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Usefulness of a new parameter in functional assessment in patients with idiopathic pulmonary fibrosis: desaturation - distance ratio from the six-minute walk test

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Abstract. *Background and aim:* New parameters in the 6-minute walk test (6MWT) are needed for assessing exercise capacity in patients with idiopathic pulmonary fibrosis (IPF). To our knowledge, no previous study has investigated the potential of using the desaturation distance ratio (DDR) to assess exercise capacity specifically in patients with IPF. This study aimed to investigate whether DDR is a potential tool for assessing the exercise capacity of patients with IPF. *Methods:* This study conducted with 33 subjects with IPF. Pulmonary function tests and a 6MWT were performed. To calculate the DDR, first, the difference between the patient's SpO_2 at each minute and the SpO_2 of 100% was summed together to determine the desaturation area (DA). Next, DDR was calculated using dividing DA by the 6-minute walk test distance (6MWD) (i.e., DA/6MWD). *Results:* When correlations of 6MWD and DDR with changes in the severity of perceived dyspnea were examined, 6MWD did not significantly correlate with ΔBorg. Conversely, there was a significant correlation between the DDR and ΔBorg (r= 0.488, p=0.004). There were significant correlations between 6MWD and FVC % (r=0.370, p=0.034), and FEV_1 % (r=0.465, p=0.006). However, DDR was significantly more correlated with FVC % (r= -0.621, p< 0.001), FEV_1 % (r= -0.648, p< 0.001). Moreover, there was a significant correlation between DDR and DL_{CO} % (r= -0.342, p=0.052). *Conclusions*: The findings of this study suggest that DDR is a promising and more useful parameter for assessing patients with IPF.

Key words: Idiopathic pulmonary fibrosis, Six-minute walk, Exercise, Desaturation, Desaturation distance ratio

Introduction

Idiopathic pulmonary fibrosis (IPF) is the relentlessly progressive chronic interstitial lung disease with a variable rate of progression (1). Patients suffering from IPF experience a persistent dry cough, tiredness and shortness of breath. As the progression of IPF is highly variable, assessments of patient status are crucial for effective clinical management of the disease. As the disease progresses, exertional dyspnea occurs exercise intolerance and is related with higher mortality. Accordingly, it is important to correctly identify the factors limiting physical activity for the clinical management of patients with IPF.

The 6-minute walk test (6MWT) is a simple and efficient test used to measure exercise capacity at submaximal exercise levels and to evaluate the effects of interventions in patients with various cardiopul-

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monary diseases, such as IPF (2-6). The original design of the 6MWT was to evaluate the comprehensive responses of the body systems engaged during exercise, such as the pulmonary and cardiovascular systems, neuromuscular units, and muscle metabolism (7). Nevertheless, the current literature debates whether the distance covered in the 6MWT is adequate and suitable for assessing the functional involvement of individual body systems during exercise (8-10).

Desaturation during 6MWT is linked to increased mortality and is associated with parameters of pulmonary function, such as forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DL_{CO}), in patients with interstitial lung diseases (11-13). In a previous study, a new index called desaturation distance ratio (DDR), which is calculated using test distance and peripheral oxygen saturation (SpO_2) during the 6MWT, was proposed in patients with interstitial lung diseases (9). The DDR was designed to provide a comprehensive assessment of the decrease in SpO_2 every 2 seconds by following the SpO_2 curve instead of considering only the change in SpO_2 between baseline and post-6MWT values. In contrast, Ijiri et al. (8), measured SpO_2 every minute, rather than every 2 seconds, during the 6MWT in a study conducted on patients with COPD. The authors believed that measuring SpO_2 every minute, rather than every 2 seconds, minimized subtle fluctuations and measurement errors in SpO_2 values and smoothed the curve of timewise changes in SpO_2 values through this modification. Ijiri et al. (8), investigated whether DDR was an estimation of exercise capacity and a potential parameter for manifold analysis of exercise capacity. They found that DDR is more informative than the 6-min walk distance for manifold analysis of exercise capacity associated with oxygen desaturation and dyspnea at the end of the test in patients with COPD.

Interstitial lung diseases are a heterogeneous group of diseases with varying progression and spread, although they show similar symptoms (14). Apart from the original study which examined DDR in patients with interstitial lung diseases, to the best of our knowledge, no previous study has investigated the potential of using the DDR to assess exercise capacity specifically in patients with IPF. The present study aimed to investigate whether DDR is a potential tool for assessing the exercise capacity of patients with IPF.

