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INTERSTITIAL LUNG DISEASE

Cardiopulmonary Exercise Testing Allows Discrimination Between Idiopathic Non-specific Interstitial Pneumonia and Idiopathic Pulmonary Fibrosis in Mild to Moderate Stages of the Disease

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Abstract

It is unclear whether there are cardiopulmonary exercise testing (CPET) parameters which may indicate poor prognosis in the early course of fibrosing interstitial lung disease. 27 untreated consecutive subjects (13 idiopathic non-specific interstitial pneumonia (iNSIP), 14 idiopathic pulmonary fibrosis (IPF); 19 male; age 69 ± 10 years) were enrolled in this observational pilot study. Subjects underwent routine pulmonary function testing and CPET. Statistically, the *t* test and the Mann–Whitney-*U* test were applied in the presence of normal and non-normal distribution (according to Shapiro–Wilk), respectively. Analyzing the whole cohort, only mild functional impairments were determined. Comparison of iNSIP and IPF groups detected significant differences for the CPET parameters V'O_2Peak[%pred] ($p = 0.011$), V'O_2/kgPeak ($p = 0.033$), Watt[%pred] ($p = 0.048$), V'E/V'CO_2 (Rest: $p = 0.016$; AT: $p = 0.011$; Peak: $p = 0.019$; Slope: $p = 0.040$), V'E/V'O_2 (Rest: $p = 0.033$ AT: $p = 0.014$; Peak: $p = 0.035$). CPET parameters may indicate IPF-specific impairments even in mild disease. It may be hypothesized that these parameters are early biomarkers of poor prognosis.

Keywords Interstitial lung disease · Lung fibrosis · Pulmonary function test · Prognosis

Abbreviations

$AaDO_2$	Alveolar-arterial oxygen partial pressure difference
AT	Anaerobic threshold
BMI	Body mass index
BR	Breathing reserve
CPET	Cardiopulmonary exercise test
DLCO	Diffusion capacity of the lung for carbon monoxide
FEV1	Forced exspiratory volume in one second
FVC	Exspiratory forced vital capacity
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
iNSIP	Idiopathic non-specific interstitial pneumonia
KCO	Transfer coefficient for carbon monoxide
OUES	Oxygen uptake efficiency slope
O_2 pulse	Oxygen pulse
PFT	Pulmonary function test
SB	Single breath
TLC	Total lung capacity
VA	Alveolar volume
VC	In inspiratory vital capacity
VE'	Minute ventilation
V'CO_2	Carbon dioxide output
V'O_2	Oxygen uptake
%pred	Percent of predicted value

Introduction

Cardiopulmonary exercise testing (CPET) is considered the gold standard for exercise intolerance evaluation, subjecting the patients to symptom-limited incremental exercise while performing breath-by-breath monitoring of cardiopulmonary variables.

Studies characterizing the specific pattern of functional limitations in interstitial lung disease (ILD) under exertion as well as those investigating the potential prognostic

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factors derived from CPET have predominantly analyzed patients with unselected or advanced stages of ILD [1–7].

The clinical behavior and the treatment response of the ILD are heterogeneous. It has been demonstrated that non-specific interstitial pneumonia (NSIP), an inflammatory-fibrosing ILD, is associated with intermediate prognosis, whereas idiopathic pulmonary fibrosis (IPF), a predominantly fibrosing ILD, is associated with a poor prognosis [8, 9].

The aims of this study were, firstly, to analyze functional impairments detectable by CPET in mild to moderate fibrosing ILD, and secondly, to determine any significant differences between the entities iNSIP and IPF.

Materials and Methods

Design and Patients

In this prospective observational pilot study, consecutive ILD subjects were enrolled in the time period October 2013 until September 2017.

Inclusion criteria were initial diagnosis of ILD (IPF, iNSIP) within the last three years, diagnosis according to the guidelines and consensus statements (high-resolution computed tomography, bronchoalveolar lavage, histology where necessary, interdisciplinary discussion) [10, 11], no prior medical treatment of ILD, written informed consent for study participation. Exclusion criteria were obstructive airway disease (forced expiratory volume in one second (FEV1) divided by forced vital capacity (FVC) < 0.7), heart failure New York Heart Association (NYHA) IV, CPET contraindication. All subjects underwent high-resolution computed tomography, bronchoalveolar lavage, clinical, and serological assessment for the identification of ILD related to exposure or rheumatological disease. Where ILD diagnosis remained inconclusive after an interdisciplinary discussion (pneumology, radiology), sampling of lung tissue by surgical lung biopsy (SLB) or transbronchial cryobiopsy (TCB) was recommended. When no definite diagnosis could be reached after TCB, SLB was recommended as invasive step up procedure. All histopathological findings were re-evaluated in an interdisciplinary discussion (pneumology, radiology, pathology). As FVC is regarded as the most robust and reproducible lung function parameter for assessment of disease severity in ILD, the disease was classified by FVC categories as mild (FVC [%pred] ≥ 70), moderate (70 > FVC [%pred] ≥ 40), and severe (FVC [%pred] < 40).

