ORIGINAL RESEARCH

Myocardial Oxygen Consumption and Efficiency in Aortic Valve Stenosis Patients With and Without Heart Failure

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***Background*—**Myocardial oxygen consumption (MVO_2) and its coupling to contractile work are fundamentals of cardiac function and may be involved causally in the transition from compensated left ventricular hypertrophy to failure. Nevertheless, these processes have not been studied previously in patients with aortic valve stenosis (AS).

***Methods and Results*—**Participants underwent ^{11}C-acetate positron emission tomography, cardiovascular magnetic resonance, and echocardiography to measure MVO_2 and myocardial external efficiency (MEE) defined as the ratio of left ventricular stroke work and the energy equivalent of MVO_2. We studied 10 healthy controls (group A), 37 asymptomatic AS patients with left ventricular ejection fraction ≥50% (group B), 12 symptomatic AS patients with left ventricular ejection fraction ≥50% (group C), and 9 symptomatic AS patients with left ventricular ejection fraction <50% (group D). MVO_2 did not differ among groups A, B, C, and D (0.105±0.02, 0.117±0.024, 0.129±0.032, and 0.104±0.026 mL/min per gram, respectively; P=0.07), whereas MEE was reduced in group D (21.0±1.6%, 22.3±3.3%, 22.1±4.2%, and 17.3±4.7%, respectively; P<0.05). Similarly, patients with global longitudinal strain greater than −12% and paradoxical low-flow, low-gradient AS had impaired MEE (P<0.05 versus controls). The ability to discriminate between symptomatic and asymptomatic patients was superior for global longitudinal strain compared with MVO_2 and MEE (area under the curve 0.98, 0.48, and 0.61, respectively; P<0.05).

***Conclusions*—**AS patients display a persistent ability to maintain normal MVO_2 and MEE (ie, the ability to convert energy into stroke work); however, patients with left ventricular ejection fraction <50%; global longitudinal strain greater than −12%; or paradoxical low-flow, low-gradient AS demonstrate reduced MEE. These findings suggest that mitochondrial uncoupling contributes to the dismal prognosis in patients with reduced contractile function or paradoxical low-flow, low-gradient AS. **(*J Am Heart Assoc.* 2017;6:e004810. DOI: 10.1161/JAHA.116.004810.)**

Key Words: aortic valve stenosis • myocardial external efficiency • myocardial metabolism • myocardial oxygen consumption • positron emission tomography

Aortic valve stenosis (AS) is characterized by progressive aortic valve narrowing with left ventricular (LV) pressure overload, concentric remodeling, and eventually heart failure. Studies trying to counteract valve degeneration have failed, underscoring the need for new therapeutic strategies.[1–3] It is proposed that the development of heart failure is multifactorial; however, the definitive mechanisms involved remain unclear. Increasing evidence of an energy-starved myocardium is emerging, suggesting that inefficient energy exploitation and mitochondrial uncoupling play crucial roles in the transition to heart failure.[4–6] Consequently, economizing myocardial energy resources seems critical for maintaining a normal contractile state in myocytes.

Myocardial oxygen consumption (MVO_2) is tightly coupled to energy turnover and can be measured noninvasively by ^{11}C-acetate positron emission tomography (PET).[7] The concept of myocardial external efficiency (MEE), defined as the ratio of LV external stroke work (EW) and the energy equivalent of MVO_2, enables evaluation of mechanoenergetic coupling.[4,7,8] Because MEE has been proven to be impaired in various cardiac diseases, this concept may provide new

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/2/e004810/DC1/embed/inline-supplementary-material-1.pdf

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information about prognosis and the transition from LV pressure overload to failure in AS patients.[6,9,10]

In the present study, we hypothesized that MVO_2 and MEE were key determinants in the process of development of symptoms, LV hypertrophy, and failure in patients with AS. We investigated MEE and MVO_2 differences in patients with increasing AS severity compared with healthy controls.

Methods

Study Population

We included 75 participants in 4 study groups: 10 healthy controls, 40 asymptomatic AS patients with LV ejection fraction (LVEF) ≥50% (AsympEF ≥50), 15 symptomatic AS patients with LVEF ≥50% (SympEF ≥50), and 10 symptomatic AS patients with LVEF <50% (SympEF <50). The major inclusion criteria for AS patients were an aortic valve area (AVA) ≤1.2 cm^2 or a transaortic maximal velocity ≥3.0 m/s, and sinus rhythm. The major exclusion criteria were known or suspected ischemic heart disease evaluated by symptoms or signs of myocardial ischemia (eg, angina pectoris, abnormal ECG, wall motion abnormalities, previously performed coronary angiography with evidence of coronary artery stenosis) or significant aortic valve regurgitation (vena contracta ≥5 mm).

Patients in the SympEF ≥50 and SympEF <50 groups had coronary angiograms without significant coronary artery stenosis (defined as coronary artery diameter stenosis >70% in a major epicardial vessel). Patients in the AsympEF ≥50 group were evaluated by a 6-minute walking test and, if required, by an additional ergometer test to ensure true asymptomatic AS before enrollment.

