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Prognostic Usefulness of Cardiopulmonary Exercise Testing for Managing Patients With Severe Aortic Stenosis

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The approach to managing asymptomatic or questionably symptomatic patients for aortic stenosis is difficult. We aimed to determine whether cardiopulmonary exercise testing (CPET) is prognostically useful in such patients. Patients judged asymptomatic or questionably symptomatic for aortic stenosis with aortic valve area index <0.6 cm^2/m^2 and left ventricular ejection fraction ≥0.50 were managed conservatively provided they had either (group 1) normal peak oxygen consumption and peak oxygen pulse (>83% and >95% of the predicted values, respectively) or (group 2) subnormal peak oxygen consumption or peak oxygen pulse but with CPET data pointing to pathologies other than hemodynamic compromise from aortic stenosis. Increase in systolic blood pressure <20 mm Hg, ST depression ≥2 mm, or symptoms during the exercise test were allowed. Unexpected events included cardiac death or hospitalization with heart failure in patients who had not been recommended valve replacement. The median age of the study population (n = 101) was 75 years (interquartile range 65 to 79 years), and 67% were judged questionably symptomatic. During a follow-up at 24 ± 6 months, the rate of unexpected cardiac death and unexpected hospitalization with heart failure was 0% and 6.0%, respectively. All-cause mortality was 4.0% compared with 8.0% in the age- and gender-matched population. For group 1, 26 of 70 (37.1%) succumbed to cardiac death, or were hospitalized because of heart failure, or underwent valve replacement, and for group 2 this was 12 of 31 (38.7%). In conclusion, if CPET does not indicate a significant hemodynamic compromise because of aortic stenosis, an initially conservative strategy results in a good prognosis and an acceptable event rate. **(Am J Cardiol 2017;120:844–849)**

For patients who are asymptomatic or questionably symptomatic for aortic stenosis, it is often difficult to determine whether or not the patient has significant hemodynamic compromise resulting from the aortic stenosis. In particular, this diagnosis is difficult for patients aged >70 years, for those who are classified as functional class II, and for patients with co-morbidities or a sedentary lifestyle.[1,2] Field exercise testing is often used,[3] but this is of limited value in such patients.[1,2] In contrast to field exercise testing, cardiopulmonary exercise testing (CPET) is a laboratory test that assays cardiopulmonary physiology during exercise in greater detail.[4] Aortic valve replacement (AVR) is not without risks or complications,[5] and patients are often reluctant to undergo this operation, causing them to postpone AVR. It is valuable for physicians and patients to possess knowledge about which parameters predict a safe initial deferral. We hypothesized that for patients judged to be asymptomatic or equivocally or mildly symptomatic for severe aortic stenosis by a cardiologist, an initial conservative treatment strategy could yield a good prognosis and acceptable event-rate after stratification by a CPET. This includes patients aged >70 years, with New York Heart Association II classification or an abnormal field exercise test.

Methods

Our primary aim was to demonstrate that if peak oxygen consumption (VO_2) and peak oxygen pulse (O_2pulse) were either (1) not subnormal or (2) subnormal, but CPET results pointed to major causes other than hemodynamic compromise from the aortic stenosis, the following end points would occur with a low and acceptable incidence.

A. Unexpected cardiac death or hospitalization with heart failure. Defined as a cardiac death or hospitalization with heart failure in a patient that had not been recommended AVR earlier in the study period.
B. Cardiac death, hospitalization with heart failure, or progression to AVR.
C. All-cause mortality. All-cause mortality was compared with the age- and gender-matched mortality in our region (similar distribution of gender and age groups in 5-year intervals), which can be calculated from Reference 6.

