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Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome

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ABSTRACT

Background: Eisenmenger syndrome (ES) represents the extreme manifestation of pulmonary arterial hypertension in patients with congenital heart disease, associated with significant exercise intolerance and mortality. Even though of six-minute-walk-test (6MWT) is routinely used in these patients, little is known about its prognostic value in comparison to functional class.

Methods and results: We included 210 adult patients with ES who underwent a total of 822 6MWTs. Median walking distance (6MWD) was 330 m [IQR 260–395], oxygen saturation (SO_2) at baseline 86% [IQR 82–91%] and SO_2 at peak-exercise 69% [IQR 60–80%]. In patients commenced on advanced therapy for pulmonary hypertension, but not in the reminder, there was a significant improvement in walking distance (297 ± 97 m vs. 325 ± 87 m,P = 0.0019), SO_2 at rest (84.9 ± 7.1 vs. 86.8 ± 5.9%,P = 0.003), SO_2 at peak exercise (69.1 ± 12.7 vs. 72.3 ± 12.2%,P = 0.04) and NYHA functional class (P = 0.0047).

During a follow up of 3.3 years, 29 patients died. On time-dependent Cox analysis, 6MWD (HR 0.94 per 10 m, 95%CI: 0.91–0.97,P < 0.001) and baseline SO_2 (HR 0.90, 95%CI:0.86–0.94,P < 0.0001) were predictors of death. In contrast, age, functional class, peak-exercise SO_2 and SO_2 change were not related to mortality. A three-fold increased risk of death was identified in patients not reaching a 6MWD of 350 m or with baseline SO_2 below 85%.

Conclusions: The 6MWD and resting SO_2, but not functional class were predictive of outcome in this contemporary cohort of Eisenmenger patients and should be incorporated in both risk stratification and management algorithms for these patients.

1. Introduction

Approximately 5–10% of patients with congenital heart disease develop pulmonary arterial hypertension (PAH), which impacts on quality of life and outcome [1–3]. Eisenmenger syndrome (ES) represents the extreme manifestation amongst them. Patients with ES are significantly impaired in their exercise capacity and have a relatively high mortality rate, particularly after the third decade of life [4]. However, patients with ES may deny significant limitations in their daily activities and, thus, be classified functional class 2 (or asymptomatic), contrary to objective evidence of severe exercise intolerance [5]. Congenital heart disease is, per definition, present from birth and PAH in patients with ES typically develops early in life, leading to adaptation of daily activities and lifestyle to patient ability [6], and thus masking objective capacity and symptoms. Assessment of functional class is broadly the basis on which physicians decide whether patients warrant initiation or escalation of advanced therapy (AT) for PAH [7]. We submit, however, that in patients with ES functional class is likely to underestimate the extent of exercise intolerance. Moreover, in patients who are already on AT, functional class alone may fail to establish adequacy of treatment and, thus, may be suboptimal for longitudinal follow-up and management of these patients. Timely initiation and escalation of treatment in ES is important, not only for improving exercise and, thus, quality of life, but also in improving prognosis [8,9]. Objective means of assessing exercise capacity have, therefore, a pivotal role for assessing disease severity, disease progression and response to AT.

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The six minute walk test (6MWT) is a simple and reliable test for patients with physical limitation; it is for this reason that it has been widely used as a primary endpoint for clinical trials in the area of PAH [10]. Furthermore, the 6MWT provides a good reflection of functional ability and limitation in everyday life. However, little information is available on the prognostic value of the 6MWT in patients with ES. Our study aimed, therefore, to assess the validity of the 6MWT distance and of other simple clinical variables, such as oxygen saturation (SO_2), in predicting outcome in a large, single-centre cohort of adults with ES.

