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Original Article

The Physiological Burden of the 6-Minute Walk Test Compared With Cardiopulmonary Exercise Stress Test in Patients With Severe Aortic Stenosis

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ABSTRACT

Background: Management of aortic stenosis (AS) relies on symptoms. Exercise testing is recommended for asymptomatic patients with significant AS but is often experienced as forbidding and/or technically unrealistic for patients who are often frail, deconditioned, and intimidated by the exercise test. We compared the physiological burden assessed with gas exchange assessments to gauge and respiratory exchange ratio (RER) of a 6-minute walk test (6MWT) to a cardiopul-

RÉSUMÉ

Introduction : La prise en charge de la sténose aortique (SA) dépend des symptômes. L'épreuve d'effort est recommandée aux patients asymptomatiques qui ont une SA significative, mais elle est souvent perçue comme dangereuse et/ou théoriquement irréaliste chez ces patients qui sont souvent fragiles, en mauvaise forme et craintifs par l'épreuve d'effort. Nous avons comparé le fardeau physiologique calculé par la consommation maximale de l'oxygène ($\dot{V}O_2$max) et le

Aortic stenosis (AS) is the most prevalent valvular disease in adults age > 65 years; 3% to 7% of this older adult population have AS.[1] Whereas medical management is generally used for those who are asymptomatic, valve replacement becomes more relevant for those with symptoms. Prognosis worsens rapidly once symptoms develop. Whereas assessment of symptoms is critical, it is not always straightforward.

Patients typically have critical AS in a larger context of multimorbidity or frailty. Sedentariness and exercise intolerance are likely in most adults with severe AS because of the intrinsic effects of valvular disease and the clinical context of multimorbidity and geriatric complexities. For many AS patients, sedentary lifestyles tend to obscure symptoms. Nonetheless, symptoms may be induced by exercise provocation, and exercise testing is an important diagnostic enhancement. Maximal exercise tests are generally restricted to asymptomatic AS patients, as maximal effort in truly symptomatic patients with AS is considered an absolute contraindication.[1,2] Strict contraindication to exercise testing becomes ambiguous in patients who are sedentary, as pertinent symptoms may only become apparent during exercise provocation[1] because one-third of patients claiming to be asymptomatic may have symptoms during exercise.[3-6] Given such a fine line between symptomatic and asymptomatic, it is important to emphasize that a meta-analysis concluded that symptom-limited stress testing is safe and has an important prognostic value in patients with severe AS.[7]

The 6-minute walk test (6MWT) has been used as an alternate to exercise testing.[8,9] In some study populations, 6MWT is found to be less physiologically burdensome than exercise testing, and other studies indicate that it is often less intimidating to many patients, especially those who are older, frailer, and burdened with disease. This test is also commonly used in AS populations and has prognostic significance.[10-12] Proponents also extol the utility of the 6MWT as an

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monary exercise stress test (CPET) in patients with severe AS. peak oxygen utilization
Methods: Adults with equivocal symptoms and severe AS (1-aortic valve area [AVA] $\leq$ 1.0 cm^2 or AVA index $\leq$ 0.6 cm^2/m^2, 2-peak aortic jet velocity $\geq$ 4.0 m/sec, 3-mean transvalvular pressure gradient $\geq$ 40 mm Hg by rest or dobutamine stress echocardiography, or 4-aortic valve calcification $\geq$ 1200 in women or $\geq$ 2000 AU in men) were studied. All participants completed both a 6MWT and symptom-limited progressive bicycle exercise testing. Breath-by-breath gas analysis and 12-lead electrocardiography were completed during 6MWT and CPET. **Results**: Eleven patients were studied. Patients walked on average 330 $\pm$ 75 m during the 6MWT and achieved a maximal workload of 48 $\pm$ 14 watts during the CPET. During the 6MWT, peak maximal oxygen uptake ($\dot{V}O_2$peak) was 12.8 $\pm$ 2.5 vs 10.8 $\pm$ 4.2 mL/kg/min during the CPET. Respiratory exchange ratio exceeded 1.1 in both the 6MWT and CPET indicating similarly high exertion. Compared with the CPET, a larger proportion of the 6MWT was performed at a high intensity level (78% $\pm$ 28% vs 33% $\pm$ 24% at $>$ 85% VO_2peak; $P = 0.004$).
Conclusions: The 6MWT with breath-by-breath gas analysis was well tolerated and able to achieve a physiological intense RER and $\dot{V}O_2$peak that are similar to symptom-limited CPET in patients with severe AS.

