




The importance of ventilatory thresholds to define aerobic exercise intensity in cardiac patients and healthy subjects

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Background: Although structured exercise training is strongly recommended in cardiac patients, uncertainties exist about the methods for determining exercise intensity (EI) and their correspondence with effective EI obtained by ventilatory thresholds. We aimed to determine the first (VT₁) and second ventilatory thresholds (VT₂) in cardiac patients, sedentary subjects, and athletes comparing VT₁ and VT₂ with EI defined by recommendations.

Methods: We prospectively enrolled 350 subjects (mean age: 50.7±12.9 years; 167 cardiac patients, 150 healthy sedentary subjects, and 33 competitive endurance athletes). Each subject underwent ECG, echocardiography, and cardiopulmonary exercise testing. The percentages of peak VO₂, peak heart rate (HR), and HR reserve were obtained at VT₁ and VT₂ and compared with the EI definition proposed by the recommendations.

Results: VO₂ at VT₁ corresponded to high rather than moderate EI in 67.1% and 19.8% of cardiac patients, applying the definition of moderate exercise by the previous recommendations and the 2020 guidelines, respectively. Most cardiac patients had VO₂ values at VT₂ corresponding to very-high rather than high EI (59.9% and 50.3%, by previous recommendations and 2020 guidelines, respectively). A better correspondence between ventilatory thresholds and recommended EI domains was observed in healthy subjects and athletes (90% and 93.9%, respectively).

Conclusions: EI definition based on percentages of peak HR and peak VO₂ may misclassify the effective EI, and the discrepancy between the individually determined and the recommended EI is particularly relevant in cardiac patients. A ventilatory threshold-based rather than a range-based approach is advisable to define an appropriate level of EI.

KEYWORDS

cardiopulmonary exercise testing, exercise intensity, exercise prescription, lactate, ventilatory threshold

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1 | INTRODUCTION

Exercise training is a crucial element in the prevention and management of cardiovascular disorders (CVD), as it is associated with proven benefits in terms of quality of life, mortality, disability, and prevention of comorbidities.¹⁻³ As a consequence, regular exercise training is highly recommended and at least 150 minutes of moderate-intensity aerobic exercise or at least 75 minutes of high-intensity exercise training throughout the week is recommended, with additional health benefits with increasing minutes per week.^{4,5} Also, strength training is recommended with a frequency of twice a week, at 30–70% of one-repetition maximum (1RM) for the upper body and 40–80% of 1RM for the lower body, with 12–15 repetitions/set.⁶ However, particularly in patients with CVD, a tailored exercise prescription is strongly recommended.^{4,5,7-9} The basic tenets of exercise prescription are usually based on the identification of four main principles: frequency, intensity, time, and type, the so-called FITT concept. EI is more important than duration to improve the life expectancy and lower the risk for chronic diseases in a primary prevention setting and can be particularly useful not only when exercising with a constant HR but also in specific training programs, such as high-intensity interval training.^{10,11} Although the prescription of frequency, time, and volume per week is intuitive and consolidated in healthy people, the methodology to determine exercise intensity (EI) aimed at prescribing exercise is still debated, particularly in patients with heart failure. Traditionally, the previous recommendations for aerobic exercise prescription identify different EI domains based on the physiological responses to exercise derived by healthy subjects or even competitive athletes: According to this approach, EI is defined based on the corresponding percentages, that is, the percentage of peak oxygen consumption (VO_2) and the percentage of peak heart rate (HR).^{7,12} Recently, the new 2020 ESC guidelines of sports cardiology proposed a new classification of EI.⁵ However, this method does not entirely reflect the individual response to exercise and, as a consequence, the effective EI can be misclassified, particularly in patients with aerobic and anaerobic thresholds influenced by clinical, pharmacological (ie, under β -blockers), or training factors, with a consequent over- or under-estimation of the intensity of exercise training.¹³⁻¹⁶

Cardiopulmonary exercise testing (CPET) is the most important tool to assess exercise intensity prescription of a tailored exercise program; however, EI is usually expressed as a percentage of maximal aerobic capacity rather than by CPET-derived individual ventilatory thresholds (VTs) that more appropriately reflect the variability of personal adaptation to exercise and better determine EI, particularly in cardiac patients with left ventricular (LV) dysfunction and β -blocker therapy.¹⁴ Unfortunately, scant data are currently

available about the determination of VTs in cardiac patients and their correspondence to EI domains.^{13,14} Therefore, this study aimed to determine the first (VT₁) and second VTs (VT₂) in cardiac patients with those obtained in healthy sedentary subjects and competitive athletes. We also compared the definition of EI by VT₁ and VT₂ with that recommended by previous and new guidelines, to investigate the correspondence between VTs and EI domains.^{7,12} The hypothesis was that recommended EI domains may misclassify the effective EI as assessed by CPET-derived VTs.

2 | METHODS

From January 2018 to June 2020, we prospectively enrolled 390 consecutive subjects referred to three centers qualified in performing CPET: the Siena Centre for Sports Cardiology, the Cardiology Department of the University Hospital of Siena, and the Sports Medicine Unit of “Toscana Centro.” Two hundred and twenty-four patients with CVD and 150 subjects without known CVD (ie, free from symptoms and evidence of CVD) were enrolled in the study. We also enrolled 33 competitive endurance athletes as a population of supranormal subjects. Patients with CVD were affected by different CVDs, including coronary artery disease, dilated cardiomyopathy, and hypertrophic cardiomyopathy. From the initial population, 26 patients were excluded because they were not in sinus rhythm (ie, atrial fibrillation) and 5 patients because of chronotropic incompetence. The VT₁ was not determined in 9 patients because of exercise oscillatory ventilation. Therefore, 350 subjects were included in the final analysis: 167 cardiac patients, 150 healthy sedentary subjects, and 33 competitive non-professional endurance athletes. Cardiac patients were also divided into 4 categories of LV systolic dysfunction, according to the guideline stratification of LV ejection fraction (EF)¹⁷: severe dysfunction (EF <30%), n=40; moderate dysfunction (30 \geq EF \leq 40%), n=82; mild dysfunction (52–54% \leq EF $>$ 40%), n=32; and preserved LVEF (EF \geq 52–54% in males and females, respectively), n=13.