The protocol was approved by the Regional Committee on Health Research Ethics (reference 1-10-72-138-13) and by the Danish Health Authority (reference 2013050476), and all patients provided written informed consent.

Imaging Protocol

All participants were evaluated by echocardiography and cardiovascular magnetic resonance (CMR) on the same day followed or preceded by an ^{11}C-acetate PET study within a median time of 2 days (interquartile range 1–7 days). All patients were clinically stable during this period. Images were stored and analyzed offline by investigators who were blinded to the clinical data.

Transthoracic echocardiography

Echocardiography was performed using a GE VIVID 9E system (GE Medical System) with a 2.5-MHz transducer and analyzed offline using EchoPAC version 113 (GE-Vingmed Ultrasound), as described previously.[11] Continuous-wave Doppler imaging from multiple acoustic windows was used to explore the highest transaortic velocity and peak and mean gradients. The mean gradients were corrected for pressure recovery according to a previously validated method.[12] Correction required measurements of the cross-sectional area of the ascending aorta that were obtained from CMR images 1 cm distal to the sinotubular junction.

The continuity equation was used to calculate the AVA from the velocity time integrals obtained across the aortic valve and in the LV outflow tract. The LV outflow tract diameter was measured from a 2-dimensional parasternal long-axis view.

Global longitudinal strain (GLS) was assessed by 2-dimensional speckle tracking (>50 frames per second) with the left ventricle automatically divided into a 17-segment model. A higher magnitude of deformation (ie, a more negative number of GLS) was referred to as "greater GLS." Pulsed-wave Doppler was used to evaluate mitral inflow patterns (E, A, deceleration time) and isovolumetric relaxation time. Mitral annular motion (s′ and e′) was assessed using tissue Doppler recordings (>150 frames per second).

CMR imaging

CMR was performed using a 1.5-T Philips Achieva dStream whole-body scanner (Philips Medical Systems) with a 32-channel coil. Image acquisition was performed according to a previously described method and analyzed using Segment v1.9 R3420 (Medviso AB).[13,14]

The degree of concentric remodeling was calculated and expressed as the ratio of LV mass/end-diastolic volume. Peak systolic wall stress was evaluated using the thick-wall sphere model assuming that peak systolic wall stress would occur one-third of the way into the ejection phase.[15,16]

Breath-hold, through-plane, phase-contrast acquisitions were performed to evaluate forward stroke volume, as described previously.[17] To avoid turbulent flow, imaging was performed at the level of the LV outflow tract where flow was laminar in all participants. Encoding velocities were set individually at 100 to 200 cm/s based on pulsed-wave Doppler imaging from echocardiography performed just prior to CMR.

^{11}C-acetate PET

All participants underwent an ^{11}C-acetate PET scan on a Siemens Biograph TruePoint TrueV 64 PET/computed tomography scanner. A catheter was placed in an antecubital vein, and after a minimum rest of 30 minutes, venous blood was collected for analysis of myocardial energy substrates: free fatty acids, glucose, ketone bodies (3-hydroxybutyrate), and lactate. Levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), hemoglobin, insulin, and catecholamine

metabolites (metanephrine and normetanephrine) were also analyzed. Subsequently, 400 MBq ^{11}C-acetate was injected, followed by list-mode PET recordings for 27 minutes. Heart rate and blood pressure were measured at 5, 10, and 20 minutes after injection.

Reconstruction of dynamic images and attenuation correction were performed according to a previously described method.[14] Dynamic data sets were analyzed using the software package Cardiac VUer, as previously described.[18] Image-derived arterial input function was obtained automatically and corrected for metabolites.[18,19] The average time–activity curve of the entire left ventricle was obtained and fitted to a 1-tissue compartment model yielding the global clearance rate (k_2) of activity from the myocardium.[20,21] Myocardial blood flow was estimated using the global uptake rate K_1, corrected for the incomplete extraction of ^{11}C-acetate.[22]

MEE and Oxygen Consumption

Average heart rate and mean arterial blood pressure measurements obtained during PET examination were used to calculate MEE according to a previously described method[7]:

$$\mathrm{MEE}(\%) = \frac{\mathrm{EW}}{\text{Total } \mathrm{MVO_2}} = \frac{\mathrm{EW} \times 1.33 \times 10^{-4}}{\text{LV mass} \times \mathrm{MVO_2} \times 20} \times 100$$

EW (mm Hg×mL/min) was calculated as the product of stroke volume, heart rate, and mean arterial blood pressure. The mean gradient was added to mean arterial blood pressure to avoid underestimating EW in AS patients. MVO_2 (mL/min per gram) was calculated from k_2 using the previously described relationship $MVO_2=(135\times k_2-0.96)/100$.[19] Finally, the caloric equivalent of 1 mL×mm Hg=1.33×10^{-4} J and 1 mL of O_2=20 J was applied to obtain units of energy.[7]

Statistical Analysis

Differences between groups are presented as mean±SD, unless stated otherwise. For continuous variables with normal distribution and variance homogeneity, 1-way ANOVA was used as the gatekeeper test. Multiple comparisons between pairs of groups were performed (by unpaired *t* tests) only if the ANOVA was significant. This testing procedure controls overall error rate (type I error) to a level of 5%.[23] If data violated the assumption of normality or variance homogeneity, they were analyzed by nonparametric tests using Kruskal-Wallis 1-way ANOVA as the gatekeeper test and the Wilcoxon-Mann–Whitney test for multiple comparisons. For dichotomous data, the chi-square test was used. Correlations for parameters of particular interest were investigated by linear regression.

