Research Square

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Appropriate selection of exercise intensity in patients with interstitial lung disease

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Abstract

Background

Training intensities in pulmonary rehabilitation are commonly based on fixed percentages of peak heart rate (HRpeak), heart rate reserve (HRR), or peak work load (Wpeak). For patients suffering from interstitial lung disease (ILD) it is unknown, whether those intensities are appropriate when compared to individual ventilatory thresholds (VT1 and VT2) derived from cardiopulmonary exercise testing (CPET). The aim of this study was to compare fixed HR percentages with HRs at VT1 and VT2.

Study Design and Methods

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.

Results

HRs at fixed percentages, i.e., at 70%HRpeak, at 70%Wpeak and at 60%HRR were significantly lower in the ILD patients compared to the control group. 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 to 18% in the control group.

Discussion

Our findings demonstrate a considerable scattering of fixed HR percentages compared to HRs at the individual VTs derived from CPET in ILD patients. Thus, the use of HRs at the individual VTs is recommended for appropriate prescription of exercise intensity in pulmonary rehabilitation of ILD patients.

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 to 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 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].

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]. CPET provides two important measures, the ventilatory threshold 1 (VT1) and 2 (VT2), that allows to differentiate between exercise intensity domains, i.e., moderate, high, severe, and extreme [21], which can be assessed reliably and reproducibly and performed safely even in patients with severe exercise intolerance [22].

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, the relationship between VT1 and VT2 derived from CPET and fixed percentages of peak heart rate (HRpeak), heart rate reserve (HRR), and peak work load (Wpeak) remains to be evaluated, especially for ILD patients.

The aim of this study was to compare the individual heart rates at VT1 and VT2 with those at 70%Wpeak, 70%HRpeak and 60%HRR. 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.

Methods

Subjects

A total of 120 patients, who were referred to the department of pulmonology, medical university of Vienna between 2018-2020, were included in this study, 80 patients with diagnosis of interstitial lung disease and 40 age-, weight- and height-matched control subjects (**table 1**). 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.

Cardiopulmonary exercise test (CPET)

All patients underwent a symptom limited CPET on an Ergoline 800 bicycle (Sensormedics, United States) with respiratory gas-exchange analysis, using a step protocol with progressive increase in workload every minute according to a total exercise time between 8-12 minutes. The increment was adapted to the expected maximum working capacity. Patients 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 minutes 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, double-checked by establishing the nadir of VE/VO_2 versus work rate relationship. VT2 was determined using the point of increase of the VE versus VCO_2, double-checked by establishing the nadir of VE/VCO_2 versus work rate relationship. Blood gas analysis was measured at rest, at VT1 and at peak exercise. Absolute values were measured and % of predictive values were assessed using reference values for CPET by Hansen and Jones.

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 (pred) *0,6 + resting HR [24].

Statistical analysis

Statistical analysis was performed by IBM SPSS version 27.0 (IBM SPSS Statistics for Windows, Chicago,IL, USA). Normal distribution of the data was verified by the Kolmogorov-Smirnov test and Shapiro-Wilk test. After a descriptive data analysis, between group differences in baseline characteristics were analysed 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. All tests were conducted as two-sided and p-value<0.05 was considered 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 was 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. Figures 1 and 2 show boxplots of the scaled HR values determined by the 3 formulas, for ILD patients and the control group, respectively.

Results

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 ± 13 years, 70 women (58%), 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 to patients with CTD and sarcoidosis. Compared to controls, resting HRs were higer 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 (TLCO) was 60.4 ± 20.8%pred. None of the patients were on long-term oxygen therapy.

Responses to maximal exercise are shown in **table 3.**

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

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 ($p<0.001$), in %Wpeak ($p<0.040$) and %HRpeak ($p<0.001$) in the patient group with ILD compared to controls, whereas both, VT1 and VT2 were significantly lower at %VO_2peakpred (**table 4**). Mean HRs at VT1 did not differ between groups, but mean HRs at VT2 were significantly lower in ILD patients. HRs at fixed percentages, i.e., at 70%HRpeak, at 70%Wpeak and at 60%HRR were significantly lower in the ILD patients compared to controls. In all patients except one the VT2 could be assessed.

