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Research Article

Is it Probably a Research to Investigate a Reproducibility of 6 Minutes Walking Distance in Patients with Pulmonary Arterial Hypertension?

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Abstract

Background: 6 minute walking distance (6-MWD) has prognostic importance and is an excellent prognostic marker. Many environmental and individual factors affect the sensitivity and objectivity of the 6-MWT, which has such an essential role in PAH. Aim of this study might be to investigate test-retest reliability of 6-MWD in patients with PAH and the responsiveness of the test to the treatment.

Methods: Fifty patients with Group I-IV pulmonary hypertension who were admitted to the outpatient clinic of the Cardiology Department were included in the study. These patients were randomly divided into pairs, and first, one by one and then, two patients simultaneously were subjected to a 6-MWT. We designed our walking area so that they can see each other.

Results: When the 6-MWT results were examined, the mean distance of the 50 patients included in the study was 348.8 ± 97.7m at the end of the first test, and 381.4 ± 95.3m at the end of the second test. The second walking test showed a mean increase of 32.6 meters or 9.3% than the first test. And this increase was found to be statistically significant ($p < 0.01$).

Conclusion: It was observed that conditioning improved the performance of the patients and increased the walking distance. It was demonstrated that conditioning could be used to increase the sensitivity and objectivity of the 6-MWT.

Keywords: *6-MWT; 6-MWD; Pulmonary Arterial Hypertension*

Abbreviations

6-MWT: 6 Minute Walking Test; 6-MWD: 6 Minute Walking Distance; PAH: Pulmonary Arterial Hypertension; CTEPH: Chronic Thrombo-embolic Pulmonary Hypertension

Introduction

Pulmonary hypertension is a deadly and progressive chronic disease characterized by an increase in pulmonary vascular resistance and presents with complaints such as shortness of breath, palpitations, angina, syncope and may lead to premature death resulting in right heart failure [1]. Pulmonary hypertension is defined as the mean resting pulmonary artery pressure (mPAP) determined by right heart catheterization ≥ 25 mmHg [2]. In the diagnosis, some patient characteristics predict a worse prognosis, including male sex, old age, some genetic mutations, and subtype of PAH (scleroderma, HIV etc.) [3,4]. More importantly, other parameters are predictors of poor survival, including worse NYHA functional class, limited 6-MWT and lower heart rate or index with right ventricular failure [5]. Therefore, the guideline proposes a regular and comprehensive assessment using a panel of multiple markers to assess the severity of PAH and right ventricular failure to determine the severity of PAH and right ventricular failure, to measure response to treatment and to guide decisions on concentration or change in therapy. The most prevalent clinical exercise tests are stair climbing, 6-MWT, shuttle walk test, detection of exercise-induced asthma, cardiac stress test (e.g. Bruce protocol) and cardiopulmonary exercise test [6,7].

The most reliable indicator of the 6-MWT is to measure the response to medical interventions in patients with moderate to severe heart or lung disease. 6-MWT has also been used to determine the functional status of patients and also as a prediction of morbidity and mortality [8]. All these indications are treatment evaluation (Lung transplantation, lung resection, lung volume reduction surgery, pulmonary rehabilitation, COPD, pulmonary hypertension, heart failure), functional status assessment (COPD, heart failure, cystic fibrosis, peripheral vascular diseases, fibromyalgia, elderly patient) and morbidity-mortality assessment (COPD, heart failure, primary pulmonary hypertension). The repeatability of the 6-MWT is correlated with functional capacity measurements. However, it is not enough objective in some patients. The walking distance of an average person within 6 minutes is 400 - 700m [8]. Although reliable individual estimates are always tricky, the estimated 1-year mortality in patients categorized as low-risk is < 5%. These patients present a non-progressive disease with 6-MWD > 440m in WHO-FC I or II and without clinically significant signs of RV dysfunction.

Aim of the Study

The study aimed to investigate whether the 6-MWT distance may undergo significant changes with conditioning (the process of training or accustoming our patients to behave in a certain way. For example you can walk more, you can do it).

Methods

This study was an experimental design study. Fifty patients who were admitted to Fırat University Research Hospital Pulmonary Hypertension Polyclinic between August 2019 and September 2019 with the diagnosis of Group I and IV PAH were included in the study. Ethical approval of the work by the local ethics committee. Inclusion criteria were diagnosis of Group I-IV PAH and the patient has previously performed 6-MWT in the course where the test will be shown. Exclusion criteria were unstable angina pectoris in the last month, myocardial infarction in the past month, resting heart rate above 120 per minute, systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 100 mmHg, oxygen saturation < 85% measured by a pulse oximeter. Our trial is an experimental research.

