


# Exercise intensity domains determined by heart rate at the ventilatory thresholds in patients with cardiovascular disease: new insights and comparisons to cardiovascular rehabilitation prescription recommendations

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## ABSTRACT

**Objectives** To compare the elicited exercise responses at ventilatory thresholds (VTs: VT1 and VT2) identified by cardiopulmonary exercise testing (CPET) in patients with cardiovascular disease (CVD) with the guideline-directed exercise intensity domains; to propose equations to predict heart rate (HR) at VTs; and to compare the accuracy of prescription methods.

**Methods** A cross-sectional study was performed with 972 maximal treadmill CPET on patients with CVD. First, VTs were identified and compared with guideline-directed exercise intensity domains. Second, multivariate linear regression analyses were performed to generate prediction equations for HR at VTs. Finally, the accuracy of prescription methods was assessed by the mean absolute percentage error (MAPE).

**Results** Significant dispersions of individual responses were found for VTs, with the same relative intensity of exercise corresponding to different guideline-directed exercise intensity domains. A mathematical error inherent to methods based on percentages of peak effort was identified, which may help to explain the dispersions. Tailored multivariable equations yielded  $r^2$  of 0.726 for VT1 and 0.901 for VT2. MAPE for the novel VT1 equation was 6.0%, lower than that for guideline-based prescription methods (9.5 to 23.8%). MAPE for the novel VT2 equation was 4.3%, lower than guideline-based methods (5.8%–19.3%).

**Conclusion** The guideline-based exercise intensity domains for cardiovascular rehabilitation revealed inconsistencies and heterogeneity, which limits the currently used methods. New multivariable equations for patients with CVD were developed and demonstrated better accuracy, indicating that this methodology may be a valid alternative when CPET is unavailable.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Exercise intensity prescription guided by cardiopulmonary exercise testing (CPET) is the gold-standard method.
- ⇒ Guideline-based exercise intensity domains for cardiovascular rehabilitation revealed marked inconsistencies and heterogeneity, limiting the heart rate ‘range-based’ current methods employed, commonly used when CPET is unavailable.

## WHAT THIS STUDY ADDS

- ⇒ A mathematical error is inherent to methods based on simple percentages of peak effort, which is minimised using multivariable equations derived from parameters that can be obtained in an ergometry test.
- ⇒ The novel equations tailored for patients with cardiovascular diseases (CVDs) demonstrated superior accuracy (mean absolute percentage error of 6.0% for the first ventilatory threshold and 4.3% for the second ventilatory threshold), indicating that these equations may be a valid alternative when CPET is unavailable.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study offers a new clinical perspective when CPET is not available. We recommend using the multivariable equations tailored to patients with CVD rather than the classic ‘range-based’ prescription that uses a percentage of peak effort. The equations presented in this study can be an interesting alternative, as demonstrated by the high  $r^2$  values and the better forecasting accuracy compared with other indirect methods.

## INTRODUCTION

Cardiovascular rehabilitation (CR) for patients with cardiovascular disease (CVD) is a consensus among international guidelines,<sup>1–5</sup> considering the reductions in morbidity and mortality rates.<sup>5–10</sup> Hence, properly determining the exercise intensity prescription for patients with CVD is a cornerstone of an efficient and safe CR.<sup>11 12</sup> Ideally, exercise intensity prescription is established by an individualised functional capacity assessment, and cardiopulmonary exercise testing (CPET) is the gold-standard method.<sup>2 3 11 13 14</sup> Indeed, evidence has demonstrated that patients with CVD have heterogeneous responses to incremental exercise, with differences in the first and second ventilatory thresholds (VT1 and VT2) when expressed in oxygen uptake ( $\text{VO}_2$ ) and heart rate (HR).<sup>3 15</sup> In addition, studies have documented great variability in individual metabolic responses when exercise intensity is performed in relation to percentages of peak effort.<sup>16–18</sup> This occurs because prescriptions based on peak exercise percentages assume all participants will experience similar physiological responses at the same relative intensity, which is not necessarily true.<sup>18 19</sup> Thus, a ‘threshold-based’ prescription rather than a ‘range-based’ approach is recommended to improve the benefits of CR.<sup>3 11 14</sup>

When CPET is unavailable, CR guidelines recommend an aerobic exercise prescription based on indices of peak effort, including percentages of peak workload, peak HR ( $\%HR_{\text{peak}}$ ) or HR reserve ( $\%HRR$ ) according to responses during an ergometry test. However, recent evidence has shown the need to carefully revise these methods currently applied in CR due to internal inconsistencies and disagreements.<sup>11 16 17</sup> Hansen *et al*<sup>16</sup> studied 272 patients with CVD assessed by CPET on a cycle ergometer. They revealed that the same relative level of exercise elicited different intensity domains, with a considerable interindividual variation ranging from low to hard intensity. Pymmer *et al*<sup>17</sup> found similar results in a study involving 112 patients, in which inaccuracy was found in many patients when HR corresponding to VT1 was compared with HR-based exercise prescription.

