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Cardiopulmonary exercise testing in aortic stenosis patients before and after aortic valve replacement

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ABSTRACT

Background Knowledge about how patients with symptomatic aortic stenosis (AS) perform on cardiopulmonary exercise testing (CPET) is sparse. Since exercise testing in patients with symptomatic AS is not advised, submaximal parameters could be of special interest. We aimed to investigate maximal and submaximal physical capacity by CPET before and 1 year after surgical aortic valve replacement (sAVR) in patients with severe AS.

Methods In this prospective longitudinal study, 30 adult patients (age 66±10 years) with severe AS referred for sAVR underwent maximal CPET (respiratory exchange ratio ≥1.05) on a bicycle ergometer before (PRE) and 1 year after (POST) sAVR. Normally distributed data are presented as mean (±SD) and non-normally distributed data are presented as median (IQR).

Results Median peak workload increased by 8% from 133 (55) watts at PRE to 144 (67) watts at POST ($p<0.001$). Median ventilatory threshold (VO_2@VT) increased from 1216 (391) to 1328 (309) mL/min ($p=0.001$, $n=28$). Mean peak oxygen uptake (peakVO_2) was not significantly different between PRE and POST; 1871±441 vs 1937±404 mL/min ($p=0.08$). The oxygen uptake efficacy slope (OUES) was significantly correlated to PeakVO2 at both PRE ($r=0.889$, $p<0.05$) and POST ($r=0.888$, $p<0.05$)

Conclusion Physical work capacity was improved 1 year following sAVR, in terms of higher median peak workload and VO_2@VT. The strong correlation between the submaximal variable OUES and peakVO_2 suggests that OUES might be a useful surrogate of peakVO_2 in this group of patients where maximal exercise testing is not always recommended.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiopulmonary exercise testing (CPET) has been shown to be prognostic for several different heart diseases but has not fully been explored in patients with severe aortic stenosis.

WHAT THIS STUDY ADDS

⇒ The study adds novel information about physical work capacity and other CPET variables in patients with severe aortic stenosis and how they are affected by aortic valve replacement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings of this study might influence the use of CPET in the preoperative evaluation of patients with aortic stenosis.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease in Europe and the prevalence increases with age.[1,2] Aortic valve replacement (AVR) is a class 1 recommendation for patients with symptomatic severe AS.[3] Due to the gradual progression of AS, symptoms may be under-reported by the patient and objective measures of cardiopulmonary function could support optimal patient management. Cardiopulmonary exercise testing (CPET) has been shown to be prognostic for several heart diseases, including the natural course of AS.[4]

In present European and American guidelines,[3,5] exercise testing is recommended in asymptomatic patients with severe AS to unmask symptoms related to AS. However, for symptomatic patients with severe AS the guidelines recommend AVR, while exercise testing is not advised. The knowledge about how patients with symptomatic severe AS perform during CPET is sparse. If exercise testing parameters that do not require maximal effort are shown to predict maximal parameters or even prognosis, then they could be of special interest in this group of patients. The oxygen uptake efficiency slope (OUES)[6] and the ventilation-carbon dioxide elimination slope (VE/VCO_2-slope) are two such parameters. They have been shown to be highly prognostic in heart failure patients[7,8] but have not been evaluated in patients with AS considered for AVR.

We aimed to investigate maximal and submaximal parameters from CPET in patients with severe AS before surgical AVR (sAVR) to further characterise their exercise response and to compare this with CPET data 1 year after sAVR.

METHODS

Study population

In this prospective longitudinal study (ClinicalTrials.gov, ID: NCT02790008), all adult patients referred for sAVR at a single department between April 2014 and February 2019 were reviewed for eligibility. Inclusion criteria were age ≥18 years and AS meeting criteria for sAVR decided by a multidisciplinary heart team. Exclusion criteria were previous or concomitant heart disease including previous cardiac surgery, myocardial infarction, coronary artery disease, other valvular heart disease or haemodynamic instability (ie, acute surgery).