Methods and Methods

Study design and subjects

In this cross-sectional study, participants were randomly included from a list of patients with IPF who had consulted the Department of Chest Diseases of Dokuz Eylül University Hospital. The inclusion criteria were volunteering for the study, having a diagnosis of IPF according to American Thoracic Society / European Respiratory Society (ATS/ERS) guidelines, and not having previous or current COVID-19. In addition, the subjects had to be in a clinically stable condition with the same medication routine and/or no acute exacerbation in the last 3 months. The subjects who require supplemental oxygen therapy were also excluded.

Once the demographic and clinical parameters were recorded, pulmonary function tests and the 6-minute walk test (6MWT) were performed. The study was conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards and approved by the institutional ethical board of Dokuz Eylül University (*approval number: 2022/16-10, date: 27 April 2022*). All subjects gave informed consent before the study.

Pulmonary Function and 6-minute Walk Test

Pulmonary function tests were assessed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines by a single trained technician using a digital spirometer *(Sensor Medics Vmax 22 machine, SensorMedics Inc., Anaheim, CA, USA)* following a standardized method (15, 16). Pulmonary function was measured as the forced expiratory volume in 1 second (FEV_1), FVC, and DL_{CO} in percentages (%) of the predicted value. The 6MWT was performed according to ATS guidelines (7). Patients were given 6 minutes to walk as far as they could along a covered, flat, 30-meter corridor. During the test the severity of perceived dyspnea was determined using a modified Borg scale, and peripheral oxygen saturation (SpO_2) were assessed using a fingertip pulse oximeter *(Beurer PO 30 Pulse oximeter, Germany)*. SpO_2 values were recorded at rest before 6MWT, and at the end of every minute during the test.

In the present study, to minimize subtle fluctuations and measurement errors in SpO_2 values, we re-

corded SpO_2 at each minute in our study, following the method used by Ijiri et al. (8), even though SpO_2 values were recorded every two seconds throughout the 6MWT in the original version of DDR calculation (9). Higher DDR values, which indicate poorer health conditions, were seen in those who covered shorter distances while experiencing a higher total amount of desaturation. To calculate the DDR, first, the difference between the patient's SpO_2 at each minute and the SpO_2 of 100% was summed together to determine the desaturation area (DA) which was initially computed as the total area above the curve generated using SpO_2 values observed at each minute during the 6MWT (Figure 1). Next, DDR was calculated using the DA to 6-minute walk test distance (6MWD) ratio. Thus, the DDR formula was as follows; DA/6MWD.

Statistical Analysis

All data were analysed using SPSS 24.0 for Windows. The Shapiro-Wilk test was used to evaluate the distribution of data. The data were expressed as mean (SD) if it is distributed normally, and as median [interquartile range (Q1, Q3)] if it is not. Categorical variables were expressed in percentages (%). Pearson correlation coefficient or Spearman rank correlation analysis was used in accordance with the distribution to assess the relationships of 6MWD and DDR with other parameters. For all statistical analyses, $p < 0.05$ was considered as statistically significant (17). The correlation between FVC % and DDR (r= -0.46, p=0.001), obtained in the study by Pimenta et al. (9), was considered for sample size calculation. The estimated sample size was 34 subjects considering a 5% α error, 85% power, and 10% increase in the sample due to possible losses.

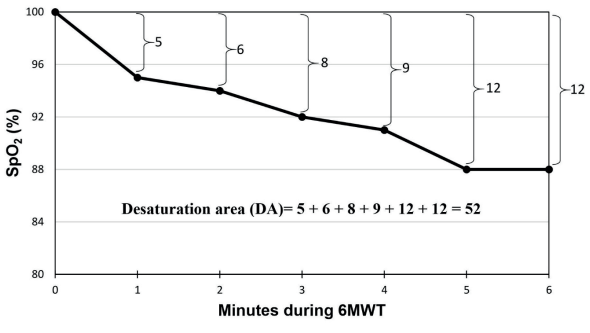

Figure 1. Desaturation area calculation sample. Notes: Desaturation area (DA) was calculated as the total area above the curve created using SpO_2 values subtracting the values at baseline from each subsequent minute during 6MWT. (i.e., summing up the differences between an SpO_2 of 100% and the patient's SpO_2 at each minute during 6MWT). Abbreviations: SpO_2, peripheral oxygen saturation; 6MWT, 6-minute walk test; DA, desaturation area; DDR, desaturation distance ratio.

