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Exercise related ventilation dynamics and clinical correlates in patients with fibrotic idiopathic interstitial pneumonias

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Abstract. Assessment of exercise performance is a key component in the management of interstitial lung diseases, as its limitation may occur very early. Aim of the present study was to assess ventilation dynamics in combination with pulse-oximetry changes in 54 clinically stable patients affected by idiopathic pulmonary fibrosis or idiopathic fibrotic nonspecific interstitial pneumonia. Testing was successfully performed with the *Spiropalm 6-MWT Hand-held spirometer* by the majority of cases (94%). End test oxygen saturation (SpO_2) values <88% were common in most of patients (76%), with a mean distance walked of 403 meters. Ventilation significantly increased due to the contribution of the tidal volume and the respiratory frequency (RF). This finding was associated with a decrease of the end of test respiratory reserve (RR), that was <20% in 9 cases (17.6%). Lung function was inversely related to the end of test RF, while a positive correlation occurred with the end of test RR and the estimated maximal voluntary ventilation (MVV). RR was also a predictive factor of declining forced vital capacity and lung diffusion capacity for carbon monoxide (DLCO) over a 6-month period. Further factors of DLCO impairment were low SpO_2 and MVV. Comparison with the cardio-pulmonary exercise test (CPET) showed that the 6-MWT end of test RR was inversely related to the CPET-derived peak RF and VE/VCO_2 suggesting RR as pivotal in exercise limitation assessment. Our results open challenging perspectives in an unexplored field. Future research will include management of latent respiratory failure and monitoring of disease progression and therapy response. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 157-165)*

Key words: 6 minute walk test, fibrotic idiopathic interstitial pneumonias, ventilation, cardio-pulmonary exercise testing, exercise limitation

Introduction

Dynamic assessment of exercise performance is a key component in the evaluation work-up of patients suffering from respiratory diseases. Exercise limitation and onset of progressive dyspnoea exert a significant clinical impact as may lead overtime to a dramatic impairment of the quality of life. This is particularly true for patients affected by interstitial lung diseases (ILDs) as reduced tolerance to any physical effort and disability may be present very

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early in the disease natural history (1). Unlike cardio-pulmonary exercise testing (CPET) that requires specialised equipment, and is time-consuming with a low reproducibility in fibrotic interstitial pneumonias (2), the 6-minute walk test (6-MWT) is recognized as a simple, efficient and low cost tool that allows the evaluation of the patient performance and the overall cardio-pulmonary fitness during a sub-maximal exercise (3). Recent evidence suggests usefulness of the 6-MWT in ILDs patients for medical treatment and rehabilitation monitoring purposes, for pre-assessment eligibility to lung transplantation and for oxygen supplementation in exercise-induced respiratory failure (4-8). However, some concerns exist as conflicting results have been reported about which 6-MWT related parameter is most effective as clinical predictor of disease outcome, that is the degree of arterial oxygen saturation (SpO_2), the heart rate (HR) recovery, or the distance walked (9-11, 2). As a consequence, more recent efforts have been focused on indices of composite variables, including the desaturation-distance ratio (DDR), that is the ratio between the distance walked and the desaturation area (12), and the distance saturation product (DSP), that is the product of the final distance walked in meters (m) and the lowest room air SpO_2 (13).

Aim of the present study was to assess 6-MWT performance along with the evaluation of dynamic changes of ventilation in a cohort of patients affected by clinically stable idiopathic fibrotic interstitial pneumonias (IIPs) in order to have a more comprehensive evaluation of exercise performance in relation to disease staging. To this end, we enrolled patients affected by idiopathic pulmonary fibrosis (IPF) and idiopathic fibrotic nonspecific interstitial pneumonia (f-NSIP) as they share some clinical similarities along with a worse prognosis (14, 15).