Cardiopulmonary exercise testing

Each patient underwent maximal CPET on a bicycle ergometer (eBike Basic, GE Medical System, Germany) before (PRE) and 12 months after sAVR (POST). Ventilation and gas exchange were measured on a breath-by-breath basis (Jaeger Oxycon Pro or Vyntus CPX, Viasys Healthcare, Hoechberg, Germany). Patients were monitored during the tests with continuous ECG (Marquette CASE 8000, GE Medical Systems, Milwaukee, Wisconsin, USA) and frequent measures of systolic blood pressure. Participants rated chest pain, dyspnoea (Borg CR-10 scale) and perceived exertion (Borg RPE scale). The test protocol included an initial 5 min of constant workload at 20, 30, 40 or 50 watts (W), followed by a continuous increase in workload by 10 or 20 W per minute. The same protocol for each patient was used at both PRE and POST, except for one patient with a different submaximal constant workload (excluded from submaximal analyses) and two patients with different ramp protocols. Peak workload was recalculated at POST for those two patients with different ramp protocols by using the following formula proposed by Brudin *et al*: $W_{max}(a_1,b_1)=(b_1/b_2)^{1/6}$, where a_1 is the initial load and b_1 is load increase per minute.[9] Each test was driven as far as possible considering standard termination criteria.[10]

Cardiopulmonary parameters

Minute ventilation (VE), oxygen uptake (VO_2) and carbon dioxide elimination (VCO_2) were measured breath by breath and presented numerically as 10 s means (excluding the highest and lowest value), using commercially available software (JLab V.5.72.1 or SentrySuite V.2.21, CareFusion, Heidelberg, Germany). Maximal CPET was defined as the peak respiratory exchange ratio (RER) ≥1.05.

PeakVO_2 (mL/min) was determined as the mean of the three highest consecutive 10 s averages recorded at or close to the end of the test. PeakVO_2 was further indexed to body mass (mL/kg/min). Predicted peakVO_2 was calculated using the reference material from Gläser *et al*.[11]

The oxygen pulse was calculated as VO_2/heart rate (HR). Two VE/VCO_2-slopes were semiautomatically determined by the software using linear regression and manually adjusted as appropriate.[12] Slope-max refers to the slope of the full curve until the end of exercise while slope submax refers to the slope confined to the linear part up until the respiratory compensation point.

The oxygen uptake at the ventilatory threshold (VO_2@VT) was manually determined at the deflection point of VO_2 relative to VCO_2 (V-slope method) and by identifying the nadir of VE/VO_2. In difficult cases, a second experienced examiner was consulted, and consensus was reached. Our research group has previously assessed and reported low interobserver variability for determining VO_2@VT and VE/VCO_2-slopes for a similar population using the same technical equipment.[13]

The OUES was determined from the log-linear relation between VO_2 and VE[14]: VO_2=a×log10 VE+b, where 'a' denotes the slope of the curve (OUES) and 'b' denotes the y-axis intercept. OUES was indexed by body surface area (BSA) and compared with predicted values from a healthy reference population taking gender, age and BSA into consideration.[15]

The CPET variables during submaximal constant workload were determined as the mean of the values during the last minute of the initial 5 min constant workload.

Statistics

Normality was assessed with a Shapiro-Wilk's test. A paired t-test was used for statistical comparisons between PRE and POST in normally distributed data and presented as mean±SD. A Wilcoxon signed rank test for related samples was used for comparisons between PRE and POST in non-normally distributed data, presented as median (IQR). Pearson's r was used for correlation analysis. McNemar's test was used for comparing proportions (categorical data). Statistica V.13.0 (TIBCO Software, Palo Alto, California, USA) and IBM SPSS Statistics for iOS V.28.0.1.0 (IBM) were used for statistical analyses. Statistical significance was set at $p<0.05$.

Patient and public involvement

Patients and the public were not involved in the design of this study.

