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Original Article

Peak Oxygen Uptake During the Six-minute Walk Test in Diffuse Interstitial Lung Disease and Pulmonary Hypertension

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ABSTRACT

Introduction: The six-minute walk test (6MWT) is widely used in evaluating diffuse interstitial lung disease (ILD) and pulmonary hypertension (PH). However, their physiological determining factors have not been well defined.
Objective: To evaluate the physiological changes that occur in ILD and PH during the 6MWT, and compare them with the cardiopulmonary exercise test (CPET).
Material and Methods: Thirteen patients with ILD and 14 with PH were studied using the 6MWT and CPET on an ergometer cycle. The respiratory variables were recorded by means of telemetry during the 6MWT.
Results: Oxygen consumption (VO_2), respiratory and heart rate reached a plateau from minute 3 of the 6MWT in both diseases. The VO_2 did not differ from the peak value in the CPET (14 ± 2 and 15 ± 2ml/kg/min, respectively, in ILD; 16 ± 6 and 16 ± 6ml/kg/min, in PH). The arterial oxygen saturation decreased in both diseases, although it was more marked in ILD (−12 ± 5%, *P*<.01). The ventilatory equivalent for CO_2 (V_E/VCO_2) in PH during the 6MWT was strongly associated with functional class (FC) (85 ± 14 in FC III-IV, 44 ± 6 in FC I-II; *P*<.001).
Conclusions: The 6MWT in ILD and PH behaves like a maximal effort test, with similar VO_2 to the CPET, demonstrating a limit in oxygen transport capacity. Monitoring using telemetry during the 6MWT may be useful for the clinical evaluation of patients with ILD or PH.

Consumo máximo de oxígeno durante la prueba de marcha de 6 minutos en la enfermedad pulmonar intersticial difusa y en la hipertensión pulmonar

Palabras clave:
Ejercicio cardiopulmonar
Fibrosis pulmonar idiopática
Consumo de oxígeno
Hipertensión pulmonar
Prueba de marcha de seis minutos

RESUMEN

Introducción: La prueba de marcha de 6 minutos (PM6M) es ampliamente utilizada en la evaluación de la enfermedad pulmonar intersticial difusa (EPID) y en la hipertensión pulmonar (HP). Sin embargo, sus determinantes fisiológicos no han sido bien caracterizados.
Objetivo: Evaluar los cambios fisiológicos que ocurren durante la PM6M en la EPID y en la HP y compararlos con la prueba de esfuerzo cardiopulmonar (PECP).
Material y métodos: Se estudiaron 13 pacientes con EPID y 14 con HP mediante PM6M y PECP en cicloergómetro. Durante la PM6M se registraron las variables respiratorias mediante telemetría.
Resultados: El consumo de oxígeno (VO_2), la ventilación y la frecuencia cardiaca mostraron una meseta desde el minuto 3 de la PM6M en ambas patologías. El valor de VO_2 no difirió del valor pico en la PECP (14 ± 2 y 15 ± 2 ml/kg/min, respectivamente, en la EPID; 16 ± 6 y 16 ± 6 ml/kg/min, en la HP). En ambas

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patologías, disminuyó la saturación arterial de oxígeno, aunque más marcadamente en la EPID (−12 ± 5%, p < 0,01). En la HP, el equivalente ventilatorio de CO_2 (V_E/VCO_2) durante la PM6M estaba fuertemente relacionado con la clase funcional (CF) (85 ± 14 en CF III-IV, 44 ± 6 en CF I-II; p < 0,001).
Conclusiones: En la EPID y en la HP la PM6M se comporta como una prueba de esfuerzo máxima, con valores de VO_2 similares a la PECP, poniendo de manifiesto limitación de la capacidad de transporte de oxígeno. La monitorización mediante telemetría durante la PM6M puede ser útil para la evaluación clínica de los pacientes con EPID o con HP.