The discriminatory performance to distinguish symptomatic and asymptomatic AS patients was assessed by area under the receiver operating characteristic curve analysis, and equality of the areas under the receiver operating characteristic curve between 2 models was tested using the method of DeLong et al.[24] $P<0.05$ was considered statistically significant. Statistical analyses were performed with STATA version 13.1 software (StataCorp).

Results

Study Population

Characteristics of the study population are presented in Table 1. Controls were younger compared with the AsympEF ≥50 and SympEF <50 groups (both $P<0.05$) but did not differ from the SympEF ≥50 group ($P=0.37$). There were no differences in mean arterial pressure or heart rate among study groups, and there was a similar disposition of men and women included in each group.

Seven patients were excluded from data analysis because of poor quality of PET data (n=2), logistic problems performing PET examination prior to subacute aortic valve replacement (n=2), missing CMR data (n=1), and unrecognized abnormal coronary angiogram (n=1) or severe aortic valve regurgitation (n=1) at the screening visit.

Transthoracic Echocardiography

Among AS patients, 95% had severe AS, defined as an indexed AVA ≤0.6 cm/m^2 or a mean gradient ≥40 mm Hg (Table 2). The indexed AVA was smaller and the mean gradient higher in the SympEF ≥50 and SympEF <50 groups than in the AsympEF ≥50 group. Controls and AsympEF ≥50 participants had greater GLS and higher s′ than the symptomatic groups. Furthermore, E/e′ was higher for all AS groups than for controls.

Cardiovascular Magnetic Resonance

LV mass index increased in all study groups, and the end-diastolic and end-systolic volume indexes were higher in the SympEF <50 group than in all other groups (Table 2). AsympEF ≥50 participants had a lower end-systolic volume index and a higher ejection fraction than controls and other AS groups. There were no differences in stroke volume index or cardiac index among groups.

MVO_2 and External Efficiency

There were no differences in MVO_2 per gram myocardium among the study groups (Table 3), and MVO_2 remained constant regardless of GLS, LVEF, and NT-proBNP (Figure 1). MVO_2 correlated with peak systolic wall stress, heart rate, and

Table 1. Demographic and Clinical Data

	Controls (n=10)	AsympEF ≥50 (n=37)	SympEF ≥50 (n=12)	SympEF <50 (n=9)	*P* Value
General					
Men, n (%)	7 (70)	25 (66)	7 (58)	7 (78)	0.87
Age, y	63±4	70±5*	67±11	75±8*†	0.002
BMI, kg/m^2	26±4	27±3	27±5	24±3	0.23
BSA, m^2	2.0±0.2	1.9±0.2	2.0±0.2	1.8±0.1	0.08
History of smoking, n (%)	6 (60)	24 (63)	6 (50)	8 (89)	0.32
Bicuspid aortic valve, n (%)	0 (0)	7 (18)	5 (42)	2 (22)	0.13‡
NYHA class, I to IV	—	1	2.3†	2.7†	<0.001‡
Systolic BP, mm Hg	129±9	142±13	139±17	138±23	0.09
Diastolic BP, mm Hg	82±6	81±8	87±12	77±10	0.74
MAP, mm Hg	97±6	102±9	104±13	98±13	0.27
HR, min^{-1}	65±9	69±7	74±13	71±8	0.09
NT-proBNP, ng/L	31 (23–74)	112 (70–278)*	664 (302–1671)*†	1343 (1231–2026)*†	<0.001
Medical history					
Hypertension, n (%)	0 (0)	21 (57)	6 (50)	5 (56)	0.92‡
Diabetes mellitus, n (%)	0 (0)	4 (11)	4 (33)	2 (22)	0.18‡
Dyslipidemia, n (%)	0 (0)	25 (68)	6 (50)	4 (44)	0.32‡
Medical treatment					
Beta-blockers, n (%)	0 (0)	0 (0)	1 (8)	2 (22)†	0.01‡
ACE/AT2 inhibitors, n (%)	0 (0)	12 (32)	0 (0)	3 (33)	0.10‡
Ca antagonists, n (%)	0 (0)	12 (32)	1 (8)	0 (0)	0.10‡
Statins, n (%)	0 (0)	23 (62)	5 (42)	4 (44)	0.87‡
Diuretics, n (%)	0 (0)	11 (30)	4 (33)	6 (66)†	0.05‡
Antidiabetic agents, n (%)	0 (0)	3 (8)	2 (17)	1 (11)	0.49‡

Values are mean±SD. NT-proBNP is presented as median (interquartile range). ACE, angiotensin-converting enzyme; AsympEF ≥50 indicates asymptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; AT2, angiotensin II; BMI indicates body mass index; BP, blood pressure; BSA, body surface area; HR, heart rate; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SympEF ≥50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%.
*P<0.05 vs controls.
†P<0.05 vs AsympEF ≥50.
‡Differences between groups excluding controls.

