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Comparison of heart rates at fixed percentages and the ventilatory thresholds in patients with interstitial lung disease

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Heart rate (HR) responses to maximal exercise are commonly used for the prescription of training intensities in pulmonary rehabilitation. Those intensities are usually based on fixed percentages of peak HR (HRpeak), heart rate reserve (HRR), or peak work load (Wpeak), and rarely on HRs at the individual ventilatory thresholds (VT1 and VT2) derived from cardiopulmonary exercise testing (CPET). For patients suffering from interstitial lung disease (ILD), data on cardiorespiratory responses to CPET are scarce. Thus, the aim of this study was to record cardiorespiratory responses to CPET and to compare fixed HR percentages with HRs at VT1 and VT2 in ILD patients. A total of 120 subjects, 80 ILD patients and 40 healthy controls, underwent a symptom-limited CPET. From the ILD patient, 32 suffered from idiopathic pulmonary fibrosis (IPF), 37 from connective tissue disease (CTD), and 11 from sarcoidosis. HRs at fixed percentages, that is, at 70%HRpeak, at 70%Wpeak, and at 60%HRR were significantly lower in the ILD patients compared with the control group (*p*-values: 0.001, 0.044, and 0.011). Large percentages of HR values at 70%Wpeak and 60%HRR ranged between the HRs at VT1 and VT2 in ILD subgroups and controls as well. HRs at 70%HRpeak were lower than HRs at VT1 in 66% of the IPF patients, 54% of the CTD patients, and 55% of patients with sarcoidosis compared with 18% in the control group. Our findings demonstrate a considerable scattering of fixed HR percentages compared with HRs at the individual VTs derived from CPET in ILD patients. These findings may provide valuable information for the prescription of exercise intensity in pulmonary rehabilitation of ILD patients.

KEYWORDS
CPET, endurance training, interstitial lung disease

1 | INTRODUCTION

Interstitial lung diseases (ILDs) are characterized by exertional dyspnea, exercise-induced hypoxemia, and exercise intolerance.[1] Thus, exercise limitation is a common feature in patients with ILD and is closely associated with increased mortality, particularly in idiopathic pulmonary fibrosis (IPF).[2] Major contributors to exercise limitation in ILD include alterations in pulmonary gas exchange, ventilatory and skeletal muscle dysfunction.[2] Reduced diffusion capacity and impaired pulmonary circulation due to capillary destruction and hypoxic pulmonary vasoconstriction result in insufficient oxygen-hemoglobin saturation during exercise.[3,4] Exertional hypoxemia was shown to attenuate cerebral oxygenation, potentially affecting exercise tolerance.[5] Beside hypoxemia, abnormal heart rate responses to exercise have been demonstrated, associated with low exercise capacity and poor prognosis.[6] Moreover, quadriceps muscle force (20%–25%) was shown to be reduced in ILD compared with healthy controls, considerably contributing to exercise impairment regardless of the underlying type of ILD.[7–9] More pronounced muscle atrophy in skeletal muscles of the lower limbs compared with upper limbs suggests physical inactivity as an important cause of muscle dysfunction and exercise limitation in ILD patients.[10]

Exercise training represents a key component of pulmonary rehabilitation for people suffering from chronic lung disease including ILD, associated with the improvement of symptoms, physical function, and quality of life.[11–13] Principles of exercise training in patients with chronic respiratory disease are comparable with those valid for healthy individuals,[14,15] including personalized exercise prescription and progression of training load.[11] The exercise intensity applied is of utmost importance for training success and is commonly set at fixed percentages of peak values of walking velocity, heart rates, or workloads.[16–19] However, such fixed percentages may not reflect optimal exercise intensities in patients suffering from various heart or lung diseases.[20,21] Unfortunately, data on cardiorespiratory responses to incremental exercise in ILD patients are scarce.

Incremental cardiopulmonary exercise testing (CPET) represents the tool of choice to assess exercise capacity, cardiovascular risk, and functional capacity, and thus, the most valuable basis for developing exercise prescription and assessing training effects on an individual basis.[21] Beside heart rate (HR) and ventilatory responses to various exercise intensities, CPET provides two important measures, the ventilatory threshold 1 (VT1) and 2 (VT2), that allows to differentiate between exercise intensity domains, that is, moderate, high, severe, and extreme,[21] which can be assessed reliably and reproducibly and performed safely even in patients with severe exercise intolerance.[22]

Traditional standards for prescribing exercise intensity are mostly based on percentages of maximal HRs or workloads. Using threshold-based training models enables to assess individually, the minimal threshold of training intensity (VT1) as well as the upper limit of training intensity (VT2). Although a threshold-based training model may be superior to the relative percentage concept,[23] it seems not to be widely applied in pulmonary rehabilitation including ILD.[16–18] Thus, cardiorespiratory responses to CPET, and in particular, the relationship between VT1 and VT2 derived from CPET and fixed percentages of peak HR (HRpeak), heart rate reserve (HRR), and peak work load (Wpeak) remains to be evaluated, especially for ILD patients.

