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Six-minute walking test and long term prognosis in patients with asymptomatic aortic valve stenosis☆

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ABSTRACT

Background: Management of asymptomatic patients with aortic valve stenosis is challenging due to the elusive relationship between symptomatic status and hemodynamic parameters in addition to the occurrence of cardiovascular death. The 6-minute walking test (6MWT) reflects overall hemodynamic function and could contribute to risk assessment in such patients.

Methods and results: One hundred sixteen asymptomatic patients (peak velocity > 2.5 m/s and left ventricular ejection fraction >50% assessed by echocardiographic screening; 85 males; aged 72 ± 8 years) underwent clinical workup, transthoracic echocardiography and a 6MWT. The mean distance covered by patients able to perform the 6MWT ($n = 107$) was 422 ± 90 m. Patients were grouped in tertiles according to distance covered in the 6MWT: *Short*, *intermediate* and *long distance* patients. During a median follow-up of 5.5 years (IQR 4.5–6.3), 29 (25%) patients died, 10 (9%) from cardiovascular causes. Multivariate analysis revealed that short distance patients (≤390 m) were at higher risk of all-cause mortality (HR: 2.44; 95% CI: 1.05–5.67; $p = 0.04$) and cardiovascular mortality (HR: 6.12; 95% CI: 1.18–31.83; $p = 0.03$). For every 100 m covered, the risk of all-cause mortality decreased by 35% (HR: 0.65; 95% CI: 0.43–0.99; $p = 0.04$). Long distance patients (>465 m) did not experience cardiovascular deaths during follow-up.

Conclusions: In asymptomatic patients with aortic valve stenosis, the 6MWT is an independent predictor of all-cause and cardiovascular mortality. It is of incremental value to the echocardiographic evaluation, suggesting that the 6MWT might be useful to guide clinical follow-up intervals and treatment strategy.

1. Introduction

In patients with aortic valve stenosis, treatment is appropriate when the risk of cardiovascular death and development of heart failure outweighs the risk of surgical or percutaneous aortic valve replacement (AVR). Untreated, severe symptomatic patients suffer an annual mortality rate of >20% [1], and in such patients indication for AVR is straightforward [2]. In contrast, the management of asymptomatic patients remains controversial due to the occurrence of cardiovascular death and irreversible myocardial damage in only some patients [3–13]. Hemodynamic progression shows marked individual variability and is *not* reflected by a single objective parameter, but instead by a complex interaction between multiple measures of the aortic valve function, left ventricle and systemic circulation [3,14]. As a consequence, surgery is often delayed until onset of cardiac symptoms even though pre-emptive AVR might be prudent in some asymptomatic patients [3–11]. Therefore, clinical tools for the timely identification of these patients in need of treatment are essential.

The 6-minute walking test (6MWT) is a physical performance test that evaluates the global and integrated responses of systems involved during physical activity, including cardiopulmonary function, systemic circulation, neuromuscular units, and metabolism [15]. It is widely available, inexpensive, has excellent reproducibility, and can be safely administered in the primary care setting [15]. The 6MWT is currently used to stratify risk and guide treatment in patients with congestive heart failure [16,17]. In symptomatic aortic valve stenosis, recent studies have suggested that the 6MWT might be used as a measure of treatment efficacy, as walking distance is often increased after AVR [18–20]. Accordingly, it appears likely that the 6MWT could contribute to risk assessment of patients without symptoms, yet with aortic valve stenosis. Thus, the aim of this study was to test the hypothesis that the 6MWT predicts long-term prognosis in asymptomatic patients with aortic valve stenosis.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study population

Patients with asymptomatic aortic valve stenosis were recruited from six hospitals in the greater Copenhagen area by screening for the diagnosis registry code for aortic valve stenosis (DI35.0) as previously described [21]. Inclusion criteria were echocardiographic peak velocity by continuous-wave Doppler >2.5 m/s and absence of symptoms assessed by the treating cardiologist at the local hospital. Patients with left ventricular ejection fraction (LVEF) < 50%, age < 50 years, and other severe heart valve disease were excluded, for details see Larsen et al. [21] Patients included in the study performed the 6MWT and underwent transthoracic echocardiography at Rigshospitalet, University of Copenhagen and were followed prospectively with regard to long term mortality and AVR (see below). Treating physicians were blinded to all data collected in this study, including the result of the 6MWT. The study was approved by the local Research and Ethics Committee (J.nr.H-B-2009-027).

2.2. Six-minute walking test

The 6-minute corridor walking test was performed in an indoor unobstructed and leveled 30 m hallway, according to current recommendations [15]. All patients were informed of the purpose of the test in a standardized manner before the test was performed. They were instructed to walk the corridor from one end to the other at their own pace, as many times as possible, within the allotted time. The patients were advised on the possibility of slowing down the pace or stopping to rest as needed to resume walking as soon as they felt they were able to do so. The test was supervised by an experienced physician who encouraged the patients at standardized intervals to improve walking performance. After 6 min had elapsed, patients were instructed to stop walking, and the total distance walked was measured. Heart rate and oxygen saturation (SpO_2) were recorded before (*pre-test*) and immediately after the test was completed (*post-test*). Patients able to perform the test were grouped according to tertiles of the distance (meters) covered in the 6MWT — *short*, *intermediate* and *long distance* patients. Patients not able to perform the test were defined as *non-performers*.