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Patients were recruited from our outpatient clinic. Inclusion criteria were as follows: asymptomatic, equivocally, or mildly symptomatic status from aortic stenosis as judged by a cardiologist, aortic valve area index <0.6 cm^2/m^2, and left ventricular ejection fraction ≥0.50. Exclusion criteria were as follows: more than trivial other valvular disease, atrial fibrillation with a resting heart rate >90 beats/min, inability to perform bicycle exercise test, and other known medical conditions or abuse that could result in survival rate <2 years. All included patients provided written informed consent, and the study was approved by the local ethics committee (1-01-83-0002-07).

Based on the outcomes and evaluations of the baseline CPET, the patients were prospectively categorized. Patients in whom peak VO_2 and peak O_2pulse were either not subnormal (group 1) or subnormal, but CPET results pointed to major causes other than hemodynamic compromise from aortic stenosis (group2), followed an initial conservative strategy. Predefined criteria for group 1 and group 2 are presented under Table 1. Patients with subnormal peak VO_2 and peak O_2pulse not explainable by causes other than hemodynamic compromise from aortic stenosis were referred for AVR. These patients were not included in the present study.

The study patients were followed with clinical evaluations at 3 months' intervals. Echocardiography and CPET were performed at 6 and 12 months' intervals, respectively. If a patient presented new or worsening symptoms, or if he or she described decreasing functional capacity, a CPET and an echocardiogram were recommended. The patient was also referred for a coronary angiogram, and a decision regarding AVR was made by an independent Heart Team (nonstudy physicians), who did not possess knowledge of the details of the CPET. Nine months post-AVR an echocardiography and a CPET were recommended. Vital status, hospitalizations, and AVR data were obtained on December 1, 2012 from the Danish National Patient Registry, hospital records, and information obtained during the study. The cause of death was determined from the primary diagnosis in the discharge summary.

CPET was performed on a bicycle ergometer with breath-by-breath measurement of the VO_2, carbon dioxide exhaustion (VCO_2), and minute ventilation (VE) (Innocor, Innovision version 6.15, Odense, Denmark) as previously described.[7] The key measurements obtained from CPET were peak VO_2 (expressing cardiac output), peak O_2pulse (expressing stroke volume), VE/VCO_2 at nadir (a higher value indicates a ventilatory/flow mismatch), and the respiratory coefficient ($R = VCO_2/VO_2$, where a value at peak exercise <1 points to inadequate effort or nonphysiological hyperventilation). An estimate of stroke volume (milliliter) at peak exercise was obtained from the following calculation (peak O_2pulse/hemoglobin in g/dL) × 100; O_2pulse/hemoglobin index). This was because hemoglobin in gram per deciliter corresponds to the milliliter of oxygen extraction per deciliter.[8,9] The predicted peak VO_2 was defined according to current recommendations.[10] A peak VO_2 <83% of the predicted value, which represents the lower 95% confidence value in a healthy sedentary population,[9,11] was regarded as abnormal. The predicted peak heart rate was calculated as 220 minus the patient's age. The predicted peak O_2 pulse was calculated as the predicted peak VO_2/predicted peak heart rate.[9] A peak O_2 pulse of <95% of the expected was regarded as abnormal.[7] An inert gas breathing test was performed as previously described.[7]