Materials and Methods

Study population

Fifty-four consecutive Italian patients affected by clinically stable fibrotic IIPs attending the Respiratory Medicine Division of the Federico II University at the Monaldi Hospital in Naples, Italy, were enrolled between January 2013 and March 2015. Diagnostic preliminaries included clinical history, physical examination, routine blood tests, complete lung function testing, arterial blood gases analysis, high resolution computed tomography scan (HRCT) of the thorax and echocardiography. Likely pulmonary hypertension was defined by echocardiography as an estimated systolic pulmonary artery pressure (esPAP) >35 mmHg at rest (16). IPF and idiopathic f-NSIP diagnosis was made according to the criteria of the International consensus statements (14, 15). Thirty-one of them were newly diagnosed cases; the remaining 23 patients (17 IPF, 6 f-NSIP) had a mean disease duration of 10.5±6 months and were referred to our Institution for re-evaluation and/or therapy purposes. Nine IPF cases among them referred to have been previously treated with high doses of N-acetylcysteine and/or oral steroids (mainly prednisone at 12.5 mg/day). All patients were naive for currently available anti-fibrotic therapies at enrolment. A 4-week wash-out period was requested for patients taking steroids. As surrogate measures of disease severity and prognosis, the composite physiologic index (CPI) and the GAP score were calculated (17, 18). The local Ethics Committee approved the study and all participants provided written informed consent. Demographics and clinical characteristics of the study population are shown in Table 1. Prevalence of current/former smokers were higher in IPF than in f-NSIP patients (82.4% *vs* 55%, p=0.03), with no differences in cigarette consumption (pack/

Table 1. Demographics and clinical characteristics of the study population

Study population	
N patients	54
IPF/ idiopathic fibrotic NSIP	34/20
Age (yrs)	66.8±7.1
Gender (M:F)	40/14
Smokers/former smokers/never smokers	1/42/11
Pack/year*	35.7±27.7
Body mass index (Kg/m²)	28±4
Co-morbidities	
• systemic arterial hypertension	16 (29.6%)
• chronic ischemic heart disease	8 (14.8%)
• type II diabetes	6 (11.1%)
• combined pulmonary emphysema	8 (14.8%)
• gastro-esophageal reflux disease	11 (20.3%)
• arterial pulmonary hypertension	13 (24%)
esPAP (mmHg)	33±7.3
Overall mortality (%)	15 (27%)

Data are expressed as mean value±SD or as absolute number (%)

Table 2. Lung function parameters and disease staging

Parameter	
FVC (% predicted)	74.4±24.9
FVC (L)	2.3±0.6
TLC (% predicted)	57.8±18.8
TLC (L)	3.3±0.9
$DLCO_{sb}$ (% predicted)	46.2±17.2
$DLCO_{sb}$ (ml/min/mmHg)	10.7±3.8
paO_2 (mmHg)	73.1±11.5
CPI	48.3±15.4
GAP stage (I/II/III)	24/20/10
GAP score	4±1.4

Data are expressed as mean value±SD

yr). Mortality was also higher in the IPF sub-group (13% *vs* 2%). Additional sub-cohort comparisons did not show any significant difference and all patients were considered as a unique group for further analysis. Main lung function parameters along with the CPI and GAP scores are reported in Table 2.

Six-minute walk test

The 6-MWT was performed by trained hospital staff according to the American Thoracic Society (ATS) guidelines on the same measured corridor (3). Patients included in the study needed to be able to maintain resting SpO_2 in room air >90% with no clinical symptoms or signs suggestive of acute exacerbation. Patients were equipped with the *Spiropalm 6-MWT Hand-held spirometer* (Cosmed, Rome, Italy) and carefully instructed to walk at his/her own pace for a maximum of 6 minutes. Test performance was assessed while patients were breathing ambient air. Testing was not terminated for saturation values below 80%, while it was symptom-limited. Pulse-oximetry data and dynamic ventilatory parameters were simultaneously recorded along with an estimation of the work expense. Additional information included the dyspnoea and fatigue level by means of the Borg scale, ranging from 0 (absence of dyspnoea) to 10 (the worst feeling of dyspnoea or fatigue). A pre-test spirometry was performed along with an inspiratory capacity (IC) manoeuvre, that was repeated at the end of testing. Calculation of the DSP was also reported (13).

Performance of conventional 6-MWT on room air was available within 10 days in a sub-group of 31 patients (20 IPF, 11 f-NSIP) with the same testing conditions. Pulse-oximetry was measured with the same oximeter (Nonin®) to minimize results variability. The distance walked (meters), the initial and end of test SpO_2, HR and dyspnoea level (Borg) were recorded. The age-standardized predicted value of the 6-MWT distance, which takes into account age, sex and height, was calculated (19).