The aim of this study was (1) to evaluate cardiorespiratory responses to CPET and (2) to compare the individual heart rates at VT1 and VT2, the physiological known intensity with exercise intensities calculated by percentages of maximum parameters (70%Wpeak, 70%HRpeak, and 60%HRR) as recommended by national and international guidelines.[1,24,25] Due to the specific limitations in ILD, we hypothesized that the relation between those intensity measures would differ within different types of ILD and from those of a sedentary healthy control population.

2 | METHODS

2.1 | Subjects

A total of 120 patients, who were referred to the department of pulmonology, Medical University of Vienna between 2018 and 2020, were included in this study, 80 patients with diagnosis of ILD and 40 age-, weight-, and height-matched control subjects (Table 1). Ten out of the 37 patients with connective tissue disease (CTD) had systemic lupus erythematosus (SLE), 6 rheumatoid arthritis, 9 scleroderma, 3 Sjögren's syndrome, and 9 patients had mixed connective tissue disease (MCTD). Five of the 80 patients with ILD suffered from pulmonary hypertension with a mean pulmonary artery pressure of 33 mmHg, and only 1 patient was on therapy with bosentan and tadalafil. Two out of the 80 patients with ILD had known cardiovascular disease, and twenty-two were on systemic corticosteroid therapy, 8 on nintedanib, 4 on ebetrexat, 9 on hydroxychloroquine, 1 on adalimumab, 6 on mycophenolat-mofetil, and 8 patients on betablocker therapy.

TABLE 1 Characteristics of study participants

	ILD-patients	Control group	*p*-value ILD versus Control	CTD	*p*-value CTD versus Control
Subjects, *n*	80	40		37	
Age, years	54.6 (13.9)	54.6 (9.2)	0.977	49.6 (11.9)	0.044
Female sex, *n* (%)	49 (61.3)	19 (47.5)	0.216	30 (81.1)	0.005
Body mass, kg	76.4 (17.2)	75.9 (15.4)	0.861	72.3 (14.3)	0.296
Height, cm	169.4 (9.0)	170.9 (9.1)	0.404	168.5 (7.6)	0.225
BMI, kg/m^2	26.6 (4.5)	25.8 (4.0)	0.341	25.5 (4.2)	0.707
Heart rate rest, bpm	78.4 (13.0)	72.9 (12.3)	0.027	76.0 (10.9)	0.249
SpO_2, rest, %	96.0 (1.6)	97.7 (1.8)	<0.001	95.7 (1.8)	<0.001

Note: Data are presented as means (±standard deviation), except for sex (frequency).

Abbreviations: bpm, beats per minute; CTD, connective tissue disease; IPF, idiopathic pulmonary fibrosis; SpO_2, peripheral oxygen saturation.

All patients included in this study had CPET assessment data available. The study was conducted in accordance with the ethical principles laid down in the declaration of Helsinki 1975, and the protocol was approved by the Ethics Committee of the Medical University of Vienna.

2.2 | Cardiopulmonary exercise test (CPET)

Before performing CPET, resting heart rates were assessed after sitting for 15 min, taken the mean of the last minute. All subjects underwent a symptom-limited CPET on an Ergoline 800 bicycle (Vyntus CPX, Vyaire Medical, Carefusion GmbH) with respiratory gas-exchange analysis, using a step protocol with progressive increase in workload every minute according to a total exercise time between 8 and 12 min. In both groups, patients and controls, the same step protocol was used; the increment was adapted to the expected maximum working capacity. The initial loading workload ranged between 20 and 40 Watt with increment steps ranging between 10 and 20 Watt per minute. Subjects were encouraged to exercise until exhaustion. A cycling frequency of 60–80 revolutions per minute (rpm) had to be maintained.

The test was ended when the subject failed to maintain a pedal frequency of at least 60 rpm. Blood pressure was measured every 2 min, and continuous 12-lead electrocardiogram and oxygen saturation (SpO_2) were recorded. Breath-by-breath minute ventilation (VE), carbon dioxide output (VCO_2), and oxygen uptake (VO_2) were measured using Sensormedics 2900 Metabolic Measurement Cart. The respiratory exchange ratio (RER) was defined as VCO_2/VO_2, the oxygen pulse was calculated by VO_2/heart rate, and the ventilatory equivalent for oxygen uptake (VE/VO_2) and the ventilatory equivalent for carbon dioxide production (VE/VCO_2) were measured. VT1 was determined using the V-slope method and double-checked by establishing the nadir of VE/VO_2 versus work rate relationship. VT2 was determined using the point of increase in VE versus VCO_2 and double-checked by establishing the nadir of VE/VCO_2 versus work rate relationship.

VTs were determined by computer analyses with different methods described above and additionally cross-checked by two different observers.

