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Six-minute walking distance and decrease in oxygen saturation during the six-minute walk test in pediatric pulmonary arterial hypertension

Johannes M. Douwes [a,*,1], Anneke K. Hegeman [b,1], Merel B. van der Krieke [a,1], Marcus T.R. Roofthooft [a,1], Hans L. Hillege [c,1], Rolf M.F. Berger [a,1]

[a] Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, The Netherlands
[b] Center for Congenital Heart Diseases, Department of Physical Therapy, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, The Netherlands
[c] Center for Congenital Heart Diseases, Department of Epidemiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, The Netherlands

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ABSTRACT

Objective: To investigate the prognostic value of the 6-minute walking distance (6-MWD), transcutaneous saturation (tcSO2) and heart rate (HR) obtained during the 6-minute walk test (6-MWT) in pediatric pulmonary arterial hypertension (PAH).
Methods: This was an observational study with forty-seven pediatric PAH patients, aged ≥7 years, and diagnosed and followed at the national referral center for pediatric PAH in the Netherlands. All patients performed a comprehensive 6-minute walk test (6-MWT), which measures 6-MWD and tcSO2 and HR before ("baseline"), during ("exercise") and 5 min after ("recovery") the walk test.
Results: The 6-MWD expressed either in meters or in sex- and age-corrected z-scores, was associated with transplant-free survival, independently from sex, age, and the presence of a shunt-defect. Shorter 6-MWD correlated with higher WHO-FC and increased NT-pro-BNP. Absolute tcSO2 at exercise and tcSO2-decrease during 6-MWT were associated with transplant-free survival, independent from 6-MWD. Combining tcSO2-decrease with 6-MWD provided the strongest prognostic model. Patients with 6-MWD > 352 m (the median 6-MWD) had a better outcome than those with smaller 6-MWD. A large tcSO2-decrease during 6-MWT (>19% for patients with and >5% for patients without a shunt defect) identified patients with worse transplant-free survival both in patients with a 6-MWD above and below the median 6-MWD.
Conclusions: The 6-MWD is an independent predictor of prognosis in pediatric PAH, that reflects disease severity and clinically relevant exercise-tolerance and therefore qualifies as a treatment goal. The magnitude of tcSO2-decrease during 6-MWT, adjusted for the presence of a shunt, indicates an additional risk factor for prognosis in children with PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by pulmonary arterial remodeling that leads to an increased pulmonary vascular resistance and pressure, eventually resulting in right ventricular failure. Despite the introduction of PAH-targeted therapies, outcome of PAH is still rather poor, especially in children [1–3]. Current guidelines recommend a goal-oriented therapy to improve outcome [4,5]. However, in pediatric PAH such treatment strategy is limited due to the lack of well-defined treatment goals. Treatment goals proposed for adult PAH patients cannot simply be translated to children with PAH [6].

In adult PAH, improvement in 6-minute walking distance (6-MWD) is regarded as a clinical meaningful treatment goal. 6-MWD has been demonstrated to correlate with other parameters of disease severity, such as WHO—functional class (WHO-FC), and has been suggested to be a predictor of outcome. Therefore the 6-MWD has been commonly used as an endpoint in treatment efficacy studies [4,7–9]. Moreover, in addition to the 6-MWD, the magnitude of desaturation during the 6-minute walk test (6-MWT) and heart rate recovery after performing the 6-MWT are reported additional predictors of outcome in adult PAH patients [10–12].

In children the use of 6-MWD is restricted to those old enough to perform the test. Data concerning the 6-MWD in these children is limited. Of recent outcome papers for pediatric PAH, three report on 6-MWD and its association with clinical outcome, however with contradictory

Abbreviations: 6-MWD, 6-minute walking distance; 6-MWT, 6-minute walk test; HR, heart rate; IPAH/HPAH, idiopathic/hereditary pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; TcSO2, transcutaneous oxygen saturation; WHO-FC, World Health Organization—functional class.

* Corresponding author at: Beatrix Children's Hospital, University Medical Center Groningen, P.O. Box 30 001, 9700 RB Groningen, The Netherlands.
E-mail address: j.m.douwes@umcg.nl (J.M. Douwes).