Considering these significant discrepancies in individual responses to effort intensity in the ‘range-based methods’ recommended by CR guidelines,<sup>2 11 20</sup> and the lack of consistent guidance regarding exercise prescriptions for patients with CVD, it is essential to explore this subject more deeply, compare different international recommendations, seek solutions to the observed inconsistencies and develop new methods.

Thus, our study aimed to compare elicited exercise responses at VT1 and VT2 (expressed as  $\%HR_{\text{peak}}$ ,  $\%HRR$  and percentage of peak  $\text{VO}_2$  ( $\%\text{VO}_{2\text{peak}}$ )) to Brazilian,<sup>2</sup> European<sup>11</sup> and American<sup>20</sup> guideline-based exercise intensity domains for CR. A further aim was to propose equations to improve HR-based prescription parameters tailored to patients with CVD using variables available in an ergometry test. We also compared the accuracy

of guideline-based prescriptions’ moderate intensity domains according to  $\%HR_{\text{peak}}$  and the novel equations.

## METHODS

### Population and design

A single-centre retrospective cross-sectional study was conducted involving the records of patients with CVD assessed by CPET in the Brazilian Midwest region between January 2011 and December 2021. Patients were primarily referred to CPET for cardiovascular risk stratification and exercise prescription. The tests were supervised and interpreted according to international recommendations.<sup>14 20–22</sup>

The inclusion criteria were treadmill CPETs performed by patients with CVD aged  $\geq 20$  years and the absence of pulmonary, neurological or severe orthopaedic diseases. The exclusion criteria were atrial fibrillation, a pacemaker or implantable cardioverter-defibrillator without sinus rhythm during exercise, a non-identified VT2 and respiratory exchange ratio (RER) $<1.10$  at peak effort.

### Patient and public involvement

As data were collected retrospectively, there was no patient or public involvement in the study.

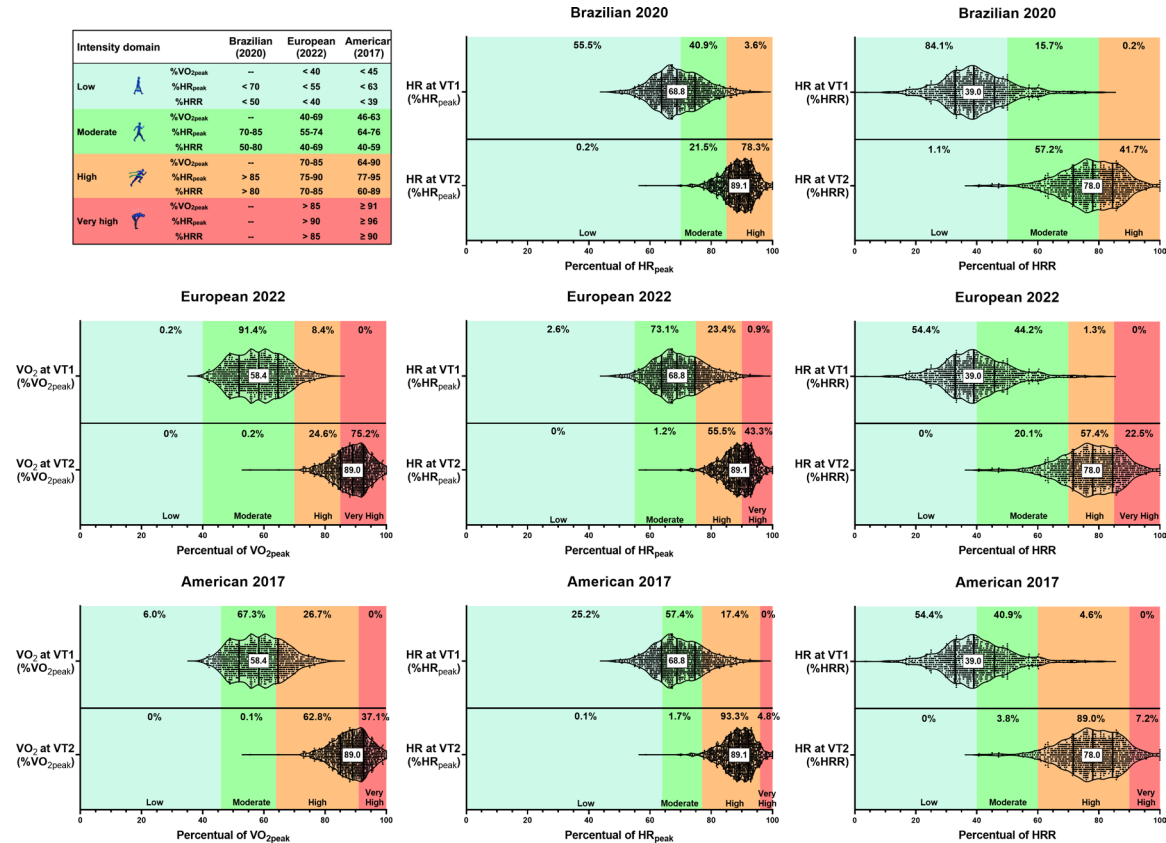
### Assessments

The subjects underwent a clinical assessment with the acquisition of demographic and anthropometric variables, clinical information about cardiovascular risk factors, previous diseases and medication use.