Blood gas analysis was measured at rest, at VT1, and at peak exercise. Absolute values were measured, and % of predictive values was assessed using reference values for CPET provided by Hansen and Jones.[26]

2.3 | Determination of heart rates at various effort intensities

Using individual CPET results, HRs were determined at VT1 and VT2. Furthermore, HRs were assessed at 70%Wpeak, at 70%HRpeak as well as at 60%HRR using the Karvonen formula: Resting HR/HRmax * 0.6 + resting HR.[27]

2.4 | Statistical analysis

Statistical analysis was performed by IBM SPSS version 27.0 (IBM SPSS Statistics for Windows) and R, release 3.6.2 Normal distribution of the data was verified by the Kolmogorov–Smirnov test and Shapiro–Wilk test. Between-group difference in baseline characteristics was analyzed using the Student ́s *t*-test for normally distributed data.

For non-normally distributed data, Mann–Whitney *U* test was used to assess the group differences. Comparison of quantitative variables among multiple groups was performed using ANOVA. All tests were conducted as

Sarcoidosis	*p*-value Sarcoidosis versus Control	IPF	*p*-value IPF versus Control	*p*-value between diagnosis groups
11		32		
51.9 (16.4)	0.606	61.2 (12.9)	0.019	0.001
8 (72.7)	0.253	11 (34.4)	0.378	0.001
72.4 (19)	0.580	82.6 (18.4)	0.104	0.031
166.6 (9.1)	0.192	171.3 (10.3)	0.841	0.245
26.7 (5.6)	0.649	27.9 (4.3)	0.042	0.087
83.5 (11.6)	0.017	79.4 (15.3)	0.055	0.211
96.4 (1.2)	0.011	96.2 (1.4)	<0.001	0.305

two-sided. Due to the exploratory character of the study, no correction for multiplicity was performed and p-value<0.05 was considered statistically significant.

Comparisons between HRs at VT1 and VT2 and HRs at 70%HRpeak, 70%Wpeak, and 60%HRR were performed using descriptive statistics presenting numbers and corresponding percentages.

To visualize the differences between HRs determined at VT1 and VT2 and HRs assessed as a percentage at 70%HRpeak, 70%Wpeak, and 60%HRR, the data were scaled using the min-max normalization, so that for every individual the values of VT1 and VT2 would correspond to the numbers 0 and 1 and the rest of the formulas was rescaled accordingly, with the same linear transformation. Min-max normalization is a scaling method used to rescale data to the range of [0.1]. In general, for a given feature "x", the min-max normalization is given by: $(x - \min(x))/(\max(x) - \min(x))$. In this case, we were interested in scaling the features with respect to VT1 and VT2 to see how the HRs at 70%HRpeak, 70%Wpeak, and 60%HRR deviate from these two values. Hence, for every patient, the scaled HR at 70%HRpeak was determined as follows: ((HR at 70%HRpeak − VT1)/(VT2 − VT1)). Scaled HRs at 70%Wpeak and 60%HRR were computed accordingly. Figure 1 shows boxplots of the scaled HR values determined by the 3 formulas, for ILD patients and the control group, respectively. Maximal RER values for the ILD subgroups are depicted by box plots in Figure 2.

3 | RESULTS

3.1 | Subjects' characteristics

Characteristics of ILD patients and controls are shown in Table 1.

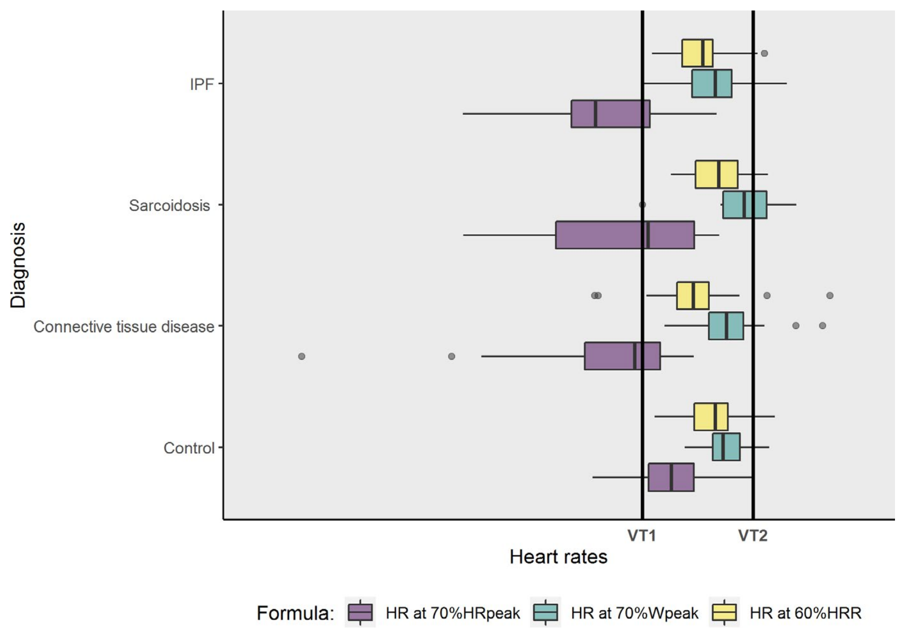

FIGURE 1 Boxplots of the scaled HR values determined by the 3 formulas for ILD patients and controls Black lines in the graphics indicate the range between VT1 and VT2

