From the 6-Minute Walk Test in Patients With Pulmonary Hypertension

Augusto G. Zapico, PhD; Darío Fuentes, MS; Miguel A. Rojo-Tirado, PhD; Francisco J. Calderón, MD, PhD; Erika B. Rosenzweig, MD; Robert P. Garofano, EdD

■ **PURPOSE:** To determine whether the 6-minute walk test (6MWT) is a predictor of peak oxygen uptake ($\dot{V}O_2$) in patients with idiopathic pulmonary arterial hypertension (IPAH).

■ **METHODS:** A total of 157 patients treated for IPAH completed a 6MWT in accordance with American Thoracic Society standards. Heart rate, pulse oximetry, and Borg rating of perceived exertion were determined at baseline and posttest. A cardiopulmonary exercise test (CPET) was performed on a cycle ergometer using a ramp protocol. Participants were stratified *post hoc* by age into 3 groups: children (n = 26), adolescents (n = 49), and adults (n = 82). Multiple linear regression analysis was performed to predict peak $\dot{V}O_2$ from the 6MWT.

■ **RESULTS:** The regression equation generated for the children was the only model to strongly predict peak $\dot{V}O_2$ ($r = 0.87$; $P < .001$). Similar models for adolescent ($r = 0.59$; $P < .001$) and adult groups ($r = 0.68$; $P < .001$) did not achieve the same level of correlation.

■ **CONCLUSION:** Six-Minute Walk Test was able to accurately predict peak $\dot{V}O_2$ in children (6-12 years) with IPAH; however, the model was weaker for predicting peak $\dot{V}O_2$ in older populations. These findings suggest that 6MWT may be as valid a test for predicting peak $\dot{V}O_2$ in children with IPAH as CPET measured peak $\dot{V}O_2$. In older IPAH populations, CPET is the only reliable method for the evaluation of peak $\dot{V}O_2$.

The cardiopulmonary response to exercise is an important clinical assessment tool, as it provides an integrated assessment of the respiratory, cardiac, and metabolic systems. The current gold standard method for assessing aerobic exercise response in humans is the maximum incremental cardiopulmonary exercise test (CPET). Peak $\dot{V}O_2$, measured by a CPET, has been widely used to assess functional capacity and predict survival in patients with advanced symptomatic heart failure and respiratory dysfunction.[1,2] However, CPET requires the use of expensive equipment and trained medical team supervision to conduct and evaluate each test.

Submaximal tests, like the 6-minute walk test (6MWT), provide useful information on daily physical performance that are safe, simple, standardized, and inexpensive. The 6MWT offers a better estimation of daily living activities than other walk tests[3] and the American Thoracic Society has endorsed and published guidelines for performing the 6MWT in clinical settings.[4]

The 6MWT is an independent predictor of morbidity and mortality in adult patients with heart failure,[1] left ventricular dysfunction,[5] chronic respiratory disease,[6] cystic fibrosis, and pulmonary hypertension.[2] In addition, the 6MWT is a significant predictor of survival in patients with pulmonary hypertension[7-11] and is used in clinical trials for IPAH medications.[12]

In addition to other health limiting and debilitating conditions, patients with lung or heart disease may show a reduced 6-minute walk distance (6MWD).[13-16] Greater pre-transplantation 6MWD also correlates with shorter intensive care unit stays after pediatric lung transplantation.[17]

Correlation between $\dot{V}o_2$ from CPET and 6MWT in healthy children[18] and correlation between CPET and 6MWT in patients with IPAH[2] has been reported by others but not prediction of $\dot{V}o_2$ peak from 6MWT. Ross et al[19] attempted to predict peak $\dot{V}o_2$ from 6MWD in patients with different cardiopulmonary disorders, suggesting poor prediction accuracy for assessing individuals for clinical purposes. In an obese nonadult group, body mass index (BMI) and 6MWD were significant factors predicting peak $\dot{V}o_2$, although no coefficient of determination for the regression equation was cited.[20] The 6MWT does not seem to predict peak $\dot{V}o_2$ in adult patients with heart failure.[21] However, no other study has tried to predict peak $\dot{V}o_2$ from 6MWT in children, adolescents, or adults with IPAH. Maximal exercise testing in IPAH populations involves a certain risk and requires supervision by well-trained and experienced health care professionals.