The tests were conducted without withdrawing cardiovascular medication and were performed on a treadmill (Centurium 200, Micromed, Brazil) using breath-by-breath gas analysis (Cortex Metalyser 3B, Germany). Symptom-limited maximal exercise testing was performed with an individualised adjusted ‘ramp protocol’. Treadmill speed started at 1.5–3 km/hour without inclination. The load increase rate was linear and adjusted according to age, sex and disease severity, with a steeper speed increase in males and younger subjects, while a steeper grade increase was applied in older subjects. This load adjustment in the ramp protocol was individualised to yield a fatigue-limited exercise test with an expected duration of 8–12 min.<sup>21 22</sup>

Variables from CPET were analysed, converting raw data to a 9-breath moving average. Peak  $\text{VO}_2$  ( $\text{VO}_{2\text{peak}}$ ) was the highest 30 s averaged sample obtained from the final test minute. At the same time frame, the highest value of RER and HR at peak effort was considered. Resting HR ( $HR_{\text{rest}}$ ) was obtained by ECG in the seated position before the beginning of CPET and after a total rest time greater than 5 min, considering the preparation for the exam.<sup>20</sup> Predicted  $HR_{\text{peak}}$  was calculated using the Tanaka equation<sup>23</sup>, and predicted  $\text{VO}_{2\text{peak}}$  was based on Brazilian reference values<sup>24</sup>.

VTs were used to define the gold-standard exercise intensity domains. VT1 marks the limit between light to moderate exercise, and VT2 marks the limit between



**Figure 1** HR at first and second ventilatory threshold (VT1 and VT2) according to obtained percentages of HRR of peak oxygen uptake ( $\%VO_{2peak}$ ), peak HR ( $\%HR_{peak}$ ) or HR reserve ( $\%HRR$ ) and different exercise intensity domains elicited according to cardiovascular rehabilitation guidelines. Data expressed as violin plots for individual values with vertical lines representing median and IQR values. The percentual number on the line above violin plots expresses the distribution of frequency of occurrence of individual responses in correspondence to recommended exercise intensity domains according to each set of guidelines (Brazilian<sup>2</sup>, European<sup>11</sup> and American<sup>20</sup>). HR, heart rate.

moderate to high-intensity effort.<sup>2 11</sup> Individual determination of VT1 and VT2 was based on the analysis of the exercise ventilation (VE),  $VO_2$  and carbon dioxide production ( $VCO_2$ ) over time, oxygen and carbon dioxide ventilatory equivalent ( $VE/VO_2$  and  $VE/CO_2$ ) over time and end-tidal partial pressure for oxygen and carbon dioxide ( $PETO_2$  and  $PETCO_2$ ) over time<sup>14</sup>.

VT1 was defined using the V-slope method ( $VCO_2$  vs  $VO_2$  plot) and was double-checked by establishing the nadir of  $VE/VO_2$  and  $PETO_2$  before rising<sup>14</sup> in the graphs over time. VT2 was defined using the VE vs  $VCO_2$  plot at the point where VE increases out of proportion to  $VCO_2$ . This threshold was double-checked by establishing the nadir of  $VE/VCO_2$  before rising and the highest  $PETCO_2$  before falling.<sup>14</sup>  $VO_2$  and HR were determined at VT1 and VT2 to calculate  $\%VO_{2peak}$ ,  $\%HR_{peak}$  and  $\%HRR$ .

### Intensity domains according to international guidelines

Obtained HR and  $VO_2$  at VT1 and VT2 were individually categorised in intensity domains according to CR guidelines<sup>2 11 20</sup> based on  $\%VO_{2peak}$ ,  $\%HR_{peak}$  and  $\%HRR$  (figure 1). These three methods report exercise intensity domains in European and American

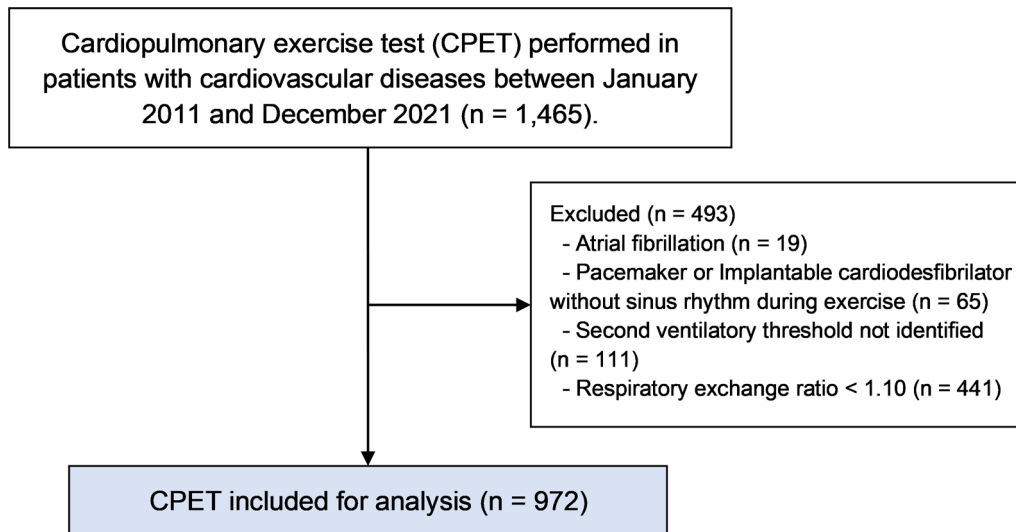
guidelines, whereas Brazilian recommendations focus only on HR methods.