quotient respiratoire (QR) d'un test de marche de 6 minutes (TM6) et d'une épreuve d'effort maximal chez des patients avec une SA sévère.
Méthodes : Tous les patients présentaient une SA symptomatique et sévère (1-aire valvulaire aortique [AVA] $\leq$ 1,0 cm^2 ouAVA $\leq$ 0,6 cm^2/m^2, 2-une vélocité maximale du flux aortique $\geq$ 4,0 m/sec, 3-un gradient de pression transvalvulaire moyen $\geq$ 40 mmHg au repos ou à l'échocardiographie à l'effort sous dobutamine ou 4-une calcification valvulaire aortique (AU) $\geq$ 1200 chez les femmes ou $\geq$ 2000 AU chez les hommes). Les participants ont effectué un TM6 et une 'épreuve d'effort maximal de type rampe sur vélo. L'analyse des échanges gazeux respiration par respiration et un électrocardiogramme à 12 dérivations ont été effectués durant le TM6 et l'épreuve d'effort maximal.
Résultats : Un total de 11 patients ont participé à l'étude. Les patients ont marché en moyenne 330 $\pm$ 75 m durant le TM6 et ont atteint une charge de travail maximale de 48 $\pm$ 14 watts durant l'épreuve d'effort maximal. Durant le TM6, le $\dot{V}O_2$max était de 12,8 $\pm$ 2,5 *vs* 10,8 $\pm$ 4,2 ml/kg/min durant l'épreuve d'effort maximal. Le QR était supérieur à 1,1 au TM6 ainsi qu'à l'épreuve d'effort maximal. Comparativement à l'épreuve d'effort maximal, un pourcentage plus important au TM6 a été réalisée à une intensité élevée (78 % $\pm$ 28 % *vs* 33 % $\pm$ 24 % à $>$ 85 % VO_2max; $P = 0{,}004$).
Conclusions : Le TM6 avec mesure directe des échanges gazeux était bien toléré et susceptible d'atteindre des valeurs physiologiques d'intensité élevée pour le QR et le $\dot{V}O_2$max. Les valeurs atteintes au TM6 étaient semblables à celles de l'épreuve d'effort maximal chez les patients avec une SA sévère.

assessment that is relatively easy to implement, low cost, requires little equipment, and reflects daily living activities, as walking requires the integration of circulatory, respiratory, nervous, and musculoskeletal systems.[13] Nevertheless, the 6MWT provides only limited information regarding patients' physiological exertion and hemodynamic adaptation, as it is performed typically in corridors with basic equipment. Therefore, a 6MWT with appraisal of the respiratory gas exchange and the measurement of peak maximal oxygen uptake (VO_2peak) may be of interest and useful for the clinician. The objective of this study was to compare the physiological burden and clinical utility of a 6MWT vs a symptom-limited cardiopulmonary exercise test (CPET) in patients with severe AS.

Materials and Methods

Study design and patients

Patients with equivocal symtoms who had severe AS (1-aortic valve area [AVA] $\leq$ 1.0 cm^2 or AVA index $\leq$ 0.6 cm^2/m^2, 2-peak aortic jet velocity $\geq$ 4.0 m/sec, 3-mean transvalvular pressure gradient $\geq$ 4 0 mm Hg by rest or dobutamine stress echocardiography, or 4-aortic valve calcification (AU) $\geq$ 1200 in women or $\geq$ 2000 AU in men)[14] (N = 11) were recruited to participate in a study focusing on 2 different modalities to evaluate functional exercise capacity. Exclusion criterion were (1) advanced cancer, (2) significant physical limitation impeding exercise, (3) severe chronic obstructive pulmonary disease and, (4) significant cognitive dysfunction according to the Mini Mental State Examination.[15] The study protocol was approved by the Ethics Committee of our Institution, and every patient provided written informed consent before study procedures.

Six-minute walk test

All patients performed a 6MWT within the same day for 7 patients (CPET first, then the 6MWT following a 3-hour rest period) or within the same week for 4 patients. Tests were conducted according to the American Thoracic Society protocol, and standardized instructions were given in the French language to each participant.[16] Patients had to walk their maximal distance in 6 minutes along a 30-meter, wide, straight, and level track. A breath-by-breath gas analysis, a 12-lead electrocardiogram, and oxygen saturation were collected throughout the test using an Oxycon Mobile device (Oxycon mobile; Vyaire, Hoechberg, Germany). The weight of this ambulatory unit did not exceed 2 kg. Because of the ambulatory nature of the test, blood pressure and perceived exhaustion scale information were taken before and immediately after the 6MWT. Maximal rate pressure product was calculated by taking the product of the maximal heart rate reached during the test and the blood pressure taken at the end of the 6 minutes. Ventilatory values were expressed as the mean value for every 15-second interval over the entire test period. Supervision was provided by the same cardiologist and an American College of Sport Medicine—certified clinical exercise physiologist that also administered the CPET.

Cardiopulmonary exercise testing

Patients underwent a symptom-limited (maximal) CPET on a recumbent ergocycle (Lode Recumbent; Groningen, The Netherlands). Patients performed a ramp exercise protocol

