV stroke volumes and peak VO_2 values were lower in patients who developed symptoms during the test. In the present study, peak VO_2 varied widely from normal to markedly reduced values (mean: 20.1 ± 5.8 mL/kg/min). Peak VO_2 values were significantly lower in older patients and in females with asymptomatic AS, in agreement with data obtained in the general population.[12] It is worth emphasizing that the present study included only patients without history of self-reported exertional dyspnoea, angina, or syncope, and no symptom development during the treadmill exercise test. Yet, one-third of the included patients had a lower than expected MEC for their age, gender, and level of training. Thus, MEC as assessed by CPET, may be used as a clinical tool to ascertain whether patients with AS are truly asymptomatic.

LVEF, diastolic function, and functional capacity in AS

Peak VO_2 is related to peak exercise cardiac output through the Fick equation. Cardiac output is related to heart rate and stroke volume, both at rest and during exercise. In our cohort, resting LV stroke volume was associated with peak VO_2, patients with lower MEC had smaller LV stroke volume, suggesting that an LV with a low stroke volume at rest does not have sufficient resources to adapt to exercise. Hence, these patients with lower LV stroke volumes at rest tend to have reduced MEC. Moreover, LV geometry seems to be related to MEC in AS patients. Despite the fact that LV mass and indexed mass were similar between groups, LVs with higher end-diastolic volumes appeared to adapt better during exercise (higher end-diastolic volume was associated with better MEC). These results can suggest that loss of 'LV filling volume' related to

Table 1 Demographic, clinical, and cardiopulmonary test data

Variable	Overall ($n = 44$)	Preserved MEC ($n = 22$)	Reduced MEC ($n = 22$)	P
Clinical and demographic data				
Age, years	66 ± 13	60 ± 12	73 ± 10	<0.001
Female gender, *n* (%)	11 (25)	3 (14)	8 (36)	0.05
Body mass index (kg/m^2)	26 ± 4	26 ± 3	26 ± 4	0.87
Heart rate (bpm)	78 ± 10	79 ± 9	79 ± 11	0.80
SBP (mmHg)	132 ± 19	131 ± 16	133 ± 23	0.85
DBP (mmHg)	72 ± 9	74 ± 9	70 ± 8	0.11
Pulse pressure (mmHg)	60 ± 17	58 ± 15	63 ± 19	0.31
Risk factors				
Diabetes mellitus, *n* (%)	6 (14)	3 (14)	3 (14)	0.90
Active smoking, *n* (%)	9 (20)	7 (32)	2 (9)	0.09
Dyslipidaemia, *n* (%)	25 (57)	11 (50)	14 (64)	0.2
Hypertension, *n* (%)	28 (64)	13 (59)	15 (68)	0.3
Mild renal failure, *n* (%)	1 (2.3)	0 (0)	1 (100)	0.3
Cardiopulmonary test data				
Test duration (min)	10 ± 4	12 ± 3	9 ± 4	0.01
Workload (W)	110 ± 38	129 ± 29	90 ± 35	0.001
Peak heart rate (bpm)	130 ± 16	135 ± 13	124 ± 17	0.02
Peak SBP (mmHg)	161 ± 23	163 ± 24	158 ± 23	0.49
Peak DBP (mmHg)	78 ± 12	81 ± 12	75 ± 12	0.15
PCP (mmHg × mL/kg/min)	3195 ± 1038	3919 ± 722	2436 ± 730	<0.001
O_2 pulse (mL/beat)	15 ± 21	20 ± 29	10 ± 4	0.13

Data are presented as mean ± SD or *n* (%).
MEC, maximal exercise capacity; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCP, peak circulatory power; O_2 pulse, oxygen pulse.