We performed test each patients twice times within two hour. The test is carried out on a 40-meters long, uneven and straight track marked with a visible, starting and ending line every 3 meters. The patient is rested in a chair for 15 minutes before starting the test. During this period, the patient's contraindications for a 6-MWT are questioned. If there is no contraindication, the patient's blood pressure, oxygen saturation by pulse oximetry, pulse rate and Borg scale are evaluated after resting.

IBM SPSS Statistics Version 22.0 package program was used for statistical analysis of the data. Continuous variables were summarized as mean and standard deviation. The Kolmogorov Smirnov test was used to test whether the continuous measurements provided the usual distribution assumption. In the comparison of continuous variables a t-test was used in two groups, and error bar graphs supported the results. Repeated measurements analysis was used to compare the variation of constant sizes over time in the same individuals. Statistical significance was taken as 0.05 in all tests. (IBM Corp. Released in 2013. IBM Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Results

Our study was included in fifty patients (40 female (80%)). The demographic characteristics and distribution of drug use of the patients are summarized in table 1. The mean NT-ProBNP is 507,66 ± 744,1. When the echocardiography results of the patients were examined, the mean LVEF was 54.7 ± 4.8 and mean sPAP value of the patients was 39.3 ± 14.1. When the catheterization results of forty patients were assessed, mean pulmonary pressure was 31.4 ± 9.3 and mean PVR value was 5.3 ± 3.2 and the mean CI value was 2.5. ± 0.7 (Table 2).

Number of Patients	50
Male, n (%)	10 (20%)
Age, mean[×] ± SD	50,68 ± 16,6
Smoking, n (%)	3 (6%)
HT, n (%)	17 (34%)
DM, n (%)	7 (14%)
HL, n (%)	4 (8%)
CAD, n (%)	8 (16%)
Group I PAH, n (%)	41 (82%)
Group IV PAH, n (%)	9 (18%)
Diuretics	20 (40%)
Beta Blocker	16 (32%)
Calcium Channel Blocker	4 (8%)
ACEi/ARB	10 (20%)
Aldosteron Receptor Antagonist	3 (6%)
Acetyl Salicylic Acid	10 (20%)
ADP Receptor Blocker	3 (6%)
Statin	4 (8%)
Oral Anticoagulant	16 (32%)
Oral Antidiabetics	7 (14%)
Endothelin Receptor Blocker	
Bosentan	9 (18%)
Macitentan	15 (30%)
Phosphodiesterase-5 Inhibitors	11 (22%)
Prostacyclin Analog	1 (2%)
Guanylate Cyclase Stimülator	5 (10%)

Table 1*: Demographic characteristics and drug characteristics of patients.*

DM: Diabetes Mellitus; HL: Hyperlipidemia; HT: Hypertension; CAD: Coronary Artery Disease; PAH: Pulmonary Arterial Hypertension; ACEi: Angiotensin Converting Enzyme Inhibitor; ADP: Adenozin Difosfat; ARB: Angiotesin Receptor Blocker.

	Mean ± Sd[×]
BUN	32 ± 15,5
Creatinine	0,69 ± 0,22
Hemoglobin	12,96 ± 1,77
Hematocrit	40,57 ± 5,55
AST	21,34 ± 11,86
ALT	18,84 ± 8,76
NT-proBNP	507,66 ± 744,1
TSH	2 ± 1,27
LVEDD (mm)	45,4 ± 5,6
LVESD (mm)	28 ± 5,3
LAD (mm)	37,5 ± 6,7
sPAB (mmHg)	39,3 ± 14,1
RA area	19,4 ± 5,6
RV-Basal Diameter	44,1 ± 7,3
RV-Mid Diameter	34,4 ± 5,5
RV-Longitudinal Diameter	69,5 ± 11,4
RA Pressure	10,3 ± 4,6
PVR	5,3 ± 3,2
CI	2,5 ± 0,7

Table 2: *Laboratory results, echocardiographic characteristics and right heart catheterization results of patients.*