All study participants underwent complete clinical and physical examination, 12-lead resting ECG, transthoracic echocardiographic examination, and CPET.

After the rationale and the study protocol were explained, all patients gave written informed consent. The study protocol was approved by the local Ethical Committee of the University of Siena.

2.1 | Physical examination and 12-lead resting ECG

Information about the presence of a known CVD, cardiovascular risk factors—family history for CVD,

hypertension, dyslipidemia, diabetes, and smoking habit—and previous implantation of pacemakers, implantable cardioverters, or cardiac resynchronization therapies was collected. Symptoms suggestive of functional capacity limitation, stratified in categories according to the New York Heart Association (NYHA), were also investigated. Information about drug therapy was also collected. Body height and weight were measured, and body mass index and body surface area were calculated. A standard 12-lead ECG was performed in all participants in the supine position during quiet respiration using a CARDIOLINE Realclick v.3.4 (Cardioline SpA, Milan, Italy). All ECGs were recorded at a paper speed of 25 mm/s and a standard gain of 1 mV/cm.

2.2 | Echocardiographic examination

Echocardiographic examination was performed by expert cardiologists using a high-quality echocardiograph (Vivid 9, General Electrics, Milwaukee, Wisconsin), equipped with an M4S 1.5-MHz to 4.0-MHz transducer, and a one-lead ECG was continuously displayed. LV end-diastolic (EDV) and end-systolic (ESV) volumes were assessed, and LV EF was calculated according to the current guidelines for chamber quantification.¹⁷

$$EF = \frac{EDV - ESV}{EDV} * 100$$

Right ventricular function was assessed as recommended by current guidelines.¹⁸ Valve diseases were reported and quantified as recommended.¹⁷

2.3 | Cardiopulmonary exercise test

All patients underwent symptom-limited CPET. All patients were carefully instructed to achieve maximal effort, and all of them were familiar with the 10-point Borg fatigue scale.¹⁹ A standard 12-lead ECG was recorded at rest, and ECG was continuously monitored during the test. Blood pressure was measured using a manual sphygmomanometer every 2 minutes. All patients were limited by fatigue, except for one patient that experienced a presyncope during the test, 2 patients had angina, and 1 patient was limited by palpitations.

The CPET data were realized on a cycle ergometer (Quark CPET, CosMed USA Inc., Concord, CA, USA), equipped with software OMNIA (CosMed USA Inc., Concord, CA, USA). At the beginning of each test day, a gas and volume calibration was performed according to the manufacturer's instructions. During the test, the environmental temperature was kept stable at 19–21°C. The exercise test (ramp protocol) included a 1-minute pre-exercise resting period sitting upright on the bike, a 2-minute unloaded warm-up cycling phase, followed by an incremental exercise cycling period with an increasing workload of 5–40W per minute, dependent on the patient's clinical status and aiming to complete the CPET within 8–12 minutes, as recommended.^{20,21} $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and ventilation (VE) during exercise were analyzed breath by breath. The VT_1 was determined according to three validated methods to determine VT_1 from incremental exercise test data²²: 1) modified V-slope method; 2) ventilatory equivalent method ($VE/\dot{V}O_2$ method); and 3) end-tidal O_2 pressure method ($PetO_2$). The VE versus W relationship was also taken into account. The V-slope was the reference method for VT_1

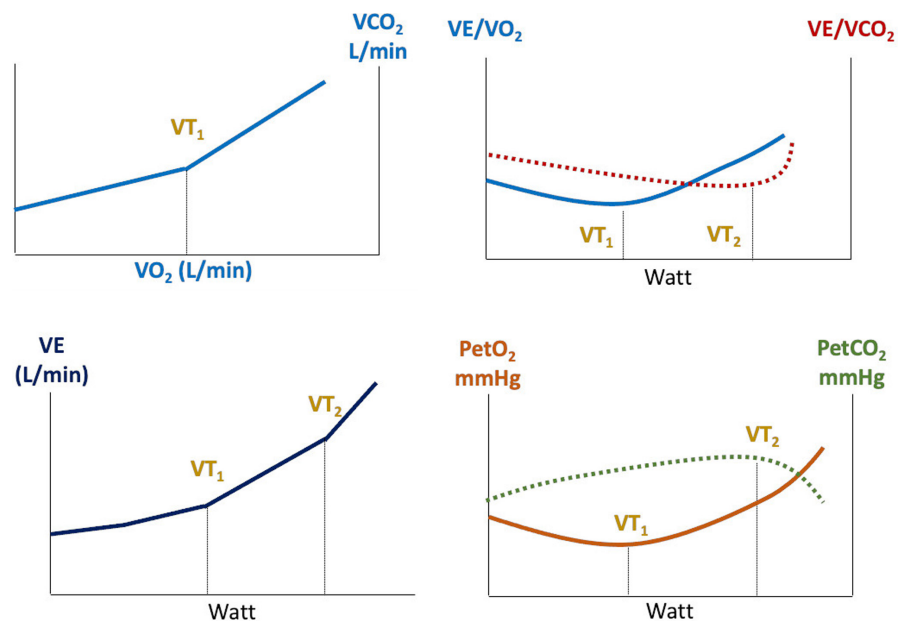


FIGURE 1 Determination of first and second ventilatory thresholds (VT_1 and VT_2) by cardiopulmonary exercise test (CPET) in a male: The VT_1 and VT_2 are usually obtained by analyzing all CPET panels, with particular attention to $\dot{V}O_2$ vs. $\dot{V}CO_2$, $VE/\dot{V}O_2$ and VE vs. power, and $PetO_2$ and $PetCO_2$ panels