RESULTS

Out of 44 patients initially enrolled in the study, four were excluded from analyses due to a submaximal exercise test at either PRE or POST (defined as a peak RER<1.05), one because of inability to perform bicycle testing, five as they could not be reached or declined the POST examination, one due to a diagnosis of malignant disease during the follow-up time, two due to myocardial infarction (Non ST-Elevation Myocardial Infarction) at the time of registration for surgery or during the follow-up respectively and one due to a diagnosis of moderate arrhythmia preoperatively. Thus, 30 patients performing both CPET (with RER ≥1.05) were included in the analyses (table 1).

Table 1 Patient characteristics (n=30)

	PRE	POST	P value
Age PRE (years)	66±10		
Time PRE to surgery (days)	7 (11)		
Time PRE to POST (weeks)	54 (3)		
Male:female (n)	22:8		
Height (cm)	176±7		
Weight (kg)	82.7±13.0	83.2±13.9	0.40
BMI	26.8±3.6	26.9±3.8	0.45
Body surface area (m^2)	1.98±0.17	1.99±0.18	0.47
Bioprosthesis (n (%))		27(90)	
Mechanical prosthesis (n (%))		3(10)	
Haemoglobin (Hb) (g/L) (n=30)	144±9		
Hb (g/L) (n=25) paired t-test	144±10	145±14	0.73
NT-ProBNP (ng/L) (n=23)	240 (250)	160 (170)	**0.005**
SBP at rest (mm Hg)	137±17	140±21	0.33
Beta-blocker treatment (n (%))*	8(27)	18(60)	**0.013**
Pacemaker (n)		1 (3)	
LVEF (%)	59 (5)	61 (9)	0.19

Data are presented as mean ±SD or median (IQR). Bold p-values = p<0.05.
*McNemar's test. Data from blood sampling regarding Hb concentration were missing at POST for five patients and regarding NT-ProBNP for seven patients.
BMI, body mass index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal probrain natriuretic peptide; SBP, systolic blood pressure.

The median peak workload increased by 8% from 133 (55) W at PRE to 144 (67) W at POST (p<0.001, table 2). The mean peakVO_2 tended to be higher at POST versus PRE, 4%, however, not statistically significant (1937±404 mL/min vs 1871±441 mL/min, p=0.08). The median VO_2@VT (determinable in 28 out of 30 patients)

Table 2 Peak values CPET (n=30)

	PRE	POST	P value
Workload (W)	133 (55)	144 (67)	**<0.001**
HR (beats/min)	142±20	142±19	0.90
BF at PeakVO_2 (breaths/min)	30±5	33±6	**<0.001**
VO_2 (mL/min)	1871±441	1937±404	0.08
% of predicted peakVO_2 (%)	95±15	100±15	**0.022**
VO_2/kg (mL/kg/min)	22.5±4.0	23.2±3.7	0.20
VCO_2 at peakVO_2 (mL/min)	2109±570	2263±532	**0.006**
VE at peakVO_2 (L/min)	66.4±16.8	75.7±18.3	**<0.001**
VE/O_2 at peakVO_2	34.2 (4.9)	38.7 (6.4)	**0.001**
VE/CO_2 at peakVO_2	30.5±2.7	32.0±3.3	**0.005**
RER	1.14±0.07	1.18±0.07	**0.014**
Oxygen pulse at peakVO_2 (mL/beat)	13.3±2.7	13.8±2.4	0.10
VO_2@VT (mL/min) (n=28)	1216 (391)	1328 (309)	**0.004**
VT % of peakVO_2 (%) (n=28)	71.0±11.1	73.0±10.4	0.36

Data are presented as mean ±SD or median (IQR). Bold p-values = p<0.05.
BF, breathing frequency; CPET, cardiopulmonary exercise testing; HR, heart rate; ΔLoad, difference between peak workload and steady state load; RER, respiratory exchange ratio; VCO_2, carbon dioxide elimination; VE, ventilatory equivalent; VO_2, oxygen uptake; ΔVO_2, Difference between peakVO_2 and steady state VO_2; VT, ventilatory threshold; W, Watt.