Cardio-pulmonary exercise testing

Symptom-limited CPET was available in a sub-cohort of 11 IPF patients tested within a period no longer than four weeks from the initial evaluation, according to the statement of the ATS/American College of Chest Physicians (20). Briefly, test was performed using a breath by breath system on a cycle ergometer (V_{max}29, Sensor Medics, Milan, Italy) calibrated in accordance with the manufacturer's specifications. Standard 12 lead electrocardiogram and pulse-oximetry were monitored along with systemic arterial blood pressure. Patients first pedaled at 55-65 revolutions per minute without any added load for 2-3 min. Then, the work rate was increased by 10 Watts/min until their maximal tolerance. The anaerobic threshold (AT) was determined by the V-slope method (21). Exercise was terminated when subjects developed severe dyspnoea or peripheral muscle fatigue and were physically exhausted.

Statistical analysis

Symmetrically distributed numerical variables were reported as mean±SD while median (min–max) was used to describe skewed numerical variables; categorical variables are reported as number of occurrences and percentages. Changes in ventilatory and pulse-oximetry parameters during the *Spiropalm*-equipped 6-MWT have been analyzed using either the student T test for paired samples or the non parametric Wilcoxon test. Concordance between the *Spiropalm*-equipped versus conventional 6-MWT have been quantified using the Lin's Concordance Correlation Coefficient (CCC) (22) and Bland-Altman analysis was used to assess the amplitude of the difference between the two procedures. Cross-sectional correlations among *Spiropalm*-equipped 6-MWT parameters and disease-related features was evaluated using the non parametric Spearman correlation coefficient. Because of the large number of the variables examined and to control the family-wise error rate at level a =0.05, the significance of the Spearman correlation p-values was assessed by using the adaptive Bonferroni procedure (23, 24). Finally, in order to define potential predictors of lung function decline, those *Spiropalm*-equipped 6-MWT parameters with a significant correlation pattern with disease-related features were entered in univariable regression models using CO lung diffusion capacity after 6 months as dependent variable. For all analyses, we used two-sided tests, with p-values <0.05 denoting statistical significance (unless otherwise specified). Modeling and statistical analyses were carried out using R 3.2.0 and SPSS 20 (SPSS Inc., Chicago, IL) software.

Table 3. Combined evaluation of pulse-oximetry and ventila tion in f-IIPs patients

Parameter	Basal	End of test	P value
A) Pulse-oximetry response			
SpO_2 (%)	93.2±1.8	84.2±6.1	<0.001
HR (pulse/min)	85±13.2	106.9±17.4	<0.001
Dyspnoea (Borg)	0 [0; 2]	6 [4; 7]	<0.001
Fatigue (Borg)	0 [0; 0]	3 [0; 6]	<0.001
B) Ventilatory response			
RR (%)	87.3±11.6	44.3±20.8	<0.001
VE (L/min)	16.6±6.3	41.6±12.2	<0.001
RF (breaths/min)	25.6±8.4	39.5±11.8	<0.001
TV (L)	0.7±0.3	1.1±0.3	<0.001
IC (L)	1.6±0.5	1.5±0.6	0.512

Data are expressed as mean value±SD or as median [min; max]. P values were obtained using either the paired T test or the non parametric Wilcoxon test.

Results

Combined evaluation of pulse-oximetry and ventilation in IIPs

Fifty-one out of 54 patients successfully completed the 6-MWT as instructed, while three of them had to prematurely stop walking (respectively, two after 2.5 min and one after 4.5 min) as felt not comfortable with the face-mask. As no significant differences of test performance and outcome were recorded in the two sub-groups of enrolled patients they were considered as a unique group for further analysis. Table 3 shows changes of pulse-oximetry (panel A) and ventilation (panel B) at baseline and at the end of test in the whole patient population. Patients who did not complete the test were excluded from analysis. Overall, end test saturation values <88% were common in most of patients as occurred in 39 cases (76%), with a SpO_2 difference of more than 4% in 45 cases (88%). The mean SpO_2 was of 85.5±4.9%, with a SpO_2 nadir of 82.6±6.1%. Mean time spent with SpO_2 <88% was of 03:30 (±02:10) min:sec. The mean distance walked was of 403±112 m (84±21% predicted) with a DSP value of 339±98 m%. Interestingly, ventilation significantly increased, through the contribution of the respiratory frequency (RF) and the tidal volume, with an estimated pre-test mean maximal voluntary ventilation (MVV, calculated as forced expiratory volume in one second x40) of 79.3±21.8 L/min. This finding was associated with a significant decrease of the respiratory reserve (RR) in all patients, with values below 20% in 9 cases (17.6%). As expected, the IC values was unchanged upon exercise. Finally, the mean work expense was of 32691±10790 Kg/m^2.