[××]Sd: Standart *Deviation; Alt: Alanine Aminotransferase; AST: Aspartat Transaminase; NT-proBNP: N-Terminal Pro-B Natriuretic Peptide; TSH: Thyroid Stimulant Hormone. LVEF: Left Ventricul Ejection Fraction; LVEDD: Left Ventricule End-diastolic Diameter; LVESD: Left Ventricule End-Systolic Diameter; LAD: Left Atrial Diameter; sPAB: Systolic Pulmonary Arterial Pressure; RA: Right Atrium; RV: Right Ventricle; mPAB: Mean Pulmonary Arterial Pressure; RA: Right Atrium; PVR: Pulmonary Vascular Resistance; CI: Cardiac Index.*

The first and second 6-MWT results of the patients included in the study are summarized in table 3 and 4. The walking distances of male and female patients in the first and second 6-MWT are summarized in figure 1. The mean walking distance of the patients who were younger than 50 years as a result of the first 6-MWT was 400.2 ± 83.4 and the distance from the second 6-MWT was 433.1 ± 80.4. The mean walking distance of the patients who were older than 50 years as 301.4 ± 86.2 was observed as 301.4 ± 86.2 and the distance from the second 6-MWT was 334.6 ± 83.7. Patients younger than fifty years of age had significantly more progress in the second 6-MWT than the first 6-MWT ($p < 0.01$). Patients older than fifty years of age also showed significant improvement in the second 6-MWT compared to the first 6-MWT ($p < 0.01$). When the patients younger than fifty years and the patients older than 50 years were compared with each other, a significant difference was observed between the two groups as the distance difference between the two tests ($p < 0.001$). It was found that patients less than fifty years of age showed a more significant increase in the second test than patients older than 50 years. The walking distances in the first and second 6-MWT of patients younger than fifty years are summarized in figure 2.

	Mean ± Sd		**N**	**%**
Walking Distance (meter)	348,8 ± 97,7	Angina	0	0,0
Systolic Pressure	118,8 ± 6,5	Dizziness	0	0,0
Diastolic Pressure	69,1 ± 4,4	Limb Ache	0	0,0
Initial Heart Rate	77,1 ± 14,7	Leg Ache	4	8
End Heart Rate	92,9 ± 20,4	Calf Ache	3	6
Starting SpO_2	94,6 ± 5,4	No complete of Test	0	0,0
End SpO_2	92,1 ± 10			
Borg Dyspne Scale	1,9 ± 1,3			

Table 3: *First six minute walking test.*

m: Metre; n: Number; Mean: Average; SpO_2: Oxygen Saturation; SS: Standard Deviation.

	Mean ± Sd		**n**	**%**
Walking Distance (m)	381,9 ± 95,3	Angina	0	0,0
Systolic Pressure	119,3 ± 6,2	Dizziness	0	0,0
Diastolic Pressure	68,8 ± 3,9	Limb Ache	0	0,0
Initial Heart Rate	77,8 ± 14	Leg Ache	4	8
End Heart Rate	92,4 ± 20,2	Calf Ache	3	6
Initial SpO_2	94,4 ± 5,7	No complete of Test	0	0,0
End SpO_2	92,6 ± 9,6			
Borg Dyspne Scale	1,9 ± 1,4			

Table 4: *Second six minute walking test.*

m: Metre; n: Number; Mean: Average; SpO_2: Oxygen Saturation; SS: Standard Deviation.