This study was approved by the Ethics Committee of the University Witten/Herdecke. ClinicalTrials.gov NCT02636452.

Examinations

All subjects underwent pre-test pulmonary function testing including body plethysmography and diffusion capacity of the lung for carbon monoxide (DLCO). The subjects underwent CPET applying a ramp protocol according to the ATS/ACCP and ERS recommendations [12, 13]. CPET was continued until the individual patient's point of exhaustion or intolerability was reached. CPET was also discontinued at the discretion of the attending clinician if medically indicated.

CPET results were analyzed by categorizing the parameters according to the compartment in which the limitations were predominantly seen. Four categories were predefined: overall exercise tolerance, cardiocirculatory, ventilatory, and gas exchange limitations.

Statistical Analysis

Categorical data were evaluated by descriptive statistics calculating percentages. These were tested for statistically significant differences using the two-proportion z test. Continuous variables are given as mean and standard deviation. Normality testing was done using the Shapiro–Wilk test. Comparison of the IPF and iNSIP group regarding continuous variables was done with the t test if normal distribution could be assumed, otherwise the Mann–Whitney-U test was applied. Minute ventilation (V'E) divided by carbon dioxide output ($V'CO_2$) slope ($V'E/V'CO_2$ slope) was calculated using linear regression of all data points recorded during exercise. The corresponding $V'E/V'O_2$ slope, expressed as oxygen uptake efficiency slope (OUES), was determined [14]. To determine whether CPET parameters correlate with FVC or DLCO, we analyzed the cohort by subdividing in FVC and DLCO quartiles. For all CPET parameters, quartile groups of baseline FVC and DLCO were analyzed irrespective of the underlying ILD entity by One-Way ANOVA or Kruskal–Wallis test, depending on actual data distribution. For correlation analysis, the Pearson correlation coefficient with corresponding two-tailed significance value was determined.

Results

Twenty-seven subjects (19 male) were included in this study in total (age 69 ± 10 years, body mass index 28 ± 4 kg/m^2). 13 subjects presented with iNSIP, 14 subjects with IPF. All subjects were diagnosed according to the guidelines and consensus statements. The diagnosis was based on clinical information, radiological data, and results from bronchoalveolar

lavage in 14 cases. Additional histological data were available from TCB alone in nine cases, from SLB alone in three cases, from both, TCB and SLB, in one case. Analyzing disease severity, 15, 12, and 0 subjects were classified as mild, moderate, and severe, respectively, with no significant difference between the IPF and iNSIP group (mild IPF 6 subjects, mild iNSIP 9, moderate IPF 8, moderate iNSIP 4). The most prevalent comorbidity was arterial hypertension. Other comorbidities differed in prevalence, but not significantly between IPF and iNSIP subjects (Table 1). When comparing the IPF and the iNSIP subgroups, age and body mass index (BMI) were comparable (Age (years): IPF group 69.1 ± 11.0, iNSIP group 69.8 ± 9.5; BMI (kg/m^2): IPF group 28.5 ± 5.5, iNSIP group 27.7 ± 3.2). None of the included subjects were active smokers, 19/27 subjects (70%) were never-smokers (IPF group 8/14, 57%, iNSIP group 11/13, 85%). The history of dyspnea showed no significant differences (overall median 14.5 months [25% quartile to 75% quartile (Q25–Q75) 6.8–36.5]; IPF 12 months [Q25–Q75 5.3–36.5 months]; iNSIP 20.5 months [Q25–Q75 8.5–52.0 months]).

Analyzing all 27 subjects, body plethysmography showed minor restrictive impairments (Table 2). CPET results demonstrated that all subjects presented with good overall exercise tolerance as determined by the mean values of the parameters Watt[%pred] (95.9 ± 39.6) and V'O_2 peak [%pred] (86.0 ± 26.7). Mean alveolar-arterial oxygen partial pressure difference ($AaDO_2$ delta) showed elevated values under exertion (26.8 ± 13.9). These results were consistent with the analysis of DLCO parameters. DLCO[%pred] was moderately (57.2 ± 19.1) impaired and the transfer coefficient for carbon monoxide (KCO) [%pred] showed minor impairments (81.9 ± 23.3).