Table 1
Baseline characteristics in the two groups

	Group 1 (n = 70)	Group 2 (n = 31)
Age (years)	73 ± 10	72 ± 7
Male/female (n)	38/32	23/8
Hypertension	36 (52%)	25 (80%)*
Diabetes mellitus	9 (13%)	3 (10%)
Prior ischemic heart disease	3 (4%)	6 (19%)
Chronic obstructive lung disease	4 (6%)	13 (42%)†
Smoker	9 (13%)	9 (29%)
Atrial fibrillation	2 (3%)	9 (29%)†
Pacemaker	2 (3%)	1 (3%)
NYHA class ≥ II	24 (34%)	21 (68%)*
Equivocally/mildly symptomatic	41 (59%)	26 (84%)*
Body mass index (kg/m^2)	27 ± 4	28 ± 5
Body surface area m^2	1.9 ± 0.2	2.0 ± 0.2
Creatinine (μmol/L)	80 ± 20	88 ± 23
LDL-cholesterol (mmol/L)	3.1 ± 1.0	2.8 ± 0.9
LDL-cholesterol (mg/dl)	120 ± 39	108 ± 35
Hemoglobin (mmol/L)	8.8 ± 0.6	8.7 ± 0.9
Brain natriuretic peptide > upper level of normal	11 (17%)	12 (39%)
Resting systolic blood pressure (mm Hg)	133 ± 14	133 ± 19
Echocardiography		
Aortic valve area index (cm^2/m^2)	0.43 ± 0.09	0.46 ± 0.08
Mean gradient (mm Hg)	42 ± 15	33 ± 11*
Left ventricular ejection fraction	59 ± 4	57 ± 5
Sa (cm/s)	5.1 ± 1.2	4.9 ± 1.2
E/e′	13.5 ± 5.0	13.7 ± 5.3
Left ventricular posterior wall thickness (cm)	1.13 ± 0.22	1.16 ± 0.30
Cardiovascular drugs		
Beta blockers	14 (20%)	15 (48%)*
Digoxin	3 (4%)	2 (7%)
Calcium-blockers	23 (33%)	5 (16%)
ACE-/AT-II-inhibitors	22 (31%)	17 (55%)
Diuretics	27 (39%)	11 (36%)
Statins	40 (57%)	19 (61%)

Data are presented as mean ± SD or n (frequency %). *p < 0.01 and † p < 0.001 compared with Group 1. Measurement of brain natriuretic peptide was not obtained in 3 and 1 patients in Group 1 and 2, respectively. NYHA = New York Heart Association. Sa = Peak systolic velocity (Color tissue Doppler). E/e′ = Peak early mitral inflow velocity/early diastolic mitral annulus velocity (Pulsed tissue Doppler).

Group 1. Normal CPX results. Peak VO_2 ≥ 83% of that predicted and peak O_2pulse ≥95% of that predicted.

Group 2. Abnormal CPX results judged not likely caused by aortic stenosis. 1) Peak VO_2 < 83% of that predicted *and* one of the following: a) normal peak O_2pulse defined as >95% of that predicted, b) low effort (respiratory coefficient <1), c) pulmonary disease with forced expiratory volume in first second to forced vital capacity ratio < 70% of that predicted, low breathing reserve, high VE/VCO_2, *and* normal O_2pulse trajectory—*or* 2) Peak VO_2 ≥ 83% and peak O_2pulse < 95% of that predicted.

All patients underwent 2-dimensional and Doppler echocardiography as previously described.[7] Lateral E/e′ was calculated as an expression of diastolic pressure. Left ventricular systolic function was assessed using the peak systolic tissue velocity (Sa) obtained by color tissue Doppler.[12] The mean of the septal and lateral Sa values was used.

For economic and logistical reasons, different assays for brain natriuretic peptide were used during the study period.

Table 2
Cardiopulmonary exercise test results in the two groups

	Group 1 (n = 70)	Group 2 (n = 31)
Peak VO_2 (mL/min/kg)	22.0 ± 6.0	16.5 ± 3.7†
Peak VO_2 (% of predicted)	110 ± 18	78 ± 12†
Peak O_2pulse (mL O_2 per beat)	12.7 ± 3.3	11.0 ± 3.0
Peak O_2pulse (% of predicted)	120 ± 19	94 ± 21†
% of predicted peak heart rate	89 ± 11	83 ± 14
Respiratory coefficient	1.07 ± 0.10	1.03 ± 0.09
Anaerobic threshold (at % of predicted peak VO_2)	71 ± 14	51 ± 9†
VE/VCO_2	30 ± 3	33 ± 6*
% of predicted forced expiratory volume first second	103 ± 30	84 ± 25†
Breathing Reserve	43 ± 20	45 ± 21
Stroke volume index resting (mL/m^2)	34 ± 9	29 ± 8*
Stroke volume index submaximal exercise (mL/m^2)	43 ± 9	36 ± 9*
PeakO_2pulse/Hemoglobin index (mL/m^2)	47 ± 8	40 ± 9†
Systolic blood pressure increase < 20 mm Hg	21 (30%)	8 (26%)
Symptoms during exercise test	3 (4%)	9 (29%)†
Valvuloarterial impedance	5.5 ± 1.7	6.1 ± 1.5

Data are presented as mean ± SD or n (%). * $p < 0.01$, † $p < 0.001$ compared with Group 1.

