

## Clinical correlation between the 6-min walk test and cardiopulmonary exercise testing in patients with pulmonary arterial hypertension

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**Background/aim:** The aims of the present study were to assess the relationship between the distance walked during the 6-min walk test (6MWT) and exercise capacity as determined by cardiopulmonary exercise testing (CPET) in patients with pulmonary arterial hypertension (PAH) and to investigate the prognostic value of the 6MWT in comparison to clinical parameters of CPET and echocardiography findings.

**Materials and methods:** Thirty PAH patients participated in the study. Subject characteristics and New York Heart Association (NYHA) classifications were recorded. All subjects completed the 6MWT and CPET. Relationships among the variables were analyzed by the Pearson correlation test. Correlation coefficients between 6MWT distance and other variables were determined by linear regression analysis.

**Results:** Distance walked in the 6MWT was significantly correlated with the following exercise parameters: peak oxygen consumption, work load, and metabolic equivalents. Additionally, cardiac index was correlated with peak oxygen consumption and metabolic equivalents. We also showed that cardiac index and age were two significant determinants for exercise performance, accounting for 35.4% of the variance in the 6MWT.

**Conclusion:** The 6MWT provides information that may be a better index for the patient's NYHA functional class determination than maximal exercise testing.

**Key words:** Six-minute walk test, cardiopulmonary exercise testing, pulmonary arterial hypertension, cardiac index

### 1. Introduction

Pulmonary arterial hypertension (PAH) is clinically defined as a mean pulmonary arterial pressure (PAP) of  $\geq 25$  mmHg at rest with a normal pulmonary capillary wedge pressure (PCWP) (1–4). The pathophysiology of PAH is characterized by progressively increasing pulmonary vascular resistance (PVR) and right ventricular heart failure in terms of insufficient oxygen supply of the right ventricle, which causes limitations in the performance of daily life activities and exercise intolerance with dyspnea and fatigue symptoms (4,5).

The New York Heart Association (NYHA) classification reflects disease severity and prognosis associated with worsening symptoms during ordinary physical activity and functional capacity in patients with PAH (6). Additionally, one of the most feasible methods for noninvasively grading the severity of exercise limitation and assessing disease symptoms in PAH is the evaluation of resting and exercise

haemodynamics by both submaximal and maximal exercise test measurements (7–10). Cardiopulmonary exercise testing (CPET) for the evaluation of disease severity is important to assess peak oxygen consumption ( $VO_{2peak}$ ), metabolic equivalents, and maximal workload during exercise tests, as well as the minute ventilation-to-carbon dioxide output ( $V_E-V_{CO_2}$ ) slope (7,8). Paolillo et al. demonstrated a reduction in  $VO_{2peak}$  and remarked on the prognostic value of the elevated  $V_E-V_{CO_2}$  slope in patients with PAH (4). The  $V_E-V_{CO_2}$  slope reflects disease severity, and it has been shown that there is a correlation between the  $V_E-V_{CO_2}$  slope and NYHA functional class (9). However, the 6-min walk test (6MWT) is commonly used in PAH patients as a submaximal exercise test to indicate the exercise capacity of patients who cannot tolerate the maximal incremental test, despite the fact that CPET has more clinical significance in terms of prognostic value and evaluation of disease severity (11,12). Although the distance

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walked in the 6MWT is significantly shorter among PAH patients than in age- and sex-matched healthy control subjects, it does not evaluate the resting hemodynamics, the response of the cardiopulmonary system, or the functional gas exchange (7,13). Furthermore, there are no studies in the literature that demonstrate the prognostic value of the 6MWT for the NYHA classification in PAH patients.

Limited data exist concerning the relation between the 6MWT and incremental CPET in patients with PAH. Thus, the aims of the present study were to assess the relation between the distance walked during the 6MWT and exercise capacity as determined by CPET in patients with PAH and to investigate the prognostic value of the 6MWT in comparison with the clinical parameters of CPET and echocardiography findings.