Table 1. Patients and tests characteristics

	All (N = 11)	Men (n = 5)	Women (n = 6)
Age (years)	79.7 ± 6.1	79.6 ± 6.2	79.8 ± 6.6
Anthropometry			
Body mass index (kg/m^2)	25.8 ± 4.5	25.9 ± 6.6	26.2 ± 4.7
Waist circumference (cm)	96.4 ± 14.8	100.3 ± 18.9	94.2 ± 15.4
Body fat (%)	30.8 ± 7.1	26.7 ± 7.7	32.8 ± 6.6
Lean body mass (kg)	45.6 ± 8.5	53.3 ± 9.8	41.7 ± 4.8*
CPET			
Test time (min:sec)	08:20 ± 02:25	08:28 ± 02:54	08:14 ± 02:12
Maximal work (watts)	48 ± 14	55 ± 12	44 ± 14
Absolute $\dot{V}O_2$peak (L/min)	0.76 ± 0.21	0.85 ± 0.29	0.68 ± 0.07
Relative $\dot{V}O_2$peak (mL/kg/min)	11.9 ± 4.2	12.3 ± 6.3	11.6 ± 2.3
Metabolic equivalent (METs)	3.4 ± 1.2	3.5 ± 1.8	3.3 ± 0.7
% of predicted $\dot{V}O_2$max (%)	85.1 ± 41.4	80.6 ± 59.5	88.9 ± 23.7
$\dot{V}E/\dot{V}CO_2$ slope	37 ± 8	39 ± 9	35 ± 7
Maximal heart rate	97 ± 16	88 ± 21	104 ± 7
Maximal respiratory exchange ratio	1.17 ± 0.07	1.20 ± 0.06	1.14 ± 0.07
Maximal ventilation (L/min)	32.7 ± 9.8	40.2 ± 10.3	26.4 ± 1.6*
Maximal systolic blood pressure (mm Hg)	159 ± 35	147 ± 47	168 ± 20
Maximal diastolic blood pressure (mm Hg)	64 ± 16	65 ± 14	63 ± 18
Rate pressure product (bpm × mm Hg)	15,604 ± 5074	17,506 ± 2680	13,322 ± 6592
6MWT			
Maximal distance walk (m)	330 ± 75	343 ± 99	318 ± 56
Maximal absolute $\dot{V}O_2$ (L/min)	0.84 ± 0.14	0.90 ± 0.17	0.79 ± 0.10
Maximal relative $\dot{V}O_2$ (mL/kg/min)	12.8 ± 2.5	12.9 ± 3.7	12.7 ± 1.3
Metabolic equivalent (METs)	3.7 ± 0.7	3.6 ± 0.4	3.7 ± 1.1
Maximal heart rate (bpm)	105 ± 17	112 ± 42	99 ± 16
Maximal respiratory exchange ratio	1.12 ± 0.10	1.13 ± 0.12	1.11 ± 0.09
Maximal reach ventilation (L/min)	32.8 ± 6.2	35.8 ± 5.5	30.3 ± 6.0
End 6MWT systolic blood pressure (mm Hg)	156 ± 27	152 ± 27	159 ± 29
End 6MWT diastolic blood pressure (mm Hg)	63 ± 13	64 ± 18	62 ± 8
Rate pressure product (bpm × mm Hg)	15,663 ± 5508	16,567 ± 3943	14,578 ± 7330

Data were expressed as mean ± standard deviation.

6MWT, 6-minute walk test; bpm, beats per minute; CPET, cardiopulmonary exercise test; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, ventilation; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_2$peak, peak maximal oxygen uptake; $\dot{V}O_2$max; maximal oxygen uptake.

* $P < 0.05$ between men and women. There was no statistical difference between 6MWT and CPET.

(linear increase in the workload). The test began with 1 minute of loadless pedaling (initiated by a 0-watt start-up motor to overcome the inertia of the flywheel up-to 50 RPM) followed by a workload increase by increments of 5, 7, or 10 watts per minute to achieve maximal exercise capacity in 8 to 12 minutes. Compared with a treadmill test, this test modality is generally considered safer for high-risk patients, as it allows a watt-by-watt progressive increment in intensity, and the test is performed seated, thus, decreasing the risk of fall and early test termination due to musculoskeletal disabilities. End-of-test criteria were used according to the American College of Sport Medicine.[17] During the entire test, breath-by-breath gas exchange (MGC Diagnostics; St Paul, MN) analysis was used to measure oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), ventilation per minute ($\dot{V}E$), and respiratory exchange ratio (RER). Ventilatory parameters were recorded breath by breath throughout the test, but gas exchange data were averaged over 15-second periods for analysis. During the test, patients wore a facemask to maintain talking ability while gas exchange data were collected. In addition, a 12-lead electrocardiogram (Cardioperfect Welch-Allyn; Skaneateles Falls, NY), heart rate, and pulse oximetry (N-395 Nellcor; Boulder, CO) were recorded continuously. Blood pressure (STBP-780, Colin Medical instruments; San Antonio, TX) and modified Borg scale[18] for perceived exhaustion were taken every 2 minutes. Tests were considered maximal if the RER was > 1.1 or if patients achieved another maximal criteria.[19] $\dot{V}O_2$peak, maximal heart rate, and maximal ventilation were defined as the highest averaged values over 15 seconds taken during loaded exercise. Maximal workload was the highest workload reached at the end of the test. $\dot{V}_E/\dot{V}CO_2$ slope was calculated using all values during the loaded exercise phase.[20] Maximal rate pressure product was calculated as the product of maximal heart rate and maximal blood pressure at the end of loaded exercise.