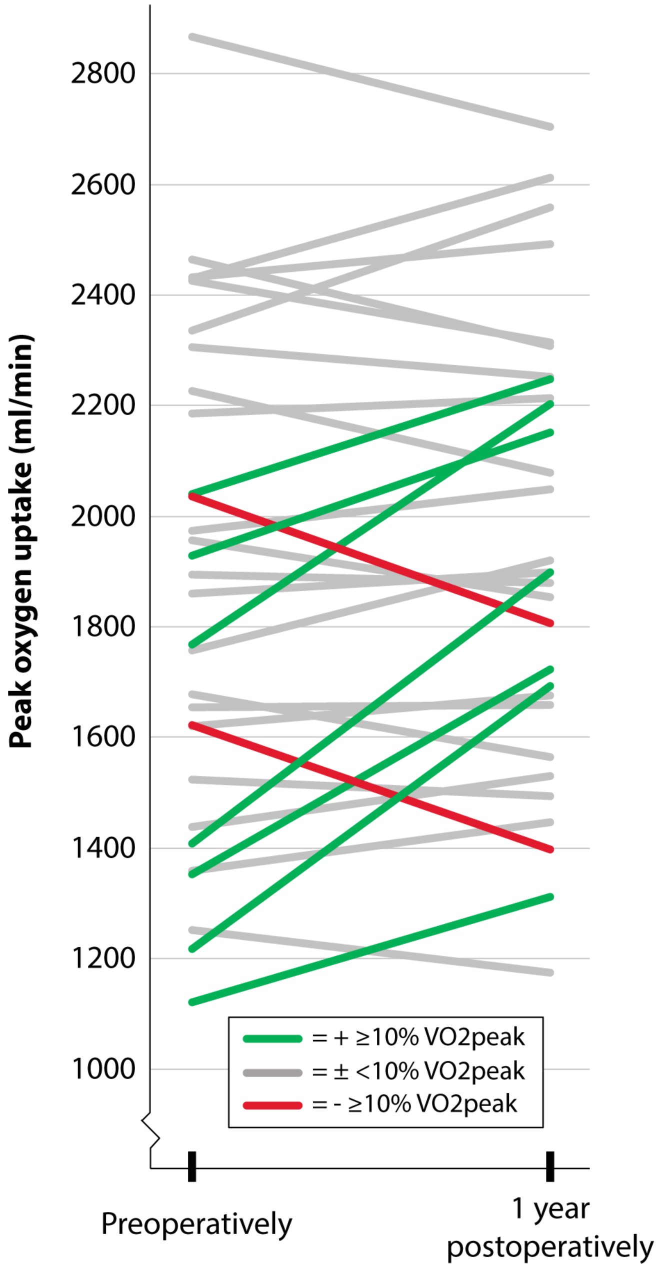

Figure 1 Individual change in peakVO_2 (mL/min) between PRE and POST. peakVO_2, peak oxygen uptake.

increased from 1216 (391) mL/min to 1328 (309) mL/min (p=0.001). Figure 1 shows the distribution of the individual change in peakVO_2 and in the peak workload between PRE and POST.

The CPET variables during submaximal constant workload are found in table 3. They were similar at PRE and POST except HR, which was significantly lower at POST compared with PRE (90±14 beats/min vs 98±20 beats/min, p=0.006). The percentage of patients treated with beta-blockers went from 27% to 60% (p=0.013) between PRE and POST. The correlation between the submaximal parameter OUES and peakVO_2 was statistically significant at PRE (r=0.89, p<0.05; figure 2) as well as at POST (r=0.89, p<0.05).