EW per gram myocardium (r^2=0.17, r^2=0.47, and r^2=0.55, respectively; P<0.001), whereas there was no correlation with AVA index, mean gradient, concentric remodeling, or LV mass index.

MEE was significantly lower in the SympEF <50 group than in the other AS groups and among controls (Figure 1A, Table 3). This was caused by an inability to maintain EW rather than changes in total MVO_2 (Table 3). MEE was reduced only in AS patients with GLS greater than −12%, LVEF <50%, and NT-proBNP >1000 ng/L (Figure 1B–1D), and there were no differences in MEE or MVO_2 when patients were grouped by AS severity (defined as AVA index or mean gradients) (Table S1).

The diagnostic accuracy to distinguish between AS patients with and without symptoms was investigated in a receiver operating characteristic curve analysis (Figure 2). MEE and MVO_2 had poor diagnostic accuracy, whereas GLS performed best (area under the receiver operating characteristic curve 0.61 [95% CI 0.45–0.77], 0.48 [95% CI 0.31–0.65], and 0.98 [95% CI 0.95–1.00]; both P<0.001). At a cutoff value of −15%, GLS displayed a positive predictive value of 86% (95% CI 64–97%) and a negative predictive value of 96% (95% CI 85–100%), resulting in correct classification of 94% of all patients.

Myocardial Blood Flow

Myocardial blood flow (mL/min per gram) did not differ significantly among groups (Table 3) but correlated with EW (r^2=0.41, P<0.001).

Table 2. Echocardiography and Cardiovascular Magnetic Resonance

	Controls (n=10)	AsympEF ≥50 (n=37)	SympEF ≥50 (n=12)	SympEF <50 (n=9)	*P* Value
Echocardiography					
AVA index, cm^2/m^2	1.5±0.2	0.5±0.1*	0.4±0.1*†	0.4±0.1*†	<0.001
Peak gradient, mm Hg‡	—	53±19	93±27†	71±29†	<0.001
Mean gradient, mm Hg‡	—	31±12	57±18†	43±19†	<0.001
GLS, %	−19±2	−18±2	−14±2*†	−11±3*†§	<0.001
LVEF, %	63±5	70±6*	58±8†	47±10*†§	<0.001
s′, cm/s	6.0±0.9	5.5±1.0	4.8±0.7*†	3.8±0.8*†§	<0.001
E/A	1.1±0.3	0.9±0.2*	1.1±0.6	0.7±0.3*	0.03
DT, ms	217±57	289±66*	243±70†	276±75	0.01
IVRT, ms	114±9	92±17*	90±39	112±25†	0.02
E/e′	9.0±1.3	16.2±5.0*	18.6±6.5*	23.2±8.3*†	<0.001
Cardiovascular magnetic resonance					
LV mass index, g/m^2	69±11	86±19*	102±29*	124±32*†	<0.001
EDV index, mL/m^2	70±13	69±16	75±23	106±30*†§	<0.001
ESV index, mL/m^2	26±6	20±9*	27±10†	62±30*†§	<0.001
LVEF, %	63±4	71±6*	65±7†	43±10*†§	<0.001
SV index, mL/m^2	38±5	42±8	41±11	37±5	0.39
Cardiac index, L/m^2 per minute	2.4±0.4	2.7±0.6	2.9±0.7	2.5±0.5	0.14
Concentric remodeling‖	1.0±0.1	1.3±0.2*	1.4±0.3*	1.2±0.2*	<0.001
Peak systolic wall stress, kPa	180±22	240±44*	273±64*	293±67*†	<0.001

Values are mean±SD. AsympEF ≥50 indicates asymptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; AVA, aortic valve area; DT, deceleration time; EDV, end-diastolic volume; ESV, end-systolic volume; GLS, global longitudinal strain; IVRT, isovolumetric relaxation time; LV, left ventricle; LVEF, left ventricular ejection fraction; SV, stroke volume; SympEF ≥50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; SympEF <50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction <50%.

*P<0.05 vs controls.

†P<0.05 vs AsympEF ≥50.

‡Without correction for pressure recovery.

§P<0.05 vs SympEF ≥50.

‖Concentric remodeling=LV mass/EDV.

Biomarkers and Substrates

NT-proBNP was higher in symptomatic AS groups than in AsympEF ≥50 participants and controls, and increasing NT-proBNP correlated with decreasing MEE (r^2=0.25, P<0.001) (Table 1). Plasma concentrations of glucose, insulin, ketone bodies, lactate, free fatty acids, and normetanephrine did not differ among study groups, whereas metanephrine was significantly higher in SympEF ≥50 and SympEF <50 participants than in controls (P=0.009 and P=0.01, respectively). Increasing levels of metanephrine and normetanephrine correlated weakly with decreasing MEE (r^2=0.09, P=0.01, and r^2=0.11, P=0.005, respectively). MVO_2 did not correlate significantly with any of the biomarkers or substrates listed.

