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FULL RESEARCH PAPER
Cardiac rehabilitation

Accurate prediction equations for ventilatory thresholds in cardiometabolic disease when gas exchange analysis is unavailable: development and validation

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Aims To develop and validate equations predicting heart rate (HR) at the first and second ventilatory thresholds (VTs) and an optimized range-adjusted prescription for patients with cardiometabolic disease (CMD). To compare their performance against guideline-based exercise intensity domains.

Methods and results Cross-sectional study involving 2868 CMD patients from nine countries. HR predictive equations for first and second VTs (VT_1, VT_2) were developed using multivariate linear regression with 975 cycle-ergometer cardiopulmonary exercise tests (CPET). 'Adjusted' percentages of peak HR ($\%HR_{peak}$) and HR reserve (%HRR) were derived from this group. External validation with 1893 CPET (cycle-ergometer or treadmill) assessed accuracy, agreement, and reliability against guideline-based $\%HR_{peak}$ and %HRR prescriptions using mean absolute percentage error (MAPE), Bland–Altman analyses, intraclass correlation coefficients (ICC). HR predictive equations (R^2: 0.77 VT_1, 0.88 VT_2) and adjusted %HRR (VT_1: 42%, VT_2: 77%) were developed. External validation demonstrated superiority over widely used guideline-directed intensity domains for $\%HR_{peak}$ and %HRR. The new methods showed consistent performance across both VTs with lower MAPE (VT_1: 7.1%, VT_2: 5.0%), 'good' ICC for VT_1 (0.81, 0.82) and 'excellent' for VT_2 (0.93). Guideline-based exercise intensity domains had higher MAPE (VT_1: 6.8–21.3%, VT_2: 5.1–16.7%), 'poor' to 'good' ICC for VT_1, and 'poor' to 'excellent' for VT_2, indicating inconsistencies related to specific VTs across guidelines.

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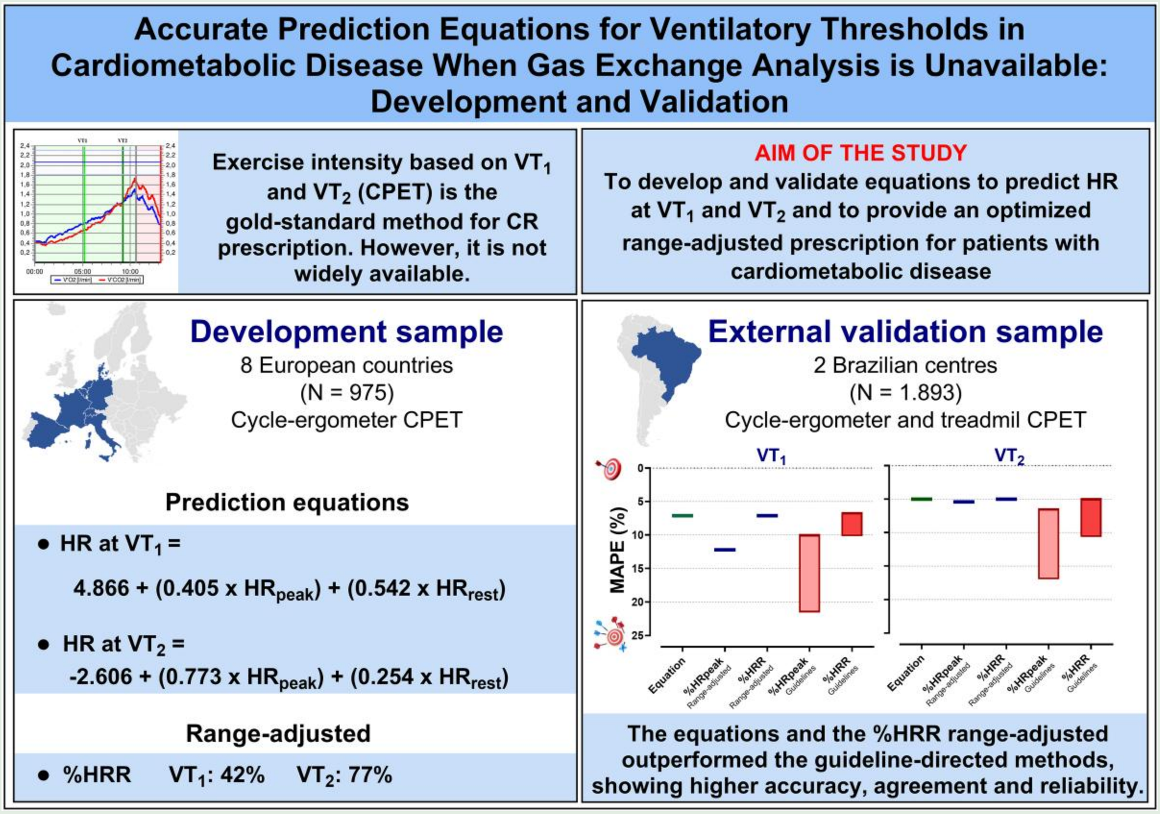
Conclusion Developed and validated HR predictive equations and the optimized %HRR for CMD patients for determining VT_1 and VT_2 outperformed the guideline-based exercise intensity domains and showed ergometer interchangeability. They offer a superior alternative for prescribing moderate intensity exercise when CPET is unavailable.

Lay summary Equations to predict heart rate at ventilatory thresholds were developed and externally validated, offering a new perspective when a cardiopulmonary exercise test is unavailable to accurately determine the aerobic exercise intensity domains. Additionally, an adjusted range for exercise intensity prescription based on the percentage of heart rate reserve (%HRR) was provided, utilizing a large sample from eight countries.

- The proposed equations and the range-adjusted %HRR significantly outperformed the guideline-directed methods for determining exercise intensity, exhibiting higher accuracy, agreement, and reliability. Exercise intensity prescription based on the percentage of heart rate peak showed higher errors, raising concerns about its clinical applicability.
- Our study may enhance the efficacy of exercise training and physical activity advice when gas exchange analysis is unavailable, potentially leading to improved clinical outcomes, even in low-resource settings. Employing these approaches in research could facilitate more tailored and consistent interventions, introducing a contemporary perspective for studies comparing exercise intensity prescriptions.

Graphical Abstract



Accurate Prediction Equations for Ventilatory Thresholds in Cardiometabolic Disease When Gas Exchange Analysis is Unavailable: Development and Validation

Exercise intensity based on VT_1 and VT_2 (CPET) is the gold-standard method for CR prescription. However, it is not widely available.

AIM OF THE STUDY
To develop and validate equations to predict HR at VT_1 and VT_2 and to provide an optimized range-adjusted prescription for patients with cardiometabolic disease

Development sample
8 European countries
(N = 975)
Cycle-ergometer CPET

Prediction equations

- **HR at VT_1 =**
  $4.866 + (0.405 \times HR_{peak}) + (0.542 \times HR_{rest})$
- **HR at VT_2 =**
  $-2.606 + (0.773 \times HR_{peak}) + (0.254 \times HR_{rest})$

Range-adjusted

- **%HRR VT_1: 42% VT_2: 77%**

External validation sample
2 Brazilian centres
(N = 1.893)
Cycle-ergometer and treadmil CPET

The equations and the %HRR range-adjusted outperformed the guideline-directed methods, showing higher accuracy, agreement and reliability.