TABLE 1 Descriptive characteristics of the population

	Overall population (N=350)	Cardiac patients (n=167)	Healthy sedentary (n=150)	Athletes (n=33)
Age, yrs	50.7 ± 12.9	54.4 ± 10.9	48.0 ± 13.2	41.9 ± 13.9
Male, n (%)	288 (82%)	147 (88%)	111 (74%)	30 (90%)
Weight, Kg	77 ± 14	81 ± 14	73 ± 14	71 ± 10
Height, cm	173 ± 8	173 ± 8	173 ± 9	176 ± 9
BMI	25.5 ± 4.1	27.0 ± 4.3	24.3 ± 3.7	22.7 ± 1.8
BSA, m ²	1.90 ± 0.2	1.94 ± 0.2	1.85 ± 0.2	1.86 ± 0.2
NYHA, n (%)				
I	215 (61%)	44 (26%)	138 (92%)	33(100%)
II	118 (34%)	106 (64%)	12 (8%)	-
III	17 (5%)	17 (10%)	-	-
IV	0 (0%)	-	-	-
Cardiovascular risk factors, n (%)				
Hypertension	43 (12%)	43 (26%)	-	-
Diabetes	27 (7%)	27 (16%)	-	-
Dyslipidemia	27 (7%)	24 (14%)	3 (2%)	-
Current smoker	21 (6%)	15 (5%)	6 (4%)	-
Previous smoker	29 (8%)	29 (17%)	-	-
Medication, n (%)				
Beta-blockers	167 (49%)	167 (100%)	-	-
ACEi	89 (25%)	89 (53%)	-	-
ARB	35 (10%)	35 (21%)	-	-
Sacubitril/valsartan	38 (11%)	38 (22%)	-	-
MRA	133 (38%)	133 (80%)	-	-
Diuretics	142 (41%)	142 (85%)	-	-
PM or ICD, n (%)	68 (19%)	68 (40%)	-	-
CRT, n (%)	54 (15%)	54 (32%)	-	-
Resting HR, bpm	70 ± 12	69 ± 11	71 ± 12	63 ± 12
LBBB, n (%)	22 (6%)	22 (13%)	-	-
RBBB, n (%)	8 (2%)	5 (3%)	3 (2%)	-
Resting SBP, mmHg	115 ± 15	108 ± 14	122 ± 10	119 ± 9
Resting DBP, mmHg	74 ± 9	71 ± 9	78 ± 7	74 ± 7

Note: Data are presented as mean ± standard deviation or as percentages.

Abbreviations: BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; HR, heart rate; LBBB, left bundle branch block; RBBB, right bundle branch block; DBP, diastolic blood pressure; METS, metabolic equivalent of task.

determination, and this point was checked with the point obtained in the other graphs. The VT₂ was determined, using the VE/VCO₂ plot, on the point where VE increases out of proportion to VCO₂, and this threshold was checked by establishing the nadir of the VE versus W relationship and the deflection point of end-tidal CO₂ pressure (PetCO₂) versus W (Figure 1).²² These points were measured according to the best agreement between two independent observers (F.A and F.V.). In case of disagreement, a third investigator was asked to assess the thresholds (F.D). In this study, the

disagreement between observers 1 and 2 was resolved by a 3rd observed in 1.5% of the cases for VT₁ and 2% of the cases for VT₂.

To ensure that peak VO₂ was attained, at least two of the following criteria had to be met: 1) maximal HR at a value close to 90% of the theoretical maximal HR, 2) respiratory exchange ratio (RER) ≥ 1.10, and 3) pedal rate note maintained at least at 60 rpm at each level of exercise.

VT₁ marks the limit between the slight and moderate intensity of exercise and exercising around this threshold allows

stimulating aerobic metabolisms while above VT_1 blood lactate and pH start to increase and decrease, respectively.^{7,14,23} VT_2 , that is, respiratory compensation point, has been proposed to be related to the so-called critical power, that is, the upper-intensity limit for prolonged aerobic exercise. VT_2 marks the limit between moderate and high-intensity of exercise.^{7,23} Therefore, the corresponding HR values obtained at VT_1 and VT_2 were considered the limit of moderate and high EI domains, respectively, and should be used to prescribe exercise in a different setting.^{14,23,24} At VT_1 and VT_2 , the percentages of peak VO_2 (%peak VO_2), peak HR (%peak HR), HR reserve (%HRR), and VO_2 reserve (% VO_2R) were extrapolated for comparison with previous recommendation-based EI domains⁷ and with the new 2020 guidelines on sports cardiology and exercise in patients with CVD by European Society of Cardiology (ESC).⁵ Supplementary Table 1 reports the definition of EI domains according to these documents.

2.4 | Statistical analysis

Normal distribution of all continuous variables was examined using the Shapiro-Wilk test, and data are presented as mean±standard deviation (95th confidence interval). Categorical variables are expressed as percentages. After the descriptive data analysis, the ANOVA test with Bonferroni post-hoc correction and the Kruskal-Wallis test were used to assess the significance between the groups of subjects, according to data distribution. A two-tailed p value <0.05 was considered significant. To identify the independent predictors of VT_1 and VT_2 , expressed as VO_2 , mL/min, in the study population individual association with clinical and demographic parameters was assessed by univariate and multivariable linear regression analysis. The model included the most important demographic and clinical variables and LVEF, while the CPET-derived parameters were excluded because of their redundant value. Two different models were set for VT_1 and VT_2 that were identified as dependent variables. Only the significant predictors identified at univariate regression analysis were included in the final model. Statistics were performed using SPSS, version 21.0 (Statistical Package for the Social Sciences Inc., Chicago, Illinois, USA).