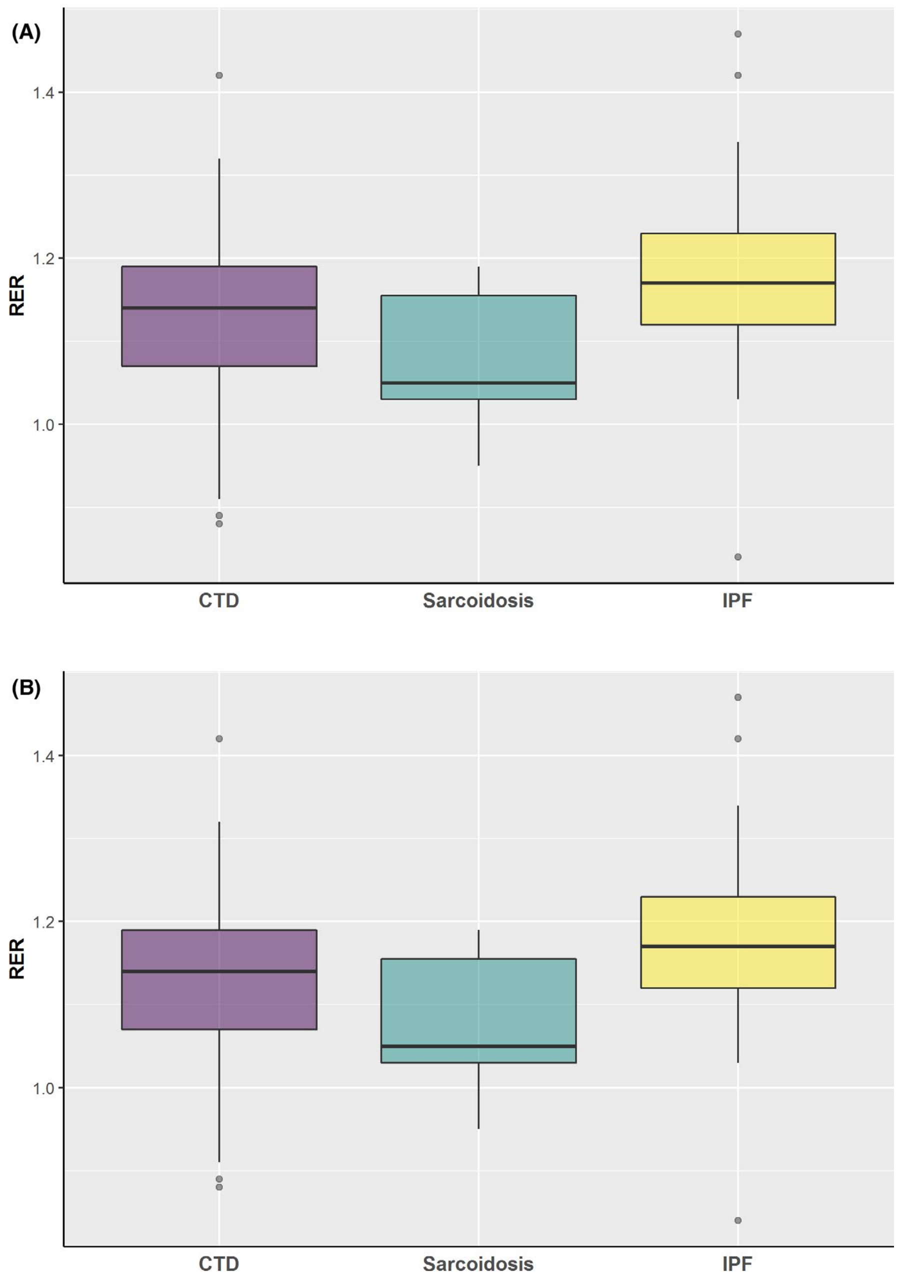

FIGURE 2 Boxplots of RER values between ILD subgroups

A total of 120 subjects were included for analysis, 80 patients with diagnosed ILD and 40 matched controls. The mean age of the ILD patients was 54.6 ± 13 years, 70 women (58%) and 50 men (42%). Anthropometric data did not differ between ILD patients and controls. Patients with IPF were older than those with CTD and had a higher body mass compared with patients with CTD and sarcoidosis. Compared with controls, resting HRs were higher in patients with sarcoidosis, and SpO_2 values were lower in those with CTD and IPF.

Included types of ILD and pulmonary function in ILD patients are shown in Table 2. Out of the 80 ILD patients, 32 suffered from IPF, 37 from connective tissue disease (CTD), and 11 from sarcoidosis. Twenty-eight (37.5%) ILD patients had restrictive lung function. In the ILD group, the mean forced ventilatory capacity (FVC) was 85.8% ± 21.4%pred and the mean carbon monoxide transfer factor (DLCO) was 60.4% ± 20.8%pred. None of the patients were on long-term oxygen therapy. Patients with IPF were significantly more limited with lower DLCO, and SO_2 and higher $AaDO_2$ at rest and peak exercise compared with patients with CTD and sarcoidosis.