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results [2,3,13–15]. Lammers and co-workers report 6-MWD to be a strong predictor of transplant-free survival, whereas van Loon et al. and Ploegstra et al. could not demonstrate a relation between 6-MWD and outcome in children with PAH [1,16]. The predictive values of desaturation during and heart rate recovery after the 6-MWT have not been previously studied in children.

The current study investigates, in children with PAH aged ≥7 years, the prognostic value of the 6-MWD and of heart rate and transcutaneous oxygen saturation (tcSO2) measured before, during and after the walk test.

2. Methods

This was an observational study within a national patient cohort. In the Netherlands, all pediatric patients suspected for PAH are referred to the National Referral Center for Pediatric Pulmonary Hypertension at the University Medical Center Groningen and undergo a standardized diagnostic work-up, including confirmation of the diagnosis by cardiac catheterization [17]. Subsequently treatment is initiated and up-titrated according to contemporary international guidelines adapted for children [4]. All patients have standardized follow-up visits at the referral center every 3–12 months, ensuring the surveillance of patients for clinical endpoints and follow-up [1,17–22]. Data concerning the diagnostic work-up, follow-up and treatment of these patients are prospectively collected within the Dutch pediatric PAH patient registry. This local electronic database system with automated data range checks and surveillance for quality control is maintained at the referral center by a dedicated coordinator. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee and written informed consent from patients/caregivers was obtained.

All included patients underwent hemodynamic assessment by right heart catheterization and fulfilled current hemodynamic criteria for diagnosis of PAH. At diagnosis and every follow-up visit, a 6-MWT is performed by all patients regarded eligible for this test. The test is conducted according to the guidelines reported by the American Thoracic Society (ATS), with adjustment of the track distance from 30 to 8 m to prevent children from getting distracted on a long track [23]. Additionally, transcutaneous oxygen saturation (tcSO2) and heart rate (HR) are measured directly before ("baseline"), during (at the end of 6 min walking: "exercise") and 5 min after the end of the 6-MWT ("recovery"), further referred to as "comprehensive 6-MWT". HR and tcSO2 were measured using a handheld pulse oximeter placed on the index finger of the patient's right hand. HR-increase is defined as HR-exercise minus HR-baseline, and tcSO2-decrease is defined as tcSO2-baseline minus tcSO2-exercise. We included patients with either idiopathic/heritable PAH (IPAH/HPAH) or PAH associated with congenital heart disease (PAH-CHD) seen between 2001–2013, who performed at least one comprehensive 6-MWT at the Dutch referral center at an age ≥ 7 years. The latter was done to ensure the ability of performing a reliable and reproducible 6-MWT [24,25]. For all included patients, the first comprehensive 6-MWT at age of ≥7 years was used for analysis. To evaluate the effect of hemodynamic significant shunt defects on the variables measured during the comprehensive 6-MWT, patients were separated in 1) patients with a hemodynamically significant intra-cardiac or arterial shunt defect (patients with shunt) and 2) patients without such a defect (patients without shunt).

2.1. Statistical analyses

The 6-MWD and HR at baseline and exercise were analyzed using absolute values and z-scores based on recently reported reference values [26]. Reference values for HR-increase and -recovery are, as far as we are aware, not available. Comparisons between shunt-groups were made using *t*-test, Mann–Whitney U and Chi-Square test. Correlations were tested using Spearman's or Pearson's correlation coefficients. Treatment was depicted at the moment of the 6-MWT and at end of follow-up, at which maximal treatment up-titration during the follow-up period for the individual patient was reached.

Transplant-free survival was determined from the time of analyzed 6-MWT to an event (death or lung transplantation) or the last follow-up visit. Cox regression analysis was used to investigate the association of the 6-MWD (meters and z-scores) and the additional comprehensive test variables with transplant-free survival. A multivariate analysis was performed to test the additional prognostic value to the 6-MWD of the comprehensive test variables with the strongest association to transplant-free survival in univariate analysis. To rule out potential confounding effects of age, sex, and shunt-defect these variables were forced into the survival model. Harrell's C-statistic was used to identify the model with the best discriminating ability between patients with worse or better outcome.