Table 3 CPET variables at submaximal constant workload (n=29)

	PRE	POST	P value
HR (beats/min)	98±20	90±14	**0.006**
BF (breaths/min)	19±3	19±3	0.76
VO_2 (mL/min)	966±148	952±129	0.41
VO_2/kg (mL/kg/min)	11.7±1.7	11.5±1.7	0.26
VCO_2 (mL/min)	888±161	871±147	0.32
VE	27.2±5.3	27.2±5.5	0.98
VE/VO_2	26.5±2.8	26.5±3.6	0.98
VE/VCO_2	28.8±2.2	28.8±2.7	0.85
RER	0.92±0.06	0.91±0.07	0.72

One patient was excluded from these analyses due to different submaximal constant workloads at PRE and POST. Data are presented as mean±SD or median (IQR). Bold p-values = p<0.05. BF, breathing frequency; CPET, cardiopulmonary exercise testing; HR, heart rate; RER, respiratory exchange ratio; VCO_2, carbon dioxide elimination; VE, ventilatory equivalent; VO_2, oxygen uptake; W, watt.

The VE/VCO_2 slope was determinable in all but one patient. The VE/VCO_2 slope max was significantly higher at POST compared with PRE (31.9±3.8 vs 29.9±3.3, p=0.002), while slope submax was similar at PRE and POST (27.6±2.8 vs 28.1±3.2, p=0.39, table 4).

To further investigate the heterogeneity of the response in peakVO_2 from PRE to POST seen in figure 1, we first performed a correlation analysis and found a significant negative correlation between peak VO_2 at PRE and the change in peakVO_2 between PRE and POST (r=–0.41, p=0.026). The 16 patients who had preoperative peakVO_2 below the mean (95%) of predicted peakVO_2 were then separately analysed. In those, the mean peakVO_2 increased significantly by 9% from 1753±426 mL/min at PRE to 1913±398 mL/min at POST (p=0.005).

The eight patients with a decrease in peakVO_2 of more than 5% between PRE and POST were further analysed. The mean decrease in peakVO_2 in these patients was 8%, from 2012±511 mL/min (99%±16% of predicted peakVO_2) at PRE to 1861±498 mL/min (93%±15% of predicted peak VO_2) at POST (p<0.001). The mean haemoglobin level (n=7) remained similar (144±13 vs 144±15 g/L, p=0.94), as well as their mean weight (80±10 vs 80±11, p=0.79). In these eight patients, the mean VO_2@VT was 1288±298 mL/min at PRE and 1338±322 mL/min at POST (p=0.39), while the mean peak RER was 1.14±0.07 at PRE and 1.19±0.05 at POST (p=0.10).

DISCUSSION

This is, to our knowledge, the first prospective study where the change in CPET parameters from before to after sAVR is evaluated in a population of patients with AS accepted for sAVR. We found that physical work capacity was improved 1 year following sAVR in terms of higher median peak workload and VO_2@VT in this group of