Anthropometrics measurements

Patients were weighted on a Tanita Body Composition Analyzer (TBF-300A Body Composition Analyzer; Tanita, Arlington Heights, IL) for assessment of body weight, body fat percentage, and fat-free mass. According to the manufacturer, bioimpedance is not indicated in patients wearing a pacemaker; such patients were weighted on a standard

Table 2. Patients, medical history

	All (N = 11)
Medical history	
Anterior thoracotomy	8 (73%)
Anterior aortic valve replacement	3 (27%)
Coronary atherosclerotic disease	9 (82%)
Peripheral vascular disease	4 (36%)
Systemic hypertension	8 (67%)
Dyslipidemia	11 (100%)
Chronic obstructive pulmonary disease	2 (18%)
Arhythmia	8 (73%)
Atrial arhythmia	6 (55%)
Ventricular arhythmia	2 (18%)
Stroke	3 (27%)
Diabetes mellitus	5 (45%)
Past history of pulmonary oedema	2 (18%)
Chronic renal failure	5 (45%)
Aortic stenosis history	
Maximal gradient	
< 50 mm Hg	7 (64%)
50-100 mm Hg	3 (27%)
> 100 mm Hg	1 (9%)
Mean gradient	
< 25 mm Hg	6 (55%)
25-40 mm Hg	3 (27%)
> 40 mm Hg	2 (18%)
Valve area	
> 1.5 cm^2	0
1.0-1.5 cm^2	3 (27%)
< 1.0 cm^2	8 (73%)
Left ventricular ejection fraction	
> 50%	6 (55%)
40%-50%	3 (27%)
< 40%	2 (18%)
Left ventricular hypertrophy	
Mild	1 (9 %)
Moderate	2 (18%)
Severe	1 (9 %)

weighing scale. Body mass index was calculated as follows: weight (in kilograms)/$height^2$ (in meters). Waist circumference was taken at the level of the iliac crest.

Statistical analysis

Results are presented as mean ± standard deviation unless otherwise specified. The normality assumption was verified with the Shapiro-Wilk tests on residuals from the statistical model. The Brown-Forsythe variation of Levene's test statistic was used to verify the homogeneity of variances. Differences between sex were analyzed using an unpaired Student *t* test, and comparison between CPET and 6MWT used a paired Student *t* test. Pearson correlation was used to highlight association between parameters. A Bland-Altman graphic was drawn to assess the relationship between CPET and 6MWT VO_2peak. Straight dark line represents the mean difference between methods, and the small dotted line represents the limits of agreement (mean ± 2 SD) (Figure 3B). A P value < 0.05 was considered significant. Statistical analysis was performed using SPSS software (IBM SPSS Statistic, Version 21).

Results

The study sample included 5 men and 6 women (Table 1). Medical history and AS severity parameters are summarized in Table 2. Most patients were taking antihypertensive medication (β blockers [n = 10], calcium channel blocker [n = 5], angiotensin-converting enzyme inhibitor [n = 2], angiotensin II receptor antagonist [n = 4], diuretic [n = 10], or others [n = 3]). All patients were taking cholesterol-lowering medication. Patients took their usual medication on the day of both tests.

During the CPET, the mean maximal workload achieved was 48 ±14 watts and a mean VO_2peak of 10.8 mL/kg/min. There were several numerical differences between men and women; only maximal ventilation reached statistical significance (Table 1). During the test, the patients reached a $V_E/VVCO_2$ slope of 37 ± 8 and a respiratory exchange of 1.17 ± 0.07. Maximal heart rate was 97 ± 16 beats per minute (bpm). Out of the 11 patients, 7 stopped the test because of exertional exhaustion, 1 for dyspnea, and 3 for both. Four patients experienced chest pain during testing. No serious adverse event was observed during exercise testing, and no test was interrupted by the physician. In particular, no acute ST segment elevation myocardial infarction, arrhythmias, or syncope were observed. Overall, 6 patients presented a blunted blood pressure response during CPET (Fig. 1). Mean blood pressure at maximal exertion was 159 ± 35/64 ± 16 mm Hg.

During the 6MWT, patients walked an average of 330 ± 75 meters with a slightly higher mean VO_2peak (12.8 mL/kg/min; Table 1). At maximum exertion, heart rate was 105 ± 17 bpm, and the RER was 1.12 ± 0.10. Patient's major limitations restraining maximal exertion were exertional exhaustion (n = 3), dyspnea (n = 4), musculoskeletal consideration (n = 2), claudication symptom (n = 1), and chest pain (n = 1). At the end of the test, mean blood pressure was 156 ± 27/63 ± 13 mm Hg.