### Multivariable equations to predict HR at VTs

Predictors were selected considering variables available in an ergometry test. This approach was chosen to create useful equations to predict HR at VT1 and VT2 when CPET cannot be performed. Thus, peak metabolic equivalent ( $MET_{peak}$ ) was calculated according to peak treadmill speed and inclination<sup>25</sup> and used as a predictor in the regression analysis rather than measured  $VO_{2peak}$ . The other predictors tested were age, sex,  $HR_{peak}$ ,  $HR_{rest}$ , HRR, beta-blocker use and beta-blockers relative dose (percentual of daily use to the maximal recommended dose).<sup>26</sup>

### Accuracy of prescription methods

To evaluate the accuracy of the prescription methods, HR values at VT1 and VT2 were compared with estimated values of each guideline-directed recommendation for moderate intensity domains according to  $\%HR_{peak}$  using measured and predicted  $HR_{peak}$ .<sup>23</sup> This approach was also used for the equations developed in the study.



**Figure 2** Study flow chart.

### Statistical analysis

Data were expressed as median and IQR or absolute and relative frequencies. Normality was assessed using the Kolmogorov-Smirnov test. Correlations between CPET variables were calculated using Spearman's correlation test since the data had a non-normal distribution. Considering variables significantly correlated with HR at VT1 and VT2, we performed linear regressions with  $HR_{peak}$  and multilinear regressions with the stepwise forward method. We selected the equation with the highest adjusted  $r^2$  value. Predictors without the ability to increase  $r^2$  by at least 0.01 were removed from the final equation.

Accuracy analysis was performed by calculating the mean absolute percentage error (MAPE; mean absolute difference of measured minus estimated values divided by measured values). Lower MAPE values indicate a lower error and greater forecasting accuracy of a model. Statistical analyses were performed using GraphPad Prism V.9 (GraphPad Software, San Diego, California, USA) or IBM-SPSS V.28.0 for Windows. All tests with a significance of  $p < 0.05$  were considered statistically significant.

## RESULTS

### Sample and subject characteristics

A total of 1465 CPETs were considered for eligibility, and 972 examinations were included (figure 2). The patients were mainly males (80.8%) with a median age of 58 (IQR: 50–66). Most patients had coronary artery disease (81.4%), and 26.6% had heart failure with a reduced ejection fraction (table 1). Median  $VO_{2peak}$  was 22.1 mL/kg/min (IQR: 17.1–27.4), corresponding to 70.7% of the predicted value (IQR: 58.8–83.4) (table 2).

### VT1 and VT2 in relation to guideline-based exercise intensity domains

VT1 was determined at 58.4% (IQR: 51.9–64.6) of  $\%VO_{2peak}$ , 68.8% (IQR: 63.8–74.7) of  $\%HR_{peak}$  and 39.0%

(IQR: 32.9–45.8) of  $\%HRR$  (table 2). For most patients, this response corresponded to moderate intensity exercise based on  $\%VO_{2peak}$  according to European and American guidelines (91.4% and 67.3%, respectively). Regarding responses related to  $\%HR_{peak}$ , most patients were performing low-intensity exercise according to the Brazilian guidelines (55.5%) and moderate intensity according to European and American guidelines (73.1% and 57.4%, respectively). The responses of most patients corresponded to the low-intensity domain for  $\%HRR$  in all three sets of guidelines (figure 1).

VT2 was determined at 89.0% (IQR: 85.0–92.6) of  $\%VO_{2peak}$ , 89.1% (IQR: 85.8–92.2) of  $\%HR_{peak}$  and 78.0% (IQR: 71.6–84.5) of  $\%HRR$  (table 2). For most patients, these responses corresponded to very high intensity for  $\%VO_{2peak}$  according to the European guidelines (75.2% of individual responses) and high intensity according to the American guidelines (62.8%). Considering  $\%HR_{peak}$ , most individual responses corresponded to high-intensity domains as stated in the Brazilian, European and American guidelines (78.3%, 55.5% and 93.3%, respectively). Lastly, individual responses corresponded to the moderate intensity domain for  $\%HRR$  according to the Brazilian guidelines (57.2%) and high intensity according to European and American guidelines (57.4% and 89.0%, respectively) (figure 1).

### HR predictive equations in VTs

HR at VT1 was strongly correlated with  $HR_{peak}$  ( $\rho = 0.764$ ), with the linear regression revealing a  $r^2$  of 0.593 (figure 3A). The following equation represents this correlation:

$$HR \text{ at VT1} = (0.4707 \times HR_{peak}) + 30.62 \quad (1)$$

Also, the linear regression of  $\%HR_{peak}$  at VT1 versus  $HR_{peak}$  (figure 3B) revealed that higher values of  $\%HR_{peak}$  at VT1 were associated with lower values of  $HR_{peak}$ .



