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Prognostic significance of six-minute walk test in non-group 1 pulmonary hypertension

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ABSTRACT

Objective: To assess the value of the six-minute walk test (6MWT) to predict outcome in non-group 1 pulmonary hypertension (PH).
Background: Distance walked during 6MWT has been widely used as a prognostic test in pulmonary arterial hypertension (group 1 pulmonary hypertension); however, little is known regarding its prognostic value in other groups of PH.
Methods: This was a retrospective study of 60 patients diagnosed of PH, Dana Point classification groups 2–5. 6MWT and echocardiography were performed in all cases.
Results: Forty patients (66.6%) were females. Mean age was 70.8 ± 10.7 years (range: 32–85). Seven patients died after a mean follow-up of 23.2 ± 16.7 months. Distance <400 m during 6MWT was associated with a higher risk for death (RR: 4.39; 95% CI: 1.13-17.05; $p = 0.03$) and for clinical deterioration (death or need for hospitalization) (RR: 2.76; 95% CI: 1.18–6.42; $p = 0.02$).
Conclusions: 6MWT is useful to predict outcome in non-group 1 PH.

Introduction

Pulmonary hypertension (PH) is an intricate disorder with multiple possible etiologies.[1] The current clinical classification of PH (Dana Point 2008)[2] designates 5 categories of PH. Group 1 PH, or pulmonary artery hypertension (PAH) is a syndrome subsequent to impaired flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance. Groups 2–5 PH cover populations with non-PAH pulmonary hypertension. These categories include PH with left heart disease (group 2), PH associated with lung disease and/or hypoxemia (group 3), PH due to chronic thrombotic and/or embolic disease (group 4), and miscellaneous causes of PH (group 5).[2]

Group 1 PH has been the main focus of cardiologists and pulmonologists specialized in the management of PH, and many studies have assessed the natural history and prognosis of this syndrome.[1,3] However, most clinicians will see non-group 1 PH much more frequently than group 1 PH. It is crucial for medical practice to use valid and reliable tests that are simple to perform to determine outcomes, in order to aid in the decision-making process. The six-minute walk test (6MWT) is an easy to perform submaximal exercise test and the distance walked correlates strongly with mortality in group 1 PH.[4] Therefore, it is usually employed as endpoint in clinical trials to assess the benefit of therapies in patients with this syndrome. This test might be also useful to direct therapy in patients with non-group 1 PH, but it is essential to determine previously whether it correlates with prognosis in these cases. It must be noted that exercise tests (including the 6MWT) seem to be less accurate predictors of outcome in a subgroup of subjects with non-idiopathic group-1 PH, like PAH associated to HIV infection or to collagen vascular diseases.[5] There is a lack of information on the prognostic value of the 6MWT in patients with non-group 1 PH. These cases are usually seen in PH clinics and several different etiopathogenic mechanisms combine frequently to produce PH. Because the 6MWT did not predict survival in the

Abbreviations: 6MWT, six-minute walk test; 95% CI, 95% confidence interval; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CT90, cumulative percentages of time at SaO_2 below 90%; CTPEH, chronic thromboembolic pulmonary hypertension; IVC, inferior vena cava; LVSF, left ventricle systolic function; OPD, other pulmonary diseases with mixed obstructive and restrictive pattern; PAH, pulmonary artery hypertension; PH, pulmonary hypertension; RR, relative risk; RV, right ventricle; RVSF, right ventricle systolic function; SaO_2, arterial oxygen saturation; SDB, sleep disordered-breathing; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

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subgroup of patients with associated medical conditions within the group-1 PH in a recent study,[5] we hypothesized that this test might also lack enough predictive capability in non-group 1 PH. Subjects with non-group 1 PH often suffer comorbid conditions that might shorten the distance walked, and this could interfere in the usefulness of the test.

The objective of this study was to assess the value of the distance walked during the 6MWT as a predictor of mortality or clinical deterioration in a group of patients admitted to the PH clinic of our hospital for study of PH that were diagnosed of groups 2–5 PH.

Material and methods

Subjects and study design

We retrospectively reviewed the computerized medical records of all the patients that were admitted to the pulmonary hypertension unit of our hospital from March 2008 to March 2012. Patients were submitted to this unit from other hospital medical services for evaluation of PH. Typically, the patients are directed to the PH clinic when there is a suspicion of group 1 PH or when a case with non-group 1 PH has values of pulmonary artery pressure that appear disproportionately high for the severity of the concomitant disease that causes PH. Due to the design of the study, information on the total population of patients with PH who were not directed to the specialized clinic was not available for analysis.

Inclusion criteria for the study were adult age (e.g. older than 18 years) and diagnosis of non-group 1 PH after a thorough evaluation that included in all cases echocardiography, and when clinically indicated, complete lung function testing, sleep studies, computed pulmonary tomography, arterial blood gas analysis and ventilation-perfusion scanning (invasive hemodynamic assessment was only performed in a minority of cases). Exclusion criteria were diagnosis of pulmonary artery hypertension (group 1 PH) and inability to perform a 6MWT (e.g. orthopedic diseases that limited walking).