2. Patients and methods

This was a retrospective study. Data on all adult patients with ES under active follow-up at our centre since 2000 to 2012 were obtained and studied. For the scope of the study we defined the start of adulthood as age > 16 years. We included patients with PAH due to a nonrestrictive intracardiac or extracardiac communication [11–13]. Patients who underwent previously corrective surgery for CHD were also included [14], provided that they had near-systemic PAH. Patients with Down syndrome who underwent 6MWT were also included into the analysis. A firm diagnosis of CHD and PAH had been established by echocardiography, cardiovascular magnetic resonance and cardiac catheterization, as previously described [14]. Demographic and clinical data were collected from a dedicated clinical database and the patients' clinical records.

Cardiac lesions were classified into 4 categories according to the shunt type: pre-tricuspid (atrial septal defect or anomalous pulmonary venous drainage), post-tricuspid (ventricular septal defect or patent ductus arteriosus in the absence of a pre-tricuspid shunt), complex anatomy (other shunt lesions including atrioventricular septal defects, univentricular physiology, transposition of the great arteries, aortopulmonary window, and common arterial trunk) and operated lesions [14–16]. In case of univentricular physiology, severe PAH was assumed when pulmonary artery was connected directly to the ventricle and there was no significant pulmonary stenosis or effective surgical banding of the pulmonary artery.

Six-minute walk test is part of the periodic follow up assessment of patients in our centre; the test is performed in agreement with standard protocols [17]. Briefly, patients are encouraged on 6MWT to walk as far as possible during a period of 6 minutes, but not run or jog. Finger pulse oximetry is performed using Massimo™ pulse oximeters model Rad-57 (Massimo International Sàrl, Switzerland) prior to 6MWT and directly at the end of the 6MWT. Dyspnea at rest and on peak exercise is assessed using the Borg dyspnea scale with 0 standing for "no dyspnea" and 10 for "maximal dyspnea" [18].

2.1. Statistical analysis

Statistical analyses were performed using MedCalc for Windows, version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium) and R-package version 2.13.0 [19]. Continuous variables are presented as mean ± standard deviation or median and inter interquartile range (IQR), presented in square brackets. Categorical variables are presented as number (percentage). Data distribution was assessed for normality using the Shapiro–Wilk test. In case of a normally distributed variable, comparison between groups was performed using unpaired two-tailed t-test or Welch-test in case of unequal variances. For data with a non-normal distribution, the Mann–Whitney test was used. For comparison of continuous variables in multiple groups, one-way analysis of variance (ANOVA) was used, with logarithmic transformation of variables when required. The relation between continuous variables was assessed using Pearson's or Spearman's rho, depending on data distribution. The relation between clinical or demographic parameters and mortality was assessed using Cox proportional-hazards regression analysis. Since most patients underwent more than one 6MWT, a Cox model with time-dependent covariates was used [14]. Locally-weighted polynomial fit was used to plot regression lines. A two-sided p-value of <0.05 was considered indicative of statistical significance.

3. Results

3.1. Demographics and mortality

In total, 210 consecutive, adult patients with ES were included in the analysis. Demographic and clinical characteristics of all patients are presented in the Table 1. Mean age at the first 6MWT was 37.1 ± 12.9 years; 33% of patients were male. Most patients had a post-tricuspid lesion (47%) followed by patients with complex cardiac anatomy (37%). Down syndrome was present in 39 (19%). Significant exercise limitation (NYHA functional class III or more) was present in over one third of patients (37%).

3.2. 6MWT

In total 822 6MWTs were analyzed. All patients underwent a 6MWT at baseline and 67% underwent at least two 6MWTs (median of 3, IQR [1–5]). The mean distance achieved at baseline 6MWT was 292 ± 120 m. Patients with Down syndrome managed significantly shorter walking distances (306 ± 121 m versus 230 ± 93 m in non-Down patients, $p < 0.001$).