Introduction

The assessment of aerobic capacity provides significant information for the diagnosis and prognosis of many respiratory diseases.[1,2] In consequence, simple exercise protocols, such as the Six-Minute Walk Test (6MWT), are being used more frequently in a clinical environment to monitor the progression of disease and evaluate the effects of therapy.[3,4] However, the routine application of the 6MWT does not provide information on the physiological variables that explain functional limitations of effort. Continual technological advances increase the reliability of telemetric measurements of O_2 consumption (VO_2) and CO_2 production (VCO_2), which can substantially increase the potential of the 6MWT for evaluating patients with chronic cardiopulmonary disorders. In patients with Diffuse Interstitial Lung Disease (DILD), the 6MWT has recently been demonstrated to be a predictive factor of mortality with a great influence on the decision making process for lung transplant.[5,6] In consequence, it is markedly advisable to include the 6MWT in the follow-up of these patients.[7] In pulmonary hypertension (PH) the 6MWT is used systematically as the main variable in most clinical trials assessing new treatments.[8-10] However, evaluation of stress by means of the 6MWT with the additional measurement of physiological variables such as VO_2, ventilation (V_E), VCO_2, etc. can improve the understanding of responses to the exercise-test in patients with PH.[11,12]

The mechanisms responsible for the limitations of tolerance to exercise in DILD[13-15] and in PH[4] have been described and correlated with the evolution and prognosis of said diseases. Recently, Deboeck et al[16] have published the fact that there is a plateau in the oxygen consumption curve during the 6MWT in patients with PH that is similar to what has been seen in patients with COPD,[17,18] with values close to those seen in the Cardiopulmonary Incremental Exercise Test (CPET). Up to date there is no information available on the behaviour of stress variables during the 6MWT in patients with DILD. Possibly, as in the case of PH,[16] in DILD, the 6MWT can cause a consumption of oxygen near to maximum oxygen consumption limited by symptoms.

This study has the aim of describing physiological responses during the 6MWT in patients with lung parenchyma disease or lung vascular disease. In this study we have compared the results obtained during the 6MWT with those obtained during CPET on the bicycle ergometer. In view of the results of previous studies,[16] we consider that differently to what happens in healthy patients or those with COPD, in patients with DILD, the 6MWT may cause a metabolic demand that is greater than the patient's oxygen transport capacity.

The clinical value of this study is that it increases our knowledge of the responses to the 6MWT of patients suffering from these 2 conditions enabling us to obtain a better understanding of the limiting factors of exercise in pathological conditions of lung parenchyma or vessels.

Patients and Methods

Subjects

A total of 27 patients were included in this study, 13 of them (10 men/3 women) diagnosed with DILD and the remaining 14 (8 men/6 women) diagnosed with PH by means of lung haemodynamic studies. The characteristics of both groups are described in Table 1.

Diagnosis of DILD was established in accordance with the American Thoracic Society (ATS) and the European Respiratory Society (ERS) consensus document.[19] In 12 cases the diagnosis was idiopathic pulmonary fibrosis (IPF) and the remaining case was a sarcoidosis with pulmonary infiltrates. Ten patients had a histological diagnosis of Usual Interstitial Pneumonia (UIP). In all patients with DILD, an ultrasound was performed at the time of diagnosis, which ruled out the existence of PH and other signs of right ventricle dysfunction such as right chamber dilatation and/or paradoxical movement of the interventricular septum.

Pulmonary hypertension (PH) was defined as the mean pulmonary arterial pressure ≥ 25mmHg at rest and a pulmonary occlusion pressure of 15mmHg. The underlying diagnoses in patients with PH were: idiopathic pulmonary arterial hypertension (n=5), associated with HIV (n=4), aorto-pulmonary hypertension (n=3) and chronic thromboembolic pulmonary disease (n=2).

Characterization of patients for the study included: 1. Clinical history and physical exam; 2. Pulmonary function tests and; 3. Diagnostic measurements carried out to support the diagnosis. Patients with continuous home portable oxygen therapy 24 hours a day were excluded from the study. The Ethics Committee of the Hospital Clínic of the University of Barcelona approved the study and the patients signed the respective informed consents.