Table 1 Comorbidities in iNSIP and in IPF subjects

Comorbidities	iNSIP ($n=13$)	IPF ($n=14$)	p
Arterial hypertension	10 (83%)	12 (80%)	0.557
Diabetes mellitus II	2 (17%)	4 (27%)	0.410
Pulmonary hypertension	1 (8%)	0 (0%)	0.290
Obstructive sleep apnea	1 (8%)	4 (27%)	0.163
Hyperlipoproteinemia	2 (17%)	3 (20%)	0.686
Chronic renal failure	1 (8%)	1 (7%)	0.957
Coronary heart disease/myocardial infarction	3 (25%)	3 (20%)	0.918
Valvular heart disease	2 (17%)	3 (20%)	0.686
History of stroke	0 (0%)	0 (0%)	–
Atrial fibrillation	1 (8%)	2 (13%)	0.568
Hypothyroidism	1 (8%)	1 (7%)	0.957
Gastroesophageal reflux disease	0 (0%)	3 (20%)	0.077
Others	9 (75%)	7 (47%)	0.310

Mean values for V'E/V'CO_2 peak, V'E/V'CO_2 at anaerobic threshold (AT) and V'E/V'CO_2 slope were elevated, whereas mean oxygen pulse at peak exercise as a percent of predicted value (O_2 Pulse peak [%pred]), mean values of breathing reserve and mean values of partial pressure of carbon dioxide at rest and under exertion were normal.

Body plethysmography parameters did not significantly differ between the iNSIP and IPF subgroups, nevertheless patients with IPF showed a trend towards more severe lung restriction (Table 2). DLCO [%pred] and KCO [%pred] were significantly lower in the IPF group.

Focusing on overall exercise tolerance, watt performance (IPF: 86.7 ± 48.5; iNSIP: 105.7 ± 25.2), peak oxygen uptake as a percent of predicted value (V'O_2 peak [%pred]) (IPF: 73.7 ± 30.5; iNSIP: 99.1 ± 14.7), and peak V'O_2 divided by body weight (V'O_2/kg peak) (IPF: 15.3 ± 6.8; iNSIP: 20.1 ± 3.7) were significantly lower in IPF subjects.

Analyzing the parameters reflecting the cardiocirculatory compartment, V'E/V'CO_2 was significantly higher in IPF subjects at rest, at anaerobic threshold and at peak exercise (IPF: 54.4 ± 12.4, 49.9 ± 14.2, 49.4 ± 16.6; iNSIP: 43.1 ± 8.6, 37.6 ± 6.3, 36.4 ± 7.0). V'E/V'CO_2 slope also differed significantly between the two groups (IPF: 49.7 ± 22.9; iNSIP: 33.8 ± 7.4) (Table 2, Fig. 1). Although O_2 Pulse peak [%pred] appears to be lower in IPF subjects, this difference was not significant.

The parameters V'E/V'CO_2 peak and V'E/V'CO_2 slope differed among DLCO quartiles ($p=0.028$), but not among FVC quartiles. According to the calculated Pearson correlation coefficient, DLCO did not correlate with the parameters V'E/V'CO_2 peak or V'E/V'CO_2 slope (data not shown).

The differences were significant for the parameters V'E divided by V'O_2 (V'E/V'O_2) at rest, at anaerobic threshold, and at peak exercise and were non-significant for OUES. The gas exchange parameters $AaDO_2$ at rest, $AaDO_2$ at peak exercise, $AaDO_2$ delta did not show significant differences between the groups.

Discussion

To the best of our knowledge, this is the first study comparing CPET data in iNSIP and IPF patients with a mild form of the disease. We found significant differences in CPET findings between iNSIP and IPF patients with comparable mild to moderate impairments of the gas exchange and extent of restriction. The anthropometric parameters and the prevalence of comorbidities were comparable in both groups, so that both groups were homogenous and well matched.