## 2. Materials and methods

### 2.1. Study subjects

This study included 30 patients with PAH (including chronic thromboembolic pulmonary hypertension, CTEPH) who were followed regularly in the pulmonary arterial hypertension outpatient clinic of our cardiology department. Among the patients, 5 (16.7%) had connective tissue disease, 10 (33.3%) had congenital heart disease, 2 (6.7%) had CTEPH, and 13 (43.3%) had idiopathic pulmonary arterial hypertension. One patient was classified as class I, 19 patients were in class II, and 10 patients were in class III according to the NYHA functional classification. All patients were treated with PAH-specific drugs, including bosentan, inhaled iloprost, sildenafil, or a combination of these drugs, in addition to other palliative treatments, such as furosemide, spironolactone, and digoxin, as needed. The diagnosis of PAH was based on right heart catheterization, with mean PAP >25 mmHg, PCWP <15 mmHg, and PVR >3 resistance units as defined by PAH guidelines (10). Patients with severe heart failure, restrictive and obstructive pulmonary disease, and acute infection were excluded from the study. All patients completed the 6MWT and cardiopulmonary exercise testing when they were clinically stable during outpatient visits. The Dokuz Eylül University Medical Ethics Committee approved the study, and all patients provided written informed consent.

### 2.2. Measurements

Subject characteristics, including age, height, body weight, and NYHA classification with PAH etiology, were recorded. The patients' dyspnea status was evaluated using the four-item Modified Medical Research Council (MMRC) Dyspnea Scale (14). Body mass index (BMI) was calculated as weight/height squared (expressed in kg/m<sup>2</sup>).

### 2.3. Right heart catheterization

A diagnostic right heart catheterization to assess pulmonary and cardiac haemodynamics was performed in all patients while they were in a stable condition during hospitalization. Baseline hemodynamic variables and mean PAP were measured in all patients. Cardiac output (CO) was measured by Fick's method (15). Total pulmonary resistance was calculated by dividing mean PAP by CO. Cardiac index (CI) was calculated by dividing CO by body surface area.

### 2.4. Six-minute walk test (6MWT)

The 6MWT was conducted for all patients according to a standardized protocol as described in the American Thoracic Society (ATS) guidelines (16). Patients were instructed to walk along a 30-m corridor to cover as much ground as possible in 6 min. They were encouraged with standardized statements. The distance covered during the test, as well as dyspnea and fatigue symptoms, were evaluated.

### 2.5. Cardiopulmonary exercise testing (CPET)

All patients performed incremental cardiorespiratory exercise testing on a cycle ergometer. Gas exchange measurements (Oxycon Pro) were taken during the following events: 3 min of rest; 3 min of unloaded leg cycling for a warm-up followed by 3 min of progressively increasing the work rate up to 20 W; and 3 min of 20-W incremental work load. After that, work load was increased by 3 W every 12 s to maximum tolerance, and gas exchange measurements were recorded until maximal exertion. Pulse oximetry (SpO<sub>2</sub>), heart rate (HR), 12-lead ECG, and blood pressure were monitored and recorded. Maximal work load and metabolic equivalent were recorded during the test. Ventilatory parameters (minute ventilation (V<sub>E</sub>), O<sub>2</sub> uptake (VO<sub>2</sub>), and CO<sub>2</sub> output (VCO<sub>2</sub>)) were interpreted by breath measurement at 6-s intervals. The anaerobic threshold (AT) percentage of O<sub>2</sub> uptake was calculated and minute ventilation-to-CO<sub>2</sub> output at AT was expressed as V<sub>E</sub>-VCO<sub>2</sub>@AT.

### 2.6. Statistical analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Analyses included frequency distribution, percentages, and calculation of means and related standard deviations (mean ± SD). Continuous variables, such as summary of demographics, resting hemodynamics, and CPET, were expressed as means and standard deviations. Frequency distributions of categorical variables and continuous variables were included as descriptive statistics. Relations between 6MWT distance and catheterization data and 6MWT distance and CPET data were analyzed for the 30 patients using the Pearson correlation test. Correlation coefficients between 6MWT distance and other variables were determined by linear

regression analysis. The independent contributors to 6MWT that were entered into the analysis were CI and age variables. Differences between the two functional classes were analyzed by the Mann–Whitney U test.