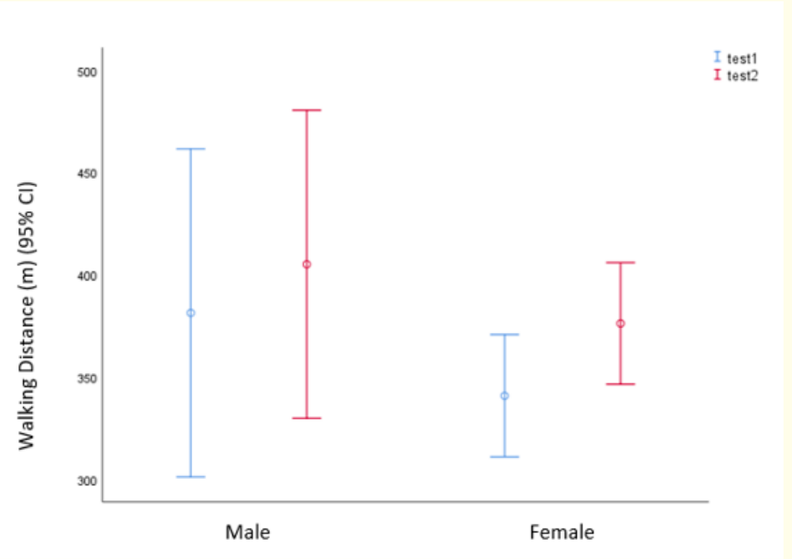

Figure 1: *According to gender disturbance of 6-MWT.*

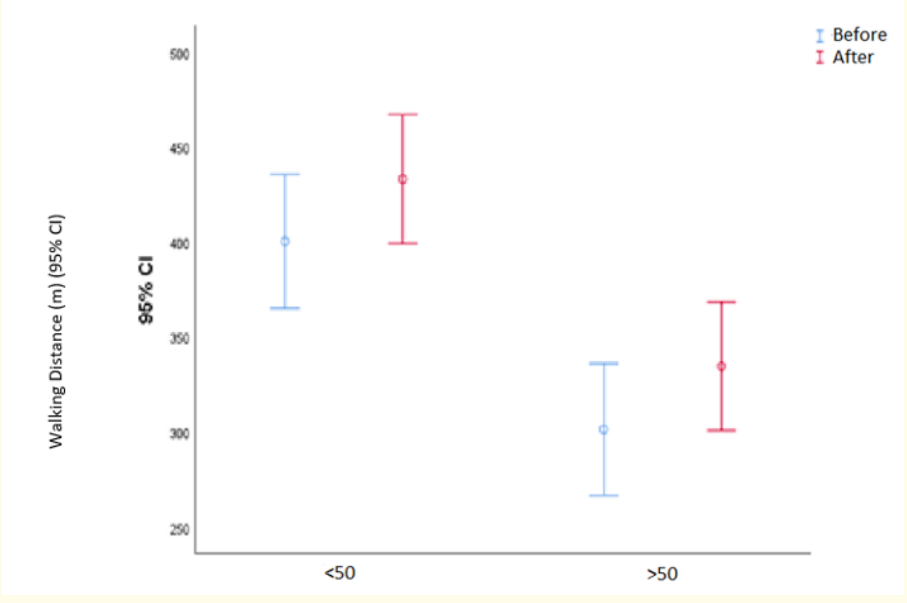

Figure 2: *According to age disturbance of 6-MWT.*

When all patients included in the study were evaluated, the patients had a significantly better distance in the second gait test than the first gait test ($p < 0.01$). The difference in length between the first and second tests is shown in figure 3 and the statistical analysis results of the 6-MWT between the groups are summarized in table 5.