VO_2 = Oxygen consumption; O_2pulse = Oxygen pulse (VO_2/heart rate); VE/VCO_2 = Ventilation/Carbon dioxide exhaustion at nadir; Valvuloarterial impedance = (Systolic blood pressure + mean gradient)/Stroke volume index at rest. Stroke volume index measured by inert gas rebreathing.

Therefore, we present data for the plasma brain natriuretic peptide levels according to the upper level of normal, incorporating age and gender. The most frequently used assay had upper levels of normal ranging from 25 pg/ml (youngest man) to 77 pg/ml (oldest woman).

For statistical calculations, SPSS Statistics software version 20 (IBM Corp., Armonk, New York) was used. Continuous variables are presented as their means ± SD if not otherwise indicated. Unpaired *t* tests and 95% confidence intervals (CI) were used to compare the means of 2 groups. Paired *t* tests were used to determine serial changes. To calculate between-group differences in categorical variables, Fisher's test was used. The 95% CI for proportions were calculated according to Newcombe.[13] The normality of the continuous variables was secured with a Shapiro-Wilk test.

Results

Over the course of 19 months (March 1 2010 to October 1 2011), 119 patients fulfilled the study criteria and consented. Eighteen patients were immediately recommended AVR because CPET suggested a significant hemodynamic compromise, likely resulting from the aortic stenosis. These patients were excluded from this study. Data for these 18 patients are presented in the supplemental material (Tables S1 and S2).

Baseline characteristics and baseline CPET results for the study population (n = 101) are presented in Table 1 and Table 2, respectively. The median age in the study population was 75 years (interquartile range 65 to 79 years). The clinical outcomes over a mean observation time of 24 months (ranging from 12 to 36 months) with complete follow-up are presented in Table 3. The impact of possible predictors on outcomes is presented in Table 4 and in the supplemental material (Table S3).

Table 3
Clinical outcome

	All study patients (n = 101)	Group 1 (n = 70)	Group 2 (n = 31)
Unexpected cardiac death	0	0	0
Unexpected hospitalization with heart failure	6 (6%)	6 (9%)	0
Cardiac death, hospitalization with heart failure or aortic valve replacement	38 (38%)	26 (37%)	12 (39%)
Deaths of all causes	4 (4%)	1 (1.4%)	3 (10%)
Cardiac death	1 (1%)	0	1 (3%)
Hospitalization with heart failure	8 (8%)	6 (9%)	2 (7%)
Cardiac death or hospitalization with heart failure	8 (8%)	6 (9%)	2 (7%)
Aortic valve replacement	36 (36%)	25 (36%)	11 (36%)

Data are presented as n (%).

Unexpected events: Events in patients not recommended aortic valve replacement earlier during the study. There were no sudden deaths.

Table 4
Odds ratios for possible predictors of outcome

	Cardiac death or Hospitalized with heart failure Odds ratio (95% confidence interval)	Cardiac death Hospitalized with heart failure or aortic valve replacement Odds ratio (95% confidence interval)
Equivocally/mildly symptomatic	0.5 (0.1–2.0)	1.0 (0.4–2.3)
NYHA class II or III	0.73 (0.2–3.2)	0.4 (0.2–1.0)*
Brain natriuretic peptide > ULN	3.5 (0.8–15)	1.8 (0.7–4.7)
Symptoms during exercise test	-†	0.5 (0.1–2.0)
Increase in SBP < 20 mm Hg	0.8 (0.2–4.3)	1.0 (0.4–2.5)
ST-depression ≥ 2 mm	-†	0.91 (0.4–2.3)
Respiratory coefficient < 1	0.5 (0.1-4-0)	0.7 (0.2–2.0)

* P = 0.04 for worse outcome in NYHA class I.

