ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Six-Minute Walk Test: How to do Guide for Performing a Reliable Test, Interpretation, and Prognostication in Pulmonary Hypertension

Altı Dakika Yürüme Testi: Pulmoner Hipertansiyonlu Hastalarda Güvenilir Bir Testi Nasıl Yapalım, Yorumlayalım ve Prognoz Tayininde Kullanalım?

ABSTRACT

Six-minute walk test (6MWT) is the most widely used exercise capacity measurement worldwide in patients with pulmonary hypertension (PH). Although cardiopulmonary exercise testing (CPET) is the gold standard for the assessment of exercise capacity in cardiovascular diseases; the limited accessibility of the device, the need for experience in interpreting the results, and the difficulties in performing CPET in advanced PH have aroused the interest in the application of easier methods for the measurement of exercise capacity. Since then, accumulated data proved that; 6-minutes walking distance (6MWD) can be used to determine exercise capacity and is highly correlated with maximum oxygen consumption (peak VO_2) detected by CPET in patients with heart failure and/or PH. Moreover, 6MWT is very easy and practical to apply in all PH subgroups. This review is focused on the application of a reliable 6MWT and the interpretation of the results in patients with PH.

Keywords: Cardiac rehabilitation, exercise, exercise testing, pulmonary arterial hypertension, six-minute walking test

ÖZET

Altı dakika yürüme testi (6DYT), pulmoner hipertansiyon (PH) tanılı hastalarda dünya genelinde egzersiz kapasitesini belirlemek için en sık olarak kullanılan yöntemdir. Kardiyopulmoner egzersiz testi (KPET), kardiyovasküler hastalıklarda egzersiz kapasitesinin değerlendirilmesinde altın standart olmakla birlikte; cihaza erişimin ve testin değerlendirilmesindeki tecrübenin kısıtlı olması ve ileri PH olgularında KPET uygulamasındaki zorluklar, egzersiz kapasitesinin belirlenmesinde daha kolay yöntemlerin arayışına girilmesine yol açmıştır. Böylece çoğalan veriler, altı dakika yürüme mesafesinin (6DYM) kalp yetmezliği ve/veya PH olan hastalarda egzersiz kapasitesini belirlemek için kullanılabileceğini ve bu hastalarda KPET ile belirlenen maksimum oksijen kullanımı (pik VO_2) ile iyi derecede korelasyon gösterdiğini bildirmiştir. Ayrıca 6DYT, PH'lı hastaların tüm alt gruplarında çok kolay ve pratik bir biçimde uygulanabilir. Bundan ötürü 6DYT, dünya genelindeki PH merkezlerinde egzersiz kapasitesini belirlemek için en sık kullanılan yöntem olmuştur. Bu derleme, PH hastalarında 6DYT'nin güvenilir bir biçimde uygulanması ve sonuçlarının yorumlanması üzerine odaklanmıştır.

Anahtar Kelimeler: Kardiyak rehabilitasyon, egzersiz, egzersiz testi, pulmoner arteriyel hipertansiyon, altı dakika yürüme testi

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Received: September 14, 2023
Accepted: September 27, 2023

Cite this article as: Meriç M, Çağlıyan CE, Eker Akıllı R, et al. Six-minute walk test: how to do guide for performing a reliable test, interpretation and prognostication in pulmonary hypertension. *Turk Kardiyol Dern Ars.* 2023;51(7):516-520.

DOI:10.5543/tkda.2023.52279

Six-minute walk test (6MWT) has become a widely accepted measure of exercise capacity in different cardiovascular diseases. Although easily applicable to different subgroups of pulmonary hypertension (PH), there are several important considerations for the performance and interpretation of the 6MWT. This review is presented as a practical guide for clinicians to perform reliable and reproducible 6MWT and highlights some basic issues and tips for evaluating the results.

Contraindications of the Six-Minute Walk Test

Universal standards for the administration of the 6MWT have been established by specialty associations.[1] The test is used to measure the distance a patient walks at a fast pace on a flat, hard surface in 6 minutes. During the test, many patients cannot achieve the highest level of exercise; instead, they are allowed to choose their own exercise

intensity and to stop and rest. This condition also applies to daily life. Definite contraindications are unstable angina pectoris and myocardial infarction within the past month. Relative contraindications are a resting heart rate >120/min and blood pressure >180/100 mmHg.[1] Stable angina pectoris induced by exertion is not a definite contraindication for 6MWT; however, these patients should take the test after having received their antianginal medication and nitrate derivatives should be made available for use as needed.