Paradoxical Low-Flow, Low-Gradient AS

A subgroup analysis was performed including AS patients only and with AVA index ≤0.6 cm^2/m^2 and preserved LVEF ≥50% in the following categories: normal flow, low gradient; normal flow, high gradient; and paradoxical low flow, low gradient (P-LFLG). Normal flow was defined as a stroke volume index ≥35 mL/m^2 and high gradient as a mean gradient ≥40 mm Hg without correction for pressure recovery.[25]

Group characteristics are presented in Table S2. MEE for patients with P-LFLG was reduced compared with those with normal flow, high gradient and normal flow, low gradient (P=0.01 and 0.003); moreover, MEE for P-LFLG was comparable to the level of MEE in patients with LVEF <50% (Figure 3). Patients with P-LFLG also had smaller end-diastolic

Table 3. ^{11}C-Acetate Positron Emission Tomography

	Controls (n=10)	AsympEF ≥50 (n=37)	SympEF ≥50 (n=12)	SympEF <50 (n=9)	*P* Value
MEE, %	21.0±1.6	22.3±3.3	22.1±4.2	17.3±4.7*†‡	0.003
k_2, /min	0.085±0.015	0.094±0.018	0.103±0.024	0.084±0.019	0.07
EW, mm Hg × mL/min × 10^3	445±93	639±189*	834±264*†	566±150*‡	<0.001
Total MVO_2, mL/min	14.1±2.6	19.2±5.8*	25.5±7.7*†	22.6±6.1*	<0.001
MVO_2, mL/min/g	0.105±0.020	0.117±0.024	0.129±0.032	0.104±0.026	0.07
MBF, mL/min/g	0.72±0.12	0.84±0.18	0.90±0.26	0.77±0.16	0.11

Values are mean±SD. AsympEF ≥50 indicates asymptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; EW indicates external stroke work; MBF, myocardial blood flow; MEE, myocardial external efficiency; MVO_2, myocardial oxygen consumption; SympEF ≥50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; SympEF <50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction <50%.
*P<0.05 vs controls.
†P<0.05 vs AsympEF ≥50.
‡P<0.05 vs SympEF ≥50.

and end-systolic volume indexes and a lower cardiac index than those with normal flow, high gradient and normal flow, low gradient. Patients with P-LFLG had a greater GLS than patients with normal flow, high gradient, whereas there were no differences in LVEF among groups.

Regression Analysis Adjusting for Age

Regression analysis adjusting for age differences between groups did not change any of the results presented in Table 3, except for eliminating the difference in MEE between controls and SympEF <50 participants (P=0.31).

Discussion

Myocardial oxidative metabolism and its coupling to contractile work are fundamentals of cardiac function and thus are of obvious interest in patients with AS. To date, the present study is the largest study of MEE and MVO_2 in patients with AS and the first to investigate patients across a wide clinical spectrum of the disease. The 2 main findings of the present study were (1) that AS patients display unaltered MVO_2 regardless of their clinical status, systolic function, and disease severity and (2) that MEE deteriorates after the onset of severely reduced systolic function, defined as GLS greater than −12% or LVEF <50, and suggests that a decline in MEE is a secondary event rather than the triggering cause of contractile dysfunction.

Myocardial Energetics in the Hypertrophied and Failing Heart of AS Patients

The pathophysiology of myocardial hypertrophy and the progression to LV failure in AS patients is a matter of ongoing debate,[26,27] and impaired MVO_2 capacity, limited substrate accessibility, and energy transfer or utilization have been proposed as responsible adverse mechanisms.[5,9,28] However, clinical studies on MVO_2 and MEE during the progression from compensated hypertrophy to heart failure are lacking.

Only a few minor studies have investigated MVO_2 in AS patients, and their conclusions are inconsistent.[28–31] These studies were also restricted by the absence of methods or by inaccurate methods to quantify stroke work, which evidently hampers any firm conclusion of how AS may affect myocardial efficiency. A more recent study found normal MVO_2 and reduced myocardial efficiency in 10 symptomatic AS patients with preserved LVEF compared with a younger control group (32% versus 49%).[28] Notably, myocardial efficiency for controls was substantially higher than that shown in previous reports (≈15–30%), and the reliability of this conclusion may be questioned.[7]

In the present study, MVO_2 was unaltered regardless of symptoms, systolic function, or degree of hypertrophy. This indicates that the rate of mitochondrial oxidative phosphorylation was preserved despite the development of hypertrophy and LV failure. We also observed that MEE declined at a rather late stage in the LV failure process, as measured by LVEF, NT-proBNP, and GLS (Figure 1, Tables 1 and 2). These observations suggest that systolic dysfunction precedes a decline in MEE and that the heart failure process is not triggered by mitochondrial dysfunction. Future studies trying to identify and target potential adverse mechanisms up- or downstream from the mitochondrion may improve outcomes in AS patients.