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 (**figure 1**) compared to 18% in the control group (**figure 2**).

Discussion

In the present study, HRs at VT1 and VT2 have been compared to fixed HR percentages, i.e., 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 characteristcs 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 cardorespiratory 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 to those with CTD, which is in agreement with other studies (2,3,31). 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 appropiate 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 [25]. Compared to the number of studies including COPD patients, clinical studies dealing with pulmonary rehabilitation in ILD is relatively small [26]. Priciples 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 [26].

Generally, VTs derived from CPET ensure individual physiological adaptations to exercise and can help to find the optimal training “zones” [27]. 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, 28]. Whereas in athletes the largest proportion of the training volume is performed at intensities below VT1 [28], in patients suffering from lung diseases, including ILD, intensities above VT1 are preferentially applied in rehabilitation [12, 16, 29]. 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 [29].

The individual application of training intensities based on CEPT 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 [27, 30, 31]. 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) [24]. 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, 32]. It was also suggested that due to the heterogenity of ILD patients, i.e., those suffering from sarcoidosis, modification and program adjustment of the standard pulmonary rehabilitation format, including individual prescription of training intensity, are required [33]. Our findings confirm the large variability of heart rate responses to exercise (CPET) and the considerable scattering of fixed HR percentages in comparison to HRs at the individual VTs in ILD patients. Thus, as claimed for cardiac rehabilitation [31], 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 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 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 ventilatory threshold. In order to minimise 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 asessed in all but 2 patients and on the other hand the relatively mild impairement in exercise capacity, which was nevertheless significantly lower compared to the control group.

Conclusions

The presented findings demonstrate large variability of HR responses to exercise (CPET) in ILD patients and a considerable scattering of fixed HR percentages in comparison to HRs at the individual VTs. Thus, when compared to fixed HR percentages, the use of individual VTs is more appropriate to prescribe exercise intensity in the rehabiltation of ILD patients.

Declarations

Ethics approval:

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 (EC 1462).

Consent for publication:

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

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The authors declare that they have no competing interests.

Author contributions:

KV designed the study, had full access to all of the data in the study, performed study examination, acquired data, analysed and interpreted data and wrote the manuscript draft.

AL, DB, MRG, SS performed study examination and acquired data. PK, RHZ, MB analysed 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

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Abbreviations

COPD Chronic obstructive pulmonary disease

CPET Cardiopulmonary exercise testing

FEVC Forced ventilatory capacity

HR Heart rate

HRR Heart rate reserve

ILD Interstitial lung disease

IPF Idiopathic pulmonary fibrosis

LVDF Left-ventricular dysfunction

PRED Predicted

RPM Rate per minute

SpO_2 Peripheral oxygen saturation

TLCO Carbon monoxide transfer factor

VE Minute ventilation

VCO_2 Carbon dioxide output

VO_2 Oxygen uptake

VT Ventilatory threshold

W Work load

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Tables

Table 1 Characteristics of study participants

	ILD-patients	Control group	p-value	Types of ILD CTD	Sarcoidosis	IPF
Subjects, n	80	40		37	11	32
Age, years	54.6 (13.9)	54.7 (9.2)	0.980	50.0 (11.8)	52.9 (17.0)	61.2 (12.9)§
Female sex, n (%)	47 (59)	19 (51)	0.980	26 (70)	6 (55)	15 (47)
Body mass, kg	76.4 (17.2)	75.9 (15.4)	0.866	72.6 (14.5)	68.1 (13.3)	82.6 (18.4)§&
Height, cm	169.4 (9.0)	170.9 (9.0)	0.402	168.4 (7.7)	165.4 (8.6)	171.3 (10.3)
Body mass index, kg/m^2	26.5 (4.6)	25.8 (4.0)	0.448	27.2 (4.5)	26.7 (4.2)	25.5 (4.3)
Heart rate, rest, bpm	78.4 (13.0)	72.9 (13.3)	0.029	76.0 (10.9)	83.5 (11.6)*	79.5 (15.3)
SpO_2, rest, %	96.0 (1.6)	97.4 (1.8)	0.001	95.7 (1.8)*	96.4 (1.2)	96.2 (1.4)*