Table 2 Resting echocardiographic data

Variable	Overall ($n = 44$)	Preserved MEC ($n = 22$)	Reduced MEC ($n = 22$)	P
LV geometry				
LV end-diastolic volume (mL)	93 ± 31	106 ± 34	78 ± 19	0.002
LV end-systolic volume (mL)	36 ± 14	41 ± 16	31 ± 10	0.02
LV mass (g)	236 ± 91	233 ± 93	240 ± 91	0.83
Indexed LV mass (g/m^2)	129 ± 47	117 ± 32	143 ± 59	0.09
LV function				
Stroke volume (mL)	85 ± 24	96 ± 27	73 ± 14	0.001
Indexed stroke volume (mL/m^2)	46 ± 10	50 ± 10	42 ± 8	0.009
Cardiac output (mL/min)	5.8 ± 1.7	6.4 ± 1.9	5.1 ± 1.3	0.01
Cardiac index (mL/min/m^2)	3.1 ± 0.7	3.3 ± 0.7	2.9 ± 0.6	0.06
LVEF (%)	62 ± 6	62 ± 5	62 ± 7	0.86
E/*e*′	10 ± 4	9 ± 2	12 ± 5	0.03
Aortic stenosis severity				
Peak gradient (mmHg)	68 ± 22	67 ± 21	68 ± 24	0.84
Mean gradient (mmHg)	41 ± 15	40 ± 14	41 ± 15	0.89
Aortic valve area (cm^2)	0.92 ± 0.31	0.99 ± 0.28	0.83 ± 0.32	0.09
Indexed aortic valve area (cm^2/m^2)	0.49 ± 0.16	0.51 ± 0.14	0.47 ± 0.18	0.35

Data are presented as mean ± SD.
MEC, maximal exercise capacity; LV, left ventricle; LVEF, left ventricle ejection fraction; *E*, peak early diastolic flow velocity measured at the mitral leaflets tip; *e*′, mitral annulus peak early diastolic velocity.

concentric remodelling/hypertrophy can be deleterious on MEC in AS. To note, a large proportion (81%) of our patients had LV concentric hypertrophy or concentric remodelling.

Interestingly, from all conventional parameters of LV systolic function, only LV stroke volume showed a significant relationship with peak VO_2, while LVEF was neither associated with lower MEC, nor different between groups. The lack of association between LVEF and peak VO_2 suggests that LVEF is a poor estimator of LV systolic performance in patients with concentric remodelling and increased LV haemodynamic afterload. In univariable analysis, reduced exercise capacity was also associated with an impaired LV diastolic function, as assessed by the *E*/*e*′ ratio—a surrogate of LV filling pressure. Patients with higher *E*/*e*′ ratio at rest had a worse adaptation to exercise, as measured by peak VO_2 values, suggesting that resting diastolic dysfunction can also have a negative impact on MEC. Our data are in line with previous studies that showed that diastolic dysfunction influences MEC.[19–21]

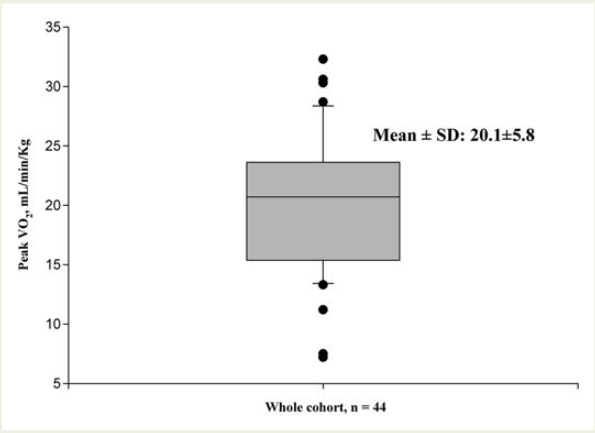

Figure 1 MEC in patients with AS.