### 3. Results

Most of the 30 PAH patients were middle-aged women (Table 1) in NYHA class II or III. Their dyspnea symptoms were mild (54.8%), moderate (22.6%), or severe (6.5%) according to the MMRC Dyspnea Scale.

At cardiac catheterization, all patients had increased resting pulmonary hypertension (mean PAP  $82.58 \pm 21.49$  mmHg), increased PVR, and reduced CI (Table 1).

All patients completed the 6MWT and CPET without incident. The duration of exercise testing in all patients averaged 9.4 (range: 3 to 15) min. The parameters of exercise gas exchange were systematically different in PAH patients. Average peak  $\text{VO}_2$  was  $12.78 \pm 4.72$  mL  $\text{kg}^{-1}$   $\text{min}^{-1}$  with a peak respiratory exchange ratio of  $0.97 \pm 0.11$ , suggesting that the majority of subjects exercised close to their maximal capacity. There was a marked decrease in peak oxygen consumption and peak heart rate and an increase in minute ventilation-to-carbon dioxide output. The mean distance covered during the 6MWT was  $404.75 \pm 104.07$  m (Table 1).

#### 3.1. Correlations

Table 2 summarizes multiple correlations between the 6MWT and other variables. Age was significantly negatively correlated with 6MWT distance. The exercise parameters of peak  $\text{VO}_2$ , peak workload, and metabolic equivalents (METs) were strongly correlated with 6MWT. Additionally, CI was correlated with peak  $\text{VO}_2$  and MET.

Linear regression analysis revealed that age and CI were significant and independent predictors of performance in the 6MWT. These two variables accounted for 35.4% of the variance in the distance covered during the 6MWT (Table 3). The distance covered during the 6MWT was predicted by the following equation:

$$\text{Distance (m)} = 455.229 + (0.382 \times \text{cardiac index}) - (0.494 \times \text{age}).$$

#### 3.2. Physiological severity of PAH

Table 4 displays the results of the NYHA gradations according to the severity of reduction in aerobic capacity. Moderate PAH patients had an end-exercise respiratory exchange ratio of  $0.95 \pm 0.98$ ; severe PAH patients had a higher end-exercise respiratory exchange ratio ( $1.00 \pm 0.12$ ) compared with moderate PAH patients, indicating that the patients with PAH had developed significant metabolic acidosis and had exercised heavily. Using this method of grading disease severity, there was a statistically significant difference between the two groups in key parameters of aerobic function (peak  $\text{VO}_2$  and MET) and distance walked in the 6MWT. The average distance

covered was equivalent for subjects with moderate and severe PAH ( $426.05 \pm 95.40$  m versus  $356.75 \pm 89.94$  m, respectively;  $P < 0.05$ ) (Table 4). Furthermore, pulmonary hemodynamic data regarding mean PAP and PVR were not statistically significantly different between the two groups.

### 4. Discussion

In the present study, we found that 6MWT distance is severely affected in patients with PAH, and we also showed that CI and age were two significant determinants for exercise performance in terms of walking distance. These two factors accounted for 35.4% of the variance in the test. Furthermore, the distance walked in the 6MWT was significantly correlated with the following exercise parameters: peak  $\text{VO}_2$ , workload, and MET. Additionally, CI was correlated with peak  $\text{VO}_2$  and MET. Although there was an increase in the  $V_E$ - $V_{\text{CO}_2}$  slope in PAH patients, there was no correlation between the other variables as a ventilatory response to the exercise test. The data between the two different NYHA classifications showed that 6MWT distance and  $\text{VO}_{2\text{peak}}$  statistically significantly decreased in proportion to the severity of NYHA functional class in patients with PAH.