Thus, the aim of this study was to determine whether the 6MWT could accurately predict peak $\dot{V}o_2$ in patients with IPAH, which could provide health care professionals an easily implemented and inexpensive tool in the evaluation and followup of patients.

METHODS

The study was conducted in accordance with the amended Declaration of Helsinki. The Columbia University Medical Center institutional review board approved the study protocol and waived the need for patient consent due to the retrospective nature of the study.

Patients

One hundred fifty-seven patients being treated for IPAH from 2003 to 2013 were included in this study. Patients were diagnosed with IPAH by right-sided heart catheterization measurement of arterial pulmonary pressures > 25 mmHg.[22,23] Subjects were stratified *post hoc* by age into 3 groups (children: 6-12 years; adolescents: 13-18 years; and adults: ≥19 years) for between-group comparisons of anthropometric and 6MWT variables.

Assessments

Subjects were tested in the pediatric exercise laboratory as part of a standard of care for IPAH visits to the Pulmonary Hypertension Center of New York Presbyterian/Columbia University Medical Center. Each patient performed a pulmonary function test, CPET, and 6MWT, all on the same day. Height, weight, and age were gathered prior to the test. Patients were familiar with the tests.

Pulmonary Function Test

Forced vital capacity, slow vital capacity, and maximum voluntary ventilation were measured. Pulmonary function tests were performed on a Breeze Suite CPX Ultima (Medgraphics, St. Paul, MN).

Cardiopulmonary Exercise Test

The CPET was performed on a Lode Corival V2 (Lode BV, Groningen, the Netherlands) cycle ergometer following a ramp protocol with increments of 5, 10, 15, 20, or 25 watts/min (depending on fitness level and/or previous tests) until volitional fatigue. Three minutes of baseline data were collected followed by 3 minutes of unloaded warm-up cycling. The ramp protocol was started after the 3-minute warm-up. Once the patient reached his or her maximum values, a 3-minute cooldown of unloaded cycling was performed as part of a 10-minute recovery period, until return to baseline levels and/or until symptoms, if any, resolved.[24] The following data were collected during the cycle ergometer test: time, work in watts, real-time 12-lead electrocardiogram including heart rate using a CardioPerfect WorkStation (Welch Allyn, Skaneateles Falls, NY), systolic and diastolic blood pressures by using the standard arm cuff technique (W. A. Baum Company, Inc, Copiague, NY), noninvasive peripheral oxygen saturation using a Datex-Ohmeda 3900P pulse oximeter (Datex-Ohmeda, Madison, WI), O_2 uptake and other gas exchange parameters through breath-by-breath analysis of expired air via Breeze Suite CPX Ultima (Medgraphics).

6MWT

The 6MWT was performed in a 30-m hallway where the patients were instructed to walk as far as possible in 6 minutes by walking back and forth in a 30-m hallway at their own speed and pace following American Thoracic Society guidelines.[4,25] Oxygen saturation using a finger sensor and a 3900P pulse oximeter (Datex-Ohmeda) and a rating of perceived

exertion (RPE) using the Borg CR10 scale[26] were collected at baseline and postwalk.

Statistical Analysis

The data were statistically analyzed using the PASW Statistics, version 18.0, for Windows (SPSS Inc, Chicago, IL). Continuous variables were presented as mean ± standard deviation. To evaluate whether anthropometric and 6MWT variables were different between the 3 groups, analysis of variance (ANOVA) was used. Finally, 3 multiple linear regression models, one for each group of participants, were determined. Variables such as weight, height, BMI, sex, walk speed, resting heart rate, and RPE were included in the analyses. A backward elimination approach was used to finalize the regression models. If the slope for an independent variable was not found to be statistically significantly different than zero at $\alpha = .05$, that independent variable was excluded from the model. To assess the fit of the predictive model, we used conventional linear regression models according to the coefficient of determination (R^2). A paired Student t test was used to compare the mean values for the measured and the estimated peak $\dot{V}O_2$ measurements. Pearson correlation coefficient (r) was used to assess the linear bivariate relationship among estimated and measured peak $\dot{V}O_2$. For all tests, a P value < .05 was considered statistically significant.

RESULTS

The baseline characteristics of the sample are shown in Table 1. Among the 26 children, mean age was 9.96 ± 1.66 years and 73% were female. In the group of adolescents (n = 49), mean age was 15.33 ± 1.80 years and 47% were female. Among the 82 adults, mean age was 27.33 ± 6.70 years and 69.5% were female.