MEE and MVO_2 in Asymptomatic and Symptomatic AS Patients

The number of elderly patients with AS is increasing, and in these patients, physical limitations often restrict the

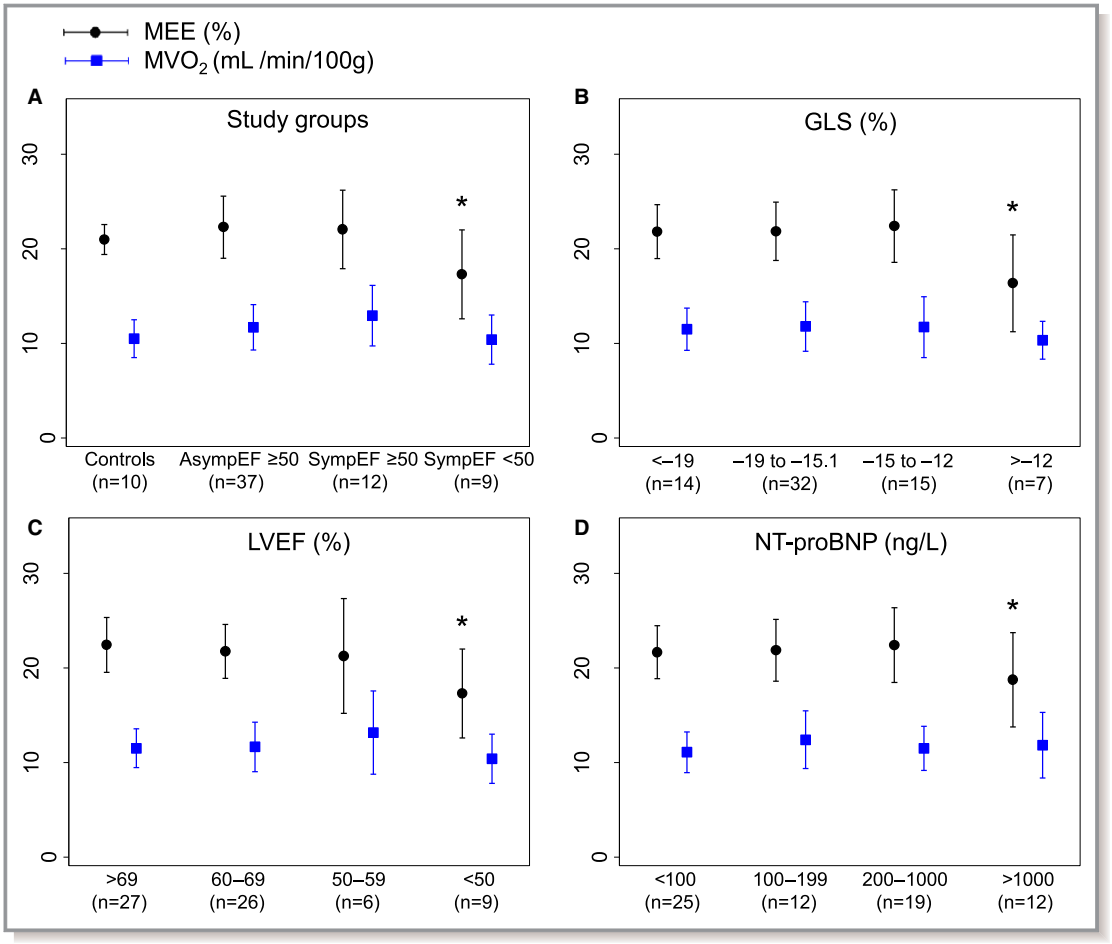

Figure 1. MEE and oxygen consumption. MEE declined late, and MVO_2 was constant regardless of study group (A), despite deteriorating GLS (B), LVEF (C), or increasing NT-proBNP (D). Values are mean±SD. *P<0.05 vs other groups (except for LVEF <50 vs 50–59 [P=0.20]). AsympEF ≥50 indicates asymptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MEE, myocardial external efficiency; MVO_2, myocardial oxygen consumption; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SympEF ≥50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction ≥50%; SympEF <50, symptomatic aortic valve stenosis patients with left ventricular ejection fraction <50%.

applicability of exercise testing. To aid correct classification of AS patients, it has been proposed to measure NT-proBNP and GLS, but their roles in clinical decision making remain controversial. Whether MEE and MVO_2 could be useful in this context has yet to be studied. The present study showed that MEE and MVO_2 had poor diagnostic accuracy for discrimination between symptomatic and asymptomatic AS patients (Figure 2). Consequently, the superior discriminatory value of GLS and NT-proBNP indicates that a single measurement of MVO_2 or MEE is of limited clinical value. The diagnostic accuracy of MEE, however, appears to be limited by large interindividual variation; therefore, longitudinal studies are warranted to investigate whether serial MEE measurements yield prognostic information in the individual asymptomatic AS patient.