Results

In total, 44 patients with IPF were invited to participate in the study. 4 did not agree to participate, 6 did not meet the inclusion criteria, 1 not completed all assessments. Therefore, 33 subjects (66.7% male) were included in the study. Figure 2 shows the flow chart of the study.

The descriptive characteristics of patients are presented in Table 1. The mean age and BMI of the patients were 68.6 ± 6.5 y and 26.1 ± 4.4, respectively. No patients received home oxygen therapy or had a baseline SpO2 below 90%.

Table 2 shows the parameters collected in the 6MWT. The mean 6MWD was 418.4 ± 75.2 m. The decrease in SpO2 values mean was -9.9% ± 2.9 and the increase in dyspnea sensation based on modified Borg was 6 (4 to 7.5).

When correlations of 6MWD and DDR with changes in the severity of perceived dyspnea were examined, 6MWD did not significantly correlate

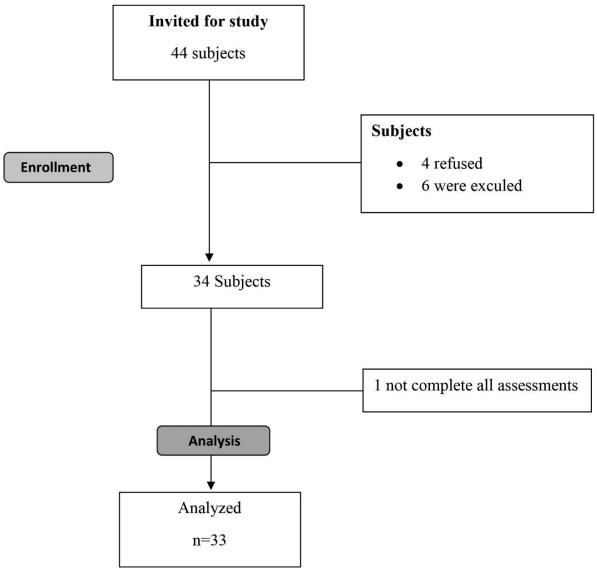

Figure 2. Flow chart of the study

Table 1. Descriptive characteristics of patients

Parameters	n (%), Mean (SD) or Median (Q1 – Q3)
Gender, % (male/female)	66.7 / 33.3
Age, years	68.6 (6.5)
BMI, kg/m^2	26.1 (4.4)
Smoking status, n (%)	
Current smokers	2 (6.1)
Ex-smokers	21 (63.6)
Non-smokers	10 (30.3)
FVC, % predicted	80.7 (16.8)
FEV_1 ,% predicted	85.4 (17.9)
DL_{CO}, % predicted	55.0 (38.0, 68.0)
SpO_2 at rest, %	97.0 (95.0, 98.0)

Data are presented as n (%) or mean (standart deviation) or median (interquartile range).
Abbreviations: BMI, Body mass index; FVC , forced vital capacity; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity of the lung for carbon monoxide; SpO_2 peripheral oxygen saturation.

Table 2. Six-minute walk test parameters of subjects

Parameters	Mean (SD) or Median (Q1 – Q3)
6MWD (m)	418.4 (75.2)
ΔSpO_2 (%)	-9.9 (2.9)
ΔBorg Dyspnea	6.0 (4.0, 7.5)
DDR	0.20 (0.07)

Data are presented as mean (standart deviation) or median (interquartile range).
Abbreviations: 6MWD, 6-minute walk distance; ΔSpO_2 change in peripheral oxygen saturations; ΔBorg, change in modified Borg scale scores; DDR, desaturation distance ratio.

with ΔBorg. Conversely, there was a significant correlation between the DDR and ΔBorg (r= 0.488, p=0.004) (Figure 3).

As for the correlations of 6MWD and DDR to the baseline pulmonary function parameters, there were significant correlations between 6MWD and FVC % (r= 0.370, p= 0.034), and FEV1 % (r= 0.465, p= 0.006). However, DDR was significantly more correlated with FVC % (r= -0.621, p< 0.001), FEV1 % (r= -0.648, p< 0.001). In addition, there was a significant correlation between DDR and DLCO % (r= -0.342, p= 0.052) (Figure 4).