ANOVA revealed significant differences between age groups for height ($F_{2,156} = 66.384$; $P < .001$), weight ($F_{2,156} = 24.453$; $P < .001$), BMI ($F_{2,156} = 11.943$; $P < .001$), and peak heart rate ($F_{2,156} = 6.8$; $P = .001$). No significant differences were found between groups for resting heart rate ($F_{2,156} = 1.91$; $P = .152$), 6MWD ($F_{2,156} = 0.195$; $P = .823$), walking speed ($F_{2,156} = 0.195$; $P = .823$), and RPE ($F_{2,156} = 1.39$; $P = .252$).

For the linear regression analysis, the 3 age groups were children, adolescents, and adults and 3 independent multiple linear regressions were modeled. The variables—sex (0 = female, 1 = male); weight; height; BMI; walk speed; resting heart rate; and RPE—were included in the models. Final models included variables that yielded the highest R^2 values.

Table 2 shows the standardized and nonstandardized coefficients for the linear regression model. Using standardized coefficients, in the first model (children), weight, BMI, and height (−4.72, 3.10, and 1.44, respectively) contributed most to the model that predicted peak $\dot{V}O_2$. The remaining variables (sex, walk speed, RPE, and resting heart rate) contributed less to the prediction. In the second model (adolescents), the walk speed contributed most to the prediction model while RPE and height contributed less. In the third model (adults), the variable that contributed the most was 6MWD (0.48), before sex (0.30), height and weight to estimate peak $\dot{V}O_2$.

Table 1 • Characteristics of Participants and 6MWT Data

	Children (n = 26)	Adolescents (n = 49)	Adults (n = 82)
Age, y	9.96 ± 1.66	15.33 ± 1.80	27.33 ± 6.70
Height, cm	140.15 ± 12.88	160.98 ± 9.48[a]	164.67 ± 8.24[a,b]
Weight, kg	35.09 ± 13.31	52.42 ± 17.80[a]	62.85 ± 19.16[a,b]
BMI, kg/m^2	17.37 ± 3.81	19.98 ± 5.47	23.02 ± 5.96[a,b]
Resting HR, bpm	90.19 ± 22.01	88.31 ± 15.95	83.84 ± 15.51
Peak HR, bpm	153.12 ± 26.22	152.04 ± 20.88	137.10 ± 28.58[a,b]
6MWD, m	471.15 ± 89.43	455.78 ± 84.63	459.77 ± 115.12
Walking speed, m/s	1.31 ± 0.25	1.27 ± 0.24	1.28 ± 0.32
Dyspnea, Borg scale 0-10	1.60 ± 2.11	0.99 ± 1.30	1.31 ± 1.44
Peak $\dot{V}O_2$, mL/kg/min	22.07 ± 6.67	20.59 ± 6.23	16.03 ± 6.33

Abbreviations: BMI, body mass index; HR, heart rate; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; $\dot{V}O_2$, oxygen uptake.

[a]Significantly different from children ($P < .05$).

[b]Significantly different from adolescents ($P < .05$).

Table 2 • Standardized and Nonstandardized Coefficients of Linear Regression Models for Peak $\dot{V}O_2$ Prediction

	Children (R^2= 0.834)			Adolescents (R^2= 0.322)			Adults (R^2= 0.479)		
	Standardized	Nonstandardized	P Value	Standardized	Nonstandardized	P Value	Standardized	Nonstandardized	P Value
Constant		−108.975		...	32.427	...	...	−21.626	...
Sex	0.342	5.043	.002	...	...	...	0.301	4.103	.002
Height	1.436	0.759	.024	−0.245	−0.167	.05	0.224	0.174	.043
Weight	−4.720	−2.366	.002	...	...	...	−0.217	−0.071	.020
BMI	3.101	5.429	.003	...	...	...	...	...	...
Walk speed	0.770	20.667	<.001	0.497	13.326	<.001	...	...	...
6MWD	...	...	...	...	...	...	0.480	0.026	<.001
RPE	−0.562	−1.78	<.001	−0.359	1.737	.006	...	...	...
Resting HR	−0.290	−0.136	.006	...	...	...	...	...	...