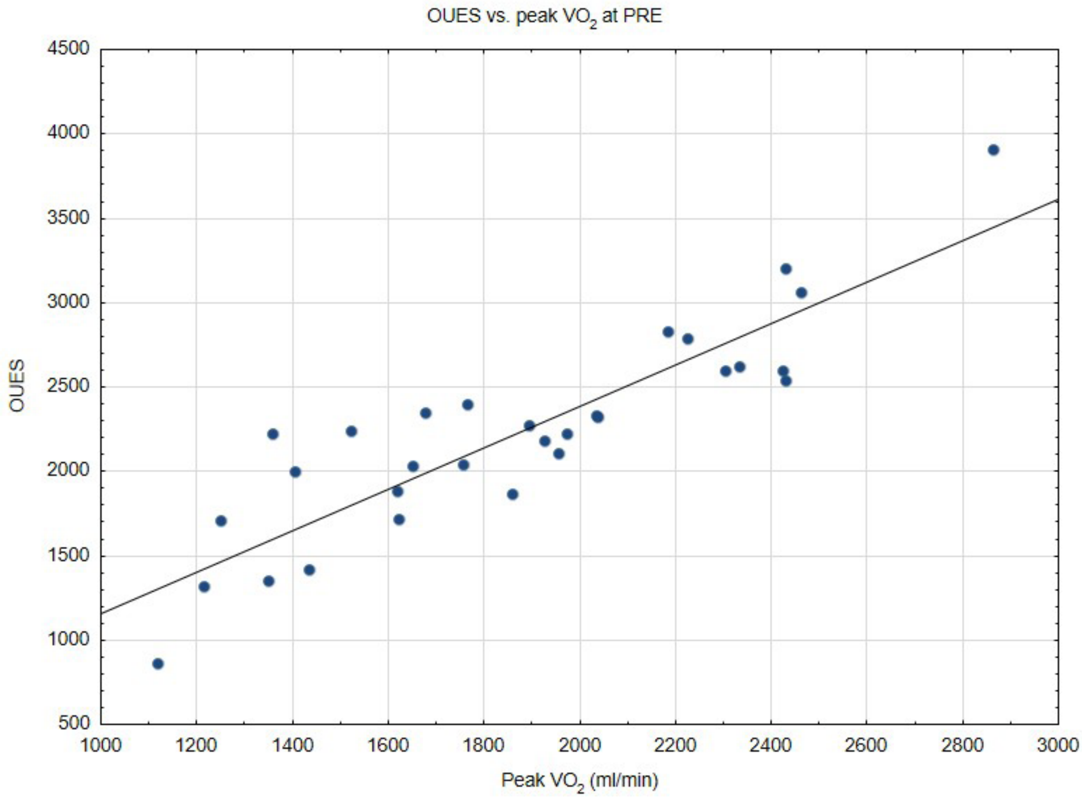

Figure 2 Scatterplot of OUES against peakVO_2 (mL/min) at PRE, r=0.889 ($p<0.05$). OUES, oxygen uptake efficacy slope; peakVO_2, peak oxygen uptake.

patients. The submaximal parameter OUES was strongly correlated with peakVO_2.

Submaximal variables

The strong correlation between peakVO_2 and OUES has been reported previously in healthy individuals[6 14] but not in patients with severe AS. This is of particular interest because of the documented relationship between OUES and clinical outcome in different heart diseases[16–18] and should be explored in future studies. Since maximal exercise testing is not advised for patients with symptomatic severe AS in clinical settings,[19] submaximal parameters could be of special interest in this population. The median VO_2@VT was 9% higher at POST compared with PRE, which supports a small but significant improvement in cardiorespiratory fitness following sAVR. Except for HR, CPET variables during submaximal constant workload in table 3 were all similar between PRE and POST. The decline in HR between PRE and POST can be explained by the more frequent use of beta-blockers at POST.

When comparing the different VE/VCO_2 slopes (slope max and slope submax) in table 4, the slope max was significantly higher at POST compared with PRE (31.9±3.8 vs 29.9±3.3, p=0.002), while slope submax (VE/VCO_2) was similar (28.1±3.2 vs 27.6±2.8, p=0.39). The difference between slope max and slope submax could be explained by the fact that the highly anaerobic phase of exercise, after the respiratory compensation point, is included in slope max, while slope submax refers to the slope confined to the linear part of the curve up until the respiratory compensation point, excluding the most anaerobic phase of the exercise. Patients might have driven their CPET a little further at POST (even though peakRER did not differ significantly), which may explain a higher slope max but not slope submax slope. We, therefore, suggest that the slope submax is the preferred VE/VCO_2 slope to use

Table 4 Calculated slopes

	PRE	POST	P value
Slope max (VE/VCO_2) (n=29)	29.9±3.3	31.9±3.8	**0.002**
Slope submax (VE/VCO_2) (n=29)	27.6±2.8	28.1±3.2	0.39
OUES (n=30)	2228±609	2205±508	0.70
OUES % of predicted (n=30)	78.9±17.2	79.1±14.4	0.94
OUES % predicted adjusted to BSA (n=30)	83.9±16.8	84.1±13.8	0.95

Data are presented as mean±SD. Bold p-values = p<0.05.
BSA, body surface area; OUES, oxygen uptake efficiency slope; VCO_2, carbon dioxide elimination; VE, ventilatory equivalent.