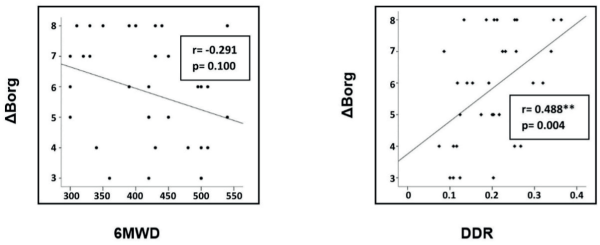

Figure 3. Correlations of 6MWD and DDR with ΔBorg dyspnea. Notes: **Spearman correlations. ΔBorg dyspnea during the 6-minute walk test was calculated by subtracting the values at baseline from those immediately after the test. Borg refers to the modified Borg scale scores of subjective sense of dyspnea. Abbreviations: ΔBorg, change in modified Borg scale scores; 6MWD, 6-minute walk distance; DDR, desaturation distance ratio.

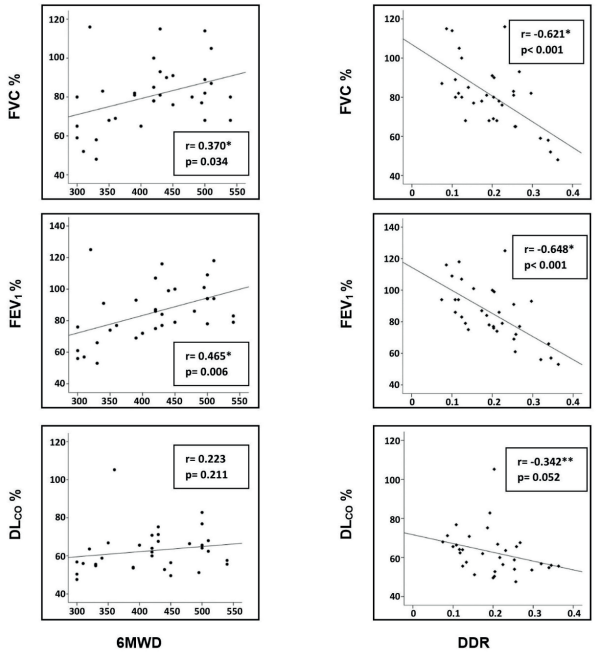

Figure 4. Correlations of 6MWD and DDR with baseline pulmonary function parameters. Notes: *Pearson correlations, **Spearman correlations. Abbreviations: 6MWD, 6-minute walk distance; DDR, desaturation distance ratio; FVC , forced vital capacity; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

Discussion

The main finding of the present study is that DDR obtained during the 6MWT is a more reliable tool linked to respiratory impairment severity and reduced pulmonary function parameters in patients with IPF than the 6MWD.

IPF has a high mortality rate and may be accompanied by a progressive reduction in exercise tolerance. Few regularly obtained measurable indicators, particularly pulmonary function parameters, can reliably predict mortality or reflect the functional limitations caused on by the disease. However, it has been demonstrated that assessments of this functional restriction (reduced exercise capacity) are important for the clinical management of patients with IPF (1, 2, 4).

The 6MWT has been demonstrated to be an effective test in assessing patients with IPF and represents a standardized, simple to apply, reproducible means to determine functional capacity. Desaturation during the 6MWT and walking distance both have a relationship with mortality (11, 18, 19). However, it is unclear which gives more reliable prognostic information: distance or SpO_2. It has been demonstrated that in patients with IPF, the distance walked during the 6MWT is less variability than the SpO_2 (18). Contrary, Lama et al. (11) demonstrated that desaturation during 6MWT better reflect mortality profile and more predictive of outcomes than 6MWD in patients with IPF.

Accordingly, Lettieri et al. (10) combined these two parameters for the first time and defined them as a new index, the distance-desaturation product (DSP), which integrates both the 6MWD and lowest SpO_2. They found that DSP is a good tool for predicting survival in IPF. Although this tool includes desaturation and 6MWD, it is limited to considering the lowest SpO_2 which does not reflect the entire oxygen saturation during the 6MWT. Flaherty et al. (13), calculated for the first time the desaturation area (DA) at the end of each minute during the 6MWT but did not take this into account along with the distance covered. They proved that even slight desaturation defined by increased DA during 6MWT increases the risk of subsequent mortality in IPF. In the light of these findings, Pimenta et al. (9) developed a new index presented as DDR. They recorded SpO_2 every 2 seconds and calculated the desaturation area accordingly. Differently, a group of researchers first recorded SpO_2 every minute, and calculated DA just like Flaherty et al. did, then use the formula of DA/6MWD ratio (8, 13). They thought that making such a modification minimized the subtle fluctuations in SpO_2 values and measurement errors. Moreover, they considered that in clinical settings, measuring SpO_2 per minute would be easier than every 2 seconds. Therefore, we used the method of DDR based on the study of Ijiri et al.(8)