† No patients with symptoms or ST-depression during exercise test suffered cardiac death or hospitalization with heart failure.

ULN = Upper level of normal according to age and gender; SBP = Systolic blood pressure.

One patient succumbed to cardiac death from progressive heart failure 17 months after the baseline CPET, but this patient had been recommended AVR for the first time 8 months earlier and again 4 months earlier during hospitalization with heart failure. Among the patients who were hospitalized for heart failure, 2 (both from group 2) had been recommended for AVR earlier during the study. However, both patients had declined the operation. In group 1, hospitalizations with heart failure were triggered by new dysregulated atrial fibrillation in 2 patients and by an anterior ST elevation myocardial infarction in 1 other patient. The all-cause mortality of 4.0% (95% CI 1.6% to 9.7%) at a mean 2-year follow-up was not

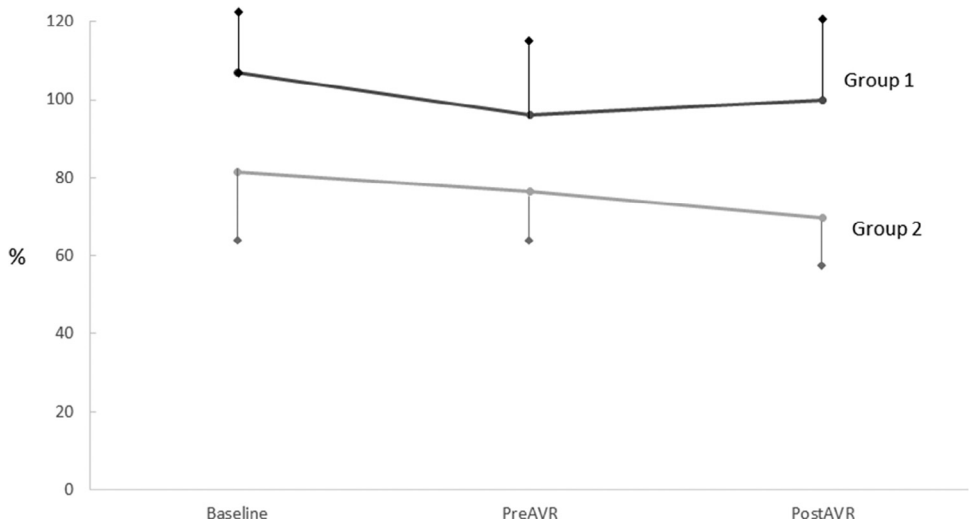

Figure 1. Serial measurements of the mean peak VO_2 as a percentage of that predicted for patients who had aortic valve replacements in the 2 groups. Bars = standard deviation. In group 1 (n = 23), the 95% CI for an increase from just pre-AVR to 9 months post-AVR was 0.0% to 7.9% (p = 0.050). In group 2 (n = 9), the 95% CI for a decrease was −12.4% to −0.62% (p = 0.034). A relative increase in peak VO_2 >5% from symptomatic pre-AVR to post-AVR, which corresponds to the coefficient of reproducibility in patients with aortic stenosis,[7] was observed in 11 of 23 in group 1 and in 2 of 9 in group 2.

higher than that of the age- and gender-matched population in our region. This was 4.0% per year,[5] amounting to 8% over 2 years. A table describing the age and gender distributions of the study population is provided in the supplemental material (Table S4). Causes of death included progressive heart failure (n = 1), ileus (n = 1), pancreatitis secondary to gallstones (n = 1), and alcoholic hepatitis (n = 1). The 30-day and 1-year mortality rates among the 582 non–high-risk patients who underwent single AVR in our country and were reported to the Danish Heart Register in 2012 were 1.5% and 5.3%, respectively.[5]