Mechanoenergetic Uncoupling in P-LFLG AS

P-LFLG AS represents a challenging category of AS patients with respect to appropriate diagnostics and therapeutic management.[32] Delay of aortic valve replacement in these patients worsens their outcome[32]; however, the group's operative risk is increased.[33]

The present study showed that MEE was significantly reduced in patients with P-LFLG AS compared with patients with normal-flow AS. Surprisingly, MEE was reduced to a level similar to that seen in symptomatic patients with reduced LVEF. The reduction in MEE was caused mainly by reduced EW, whereas MVO_2 remained unaltered (Figure 3, Table S2). This finding suggests that patients with P-LFLG AS should be characterized by energy-inefficient LV remodeling,

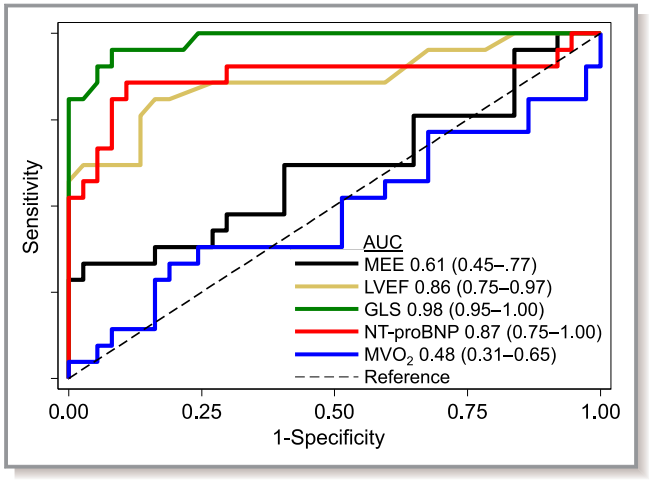

Figure 2. Diagnostic accuracy to distinguish between asymptomatic and symptomatic aortic valve stenosis (AS) patients. Receiver operating characteristic curve analysis illustrating the diagnostic accuracy to distinguish between AS patients with and without symptoms. GLS vs MEE, GLS vs MVO_2, and GSL vs LVEF, all $P<0.05$. GLS vs NT-proBNP, $P=0.10$. Values are AUC (95% CI). AUC indicates area under the receiver operating characteristic curve; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MEE, myocardial external efficiency; MVO_2, myocardial oxygen consumption; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

which offers a mechanoenergetic explanation of the so far inexplicably poor prognosis observed in patients with P-LFLG.

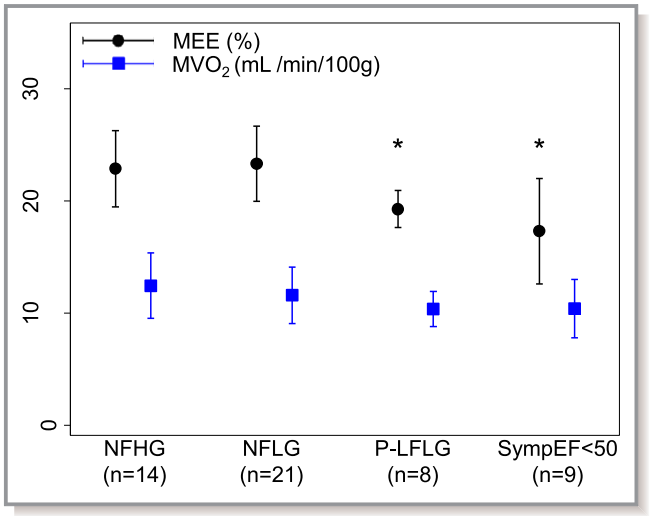

Figure 3. Reduced MEE and MVO_2 in patients with paradoxical low-flow low-gradient aortic valve stenosis (AS). Reduced MEE in patients with P-LFLG compared with AS patients with NFHG and NFLG AS. Mean±SD. *$P<0.05$ compared with NFHG and NFLG. MEE indicates myocardial external efficiency; MVO_2, myocardial oxygen consumption; NFHG, normal-flow, high-gradient; NFLG, normal-flow, low-gradient; P-LFLG, paradoxical low-flow, low-gradient aortic valve stenosis.

Study Limitations

Evaluation during rest minimized motion artifacts and ensured high-quality PET and CMR images but restricted the conclusions to resting conditions only. Future studies should include myocardial stress testing that seeks to expose differences in mechanical and metabolic reserves in AS patients. This approach could yield important information.

A precondition for noninvasive quantification of EW is the assumption that the LV pressure–volume loop has a rectangular shape. Such simplification of the true relation is well accepted despite the risk of minor methodological inaccuracies.[7] This assumption, however, is further challenged by the presence of a pressure gradient across the stenotic aortic valve in AS patients. To minimize the risk of underestimating EW, mean arterial blood pressure was corrected for mean gradients. This is believed to have improved accuracy.

Transmural perfusion was not different among study groups; however, AS patients' vulnerability to subendocardial ischemia is well recognized and suspected to play a role in the pathophysiology of AS.[34] Assessment of blood flow in the subendocardial layer of the myocardium by PET is limited by low spatial resolution. Consequently, subendocardial ischemia could contribute to LV contractile dysfunction despite a preserved rate of oxidative phosphorylation as measured by MVO_2.

This study was restricted by the numbers of symptomatic patients included. Consequently, it was not possible to apply a statistical model correcting for multiple variables; however, we performed a regression analysis adjusting for age differences among groups. This did not affect the overall result of deteriorating MEE for AS patients with LVEF <50, a finding supported by the fact that no evidence suggests age affects MEE, MVO_2, or EW when examined during rest.