Study Design

The subjects carried out two exercise protocols on the same day, a CPET and a 6MWT, with a minimum time between both tests of 1

Table 1
Anthropometric and Functional Characteristics of the Population

	DILD Mean ± SD	PH Mean ± SD
Gender, M/F	10/3	8/6
Age, years	63 ± 9	42 ± 15
BMI, kg/m^2	27 ± 4	22 ± 3
FVC, l	2.86 ± 0.71	3.78 ± 0.82
FVC, % ref.	73 ± 22	92 ± 15
FEV_1/FVC, %	84 ± 6	79 ± 8
TLC, % ref.	70 ± 18	98 ± 15
DLCO, % ref.	47 ± 18	61 ± 14
PaO_2, mmHg	83 ± 15	92 ± 13
$PaCO_2$, mmHg	39 ± 3	33 ± 4
$AaPO_2$, mmHg	20 ± 10	23 ± 14
PAP, mmHg		49 ± 11
CI, Lmin^{-1}m^2		2.38 ± 0.72
PVR, dinscm^{-5}		999 ± 345

$AaPO_2$: alveolo-arterial oxygen gradient at rest; DLCO: diffusion *lung* capacity for carbon monoxide; DILD: diffuse interstitial lung disease; FEV_1: forced expiratory volume in one second, FEV_1/FVC: forced expiratory volume in one second and forced vital capacity expressed as an absolute percentage; FVC: forced vital capacity; PH: pulmonary hypertension; CI: cardiac index; BMI: body mass index; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; TLC: Total lung capacity.
Data are presented as mean ± SD (standard deviation).

hour to ensure a return to basal conditions before beginning the second exercise protocol. The order in which both exercise protocols (CPET and 6MWT) were performed was random.

Pulmonary Function at Rest. All patients underwent forced spirometry, pulmonary volume by plethysmography and Lung Diffusion Capacity for Carbon Monoxide (LDCO) determinations (Jaeger, MasterScreen; Wüerzburg, Germany).[20,21] In all of these we analysed a sample of arterial blood, partial oxygen pressure (PaO_2), carbon dioxide pressure ($PaCO_2$), and blood pH and lactate (Ciba Corning 800, USA)

Ultrasound. Patients diagnosed with DILD underwent a screening test by means of a Doppler colour flow transthoracic ultrasound (ACUSON, Sequoia C256, Siemens, CA, USA) to exclude PH. All patients with PH had an ultrasound that indicated suspicion of PH with a systolic arterial pulmonary pressure above 40mmHg.

Pulmonary haemodynamics. Right heart catheterisation was performed only on patients with suspected PH prior to their inclusion in the study. Haemodynamic measurements were only carried out at rest.[22]

6MWT. The 6MWT[23] was performed with a simultaneous register of heart rate (HR), V_E, VO_2, VCO_2, Respiratory Exchange Ratio (RER), ratio between minute ventilation and VCO_2 (V_E/VCO_2) and ratio between minute ventilation and oxygen consumption (V_E/VO_2), using a portable telemetric system (K4b[2]; Cosmed; Pavona di Albano, Italy). The value of physiological variables during the 6MWT is that of the average during the last 30 seconds of each minute. Samples of arterial blood were taken at rest after the end of the test using an arterial catheter to analyse respiratory gases (PaO_2 and $PaCO_2$) and lactic acid. Oxygen saturation was also measured by pulse oxymetry (SpO_2) during both exercise protocols (PulsoX-31, Minolta, Japan). In the case of the 6MWT the extraction of the blood sample to measure gases was done immediately after ending the test. All patients had previously carried out a 6MWT as part of their routine follow-up.

Cardiopulmonary Exercise Test. All patients carried out an incremental exercise test on a bicycle,[24] with a *breath by breath* calculation of the variables described in the 6MWT with the portable telemetric system. An electronically controlled bicycle ergometer was used (CardiO2 cycle Medical Graphics Corporation, St. Paul, Mn, USA). The value of physiological variables during CPET corresponded to the average of 15 second intervals. Arterial blood samples at rest were taken (at the beginning), at one minute and every 3 minutes during the test to measure respiratory gases and lactate levels.