CPET, cardiopulmonary exercise test; HR, heart rate; MAPE, mean absolute percentage error; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold; $\%HR_{peak}$, percentage of peak heart rate; %HRR, percentage of heart rate reserve.

Keywords Cardiac rehabilitation • Exercise • Exercise therapy • Exercise test • Cardiovascular diseases • Metabolic diseases • Health planning guidelines • Validation study

Introduction

Exercise therapy consistently demonstrates benefits for patients with cardiometabolic diseases (CMD) (e.g. improving physical fitness and cardiovascular risk, quality of life, and reducing morbi-mortality).[1–3] The determination of an optimal aerobic exercise intensity is essential for a safe and efficient exercise intervention,[4–6] as existing evidence emphasizes its importance for best clinical outcomes.[6–10] A 'threshold-based' exercise prescription, derived from the gold-standard cardiopulmonary exercise test (CPET) at the first and second ventilatory thresholds (VT_1, VT_2), may enhance intervention benefits, feasibility, and safety.[5,11–14] In the absence of CPET, international guidelines recommend exercise prescriptions based on ergometry tests, as first following alternative, using intensities expressed as percentages of peak heart rate (%HR$_{peak}$) or heart rate reserve (%HRR).[5,11,15]

Notably, significant discrepancies between heart rate (HR) or workload at the ventilatory thresholds (VTs) and those based on widely used guideline-directed exercise intensity domains have been observed.[16–23] Such inappropriate exercise intensity setting could potentially cause under- or overtraining and may affect patient motivation, emphasizing the need for a careful and critical revision of this widely used method.[5,16–19,21,22]

Milani *et al.*[21] recently reported a mathematical error in %HR$_{peak}$-based exercise prescription, which can be minimized using multivariable equations to estimate HR at the VTs. This approach demonstrated superior accuracy (mean absolute percentage error, MAPE: 6.0% for VT$_1$, 4.3% for VT$_2$) compared to other indirect methods (guideline-directed intensity domains: MAPE: 9.5–23.8% for VT$_1$, 5.8–19.3% for VT$_2$) utilizing simple treadmill test parameters, in patients with cardiovascular diseases (CVD). While indicating potential validity when gas exchange analysis is unavailable, further studies are needed to develop and validate VTs' predictive equations on cycle-ergometry tests in a diverse multinational cohort of CMD patients with varying phenotypes.

Hence, our aims were:

1. To develop equations for predicting HR at VTs during cycle-ergometry CPET in patients with CMD (i.e. development study).
2. To generate an 'optimal' range-adjusted exercise intensity prescription (%HR$_{peak}$ and %HRR).
3. To externally validate these predictive equations and the range-adjusted prescriptions, comparing their accuracy, agreement, and reliability with current guideline-based %HR$_{peak}$ and %HRR prescriptions (i.e. external validation study).

Methods

The current research was structured in two independent studies. The first, termed the 'Development study', utilized European data and focused on the formulation of the equations and the adjustment of ranges for prescription purposes. The second, labelled as the 'External validation study', involved the validation process and utilized a sample from a different continent, South America.

Ethics approval

Our retrospective study was based on previously obtained data from prospective studies[16,17,23–26] and was approved by all relevant medical ethics committees. EU-CaRE prospective cohort study: Landesärztekammer Rheinland Pfalz, Germany (Nr. 837.341.15, (10109)); Comission Nationale de l'Informatique et de Libertés, France (DR-2016-021); medisch-ethische toetsingscomissie METC Isala Zwolle, The Netherlands (15.0350); Secretario do Comité de Ética da Investigación de Santiago-Lugo, Spain (2015/486); Comitato Ethico per Parma, Italy (34360); Videnskabsetiske Komite C for Region Hovedstaden, Denmark (593); Kantonale Ethikkomission Bern, Switzerland (290/15). Belgium: (Medical ethical committee of Jessa Hospital, B243201629466). Brazil: (Comitê de Ética da Universidade de Brasília, CAAE: 35706720.4.1001.8093). Informed consent was waived since the data were collected retrospectively or relied on informed consent obtained in the original prospective studies.

Development study

A retrospective cross-sectional study involved 975 patients with CMD who underwent cycle-ergometer CPET in eight European countries: Denmark, France, Germany, the Netherlands, Italy, Spain, Switzerland (EU-CaRE study), and Belgium. Inclusion criteria encompassed individuals aged ≥20 years without pulmonary, neurological, or severe orthopaedic disorders. Exclusion criteria included pacemakers or implantable cardioverter devices, unidentified VTs, and peak respiratory exchange ratio (RER$_{peak}$) below 1.10 (cut-off value for maximal metabolic effort[27]).

Assessments

Patients underwent a symptom-limited CPET on a cycle-ergometer with breath-by-breath gas analysis and electrocardiographic monitoring. Medications were not withdrawn, and testing was performed until volitional fatigue. CPET was performed with an individualized ramp protocol to yield a fatigue-limited exercise test with an expected duration of 8–12 min. The obtained CPET variables included HR at rest (HR$_{rest}$), at VTs and at peak (HR$_{peak}$); oxygen uptake (VO$_2$) at VTs and at peak (VO$_{2peak}$); RER$_{peak}$; and peak workload (W$_{peak}$).

VTs identification followed established recommendations.[5,14,28] VT$_1$ marks the limit between light to moderate exercise, and VT$_2$ marks the limit between moderate to high-intensity effort.[5,11] Individual determination of VT$_1$ and VT$_2$ was made by experienced personal and based on the analysis of the exercise ventilation (VE), oxygen uptake (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.[14]

All laboratories followed international recommendations regarding device's calibration, exercise protocols, and analyses.[5,14,27,28] Data acquisition and management have been reported in previous publications.[16,17,23–26]

Predictive equations and optimal range-adjusted prescription

The CPET variables along with clinical information were used to develop the multivariate equations outlined in the statistical section. The values determined in the development sample as %HR$_{peak}$ and %HRR for VTs were considered the optimal range-adjusted prescription.

External validation study

The equations from the development study were cross-validated in a Brazilian database ($n = 1893$ patients) incorporating two datasets from different ergometers (treadmills or cycle-ergometers), aligned with international recommendations for device calibration, exercise protocols, and analyses.[14,28] The inclusion and exclusion criteria matched, apart from RER$_{peak}$ (cut-off value 1.00 instead of 1.10), simulating real-life ergometry assessments without gas exchange analysis where RER$_{peak}$ is unknown.

The measured values obtained from the external validation sample were compared with the estimations using the equations and the range-adjusted prescriptions within the same dataset. Furthermore, these parameters were compared with the estimated values recommended by the European,[15] American,[28] and Brazilian[11] guidelines for moderate-intensity HR ranges:

- %HR$_{peak}$: European: 55–74%; American: 64–76%; Brazilian: 70–85%.
- %HRR: European: 40–69%; American: 40–59%; Brazilian: 50–80%.

Statistical analysis

We assessed normality using the Kolmogorov–Smirnov test and presented data as medians with interquartile ranges (IQR) or absolute and relative frequencies.