3 | RESULTS

3.1 | Subjects characteristics

The demographic and clinical characteristics of the study population are reported in Table 1. The majority of patients were male (82%). The mean age was 50.7 ± 12.9 years. Hypertension was the most common cardiovascular risk factor. All cardiac patients were on β -blocker therapy, although the type

of β -blocker and the dosage differs significantly among the patients. Bisoprolol was the most commonly prescribed β -blocker, with an average dosage of 5 mg/die, followed by carvedilol and less commonly metoprolol. One hundred and twenty-two subjects had cardiac stimulation devices (34%), but all of them had sinus rhythm during exercise.

3.2 | Cardiopulmonary exercise test

CPET peak parameters in the overall study population and different categories of patients are shown in Table 1 and Table 2, respectively. Mean peak VO_2 was reduced in cardiac patients and preserved in healthy sedentary and competitive athletes (overall $p<0.0001$). All variables showed significant differences among the three different groups of subjects (overall p value <0.0001 for most parameters). The differences between groups are reported in detail in Table 2.

3.3 | Ventilatory thresholds and correspondence with exercise intensity domains

The determination of VT_1 and VT_2 in different categories of patients and the corresponding values of CPET parameters are reported in Table 3. The VT_1 was identified at higher VO_2 in athletes as compared to sedentary subjects and cardiac patients (overall $p<0.0001$). The percentage of peak HR and peak VO_2 demonstrated a trend toward a decrease in cardiac patients, sedentary subjects, and competitive athletes ($p<0.0001$), while the percentage of predicted VO_2 demonstrated an opposite trend. The same trend was demonstrated also for VT_2 and corresponding peak VO_2 and percentage of peak VO_2 . The difference between HR values corresponding to VT_1 and VT_2 was the lowest in cardiac patients and the highest in competitive athletes.

Recommendations of exercise intensity in cardiac patients seem to be partly incorrect in the current guideline. Table 4 reports the EI defined by VT_1 and VT_2 in cardiac patients, healthy sedentary subjects, and competitive athletes and its correspondence to the definition proposed by the previous recommendations and by 2020 ESC guidelines. For the majority of cardiac patients, moderate EI defined by VO_2 at VT_1 corresponded to high EI domains, applying the cutoffs proposed by the previous recommendations (67.1%), while moderate EI when the 2020 ESC guidelines were considered (79.6%). Similarly, the percentage of sedentary subjects and athletes with moderate EI defined by VO_2 at VT_1 corresponding to moderate EI cutoffs based on percentages was higher with the ESC 2020 classification than with the previous recommendations. In all groups, the percentage of subjects with VO_2R at VT_1 corresponding to moderate EI was higher when applying the 2020 ESC guidelines rather than the previous recommendations (90.4% vs. 67.1% for cardiac patients,

TABLE 2 Peak cardiopulmonary parameters in different categories of subjects

	Cardiac patients	Healthy sedentary	Athletes	p value
Peak Cycling Power Output, watt	113.0 ± 36.0 (108–119)	183.2 ± 63.1* (173–193)	295.4 ± 54.3* (276–314)	<0.0001
Peak SBP, mmHg	137.1 ± 23.9* (133–141)	179.0 ± 29.4 (174–184)	187.7 ± 24.9 (179–196)	<0.0001
Peak DBP, mmHg	77.6 ± 10.6^ (76–79)	82.7 ± 8.9 (81–84)	78.5 ± 8.3 (75–81)	<0.0001
Peak Borg Scale Dyspnea	5.9 ± 1.8 (5.6–6.2)	5.1 ± 1.8° (4.6–5.7)	8.3 ± 0.8* (7.8–8.8)	<0.0001
Peak METS	5.5 ± 1.4 (5.3–5.7)	8.7 ± 2.2* (8.4–9.1)	14 ± 2.2* (13.2–14.8)	<0.0001
Peak RER	1.11 ± 0.08^ (1.09–1.12)	1.14 ± 0.08 (1.12–1.15)	1.11 ± 0.07 (1.08–1.14)	0.003
Peak HR, bpm	118 ± 20* (115–121)	153 ± 19 (150–156)	162 ± 14§ (157–168)	<0.0001
Peak HR, %	70.8 ± 11.3^ (69–75)	88.9 ± 10.4 (87–91)	91.2 ± 7.6* (88–94)	<0.0001
Peak VO ₂ , mL/min	1533 ± 410 (1471–1596)	2215 ± 680* (2105–2325)	3464 ± 562* (3264–3662)	<0.0001
Peak VO ₂ /Kg, mL/min/Kg	19.0 ± 4.9 (18.3–19.8)	30.5 ± 7.9* (29–32)	49.0 ± 7.7* (46–52)	<0.0001
Peak VO ₂ , %	67.9 ± 14.1 (66–70)	99.0 ± 22.1* (95–103)	142.7 ± 30.9* (132–154)	<0.0001
VE/VCO ₂ slope	31.8 ± 7.4* (30.6–32.9)	27.1 ± 3.6 (26.5–27.7)	25.9 ± 3.1 (24.8–27.1)	<0.0001
Peak VE, l/min	58.4 ± 13.9 (56.3–60.5)	75.5 ± 23.0* (71.8–79.2)	115.1 ± 26.0* (105.8–124.3)	<0.0001
Peak VO ₂ /HR	13.3 ± 3.2 (12.8–13.7)	14.6 ± 4.1* (13.9–15.3)	21.5 ± 3.5* (20.3–22.7)	<0.0001
Peak VO ₂ /HR, %	98.7 ± 20.6 (96–102)	112.5 ± 21.6* (109–116)	152.5 ± 30.6* (142–163)	<0.0001
Peak VO ₂ /WR	9.6 ± 1.3 (9.4–9.8)	9.9 ± 0.8 (9.7–10.0)	10.6 ± 0.6* (10.3–10.8)	<0.0001
HRR, bpm	48 ± 18 (45–51)	82 ± 19* (79–86)	100 ± 14* (95–105)	<0.0001
VO ₂ R, mL/min	15.5 ± 4.9 (14.8–16.3)	27.0 ± 7.9* (25.7–28.3)	45.5 ± 7.7* (42.8–48.2)	<0.0001

Note: Data are presented as mean ± standard deviation (95% confidence interval). * $p \leq 0.001$ vs. other groups; ^ $p \leq 0.001$ vs. healthy sedentary; ° $p < 0.05$ vs. cardiac patients; and § $p < 0.05$ vs. healthy sedentary.