Features of the Place where the Test Will be Performed

This test should be performed in a center where emergency cases can be treated quickly and appropriately. The location of the hospital bed for emergency admission should also be determined in advance by the physician in charge of this department. Oxygen, sublingual nitroglycerin, aspirin, and albuterol (metered dose inhaler or nebulizer) should be available in the test room. A telephone should also be available to call for further assistance if necessary. The technician performing the test must have at least a basic life support certificate and preferably an advanced life support certificate. An accessible defibrillator and crash cart should be available in the testing area. Physicians do not need to be present during the test; however, in special circumstances, the physician requesting the test may decide whether a physician should be present. Patients receiving continuous oxygen therapy can still be tested under oxygen. In this case, the patient is walked while oxygen is given at the standard rate or the rate determined by the physician. A wheelchair or stool that can be moved along the corridor can be kept so that the patient can take a break and rest when necessary. There should also be a stopwatch for time measurement. The 6MWT should be performed indoors, along a horizontal, straight, enclosed, hard-floored corridor with minimal passage. The test can also be performed outdoors if the weather allows. The walkway should be 30 m long,[2] and the length of the corridor should be marked every 3 m. Turn points should be marked with a cone (e.g., an orange traffic cone). A starting line indicating the beginning and end of each 60 m round should be marked on the ground using bright colored tape. Standards require a 30-m corridor, but depending on the conditions, the test can also be performed in a 20- or 50-m corridor.[3,4] It should be noted that when the corridor is shorter, as the patients will take more time to change direction, the walking distance will also be shorter. Walking patients on a treadmill instead of corridor is not recommended. Because patients can walk less on the treadmill compared to their usual physical condition.

The medications that the patient uses regularly and their regimen should be noted in advance and should not be changed for the test. It is recommended that patients wear comfortable clothes and shoes and use their usual walking apparatus (cane, walker, etc.) for the test. A light meal in the early morning or early afternoon before the test is acceptable. The patient should not do vigorous exercise within 2 hours before starting the test. The patient should be seated in a chair close to the starting position for at least 10 minutes before starting the test. Meanwhile, the patient contraindications, heart rate, blood pressure, clothing, and shoes should be checked for test suitability.

Preparation of the Patient and Implementation of the Test

Monitoring of the patient's oxygen saturation by "pulse oximetry" during the test is not mandatory.[1] If a pulse oximeter is to be used, it should not be used for continuous control and the technician should not be walking near the patient with the oximeter in hand (because the technician's own speed may affect the patient's speed). The oximeter should therefore be portable on the patient. It should also be noted that most oximeters produce motion artifacts. Before the test, the sitting patient is asked to stand up and evaluated for dyspnea and general fatigue using the Borg scale. Borg scale is summarized in Table 1. The round counter is set to zero, the stopwatch is set to 6 min, all necessary equipment is checked and information and instructions about the test are given to the patient at the starting point. For example "The goal of this test is to walk as far as possible for 6 minute. You will walk back and forth in this corridor. Six minutes is a long walking time, so you will be tired, likely out of breath, and fatigued. You can rest whenever you need to slow down or stop. You can lean against the wall while resting, but as soon as you feel better you should keep walking again. You will go back and forth around the cones. When going around the cones you should turn quickly and keep walking to the other side without hesitation. I will show you now, please watch how I turn quickly and keep going." The technician should walk one round to demonstrate and turn quickly around the cone. Now "Are you ready to start? I will use this counter to follow the number of rounds you have completed. I will click it every time you go around this starting line. Remember that your goal is to walk as many rounds as possible in 6 min, but do not run. You can start when you are ready." Once the technician is sure that the patient has understood the instructions, the patient is instructed to start the test and the stopwatch is started as soon as the patient starts walking. The technician should not walk with the patient and should watch the patient carefully from the starting point of the