Data Analysis

The results in this text are expressed as mean ± standard deviation (SD). The comparisons between exercise protocols (6MWT and CPET) were made using a paired t Student test. Furthermore, peak VO_2 during the CPET and also during the last 3 minutes of the 6MWT was compared by means of a Bland & Altman analysis. Statistical significance was fixed for values of $P<.05$ in all cases.

Results

Characteristics at Rest

The anthropometric and functional characteristics of patients with DILD and PH can be seen separately in Table 1. At rest, the patients with PH presented severe PH, with a low cardiac index and an increase of pulmonary vascular resistance, of severe intensity (Table 1). Ten of the 14 patients with PH were in functional class (FC) I:II of the World Health Organisation-New York Heart Association (WHO-NYHA) scale[25] and the remaining 4 were in FC III-IV. The two groups of patients diagnosed with DILD and PH presented a similar reduction of their aerobic capacity, as can be seen in Table 2. With CPET, the maximum load achieved was 44% (in men) and 56% (in women) of the values of reference[26] in patients with DILD, and 46% and 59%, respectively, in patients with PH. In the 6MWT the final distance walked was 62% and 67% of the reference values[27] for men and women, respectively, in patients with DILD, and 64% and 68% in those with PH.

Diffuse Interstitial Lung Disease

The respective curves of VO_2, V_E and heart rate flattened to a plateau in relation to time during the last 3 minutes of the 6MWT (Figure 1, left panels). SpO_2 decreased significantly during the walk, from a mean value at rest of 95 ± 2% up to 84 ± 10%, at the end of the test (ΔSpO_2 −12 ± 5%) ($P<.01$). The value of the PaO_2 during the 6MWT fell up to 64 ± 19mmHg ($P=.001$), without changes in the $PaCO_2$ in comparison with the value at rest. During exercise, the V_E/VCO_2 ratio showed a tendency to decrease during the 6MWT. 2). However, the values achieved at the end of the test (43 ± 11) were significantly higher than the reference values for this variable at the anaerobic threshold (29 ± 4) ($P<.05$).[28-30] The VO_2 achieved during the last 3 minutes of the 6MWT (14 ± 2ml/kg/min) was near to the maximum VO_2 value on the bicycle ergometer (15 ± 2ml/kg/min) (Table 2). The lactic acid threshold during the CPET was identified at 34 ± 9% of the predicted VO_2 maximum. As was only to be expected, the V_E, the RER and the levels of arterial lactate were clearly lower during the 6MWT than those achieved

Table 2
Physiological responses during the 6 minute walk test and the cardiopulmonary effort test in diffuse interstitial lung disease and in pulmonary hypertension

	DILD Mean ± SD	PH Mean ± SD
Charge, watts		
CPET	63 ± 15	78 ± 24
Distance, m		
6MWT	451 ± 80	542 ± 100
VO_2, ml/kg/min		
6MWT	14 ± 2	16 ± 6
CEPT	15 ± 2	16 ± 2
RER		
6MWT	0.94 ± 0.11	1.00 ± 0.12
CPET	1.02 ± 0.07[a]	1.17 ± 0.08[a]
V_E, l/min		
6MWT	46.4 ± 15.1	52.2 ± 15.2
CEPT	53.8 ± 14.6[a]	68.8 ± 21.2[a]
HR, beats/min		
6MWT	112 ± 19	142 ± 24
CEPT	125 ± 20[a]	146 ± 23
Pulse O_2, ml		
6MWT	9.5 ± 1.3	6.8 ± 1.9
CEPT	9.6 ± 1.6	7.2 ± 1.5
[La]art, mol/l		
6MWT	2.82 ± 1.46	4.56 ± 2.43
CEPT	4.73 ± 1.38[a]	7.14 ± 2.29[a]

DILD: Diffuse Interstitial Lung Disease; HR: heart rate; PH: Pulmonary hypertension; [La]art: lactate in arterial blood; CEPT: Cardiopulmonary exercise test; 6MWT: 6 minute-walk test; O_2 pulse: oxygen pulse; RER: respiratory rate; V_E: ventilation per minute; VO_2: oxygen consumption.
Data are presented as mean ± SD (standard deviation). The values registered during the 6MWT correspond to average values during the last 30 seconds of the test. In the CPET the values shown correspond to maximum exercise.
[a] $P<.05$ compared with the 6MWT.