Conclusions

AS patients displayed unaltered MVO_2 and MEE despite onset of symptoms and moderate systolic dysfunction. These results indicate preserved mitochondrial function with a persistent ability to convert energy into EW in AS patients and suggest that MEE deteriorates late in the heart failure process. MVO_2 and MEE could not discriminate between asymptomatic and symptomatic patients, whereas GLS and NT-proBNP displayed excellent discriminatory performance. In contrast, patients with P-LFLG AS displayed prematurely reduced MEE compared with normal-flow AS patients. These findings may contribute to a poor clinical outcome.

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Disclosures

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SUPPLEMENTAL MATERIAL

TABLE S1. PATIENTS GROUPS ACCORDING TO AORTIC VALVE CHARACTERISTICS

		Aortic valve area index (cm^2/m^2)				
	Controls	**>0.52**	**0.46-0.52**	**0.36-0.45**	**<0.36**	**p**
MEE, %	21.0 ± 1.6	20.7 ± 3.6	21.7 ± 3.4	22.4 ± 3.6	21.1 ± 5.3	0.76
MVO2, mL/min/g	0.105 ± 0.020	0.122 ± 0.028	0.106 ± 0.021	0.119 ± 0.026	0.122 ± 0.030	0.26
GLS, %	-19 ± 2	-19 ± 3	-16 ± 2	-17 ± 3	-13 ± 4	<0.001
NT-proBNP, ng/L	31 (23-74)	88 (34-2111)	149 (50-1343)	256 (53-2026)	1030 (46-12677)	<0.001
		Mean gradient (mmHg)				
	Controls	**<24.6**	**24.6-33.2**	**33.3-47.6**	**>47.6**	**p**
MEE, %	21.0 ± 1.6	20.2 ± 3.3	22.1 ± 3.6	23.0 ± 4.2	20.5 ± 4.7	0.23
MVO2, mL/min/g	0.105 ± 0.020	0.114 ± 0.027	0.118 ± 0.029	0.114 ± 0.021	0.125 ± 0.030	0.42
GLS, %	-19 ± 2	-17 ± 3	-18 ± 3	-15 ± 3	-13 ± 3	<0.001
NT-proBNP, ng/L	31 (23-74)	74 (38-2111)	149 (34-401)	300 (46-1243)	1169 (112-12677)	<0.001

Patients with aortic valve stenosis (n=58) were subdivided into 4 groups according to interquartile range of aortic valve area index and mean gradient, respectively. Values are mean ± SD. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is presented as median (interquartile range). Global longitudinal strain (GLS). Myocardial external efficiency (MEE). Myocardial oxygen consumption (MVO_2).

TABLE S2. PARADOXICAL LOW FLOW, LOW GRADIENT VS. NORMAL FLOW AS

	NFHG (n=14)	**NFLG (n=21)**	**P-LFLG (n=8)**	**p**
MEE, %	22.9 ± 3.4	23.3 ± 3.4	19.3 ± 1.7*†	0.01
EW, mmHg x mL/min x 10^3	884 ± 213	661 ± 165	442 ± 815*†	<0.001
Total MVO_2, mL/min	26.1 ± 6.8	19.3 ± 5.8	15.3 ± 2.9*	<0.001
MVO_2, mL/min/g	0.124 ± 0.029	0.116 ± 0.025	0.104 ± 0.016	0.19
NYHA class I/II/III/IV, n	7/6/1/0	20/1/0/0	7/0/1/0	0.02
NT-proBNP, ng/L	463 (46-2379)	127 (53-682)	82 (50-401)*	0.003
AVA index, cm^2/m^2	0.3 ± 0.1	0.5 ± 0.1	0.5 ± 0.1*	<0.001
GLS, %	-15 ± 3	-18 ± 2	-17 ± 2*	0.002
LVEF, %	67 ± 7	71 ± 5	71 ± 5	0.26
LV mass index, g/m^2	109 ± 24	87 ± 19	75 ± 11*	<0.001
EDV index, mL/m^2	84 ± 20	72 ± 13	51 ± 5*†	<0.001
ESV index, mL/m^2	28 ± 11	21 ± 7	15 ± 3*†	<0.001
Cardiac index, $L/m^2/min$	3.1 ± 0.5	2.8 ± 0.5	2.0 ± 0.2*†	<0.001
Concentric remodeling‖	1.3 ± 0.2	1.2 ± 0.2	1.5 ± 0.3†	0.02

*Values are mean ± SD. *p < 0.05 vs. normal flow, high gradient (NFHG). †p < 0.05 vs. normal flow, low gradient (NFLG). Paradoxical low flow, low gradient (P-LFLG). N-terminal pro-B-type natriuretic peptide (NT-proBNP) is presented as median (interquartile range). ‖Concentric remodeling = LV mass/ EDV. Aortic valve area (AVA). End-diastolic volume (EDV). End-systolic volume (ESV). Global longitudinal strain (GLS). Left ventricle (LV). Left ventricular ejection fraction (LVEF). Mechanical external work (EW). Myocardial external efficiency (MEE). Myocardial blood flow (MBF). Myocardial oxygen consumption (MVO_2)*