Patients experienced comparable levels of exertion during both tests; mean maximal heart rate (P = 0.32), mean maximal ventilation (P = 0.96), mean maximal blood pressure (P = 0.70), and mean maximal rate pressure product (P = 0.59) were all comparable. While performing the 6MWT, patients reached a relative VO_2peak 9.4% higher than that during the CPET (P = 0.06). In both tests, RER was over the maximal exertion criteria of > 1.1 (CPET, 1.17 ± 0.07 vs 6MWT, 1.12 ± 0.10; P = 0.21). Patients felt comparable levels of exhaustion during both tests reaching 7 ± 2 for the CPET and 6 ± 2 for the 6MWT on the modified Borg scale (measured over a 10-point scale) (P = 0.18). However, a higher proportion of the 6MWT (78%) was performed at a higher intensity level compared with the CPET (32%) on the basis of heart rate (P = 0.025) and VO_2 (P = 0.004) (Fig. 2). During the 6MWT, 88% of the test duration was performed above the ventilatory threshold. VO_2peak during the CPET was strongly correlated to the highest VO_2 reached during the 6MWT (r = 0.88; P < 0.001) (Fig. 3A). Agreement between the 6MWT and CPET for VO_2peak is shown using a Bland-Altman representation (Fig. 3B). In accordance with the findings, relative VO_2peak was 9.4% during 6MWT; the Bland Altman showed that for all patients (except 1), the 6MWT slightly overestimate the VO_2peak compared with the CPET. No correlation was found between a longer distance achieved during the 6MWT with either the VO_2peak (r = 0.49; P = 0.12) nor with maximal workload (r = 0.49; P = 0.12) during the CPET. Lower body mass index was associated with a higher VO_2peak during the CPET (r = −0.67; P = 0.02). We found no parameter that predicts exercise performance from the 6MWT.

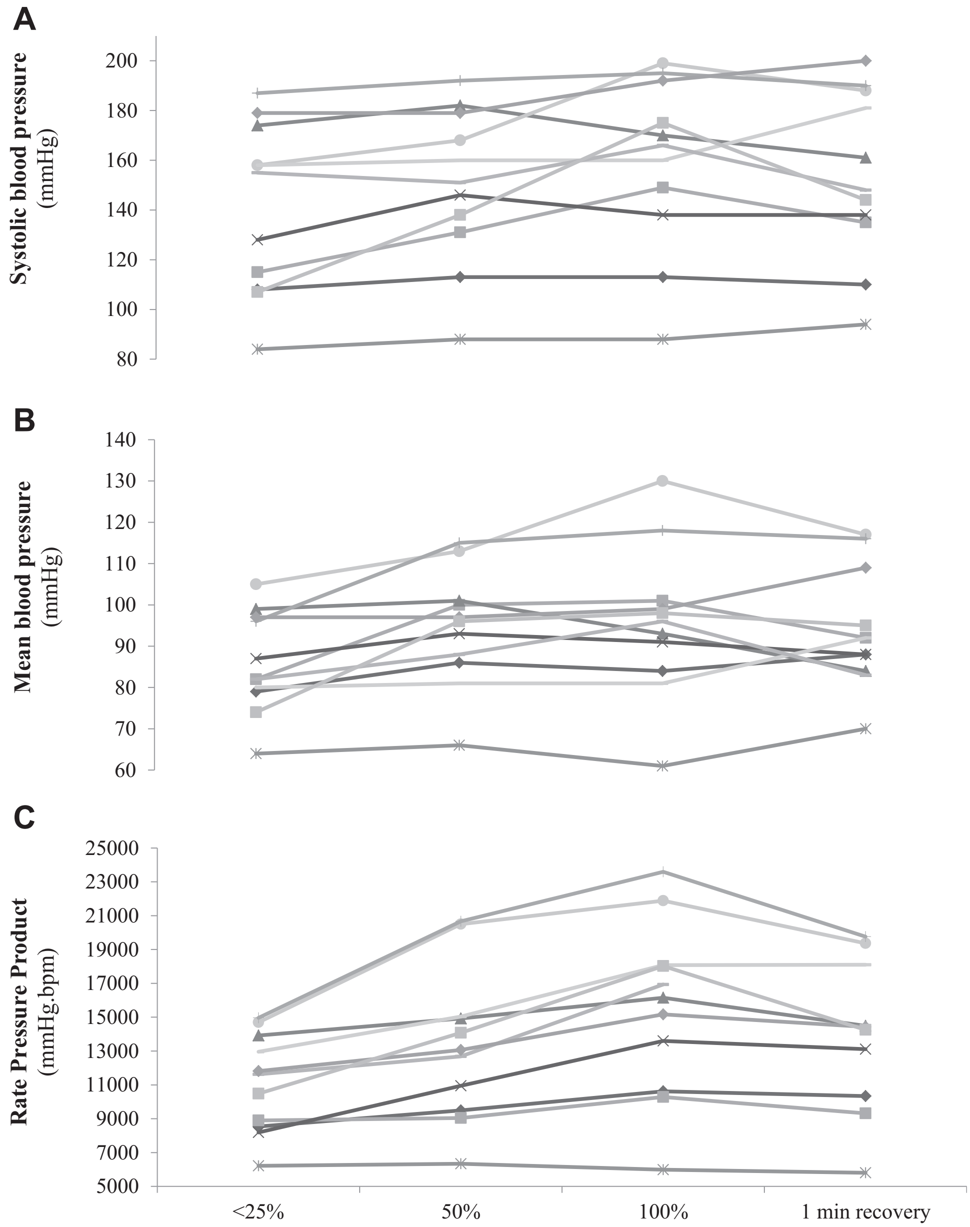

Figure 1. Evolution of cardiac parameters during cardiopulmonary exercise test. (**A**) n = 2, drop in systolic blood pressure (8 and 12 mm Hg); n = 3: reached maximal systolic blood pressure during recovery; and n = 6: normal progression during the CPET. (**B**) n = 2, decrease mean blood pressure; n = 3, maximal mean blood pressure during recovery; n = 1, both patterns; and n = 6, normal progression during the CPET. (**C**) Most patients presented normal progression of cardiac work; n = 1, drop in cardiac work and n = 1, maximal cardiac work during recovery.