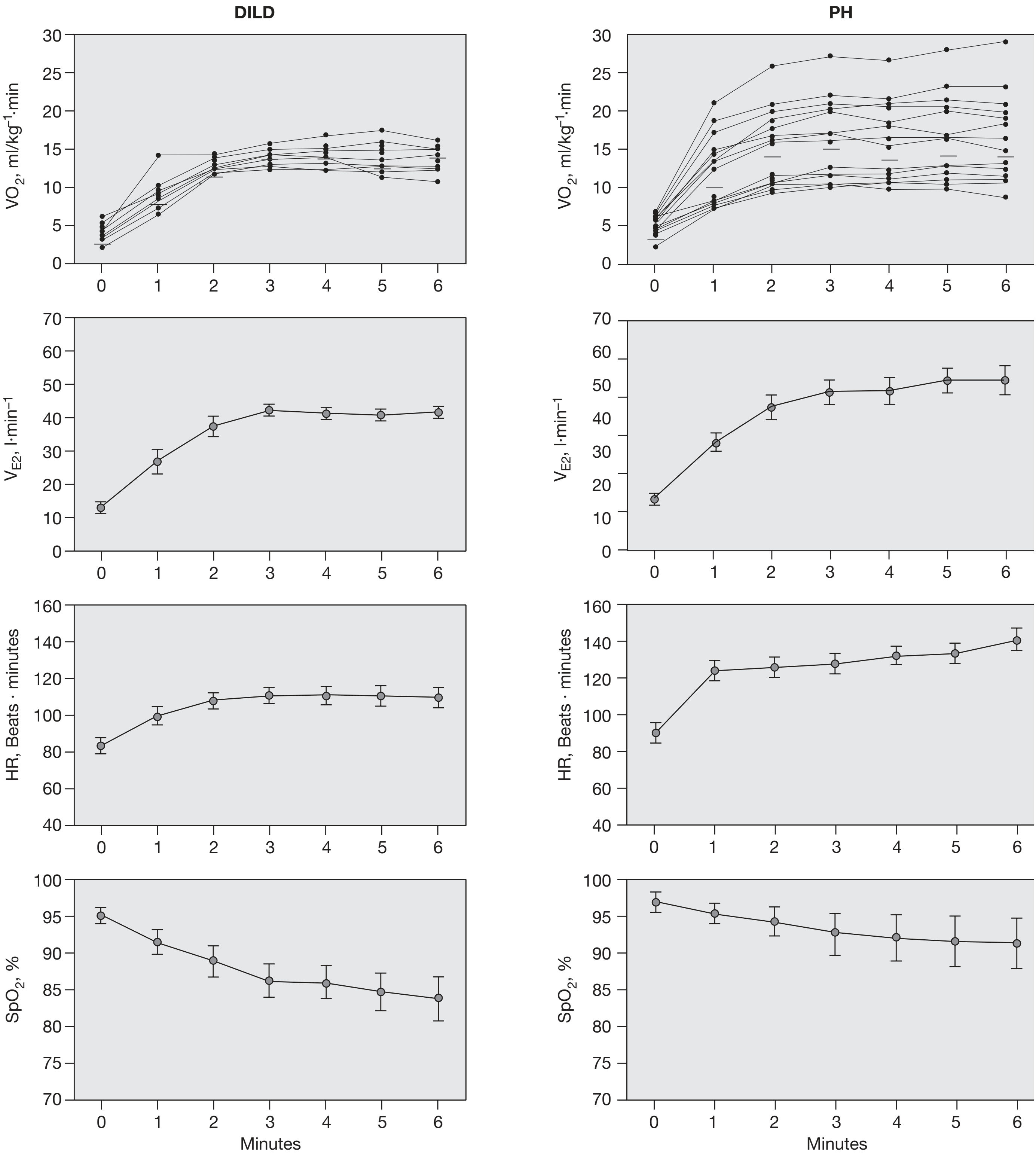

Figure 1. Cardiopulmonary response during the 6-minute walk test (6MWT) in diffuse interstitial lung disease (DILD), left panels, and in pulmonary hypertension (PH), right panels. The results are expressed as mean ± standard deviation for all variables. In the case of values of oxygen consumption (VO_2) individual responses are shown.