LV longitudinal function and functional capacity in AS

In the current guidelines, LVEF is the only LV function parameter used to recommend AVR in asymptomatic patients with severe AS.[1] However, there is unquestionable evidence that LVEF can be misleading in the assessment of LV systolic performance in AS.[22–24] In AS, the presence of LV hypertrophy, through a simple geometrical effect, can generate a confusing impression of 'normal' LV systolic performance, despite a progressive decline in LV contractility. In contrast, as highlighted in previous studies,[6,25–27] LV longitudinal systolic function is impaired earlier in conditions

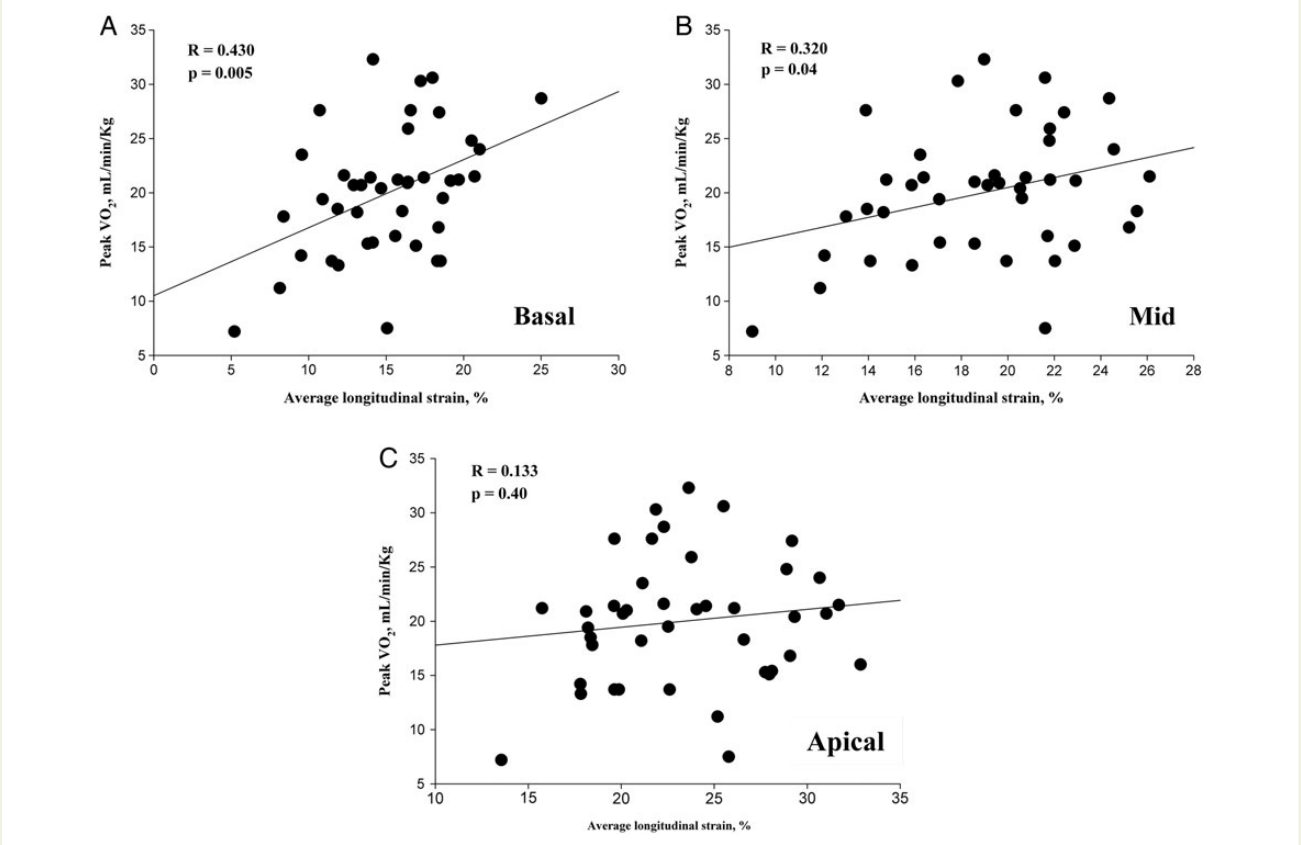

Figure 2 Relationship between MEC (Peak VO_2) and basal (*A*), mid (*B*) and apical strains, as assessed by STE (*C*).