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; HRR, heart rate reserve; METS, metabolic equivalent of task; RER, respiratory exchange ratio; SBP, systolic blood pressure; VCO₂, exhaled carbon dioxide; VE, ventilation; VO₂, oxygen uptake; VO₂R, VO₂ reserve; WR, work rate.

92.7% vs. 72% for healthy sedentary subjects, and 72.7% vs 60.6% for competitive athletes).

The VT₂ was identified at higher VO₂ in athletes as compared to sedentary subjects and cardiac patients (overall $p < 0.0001$). The percentage of peak VO₂ demonstrated a trend toward a decrease in cardiac patients, sedentary subjects, and competitive athletes ($p < 0.0001$) (Table 3). For the majority of cardiac patients, VO₂ values at VT₂ corresponded to very-high EI when both recommendations were applied. Conversely, a higher percentage of healthy sedentary subjects

and competitive athletes showed VO₂ at VT₂ corresponding to high EI domain according to both previous recommendations and 2020 ESC guidelines.

3.4 | Comparison between left ventricular systolic function categories

The EI defined by VT₁ and VT₂ in subjects stratified according to LV EF and its correspondence to current recommendations

TABLE 3 First and second ventilatory thresholds and their respective parameters determined by cardiopulmonary testing in different categories of subjects

		Cardiac patients	Healthy sedentary	Athletes	p value
VT ₁	VO ₂ , mL/min	955 ± 230 (920–990)	1286 ± 359* (1228–1344)	1828±454* (1667–1989)	<0.0001
	VO ₂ /Kg, mL/min/Kg	11.9 ± 2.8 (11.4–12.3)	17.8 ± 4.4* (17.1–18.5)	26.2±7.6* (23.5–28.9)	<0.0001
	Peak VO ₂ , %	63.1 ± 7.8 (62–64)	59.1 ± 8.3* (58–60)	52.8±10.0* (49–56)	<0.0001
	Predicted VO ₂ %	42.6 ± 9.2 (41–44)	58.0 ± 13.5* (56–60)	76.8±27.2* (67–86)	<0.0001
	HR, bpm	88 ± 13^ (86–90)	107 ± 17 (104–110)	111±16* (106–117)	<0.0001
	Peak HR, %	75.1 ± 8.1^ (74–76)	70.0 ± 7.3 (69–71)	68.8±6.9* (66–71)	<0.0001
	Work Rate, watt	53.0 ± 21.9 (50–56)	87.3 ± 32.9* (82–93)	139.2±38.6* (125–153)	<0.0001
	VO ₂ /HR	11.0 ± 2.5 (10.6–11.4)	12.2 ± 3.4* (11.6–12.7)	16.5±3.6* (15.2–17.8)	<0.0001
	PetCO ₂ , mmHg	35.8 ± 4.8 (35–37)	40.6 ± 4.5* (39–41)	43.8±3.5* (43–45)	<0.0001
VT ₂	VO ₂ , mL/min	1301 ± 323 (1252–1350)	1833 ± 561* (1743–1923)	2811±505* (2632–2990)	<0.0001
	VO ₂ /Kg, mL/min/Kg	16.3 ± 3.9 (15.7–16–9)	25.1 ± 6.4* (24.1–26.2)	40.4±7.5* (38–43)	<0.0001
	Peak VO ₂ , %	85.4 ± 4.9* (84–86)	83.1 ± 7.7 (82–84)	81.0±6.2 (79–83)	<0.0001
	Predicted VO ₂ , %	57.9 ± 12.0 (56–60)	82.3 ± 19.5* (79–85)	116.8±28.6* (107–127)	<0.0001
	HR, bpm	104 ± 16 (101–106)	133 ± 19* (130–136)	144±15* (139–150)	<0.0001
	Peak HR, %	88.2 ± 5.8 (87–89)	87.1 ± 5.6 (86–88)	89.4±4.3 (88–91)	0.053
	Work Rate, watt	86.8 ± 29.1 (82–91)	144.0 ± 51.6* (136–152)	237.1±43.5* (221–252)	<0.0001
	VO ₂ /HR	12.7 ± 2.9 (12.2–13.1)	13.8 ± 3.8° (13.2–14.4)	19.5±3.6* (18.2–20.8)	<0.0001
	PetCO ₂ , mmHg	36.6 ± 5.3* (35–37)	42.0 ± 4.8 (41–43)	39.7±5.9§ (39–41)	<0.0001
Delta HR (VT ₂ -VT ₁), bpm	16±8 (15–17)	26 ± 10* (25–28)	33 ± 11* (30–37)	<0.0001	

Note: Data are presented as mean±standard deviation (95% confidence interval). * $p \leq 0.001$ vs. other groups; ^ $p \leq 0.001$ vs. healthy sedentary; ° $p < 0.05$ vs. cardiac patients; and § $p < 0.05$ vs. healthy sedentary.