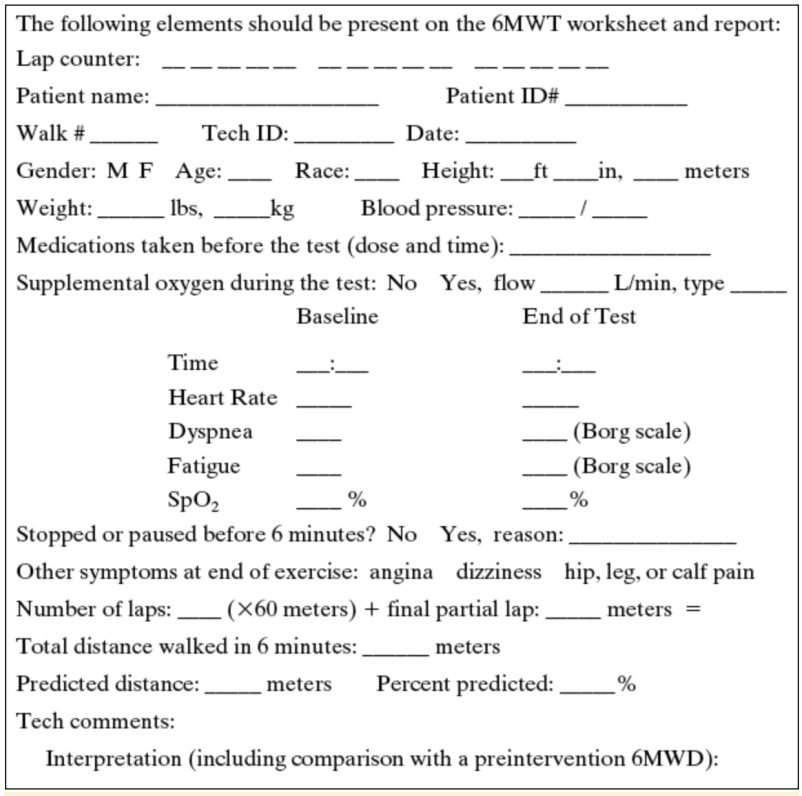
ABBREVIATIONS

6MWT	Six-minute walk test
6MWD	6-minute walking distance
CPET	Cardiopulmonary exercise testing
ERS	European Respiratory Society
ESC	European Society of Cardiology
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension

Table 1. Borg dyspnea scale

0	No dyspnea
0,5	Very, very mild
1	Very mild
2	Mild
3	Moderate
4	Slightly severe
5	Severe
6	....
7	Very Severe
8	....
9	Very, very severe
10	Maximum

test, should speak to the patient in a flat voice while using standard words of encouragement, should keep an eye on the patient, should not talk to anyone else, should not be occupied with other activities and should be careful not to miss the number of rounds. Each time the patient reaches the starting line, the technician should click on the round counter and make sure that the patient can see this action or inform the patient of the number of rounds. After the 1st min, the technician should say to the patient in a flat voice: "You are doing well, you have 5 minutes left." When the timer shows 4 minutes left, the patient should be told: "Keep up the good work, you have 4 minutes left." When the timer shows 3 minutes left, the patient should be told: "You are doing well, you are already halfway there." When the timer shows 2 minutes left, the patient should be told: "Keep up the good work, you have only 2 minutes left". When the timer shows 1 minute left, the patient should be told: "You are doing well, you only have 1 minute left". No other words of encouragement or body language should be used to speed up. If the patient needs to stop walking and rest during the test, say: "If you wish, you can rest by leaning against the wall, then resume walking when you feel you can." The timer should not be stopped at this point. If the patient stops before the end of 6 minutes and refuses to continue (or the technician decides not to), the wheelchair is approached to the patient so that he/she is seated and the test is terminated. The time of the termination the test and the reason for premature termination are noted on the worksheet. When 15 s remain until the end of the test, the patient should be told: "I will tell you to stop in a moment." When I tell you, stay where you are and I will come to you." When the stopwatch time reaches 6 minutes and the alarm sounds, the patient should be told: "Stop!". The technician walks toward the patient and considers taking the wheelchair to the patient if the patient looks exhausted. The technician marks the patient's position with a tape or object. At the end of the test, Borg dyspnea and fatigue levels are remeasured and recorded. If a pulse oximeter was used, the pulse rate and oxygen saturation at the end of the test are recorded. Finally, the absolute 6-minutes walking distance (6MWD) is recorded on the worksheet by measuring the total number of rounds covered by the patient and the distance covered in the incomplete round in the last round. A sample of a 6MWT worksheet is illustrated in Figure 1.[5] The test is terminated by congratulating the patient for their effort and offering some rest and water to drink. If it is necessary to administer oxygen at a rate higher than the maintenance dose to patients who have previously received continuous oxygen therapy during the test, this should be stated in the study report. The type of equipment used to administer oxygen to the patient during the test should also be recorded (e.g., patient carried liquid oxygen or pushed or pulled an oxygen tank). During the test, the technician walking behind the patient with an oxygen source to provide oxygen support is not recommended. The 6MWT may also be terminated early by the technician if the technician detects any urgent condition (chest pain, intolerably severe dyspnea, leg cramps, stumbling, or a pale or ash-colored appearance) in the patient, noting the reason for termination. If the test is stopped for these emergency reasons, depending on the severity of the event, the patient should be appropriately seated or laid on their back to avoid the risk of fainting. Technicians should be trained by standard pre-prepared protocols to recognize and deal with such emergencies and should be supervised in multiple tests before administering the 6MWT alone.