during the CPET (*P*<.05). Although there were no differences between the 6MWT and the CPET in initial SpO_2, this variable was significantly lower at the end of the 6MWT (84 ± 10% versus 88 ± 8%) (*P*<.005). In the CPET, the inability of the lung to carry out gas exchange was made apparent by the significant increase in the increased alveolo-arterial oxygen gradient ($AaPO_2$), that reached a maximum difference at the end of exercise ($\Delta AaPO_2$ 23 ± 11mmHg) (*P*<.001).

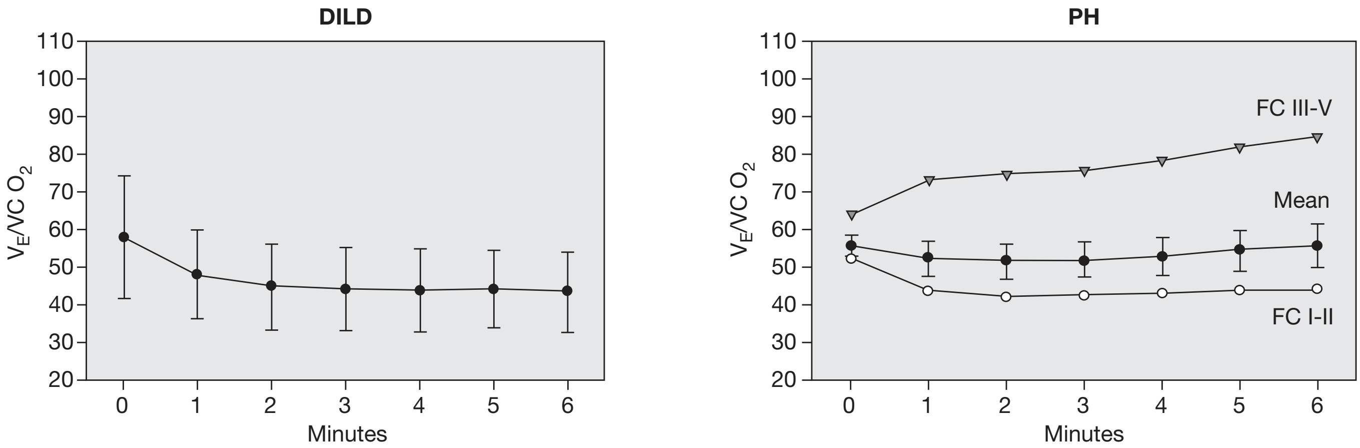

Figure 2. Ventilation equivalent of CO_2 in diffuse interstitial lung disease (DILD), left panel, and in pulmonary hypertension (PH), right panel. The results are expressed as mean ± standard deviation. In PH, the results are also expressed grouped according to FC (FC: I-II and III-IV).

Pulmonary Hypertension

The VO_2 and V_E curves in relation to time also reached a plateau during the 6MWT in patients with PH, but heart rate did not (Figure 1, right panels). No differences were seen in VO_2 between the 6MWT (16 ± 6ml/kg/min) and the CEPT (16 ± 6ml/kg/min). The lactic acid threshold during the CEPT was identified at 34 ± 13% of the maximum predicted VO_2. PaO_2 during the 6MWT fell moderately until it reached 80 ± 20mmHg (P<.05) with a significant descent of the $PaCO_2$ up to 31 ± 5mmHg (P<.05), in relation to the situation at rest. The respiratory rate and lactate levels in blood during the 6MWT were also significantly lower than in the CPET (P<.01). These patients also had a significant increase of $AaPO_2$ during the CPET ($\Delta AaPO_2$ 14 ± 15mmHg) (P<.05). The decrease of SpO_2 during exercise was less during the CPET (from 98 ± 1% up to 95 ± 3%, ΔSpO_2 −3 ± 3%) than during the 6MWT (ΔSpO_2 −5 ± 3%) (P<.05).