Table 3 LV myocardial deformation parameters

Variable	Overall ($n = 44$)	Preserved MEC ($n = 22$)	Reduced MEC ($n = 22$)	P
LV function (deformation imaging derived parameters)				
Average basal longitudinal strain (%)	15.2 ± 4	16.7 ± 3.7	13.5 ± 3.8	0.01
Average mid longitudinal strain (%)	19 ± 4.1	20 ± 3.3	17.9 ± 4.7	0.09
Average apical longitudinal strain (%)	23.4 ± 4.7	23.7 ± 4.4	23.1 ± 5.2	0.68
Average circumferential strain (%)	20 ± 4	20 ± 2.9	19.9 ± 5.5	0.94
Average radial strain (%)	51.1 ± 24.4	55.9 ± 24.3	42.2 ± 23.7	0.21

Data are presented as mean ± SD.
MEC, maximal exercise capacity; LV, left ventricle; LVEF, left ventricular ejection fraction.

with high afterload, as in AS. Global LV longitudinal shortening is more closely associated with changes in symptomatic status, abnormal exercise response, and outcome than LVEF in asymptomatic AS.[10,11,28]

This study shows, for the first time to our knowledge, that LV longitudinal systolic function represents a major determinant of MEC in asymptomatic AS; longitudinal function in the basal, but not in the mid and apical myocardial segments being a predictor of MEC. The base-to-apex gradient in LS described in AS was more pronounced in patients with reduced MEC.[10,11,25,29,30] LS was significantly lower in the basal segments compared with the apex. It is well known that longitudinal function is governed by the subendocardial myocardial fibres, which are more likely to be affected by microvascular ischaemia. However, basal segments, due to their higher systolic wall stress, are even more susceptible to elicit early systolic dysfunction than the mid and apical segments.[11,31,32] This could explain why GLS, averaging base-to-apex strains, weakly predicted reduced MEC in our population. Reduced bLS has emerged in a few studies as an important determinant of low-flow state, poor LV adaptation to exercise, and global cardiac events in AS.[29,30] bLS has also been constantly found to be a more powerful predictor of outcome than GLS, suggesting that it could be a more sensitive marker of LV dysfunction. Recent cardiac magnetic resonance studies have shown that myocardial fibrosis is predominantly found in the basal segments of the LV, which can contribute to impaired bLS.[7] After AVR, the recovery of longitudinal function may still occur but it mainly results from improvement of the basal and mid segmental function.[33] Although reduced bLS is a marker of limited MEC, it may identify a subgroup of patients with less advanced disease process. It may thus precede the diffuse alteration in intrinsic myocardial function, which is often associated with a more significant decrease in GLS and diffuse myocardial fibrosis.[7] Whether bLS could be used to optimize the timing of AVR needs to be addressed in a larger series of patients.

The fact that this difference was particularly evidenced on LS, and absent in its radial and circumferential component, probably reflects the earlier impairment of longitudinal function in these patients.[30] In addition, the better intra-observer and inter-observer reproducibility reported for LS when compared with RS and CS could also have contributed to this observation.[9]

Table 4 Relationship among peak VO_2, age, and echocardiographic parameters

Variables	r	P
Age	−0.44	0.003
LV geometry		
LV end-diastolic volume	0.35	0.02
LV end-systolic volume	0.26	0.10
LV mass	0.04	0.79
Indexed LV mass	−0.11	0.52
LV systolic function		
LV stroke volume	0.37	0.02
Indexed LV stroke volume	0.32	0.04
Cardiac output	0.25	0.11
Cardiac index	0.19	0.24
LVEF	0.04	0.81
Average basal longitudinal strain	0.43	0.005
Average mid longitudinal strain	0.32	0.04
Average apical longitudinal strain	0.13	0.40
Average circumferential strain	0.11	0.61
Average radial strain	0.24	0.28
LV diastolic function		
E/*A* ratio	−0.12	0.48
E/*e*′ ratio	−0.37	0.02
AS severity		
Peak aortic pressure gradient	0.02	0.88
Mean aortic pressure gradient	−0.01	0.97
Aortic valve area	0.23	0.13
Indexed aortic valve area	0.15	0.32

LV, left ventricle; LVEF, left ventricle ejection fraction; *E*, peak early diastolic flow velocity measured at the mitral leaflets tip; *A*, peak late diastolic flow velocity measured at the mitral leaflets tips; *e*′, mitral annulus peak early diastolic velocity.