Maximal variables

In the present study, follow-up CPET was conducted 1 year after sAVR, the aim being to perform the evaluation after the period of detraining and normal rehabilitation after cardiac surgery. In order to include maximal exercise tests, only patients with peak RER ≥1.05 were included in the analysis.

We found some improvement in physical work capacity. There was a significant improvement measured as peak workload and VO_2@VT, and a slight but not significant improvement for peakVO_2. Lack of improvement in peakVO_2 has also previously been shown in patients after sAVR or transcatheter aortic valve implantation in a study by Le *et al*.[20] They found a heterogeneous change in peakVO_2 without a significant improvement in mean peakVO_2. They also found that less severe AS (lower mean gradient) and elevated brain natriuretic peptide predicted an unfavourable outcome for change in peakVO_2.

Since patients with severe AS undergoing sAVR probably have a cardiac limitation to their physical work capacity, one might expect an improvement in peak VO_2 after sAVR. Possibly, the cohort of patients accepted for sAVR is heterogeneous in terms of the degree of physical limitation due to their AS, and the patients in the present study reached a relatively high % of their predicted peak VO_2 during the preoperative CPET (95%±15%), indicating that a relatively fit study population agreed to participate in the study.

The mean postoperative % of predicted peakVO_2 was 100%±15%, indicating a normal physical work capacity post-sAVR. This was also shown in previous results by Becassis *et al* where no difference in peakVO_2 was seen between patients 1-year post-sAVR (both AS and aortic regurgitation) and a matched controlled group with no history of heart disease.[21] However, the pattern of the change in peakVO_2 between PRE and POST (figure 1) highlights the heterogeneity of the response in that parameter following sAVR. The bivariate correlation analysis between peakVO_2 and the change in peakVO_2 between PRE and POST as well as the subgroup analysis of the patients improving and decreasing their peakVO_2 implies that the patients with the lowest preoperative peak VO_2 were the ones more likely to improve in peakVO_2 following sAVR. As patients on average achieved a relatively high mean % of predicted peakVO_2 at the preoperative CPET (95%±15%), this could suggest that the improvement in peakVO_2 would have been greater if the mean % of predicted peakVO_2 at PRE had been lower. In this population with AS patients accepted for sAVR, the patients most affected by their AS are likely to be the ones with the lowest peakVO_2 at PRE. As remodelling of the left ventricle following sAVR may continue over several years,[22] there is also a possibility that further improvements in aerobic physical work capacity may occur even later after surgery.

The use of CPET is not suitable for all patients with AS. But a more accurate preoperative evaluation of cardiopulmonary function could be useful in patients that are on the borderline area between watchful waiting and sAVR. Our results indicate a favourable outcome in CPET parameters especially among the patients with the lowest preoperative peakVO_2, which can be helpful in making informed decisions. While the use of the 6 min walk test has shown to be of use in patients with TAVI to predict postoperative outcomes,[23 24] this remains to be evaluated for submaximal CPET variables. The question of whether high peak VO_2 or even OUES provides sufficient information to justify watchful waiting, even in the presence of other indications for surgery, remains a subject for future studies.

Limitations

The narrow inclusion criteria with no other concomitant heart disease led to a well-defined study population, which infers that the results may be difficult to extrapolate to a broader population with accompanying cardiopulmonary comorbidities. The design with repeated CPET might have influenced the selection of patients, with the most healthy and fit patients agreeing to participate.

CONCLUSIONS

In patients with severe AS accepted for surgery, physical work capacity was improved 1-year post-sAVR compared with the preoperative examination in terms of higher VO_2@VT and peak workload. The submaximal parameter OUES was strongly correlated to peak VO_2, which makes this variable of special interest in this patient population where maximal CPET is not always feasible. Patients with low preoperative peak VO_2 were most likely to improve their peakVO_2 after sAVR. Further research is warranted to study the outcome during longer follow-up after sAVR in relation to CPET variables.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the regional ethical review board in Linköping, Sweden (No. 2011/105-31). Participants gave written informed consent to participate in the study before taking part.

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