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

Karin Vonbank¹ | Antje Lehmann¹ | Dominik Bernitzky¹ | Maximilian Robert Gysan¹ | Stefan Simon¹ | Pavla Krotka² | Ralf-Harun Zwick³ | Marco Idzko¹ | Martin Burtscher⁴

¹Department of Pulmonary Medicine, Medical University of Vienna, Vienna, Austria
²Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria
³ThermeWienMed, Ludwig Boltzmann Institute for Rehabilitation Research, Vienna, Austria
⁴Department of Sports Sciences, Medical Section, University of Innsbruck, Innsbruck, Austria

Correspondence
Karin Vonbank, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.
Email: karin.vonbank@meduniwien.ac.at

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.\(^1,12,24,25\) 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 mycophenolate-mofetil, and 8 patients on betablocker therapy.
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 (SpO₂) were recorded. Breath-by-breath minute ventilation (VE), carbon dioxide output (VCO₂), and oxygen uptake (VO₂) were measured using Sensormedics 2900 Metabolic Measurement Cart. The respiratory exchange ratio (RER) was defined as VCO₂/VO₂, the oxygen pulse was calculated by VO₂/heart rate, and the ventilatory equivalent for oxygen uptake (VE/VO₂) and the ventilatory equivalent for carbon dioxide production (VE/VCO₂) were measured. VT1 was determined using the V-slope method and double-checked by establishing the nadir of VE/VO₂ versus work rate relationship. VT2 was determined using the point of increase in VE versus VCO₂ and double-checked by establishing the nadir of VE/VCO₂ 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%Hpeak 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
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: \(((HR \text{ at } 70\%\text{HRpeak} - \text{VT1})/(\text{VT2} - \text{VT1}))\). 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.
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 \(54.6 \pm 13\) 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 \(\text{SpO}_2\) 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 \(85.8\% \pm 21.4\%\) pred and the mean carbon monoxide transfer factor (DLCO) was \(60.4\% \pm 20.8\%\) pred. None of the patients were on long-term oxygen therapy. Patients with IPF were significantly more limited with lower DLCO, and \(\text{SpO}_2\) 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 (\(\text{VO}_2\), \(W\), \(\text{SpO}_2\), 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. \(\text{VO}_2\)peak
(\%\text{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/VO₂ values in ILD patients and higher VE/VCO₂ values, except for patients with sarcoidosis, compared with controls. PETO₂ was significantly higher in CTD and IPF patients compared with controls. No significant differences were found between PETCO₂ and RER in both groups, but RER values are different between ILD subgroups (Table 3, Figure 2). With regard to sex-specific differences, relative VO₂peak did not differ between males and females and VO₂\%\text{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 VO₂peak 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 %VO₂peak \((p < 0.001)\), %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 %VO₂peak\%\text{pred} (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 (VO₂peak and Wpeak) and lower cardiorespiratory responses (HRpeak and SpO₂peak) to maximal exercise than controls.

Comparisons between ILD types revealed higher VO₂peak (\%\text{pred}) and peak HRs in patients with sarcoidosis compared with those with CTD, which is in agreement with other studies. In contrast to the control group, relative VO₂peak did not differ between males and females and VO₂\%\text{pred} was higher in females within the ILD patients. This observation might indicate that aerobic capacity in males...
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/VCO₂ values, considered as an index of the degree of V/Q inequality, were significantly higher in the CTD and IPF groups. Whereas the PETO₂ was significantly lower in the CTD and IPF patients of the present study is an interesting observation of significantly higher in the CTD and IPF groups. Whereas the PETO₂ was significantly lower in the CTD and IPF group, the PETCO₂, 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.³¹,³⁵ Whereas in athletes the largest proportion of the
**TABLE 4**  Sex-specific responses to maximal exercise

|        | ILD                      | Control group            |        |       |        |        |        |        |        |        |        |
|--------|--------------------------|--------------------------|--------|-------|--------|-------|--------|--------|--------|--------|--------|
|        | **Subjects, n**          | **Males**                | **Females** | **M versus F** | **Males** | **Females** | **M versus F** | **p-value** | **p-value** | **p-value** | **p-value** |
|        |                          |                          |         |       |        |       |        |        |        |        |        |
|        |                          | 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/VO_{2}, ventilatory equivalent for carbon dioxide production; VE/VCO_{2}, ventilatory equivalent for oxygen uptake; VO_{2}, oxygen uptake; W, power output.
training volume is performed at intensities below VT1,\(^\text{35}\) in patients suffering from lung diseases, including ILD. Intensities above VT1 are preferentially applied in rehabilitation.\(^\text{12,16,36}\) 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.\(^\text{36}\)