The mean time interval from baseline CPET to clinical progression leading to AVR was 18 ± 6 and 14 ± 7 months in groups 1 and 2, respectively. AVR was performed at a mean of 2.0 ± 1.5 months thereafter. The clinical progression leading to AVR included the following: hospitalization with heart failure (n = 6), new or progressing exercise-induced symptoms (dyspnea or syncope) or decreasing threshold for symptoms (n = 25), new atrial fibrillation and progression in dyspnea (n = 2), angina pectoris or acute coronary syndrome (n = 2), and progressive worsening of CPET results in an asymptomatic patient with very severe aortic stenosis (n = 1). Surgical AVR, surgical AVR with coronary artery bypass, and transfemoral AVR were performed in 21, 11, and 4 patients, respectively. Transfemoral AVR was not performed for clinical reasons, but as part of a randomized study of patients older than 70 years eligible for surgical AVR that showed neutral outcome.[14]

Serial measurements of peak VO_2 at baseline, pre-AVR ("symptomatic state"), and 9 months post-AVR were available for 23 of 25 patients in group 1 and for 9 of 11 patients in group 2 (Figure 1). Serial echocardiographic data were available in 22 of 25 patients and 8 of 11 patients in groups 1 and 2, respectively: From immediately preoperatively (symptomatic state) to 9 months postoperatively, Sa increased from 4.8 ± 1.1 cm/s to 5.5 ± 1.4 cm/s (95% CI for an increase 0.22 to 1.12 cm/s, p = 0.006) in group 1 and from 4.2 ± 1.2 cm/s to 5.1 ± 0.74 cm/s (95% CI for an increase −0.34 to 2.01 cm/s, p = 0.13) in group 2. The E/e′ decreased from 17.6 ± 7.0 to 13.3 ± 5.4 (95% CI for a decrease −7.3 to −1.4 cm/s, p = 0.006) in group 1 and 14.4 ± 5.3 to 13.6 ± 5.3 (95% CI for a decrease −5.87 to 4.13 cm/s, p = 0.68) in group 2. Among the patients who had AVR and a plasma brain natriuretic peptide measurement obtained at baseline and post-AVR, the number of patients with a value greater than the upper level of normal was 11 of 32 at baseline and 13 of 32 post-AVR.

Discussion

According to our predefined criteria, we found that if CPET did not indicate significant hemodynamic compromise resulting from aortic stenosis, an initially conservative treatment strategy had a good prognosis for subsequent years with no unexpected cardiac deaths. Patient survival rate was comparable with the age- and gender-matched population, and only 35% of patients required an AVR during a mean follow-up period of 2 years.

A normal CPET (group 1) did not prevent unexpected hospitalization with heart failure, and the rate of hospitalization with heart failure or AVR was similar to group 2. Obviously, a peak VO_2 of 90% of the predicted is abnormal if the patient's normal peak VO_2 was 120%. However, we do not think that a patient with such a decrease would be regarded as asymptomatic or questionably symptomatic by a cardiologist. Thus, they would not represent the typical patient included in our study. Mortality was low in group 1, which is unsurprising because of the close relation between peak VO_2 and survival. Significant improvements in peak VO_2 after AVR were observed, suggesting the valve disease was a major cause of symptoms in those who progressed to AVR in this group.