**Table 1** General characteristics of the study sample

Characteristic	All sample (n=972)
Male	785 (80.8%)
Age, year	58 (50, 66)
Risk factors	
Hypertension	521 (53.6%)
Diabetes mellitus	172 (17.7%)
Tobacco use (actual)	14 (1.4%)
Previous cardiovascular disease	
Coronary artery disease	791 (81.4%)
Coronary angioplasty	502 (51.6%)
Myocardial infarction	411 (42.3%)
Heart surgery	279 (28.7%)
Heart failure	259 (26.6%)
Anthropometry	
Weight, kg	77.0 (68.0, 86.6)
Height, m	1.70 (1.64, 1.76)
Body mass index, kg/m <sup>2</sup>	26.5 (24.5, 29.2)
Medications, percentual of use	
ACEi/ARB	376 (38.7%)
Diuretics	307 (31.6%)
Beta-blockers	765 (78.7%)
Atenolol	98 (10.1%)
Bisoprolol	240 (24.7%)
Carvedilol	161 (16.6%)
Metoprolol	240 (24.7%)
Nebivolol	20 (2.1%)
Propranolol	6 (0.6%)
Medications' dose, mg per day	
Atenolol	50 (25, 50)
Bisoprolol	2.5 (2.5, 5.0)
Carvedilol	25 (12.5, 50)
Metoprolol	50 (25, 100)
Nebivolol	5.0 (2.5, 5.0)
Propranolol	80 (80, 80)

Data expressed as median and IQR or absolute and relative frequencies n (%).  
ACEi/ARB, ACE inhibitors/angiotensin receptor blockers.

HR at VT2 strongly correlated with HR<sub>peak</sub> (rho=0.941), with the linear regression revealing a r<sup>2</sup> of 0.890 (figure 3C). Less variability in %HR<sub>peak</sub> at VT2 when analysed according to HR<sub>peak</sub> (figure 3D). The following equation represents this correlation:

$$\text{HR at VT2} = (0.8544 \times \text{HR}_{\text{peak}}) + 4.397 \quad (2)$$

Nearly all correlations between CPET variables and HR at VT1 and VT2 were significant. Thus, multivariable linear regression with predictors available in an ergometry test was used to estimate HR at VT1 and VT2, which yielded the following novel equations tailored to patients with CVD with relevant r<sup>2</sup> values:

**Table 2** Cardiopulmonary exercise test variables of the study sample

CPET variables	All sample (n=972)
VO <sub>2peak</sub> , mL/kg/min	22.1 (17.1, 27.4)
VO <sub>2peak</sub> , percentual of predicted*	70.7 (58.8, 83.4)
HR <sub>peak</sub> , bpm	144 (125, 160)
HR <sub>peak</sub> , percentual of predicted†	89.0 (78.3, 97.5)
HR <sub>rest</sub> , bpm	68 (61, 75)
HRR, bpm	76 (57, 91)
Peak RER	1.20 (1.15, 1.27)
VO <sub>2</sub> at VT1, mL/kg/min	12.4 (10.6, 14.5)
VO <sub>2</sub> at VT1, %VO <sub>2peak</sub>	58.4 (51.9, 64.6)
HR at VT1, bpm	96 (88, 107)
HR at VT1, %HR <sub>peak</sub>	68.8 (63.8, 74.7)
HR at VT1, %HRR	39.0 (32.9, 45.8)
VO <sub>2</sub> at VT2, mL/kg/min	19.1 (15.2, 24.3)
VO <sub>2</sub> at VT2, %VO <sub>2peak</sub>	89.0 (85.0, 92.6)
HR at VT2, bpm	125 (109, 142)
HR at VT2, %HR <sub>peak</sub>	89.1 (85.8, 92.2)
HR at VT2, %HRR	78.0 (71.6, 84.5)

Data expressed as median and IQR.  
\*According to Brazilian reference values.  
†According to Tanaka *et al.*<sup>23</sup>  
HR, heart rate; HR<sub>peak</sub>, peak heart rate; %HR<sub>peak</sub>, percentage of peak HR; %HRR, percentage of HR reserve; HR<sub>rest</sub>, rest HR; RER, respiratory exchange ratio; VO<sub>2</sub>, oxygen uptake; VO<sub>2peak</sub>, peak VO<sub>2</sub>; %VO<sub>2peak</sub>, percentage of VO<sub>2peak</sub>; VT1, first ventilatory threshold; VT2, second VT.