We registered the following variables: sex and age of the patient, the primary diagnosis, the date and results of the echocardiography and the 6MWT (see below), the comorbid conditions (assessed by means of the non-age adjusted Charlson comorbidity index[6]), the number of hospital admissions after the 6MWT, and the vital status at the time of data analysis. The date and cause of death were obtained reviewing the death certificates. Approval for the use of the data was obtained from our local ethical committee (Reg. N° CEIC Galicia 2012/229).

Echocardiography

The study was done using a SONOS 5500 (Hewlett Packard, Palo Alto, CA) ultrasound imaging system with an S4 transducer. In all cases M-mode, 2-dimensional, Doppler (continuous and pulsed wave), and color Doppler were performed with the patient in the left lateral position. The structure of the mitral, aortic, tricuspid, and pulmonary valves, and the systolic and diastolic function of the left ventricle were systematically assessed. PH was defined as systolic pulmonary artery pressure (SPAP) $>$ 40 mm Hg.[7] Doppler derived right ventricle (RV) systolic pressure was calculated from the peak velocity of tricuspid flow regurgitation with continuous wave Doppler in the apical four chamber view and the modified Bernoulli equation.[8] Right atrial pressure was considered equal to 5 mm Hg or 10 mm Hg according to whether or not the inferior vena cava collapsed during inspiration, respectively.[9] Because no patient had right ventricular outflow obstruction, SPAP was considered equivalent to RV systolic pressure. We registered the value of SPAP, and the presence or absence of the following variables: right ventricle (RV) dilatation (end-diastolic diameter $>$ 30 mm or right to left ventricular end-diastolic diameter ratio $\geq$ 1 in apical 4-chamber view), RV systolic function (RVSF) depression, left ventricle systolic function (LVSF) depression (LV ejection fraction $<$ 50%), paradoxical septal systolic motion, pericardial effusion and inferior vena cava dilatation. Left ventricular systolic function was assessed in most cases by Teichholz method and Simpsons's biplane method. In some cases, the LV function was assessed by visual estimation. RV systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE) and lateral RV annular peak systolic velocity by pulse wave tissue Doppler. TAPSE was calculated as index of right ventricular global systolic function by the difference between end-diastolic and end-systolic measurements (in millimeters). Patients were considered to have abnormal RVSF if they had reduced values of TAPSE ($<$15 mm).

6MWT

A 6MWT was performed as part of the initial evaluation in all patients with echocardiography-confirmed PH, unless they were unable to carry out the test. The 6MWT was performed according to the ATS statement, in a 30 m corridor.[10] The primary variable was total distance walked during the test.[4] Additionally, continuous pulse oximetry was recorded during the test using a wrist oximeter with a finger probe (Pulsox 3i; Minolta, Ramsey, NJ, USA). Pulse oximetry variables were calculated using computer software (Pulsox SaO_2 analysis software DS-3; Minolta, Ramsey, NJ, USA). We registered the following variables: total distance walked, resting SaO_2 before walking, mean and lower SaO_2 during the test, cumulative percentages of time at saturation below 90% (CT90) while walking, mean and higher pulse rate during the 6MWT. The chronotropic response was calculated as peak pulse rate minus resting pulse rate.

Statistical analysis

The primary endpoint was all-cause mortality. The secondary endpoint was a combined adverse events outcome that included death and/or need for hospitalization after the 6MWT. We assessed the time from the date of the 6MWT to the date of death and/or the date of the first hospitalization. The patients were censored at the end of the study if the primary or secondary endpoints had not been reached. Vital status, ascertained as of January 2013 was

Table 1
Categorization of patients according to the Dana Point updated classification of pulmonary hypertension.

PH group	*N*	Detailed (subgroup)	*N*
2	29	Systolic left heart dysfunction (2.1)	5
		Diastolic left heart dysfunction (2.2)	10
		Valvular disease (2.3)	14
3	7	COPD (3.1)	5
		Interstitial lung disease (3.2)	2
4	6	CTEPH	6
5	1	Chronic renal failure on dialysis (5.4)	1
2 + 3	17	Valvular disease plus SDB	5
		Diastolic left heart dysfunction plus COPD plus SDB	3
		Valvular disease plus COPD	2
		Systolic left heart dysfunction plus COPD plus SDB	2
		Diastolic left heart dysfunction plus SDB	2
		Systolic left heart dysfunction plus valvular disease plus OPD	1
		Systolic left heart dysfunction plus SDB	1
		Systolic left heart dysfunction plus interstitial lung disease	1

COPD: chronic obstructive pulmonary disease; CTPEH: chronic thromboembolic pulmonary hypertension; SDB: sleep disordered-breathing; OPD: other pulmonary diseases with mixed obstructive and restrictive pattern.