We assessed functional exercise capacity using the 6MWT, which primarily evaluates pulmonary and cardiac impairments in patients with PAH. The self-paced 6MWT evaluates the global and integrated responses of all the systems involved during exercise (16–18). It has been shown that the 6MWT test has prognostic value in disease severity and mortality by revealing decreased distance in patients with heart failure (19). Additionally, it was previously shown by Miyamoto et al. that a 6MWT distance below 332 m is an indicator of poor prognosis in PAH (7). The moderate and severe PAH patients in our study demonstrated 6MWT distances of 426.05 and 356.75 m, respectively; these distances were greater than expected according to their disease severity compared to the cut-off point of 332 m reported by Miyamoto et al. for poor prognosis in functional class II and III patients. Nearly all of the patients in our study walked farther than in that study (404.75 m).

Linear regression analysis in this study showed that a large portion of the variance in the 6MWT distance of the PAH patients was explained by age and CI. This finding revealed that higher age and lower CI values resulted in lower functional capacity in patients with PAH. In the literature, there is only one study, by Britto et al. (20), reporting that the distance covered during the 6MWT is significantly associated with age and heart rate variability; in another study, Miyamoto et al. found that 6MWT distance is correlated with CO (6). However, there are no data concerning the relation between 6MWT distance and

**Table 1.** Summary of demographics, resting hemodynamics, 6MWT, and CPET in 30 PAH patients.

	Mean $\pm$ SD (n = 30)
Demographics	
Age, years	51.93 $\pm$ 17.39
Sex, %	
Female	77.4
Male	22.6
Height, cm	163.29 $\pm$ 10.12
Weight, kg	69.80 $\pm$ 15.01
Body mass index, kg/m <sup>2</sup>	24.46 $\pm$ 8.10
NYHA class	2.3 $\pm$ 0.4
Dyspnea, %	
Mild	54.8
Moderate	22.6
Severe	6.5
Resting hemodynamics	
Systolic pulmonary arterial pressure, mmHg	76.09 $\pm$ 25.66
CI, L min <sup>-1</sup> m <sup>-2</sup>	3.13 $\pm$ 1.17
Pulmonary vascular resistance, mmHg L <sup>-1</sup> min <sup>-1</sup>	6.29 $\pm$ 2.84
Walk test distance, m	404.75 $\pm$ 104.07
CPET	
RER maximal work load Ratio	0.97 $\pm$ 0.11
Peak VO <sub>2</sub> mL kg <sup>-1</sup> min <sup>-1</sup>	12.78 $\pm$ 4.72
Peak work rate W	132.13 $\pm$ 69.86
Peak ventilation L min <sup>-1</sup>	40.93 $\pm$ 19.55
Metabolic equivalents Ratio	3.65 $\pm$ 4.72
Peak heart rate bpm	130.89 $\pm$ 31.06
V <sub>E</sub> -V <sub>CO2</sub> @AT	57.10 $\pm$ 23.22

NYHA = New York Heart Association, CPET = cardiopulmonary exercise testing, RER = respiratory exchange ratio, Peak VO<sub>2</sub> = peak oxygen consumption, V<sub>E</sub>-V<sub>CO2</sub>@AT = minute ventilation-to-carbon dioxide output at anaerobic threshold, CI: cardiac index.

CI. In our study, CI was the first variable that explained the variance in 6MWT distance, indicating that lower CI was associated with shorter 6MWT distance or functional capacity. In addition, PAH patients in our study had a

higher CI (over 2.5 L min<sup>-1</sup> m<sup>-2</sup>) with a mean value of 3.13 L min<sup>-1</sup> m<sup>-2</sup>. Age was the second variable that explained the variance in 6MWT distance in our study, indicating that older age was associated with shorter 6MWT