The significant differences in the overall exercise capacity between iNSIP and IPF subjects and the global parameters for exercise tolerance VO_2 peak [%pred], VO_2/kg

Table 2 Anthropometric data as well as selected results of body plethysmography, diffusing capacity of the lung for carbon monoxide and cardiopulmonary exercise testing

	All subjects	iNSIP	IPF	*p* (iNSIP versus IPF)
No. of patients*	27	13 (48%)	14 (52%)	
Women*	8 (30%)	5 (38%)	3 (21%)	
Body plethysmography				
FEV1 [%pred]	79.6 ± 19.4	86.4 ± 24.5	73.4 ± 10.6	0.095
FVC [%pred]	72.2 ± 19.2	80.0 ± 22.7	64.9 ± 12.0	0.054
TLC [%pred]	70.0 ± 13.8	74.3 ± 16.1	66.1 ± 10.4	0.126
Diffusion capacity of the lung for carbon monoxide				
DLCO [%pred]	57.2 ± 19.1	62.2 ± 15.6	51.7 ± 21.8	*0.037*
KCO [%pred]	81.9 ± 23.3	93.3 ± 24.2	70.4 ± 16.3	*0.013*
Cardiopulmonary exercise testing				
Watt [%pred]	95.9 ± 39.6	105.7 ± 25.2	86.7 ± 48.5	*0.048*
V'O_2 peak [%pred]	86.0 ± 26.7	99.1 ± 14.7	73.7 ± 30.5	*0.011*
V'O_2/kg peak [(mL/min)/kg]	17.6 ± 5.9	20.1 ± 3.7	15.3 ± 6.8	*0.033*
O_2 Pulse peak [%pred]	99.3 ± 25.6	108.7 ± 19.7	91.4 ± 27.9	0.085
$AaDO_2$ peak (mmHg)	60.1 ± 13.1	55.2 ± 13.5	64.9 ± 11.1	0.059
$AaDO_2$ delta (mmHg)	26.8 ± 13.9	26.3 ± 15.9	27.3 ± 12.5	0.857
V'E/V'O_2 peak [(L/min)/(L/min)]	45.5 ± 15.6	38.8 ± 8.3	51.7 ± 18.4	*0.035*
OUES [(mL/min)/(L/min)]	1730 ± 667	1955 ± 576	1522 ± 699	0.107
V'E/V'CO_2 rest [(L/min)/(L/min)]	49.0 ± 12.0	43.1 ± 8.6	54.4 ± 12.4	*0.016*
V'E/V'CO_2 peak [(L/min)/(L/min)]	43.2 ± 14.3	36.4 ± 7.0	49.4 ± 16.6	*0.019*
V'E/V'CO_2 slope [(L/min)/(L/min)]	42.1 ± 18.8	33.8 ± 7.4	49.7 ± 22.9	*0.040*
BR (%)	22.8 ± 18.8	27.0 ± 13.5	19.3 ± 22.2	0.347

$p < 0.05$ is assumed to be statistically significant, significant p values are marked in italics

AT anaerobic threshold, *BMI* body mass index, *BR* breathing reserve, *DLCO* diffusion capacity of the lung for carbon monoxide, *FEV1* forced exspiratory volume in one second, *FVC* exspiratory forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *iNSIP* idiopathic non-specific interstitial pneumonia, *KCO* transfer coefficient for carbon monoxide, *OUES* oxygen uptake efficiency slope, *SB* single breath, *TLC* total lung capacity, *VA* alveolar volume, *VC* in inspiratory vital capacity, *V'CO2* carbon dioxide output, *V'O2* oxygen uptake, *%pred* percent of predicted value

*Number (percentage)

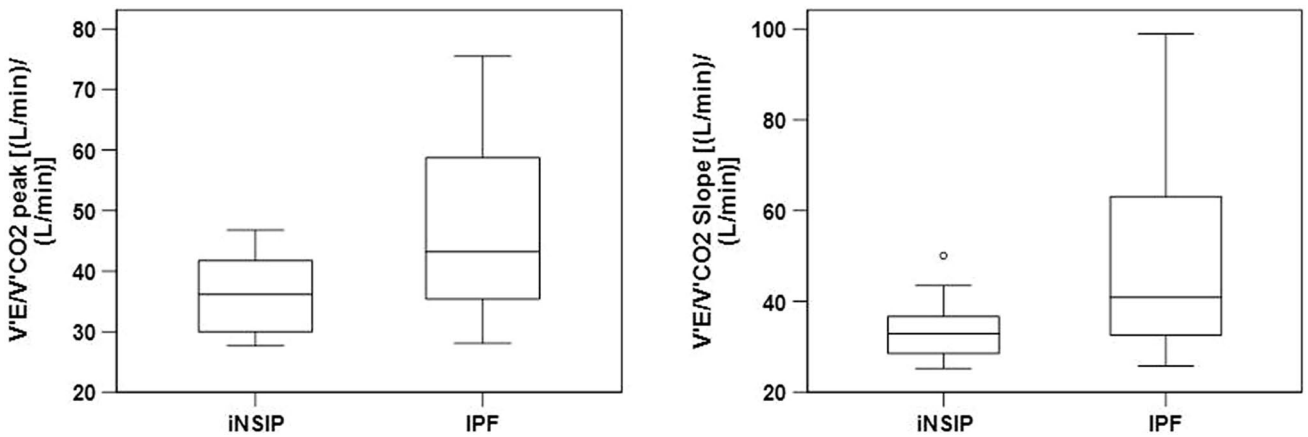

Fig. 1 Parameters V'E/V'CO_2 peak and V'E/V'CO_2 slope: Comparison of IPF and iNSIP group

peak, and Watt [%pred] suggest that there are functional impairments even in early IPF affecting the overall exercise tolerance.