The following elements should be present on the 6MWT worksheet and report:
Lap counter: _____ _____ _____
Patient name: _____ Patient ID# _____
Walk # _____ Tech ID: _____ Date: _____
Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters
Weight: _____ lbs, _____kg Blood pressure: _____ / _____
Medications taken before the test (dose and time): _____
Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____ (Borg scale)
Fatigue	____	____ (Borg scale)
SpO_2	____ %	____%

Stopped or paused before 6 minutes? No Yes, reason: _____
Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain
Number of laps: ____ (×60 meters) + final partial lap: _____ meters =
Total distance walked in 6 minutes: _____ meters
Predicted distance: _____ meters Percent predicted: _____%
Tech comments:
Interpretation (including comparison with a preintervention 6MWD):

Figure 1. A sample of a worksheet for reporting 6MWT findings.[5]

Interpretation of the 6MWT

6MWT results, like other PH assessment tests, should always be interpreted in a clinical context. 6MWD is influenced by factors including gender, age, height, weight, comorbidities, oxygen demand, learning curve, and motivation. Test results are usually expressed as absolute distance (meters) rather than as a percentage of predicted values. These results provide a convenient and comparable measure of exercise capacity for an individual PH patient in his long-term follow-up; however, it should be noted that expected absolute and predicted percentage values are not exactly same for different patients with different PH etiologies or for patients with different comorbidities. Because there are numerous interacting variables that influence these results for individual patients. Hence, factors affecting 6MWD should be known to be able to evaluate and compare test results: Advanced age, short stature, obesity, female gender, impaired perception, a corridor shorter than 30 m, pulmonary diseases (chronic obstructive pulmonary disease, asthma, cystic fibrosis, and interstitial lung disease), cardiovascular diseases (angina pectoris, myocardial infarction, and congestive heart failure), and the presence of musculoskeletal diseases reduce 6MWD. However, factors such as being tall, male sex, high motivation, previous test performance, walking with supplemental oxygen in patients with hypoxemia, and taking maintenance medications before the test have an increasing effect on 6MWD.

Prognostic Value of the 6MWT in Patients with PAH

Despite some limitations, 6MWT now plays a key role in the evaluation and management of patients with PH. Pulmonary arterial hypertension (PAH) is a life-shortening condition and a patient-based risk assessment is strongly recommended to inform treatment decisions. Exercise limitation is an early presenting symptom in PAH and measures of exercise capacity are typically severely reduced.[6,7] The risk stratification tables in the European Society of Cardiology (ESC) and European Respiratory Society (ERS) PH guidelines and the REVEAL 2.0 risk scores recommend exercise testing for all PAH patients as part of a multiparametric assessment and this has often been used as an endpoint in clinical trials.[8,9] The most commonly used exercise test in PH, the 6MWT, is a low-cost and easy to perform walking test. According to the latest PH guidelines of the ESC/ERS published past year, 6MWT should be performed. At baseline and repeated 3–4 months after the initiation or change of PAH-specific treatment and at each clinical worsening; in addition, 6MWT should be monitored regularly at 3–6-month intervals in patients who remain stable.[9]