Data are presented as means (± standard deviation), except for sex (frequency), SpO_2: peripheral oxygen saturation, bpm: beats per minute; IPF: idiopathic pulmonary fibrosis, CTD: connective tissue disease

* different vs. control, § different vs. CTD, & different vs. Sarcoidosis,

Table 2 Characteristics of ILD patients

Interstitial lung disease	
IPF n (%)	32 (40.0)
CTD n (%)	37 (46.3)
Sarcoidosis n (%)	11 (13.7)
Patients with restriction, n (%)	38 (37.5)
TLC, L	6.1 (4.3)
FVC, %	85.8 (21.4)
FEV1, %pred	84.9 (21.2)
FEV1/FVC, %	78.6 (8.6)
RV/TLC, %	41.0 (7.7)
DLCO, %	60.4 (20.8)
$AaDO_2$ rest, mmHg	24.0 (12.0)
$AaDO_2$ exercise, mmHg	30.6 (18.1)
SaO_2 rest, %	96.0 (1.6)
SaO_2 exercise, %	93.7 (4.4)

Data are presented as means (± standard deviation) or frequencies and percentages (n, %),IPF: idiopathic pulmonary fibrosis, CTD: connective tissue disease,TLC: total lung capacity, FVC: forced vital capacity, FEV 1: forced expired volume in one second, RV: residual volume, DLCO: diffusion capacity of lung for carbon monoxide, $AaDO_2$: alveolar-arterial oxygen difference, SaO_2: arterial oxygen saturation

Table 3 Responses to maximal exercise

	ILD-patients	Control group	p-value	Types of ILD CTD	Sarcoidosis	IPF
Subjects, n	80	40		37	11	32
VO_2peak, ml/kg/min	20.2 (7.4)	30.4 (8.6)	0.001	20.5 (8.7)*	24.2 (8.0)*	18.4 (4.8)*
VO_2peak, %pred	83.4 (23.6)	119.0 (24.0)	0.001	82.8 (26.9)*	94.3 (15.4)*[§]	80.3 (21.1)*
Wpeak, watt	106.9 (51.6)	191.9 (59.4)	0.001	106.0 (53.6)*	122.6 (68.7)*	102.6 (68.7)*
Wpeak, %pred	75.3 (30.6)	131.2 (25.8)	0.001	77.7 (35.4)*	85.6 (31.0)*	69.1 (23.3)*
SpO_2peak, %	93.7 (4.4)	98.1 (0.9)	0.001	92.6 (4.9)*	95.7 (2.1)*	94.2 (4.1)*
HRpeak, bpm	145.4 (23.9)	162.5 (18.3)	0.001	148.3 (21.6)*	162.3 (21.0)[§]	136.2 (24.2)*
HRpeak, pred, %	87.8 (12.1)	98.3 (10.0)	0.001	88.2 (13.3)*	87.6 (11.5)*	86.5 (11.4)*

Data are presented as means (± standard deviation), except for sex (frequency), VO_2: oxygen uptake, W: power output, HR: heart rate, SpO_2: peripheral oxygen saturation, pred: predicted, bpm: beats per minute; * different vs. control, [§] different vs. IPF

Table 4 Intensity domains based on ventilatory thresholds and fixed heart rate percentages

	ILD-patients	Control group	p- value
Subjects, n	80	40	
VT1, %VO_2peak	57.1 (9.2)	47.8 (7.3)	0.001
VT1, %VO_2peak pred	45.4 (11.0)	57.0 (13.5)	0.001
VT1, %Wpeak	42.1 (21.3)	38.4 (7.8)	0.040
VT1, %HRpeak	72.5 (8.1)	63.7 (6.9)	0.001
VT2, %VO_2peak	82.8 (8.9)	79.2 (9.2)	0.044
VT2, %VO_2peak pred	67.2 (18.3)	93.8 (20.5)	0.001
VT2, %Wpeak	82.6 (12.5)	77.9 (9.7)	0.031
VT2, %HRpeak	90.5 (6.3)	87.1 (6.5)	0.005
HR at VT1, bpm	103.1 (14.4)	104.6 (16.4)	0.629
HR at VT2, bpm	131.2 (21.4)	141.1 (17.5)	0.012
HR at 70%HRpeak, bpm	101.8 (16.8)	113.8 (12.8)	0.001
HR at 70%Wpeak, bpm	123.5 (21.1)	131.1 (14.4)	0.044
HR at 60%HRR, bpm	118.6 (17.4)	126.7 (13.4)	0.011