**Table 2.** Correlation r matrix of independent variables and 6-min walk test.

	6MWT	Age	CI	MET	V <sub>E</sub> -V <sub>CO<sub>2</sub></sub> @AT	V <sub>O<sub>2</sub></sub> peak
Age (years)	r = 0.56** P = 0.002	-				
Cardiac index (L min <sup>-1</sup> m <sup>-2</sup> )	r = 0.27 P = 0.186	r = -0.08 P = 0.683	-			
Metabolic equivalents	r = 0.74** P = 0.001	r = 0.56** P = 0.002	r = 0.62** P = 0.038	-		
V <sub>E</sub> -V <sub>CO<sub>2</sub></sub> @AT	r = 0.13 P = 0.634	r = -0.14 P = 0.827	r = 0.29 P = 0.588	r = 0.14** P = 0.050	-	
Peak VO <sub>2</sub> (mL kg <sup>-1</sup> min <sup>-1</sup> )	r = 0.75** P = 0.001	r = 0.56** P = 0.002	r = 0.42** P = 0.032	r = 1.00** P = 0.001	r = 0.14 P = 0.052	-
Peak work rate (W)	r = 0.57** P = 0.002	r = 0.69** P = 0.001	r = 0.19 P = 0.348	r = 0.62** P = 0.001	r = 0.26 P = 0.291	r = 0.62** P = 0.001

Cardiac index = CI, Metabolic equivalent = MET, V<sub>E</sub>-V<sub>CO<sub>2</sub></sub>@AT = minute ventilation-to-carbon dioxide output at anaerobic threshold, Peak VO<sub>2</sub> = peak oxygen consumption, \*\* = statistically significant.

**Table 3.** Linear regression model. Variables in the model.

	β	t	P-value
CI	0.382	2.198	0.041
Age	0.494	2.840	0.010

**Table 4.** Exercise values in PAH patients categorized according to severity of reduction in 6MWT and CPET aerobic capacity.

	n = 19 Moderate PAH, NYHA class II	n = 10 Severe PAH, NYHA class III	P-value
RER maximal anaerobic threshold Ratio	0.95 ± 0.98	1.00 ± 0.12	0.172
Peak VO <sub>2</sub> mL min <sup>-1</sup> kg <sup>-1</sup>	13.55 ± 4.57	10.10 ± 3.21*	0.025*
Peak work rate W	122.21 ± 60.90	132.44 ± 64.69	0.498
Peak ventilation L min <sup>-1</sup>	38.47 ± 17.65	40.66 ± 17.92	0.562
Metabolic equivalents Ratio	3.87 ± 1.30	2.87 ± 0.91*	0.025*
Peak heart rate bpm	136.68 ± 26.50	114.0 ± 34.27	0.129
V <sub>E</sub> -V <sub>CO<sub>2</sub></sub> @AT Ratio	51.64 ± 18.11	65.50 ± 29.75	0.154
Systolic PAP, mmHg	77.26 ± 26.41	77.60 ± 24.60	0.059
CI, L min <sup>-1</sup> m <sup>-2</sup>	3.21 ± 1.09	2.75 ± 1.24	0.329
PVR, mmHg L <sup>-1</sup> min <sup>-1</sup>	5.70 ± 2.81	7.38 ± 2.79	0.200
6MWT, m	426.05 ± 95.40	356.75 ± 89.94*	0.041*

\*Each 6MWT and CPET parameter of all class II and class III PAH patients was significantly different between the groups (P < 0.05). Systolic PAP = Systolic pulmonary arterial pressure, Cardiac index = CI, PVR = pulmonary vascular resistance, 6MWT= 6-min walk test.

distance. These results are consistent with those of Enright et al., who demonstrated that 6MWT distance is strongly associated with age and that elderly subjects had lower walking distances (18).

In the present study, we first demonstrated that the distance walked in 6 min decreased in proportion to the decrease in peak  $\text{VO}_2$  and MET determined by maximal CPET. Maximal CPET results showed that patients with PAH had reduced peak  $\text{VO}_2$  values. Peak  $\text{VO}_2$  assesses the subject's maximal work ability and maximal ability of the circulatory system to increase CO. In PAH, this relates to pulmonary vasculopathy, which limits blood flow through the lungs (7). On the other hand, 6MWT distance correlated modestly with  $\text{VO}_{2\text{peak}}$ , MET, and workload in the present study.

Additionally, considering the increased demand of ventilatory deficiency, the minute ventilation-to-carbon dioxide output slope increased in our PAH patients. Previously, it was shown that 6MWT distance was negatively correlated with VE-VCO<sub>2</sub> slope in patients with PAH (7). However, our findings did not show a similar correlation. Only the hemodynamic parameter of CI showed a statistically significant correlation with peak  $\text{VO}_2$ . This result shows that decreased CI causes reduced oxygen consumption or functional capacity (21).