We conducted multiple regression analyses using the stepwise forward method, selecting predictors available during an ergometry test to develop practical equations for predicting HR at VTs when gas exchange analysis is unavailable.[21] Potential predictors included age, sex, weight, height, W$_{peak}$, HR$_{peak}$, HR$_{rest}$, beta-blocker usage, and the presence of hypertension, diabetes, coronary artery disease, and heart failure.

We verified model assumptions, addressing independence of residuals, linearity, homoscedasticity, multicollinearity, and residual normality. Independence of residuals was evaluated by Durbin–Watson statistic. Linearity was analysed by partial regression plots and a plot of studentized residuals against the predicted values. Homoscedasticity was examined by plots' visual inspection of studentized residuals vs. unstandardized predicted values. Multicollinearity was assessed by tolerance values greater than 0.1. Leverage was verified by individual values greater than 0.2. Cook's distance was calculated to search for individual values above 1. Outliers were removed due to their impact on model accuracy and the criteria for exclusion

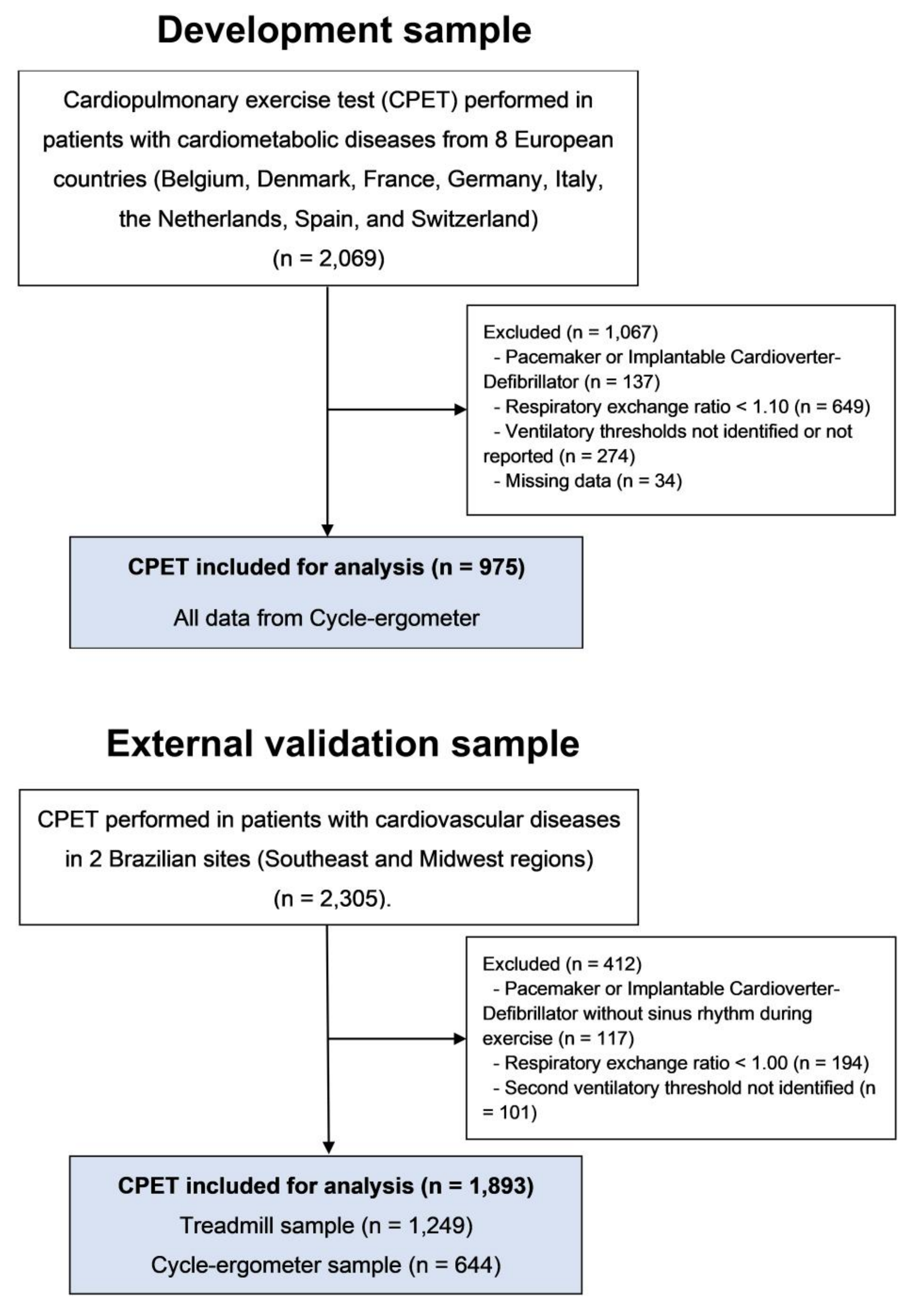


Figure 1 Flowchart of the study development and validation samples.

was the presence of individual values for studentized deleted residual or standardized residual greater than ±3 standard deviations. The model selection prioritized the highest adjusted *R*-squared, eliminating non-significant predictors and those unable to increase R^2 by at least 0.01.

Accuracy and agreement were assessed using MAPE (absolute difference between measured and estimated values divided by measured values) and Bland–Altman analysis. Lower MAPE indicates better accuracy. Reliability was determined using the intraclass correlation coefficient (ICC), two-way random and absolute agreement, with 95% confidence interval, employing benchmarks of: <0.50 'poor,' 0.50–0.75 'moderate,' 0.75–0.90 'good,' and >0.90 'excellent'.[29]

Statistical analyses, conducted with GraphPad Prism and IBM-SPSS for Windows, considered significance at $P < 0.05$.

Ancillary analyses

For sensitivity analysis, we categorized the sample according to individuals' errors below or above the MAPE for each VT, comparing associated clinical characteristics by Mann–Whitney test for continuous variables and χ^2 test for categorical variables. Moreover, we split the validation sample into cycle-ergometer and treadmill assessments to perform the external validation analyses as previously described, exploring responses in each ergometer.

Equity, diversity, and inclusion statement

Our study included databases from diverse countries, covering different income levels, ethnicities, and socioeconomic backgrounds. The author group comprises senior and less-experienced investigators from various countries,

Table 1 General characteristics and cardiopulmonary exercise test variables of the study sample