Responses to maximal exercise are shown in Tables 3 and 4.

Physiological responses (VO_2, W, SpO_2, and HR) determined at maximal exercise were all significantly lower in ILD patients compared with controls. This is true for all types of ILD with the exception of sarcoidosis patients, who had similar HRpeak values as controls. VO_2peak

TABLE 2 Characteristics of ILD patients

	ILD-patients	CTD	Sarcoidosis	IPF	*p*-value
Subjects, *n* (%)	80	37 (46.3)	11 (13.7)	32 (40.0)	
TLC, L	6.1 (4.3)	6.5 (6.0)	6.2 (1.9)	5.5 (1.3)	0.634
FVC, %	85.8 (21.4)	82.2 (18.5)	98.4 (20)	85.6 (23.8)	0.087
FEV1,%pred	84.9 (21.2)	80.8 (18.8)	95.2 (23.7)	86.2 (22.3)	0.129
FEV1/FVC, %	78.6 (8.6)	78.5 (9.2)	77.1 (8.3)	79.2 (8.2)	0.784
RV/TLC, %	41.0 (7.7)	41.8 (9.0)	40.0 (6.1)	40.2 (6.4)	0.633
DLCO, %	60.4 (20.8)	63.1 (18.4)	75.9 (25.0)	51.3 (18.0)	0.001
$AaDO_2$ rest, mmHg	23.9 (11.9)	19.7 (11.0)	18.1 (9.8)	30.7 (10.6)	<0.001
$AaDO_2$ peak, mmHg	30.3 (18.3)	22.6 (14.9)	20.3 (12.4)	42.5 (17.0)	<0.001
SpO_2, peak, %	93.6 (4.4)	95.2 (3.0)	96.7 (1.5)	90.6 (4.7)	<0.001

Note: Data are presented as means (±standard deviation) or frequencies and percentages (*n*, %). *p*-values for differences between ILD subgroups.

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; CTD, connective tissue disease; DLCO, diffusion capacity of lung for carbon monoxide; FEV 1, forced expired volume in one second; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; RV, residual volume; SpO_2, peripheral oxygen saturation; TLC, total lung capacity.

(%pred) was also higher in patients with sarcoidosis compared with IPF (Table 3).

VE was significantly higher in CTD and IPF patients compared with controls with higher VE/VO_2 values in ILD patients and higher VE/VCO_2 values, except for patients with sarcoidosis, compared with controls. $PETO_2$ was significantly higher in CTD and IPF patients compared with controls. No significant differences were found between $PETCO_2$ and RER in both groups, but RER values are different between ILD subgroups (Table 3, Figure 2). With regard to sex-specific differences, relative VO_2peak did not differ between males and females and VO_2%pred was higher in females within the ILD patients, which is in contrast to controls (Table 4). Group * sex interactions were found for relative and absolute VO_2peak values and Wpeak values (Table 4).

3.2 | Ventilatory thresholds and heart rates at fixed percentages of peak heart, peak power output, and heart rate reserve

Ventilatory thresholds were significantly higher in %VO_2peak ($p < 0.001$), %Wpeak ($p < 0.040$), and %HRpeak ($p < 0.001$) in the patient group with ILD compared with controls, whereas both VT1 and VT2 were significantly lower at %VO_2peakpred (Figure 1). Mean HRs at VT1 did not differ between groups, but mean HRs at VT2 were significantly lower in ILD patients. HRs at fixed percentages, that is, at 70%HRpeak, 70%Wpeak, and 60%HRR, were significantly lower in the ILD patients compared with controls. In all patients except one, the VT2 could be assessed. However, those HRs did not differ between males and females of ILD patients (Table 5).

HRs at 70%HRpeak were lower than the HRs at VT1 in 66% of the IPF patients, 54% of the CTD patients, and 55% of the patients with sarcoidosis compared with 18% in the control group (Figure 1).

4 | DISCUSSION

In the present study, cardiorespiratory responses to CPET have been recorded, and HRs at VT1 and VT2 have been compared with fixed HR percentages, that is, of 70%HRpeak, 70%Wpeak, and 60%HRR in patients with ILD, ILD subgroups and an age-matched healthy control group. Our findings demonstrate differences in performance characteristics and the related scattering of fixed HR percentages when compared to the individual VT1 and VT2. Patients with ILD had lower exercise capacity (VO_2peak and Wpeak) and lower cardiorespiratory responses (HRpeak and SpO_2peak) to maximal exercise than controls.