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.\(^\text{34,37,38}\) 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).\(^\text{27}\) Even in healthy subjects, it was shown that exercising according to a fixed HRR for 12 weeks, VO\(_2\)peak was increased in only 42% of the total group when compared to a significantly improved VO\(_2\)peak in all individuals exercising according to the range between VT1 and VT2.\(^\text{23,39}\) 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.\(^\text{40}\) 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,\(^\text{38}\) 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.\(^\text{34}\) Training intensities in pulmonary rehabilitation are commonly based on fixed percentages of Wpeak, HRpeak, or HRR.\(^\text{16–19}\) 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.

| Abbreviations: HR, heart rate; HRR, heart rate reserve; VT1, first ventilatory threshold; VT2, second ventilatory threshold; Wpeak, watt peak. |
|---|
| **p-value** for sex differences. |
| **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) |  |
| 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 |
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 VTI 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 LVDF27 and even for healthy subjects.23,32 Our findings suggest that in comparison with fixed HR percentages, the use of individual 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.

ORCID
Karin Vonbank https://orcid.org/0000-0003-2930-7252
Martin Burtscher https://orcid.org/0000-0002-5232-3632

REFERENCES
1. Holland AE, Dowman LM, Hill CJ. Principles of rehabilitation and reactivation: interstitial lung disease, sarcoidosis and rheumatoid disease with respiratory involvement. Respiration. 2015;89(2):89-99.
2. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7(2):101-111.
3. Agusti AG, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1991;143(2):219-225.
4. Gläser S, Noga O, Koch B, et al. Impact of pulmonary hypertension on gas exchange and exercise capacity in patients with pulmonary fibrosis. Respir Med. 2009;103(2):317-324.
5. Marillier M, Bernard AC, Verges S, Moran-Mendoza O, O’Donnell DE, Neder JA. Influence of exertional hypoxemia on cerebral oxygenation in fibrotic interstitial lung disease. Respir Physiol Neurobiol. 2020;285:103601.
6. Holland AE, Hill CJ, Glaspole I, Goh N, Dowman L, McDonald CF. Impaired chronotropic response to 6-min walk test and reduced survival in interstitial lung disease. Respir Med. 2013;107(7):1066-1072.
7. Watanabe F, Taniguchi H, Sakamoto K, et al. Quadriceps weakness contributes to exercise capacity in nonspecific interstitial pneumonia. Respir Med. 2013;107(4):622-628.
8. Nishiyama O, Taniguchi H, Kondoh Y, et al. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. Chest. 2005;127(6):2028-2033.
9. Guler SA, Hur SA, Lear SA, Camp PG, Ryerson CJ. Body composition, muscle function, and physical performance in fibrotic interstitial lung disease: a prospective cohort study. Respir Res. 2019;20(1):56.
10. Mendes P, Wickerson L, Helm D, et al. Skeletal muscle atrophy in advanced interstitial lung disease. Respirology. 2015;20(6):953-959.
11. Armstrong M, Vogiatzis I. Personalized exercise training in chronic lung diseases. Respirology. 2019;24(9):854-862.
12. Dowman LM, McDonald CF, Hill CJ, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax. 2017;72(7):610-619.
13. Perez-Bogerd S, Wuyts W, Barbier V, et al. Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. Respir Res. 2018;19(1):182.
14. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.
15. Spruit MA, Rochester CL, Pitta F, et al. Pulmonary rehabilitation, physical activity, respiratory failure and palliative respiratory care. Thorax. 2019;74(7):693-699.
16. Ward TJ, Plumptre CD, Dolmage TE, et al. Change in V˙O. Chron. 2020;158(1):131-144.
17. Vainsheboim B, Oliveira J, Fox BD, Soreck Y, Fruchter O, Kramer MR. Long-term effects of a 12-week exercise training program on clinical outcomes in idiopathic pulmonary fibrosis. Lung. 2015;193(3):345-354.
18. Jackson RM, Gómez-Marin OW, Ramos CF, et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung. 2014;192(3):367-376.