Patients in group 2 had subnormal values of peak VO_2 and/or peak O_2pulse. Thus, they displayed objectively decreased exercise capacity. Furthermore, 84% had some symptoms in

daily life, and 68% were deemed New York Heart Association functional class II. Therefore, a physician could have referred nearly all of these patients for AVR because of severe aortic stenosis and symptoms or decreased exercise capacity. Nevertheless, the rate of unexpected cardiac death or hospitalization with heart failure was 0% in group 2. For patients in group 2 who had an AVR, improvements in peak VO_2 were not observed. Because Sa and E/e′ tended to improve, this suggest that the timing of AVR was not overdue. The low peak VO_2 and lack of improvements in peak VO_2 suggest that causes other than the valve disease were the major reasons for symptoms and low functional capacity. The mean gradient was low compared with the aortic valve area index, although the mean Sa and left ventricular ejection fraction values were comparable with those in group 1. This is well explained by the resting stroke volume that was clearly lower, as assessed by inert gas rebreathing (Table 1). A lower resting stroke volume is a key finding in unfit subjects with normal left ventricular ejection fraction.[15] The mortality in this group was 9.9%. Although there is uncertainty because of the low n, this is acceptable compared with the expected 8% in the age- and gender-matched population because of the high rate of co-morbidities.

How does this study expand upon previous studies? Das et al[1] found that field exercise testing was not useful in patients >70 years or in those deemed functional class II. Patients with co-morbidities,[1,16] symptoms during the test[16,17]—a subjective criterion,[2] or a low exercise capacity[17] were excluded in many studies. However, patients with aortic stenosis are often older. They also tend to have co-morbidities and symptoms that are difficult to assess. It is for these patients that decisions regarding treatment strategies are difficult and ambiguous. Our study suggests that CPET is useful in such patient groups. This included patients with revealed symptoms, ST depression >2 mm, decreased blood pressure response during exercise test, low exercise capacity, respiratory coefficient <1, or brain natriuretic peptide greater than the upper level of normal. In a cohort with a mean age of 64 years and 53% (n = 71) with an aortic valve area <1 cm^2/m^2, Marechaux et al[16] found an event rate of cardiac death, heart failure, or AVR of 50% after a mean follow-up of 20 months after a normal field exercise test result, that is, a negative predictive value of 50%. In the older population in our study, all of them had an aortic valve area index <0.6 cm^2/m^2, and the event rate at a mean follow-up of 24 months was 37%. This presents a negative predictive value for a CPET without suggesting a significant hemodynamic compromise of 63%. In a meta-analysis that included 491 largely asymptomatic patients with a mean age of 62 years and a mean aortic valve area index of 0.47 cm^2/m^2, the rate of cardiac death or symptoms leading to AVR was 42% at a mean follow-up of 14 months.[18] These observations suggest that a CPET-guided strategy may lead to a lower event rate (higher negative predictive value) than that obtained using a field exercise test strategy without sacrificing safety.

Our study had some limitations. Only a few patients in our cohort (9%) had very severe aortic stenosis with peak gradients >100 mm Hg.[7] However, only in cases when the cardiologist judges the patient asymptomatic or equivocally symptomatic for severe or borderline to severe aortic stenosis is assessment ambiguous, requiring additional diagnostic information. Furthermore, patients who were not able to perform an exercise test were not referred or included. However, such frail patients are seldom considered for AVR if they are only asymptomatic or questionably symptomatic. No randomization against field exercise testing was done. However, the limitations of field exercise testing in patients aged >70 years with co-morbidities or with some symptoms or functional limitation are well-recognized.[1] Therefore, we feel that our finding that a CPET-guided strategy was followed by a good prognosis and an acceptable event rate, in such patients who are difficult to assess, provides new and useful information. To compare mortality with that in the background population would ideally also demand a match in peak VO_2, because some patients can be supervariants with aortic stenosis. Obviously, this is a nearly impossible task. The cause of death and hospitalizations for heart failure was not determined by an independent assessment committee. However, all deaths occurred in the hospital at other institutions, and the cause of death was determined by local physicians and stated in the discharge summary.

In conclusion, we examined a study population with a median age of 75 years that displayed echocardiographically severe aortic stenosis, including two-thirds who had some symptoms. If CPET did not indicate primary significant hemodynamic compromise from the aortic stenosis, we found that an initially conservative treatment strategy was associated with a good prognosis and an acceptable rate of cardiac events.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2017.05.047.

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