Data are presented as means (± standard deviation)

VT1 and VT2: first and second ventilatory threshold, VO_2: oxygen uptake, W: power output,

HR: heart rate, HRR: heart rate reserve, pred: predicted, bpm: beats per minute

Figures

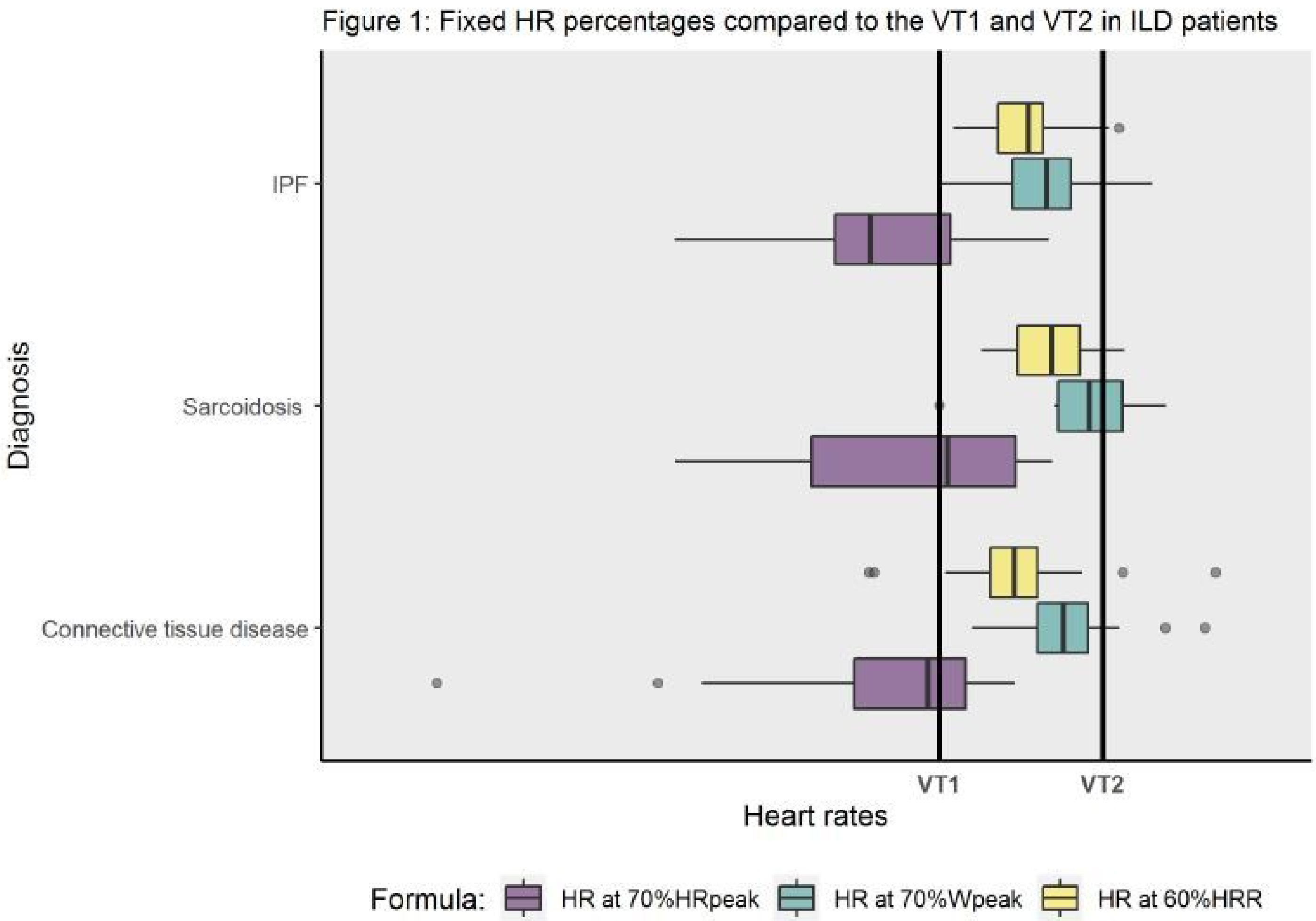

Figure 1

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

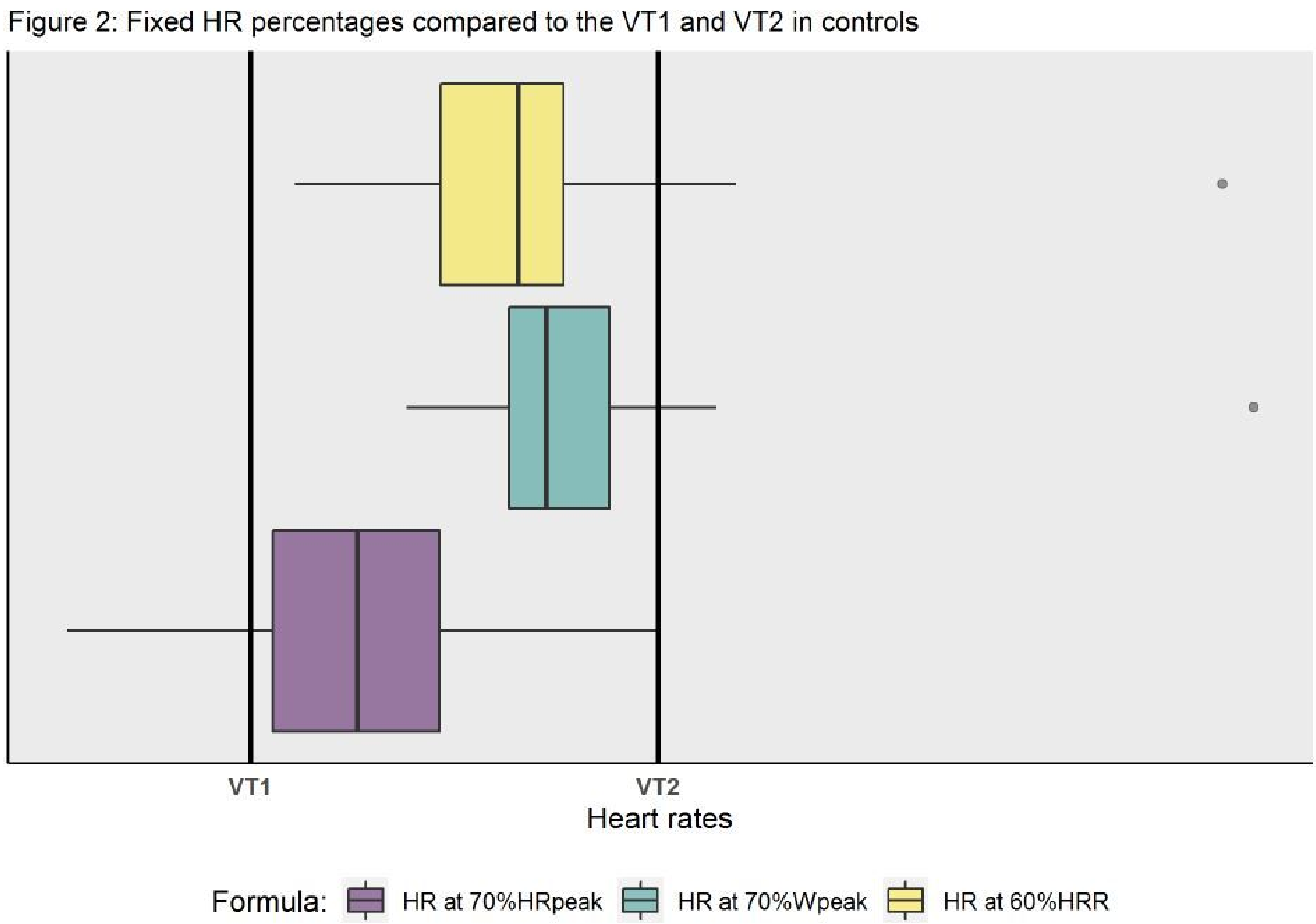

Figure 2

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