19. Combes A, Dekerle J, Dumont X, et al. Continuous exercise induces airway epithelium damage while a matched-intensity and volume intermittent exercise does not. Respir Res. 2019;20(1):12.
20. Luan X, Tian X, Zhang H, et al. Exercise as a prescription for patients with various diseases. J Sport Health Sci. 2019;8(5):422-441.
21. Palermo P, Corrà U. Exercise prescriptions for training and rehabilitation in patients with heart and lung disease. Ann Am Thorac Soc. 2017;14(Supplement_1):S59-S66.
22. Hansen JE, Sun X-G, Yasunobu Y, et al. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. Chest. 2004;126(3):816-824.
23. Wolpern AE, Burgos DJ, Janot JM, Dalleck LC. Is a threshold-based model a superior method to the relative percent concept for establishing individual exercise intensity? A randomized controlled trial. BMC Sports Sci Med Rehabil. 2015;7:16.
24. Nakazawa A, Cox NS, Holland AE. Current best practice in rehabilitation in interstitial lung disease. Ther Adv Respir Dis. 2017;11(2):115-128.
25. Kenn K, Gloeckl R, Behr J. Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis—a review. Respiration. 2013;86(2):89-99.
26. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. Am Rev Respir Dis. 1984;129(2 Pt 2):S49-S55.
27. Strzelczyk TA, Quigg RJ, Pfeifer PB, Parker MA, Greenland P. Accuracy of estimating exercise prescription intensity in patients with left ventricular systolic dysfunction. J Cardiopulm Rehabil. 2001;21(3):158-163.
28. Bonini M, Fiorenzano G. Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing. Eur Respir Rev. 2017;26(143):160099.
29. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA. 1999;281(6):524-529.
30. Bartels M, Armstrong H, Layton A, Lederer D. Does chronotropic incompetence occur in interstitial lung disease? Eur Respir J. 2011;38(Suppl 55):464.
31. Liu H-J, Guo J, Zhao Q-H, et al. Chronotropic incompetence and its relation to exercise intolerance in chronic obstructive pulmonary disease. Am J Med Sci. 2017;353(3):216-223.
32. Cherneva RV, Youroukova VM, Cherneva ZV. Dynamic hyperinflation, chronotropic intolerance and abnormal heart rate recovery in non-severe chronic obstructive pulmonary disease patients—reflections in the mirror. Pulmonology. 2021;S2531-0437(20):30264-6.
33. Wytrychowski K, Hans-Wytrychowska A, Piesiak P, Majewska-Pulsakowska M, Rożek-Piechura K. Pulmonary rehabilitation in interstitial lung diseases: a review of the literature. Adv Clin Exp Med. 2020;29(2):257-264.
34. Meyer T, Lucia A, Earnest CP, Kindermann W. A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters—theory and application. Int J Sports Med. 2005;26(Suppl 1):S38-S48.
35. Seiler KS, Kjerland G. Quantifying training intensity distribution in elite endurance athletes: is there evidence for an “optimal” distribution? Scand J Med Sci Sports. 2006;16(1):49-56.
36. Casaburi R, Wasserman K, Patessio A, Ioli F, Zanaboni S, Donner CF. A new perspective in pulmonary rehabilitation: anaerobic threshold as a discriminant in training. Eur Respir J Suppl. 1989;7:618S-623S.
37. Hansen D, Bonné K, Alders T, et al. Exercise training intensity determination in cardiovascular rehabilitation: should the guidelines be reconsidered? Eur J Prev Cardiol. 2019;26(18):1921-1928.
38. Pymer S, Nichols S, Prosser J, Birkett S, Carroll S, Ingle L. Does exercise prescription based on estimated heart rate training zones exceed the ventilatory anaerobic threshold in patients with coronary heart disease undergoing usual-care cardiovascular rehabilitation? A United Kingdom perspective. Eur J Prev Cardiol. 2020;27(6):579-589.
39. Weatherwax RM, Harris NK, Kilding AE, Dalleck LC. Incidence of V˙O2max responders to personalized versus standardized exercise prescription. Med Sci Sports Exerc. 2019;51(4):681-691.
40. Strokappke B, Saketkoo LA, Elfferich M, et al. Physical activity and training in sarcoidosis: review and experience-based recommendations. Expert Rev Respir Med. 2016;10(10):1057-1068.

How to cite this article: Vonbank K, Lehmann A, Bernitzky D, et al. Comparison of heart rates at fixed percentages and the ventilatory thresholds in patients with interstitial lung disease. Scand J Med Sci Sports. 2022;32:754–764. doi:10.1111/sms.14117