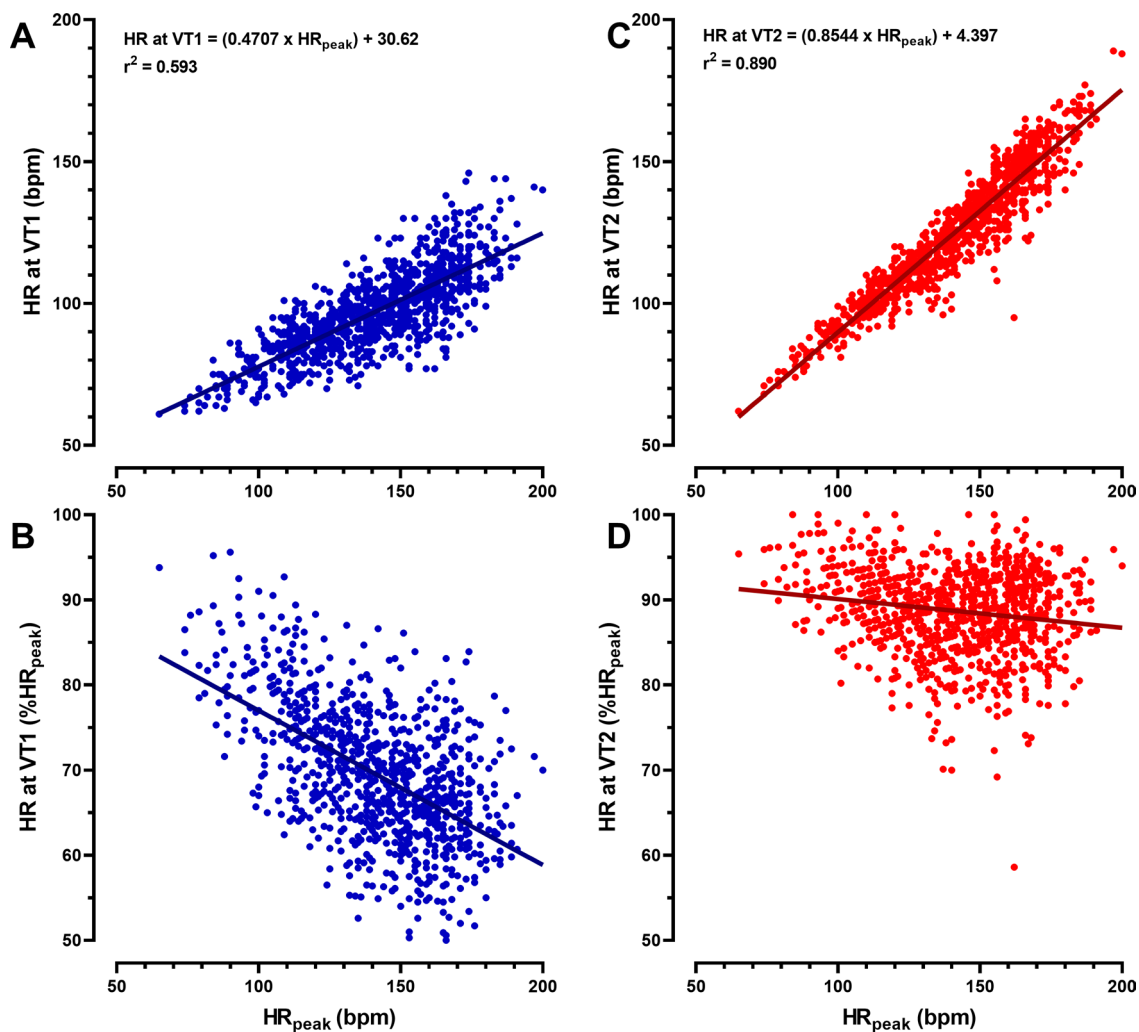
$$\begin{aligned} \text{HR at VT1} = & 3.453 + (0.887 \times \text{HR}_{\text{peak}}) - (0.555 \times (\text{HR}_{\text{peak}} - \text{HR}_{\text{rest}})) + \\ & (1.044 \times \text{MET}_{\text{peak}}), r^2 = 0.726 \end{aligned} \quad (3)$$

$$\begin{aligned} \text{HR at VT2} = & -8.256 + (0.979 \times \text{HR}_{\text{peak}}) - (0.232 \times (\text{HR}_{\text{peak}} - \text{HR}_{\text{rest}})) + \\ & (1.418 \times \text{MET}_{\text{peak}}), r^2 = 0.901 \end{aligned} \quad (4)$$

Of note, beta-blockers use, age and sex were imputed as predictors in the model construction; however, they did not reveal significant influences and were removed from the equations.

### Accuracy of prescription methods

Forecasting accuracy was assessed using MAPE calculations (figure 4). MAPE of the novel VT1 equation was 6.0%, lower than values calculated using the guideline-based prescription methods considering measured HR<sub>peak</sub> (9.5%–20.0%) or predicted HR<sub>peak</sub> (11.4%–23.8%). MAPE was even lower for the novel VT2 equation (4.3%), which was also lower than values determined using the guideline-based methods (5.8%–16.4% for measured HR<sub>peak</sub> and 13.7%–19.3% for predicted HR<sub>peak</sub>).



**Figure 3** Correlations between heart rate at ventilatory thresholds (VTs) and peak heart rate (HR). (A) Correlation for HR at VT1 (expressed as absolute value) and HR<sub>peak</sub>; (B) correlation for HR at VT1 (expressed as %HR<sub>peak</sub>) and HR<sub>peak</sub>; (C) correlation for HR at VT2 (expressed as absolute value) and HR<sub>peak</sub>; (D) correlation for HR at VT2 (expressed as %HR<sub>peak</sub>) and HR<sub>peak</sub>. HR<sub>peak</sub>, peak HR; %HR<sub>peak</sub>, percentage of HR<sub>peak</sub>.