Abbreviations: HR, heart rate; PetCO₂, CO₂ end-tidal pressure; VCO₂, exhaled carbon dioxide; VE, ventilation; VO₂, oxygen uptake; VT₁, first ventilatory threshold; VT₂, second ventilatory threshold; WR, work rate.

and the proposed classification is reported in Table 5. Most of the frequencies did not significantly differ among the groups with different LVEF. Irrespective of the degree of LV systolic dysfunction, the majority of cardiac patients had VO₂ values at VT₁ corresponding to high EI when the previously recommended classification was applied, while to moderate EI when

the definition was based on the 2020 ESC guidelines. Almost all groups of patients had VO₂ values at VT₂ corresponding mostly to very-high EI recommendation-based domain, while the groups with mildly depressed EF and preserved EF had VO₂ values at VT₂ corresponding mostly to high exercise bases on the 2020 ESC guidelines domains.

TABLE 4 Exercise intensity defined by first and second ventilatory thresholds in cardiac patients, healthy sedentary subjects, and athletes and its correspondence to previous recommendations and 2020 guidelines

	First ventilatory threshold			Second ventilatory threshold		
	Cardiac patients	Healthy sedentary	Athletes	Cardiac patients	Healthy sedentary	Athletes
<i>Correspondence of exercise intensity according to previous recommendations</i>						
% Peak VO₂						
Light	0.6%	2.7%	27.3%*	-	-	-
Moderate	31.7%	53.3%^	48.5%	-	-	-
High	67.1%	43.3%	24.2%	40.1%*	55.3%	69.7%
Very high	0.6%	0.7%	-	59.9%*	44.7%	30.3%
% Peak HR						
Light	1.2%	0.7%	-	-	-	-
Moderate	24%*	47.3%	45.5%	1.2%	0.7%	-
High	73.7%	50.7%^	54.5%	48.5%	61.3%	48.5%
Very high	1.2%	1.3%	-	50.3%	38%	51.5%
% HRR						
Light	57.5%*	34.7%	24.2%	1.8%	-	-
Moderate	37.1%*	56%	63.6%	12.6%	7.3%	3%
High	5.4%	9.3%	12.2%	76.6%	71.3%	57.6%
Very high	-	-	-	9%*	21.3%	42.4%
<i>Correspondence of exercise intensity according to 2020 guidelines</i>						
% Peak VO₂						
Light	-	0.7%	3%	-	-	-
Moderate	79.6%	90%	93.9%^	0.6%	6%	-
High	19.8%	8.7%^	3%	49.1%	56.7%	75.8%^
Very high	0.6%	0.7%	-	50.3%	37.3%	24.2%
% Peak HR						
Light	1.2%	0.7%	-	-	-	-
Moderate	43.1%*	73.3%	84.8%	0.6%	2.7%	-
High	54.5%*	26%	15.2%	58.1%	69.3%	57.6%
Very high	1.2%	-	-	41.3%	28%	42.4%
% HRR						
Light	58.7%*	34.7%	24.2%	1.8%	-	-
Moderate	41.3%*	62.6%	66.7%	38.9%	24.7%	3%
High	-	2.7%	9.1%	51.5%	56%	66.7%
Very high	-	-	-	8.4%*	19.3%	30.3%

Note: Data are expressed as percentages of subjects stratified according to exercise intensity for each cardiopulmonary exercise testing parameter. * $p < 0.05$ vs. other groups and ^ $p < 0.05$ vs. cardiac patients.

Abbreviations: HR, heart rate; HRR, heart rate reserve; VO₂, oxygen uptake.

3.5 | Regression analysis

To determine the independent predictors of VT₁ and VT₂, expressed as VO₂, mL/min, a multivariate linear regression analysis was performed. The predictors of VT₁ were age, gender, height, LVEF, and β -blocker therapy (R=0.62, adjusted R squared 0.36, $p < 0.0001$, for the entire model). The predictors of VT₂ expressed as VO₂, mL/min were age, gender,

weight, height, LVEF, and β -blocker therapy (R=0.71, adjusted R squared 0.48, $p < 0.0001$, for the entire model).

4 | DISCUSSION

The present study demonstrates that in cardiac patients, the use of EI domains proposed by the previous recommendations

TABLE 5 Exercise intensity defined by first and second ventilatory thresholds in subjects stratified according to left ventricular ejection fraction and its correspondence to previous recommendations and 2020 guidelines

	First ventilatory threshold				Second ventilatory threshold			
	Severely depressed	Moderately depressed	Mildly depressed	Preserved	Severely depressed	Moderately depressed	Mildly depressed	Preserved
<i>Correspondence of exercise intensity according to previous recommendations</i>								
% Peak VO₂								
Light	-	1.2%	-	-	-	-	-	-
Moderate	32.5%	32.5%	25.8%	46.2%	-	-	-	-
High	67.5%	65.1%	74.2%	53.8%	32.5%	41%	41.9%	53.8%
Very high	-	1.2%	-	-	67.5%	79%	58.1%	46.2%
% Peak HR								
Light	5%	-	-	-	-	-	-	-
Moderate	27.5%	26.5%	19.4%	15.4%	2.5%	1.2%	-	-
High	67.5%	71.1%	80.6%	84.6%	47.5%	50.6%	41.9%	53.8%
Very high	-	2.4%	-	-	50%	48.2%	58.1%	46.2%
% HRR								
Light	62.5%	61.4%	45.2%	46.1%	2.5%	2.4%	-	-
Moderate	37.5%	30.1%	51.6%	46.2%	20%	12%	6.5%	7.7%
High	-	8.4%	-	7.7%	70%	77.1%	83.9%	76.9%
Very high	-	-	-	-	7.5%	8.4%	9.7%	15.4%
<i>Correspondence of exercise intensity according to 2020 guidelines</i>								
% Peak VO₂								
Light	-	-	-	-	-	-	-	-
Moderate	77.5%	75.6%	93.8%*	76.9%	-	1.2%	-	-
High	22.5%	23.2%	6.2%	23.1%	47.5%	45.1%	53.1%	69.2%
Very high	-	1.2%	-	-	52.5%	53.7%	46.9%	30.8%
% Peak HR								
Light	5%	-	-	-	-	-	-	-
Moderate	40%	42.7%	43.8%	53.8%	2.5%	-	-	-
High	55%	54.9%	56.2%	46.2%	55%	61%	53.1%	61.5%
Very high	-	2.4%	-	-	42.5%	39%	46.9%	38.5%
% HRR								
Light	62.5%	62.2%	50%	46.2%	2.5%	2.4%	-	-
Moderate	37.5%	37.8%	50%	53.8%	50%	39%	28.1%	30.8%
High	-	-	-	-	42.5%	51.2%	62.5%	53.8%
Very high	-	-	-	-	5%	7.3%	9.4%	15.4%

Note: Data are expressed as percentages of subjects stratified according to left ventricular ejection fraction. * $p < 0.05$ vs. other groups.

