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Six-minute walk test in patients with idiopathic pulmonary fibrosis

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The six-minute walk test (6MWT) is a simple method for investigating exercise capacity in patients with advanced lung disease.[1,2] Unlike patients undergoing traditional cardiopulmonary exercise testing, those undergoing the 6MWT do not, as a rule, reach maximal respiratory and heart rates, the 6MWT therefore being a submaximal test. The 6MWT is advantageous because walking is a task that patients are familiar with and because the 6MWT is inexpensive, requiring only a trained health professional, a flat corridor of approximately 30 m in length, a sphygmomanometer, and a pulse oximeter.

Although the 6MWT does not allow identification of the mechanisms involved in exercise limitation, the six-minute walk distance (6MWD) is an overall measure of integration among systems (i.e., the respiratory, cardiovascular, and locomotor systems). There is increasing evidence that a low 6MWD is strongly associated with an increased risk of hospitalization and mortality in patients with advanced lung disease.[1,2]

Although the 6MWT has good test-retest reliability, there is a learning effect with repeated testing. Therefore, at least two tests should be performed on the same day, at least 30 min apart (in order to allow for rest between tests), the longest 6MWD being selected for analysis.[2,3]

Although the primary physiological measure of interest is the 6MWD, other parameters of interest include the SaO_2 nadir, heart rate recovery at 1 min after exercise, and the product of the 6MWD by the lowest measured SpO_2.[4]

Although the 6MWT is easily performed, it should not be performed in patients with disabling dyspnea, in those with significant orthopedic abnormalities, or in those with cardiovascular conditions such as recent myocardial infarction, severe aortic stenosis, and decompensated heart failure.[2,3] Patients showing an SpO_2 of < 88% on room air should receive supplemental oxygen during the test, which should be interrupted if the SpO_2 on room air falls below 80% for 6 s or more; the test can be resumed when SpO_2 is ≥ 85% on room air.[2,3]

In recent years, there has been increasing interest in using the 6MWT in patients with idiopathic pulmonary fibrosis (IPF) not only in routine clinical practice but also in controlled clinical trials.[4,5] An initial test, performed at the first consultation, can provide information on exercise capacity and the need for supplemental oxygen during physical activity, as well as prognostic data. It is well recognized that an SpO_2 of ≤ 88% is a reliable indicator of poor survival in IPF patients undergoing a 6MWT without supplemental oxygen.[6]

Although there have been quite a few studies involving patients with IPF and the 6MWT, the most reliable data were provided by two large clinical trials of new drugs for the treatment of IPF, a substantial number of patients having been included in those trials.[7-9] The studies showed that the 6MWD correlated significantly with quality of life and dyspnea, as well as with lung function variables.

An analysis of 748 volunteers included in one of the aforementioned studies[7] showed that a 6MWD of < 250 m on the initial test was associated with double the risk of mortality after approximately one year of follow-up. In addition, decreases of more than 50 m in the 6MWD on tests performed 24 weeks after the first resulted in a three-fold increased risk of death in the following 24 weeks. Minimal clinically important differences were calculated from data from the aforementioned studies[8,9] and were found to be 24-45 m and 21.7-37.0 m. The results of the two aforementioned clinical trials[7-9] clearly show that the 6MWT is a valid and useful tool for the management of patients with IPF.

In the current issue of the JBP, Mancuso et al.[10] report the 6MWD in 70 IPF patients retrospectively selected from among those treated at either of two referral centers for interstitial lung disease in Brazil. The major finding of the study is that a 6MWD of < 330 m or < 70% of the predicted value is associated with a substantially decreased survival rate and should be considered an indicator of poor prognosis in patients with IPF in Brazil.

The first question is why the indicator of poor prognosis found in a study conducted in Brazil[10] is significantly different from those found in studies conducted elsewhere.[7,11-13] According to Mancuso et al.,[10] this might be due to differences in reference values for the 6MWT across countries.[14] There is evidence that the 6MWD is longer in individuals living in Latin America than in those living in Europe or the USA.[14] This appears to be due to the fact that physical demands are higher in individuals living in developing countries, with lower socioeconomic status. It appears that such an association also applies to respiratory diseases such as COPD and IPF. However, the difference between the values found by Mancuso et al.[10] and those found by other authors might be due to the study design and the analyses performed in the study. Because it is impossible to compare the study conducted by Mancuso et al.[10] with all previous studies, I will compare it with the study involving the highest number of patients and based on data from the study by du Bois et al.[7]

In the study by Mancuso et al.,[10] patients presenting with an SpO_2 of < 89% were excluded, whereas, in the

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study by du Bois et al.,[7] 11.5% of the participants were receiving oxygen therapy. The difference in findings between the two studies might be explained, at least in part, by the fact that the latter study included patients who were more severely ill, including patients with severe pulmonary hypertension. Although this is a reasonable explanation, it should be noted that the mean 6MWD is very similar between the two studies. In fact, the mean 6MWD was higher in the study by du Bois et al. than in the study by Mancuso et al. (397 ± 107 m vs. 380 ± 115 m).[7,10]

The difference in findings between the two studies might also be due to different follow-up periods. In the study by du Bois et al.,[7] patients were followed for 48 weeks, whereas, in the study by Mancuso et al.,[10] the median follow-up period was 37.6 months (range, 5-129 months). Therefore, it is possible that the results were affected by the fact that follow-up was limited to the duration of the trial and therefore prevented a more detailed characterization of patients in whom the disease behaved in a more benign manner.

Differences between the two studies regarding the statistical methods used and how the results were reported should also be taken into account. According to du Bois et al.,[7] a 6MWD of < 250 m is associated with double the risk of mortality after 48 weeks of follow-up. According to Mancuso et al.,[10] a 6MWD of < 330 m is associated with a survival of 24 months, whereas a longer 6MWD is associated with a median survival of 59 months.

The study by Mancuso et al.[10] reinforces the prognostic importance of the 6MWT in patients with IPF. However, the 6MWD should be evaluated in conjunction with other clinical and physiological data, such as dyspnea intensity, FVC, and DLCO.

Pulmonologists in Brazil should be alert to the possibility of encountering IPF patients with absolute 6MWD values indicating a poor prognosis, these values being higher than those recommended in the international literature. If we analyze the 6MWD in isolation and use as an indicator of poor prognosis any of the absolute 6MWD values recommended in the international literature, we run the risk of underestimating the severity of lung disease.

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