2.3. Transthoracic echocardiography

All examinations were performed on a Vivid E9 scanner (GE Healthcare, Horten, Norway) with a 3.5 MHz transducer. Images were obtained and digitally transferred to a remote workstation for offline analysis (EchoPac BT 11.1.0, GE Healthcare, Horten, Norway). All measures regarding the aortic valve, LVEF, left ventricular mass, and relative wall thickness were performed and calculated as recommended [22,23]. Calcification of the aortic valve were assessed and visually graded as previously described [5]. Severity of aortic valve stenosis was graded according to Doppler estimated effective orifice area (AVA) in mild (>1.5 cm^2), moderate (1.0–1.5 cm^2), and severe (<1.0 cm^2) as recommended [22].

2.4. Clinical variables

Clinical data recorded at study entry included prior evidence of coronary artery disease, a history of hypertension, systemic embolic events, other chronic diseases (diabetes and pulmonary disease), and current medication.

Diagnostic work-up included N-terminal pro brain-type natriuretic peptide (NT-proBNP) and pulmonary function tests. Maximally forced expired flow volume loops were performed prior to the 6MWT using a standard spirometer. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were reported from the same loop according to guidelines [24]. The percentages of maximum age-gender-height-adjusted FEV_1 and FVC were obtained automatically from the spirometer.

2.5. Study endpoints

The primary endpoint of the study was all-cause mortality. The secondary endpoint was cardiovascular mortality. The tertiary endpoint was AVR (surgical or percutaneous). Endpoints were collected 4 years after inclusion of the last patient. Information on mortality and AVR was obtained from electronic health records. Cause of death was established from medical records and adjudicated as cardiovascular death, non-cardiovascular or unknown, blinded to all data collected in the study.

2.6. Statistical analysis

All statistical analysis was completed using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Normal distribution was examined by Q-Q plots and normality tests (Kolmogorov-Smirnov, Shapiro-Wilk). Continuous variables with normal distribution are presented as mean ± SD and compared using Student's *t*-test for two groups and one-way analysis of variance for multiple groups. Variables with non-normal distribution are presented as median (interquartile range; IQR) and compared using Mann-Whitney *U* test for two groups and Kruskal-Wallis for multiple groups. Categorical variables are presented as n (%) and compared using Fisher's exact test.

The time-related outcome distribution according to the distance walked in the 6MWT was estimated using Kaplan-Meier curves and log-rank tests were used to estimate the difference. Proportional hazards were verified with Schoenfeld residuals. Univariate and multivariate Cox regression models were used to estimate predictors of the endpoints. Variables with a univariate value of $p < 0.05$ were incorporated into the multivariate models. NT-proBNP and LVEF were right-skewed and therefore log transformed before regression analysis. To assess the effect on mortality in patients not undergoing AVR, a subgroup analysis was performed. p-Values < 0.05 in two-sided tests were considered statistically significant.

3. Results

One hundred and sixteen eligible patients were included in the study. Mean age of the patients was 72 ± 8 years, 85 (73%) were male. The severity of aortic valve stenosis by Doppler estimated effective orifice area ranged from 0.5 to 2.0 cm^2, with 10 (9%) having mild, 41 (35%) moderate, and 65 (56%) severe AS.

3.1. 6-minute walk test

All except 9 (8%) patients were able to perform the test (2 were wheelchair-bound, 2 had recent injury of the lower extremities, and 5 did not consent due to non-specific disabilities). The mean distance of the 6MWT in patients performing the test was 422 ± 90 m (range 120–625 m). Six patients (6%) required a rest stop during the test. No patients experienced adverse events as a result of the test.

Short, *intermediate* and *long distance* tertiles of the 6MWT were ≤390, 390 to 465, and >465 m respectively. Clinical characteristics, echocardiographic findings and pulmonary function tests, according to distance walked during the 6MWT in addition to non-performers are given in Table 1. Clinical characteristics and echocardiographic findings were overall similar between the three groups performing the 6MWT, however short distance patients were significantly older, and had higher levels of NT-proBNP. A significant difference in FEV_1 between groups was noted, however, when adjusting for predicted normal values this did not remain significant. During the 6MWT, short distance patients experienced a smaller increase in heart rate than other patients (Table 2). No difference in pulse oximetry was measured between the groups (Table 2).

3.2. Clinical outcome

Patients were followed for a median of 5.5 years (IQR 4.5–6.3). Of the 107 patients performing the 6MWT, 23 (21%) patients died during follow-up with cause of death being cardiovascular in 10 (9%), non-cardiovascular in 12 (11%) and unknown in 1 (1%). Six (67%) of the 9 non-performers died during follow-up, all from non-cardiovascular ($n = 4$) or unknown causes ($n = 2$). During follow-up 46 of 116 (40%) patients underwent AVR. The clinical indications for AVR were development of symptoms in 42 (91%), reduced LVEF in 3 (7%) and severe AS with 3-vessel disease in 1 (2%). No patients were lost to follow-up. An additional of 12 patients developed symptoms but did not undergo AVR due to severe comorbidity.

3.3. All-cause mortality

Kaplan-Meier curves for all-cause mortality in the 3 groups performing the 6MWT ($n = 107$) are given in Fig. 1A. Univariate analysis revealed that walking a short distance in the 6MWT and COPD were predictors of all-cause mortality (Table 3, left). No significant interactions existed between these parameters and any other parameter given in Table 3. In multivariate analysis, walking a short distance remained the only independent predictor of all-cause mortality (Table 3, right). Fig. 1C illustrates the estimated survival probability according to the distance walked. For every 100 m covered in the 6MWT, the risk of all-cause mortality decreased by 35% (HR: 0.65; 95% CI: 0.43–0.99; $p = 0.04$) in an unadjusted model. Of all patients included ($n = 116$), non-performers ($n = 9$) had a poorer prognosis than those who performed the test ($n = 107$) (HR: 5.54; 95% CI: 2.19–14.06; $p < 0.001$).

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