Characteristic	Development sample ($n = 975$)	Validation sample ($n = 1893$)
Male	794 (81.4%)	1501 (79.3%)
Age, year	69 (65, 74)	60 (50, 68)
Anthropometry		
Weight, kg	79.9 (71.1, 89.7)	77.8 (68.6, 87.8)
Height, cm	173 (167, 178)	171 (165, 177)
Body mass index, kg m^{-2}	26.8 (24.5, 29.7)	26.5 (24.3, 29.3)
Risk factors		
Hypertension	576 (59.1%)	1004 (53.0%)
Diabetes mellitus	194 (19.9%)	321 (17.0%)
Current smoking	151 (15.5%)	35 (1.8%)
Obesity	220 (22.6%)	396 (20.9%)
Previous cardiovascular disease		
Coronary artery disease	663 (68.0%)	1528 (80.7%)
Coronary angioplasty	562 (57.6%)	934 (49.8%)
Coronary artery bypass graft	201 (20.6%)	429 (22.7%)
Heart failure	37 (3.8%)	458 (24.2%)
Medications, percentual of use		
Statins	831 (85.2%)	—
Beta-blockers	723 (74.2%)	1365 (72.1%)
ACEi/ARB	557 (57.2%)	926 (48.9%)
Diuretics	179 (18.4%)	644 (34.0%)
Calcium-antagonist	158 (16.2%)	—
Nitrate	74 (7.6%)	—
Insulin	48 (4.9%)	—
Cardiopulmonary exercise testing		
VO_{2peak}, L min^{-1}	1.49 (1.19, 1.85)	1.72 (1.27, 2.28)
VO_{2peak}, mL kg^{-1} min^{-1}	18.5 (15.7, 22.4)	21.7 (16.9, 27.5)
HR_{peak}, b.p.m.	122 (109, 138)	140 (122, 159)
RER_{peak}	1.20 (1.10, 1.24)	1.15 (1.08, 1.22)
W_{peak}, Watts	120 (95, 153)	—
HR_{rest}, b.p.m.	66 (59, 75)	68 (62, 76)
HRR, b.p.m.	55 (41, 69)	71 (53, 88)
VO_2 at VT_1, $mL.kg^{-1}.min^{-1}$	11.0 (9.4, 13.0)	12.3 (10.3, 14.7)
VO_2 at VT_1, $\%VO_{2peak}$	60.2 (53.4, 67.1)	58.5 (51.7, 65.2)
Load at VT_1, W	56 (42, 73)	—
Load at VT_1, $\%W_{peak}$	45.9 (38.0, 54.8)	—
HR at VT_1, b.p.m.	91 (82, 100)	96 (87, 107)
HR at VT_1, $\%HR_{peak}$	75.2 (69.2, 81.0)	69.9 (64.5, 76.6)
HR at VT_1, %HRR	42.2 (34.3, 52.2)	39.1 (32.1, 47.2)
VO_2 at VT_2, $mL.kg^{-1}.min^{-1}$	15.4 (13.1, 18.6)	18.6 (14.8, 23.9)
VO_2 at VT_2, $\%VO_{2peak}$	84.8 (79.6, 89.9)	88.4 (82.9, 92.9)
Load at VT_2, W	94 (74, 120)	—
Load at VT_2, $\%W_{peak}$	79.8 (73.3, 85.6)	—
HR at VT_2, b.p.m.	108 (97, 121)	123 (107, 141)
HR at VT_2, $\%HR_{peak}$	90.1 (85.7, 93.7)	89.6 (85.5, 93.2)
HR at VT_2, %HRR	76.6 (68.0, 84.5)	78.0 (70.5, 85.7)

Continued

Table 1 *Continued*

Data expressed as median and IQR or absolute and relative frequencies *n* (%). ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; HR, heart rate; HRR, heart rate reserve; HR_{rest}, rest heart rate; HR_{peak}, peak heart rate; RER_{peak}, peak respiratory exchange ratio; VO_2, oxygen uptake; VO_{2peak}, peak oxygen uptake; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold; % HR_{peak}, percentage of peak heart rate; %HRR, percentage of heart rate reserve; % VO_{2peak}, percentage of peak oxygen uptake; W_{peak}, peak load.

including researchers from the Global South. We applied consistent methods across different regions, educational levels, and socioeconomic backgrounds.

Results

Samples

A total of 2868 CPETs were included: 975 in the development study and 1893 in the external validation study (*Figure 1*).

The development sample predominantly comprised males (81%), with a median age of 69 years (IQR: 65, 74). The majority had coronary artery disease (68%) and were using beta-blockers (74%). The median VO_{2peak} was 18.5 mL kg^{-1} min^{-1} (IQR: 15.7, 22.4), and the median HR_{peak} was 122 b.p.m. (IQR: 109, 138). The validation sample also consisted mainly of males (79%) with a median age of 60 years (IQR 50, 68). Approximately 81% had coronary artery disease, and 72% were on beta-blockers. Median VO_{2peak}: 21.7 mL kg^{-1} min^{-1} (IQR: 16.9, 27.5), and the median HR_{peak}: 140 b.p.m. (IQR: 122, 159) (*Table 1*).

Predictive equations for HR at VT_1 and VT_2

A multiple regression analysis was conducted to predict HR at VTs. Potential predictors included age, sex, weight, height, W_{peak}, HR_{peak}, HR_{rest}, beta-blocker usage, and the presence of hypertension, diabetes, coronary artery disease, and heart failure. HR_{peak} and HR_{rest} emerged as the most significant predictors, contributing to the highest *R*-squared values, and thus remaining in the final equation. Conversely, the other predictors did not exhibit significant influences and were subsequently removed.

All assumptions for multiple regression were met in the final models, including independence of residuals, linearity, homoscedasticity, multicollinearity, and normality of residuals. A few individual cases were excluded based on the criterion of studentized deleted residual values exceeding ±3 standard deviations (10 cases for the VT_1 equation and 6 for the VT_2 equation). The multiple regression models significantly predicted HR at both VT_1 [F (2, 962) = 1615.9, $P < 0.001$] and VT_2 [F (2, 966) = 3610.0, $P < 0.001$].

The following equations were generated:

$$HR\ at\ VT_1 = 4.866 + (0.405 \times HR_{peak}) + (0.542 \times HR_{rest}) \quad (1)$$

$$R^2 = 0.77$$

$$MAPE = 6.2\%.$$

$$HR\ at\ VT_2 = -2.606 + (0.773 \times HR_{peak}) + (0.254 \times HR_{rest}) \quad (2)$$

$$R^2 = 0.88$$

$$\text{MAPE} = 4.7\%$$

An automated calculation spreadsheet is available in Supplementary material.

Range-adjusted prescription

Based on the measured values of HR_{rest}, HR_{peak}, HR at VT_1 and VT_2 obtained in the development sample (*Table 1*), we set the optimal range-adjusted prescriptions for $\%HR_{peak}$ and %HRR for both VTs:

$$\%HR_{peak}{:}VT_1 = 75\%;\ VT_2 = 90\%.$$

$$\%HRR{:}VT_1 = 42\%;\ VT_2 = 77\%.$$

External validation

First ventilatory threshold—VT_1

The median HR at VT_1 was 96 b.p.m. (IQR: 87, 107), estimated at 100 b.p.m. (IQR: 89, 108) by the equation. Range-adjusted estimations: 105 b.p.m. (IQR: 92, 119) for $\%HR_{peak}$ and 99 b.p.m. (IQR: 87, 109) for %HRR (*Table 2*).

According to European,[5,15] American,[28] and Brazilian[11] guidelines, the estimated lower limit for moderate exercise ranged from 77 to 98 b.p.m. ($\%HR_{peak}$) and 98 to 105 b.p.m. (%HRR). Accuracy analysis demonstrated a 7.1% MAPE for the equation and the range-adjusted %HRR, while the $\%HR_{peak}$ varied from 10.1% to 21.3%, which is notably higher. %HRR-based recommendations ranged from 6.8% (European and American) to 9.9% (Brazilian) (*Table 2*).