Abbreviations: HR, heart rate; HRR, heart rate reserve; VO₂, oxygen uptake.

determines a misclassification of the effective level of EI assessed by CPET-derived ventilatory thresholds (ie, VT₁ and VT₂). In particular, when the percentage of peak VO₂ was considered, the majority of cardiac patients had an intensity at VT₁ wrongly classified as “high” and an intensity at VT₂ wrongly defined as “very high” (67.1% and 59.9%, respectively). Notably, the previously recommended classification defined different levels of EI validated on cohorts of healthy subjects^{7,25} but there are concerns about their performance on

healthy subjects²⁶ and they may not perform well in patients with CVD, taking medications and having a cardiac or ventilatory deficiency. Indeed, the present study demonstrates that the discrepancy between the individually determined EI and the previously recommended EI levels was less evident in healthy sedentary subjects and competitive athletes. Nevertheless, also in these groups, the same level of effort at VT₁ and VT₂ corresponded to different levels of EI. The new ESC 2020 ESC guidelines reported a different classification

that showed in this study a better correspondence between VT_1 parameters and moderate EI domain, especially when the percentage of peak VO_2 was considered. However, also applying these guidelines, in cardiac patients HR parameters (ie, % peak HR and %HRR) failed to demonstrate a proper matching between VTs and EI domains. In particular, most cardiac patients had an erroneous classification of the intensity of exercise, when % peak HR and %HRR at VT_1 were used.

Previous studies demonstrated that prescribing EI as a fixed percentage of peak VO_2 is not a proper method to obtain homogeneous EI grades in different individuals. In particular, the prescription of EI at 70% of peak VO_2 resulted in higher concentrations of plasma lactate in untrained rather than in trained subjects.²⁷ Another study reported a large intra-subject variability in blood lactate observed during an exercise performed at 60 and 75% of peak VO_2 , highlighting the absence of a lactate steady state at the same presumed level of EI.²⁸ Moreover, a high inter-subject variability has been observed in highly trained cyclists for RER when cycling at 79% of peak VO_2 .²⁹ In our population, for the definition of EI based on the percentage of peak HR and of peak VO_2 , we observed a similar trend: Indeed, the majority of cardiac patients reported a percentage of peak HR at VT_1 corresponding to the definition by previous recommendations of high rather than moderate intensity. Moreover, comparing the 2020 ESC guideline-based classification to the confidence interval of % peak VO_2 at VTs reported in Table 3, we observed that the range of % peak VO_2 at VT_1 (ie, 62–64%) and VT_2 (84–86%) are consistent with the moderate and high EI domains, respectively. However, these values are near to the upper limits of these ranges, suggesting that prescribing exercise with guidelines-domain may underestimate the desired intensity, particularly in some categories of individuals. Despite its common use, only one study investigated the validity of the percentage of peak HR to normalize EI and there is no evidence that prescribing EI to fixed percentages of peak HR could be a valid method to achieve homogeneous domains of EI,^{30,31} particularly in patients under β -blocker therapy. Moreover, a loss of linearity of HR versus WR relationship has been reported as peak VO_2 is approached in cardiac patients,³² in whom chronotropic incompetence is a frequent finding due to age-, pathology-, and drug-related sinus node dysfunction. Consequently, in cardiac patients, both on- and off- β -blockers, high uncertainty in predicting % VO_2R based on %HRR has been reported.^{33–35} In the present study, a population of cardiac patients on β -blocker therapy was examined and it was observed that a great majority of subjects presented a %HRR at VT_1 below the expected level of EI (ie, less than moderate). Thus, our results demonstrated that in cardiac patients, the HR recommendation-based parameters of EI may not correspond to the ventilatory threshold-based intensity of exercise and may misclassify

the proper level of EI, leading to the absence of benefit or potential harm of exercise prescription.

Previous recommendations reported also the cutoffs for EI domains for the percentage of VO_2R , which has been found to correspond to the same thresholds of %HRR, both in healthy individuals and in cardiac patients.^{36,37} Although the 2020 ESC guidelines did not report this parameter in EI classification, when assuming for % VO_2R the same cutoffs of %HRR as previously recommended, we observed that a high percentage of subjects in all categories had values of % VO_2R at VT_1 correctly corresponding to “moderate” EI.

Recently, Hansen et al. observed that, in a population of patients with CVD, at the same level of effort (both at VT_1 and VT_2) different recommendation-based EI domains were obtained, suggesting the need for an adjustment of the recommendations.¹⁴ Moreover, they demonstrated that patients with lower peak VO_2 had a higher level of EI than those with greater peak VO_2 .¹⁴ Only a minority of patients showed VT_1 and VT_2 parameters corresponding to moderate and high recommendation-based EI, respectively. Our results are consistent with those reported by this study and provide further information about individual responses and their correspondence to previous recommendations and 2020 ESC guidelines in patients with CVD, in healthy sedentary subjects and athletes.