Comparisons between ILD types revealed higher VO_2peak (%pred) and peak HRs in patients with sarcoidosis compared with those with CTD, which is in agreement with other studies.[2,3]

In contrast to the control group, relative VO_2peak did not differ between males and females and VO_2%pred was higher in females within the ILD patients. This observation might indicate that aerobic capacity in males

TABLE 3 Responses to maximal exercise

	ILD-patients	Control group	*p*-value ILD versus Control	CTD	*p*-value CTD versus Control
Subjects, *n*	80	40		37	
VO_2peak, ml/kg/min	20.2 (7.4)	30.4 (8.6)	<0.001	20.5 (8.7)	<0.001
VO_2peak, ml	1497.5 (536.4)	2269.6 (672.2)	<0.001	1439.1 (574.9)	<0.001
VO_2peak, %pred	83.4 (23.6)	119.0 (24.0)	<0.001	82.8 (26.9)	<0.001
Wpeak, watt	106.9 (51.6)	192.0 (59.5)	<0.001	106.0 (53.6)	<0.001
Wpeak, %pred	75.3 (30.7)	131.2 (25.8)	<0.001	77.7 (35.4)	<0.001
SpO_2peak, %	93.7 (4.4)	98.0 (0.8)	<0.001	92.6 (4.9)	<0.001
HRpeak, bpm	145.4 (23.9)	162.5 (18.3)	<0.001	148.3 (21.6)	0.003
HRpeak, pred, %	87.8 (12.1)	98.3 (10.0)	<0.001	88.2 (13.3)	<0.001
VE,Ll/min	66.7 (21.1)	89.6 (26.5)	<0.001	61.8 (18.5)	<0.001
VE/VO_2	42.2 (9.3)	37.0 (5.9)	<0.001	41.3 (9,1)	0.018
VE/VCO_2	36.9 (8.3)	32.6 (4.5)	<0.001	35.0 (6.4)	0.069
$PETO_2$, mmHg	117.3 (6.2)	120.8 (4.6)	<0.001	116.8 (6.5)	0.003
$PETCO_2$, mmHg	32.5 (5.5)	33.9 (4.0)	0.128	33.0 (5.7)	0.466
RER	1.14 (0.1)	1.14 (0.1)	0.846	1.17 (0.1)	0.152

Note: Data are presented as means (±standard deviation).

Abbreviations: bpm, beats per minute; HR, heart rate; $PETCO_2$, end-tidal carbon dioxide tension; $PETO_2$, end-tidal oxygen tension; pred, predicted; RER, respiratory exchange ratio; SpO_2, peripheral oxygen saturation; VE, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide production; VE/VO_2, ventilatory equivalent for oxygen uptake; VO_2, oxygen uptake; W, power output.

suffering from ILD is more severely affected compared with females.

Augmented ventilatory demand during exercise with higher VE and ventilatory equivalents were found in ILD patients compared with controls. VE/VCO_2 values, considered as an index of the degree of V/Q inequality, were significantly higher in the CTD and IPF groups. Whereas the $PETO_2$ was significantly lower in the CTD and IPF group, the $PETCO_2$, which has been suggested as a marker for pulmonary hypertension connected to ILD, was not significantly elevated in the ILD patients compared with the controls.[28]

Chronotropic incompetence (CI) observed in ILD patients of the present study is an interesting observation of clinical importance. CI is defined as the inability to reach the target heart rate during CPET, likely representing an impaired sympathetic response, constitutes an independent predictor of cardiovascular diseases and mortality.[29] CI has been repeatedly reported in patients suffering from lung diseases, including ILD patients.[30] CI has been demonstrated to be present in a large proportion of COPD patients (62%)[31] and was recently reported in those suffering non-severe COPD, due to autonomic dysfunction and associated with lung hyperinflation.[32] Thus, autonomic dysfunction is the likely pathophysiological mechanism explaining CI in ILD patients, particularly in those with CTD and IPF.

Scattering of fixed HR percentages is rather small for HRs at 70%Wpeak and 60%HRR but comparatively large for HR at 70%HRpeak (Figure 1). In contrast to the control group, HR at 70%HRpeak in ILD is at or slightly below the HR at VT1. However, the scatter range is probably too large to generate optimal individual training effects, because exercise intensity may be below VT1 in some ILD patients or above VT1 in others.

Assessment of appropriate exercise intensities in patients with chronic diseases becomes more and more important. It has been suggested that people with ILD may need more careful planning and modification of their exercise prescription than healthy subjects or even patients with COPD.[24] Compared with the number of studies including COPD patients, clinical studies dealing with pulmonary rehabilitation in ILD are relatively small.[33] Principles of pulmonary rehabilitation are similar for both groups of diseases. However, exercise-induced desaturation and related complications occur more frequently in ILD patients, emphasizing the importance of proper training intensity selections.[33]

Generally, VTs derived from CPET ensure individual physiological adaptations to exercise and can help to find the optimal training "zones".[34] VT1 and VT2 form boundaries for the determination of 3 training zones (from low to high) successfully applied in athletes and patients as well.[21,35] Whereas in athletes the largest proportion of the