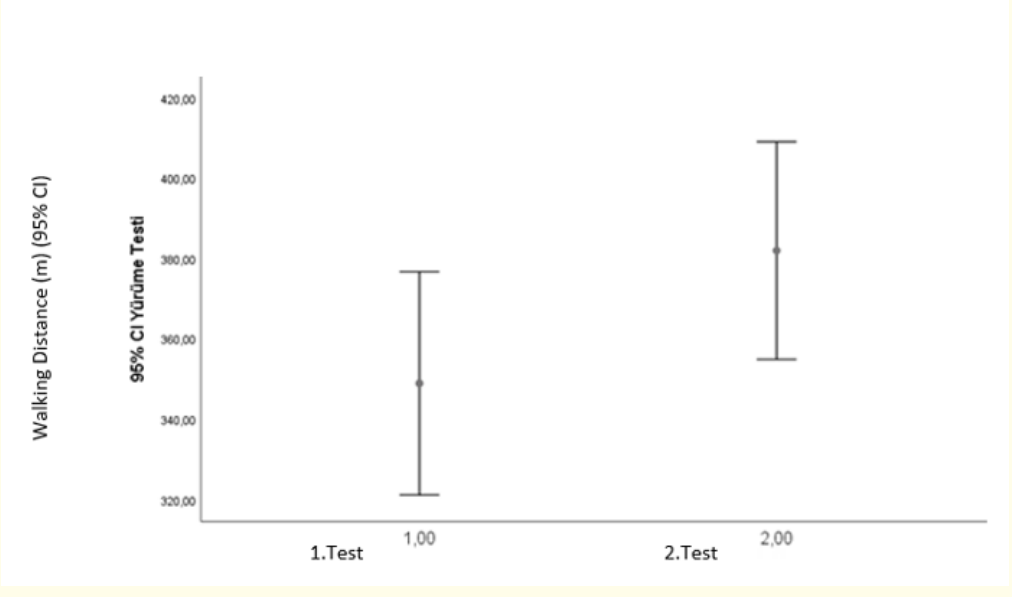

Figure 3: *According to first and second test disturbance of 6-MWT.*

	First Walking Distance	Second Walking Distance	p
	Mean ± Sd	Mean ± Sd	
Male	381,3 ± 112,1	405,1 ± 105,3	0,01
Female	340,7 ± 93,5	376,1 ± 93,1	< 0,01
< 50 age	400,2 ± 83,4	433,1 ± 80,4	< 0,01
> 50 age	301,4 ± 86,2	334,6 ± 83,7	< 0,01
Total	348,8 ± 97,7	381,9 ± 96,3	< 0,01

Table 5: *Statistical analyses results of 6-MWT.*

Discussion

Exercise intolerance is the main feature of PAH. The 6-MWT and cardiopulmonary exercise test is commonly used to evaluate exercise capacity in patients with PAH. The 6-MWT was the primary clinical outcome measure in PAH and was used as the primary endpoint in many studies for new PAH treatments. The use of 6-MWT as an endpoint in clinical trials has many advantages. 6-MWT is a standardized test that is simple, inexpensive, easy to administer, reproducible and well tolerated by patients with PAH. It is also a valid measure of symptomatic recovery. It correlates with the variables of maximal cardiopulmonary exercise test as a measure of submaximal exercise capacity, as well as markers of disease severity such as functional class and pulmonary hemodynamics. It is widely used in clinical practice to evaluate disease progression and response to treatment with other markers of invasive and noninvasive disease. It also has prognostic significance, a good indicator of prognosis. In recent years, however, there have been objections to the use of 6-MWT as the primary endpoint in the field of PAH. It has decreased sensitivity in people with less severe disease with high initial walking distances and reduced ability to determine the treatment effect in patients receiving PAH. Despite its limitations, 6-MWT plays a vital role in the evaluation and management of patients with PAH [9].

Many environmental and individual factors affect the sensitivity and objectivity of the 6-MWT, which has such an important role in pulmonary arterial hypertension. In the previous studies [10,11], taking into account these factors, it was shown that two walking tests performed on different days on the same track were able to isolate influential factors such as the effect of training, ensuring coordination, reducing anxiety and finding the appropriate step interval and maximizing patient performance. There are also studies in which the same patients undergo a 6-MWT at different times (twice on the same day or twice in the same week) to compare post-test distances and to increase the sensitivity and objectivity of 6-MWT. In a study by Hernandes., *et al*. It was stated that the walking distance could be increased to 27 meters by repeating the 6-MWT [12]. In this study conducted by Hernandes., *et al*. 1514 patients followed by COPD underwent a 6-MWT on different days in the same week. Patients walked an average of 381 meters in the first test, while the percentage of 418 meters in the second test. In other words, an increase of 27 meters (7%) was observed (p: 0.0001). The reason for this increase was thought to be a learning effect. In a study involving 103 children with cystic fibrosis [13], it was shown that there was no significant difference between the two walking distances achieved in the 6-minute walk test performed one week apart (737 ± 85, 742 ± 90 p = 0.56). Similarly, in many studies questioning the objectivity of 6-MWT, the reported increase in mean walking tests of patients with one or several day intervals ranges between 0 - 17% [13-17].

Conclusion

In our study, to reduce the effect of the factors emphasized in the previous studies, the same element was used for testing the same course and the same patients who knew the course and especially the conditioning factor that was not used in the previous studies was taken into consideration. As a result, it was observed that conditioning improves the performance of the patients and increases the wal-

king distance. As a result of the study, it was demonstrated that conditioning could be used to increase the sensitivity and objectivity of the 6-MWT. In our study, although it was shown that conditioning affected 6-MWT distance and performance, the relationship between this indicator, which increases sensitivity and objectivity, and its involvement with prognosis and treatment could not be evaluated. Therefore, in future prospective studies, this relationship will be emphasized; its use in larger patient populations and performed over a more full-time interval will provide more beneficial results. At the same time, geographic and cultural factors should be supported with multicenter studies considering that the test may affect the sensitivity and objectivity of the test. As a result of the study, it was demonstrated that conditioning could be used to increase the sensitivity and objectivity of the 6-MWT.

Conflict of Interest

There is no conflict of interest.

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