Performance comparison with conventional 6-minute walk test

To address whether *Spiropalm*-equipped 6-MWT results differ from conventional pulse-oximetry, 31 patients (20 IPF and 11 f-NSIP) successfully repeated conventional 6-MWT within 10 days from initial evaluation. Basal and end test SpO_2, HR and dyspnoea level (Borg), along with the distance (m) walked were collected. Test concordance is reported in Table 4. As shown, baseline SpO_2 recorded by *Spiropalm*-equipped 6-MWT was significantly lower (-1.04%) than that obtained with the conventional test. However, such a difference was not clinically relevant. Recording variations of all the other parameters analysed were not significant as well.

Correlation analysis of 6-MWT performance and disease-related features

Correlation analysis revealed significant and strong correlations between SpO_2 levels (end of test, nadir or mean) and ventilation variables, including the end of test RF and RR, and the MVV with lung function parameters and disease scoring indices (Figure 1). A weak correlation was found between the DSP and the sole absolute values of the forced vital capacity (FVC), the total lung capacity (TLC)

Table 4. Results concordance of *Spiropalm*-equipped *versus* conventional 6-MWT

Parameter	CCC [95% CI]	Mean difference [95% CI]	Lower LoA [95% CI]	Upper LoA [95% CI]
Basal SpO_2 (%)	0.31 [-0.04; 0.59]	-1.04 [-2.02; -0.06]	-5.78 [-7.48; -4.09]	3.7 [2.01; 5.4]
End of test SpO_2 (%)	0.59 [0.32; 0.77]	-1.72 [-3.83; 0.39]	-11.94 [-15.6; -8.29]	8.5 [4.85; 12.16]
Δ SpO_2 (%)	0.21 [-0.11; 0.5]	-0.68 [-3.34; 1.98]	-13.56 [-18.16; -8.96]	12.2 [7.6; 16.8]
Basal HR (pulse/min)	0.32 [-0.05; 0.61]	4.24 [-2.32; 10.8]	-27.53 [-38.88; -16.17]	36.01 [24.65;47.36]
End of test HR (pulse/min)	0.31 [-0.07; 0.62]	-0.64 [-8.26; 6.98]	-37.58 [-50.78; -24.37]	36.3 [23.09; 49.5]
ΔHR (pulse/min)	0.26 [-0.12; 0.57]	-4.88 [-13.83; 4.07]	-48.26 [-63.76; -32.75]	38.5 [22.99; 54]
Basal dyspnoea score (Borg)	0.04 [-0.27; 0.34]	0.48 [-0.26; 1.21]	-2.93 [-4.2; -1.65]	3.88 [2.61; 5.16]
End of test dyspnoea score (Borg)	0.45 [0.06; 0.72]	-0.09 [-1.42; 1.24]	-6.07 [-8.37; -3.78]	5.89 [3.59; 8.19]
Ddyspnoea score (Borg)	0.37 [-0.03; 0.68]	-0.59 [-1.97; 0.79]	-6.81 [-9.2; -4.42]	5.63 [3.24; 8.02]
Distance walked (m)	0.52 [0.19; 0.74]	27.2 [-11.25; 65.65]	-159.11 [-225.71; 92.51]	213.51 [146.91; 280.11]

CCC: Lin's Concordance Correlation Coefficient.
Lower LoA: Lower limit of agreement according to Bland-Altman Analysis. Denotes the value under which individual differences between the two methods can occur with probability of 0.025.
Upper LoA: Upper limit of agreement according to Bland Altman Analysis. Denotes the value above which individual differences between the two methods can occur with probability of 0.02.

and the lung diffusion capacity for carbon-monoxide (DLCO). The distance walked was not correlated with any of disease-related features.

Predictive factors of mortality and of lung function decline

A panel of measured variables, including the time spent with a SpO_2 <88%, the DSP, the work expense, the end of test, nadir and mean SpO_2, the end of test RF and RR, and the MVV, were analysed to assess their predictive value. No one of these was associated with mortality. Conversely, the end of test RR was predictive of the FVC decline (as % predicted) at 6 months (p=0.01) in a sub-cohort of 26 patients, including 11 untreated and 9 pirfenidone-treated IPF cases and 6 f-NSIP patients. Factors predictive of impairment of DLCO impairment (as % predicted) are reported in Table 5 (sub-group analysis of treated *versus* untreated patients did not show differences, not reported).