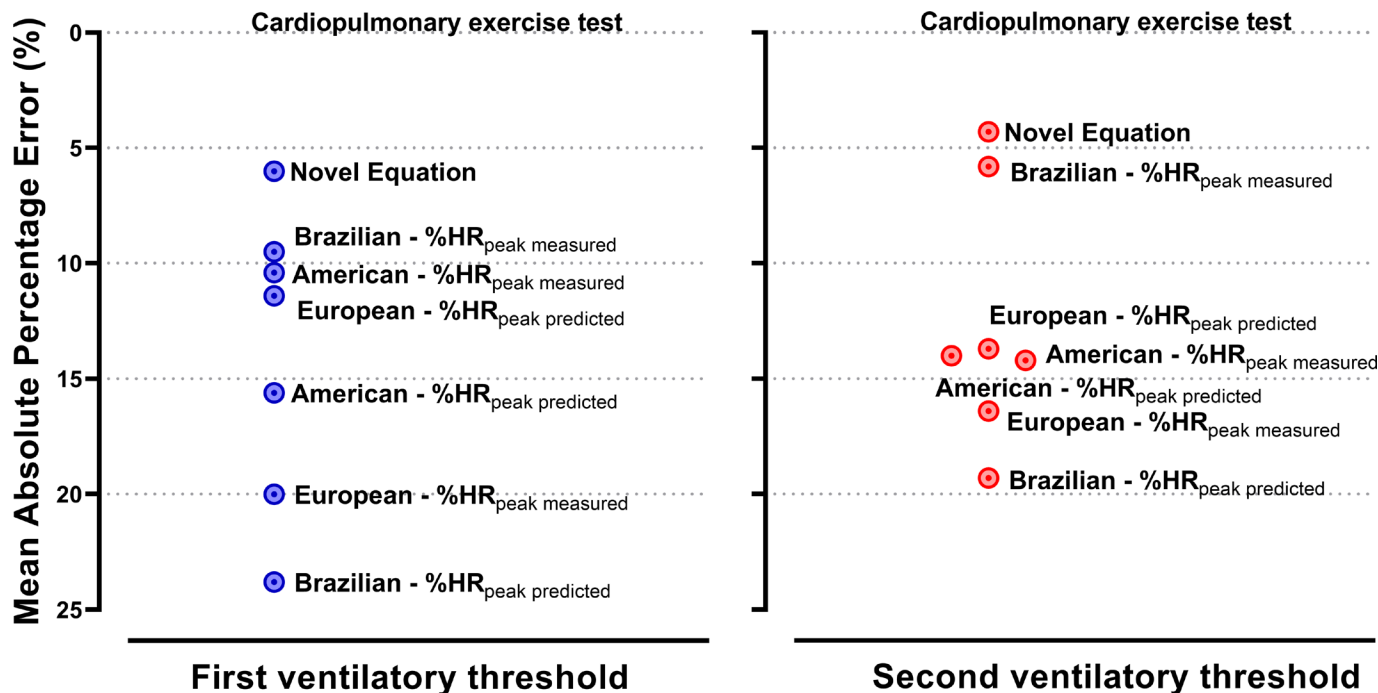
## DISCUSSION

This study reported results from a large sample of CR patients, in which we found that different guideline-based exercise intensity domains were elicited for the same relative level of exercise, whether at VT1 or VT2 (figure 1). Considering Brazilian, European and American guidelines, the results corresponded to low to moderate exercise intensity domains for VT1 and to moderate to very high-intensity exercise domains for VT2. The results showed that the relations between %HR<sub>peak</sub> at VTs and HR<sub>peak</sub> are not constant (figure 3), especially for VT1, which mathematically limits the applicability of the prescription methods based on a percentage of peak effort variables. We also offer greater insight into improving CR exercise prescription when CPET is unavailable by providing VT1 and VT2 equations tailored to patients with CVD using variables assessed during an ergometry test. Moreover, MAPE analyses revealed that the novel equations have greater accuracy than other methods generally used in CR to prescribe the exercise intensity targets based on

%HR<sub>peak</sub>, indicating that our proposal is the closest to metabolic thresholds of CPET (figure 4).

## VT1 and VT2 in relation to guideline-based exercise intensity domains

The correspondence of different exercise intensity parameters has been studied. Considerable variation is found in recommendation targets for prescription,<sup>13 16 27-30</sup> since the same relative %HR<sub>peak</sub>, %HRR and/or %VO<sub>2peak</sub> elicited different guideline-based exercise intensity domains (which could be considered low to moderate intensity for VT1 and moderate to high intensity for VT2). Consequently, an important percentage of subjects will be trained below VT1 or above VT2 when HR-based methods are used, as demonstrated by the high dispersion found in the individual responses of the patients (figure 1). Hansen *et al*<sup>16</sup> also found considerable variation in guideline-based exercise intensity domains at the same relative level of exercise, and Díaz-Buschmann *et al*<sup>13</sup> pointed out the substantial interpatient variance



**Figure 4** Forecasting accuracy calculated by mean absolute percentage error of exercise prescription using indirect methods for first and second ventilatory thresholds. Gold standard (MAPE equals zero) considered ventilatory thresholds identified by cardiopulmonary exercise testing. Guideline references: Brazilian<sup>2</sup>, European<sup>11</sup> and American.<sup>20</sup> %HR<sub>peak</sub>, percentage of peak heart rate, measured or predicted; MAPE, mean absolute percentage error.