Bland–Altman plots (*Figures 2A, 3A,* and *4A*) revealed an equation bias of 1.7 b.p.m., similar to the range-adjusted %HRR bias of 1.5 b.p.m. European and American %HRR guidelines displayed a minimal bias (0.1 b.p.m.), near $\%HR_{peak}$ Brazilian recommendations (0.2 b.p.m.). Biases were greater in range-adjusted $\%HR_{peak}$ (7.3 b.p.m.), European and American $\%HR_{peak}$ guidelines (−20.7 and −8.2 b.p.m.) and Brazilian %HRR guideline (7.1 b.p.m.).

ICC showed 'good' reliability for the equation, range-adjusted %HRR, European, and American %HRR estimates. Brazilian recommendations had 'moderate' reliability, while other $\%HR_{peak}$ estimations varied from 'poor' to 'moderate' (*Table 2*).

Second ventilatory threshold—VT_2

The median HR at VT_2 was 123 b.p.m. (IQR: 107, 141), estimated as 124 b.p.m. (IQR: 108, 139) by the equation. Range-adjusted estimations were 126 b.p.m. ($\%HR_{peak}$, IQR: 110, 143) and 124 b.p.m. (%HRR, IQR: 109, 139) (*Table 2*).

Per guidelines, moderate-intensity upper limits ranged from 104 to 119 b.p.m. ($\%HR_{peak}$) and 111 to 126 b.p.m. (%HRR). Accuracy analysis indicated a 5.0% MAPE for the equation and the range-adjusted %HRR, while $\%HR_{peak}$ estimations varied from 5.4% (range-adjusted) to 16.7% (European). %HRR-based guideline extended from 5.1% (Brazilian) to 10.4% (American) (*Table 2*).

The Bland–Altman plots (*Figures 2B, 3B, and 4B*) indicated a −1.2 b.p.m. bias for the equation, with the range-adjusted %HRR exhibiting the smallest bias (−0.6 b.p.m.). Guidelines' estimations based on $\%HR_{peak}$ showed the poorest agreement (bias: −5.5 to −20.8 b.p.m.). Concerning %HRR-based prescription, European and American guidelines had the greatest bias (−6.2 and −13.2 b.p.m., respectively), while the Brazilian guidelines showed a more favourable result (1.4 b.p.m.), contrary to VT_1 observations.

Table 2 Heart rates at ventilatory thresholds: measurement, estimation, accuracy, and reliability across different methodologies in the validation sample

Variables	VT_1 ($n = 1893$)	VT_2 ($n = 1893$)
HR at VTs, b.p.m. (median and IQR)		
Measured	96 (87, 107)	123 (107, 141)
New equation	100 (89, 108)	124 (108, 139)
Estimation by $\%HR_{peak}$—Adjusted	105 (92, 119)	126 (110, 143)
Estimation by $\%HR_{peak}$—European	77 (67, 87)	104 (90, 118)
Estimation by $\%HR_{peak}$—American	90 (78, 102)	106 (93, 121)
Estimation by $\%HR_{peak}$—Brazilian	98 (85, 111)	119 (104, 135)
Estimation by %HRR—Adjusted	99 (89, 109)	124 (109, 139)
Estimation by %HRR—European	98 (87, 107)	119 (104, 132)
Estimation by %HRR—American	98 (87, 107)	111 (99, 123)
Estimation by %HRR—Brazilian	105 (94, 116)	126 (110, 142)
MAPE of HR estimation at VTs, %		
New equation (HR_{peak} and HRR)	7.1	5.0
Estimation by $\%HR_{peak}$—Adjusted	12.2	5.4
Estimation by $\%HR_{peak}$—European	21.3	16.7
Estimation by $\%HR_{peak}$—American	11.6	14.5
Estimation by $\%HR_{peak}$—Brazilian	10.1	6.6
Estimation by %HRR—Adjusted	7.1	5.0
Estimation by %HRR—European	6.8	6.4
Estimation by %HRR—American	6.8	10.4
Estimation by %HRR—Brazilian	9.9	5.1
ICC[a] measured vs. estimated HR at VTs		
New equation	0.81 (0.79, 0.83)	0.93 (0.92, 0.93)
Estimation by $\%HR_{peak}$—Adjusted	0.68 (0.47, 0.80)	0.93 (0.92, 0.94)
Estimation by $\%HR_{peak}$—European	0.38 (0.00, 0.71)	0.60 (0.00, 0.87)
Estimation by $\%HR_{peak}$—American	0.66 (0.32, 0.81)	0.67 (0.00, 0.89)
Estimation by $\%HR_{peak}$—Brazilian	0.75 (0.73, 0.77)	0.90 (0.75, 0.95)
Estimation by %HRR—Adjusted	0.82 (0.80, 0.83)	0.93 (0.92, 0.93)
Estimation by %HRR—European	0.82 (0.80, 0.83)	0.87 (0.65, 0.94)
Estimation by %HRR—American	0.82 (0.80, 0.83)	0.72 (0.00, 0.90)
Estimation by %HRR—Brazilian	0.75 (0.39, 0.87)	0.93 (0.92, 0.94)

Data expressed as median and interquartile range.
Recommendations for moderate exercise intensity according to $\%HR_{peak}$ (VT_1 and VT_2). Adjusted: 75–90%; European: 55–74%; American: 64–76%; Brazilian: 70–85%.
Recommendations for moderate exercise intensity according to %HRR (VT_1 and VT_2): Adjusted: 42–77%; European: 40–69%; American: 40–59%; Brazilian: 50–80%.
[a]Intraclass correlation coefficient and 95% confidence interval (two-way random and absolute agreement).
HR, heart rate; ICC, intraclass correlation coefficient; MAPE, mean absolute percentage error; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold; $\%HR_{peak}$, percentage of peak heart rate; %HRR, percentage of heart rate reserve.

ICC demonstrated 'excellent' reliability for the equation and both range-adjusted estimations. Guideline-based $\%HR_{peak}$ varied from 'moderate' to 'good,' while for %HRR, ICC was 'good' for European, 'moderate' for American, and 'excellent' for Brazilian guidelines.

Ancillary analyses

Patient characteristics influencing equation accuracy

The individuals with the most accurate HR prediction at VTs had the lowest VO_{2peak}, HR_{peak}, and HRR, alongside the highest HR_{rest} (see