Sarcoidosis	*p*-value Sarcoidosis versus Control	IPF	*p*-value IPF versus Control	*p*-value between diagnosis groups
11		32		
24.1 (8.0)	0.036	18.4 (4.8)	<0.001	0.084
1691.8 (609.5)	0.014	1498.2 (460.4)	<0.001	0.395
94.3 (15.4)	<0.001	80.3 (21.1)	<0.001	0.236
122.6 (68.7)	0.008	102.6 (42.6)	<0.001	0.539
85.6 (31.0)	<0.001	69.1 (23.3)	<0.001	0.249
95.7 (2.1)	0.006	94.2 (4.1)	<0.001	0.103
162.3 (21.0)	0.974	136.2 (24.2)	<0.001	0.004
87.4 (10.9)	0.009	87.2 (11.4)	<0.001	0.888
76.4 (29.7)	0.202	69.2 (19.5)	<0.001	0.090
42.7 (7.5)	0.035	43.1 (10.2)	0.005	0.707
36.5 (6.0)	0.068	39.4 (10.4)	0.001	0.085
118.8 (4.3)	0.191	117.5 (6.5)	0.018	0.650
31.5 (4.4)	0.129	32.2 (5.7)	0.173	0.676
1.17 (0.1)	0.305	1.09 (0.1)	0.042	0.011

TABLE 4 Sex-specific responses to maximal exercise

	ILD		*p*-value	Control group		*p*-value	*p*-value
	Males	Females	M versus F	Males	Females	M versus F	Interaction Group*Sex
Subjects, *n*	31	49		21	19		
VO_2peak, ml/kg/min	19.4 (6.2)	20.7 (8.2)	0.432	33.3 (8.3)	27.2 (7.9)	0.024	0.017
VO_2peak, ml	1717.3 (659.2)	1358.5 (388.6)	0.009	2702 (585.5)	1791.7 (372.9)	<0.001	0.006
VO_2peak, %pred	74.4 (19.5)	89.0 (24.3)	0.004	114.8 (20.2)	123.6 (27.5)	0.259	0.521
Wpeak, watt	123.3 (63.9)	96.6 (39.3)	0.042	232.5 (49.4)	147.2 (30.1)	<0.001	0.002
Wpeak, %pred	69.6 (27.2)	79.0 (32.4)	0.167	132.8 (24.5)	129.4 (27.7)	0.686	0.264
SpO_2peak, %	94.2 (4.1)	93.3 (4.6)	0.450	98.2 (0.7)	97.9 (0.9)	0.281	0.706
HRpeak, bpm	141.4 (27.1)	147.9 (21.7)	0.261	164.2 (18.1)	160.6 (18.6)	0.548	0.248
HRpeak, pred, %	86.0 (11.3)	89.0 (12.6)	0.274	99.5 (10.6)	97.0 (9.4)	0.430	0.222
VE, L/min	80.4 (24.3)	58.3 (13.2)	<0.001	105.5 (22.8)	71.1 (16.7)	<0.001	0.102
VE/VO_2	44.8 (11.2)	40.6 (7.6)	0.078	38.0 (6.3)	35.9 (5.2)	0.262	0.525
VE/VCO_2	39.6 (11.1)	35.3 (5.7)	0.056	33.7 (4.8)	31.3 (3.8)	0.086	0.513
$PETO_2$, mmHg	117.3 (7.4)	117.4 (5.4)	0.949	122.0 (4.8)	119.5 (4.1)	0.090	0.259
$PETCO_2$, mmHg	32.4 (6.8)	32.5 (4.5)	0.921	33.2 (4.6)	34.6 (3.2)	0.287	0.545
RER	1.15 (0.1)	1.13 (0.1)	0.555	1.15 (0.1)	1.13 (0.1)	0.600	0.967
Lactate, mmol/L	6.1 (2.2)	6.1 (2.1)	0.905	8.9 (2.2)	8.9 (2.6)	0.971	0.973
Beta-blocker use	4 (12.9%)	6 (12.2%)	1.000				

Note: Data are presented as means (±standard deviation).

Abbreviations: bpm, beats per minute; HR, heart rate; $PETCO_2$, end-tidal carbon dioxide; $PETO_2$, end-tidal oxygen tension; pred, predicted; SpO_2, peripheral oxygen saturation; tension RER, respiratory exchange ratio; VE, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide production; VE/VO_2, ventilatory equivalent for oxygen uptake; VO_2, oxygen uptake; W, power output.