Analyzing the compartment-specific parameters, differences between the two groups are significant for the parameters V'E/V'CO_2 rest, V'E/V'CO_2 AT, V'E/V'CO_2 peak, and V'E/V'CO_2 slope. O_2 pulse peak [%pred] appears to be lower in IPF subjects by trend.

These parameters allow the detection of impairments within the cardiocirculatory compartment. Circulatory impairment results from pulmonary capillary destruction and hypoxic pulmonary vasoconstriction, the latter occurring mainly to counteract against the effects of heterogeneous intrapulmonary ventilation/perfusion mismatch [15]. Exaggerated ventilatory response in ILD may therefore not only be caused by hypoxia and the stimulation of pulmonary stretch receptors but may also be due to the inadequate pulmonary perfusion. It has been demonstrated in previous studies that in advanced IPF, decreased O_2 pulse peak [%pred] and elevated V'E/V'CO_2 correlate with prognosis in IPF patients and may be an indicator for mortality [7, 16, 17].

In the context of this evidence the data of our study suggest that even in mild and moderate IPF, disturbances in the cardiocirculatory compartment are evident and clinically relevant. It may be hypothesized that V'E/V'CO_2 rest, V'E/V'CO_2 AT, V'E/V'CO_2 peak, V'E/V'CO_2 slope, V'O_2 peak [%pred], V'O_2/kg peak, and Watt [%pred] are useful discriminators between iNSIP with good to moderate prognosis and IPF with poor prognosis. Future prospective larger studies are necessary to prove this hypothesis.

Differences were significant for the parameter V'E/V'O_2 at rest, at the anaerobic threshold and at peak exercise but not significant for the parameter OUES. These and the DLCO data from this study may reflect the influence of multifactorial variables for reduced oxygen uptake (gas exchange disturbances, ventilation/perfusion mismatch, heart failure). Overall, the gas exchange values did not show consistent results and there remain methodological concerns upon reliability and reproducibility of the tests. In clinical practice, the intraindividual and interinstitutional reproducibilities of DLCO and KCO values are limited. The reliability of DLCO and KCO values may be limited, as the measurement requires a breath hold that can be difficult for symptomatic patients and test results have a relevant intrinsic variability. The variability has been described to be as high as 15%, which is the threshold that has commonly been used to indicate a significant deterioration or improvement [18]. Studies analyzing the predictive value of gas exchange parameters showed inconsistent results [19, 20].

This pilot study is limited due to the low number of recruited subjects. However, the analyzed study cohort is clearly defined by the prespecified algorithm as well as the inclusion/exclusion criteria and represents a relevant group of patients in clinical practice.

Conclusion

Overall, data from this study suggest that CPET allows for the detection of functional impairments in mild fibrosing ILD. Limitations of the cardiocirculatory compartment may occur in mild and moderate disease more likely in IPF than in iNSIP. Longitudinal studies have to determine intraindividually whether the occurrence of these specific limitations may predict worse prognosis and mortality in mild and moderate ILD.

Author Contributions LH was involved in study conception and design, data acquisition, data analysis and interpretation, manuscript drafting, critical revision, and final approvement. SH was involved in data acquisition, data analysis and interpretation, critical revision of the manuscript, and final approvement. NA was involved in data acquisition, data analysis and interpretation, critical revision of the manuscript, and final approvement. MT was involved in data analysis and interpretation, manuscript drafting, critical revision of the manuscript, and final approvement. WR was involved study conception and design, data analysis and interpretation, critical revision of the manuscript, and final approvement.

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Compliance with Ethical Standards

Conflict of interest Lars Hagmeyer reports travel grants and speaking fees by Roche and Boehringer Ingelheim. Simon Herkenrath, Norbert Anduleit, Marcel Treml states that there is no conflict of interest. Winfried Randerath reports travel grants and speaking fees by Roche.

Ethical Approval This study was approved by the Ethics Committee of the University Witten/Herdecke. ClinicalTrials.gov NCT02636452.

Informed Consent All subjects have given their written informed consent.

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