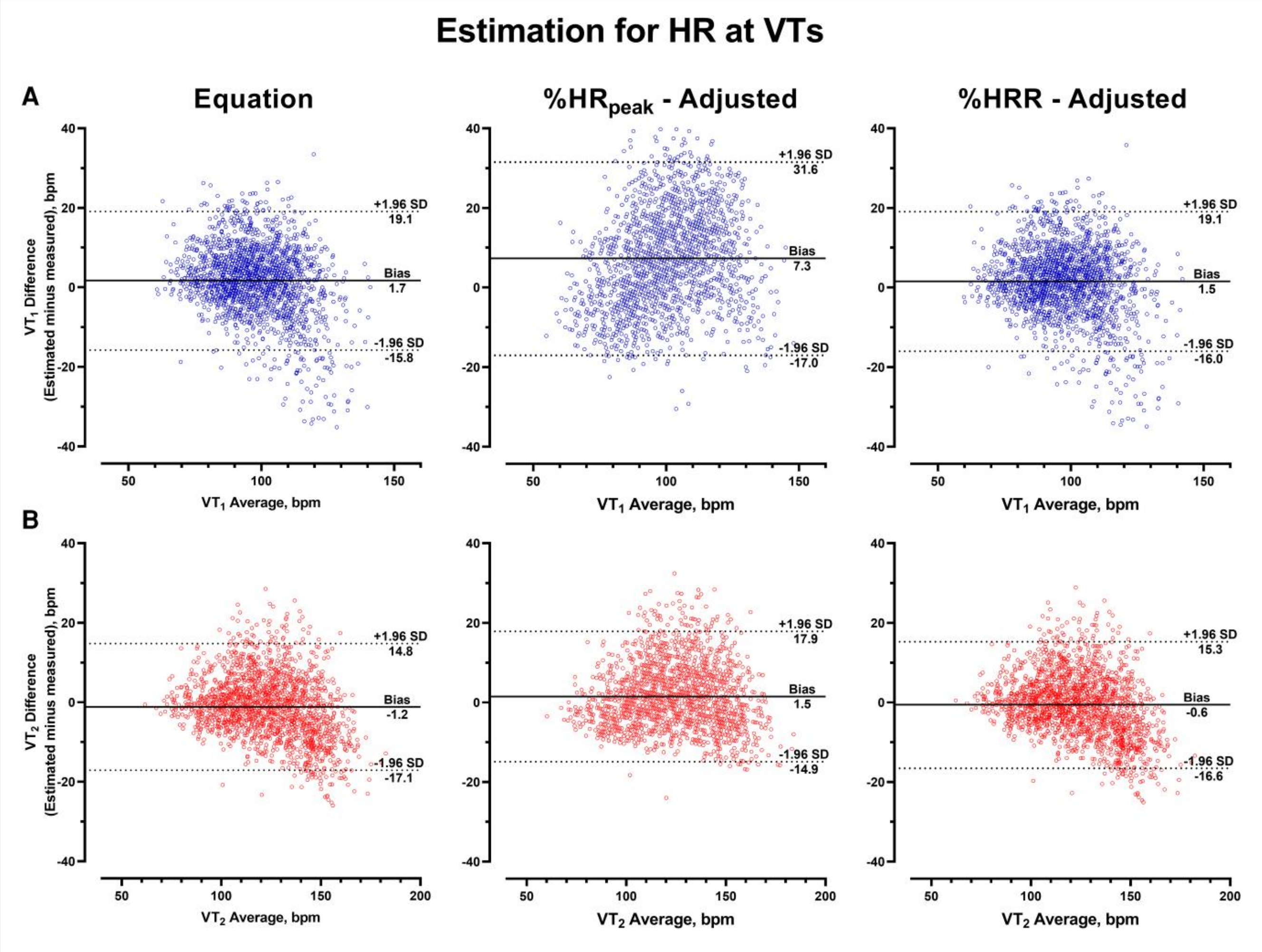


Figure 2 Bland–Altman plots of measured vs. estimated heart rates at the ventilatory thresholds according to the novel equations, and adjusted percentages of peak heart rate and heart rate reserve. (*A*) Data for the first ventilatory threshold; (*B*) data for the second ventilatory threshold. VT$_1$, first ventilatory threshold; VT$_2$, second ventilatory threshold; %HR$_{peak}$, percentage of peak heart rate; %HRR, percentage of heart rate reserve.

Supplementary material online, *Figure S1*, *Tables S1*, and *S2*)—indicative of deconditioned patients. Additionally, they were older with a higher hypertension prevalence.

Difference between ergometers

The treadmill and cycle-ergometer assessments showed similar accuracy and reliability patterns, with surprisingly better performance in the treadmill group. For VT$_1$, the treadmill group had a 6.4% MAPE for the equation and 6.3% for the adjusted %HRR range, while the cycle-ergometer group displayed an 8.7% MAPE for the equation and 8.5% for the adjusted %HRR range, both with ‘good’ reliability. For VT$_2$, the treadmill group demonstrated a 4.9% MAPE for the equation and 4.7% for the adjusted %HRR range, while the cycle-ergometer group had a 5.4% MAPE for the equation and 5.5% for the adjusted % HRR. Both ergometers demonstrated ‘excellent’ reliability (see Supplementary material online, *Tables S3–S6*).

Discussion

Our study contributes to cardiovascular rehabilitation (CR) and exercise interventions or physical activity advice by offering more accurate exercise prescriptions when gas exchange analysis during exercise testing is unavailable. For the first time, HR at VTs predictive equations were developed using multicenter cycle-ergometer data from eight countries. Additionally, an optimized range-adjusted %HRR was provided. Our equations demonstrated notable R^2 values and, like the adjusted %HRR, exhibited greater measurement quality compared to the widely used guidelines. Particularly, %HR$_{peak}$-based prescriptions showed the poorest performance. External validation confirmed that our proposals closely approximate the CPET’s VTs.

Predictive equations and range-adjusted prescription

Optimizing exercise prescription is crucial for consistent positive outcomes, as physiological adaptations depend on exercise stimuli. Our equations offer an alternative indirect method to determine moderate-intensity aerobic exercise levels if gas exchange analysis during exercise testing is not possible/feasible.

Our results align with another study, which involved treadmill CPET assessments of 972 CVD patients.[21] This previous study also provided HR predictive equations for VT$_1$ and VT$_2$ with R^2 values of 0.73 and 0.90, respectively, similar to the present study (R^2= 0.77 for VT$_1$;