among patients with CVD about HR-based prescription. These findings could partially be explained by the non-linearity and high variability of the relation between  $\text{VO}_2$  and workload in patients with CVD,<sup>31 32</sup> chronotropic incompetence and the use of beta blockers, which influence the relation between HR and  $\text{VO}_2$ .<sup>33</sup> Additionally, Iannetta *et al*<sup>34</sup> recently reported that the intensity of exercise training during CR predicts the increase of MET peak, highlighting that the heterogeneity in the metabolic stimulus of each exercise session can generate individual variation in training adaptations.<sup>34–36</sup>

#### Novel equations for patients with CVD

This study revealed a simple but crucial mathematic limitation inherent to the method for seeking a fixed percentage of peak parameters for prescribing exercise intensity. For example, if we consider 69% of  $\text{HR}_{\text{peak}}$  as the lower limit of exercise prescription (value for HR at VT1 in our data), we will assume that the equation follows a linear equation ( $Y=A*X+B$ ), in which  $Y=\text{HR}$  at VT1,  $A=0.69$ ,  $X=\text{HR}_{\text{peak}}$  and  $B=0$  ( $\text{HR}$  at VT1= $0.69 * \text{HR}_{\text{peak}}+0$ ). Thus, the mathematical concept suggests that the relation between HR at VT1 and  $\text{HR}_{\text{peak}}$  (or  $Y/X$ ) is constant when plotted against  $\text{HR}_{\text{peak}}$  (or  $X$ ). In other words, when using the % $\text{HR}_{\text{peak}}$  method, we assume that intercept (B) equals zero without considering any correction for the data dispersion.

However, when we analyse the plotted curve of our data (figure 3A), we observe that the intercept (B) is 30.62, strongly different from zero. Moreover, the coefficient (A) is 0.4707, which is also very different from the value

considered for moderate-intensity exercise in the guidelines (Brazilian: 0.70; European: 0.55; American: 0.64). We also noticed a significant association between higher values of % $\text{HR}_{\text{peak}}$  at VT1 and lower  $\text{HR}_{\text{peak}}$  values (figure 3B). Regarding VT2, our intercept (B) is much more like previously assumed values (4.397 vs 0), and the same is true for the coefficient (A) (0.8544 vs Brazilian: 0.85; European: 0.7; American: 0.76).

Thus, applying this simple math problem to the real world, we can see that the widely used method of prescribing exercise intensity according to percentages of  $\text{HR}_{\text{peak}}$  has an important limitation. The greater observed error can be related to the method itself and not the percentage values, as we cannot assume that the intercept of the equation is zero, especially concerning VT1, which is considered the lower limit for a moderate-intensity exercise prescription.

#### Accuracy of prescription methods

Another important contribution of this study is the accuracy approach by MAPE, in which lower values indicate greater forecasting accuracy of a model. MAPE of the VT1 equation was 6.0%, lower than guideline-based prescription methods (9.5%–23.8%). Moreover, the MAPE for the VT2 equation was 4.3%, which was also lower than guideline-based methods (5.8%–19.3%). These results suggested that the novel equations can be used as an alternative for patients with CVD, defining an intensity closer to the parameter determined by the CPET. The approach by MAPE was recently also used in a study comparing the accuracy of different predictive equations

applied to CR.<sup>32</sup> The reported MAPE for VT1 estimation ranged from 11.3 to 16.5% in patients with heart failure.

### Clinical implications

Similarly to others,<sup>13 16 17</sup> our study has demonstrated that currently employed methods using percentages of peak exercise ('range-based' approach) can be inaccurate for exercise intensity prescription, which may influence clinical outcomes. Hence, the HR predictive equations proposed in this study, primarily developed for VTs identification and using parameters available on the ergometry test, recognised as a minimum standard, demonstrated higher  $r^2$  and a lower error measured by MAPE than previously adopted indirect methods.

Thus, this new approach has great clinical applicability and may be a useful alternative when only an ergometry test is available, providing an indirect prescription closer to VTs of the CPET, which remains the gold-standard method.

### Limitations

First, although including a large sample, the data were provided from a single centre. However, our sample is from Brasilia (the capital of Brazil). It may constitute casual pooled data from different Brazilian regions as the area received intense migration in the mid-1960s due to the relocation of the capital, as previously reported.<sup>24</sup> External validity in other population samples remains to be tested to assure international applicability. Lastly, our study only included data from CPET performed on a treadmill; thus, our equations may not apply to exercise tests obtained from cycle ergometers.

### CONCLUSION

The analysis of guideline-based exercise intensity domains for CR revealed inconsistencies and heterogeneity among current international guidelines recommendations, which limits usually used methods since the dispersion of individual data is considerable. Our results demonstrated that prescribing exercise intensity according to percentages of  $HR_{peak}$  has an important mathematical limitation related to the method itself. Novel equations tailored to patients with CVD were developed, which revealed greater accuracy than other indirect methods, indicating that this methodology may be a valid alternative when CPET is unavailable.

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