Abbreviations: BMI, body mass index; HR, heart rate; RPE, rating of perceived exertion; 6MWD, 6-minute walk distance.

Assessment by the Student t test showed no significant differences between the measured and the estimated peak $\dot{V}O_2$ for children, adolescents, and adults. There were significant correlations between measured and estimated peak $\dot{V}O_2$ in the 3 groups (children, $r^2 = 0.873$; adolescents, $r^2 = 0.591$; and adults, $r^2 = 0.681$, $P < .001$ for all). Figure 1 shows this correlation between measured peak $\dot{V}O_2$ from the exercise test (peak $\dot{V}O_2$-CPET) and estimated peak $\dot{V}O_2$ from 6MWT (peak $\dot{V}O_2$-6MWT) for all 3 groups (children, adolescents, and adults) expressed in mL/kg/min.

DISCUSSION

The primary result of this study was that a simple 6MWT may be able to predict peak $\dot{V}O_2$ in children with IPAH. However, the 6MWT was not able to predict peak $\dot{V}O_2$ in other patients with IPAH. This is the first study that attempted to predict peak $\dot{V}O_2$ from 6MWT solely in patients with IPAH. Being able to predict peak $\dot{V}O_2$ from 6MWT would give physicians and other health care professionals an easy, inexpensive, and simple tool for the followup of the disease. The 6MWT was a strong predictor of peak $\dot{V}O_2$ in children; however, the predictions were weaker in adolescents or adults.

Although peak $\dot{V}O_2$ was predicted ($r^2 = 0.83$) in the children's group, peak $\dot{V}O_2$ alone does not provide enough information for the treatment and prognosis of patients with IPAH. Peak $\dot{V}O_2$ is only 1 of the many variables obtained from a CPET. Peak $\dot{V}O_2$ would only show a decrease in aerobic fitness in these patients but it would not determine what contributed to the decrease. In children, up to 12 years of age, the 6MWT may be used to predict peak $\dot{V}O_2$, although a previous CPET would always be highly recommended and the 6MWT could be used as a followup assessment until adolescence.

Correlation between $\dot{V}O_2$ from CPET and 6MWT in healthy children[18] and correlation between CPET and 6MWT in patients with IPAH[2] have been reported by others, but no correlation between 6MWT predicted $\dot{V}O_2$ and measured $\dot{V}O_2$ has been reported. However, Ross et al[19] attempted to predict peak $\dot{V}O_2$ from 6MWD in patients with different cardiopulmonary disorders and reported poor prediction accuracy for assessing individuals for clinical purposes. Body mass index and 6MWD were the only significant factors to predict peak $\dot{V}O_2$, in obese nonadult patients, although no coefficient of determination for the regression equation was reported.[20] 6MWT does not appear to accurately predict peak $\dot{V}O_2$ in adult patients with heart failure.[21]
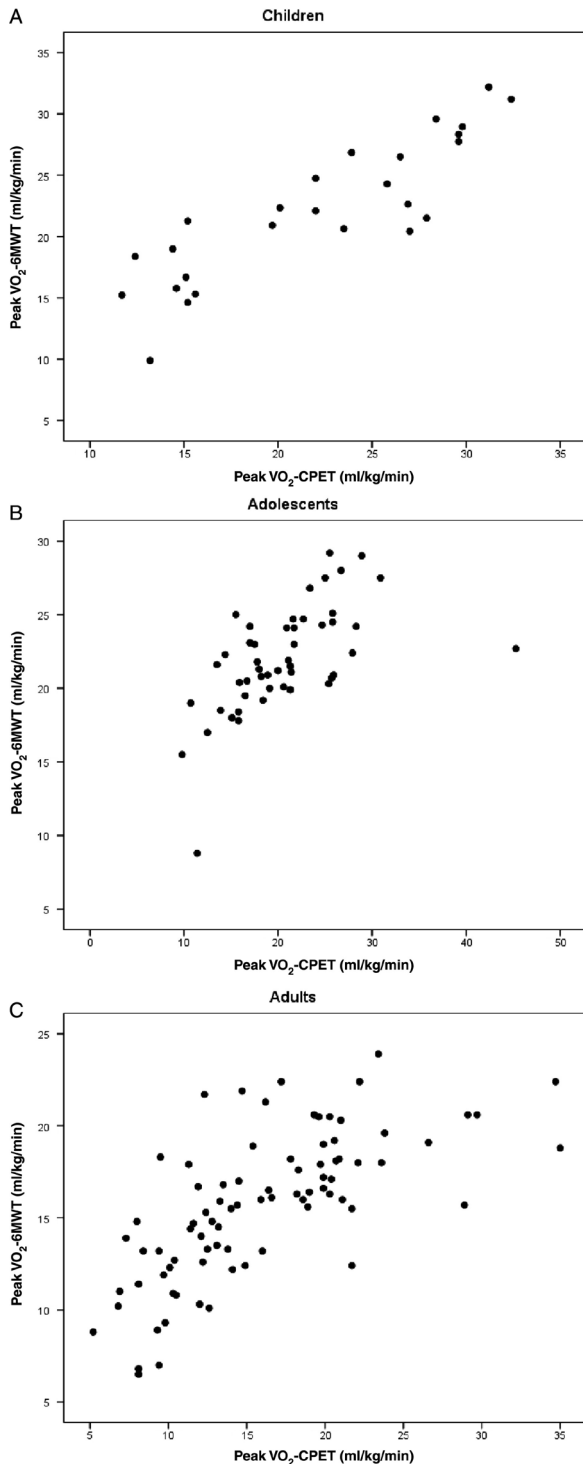
Figure 1. Measured (CPET) versus predicted (6MWT) values for peak $\dot{V}O_2$ in (A) children, (B) adolescents, and (C) adults. CPET indicates cardiopulmonary exercise test; $\dot{V}O_2$, oxygen uptake; 6MWT, 6-minute walk test.