Performance of cardio-pulmonary exercise testing and comparison with ventilation changes upon 6-MWT

CPET was performed in a sub-cohort of 11 IPF patients who successfully completed the test within four weeks from study enrolment. As shown in Table 6 (panel A), test performance was suboptimal as assessed by VO_2 along with a work expense less than 50% of predicted. The mean AT was within the reference values suggesting that muscle de-conditioning not occurred. No early plateau of the O_2 pulse was observed as well. Ventilation increased upon testing with a mean peak estimated at the 70% of predicted. As expected, we observed a deeper reduction of the mean peak RR, with complete exhaustion in 6 patients (54.5%). Overall, testing was completed by means of a maximal effort, with limitation occurring by ventilatory impairment in all cases (along with a likely ventilation/perfusion mismatch), as assessed by the VE/VCO_2 slope. Comparison of selected *Spiropalm*-equipped 6-MWT derived variables not surprisingly revealed a significant discrepancy between the end of test RR and VE with their peak values recorded at CPET (Table 6, panel B).

Correlation analysis of 6-MWT with CPET performance

Correlation analysis showed that the DSP and MVV were significantly correlated with the VO_2, the O_2 pulse and peak VE (Figure 2). 6-MWT-derived

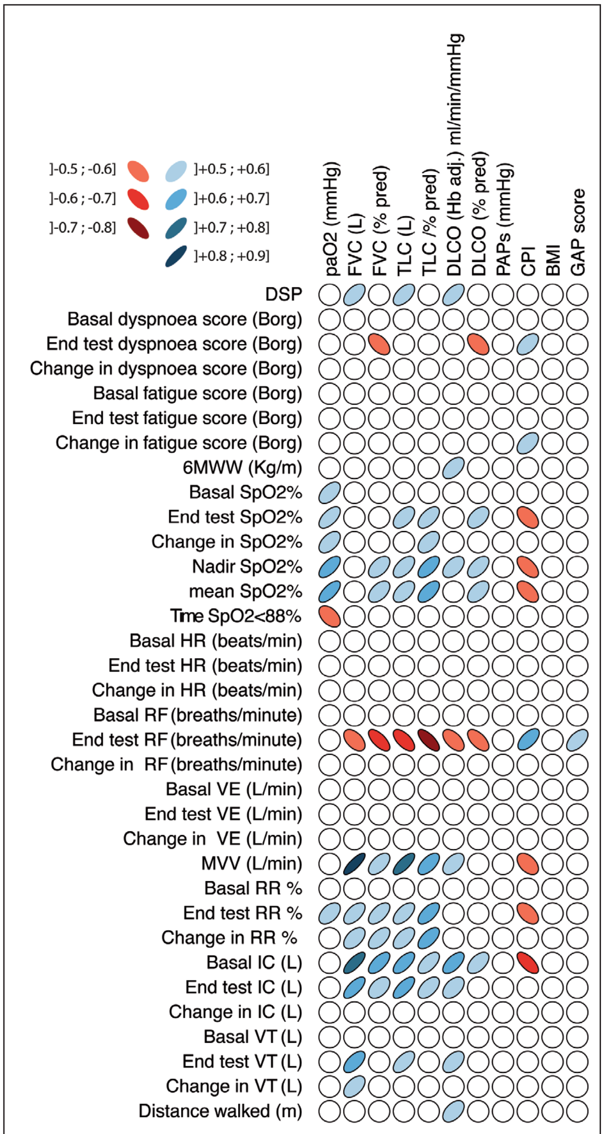

Fig. 1. Correlation of *Spiropalm*-equipped 6-MWT variables with lung function and disease staging.
Two-dimensional graphical representation of the Spearman r non-parametric correlations among the study variables. The presence of a significant correlation between two variables is expressed by means of a red (negative correlation) or blue (positive correlation) ellipse, and an empty circle refers to a non significant correlation. The color intensity and the thickness of each ellipse are proportional to the correlation value (see graphic legend for numeric values). Significance of the p-values was assessed using the Bonferroni adaptive procedure

MVV and RR were inversely related to the VE/VCO2 slope, while the last one had a positive correlation with the end of test RF.