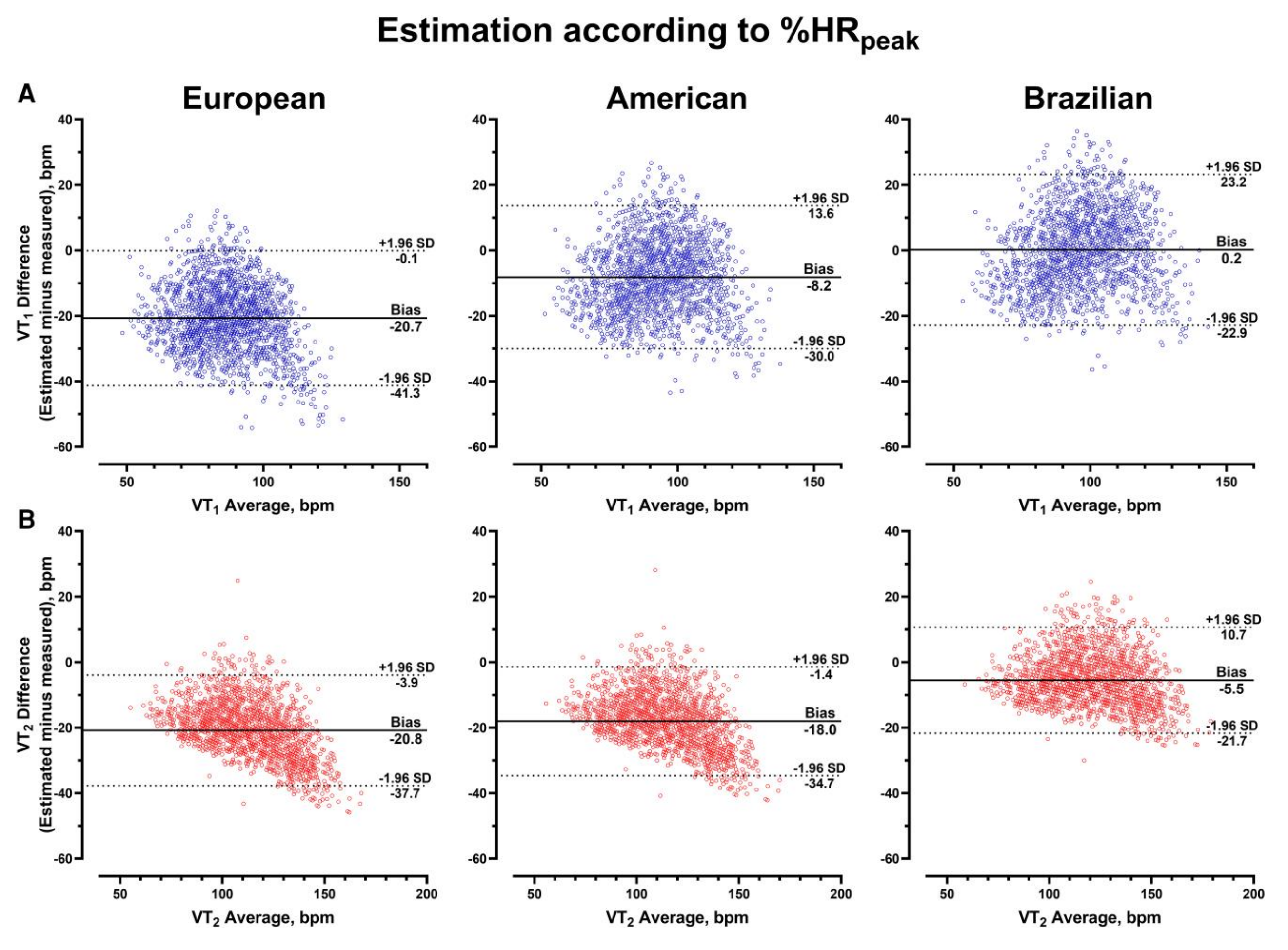


Figure 3 Bland–Altman plots of measured vs. estimated heart rates at the ventilatory thresholds according to the percentage of peak heart rate recommended in European, American, and Brazilian current guidelines. (*A*) Data for the first ventilatory threshold; (*B*) data for the second ventilatory threshold. VT$_1$, first ventilatory threshold; VT$_2$, second ventilatory threshold; %HR$_{peak}$, percentage of peak heart rate.

0.88 for VT$_2$). To our knowledge, these are the sole equations predicting HR at VTs developed thus far. Other equations estimating HR responses during exercise mainly rely on non-effort parameters to predict peak values,[30,31] and the suggested %HR$_{peak}$ based on guidelines is frequently inaccurate, even with measured values.[17,21] This discrepancy might result in significant prescription errors when applied to a non-measured HR$_{peak,}$ compromising patient outcomes.

The exclusion of age and beta-blocker usage as predictors in the final equation is notable. These variables could have affected HR$_{peak}$ and HR$_{rest}$ responses, which were among the retained predictors. Thus, their influence might persist in the models, resembling prior equations with treadmill assessments that incorporated HR$_{peak}$, HR$_{rest}$, and MET$_{peak}$.[21]

Besides the equations and considering the classical indirect approaches described in the guidelines,[5,11,15,28] the present study also provided adjusted-range prescriptions. Despite being widely used and recommended by guidelines,[5,11,15,28] we advise against using the %HR$_{peak}$ method, as evidence has shown that these percentages for prescriptions may not consistently guarantee uniform exercise intensity ranges.[17,19,21,22,32]

Another significant challenge in the current global CR scenario is that, despite recommending minimal patient evaluation using an ergometric test for enhanced rehabilitation outcomes,[5] this approach is not widely implemented in most rehabilitation services. Krieger *et al.*[33] recently reported that only 2% of 91 American programs conducted incremental exercise tests.

Moreover, it is important to emphasize that in clinical practice, supplementary methods are necessary to manage and regulate exercise intensity during exercise sessions. These can involve the 'Talk Test' or self-rated perceived exertion.[5] Supplementary material online, *Figure S2S* provides a practical guide for prescribing moderate aerobic exercise for CR.

External validation

The equations and range-adjusted %HRR performed better in terms of measurement quality and consistency compared to the guidelines. Patients with RER$_{peak}$ < 1.00 in the validation sample mimic routine cases, where achieving RER$_{peak}$ > 1.10 without gas exchange analysis is uncertain. Consequently, given reports that many CMD patients, especially older adults, may not reach this level,[23] these equations find practical relevance.

The predictive equations closely mirrored the adjusted %HRR, exhibiting precisely the same MAPE for both VTs (VT$_1$: 7.1%, VT$_2$: 5.0%), as well as reliability (VT$_1$: 'good', VT$_2$: 'excellent'). These approaches consistently outperformed the guidelines due to notable variations in