Discussion

In this study, we found that, in elderly patients with severe AS, both 6MWT and CPET with appraisal of the respiratory gas exchange were feasible, were well-tolerated, and induced similar high-intensity exercise stimulus when patients were monitored appropriately. Contrary to the presumption of many that 6MWT is a submaximal exercise stimulus,[21] our findings showed that the 6MWT was more physiologically demanding in this population, as 88% of the test duration was performed above the ventilatory threshold, and approximately 75% of the test was performed at $\geq$ 85% of VO_2peak. During the CPET, on average, patients reached $\geq$ 85% of VO_2peak and heart rate reserve during 22% and 38% of the CPET time, respectively. This finding is in great contrast to those of patients during the 6MWT reaching $\geq$ 85% of VO_2peak and heart rate reserve during 68% and 72% of the 6MWT time, respectively. Moreover, the time spent over the ventilator threshold by the patients during the 6MWT was 88% of the test duration. VO_2peak observed during the 6MWT also tended to be higher than during the CPET. These data are consistent with those of a previous study showing a 10% higher VO_2peak during a CPET performed with a treadmill vs CPET on an ergocycle.[22] During the 6MWT, progression of intensity was abrupt, and patients maintained a high exercise intensity level for a longer period than in the CPET.

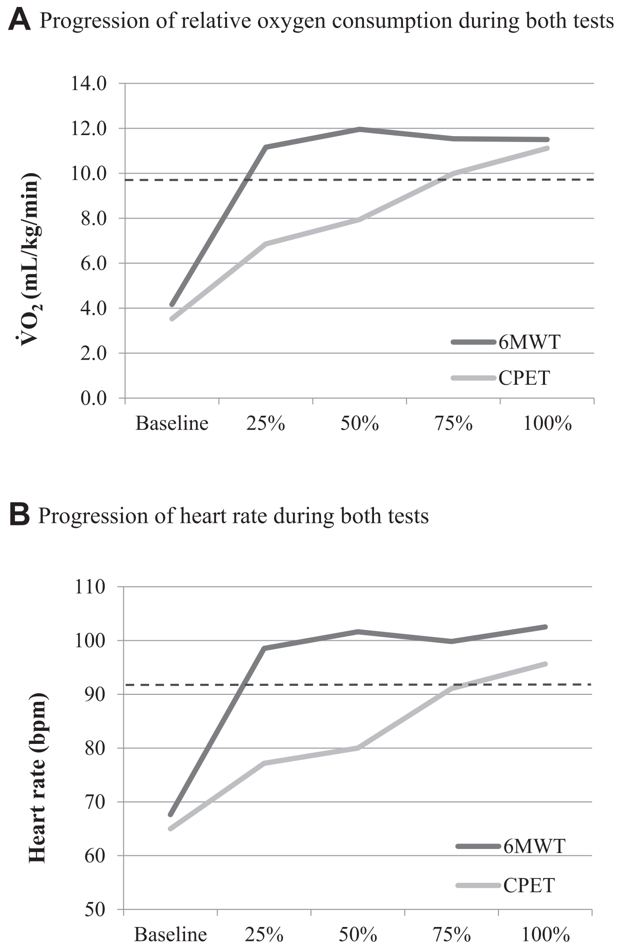

Figure 2. Intensity progression during both tests. (**A**) After 22% into the 6MWT, patients reached a high-intensity level of exertion characterised as 85% of the $\dot{V}O_2$peak measured during the CPET (dotted line at 9.9 mL/kg/min). In contrast, the progression of the CPET was linear, and patients reached 85% of their $\dot{V}O_2$peak at 68% of the test ($P = 0.004$). (**B**) The same pattern was observed for heart rate evolution. Patients reached an intensity of 85% of their cardiac heart rate reserve obtained during CPET (92 ± 14 bpm) at 38% during the 6MWT compared with 72% during the CPET ($P = 0.025$). 6MWT, 6-minute walk test; bpm, beats per minute; CPET, cardiopulmonary exercise test; $\dot{V}O_2$peak, peak maximal oxygen uptake.