Table 5. Predictive factors of CO lung diffusion capacity decline

Parameter	Beta [95% CI]	p value
T<88%	-2.12 [-4.75; 0.52]	0.108
DSP (m%)	0.05 [-0.01; 0.11]	0.114
Work (Kg/m^2)	0.26 [-0.44; 0.97]	0.444
End of test SpO_2 (%)	1.15 [0.2; 2.11]	0.021
Nadir SpO_2 (%)	1.2 [0.29; 2.11]	0.013
Mean SpO_2 (%)	1.5 [0.47; 2.54]	0.007
End of test RF (breaths/min)	-0.51 [-1.14; 0.11]	0.100
End of test RR (%)	0.44 [0.15; 0.73]	0.005
Δ RR (%)	0.39 [0.04; 0.74]	0.030
MVV (L/min)	0.32 [0.07; 0.58]	0.016

Beta coefficients are derived using univariable regression models with CO lung diffusion capacity at 6 month as dependent variable and adjusting for baseline DLCO values

Discussion

To our knowledge this is the first effort to characterize exercise limitation in fibrotic IIPs through a combined evaluation of pulse-oximetry and ventilation. This is actually evaluable by means of new diagnostic devices offering to clinicians the challenge to assess ventilation dynamics while patients are performing a routine 6-MWT. Walking is a physiological parameter that characterizes the individual ability to perform daily activities. The simple, safe and self-paced 6-MWT has been widely used in routine practice to address patient sub-maximal effort by means of SpO_2 and HR changes, along with the distance walked. Any fall of O_2 saturation to 88% or less has been associated with significantly higher mortality in 83 IPF and 22 NSIP patients (25), with further suggestion of stratifying patients for prognosis purposes (26). Despite this, Eaton *et al.* have reported that distance walked had a better reproducibility than the amplitude of SpO_2 changes in 53 patients with fibrotic IIPs (27). In this issue, 6-MWT distance has been shown as a better predictor of mortality in waiting list patients for lung transplantation, being superior to FVC % predicted (28). IPF patients that walked less than 212 m have been shown to have a reduced survival (29), with an estimation of the minimum important difference of 28 m (30). A 24-week decline of greater than 50 m has been associated with a fourfold increase in risk of death at 1 year in a cohort of 822 IPF patients

Table 6. Performance of CPET (A) and concordance analysis with 6-MWT derived parameters (B)

A)

Peak cardiovascular response	
VO_2 (ml/Kg/min)	15.4±3.2
% predicted	63.9±16.2
VO_2 (L/min)	1.2±0.3
VCO_2 (L/min)	1.4±0.3
Work (Watt)	54.2±19
% predicted	41.6±16
AT (L/min)	0.9±0.3
% predicted max VO_2	46±14.6
O_2 pulse (ml/beats)	9.5±2.7
% predicted	71.5±14.1
Peak ventilatory response	
VE max (L/min)	58.4±15.9
% predicted	70.9±13.2
RR (%)	19±17.5
Gas exchange response	
VE/VCO_2 at AT	39±5.4
Respiratory quotient (RQ)	1.1±0.1

Data are expressed as mean value±SD

B)

Parameter	CCC [95% CI]	Mean difference [95% CI]	Lower LoA [95% CI]	Upper LoA [95% CI]
VE (L/min)	0.12 [-0.14; 0.36]	18.14 [6.1; 30.18]	-15.52 [-36.37; 5.33]	51.8 [30.95; 72.65]
RR (%)	0.22 [-0.15; 0.53]	-23.7 [-38.21; -9.19]	-64.26 [-89.39; -39.13]	16.86 [-8.27; 41.99]
RF (breaths/min)	0.61 [0.13; 0.86]	5.14 [-0.49; 10.77]	-10.6 [-20.36; -0.85]	20.88 [11.13; 30.64]

CCC: Lin's Concordance Correlation Coefficient.
Lower LoA: Lower limit of agreement according to Bland-Altman Analysis. Denotes the value under which individual differences between the two methods can occur with probability of 0.025.
Upper LoA: Upper limit of agreement according to Bland Altman Analysis. Denotes the value above which individual differences between the two methods can occur with probability of 0.02.

included into a clinical trial (31). Despite distance was not correlated with functional parameters, the estimated minimal clinical important difference was of 24-45 m, as also recently confirmed (32, 33). Finally, among composite indices, the DDR has been found to be better correlated than either SpO_2 and distance walked with the DLco in 49 ILDs patients (12). A DSP value <200m% has been associated with a seven fold increased risk of death at 12 months, predicting mortality better than individual 6-MWT components (13).