Baseline SO_2 on air at baseline was 84.9 ± 8.0% whereas peak exercise SO_2 68.7 ± 14.4%. Oxygen saturations below 70%, the limit of accurate measurement suggested by manufacturers of pulse-oximeters, were recorded at rest in 1% of tests and in 50% of tests at peak exercise [20]. Significant differences in both baseline SO_2 ($p < 0.0001$) and 6MWT distance ($p = 0.037$) were detected between anatomical subgroups: patients with complex cardiac lesions had the shortest median 6MWT distance (271 m [196–350]) and lowest baseline SO_2 (83% [77–86]) compared to all other groups (Fig. 1).

There was a weak, but statistically significant correlation between 6MWT distance and NYHA functional class ($r = 0.31$, $p < 0.0001$), baseline and peak saturations on 6MWT ($r = 0.36$, $p < 0.0001$ and $r = 0.20$, $p < 0.0001$, respectively).

Out of 146 patients who underwent more than one 6MWT 46 patients (32%) were at the time of first 6MWT on AT. Overall, there was no significant change in 6MWT distance (304.9 ± 118.8 m vs. 308.1 ± 109.9 m, $P = 0.65$), baseline SO2 (85.5 ± 7.2% vs. 85.6 ± 6.6%, $P = 0.81$) and peak SO2 (67.8 ± 14.0% vs. 69.4 ± 13.9%, $P = 0.09$) between the first and second 6MWT.

At the time of first 6MWT 35% patients were on AT. The median time of AT therapy at the time of first 6MWT was 106 days and 48% patients were treated with endothelin receptor antagonists and 52% with phosphodiesterase-5 inhibitors. In patients started on AT (Fig. 2) there was a significant improvement in walking distance (297 ± 97 m vs. 325 ± 87 m, $P = 0.0019$), SO_2 at rest (84.9 ± 7.1 vs. 86.8 ± 5.9%, $P = 0.003$), SO_2 at peak exercise (69.1 ± 12.7 vs. 72.3 ± 12.2%, $P = 0.04$) and NYHA functional class ($P = 0.0047$).

3.3. Predictors of outcome

The median follow-up time from first 6MWT was 3.3 [2.0–7.1] years. Overall, 29 (14%) of patients died: 14 (48%) were on AT at the time of death (overall mortality rate of 30.7/1000 patients per year). One patient had heart-lung transplantation during follow-up and was censored at the time of transplantation.

On univariate Cox analysis, several parameters emerged as predictors of death (Table 2, Fig. 3). These included 6MWT distance, distance change, defined as difference between the 6MWT distance on consecutive tests, distance change rate, as well as baseline SO_2. When patients with Down syndrome were excluded, 6MWT distance and baseline SO_2 were the only predictors of outcome (HR = 0.94, 95% CI 0.91–0.97 per 10 m, $P = 0.0006$ and HR = 0.90, 95% CI 0.86–0.94 per 1% SO_2, $P < 0.0001$, respectively), while in patients with Down syndrome 6MWT distance was the only predictor of mortality (HR = 0.82, 95% CI 0.68–0.98, $P = 0.03$).

Overall, patients with 6MWT distance in the lowest quartile (<260 m) were at three-fold higher risk of mortality when compared to patients in the highest quartile (>395 m) on the Cox regression analysis (HR 3.00, 95% CI 1.38–6.48, $P = 0.005$). Similarly, patients with baseline SO_2 in the lowest quartile (<82%) had an over three-fold higher risk of mortality (HR 3.3, 95% CI 1.48–7.36, $P = 0.0035$) when compared to patients in the highest quartile (>91%).

Analysis of cut-off values for walking distance and baseline saturation as predictors of mortality in the entire cohort revealed values of 350 m for distance (HR 3.06, 95% CI 1.16–8.08, $P = 0.024$) and 85% for baseline saturation (HR 2.80, 95% CI 1.22–6.46, $P = 0.016$; Fig. 4).

On bivariate Cox analysis both 6MWT distance and baseline SO_2 were significant predictors of outcome, even after adjusting for AT