However, no other study has tried to predict peak $\dot{V}O_2$ from 6MWT in children, adolescents, or adults with IPAH.

Weight, BMI, and height have been cited as the most important variables affecting 6MWD.[27,28] Consistent with these findings, our models showed that these 3 variables have the strongest effect on the linear regression to predict peak $\dot{V}O_2$ in children.

As expected, IPAH subjects showed lower 6MWD than healthy patients from other studies: children with IPAH averaged 471.15 ± 89.43 meters versus 664 ± 65.3 meters[29] and 619.2 ± 115.2 meters[30] in healthy children; adolescents with IPAH walked 455.78 ± 84.63 meters versus 699.2 ± 87 meters[30] found in healthy adolescents; IPAH adults averaged a 6MWD of 459.77 ± 115.12 meters versus the distances averaged by other healthy adults of 615.5 ± 44 meters[31] and 672 ± 83 meters.[32]

Although a 6MWT may not be robust enough to predict peak $\dot{V}O_2$ in adolescents and adults, it remains a very important tool to predict morbidity and mortality in a clinical setting. It is also important in predicting shorter intensive care unit stays after pediatric lung transplantation,[17] as well as predicting morbidity and mortality in adult patients with left ventricular dysfunction.[5] The 6MWT is a significant predictor of survival in patients with IPAH.[7-11] It is still used in clinical trials for IPAH medication use.[12]

Although performing a simpler submaximal test, like the 6MWT, with children with IPAH may predict peak $\dot{V}O_2$, it would not give health care professionals the necessary information to evaluate functional capacity. The 6MWT is not able to predict peak $\dot{V}O_2$ in most patients with pulmonary hypertension, but it is an important tool for the evaluation and followup of patients with IPAH.

The small sample size, specifically in the children's group (n = 26, with only 7 males), is a limitation of this study. In future research, a larger sample size, especially in the children's group, is needed. The small sample size in this study prevented us from validating the regression equations. Also, future studies comparing each group with a control group could shed more light on how and what prediction equations used in the study would apply to a normal or healthy population.

CONCLUSION

The measured peak $\dot{V}O_2$ of the patients varied greatly by age. A linear regression equation developed from the 6MWT was able to accurately predict peak $\dot{V}O_2$ in children (6-12 years) with IPAH; however, the model failed to predict peak $\dot{V}O_2$ in older populations. These findings suggest that peak $\dot{V}O_2$ measured by CPET is still the gold standard for assessing aerobic exercise capacity in patients with IPAH. However, the 6MWT

could still be a valuable test for prognostic purposes when performing a CPET is not an option. It could also be of great value as a complement to the CPET. Future research should be conducted to validate the regression equations.

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