Kaplan–Meier curves with log-rank tests were plotted for patients below and above the median 6-MWD. To identify patients with a worse prognosis Kaplan–Meier curves were plotted for the highest versus the two lower tertiles (thereby choosing the cut-off value at the second tertile of the variable) of the additional comprehensive test variable that was identified to be the strongest predictor of outcome in addition to the 6-MWD in the Cox-regression analysis [22,27]. To illustrate the prognostic value in addition to the 6-MWD, these curves were plotted for patients with a 6-MWD below and above the median 6-MWD separately. Tertiles of the additional comprehensive test variable were determined separately for the patients with and without a shunt defect. Analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA) and STATA 11.0 (Stata Corp., Texas, USA). The level of significance was defined as $p < 0.05$, two-sided.

3. Results

The study included 47 patients, 15 with PAH-CHD and a shunt defect and 32 without a shunt defect; including 2 PAH-CHD patients with PAH > 1 year after complete closure of a shunt-defect and 30 patients with IPAH/HPAH (Table 1). PAH was diagnosed by cardiac catheterization (mPAP ≥ 25 mm Hg, pulmonary capillary wedge pressure (mPCWP) ≤ 15 mm Hg and PVRi ≥ 3 WU m^2) in all patients but one. In this latter patient with severe PAH based on Eisenmenger's syndrome, cardiac catheterization was not performed because the procedural risk was considered too high. The diagnosis was confirmed by echocardiography. There was a slight female predominance. Three Down syndrome patients were included, that were regarded to be able to perform a reliable 6-MWT (Table 2). Patients with a shunt-defect had lower systemic arterial and transcutaneous oxygen saturations and a higher baseline heart rate.

The tcSO2 decreased significantly after 6 min of walking (tcSO2-exercise) in both the patients with and without a shunt, and had recovered 5 min after the end of the test (tcSO2-recovery) (Fig. 1). The tcSO2-decrease was significantly more pronounced in patients with shunt-defects compared to those without shunt-defects (Table 2). The HR increased significantly during 6-MWT (HR-exercise) in both patient groups and had recovered 5 min after the end of the test (HR-recovery) (Fig. 1). The HR-increase did not differ between both patient groups (Table 2).

3.1. Comprehensive 6-MWT and disease severity

The 6-MWD correlated negatively with WHO-FC and log10NT-proBNP ($r = -0.402$ $p = 0.005$; $r = -0.439$ $p = 0.011$ respectively). The tcSO2-exercise correlated negatively with WHO-FC ($r = -0.363$ $p = 0.013$), whereas tcSO2-decrease correlated positively with WHO-FC ($r = 0.316$ $p = 0.032$). Both were not correlated with age and NT-proBNP. HR-increase was larger in older patients ($r = 0.379$ $p = 0.009$), but did not correlate with WHO-FC or NT-proBNP. TcSO2-baseline, tcSO2-recovery, HR-baseline, HR-exercise, and HR-recovery (absolute values) did not correlate with age, WHO-FC or NT-proBNP.

3.2. Comprehensive 6-MWT and outcome

Patients were treated according to contemporary treatment guidelines adapted for children (Table 3). Of the 47 patients, 17 reached an endpoint (11 died, 6 underwent lung transplantation). Of the 30 IPAH/HPAH patients 6 died and 4 had a lung transplantation. Of the 17 PAH-CHD patients 5 died, 1 had a lung transplantation and 1 a heart–lung transplantation. All deaths were PAH related or PAH treatment related. Reasons of death include progressive right ventricular failure (n = 4), hemoptoe with circulatory failure (n = 5), circulatory failure during sepsis due to venous access port infection and peri-operative death during a lung transplantation procedure. Median time to reaching the endpoint was 2.8 (0.7–4.9) years. All deaths were PAH-related.

Cox regression analyses were performed and corrected for age, sex, and shunt-defect to rule out their potential confounding effects. Longer

Table 1
Characterization of shunt defects.

Pre-tricuspid shunt:
Atrial septal defect (n = 2)
Post-tricuspid shunt:
Ventricular septal defect (VSD) (n = 3)
Persistent ductus arteriosus (PDA) (n = 5)
VSD, PDA, and partial abnormal pulmonary venous return (n = 1)
Complete atrioventricular septal defect (n = 2)
Univentricular heart with PDA (uncorrected) (n = 1)
Double inlet left ventricle, double outlet right ventricle with a straddling tricuspid valve and side-by-side transposition of the great arteries (uncorrected) (n = 1)