It is well recognized that a maximal exercise test should not be performed in patients with symptomatic AS because of a high risk of serious complications.[2,23] Hence, the 6MWT may be an alternative to assess functional capacity/impairment in this frail population, as many patients who have symptoms remain undetected in clinical practice because patients have adapted by decreasing their level of activity to avoid symptoms. The 6MWT distance is often used for independent prognostic information before aortic valve replacement[10,11] and provides useful preoperative information.[12,24] In patients with symptomatic severe AS eligible for a transcatheter aortic valve implantation procedure, a 6MWT distance > 182 meters has been reported to be associated with higher survival at 1-year follow-up.[12] Although the overall 6MWT distance may increase after a transcatheter aortic valve implantation procedure, a significant proportion of patients may not improve their distance at follow-up vs baseline.[25,26]

Following our findings, and considering that our patients with severe AS sustained a high intensity for a long period during the 6MWT and reached comparable VO_2peak values in both the 6MWT and CPET, one may speculate that the prognostic value of the 6MWT may be explained by the fact that in this population, the 6MWT may be very demanding and should be considered as a maximal exercise test[27,28] as it is the case in patients with heart failure.[9] It must be emphasized that 6MWT has a very different methodology compared with the CPET. 6MWT resembles more a constant work rate test (ie, endurance test) than a ramp test, as is the CPET in this study. For this reason, the 6MWT produced a higher proportion of time at higher levels of intensity. The patients are capable of sustaining this high intensity for longer periods during the 6MWT probably because there is no externally imposed workload as there is during the CPET. Along with the course-imposed turning around the cones, which requires deceleration and acceleration, patients are able to modulate their exertion to be able to continue without stopping because of the ever-increasing imposed workload of a ramp protocol on a cycle ergometer. We observed no serious adverse event related neither to CPET nor to the 6MWT. Regarding the risk of exhaustion, experts agreed that patients with severe AS should not be excluded from exercise testing, as patients probably experienced exhaustion in their everyday lives as documented here by the 6MWT.[23] Besides its use for symptomatic status assessment, CPET is used in clinical practice to assess the hemodynamic response to exercise and for prognostic purpose.[23,29] Not surprisingly, our data describe a population with a poor prognosis and a very high 1-year risk of hospitalisation as failure to achieve 5 Metabolic equivalents (or $\dot{V}O_2$peak $\leq$ 14 mL/kg/min), and a VE/VCO_2 slope $\geq$ 34 during exercise testing is associated with a worse prognosis.[30-32] Therefore, systematic CPET before a valve replacement procedure may be of importance to stratify those high-risk patients in attempt to prioritize patients for surgery.[23] Although, one may argue that there was no reason to perform exercise tolerance tests in our patients showing these features of AS. The aim of our study was to assess in patients with severe AS (Table 2) the ventilatory and hemodynamic responses during the 6MWT compared with a ramp CPET. In clinical practice, symptoms are often underestimated in patients with severe AS. Dyspnea is one of the most prognostically important symptoms in patients with AS and may be particularly difficult to detect, as patients may relate their shortness of breath to other medical conditions and aging. Moreover, they may reduce their daily activities to avoid symptoms. Self-reported symptoms may also be difficult to interpret by treating physicians.[23]

Local parameters, such as the availability or quality of equipment and personnel, may influence the selection of certain tests, as relatively few patients with asymptomatic AS undergo routine stress testing.[33] From a follow-up or a preoperative perspective, the CPET using a recumbent ergocycle (as oppose to a treadmill) may represent a safer way to integrate functional assessment with the use of imaging techniques during testing, which allows a full evaluation of the physiology and morphology of a stenotic valve benefiting valve replacement workup. It is recognized that frailty falls along a spectrum, and an approach incorporating both anatomic (echocardiogram) grading criteria and physiological (stress