To the best of our knowledge, this is the first study to explore the roles of DDR in assessing exercise capacity in a population consisting purely of patients with IPF, even though it was previously used in a study conducted by Pimenta et al. (9) on a heterogeneous group of patients with various interstitial lung diseases. They showed that there were higher correlations between DDR and DL_{CO} %, FVC %, and FEV_1 % than 6MWD. Even there was no significant correlation between 6MWD and FEV_1 % in their study. Similarly, Ijiri et al. (8) examined the role of DDR in COPD patients and found higher correlations between DDR and FEV_1% compared to 6MWD. In contrast, DL_{CO}% was almost equally correlated with DDR and 6MWD in their study. Moreover, both ΔSpO_2 and ΔBorg were not significantly correlated with the 6MWD in the mentioned study. Conversely, significant correlations were found between the DDR with both ΔSpO_2 and ΔBorg by Ijiri et al. (8) In another study, Fujimoto et al. (20) used two ways of calculating DA: the method used by Pimenta et al. as DDR-original, which records SpO_2 every 2 seconds and the method used by Ijiri et al. as DDR-simple, which records SpO_2 per minute (8, 9). Fujimoto et al. (20), examined the usefulness of the DDR in patients with COPD. Surprisingly, they showed that the correlations between DDR and FEV_1% and DL_{CO}% were almost the same in both calculation methods. Moreover, they show higher correlations with DDR compared to 6MWD. In our study we found that DDR higher correlated with FVC%, and FEV_1% compared to 6MWD. Moreover, although DL_{CO}% showed a significant correlation with DDR, it did not show a significant correlation with 6MWD. We consider that since the above studies using DDR were conducted in different or heterogeneous patient groups, the presence of varied but similar findings. In this regard, our study is noteworthy in that it focused only on patients with IPF in terms of the usefulness of the DDR tool.

Desaturation of oxygen during the 6MWT is related to a poorer prognosis and higher mortal-

ity, and it correlates well with pulmonary function parameters such as DL_{CO}, and FVC in interstitial lung disease patients (11-13, 21). A previous study showed that mortality in individuals with idiopathic pulmonary fibrosis was related to the desaturation area, which is expressed as the total area above the curve generated using SpO_2 values observed at each minute during the 6MWT (13). However, to the best of our knowledge, no previous study has investigated the relationship of DDR to oxygen desaturation and perception of dyspnea during the 6MWT specifically in patients with IPF. This study is therefore unique in its focus on the relationship between these variables in this specific patient population. In our study, we found a significant association between DDR and the reduction in dyspnea during 6MWT in patients with IPF. However, the reduction in dyspnea during 6MWT was not significantly associated with 6MWD. This finding is consistent with the findings of previous studies in patients with COPD (8, 22).

Our study has several limitations. First, a small sample size possibly results in a lack of sufficient statistical power. To support our findings, large population studies including more current smokers should be conducted. Second, we excluded patients who needed supplemental oxygen. Given that advanced patients with IPF frequently require supplemental oxygen, this exclusion may appear to limit the generalizability of our findings to the IPF population. However, in this way, we have obtained a more homogeneous population. Moreover, patients who use supplementary oxygen were not included in earlier 6MWT studies (10, 11). To determine whether the trend of SpO_2 values with oxygen supplementation during the 6MWT in these patients is similar to that in patients who do not need it, further studies should be conducted on the current method in patients with IPF who need oxygen supplementation. Lastly, the exertion of the patient may have an impact on the 6MWT, which could change the overall distance walked and the accompanying desaturation. This is a limitation of all exercise tests, not just the 6MWT specific to DDR.

Conclusions

In conclusion, the DDR and 6MWD obtained during the 6MWT correlated to baseline pulmonary function parameters. Moreover, DDR provides more valuable insight into the exercise capacity of patients with IPF, linked to the perception of dyspnea, than the 6MWD. Therefore, the findings of this study suggest that DDR is a promising and more useful parameter for assessing patients with IPF. Further studies should investigate the relationship of DDR with physical activity and mortality as well as provide information about responses to interventional studies.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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