In clinical trials of PAH, "change in 6MWD" is one of the most widely used follow-up parameters as a primary endpoint, important secondary endpoint, or as a component of clinical worsening.[10,11] A recent study showed that the best absolute thresholds for 1-year mortality and 1-year survival are 165 m and 440 m, respectively.[12] However, no single threshold is applicable to all patients.[13] The use of oximetry during the 6MWT is optional; however, some recent studies have suggested that in addition to 6MWD, studying the heart rate response measured during the exercise test, the lowest SpO_2 value during exercise or the excess of "desaturation" (the difference between the lowest SpO_2 at rest and during exercise) during exercise may improve the prognostic association.[14-16] Given that exercise intolerance is one of the main symptoms of PAH, a correlation of absolute 6MWD, a measure of the patient's exercise capacity, with hemodynamic parameters in patients with idiopathic PAH is not surprising and can predict survival both at the time of diagnosis and during clinical follow-up.[16-19] However, improvement in 6MWD as a response to treatment has not been demonstrated to be independently prognostic for PAH patients.[20,21] Six-minute walk distance has been identified as the main clinical outcome in PAH studies and has been used as the primary endpoint in many studies of new PAH therapies. There are several advantages to using 6MWD as an endpoint in clinical studies; it is at least a simple, low-cost, reproducible tool that is a validated measure of exercise capacity in patients with idiopathic PAH and is accepted by regulatory authorities for the registration of PAH medications. In addition, a comprehensive experience with 6MWT in idiopathic PAH and connective tissue disease-associated PAH is available. As typical in a rare disease such as PAH, using change from baseline in 6MWD as the primary outcome measure in short-term studies with small patient numbers has resulted in statistically significant differences between placebo and study drugs, leading to their approval. Deterioration of 6MWD, on the other hand, is strongly associated with poor prognosis.[21,22] Nevertheless, the role of 6MWD as an endpoint, especially in clinical studies, has been criticized, as prospective and retrospective studies have failed to show that improvements in 6MWD are independently associated with survival.[20-23] Eventually, a consensus was reached for the use of primary endpoints in clinical studies that reflect long-term disease progression and the morbidity of PAH. Using 6MWT alone as a primary endpoint in the treatment of PAH has its limitations. Gaine and Simonneau[20] discussed the limitations of the 6MWT and reported reduced sensitivity of the 6MWD in patients with milder symptoms and walking longer distances (ceiling effect), and reduced adequacy in patients currently on PAH therapy. For example, a "ceiling effect" in the 6MWD may mask treatment efficacy in patients with less severe symptomatic disease and high baseline walking distances. The specificity of 6MWD as a measure of exercise capacity may also be confounded by reasons unrelated to PAH, especially at low walking distances.[20,24] For instance, a patient with scleroderma may have compromised walking distance as a result of frailty and other comorbidities. Loss of fitness, that is, loss of muscle tone and endurance, can also occur in patients with chronic disease and affect the distance the patient can walk.

In PAH, three parameters of 6MWT have been evaluated for their association with post-treatment outcomes: (1) The absolute 6MWD value at baseline; (2) the absolute 6MWD value at a predefined time point post-treatment; and (3) the absolute change in 6MWD between pre- and post-treatment 6MWD values at a pre-defined time point. All these parameters were found not to be equally valid as prognostic indicators. Both systematic reviews and meta-analyses of randomized trials on PAH-specific therapies have shown that absolute changes in 6MWD from baseline do not predict a survival benefit or the incidence of clinical events.[20] In conclusion, based on all these data, it is recommended to use the 6MWD in clinical trials as one of the parameters that make up the "composite primary endpoints" defined under the name of clinical deterioration, rather than as a stand-alone clinical endpoint due to its limitations.[25] Therefore, clinical trials of newly developed drugs for PAH are now based on

combined clinical endpoints including morbidity and mortality events. These usually include all-cause mortality, hospitalization, switching to a new PAH treatment, and worsening of PAH, and studies assess time to first occurrence. However, for studies addressing subpopulations of PAH patients, such as congenital heart disease, where morbidity and mortality studies are unlikely, 6MWD still has a place as a primary endpoint.

Conclusion

Determining and eliminating exercise limitation are of great importance in PAH patients. 6MWD has become a widely accepted measure of exercise capacity in PAH patients. Careful and standardized implementation and appropriate interpretation of 6MWT provide prognostic insight and a reliable tool to monitor individual patients' treatment response.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Design – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Supervision – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Resource – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Materials – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Data Collection and/or Processing – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Analysis and/or Interpretation – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Literature Review – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Writing – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.; Critical Review – M.M., Ç.E.Ç., R.E.A., B.K.A., Ü.Y.S., P.D.Ç., R.D., İ.B., M.A.

Conflict of Interest: No conflict of interest disclosure has been received from the authors.

Funding: The authors declared that this study received no financial support.

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