TABLE 5 Intensity domains based on ventilatory threshold and fixed heart rate percentages for both sexes

	ILD patients ($n = 80$)	Males ($n = 31$)	Females ($n = 49$)	p-value
HR, rest	78.4 (13.0)	81.9 (15.6)	76.2 (10.6)	0.079
HR, peak	145.4 (24.0)	141.4 (27.1)	147.9 (21.7)	0.261
HR at 60%HRR	118.6 (17.4)	117.6 (20.4)	119.2 (15.4)	0.702
HR at 70% HRpeak	101.8 (16.8)	99.0 (19.0)	103.6 (15.2)	0.261
HR at 70% Wpeak	123.5 (21.1)	120.2 (23.0)	125.7 (19.7)	0.279
HR at VT1	104.6 (16.4)	103.6 (18.8)	105.2 (14.8)	0.689
HR at VT2	131.2 (21.4)	128.9 (25.5)	132.6 (18.5)	0.495
RER	1.14 (0.1)	1.15 (0.1)	1.13 (0.1)	0.555
Lactate at rest	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)	0.302

Abbreviations: HR, heart rate; HRR, heart rate reserve; VT1, first ventilatory threshold; VT2, second ventilatory threshold; Wpeak, watt peak.

p-value for sex differences.

training volume is performed at intensities below VT1,[35] in patients suffering from lung diseases, including ILD, intensities above VT1 are preferentially applied in rehabilitation.[12,16,36] This is at least partly based on the early study by Casaburi et al., who evaluated effects of various training intensities in COPD patients. These authors found reduced ventilatory requirements and improved exercise tolerance after training at intensities above VT1, due to metabolic adaptations within the working muscles resulting in lower blood lactate concentration, diminished carbon dioxide production, and associated lower exercise ventilation.[36]

The individual application of training intensities based on CPET is particularly needed by patients suffering from different diseases. For instance, several training studies in chronic heart failure patients implicated the VT1 as an useful and valid method for individual training prescription.[34,37,38] In those patients, the proper assessment of training intensity was emphasized because of the high inter-patient variance. Similarly, intensity prescription based on HR identification at the VT was also highlighted for patients with left ventricular dysfunction (LVDF).[27] Even in healthy subjects, it was shown that exercising according to a fixed HRR for 12 weeks, VO_2peak was increased in only 42% of the total group when compared to a significantly improved VO_2peak in all individuals exercising according to the range between VT1 and VT2.[23,39] It was also suggested that due to the heterogeneity of ILD patients, that is, those suffering from sarcoidosis, modification and program adjustment of the standard pulmonary rehabilitation format, including individual prescription of training intensity, are required.[40] Our findings confirm the large variability of heart rate responses to exercise (CPET) and the considerable scattering of fixed HR percentages in comparison with HRs at the individual VTs in ILD patients. Thus, as claimed for cardiac rehabilitation,[38] or even more important, the approach of fixed HR percentages may be inaccurate in a large proportion of ILD patients undertaking rehabilitation and should be replaced by individual VTs determined by CPET.

To the best of our knowledge, this is the first study reporting cardiorespiratory responses to CPET and comparing HRs at the individual VTs and fixed HR percentages. Thus, the presented findings derived from a relatively large cohort of ILD patients not only highlight the importance of CEPT but may also provide valuable basis for training intensity prescription for those patients.

This study may be limited by the inter-observer variability in the determination of ventilator threshold. In order to minimize the bias, the ventilatory thresholds were determined and cross-checked by two different observers. The patients in our study were only mild-to -moderately limited, which explain on one side that the VT2 could be assessed in all but 2 patients and on the contrary the relatively mild impairment in exercise capacity, which was nevertheless significantly lower compared with the control group.

4.1 | Perspectives

Our findings may be of interest as optimal training prescriptions are of utmost importance in therapy and rehabilitation of most chronic diseases.[34] Training intensities in pulmonary rehabilitation are commonly based on fixed percentages of Wpeak, HRpeak, or HRR.[16–19] The present study reports cardiorespiratory responses to CPET and compared the individual HRs of ILD patients at VT1 and VT2 with those at 70%Wpeak, 70%HRpeak, and 60%HRR.

Findings demonstrate significant deviations of cardiorespiratory responses in ILD patients compared with healthy controls. CI in CTD and IPF subgroups is especially noteworthy.

In addition, we demonstrate large variability of HR responses to exercise (CPET) in ILD patients and a considerable scattering of fixed HR percentages in comparison with HRs at the individual VTs. Similar results have been reported from training studies in chronic heart failure patients, demonstrating the VT1 as an useful and valid method for individual training prescription.[27,30,31] Moreover, intensity prescription based on HR identification at the VTs was also emphasized in LVDF[27] and even for healthy subjects.[23,32] Our findings suggest that in comparison with fixed HR percentages, the use of individual VTs is more appropriate to prescribe individually tailored exercise intensity in the rehabilitation of ILD patients. However, further confirmation will be necessary by well-designed, large-scaled intervention studies.

CONFLICT OF INTEREST

The authors declare that there are no conflicts existing for any authors.

AUTHOR CONTRIBUTIONS

Karin Vonbank designed the study, had full access to all of the data in the study, performed study examination, acquired data, analyzed and interpreted data, and wrote the manuscript draft. Antje Lehmann, Dominik Bernitzky, Maximilian Robert Gysan, and Stefan Simon performed study examination and acquired data. Pavla Krotka, Ralf-Harun Zwick, and Martin Burtscher analyzed and interpreted data and wrote manuscript draft. All listed authors read, revised, and finally approved the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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