As can be seen in Figure 2 (right panel), the values of the V_E/VCO_2 ratio in patients with PH were markedly higher than the reference values for the anaerobic threshold during CPET.[28-30] The increase of the V_E/VCO_2 ratio was greater in patients with FC III-IV (85 ± 14), than in those with FC I-II (44 ± 6) (P<.01). Furthermore, the V_E/VCO_2 ratio had a significant negative correlation with the cardiac index (r = −0.65) (P<.05).

Comparisons Between DILD and PH in Stress Tests

Individual responses of VO_2 during the 6MWT were more heterogeneous in PH than in the group of patients with DILD (Figure 1). V_E was lower in DILD (44 ± 13L/min) than in patients with PH (52 ± 15L/min). Heart rate also achieved higher values in patients with PH in comparison with patients with DILD. In spite of the fact that arterial oxygenation at rest was similar in both groups of patients with DILD and PH, the fall of SpO_2 at the end of the 6MWT was significantly less in patients with PH (ΔSpO_2 −5 ± 3%, P<.001) than in the DILD group (ΔSpO_2 −12 ± 5%).

Discussion

This study demonstrates that the 6MWT generated maximum aerobic capacity in both groups of patients, with DILD and with PH. This statement is based on two main observations, first, there is a clear limitation of the oxygen transport capacity induced by exercise assessed by desaturation of arterial oxyhaemoglobin (Figure 1). Second, and not less important, VO_2 values at the end of the two exercise protocols were similar (Table 2), in spite of the fact that the workloads generated by the 2 exercise protocols were undoubtedly different.[1] The limitation of oxygen transport capacity observed in both diseases (DILD and PH) indicates that pulmonary factors and non-pulmonary factors that determine arterial blood oxygenation are incapable of covering the oxygen demand of muscle during exercise.

The VO_2 responses described in this study are a new contribution to information on patients with DILD, whereas the information obtained in patients with PH is consistent with the information published by Deboeck et al.[16] The results in DILD and PH in our groups of subjects show a significant difference in relation to the results seen in patients with COPD[18] in whom the 6MWT is consistently a high intensity submaximal exercise. Similarly, an acceptable association was seen between maximum VO_2 and VO_2 at the end of the 6MWT, assessed by means of a Bland & Altman analysis.

In both diseases studied, the differences in physiological response between the two exercise protocols (Table 2) were similar to those published in the medical literature for other diseases.[29] The internal consistencies of our observations are a significant contribution which indicate the need to reassess the clinical use of the 6MWT in the two diseases studied. It seems reasonable to suppose that physiological measurements during the 6MWT of the type carried out in this study can improve the decision making process both in DILD and in PH.

Patients with Diffuse Interstitial Lung Disease

In patients with DILD the alterations which take place at gas exchange level during exercise constitute a prognostic factor to be taken into account when monitoring disease progression and to regulate treatment.[5,6,15,31] This study indicates that the 6MWT systematically showed a greater sign of lack of efficacy in gas exchange than the cardiopulmonary incremental test. Both the increase of $AaPO_2$ induced by exercise as the fall of SpO_2 were more pronounced during the 6MWT than during the CPET, which could be partly explained by the fact that during the 6MWT more muscle mass is exercised. It is known that exercise limitation in patients with DILD is explained by alteration of arterial blood oxygenation.[14] The main pulmonary mechanisms that cause arterial hypoxia in patients with DILD are the imbalance between the ventilation-perfusion ratio (V_A/Q) and the limitation of oxygen diffusion from the alveoli to the capillaries.[13] During exercise the imbalance between this V_A/Q ratio persists, oxygen diffusion worsens and partial oxygen pressure in mixed venous blood decreases. All these factors together explain the exercise induced fall of PaO_2, observed in patients with DILD that, as has been mentioned before, constitutes a marker for a poor prognosis in this disease.