Limitations

The sample size of the present study is relatively small but all patients included had a CPET. Diabetes and hypertension may influence strain values; however, there were no significant differences in these parameters between groups. Peak VO_2 may also be affected

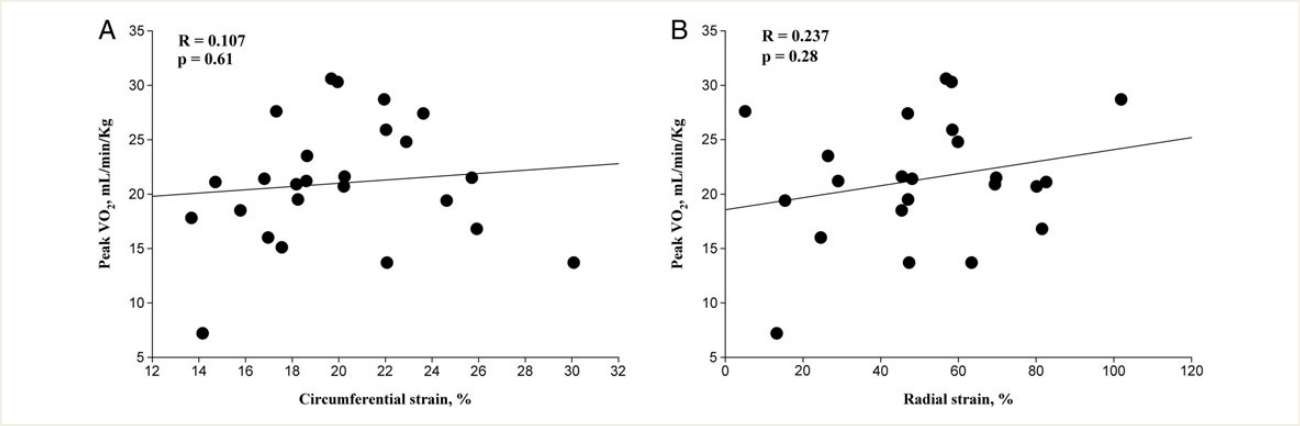

Figure 3 Relationship among MEC (Peak VO_2), CS (*A*), and RS (*B*).

Table 5 Multiple linear regression analysis for prediction of MEC: average LV mid longitudinal and basal strains model (total $r^2 = 0.393$)

	B	SE	*P*
Age	−0.08	0.08	0.30
Sex	5.09	1.9	0.01
LV stroke volume	0.003	0.04	0.95
Average basal longitudinal strain	0.86	0.42	0.046
Average mid longitudinal strain	−0.27	0.39	0.51

LV, left ventricle.

Table 6 Multiple linear regression analysis for prediction of MEC: basal LV longitudinal strain model (total $r^2 = 0.423$)

	B	SE	*P*
Age	−0.12	0.07	0.08
Sex	4.98	1.74	0.008
LV stroke volume	–	–	NS
Average basal longitudinal strain	0.50	0.21	0.03
E/*e*′	–	–	NS

LV, left ventricle; *E*, peak early diastolic flow velocity; *e*′, mitral annulus peak early diastolic velocity.

by pulmonary diseases, neuromuscular, or musculoskeletal disease, anaemia or any other pathology that decreases the oxygen transport capacity of blood. However, none of the patients included in the present study had symptoms or any of the above-mentioned pathologies. Exercise-induced myocardial ischaemia may be a limiting factor of MEC. However, none of our patients had a history of coronary artery disease, or presented angina or significant ST changes suggestive of active myocardial ischaemia during exercise.

Conclusion

In asymptomatic patients with moderate to severe AS and preserved LVEF, LV myocardial longitudinal function is the main determinant of reduced MEC. bLS was the only parameter of LV regional function, as assessed by STE, independently associated with MEC. Further studies are needed to explore the potential role of MEC and LV longitudinal systolic dysfunction in the risk stratification of asymptomatic AS.

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