Our results show that the majority of patients (94%) included in the study successfully completed testing while equipped with the *Spiropalm* device. The face-mask was well tolerated with no significant differences of pulse-oximetry in comparison with conventional 6-MWT. This is an important finding in our opinion as invites to the implementation of such an approach in routine clinical practice. As expected, ventilation significantly increased upon exercise due to the combined contribution of the TV and RF, with no dynamic IC changes. Conversely, a significant RR reduction was observed with 5 cases (9.8%) reaching a complete exhaustion. Interestingly, we identified additional clinical correlates among ventilation-related variables that included the end of test RF and RR, and the MVV. The former was inversely correlated with the FVC, TLC and DLCO, while a positive relation was found between the end of test RR and MVV and the FVC and TLC. In addition, the end of test RR was also identified as the sole predictive factor of both FVC and DLCO decline over a six-month period. Further factors predictive of DLCO decline were low SpO_2 and MVV

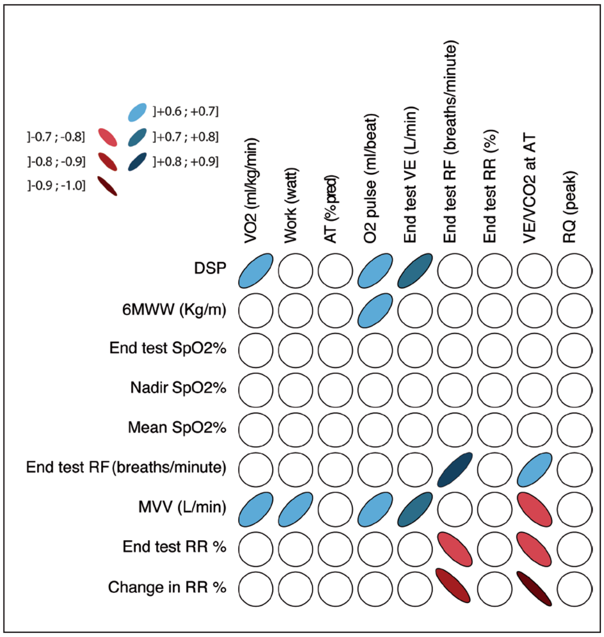

Fig. 2. Correlation of *Spiropalm*-equipped 6-MWT variables with CPET performance indices.
Two-dimensional graphical representation of the Spearman r non-parametric correlations among the study variables. The presence of a significant correlation between two variables is expressed by means of a red (negative correlation) or blue (positive correlation) ellipse, and an empty circle refers to a non significant correlation. The color intensity and the thickness of each ellipse are proportional to the correlation value (see graphic legend for numeric values). Significance of the p-values was assessed using the Bonferroni adaptive procedure

values. We believe that this preliminary finding may be of clinical interest. However, as pulmonary functional assessment may be influenced by reproducibility issues, such an observation needs to be further confirmed across longer monitoring periods. Unlike previous reports, neither the DSP nor any other parameter was predictive of mortality.

CPET is not routinely used in the management of ILD patients unless required prior to lung transplantation. Recent efforts have suggested CPET as a useful tool for distinguishing pulmonary hypertension (PH) in ILD cases through the measurement of ventilation and perfusion defects (34). Peak oxygen uptake has indeed been validated as good predictor of both PH and survival in 135 IPF patients (35). Keyser *et al.* have more recently reported an ameliorated CPET performance in a small cohort of 13 ILD patients after aerobic exercise training, that occurred through an increased peripheral O_2 extraction at the muscle level (36). In our setting, CPET was available for comparison purposes in 11 IPF patients that completed testing through a maximal effort. Overall performance was sub-optimal with test limitation occurring due to ventilation impairment along with a very severe reduction of the RR in the half of cases. As expected, 6-MWT and CPET performance was not overlapping. However, the 6-MWT end of test RR was inversely related to the CPET-derived peak RF and VE/VCO_2 suggesting such a parameter as pivotal in the assessment of exercise limitation at different intensity levels. Interestingly, the DSP and MVV were related to CPET overall performance. This finding is not surprising; however, it provides an additional clinical value to simple to calculate parameters in the daily management of these patients.

In conclusion, our study opens appealing perspectives in a still unexplored field. It has some limitations, and additional efforts are needed in larger patient populations. Future research directions will include assessment of best exercise performance with oxygen supplementation and monitoring purposes of disease progression and therapy

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