Patients with Pulmonary Hypertension

The response to exercise of patients with PH indicates a cardiovascular limitation due to a right ventricle post-load increase that plays an important role modulating exercise tolerance in patients with pulmonary vascular disease. In these patients, the existence of a V_A/Q ratio imbalance also plays an important role; however, in this case, the impact on arterial blood oxygenation is increased by a lower oxygen partial pressure in mixed venous blood caused by a reduction of cardiac output, that increases during exercise with the increase in oxygen demand.[32] It must be highlighted that the V_E/VCO_2 ratio during exercise underwent greater abnormal elevation in PH than in patients with DILD. Furthermore, patients with PH presented a significant negative correlation between said ratio and the cardiac index, consistent with physiological mechanisms. Similarly, patients with more severe PH (FC III-IV) presented V_E/VCO_2 ratio values significantly higher than those with a slight to moderate (FC I-II). A recent retrospective study published by Hoeper et al[33] reveals that both the distance walked during the 6MWT, pressure in the right atria, and the existence of low $PaCO_2$, at rest and during effort, are independent predictive factors of survival in patients with PH. Our results suggest that the VE/VCO_2 ratio during the 6MWT could be a useful and non-invasive indirect measurement of cardiac output, and, in consequence, could be a practical and effective marker for clinical monitoring of these patients. More studies are necessary to confirm that clinical improvement and the increase of distance walked during the 6MWT seen with new treatments[8,34] are accompanied by an increase in VO_2 together with a fall in the V_E/VCO_2 ratio.

In spite of the fact that both diseases cause similar alterations of the lungs in relation to oxygen exchange assessed as the difference in $AaPO_2$, the decrease of arterial blood oxygenation during the 6MWT is more pronounced in DILD than in PH (Figure 1). In DILD it is justified by the fact that PaO_2 during exercise is near to the most pronounced part of the oxyhaemoglobin saturation curve, without accompanying changes in $PaCO_2$, when going from rest to exercise; however, in patients with PH, there was a marked fall in $PaCO_2$ during exercise that maintained arterial blood oxygenation in the flat part of the oxyhaemoglobin saturation curve and partially prevented a fall of exercise induced SpO_2.

Limitations of the Study

We recognise that our study presents some limitations that condition generalization of our results. Firstly, a retrospective cohort was evaluated, this could introduce limitations in the analysis of the data collected at the time the tests were performed. Secondly, we studied 2 heterogeneous relatively small groups of patients with the consequent limitations in the comparisons performed and the generalization of results. However, the main purpose of the study was the description of physiological variables in both groups of patients. In the first group (DILD), the physiological responses during the 6MWT were not described. In the second group of patients (PH) we compared a cohort of ours with the results described by Deboeck et al,[16] confirming the findings of these authors. Thirdly, carrying out both effort protocols during the same day could have influenced the second one performed. However, by design, the second exercise protocol was delayed until the patient's physiological parameters had returned to basal values. Furthermore, the order in which the 2 exercise protocols were performed was random so that the influence of this potential problem on our final results is negligible and does not alter the conclusions of our research.

Clinical Implications

Our study highlights the potential possibility of extending physiological measurements during the 6MWT to monitor patients with DILD and PH in clinical practice. The limitation of aerobic capacity during the 6MWT in both diseases is clearly the result of different physiological mechanisms. In patients with DILD, the exercise induced fall of SpO_2 seems to play a decisive role that limits behaviour whereas the increase in right ventricle post-load is a mechanism that leads to exercise limitation in patients with PH. In spite of the fact that this research was conducted on a rather small study group, the characteristics of the results firmly support the clinical relevance of the study. The clinical applicability of the 6MWT and its suitability for longitudinal control, both of disease evolution as of the effect of treatments, mean this study is of great clinical relevance.

The continuous advances of mobile technologies make it easier to carry out remote measurements of physiological variables during walking and other activities of daily living, which opens up new possibilities for patients' clinical evaluation, both with reference to innovative treatments and for follow-up. However, we are aware that the clinical impact of these observations will require subsequent prospective trials to substantiate them.

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