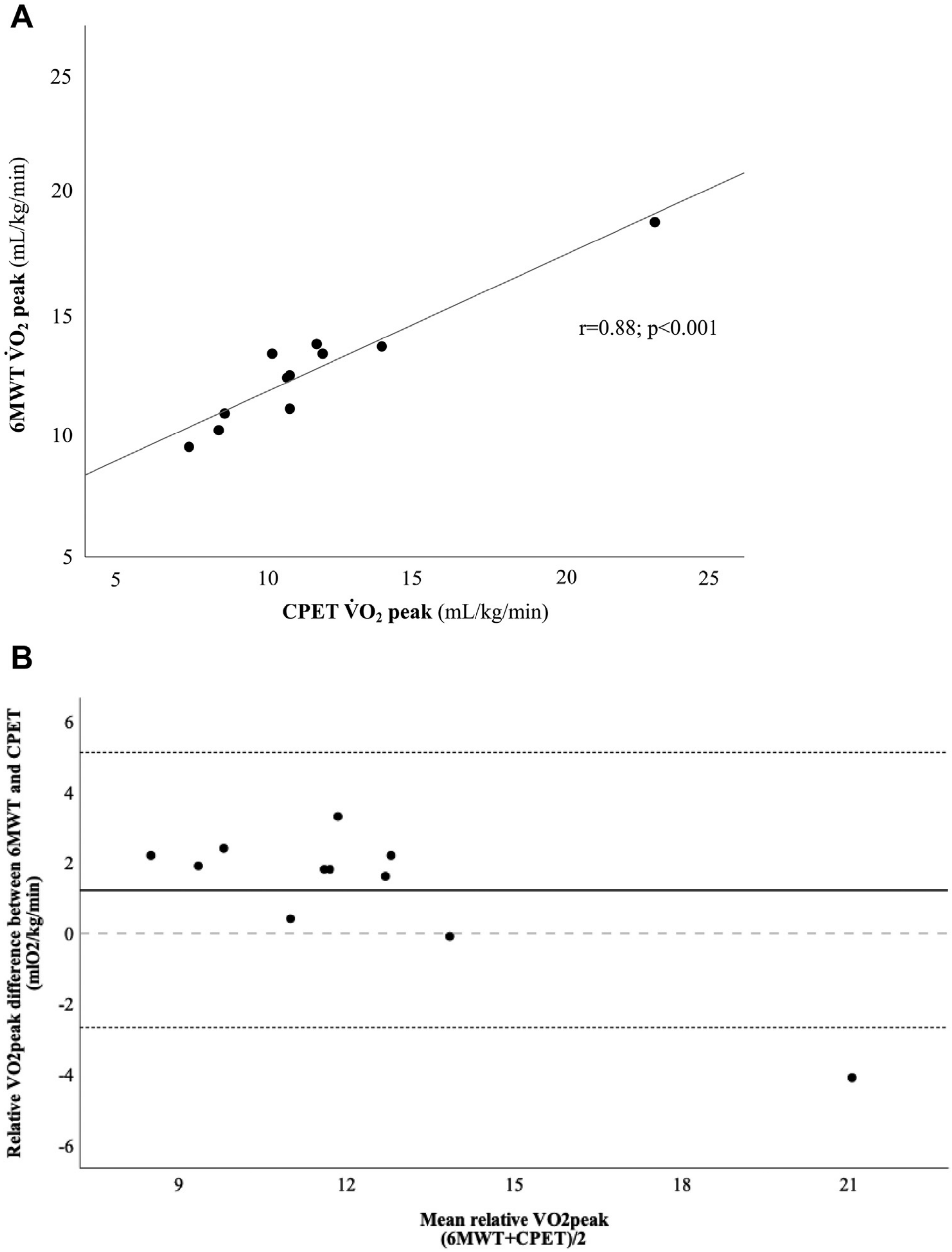

Figure 3. Correlation and Bland Altman representation between 6-minutes walk test (6MWT) and cardiopulmonary exercise test (CPET) $\dot{V}O_2$ peak. (**A**) Correlation between 6MWT and CPET $\dot{V}O_2$ peak. (**B**) Bland-Altman representation showing agreement between 6MWT and CPET $\dot{V}O_2$ peak. $\dot{V}O_2$peak, peak maximal oxygen uptake.

test) assessments of the aortic valve might represent a more appropriate investigational strategy when facing patients with severe or even moderate asymptomatic AS.[34] Maximal exercise testing by itself will provide information about the origin of the exercise intolerance, which might not be coming entirely from the severely stenotic valve. However, many patients with severe AS cannot even perform a 5-meter gait speed assessment[35] or a treadmill exercise test, as frailty is highly prevalent in the AS population and is emerging as an important predictor of outcomes.[35,36] This is the reason we wanted to assess the cardiopulmonary adaptation during a 6MWT using a breath-by-breath gas analysis device ambulatory unit weighting approximately 2 kg. We used the recumbent ergocycle for the CPET to assure better safety during the test.

Our study results should be viewed in the light of some inherent limitations. First, the relative small number of patients limits the strength of the study and limits our power to detect significant sex-difference effects. Although all patients in our study shared the common denominator of severe AS, the population was quite heterogeneous. There was a high prevalence of coronary artery disease (82%). Our findings do not rule out the possibility that revealed symptoms during testing may also reflect clinically significant coronary artery disease. However, AS is commonly associated with coronary artery disease, and decisions for surgery need to take into account a patient's combined effect on symptoms. Aortic stenosis severity was mostly based on 2-dimensional transthoracic echocardiography imaging, whereas confirmation of severity using another modality, such as dobutamine stress echo or computed tomography calcium score, was also used in some patients for the heart team to make a decision regarding AS valve management. Because it has been shown that walking distance tends to increase with repeated test administration, a learning effect occurs because of test familiarization. One may argue that it is difficult to compare recumbent bicycle to upright walking; however, we are confident that our data are relevant, as the breath-by-breath gas analysis showed similar exercise exertion during both tests. The potential effect of performing both tests on the same day may result in an increase level of fatigue, which is more likely to decrease a patient's ability to reach higher VO_2peak. Our results showed a nonsignificant higher VO_2peak reached during 6MWT compared with CPET. Future studies with more patients are necessary to confirm our data. Nevertheless, this study provides important clinical information on safety and highlights the importance of the exercise testing physiological burden during a 6MWT in patients with AS for a comprehensive evaluation by the heart team in this often frail population.

Conclusions

The 6MWT and the CPET may be used for assessment of exercise capacity in patients with severe AS, as both tests were performed without any events and were performed at a high level of exertion. During the 6MWT, a high intensity ($\geq$ 85% VO_2peak) was maintained for $>$ 75% of the test in contrast to only 33% of the time during the CPET. This may contribute to the high prognostic value of the 6MWT documented in clinical studies. The 6MWT, with proper supervision and equipment (breath-by-breath gas analysis and 12-lead ECG), may be an alternative to better assess symptoms in these patients.

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