Several authors reported a close association between 6MWT distance and maximal exercise testing in patients with heart failure, heart transplantation, and primary pulmonary hypertension (7,22). Our analysis showed that there were significant differences between the NYHA class II and class III patients in terms of 6MWT distance, peak  $\text{VO}_2$ , and MET. Reduction and association among these variables reflect right ventricle dysfunction, reduced CI, and oxygen deficit during exercise (9). Concerning the prognostic value of the submaximal 6MWT, it may be concluded that the 6MWT can be used as an equivalent to the peak  $\text{VO}_2$  parameter of maximal exercise testing.

In conclusion, submaximal exercise testing can be used safely and easily to assess decreased functional capacity in patients with PAH. The 6MWT provides information that may be a better index for the patient's NYHA functional class determination than maximal exercise testing. The determination of walking distance by CI and age indicators enables patient-specific assessment of prognosis and disease severity.

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#### References

- Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 2011; 336: 111-117.
- Olschewski H, Kovacs G. ESC guidelines 2015 on pulmonary hypertension. *Herz* 2015; 4: 1055-1060.
- McLaughlin VV, Davis M, Cornwell W. Pulmonary arterial hypertension. *Curr Probl Cardiol* 2011; 36: 461-517.
- Paolillo S, Farina S, Bussotti M, Iorio A, Perrone Filardi P, Piepoli MF, Agostoni P. Exercise testing in the clinical management of patients affected by pulmonary arterial hypertension. *Eur J Prev Cardiol* 2011;19: 960-971.
- Naeije R. Breathing more with weaker respiratory muscles in pulmonary arterial hypertension. *Eur Respir J* 2003; 25: 6-8.
- McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS et al. ACC/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association. *Circulation* 2009; 119: 2250-2294.
- Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 48-492.
- Sun X, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429-435.
- Fowler RM, Gain KR, Gabbay E. Exercise intolerance in pulmonary arterial hypertension. *Pulmonary Medicine* 2012; 2012: 359204.
- Groepenhoff H, Vonk-Noordegraaf A, van de Veerdonk MC, Boonstra A, Westerhof N, Bogaard HJ. Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. *PLoS One* 2013; 8: e72013.
- Guazzi M, Opasich C. Functional evaluation of patients with chronic pulmonary hypertension. *Ital Heart* 2005; 6: 789-794.
- Demir R, Küçüköğlü MS. Six-minute walk test in pulmonary arterial hypertension. *Anatol J Cardiol* 2015; 15: 249-254.
- Neal JE, Lee AS, Burger CD. Submaximal exercise testing may be superior to the 6-min walk test in assessing pulmonary arterial hypertension disease severity. *Clin Respir J* 2014; 8: 404-409.
- Inal-Ince D, Savci S, Saglam M, Calik E, Arikan H, Bosnak-Guclu M, Vardar-Yagli N, Coplu L. Fatigue and multidimensional disease severity in chronic obstructive pulmonary disease. *Multidiscip Respir Med* 2010; 5: 162-167.
- Selzer A, Sudrann RB. Reliability of the determination of cardiac output in man by means of the Fick principle. *Circ Res* 1958; 6: 485-490.

16. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111-117.
17. Enright PL, McBurnie MA, Bittner V. The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003; 123: 387-398.
18. Farber HW, Miller DP, McGoon MD, Frost AE. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant* 2015; 34: 362-368.
19. Britto RR, Probst VS, Andrade AFD. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. *Braz J Phys Ther* 2013; 17: 556-563.
20. Galie N, Simonneau G. The Fifth World Symposium on Pulmonary Hypertension. *J Am Coll Cardiol* 2013; 24: 1-3.
21. Jefferson AL, Himali JJ, Beiser AS. Cardiac index is associated with brain aging: The Framingham Heart Study. *Circulation* 2010; 122: 690-697.
22. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, Di-Salvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996; 110: 325-332.