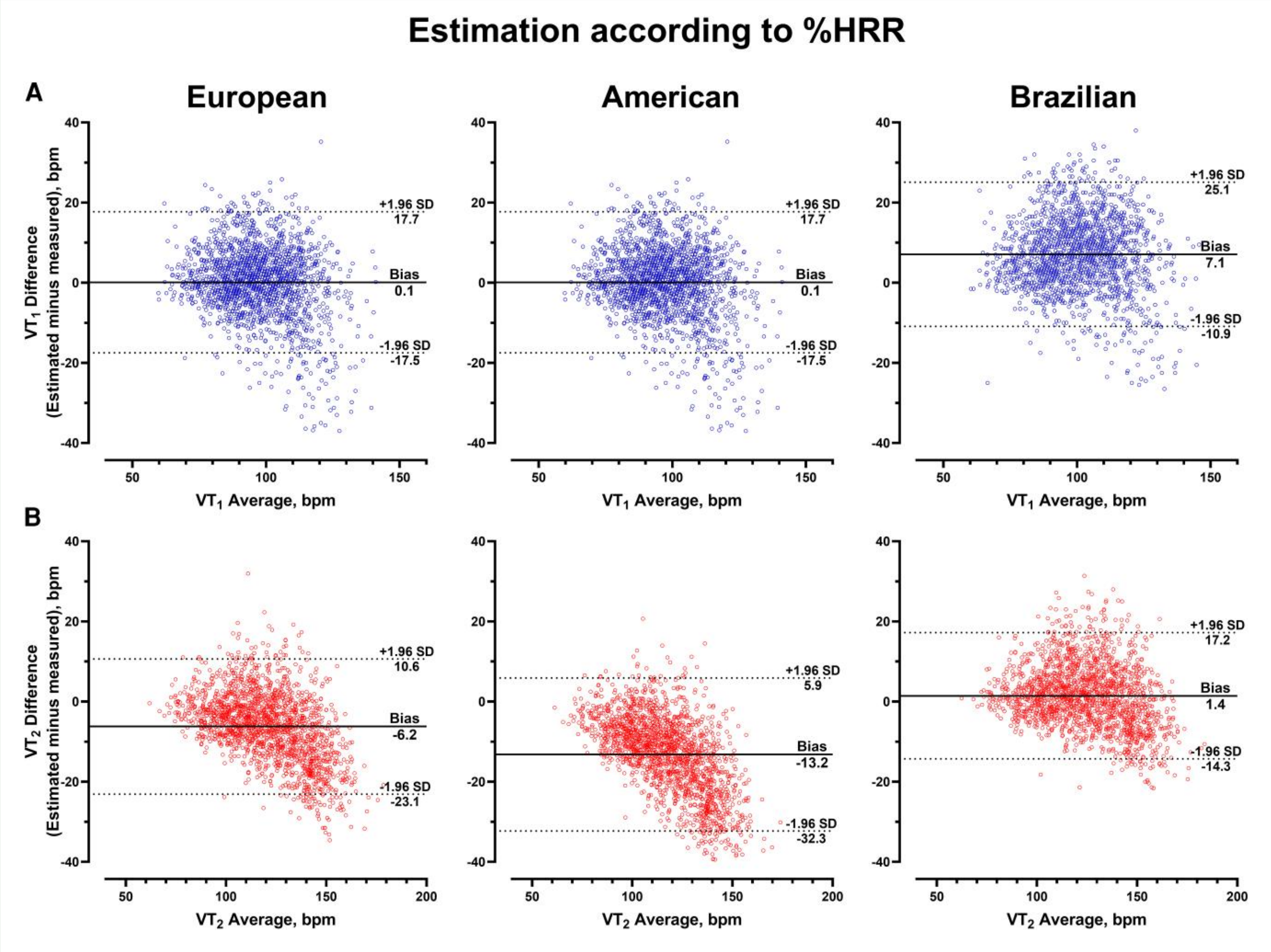


Figure 4 Bland–Altman plots of measured vs. estimated heart rates at the ventilatory thresholds according to the percentage of heart rate reserve recommended in European, American, and Brazilian current guidelines. (*A*) Data for the first ventilatory threshold; (*B*) data for the second ventilatory threshold. VT_1, first ventilatory threshold; VT_2, second ventilatory threshold; %HRR, percentage of heart rate reserve.

recommendations, resulting in accuracy differences based on the considered guideline and VT. For example, in estimating VTs using guidelines-directed %HRR, both the European and American demonstrated superior accuracy, reliability, and agreement for VT_1, while the Brazilian guideline proved to be superior for VT_2 (*Table 2*, *Figure 4*).

Notably, the $\%HR_{peak}$ estimations had the poorest performance, raising doubts about its validity, given the absence of physiological evidence supporting uniform responses to metabolic stress at the same $\%HR_{peak}$.[19,32] This implies that fixed percentage-based exercise prescriptions might not consistently achieve uniform exercise intensity domains.[19,32] Furthermore, discrepancies in the relationship between $\%HR_{peak}$ at VTs and HR_{peak}, particularly at VT_1, limit the mathematical applicability of percentage-based peak effort prescriptions.[21] These differences could arise from heterogeneous HR and VO_2 responses during incremental effort in cardiovascular disease patients[34] and the variable relationship between VO_2 and workload.[35]

These findings suggest that utilizing two variables (HR_{peak}, HR_{rest}) enhances the ability to predict HR within the moderate intensity domain. Consequently, estimations using either the predictive equation or adjusted %HRR provide greater consistency compared to other indirect methods typically recommended when CPET is unavailable.

Notably, even with gas exchange analysis, identifying VTs may not be achievable. Marcin *et al.*[23] analysing 1527 CVD patients (EU-CaRE Study) reported that VT_1 could not be identified in approximately 25% of the sample, and VT_2 was not reached or detectable in 50%. In this scenario, the equations or range-adjusted %HRR might have other potential clinical applications, serving as a complementary strategy to assist in identifying the region of the VTs in cases where it is unclear using standard methods.

Ancillary analyses

The sensitivity analysis suggested a specific patient profile in which the equations exhibited greater potential applicability: lower VO_{2peak}, HR_{peak}, and HRR; higher HR_{rest}; older age; and hypertension presence. Remarkably, these characteristics were more prevalent in the development sample compared to the validation sample (*Table 1*), aligning with these findings.

Interestingly, the equations performed better in the validation sample subgroup assessed on treadmills compared to the cycle-ergometer patients. We attribute this result to unreported sample characteristics rather than the type of ergometer, considering the equations were developed on cycle-ergometer data. Thus, the prediction equations for HR at VTs revealed ergometer interchangeability, as our equations' applicability remained acceptable in both modes of exercise, despite the known differences in HR_{peak} and VO_{2peak} between cycle-ergometer and treadmill-based assessments.[36] This result may be attributed to the predictors obtained through effort assessment. Consequently, the actual patients' HR_{peak} (on treadmill or cycle-ergometer) was imputed into the equation, automatically adjusting the measurement according to the ergometer used for obtaining HR_{peak}.

Clinical implications

Best practices for exercise prescription should consider individual physiological responses,[37] as distinct exercise intensities cause specific homeostatic disturbances.[38] Hence, aligning indirect prescription with the gold-standard provides a comparable relative metabolic stimulus for patients helping to identify the most effective training stimulus[32,39,40] to promote desired adaptations, enhance effectiveness, and reduce non-responsiveness.[37] Accordingly, the externally validated predictive equations for HR at VTs and the range-adjusted %HRR (42 to 77%) provided in this study offer valuable clinical utility, bridging the gap between indirect prescription and 'threshold-based' prescription.

Limitations

We used reported variables, and certain data, such as daily activity levels, were unavailable and could be other potential predictors. Despite this, we developed equations with a notable R^2.

Regarding generalizability, our equations were developed using European data and validated on South American databases. Further validation in diverse ethnic populations (e.g. Asian, African) is necessary. However, the European sample comprised eight different countries, and the external validation involved a completely different sample from another continent, totalling 2868 examinations.

Additionally, patients with heart failure were under-represented in our development sample (prevalence of only 3.8%). Thus, future studies may be necessary to better explore this subset of patients.

Conclusion

Our study presented externally validated predictive equations for HR at VTs in individuals with CMD, utilizing exercise testing variables without gas exchange analyses. Additionally, it provided an adjusted and validated %HRR range (42–77%). These approaches demonstrated superior consistency, accuracy, agreement, and reliability, outperforming the guideline-directed $\%HR_{peak}$ and %HRR prescriptions. While $\%HR_{peak}$-based prescription remains widely used, our findings challenge their clinical applicability and robustness. Importantly, these equations exhibited consistent performance across different exercise testing modes, indicating ergometer interchangeability.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Authors' contributions

J.G.P.O.M.: conception and design, analysis and interpretation of the results, drafted the article; M.M.: conception and design, analysis and interpretation of the results, revised it critically; F.V.C.M., G.F.B.C., K.V.: interpretation of the results, revised it critically; M.W., T.M., F.D.A., L.C., C.K., M.F., B.B., R.M., F.B., V.C.: acquisition of data, revised it critically; G.C.J., D.H.: conception and design, analysis and interpretation of data, revised it critically, supervision. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflicts of interest: No potential conflict of interest is reported by the authors.

Data availability

Data cannot be shared publicly because of legislative restrictions in some of the participating countries. Data is available upon reasonable request for researchers who meet the criteria for access to confidential data.

Information about previous presentations

None of the contents of this paper have previously been published or presented.

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