The lack of correspondence between guideline-based and ventilatory threshold-based EI domains highlights the need for individualized exercise prescription based on objective parameters derived from quantitative assessment of CPET values. As a consequence, a shift from a “range-based” to a “ventilatory threshold-based” EI prescription is advisable to prescribe an appropriate level of intensity associated with proven benefits.^{7,23} The use of CPET is well established for tailored exercise prescription, as the determination of VTs represents the gold standard for assessment of EI and helps set EI in a highly individualized manner.²² Although CPET gives the unique opportunity to define EI for each specific patient, determining the VTs and identifying the most appropriate target for aerobic exercise³⁸ also in patients with CVD,¹³ the % of VO_2 peak is frequently used to prescribe exercise. However, this study demonstrates the importance of prescribing aerobic exercise according to VT_1 and VT_2 , to obtain the appropriate level of moderate and high EI and to avoid levels of intensity potentially associated with harmful outcomes. Indeed, it has been demonstrated that in patients with hypertrophic cardiomyopathy during incremental effort exercise, concentrations of adrenaline and noradrenaline were stable at a light and moderate EI, whereas above VT_2 plasma catecholamine levels rose rapidly.³⁹ Therefore, an EI not exceeding VT_2 seems to represent the best and safest exercise option in patients with known CVD and an accurate definition of EI based on VT_2 is crucial. This approach should be followed particularly in cardiac patients under β -blocker

therapy, as the misclassification of EI is particularly evident in this group of patients: Indeed, our study demonstrates that, when a certain percentage of VO_2 max and HR is used to prescribe moderate EI in a cardiac patient under β -blocker therapy, in 67% and 74% the EI corresponds to high rather than moderate intensity, failing to identify the appropriate EI suggested by international guidelines and leading to a wrong prescription with a higher than recommended EI. Conversely, if the percentage of HRR is used in a β -blocked patient, a light EI is prescribed in 58% of the cases, leading to an EI that is below the threshold recommended and that should not allow reaching the established benefits of exercising, given the inappropriateness of EI definition. Accordingly, based on the results of the present study, we strongly encourage physicians prescribing exercise to use an approach based on the determination of ventilatory threshold, that should more appropriately classify EI, particularly in patients under β -blocker therapy.

In case of impossibility to determine VTs, we suggest the use of the 2020 ESC guideline classification of EI, which at least partially overcomes the limitations of the previously recommended classification and has shown a better correspondence with individual responses, particularly in cardiac patients.

5 | LIMITATIONS

This study has some limitations. Firstly, the study population included mostly patients with coronary artery disease, dilated cardiomyopathy, and hypertrophic cardiomyopathy. As a consequence, our results cannot be directly applied to the entire spectrum of CVDs, although the CVDs included in this study represent most of the cardiac patients with an indication to CPET. Secondly, the population of competitive athletes is relatively small. However, these subjects were enrolled to compare VTs obtained in cardiac patients to those identified in competitive athletes, to provide a comprehensive description of the effects of CVDs, sedentary and training on the determination of VTs.

Data on RER and Borg scale values at corresponding first and second VTs were not reported in the present study, and this represents a limitation. However, in Table 3 the corresponding values of the percentages of max HR were reported in the three different groups of subjects to provide informative data also for physicians and centers that cannot use CPET to prescribe exercise.

The population of cardiac patients selected in our study was relatively well compensated and with a less advanced stage of the disease: Accordingly, the VT_1 was undeterminable only in 5% of cardiac patients, while some authors found that VT_1 was not determinable in a greater proportion of patients (>15%) with more advanced cardiac disease.⁴⁰

Therefore, the present results cannot be generalized to the entire population of cardiac patients.

Lastly, although we demonstrated that the determination of VTs is crucial to appropriately prescribe exercise, particularly in cardiac patients under β -blocker therapy, we recognize that the manual analysis is time-consuming and is affected by a non-negligible intra- and inter-observer variability.⁴⁰ However, if VTs are determined by highly experienced clinicians, as in this and other studies by research groups well trained in prescribing exercise by CPET, the CV is rather low (around 2–3.5% for VT_1 and 1.9–2.1% for VT_2).^{41–44} It is therefore essential that physicians are aware of the importance to obtain VTs during CPET and that training is essential to appropriately interpret CPET data. Recently, artificial intelligence has been applied to the determination of VTs demonstrating that neural network achieved expert-level performances across the tasks (mean absolute error was 9.5% ($r=0.79$) and 4.2% ($r=0.94$) for VT_1 and VT_2 , respectively).⁴⁵ Therefore, to overcome the current limitations, neural networks could potentially be embedded in CPET hardware/software to extend the reach of exercise physiologists beyond their laboratories.

6 | PERSPECTIVE

The definition of exercise intensity is crucial to properly prescribe exercise, particularly in cardiac patients under β -blocker therapy. Exercise intensity defined by percentages of peak HR and peak VO_2 may misclassify the effective intensity. Conversely, in this study on 350 patients, we found that in cardiac patients, the use of EI domains proposed by the previous recommendations determines a misclassification of the effective level of EI assessed by CPET-derived ventilatory thresholds.

The 2020 ESC guideline-based EI domains present a better correspondence with EI derived from VT_1 and VT_2 , as compared to the previous recommendations. However, a shift from a “range-based” to a “ventilatory threshold-based” EI determination is advisable to prescribe an appropriate level of EI for each individual, according to individual characteristics, personal clinical history, and therapy, particularly in cardiac patients under β -blocker therapy.

Every approach to prescribe aerobic EI may have some limitations. Indeed, when aerobic EI is prescribed using indices of peak effort (eg, % $\text{VO}_{2\text{peak}}$), one of the main limitations is represented by the fact that not all cardiac patients can achieve a near-maximal effort during CPET and, therefore, this may have a relevant impact on the determination of the appropriate EI. Conversely, VT_1 and VT_2 are effort-independent and can be achieved by the vast majority of cardiac patients. Nevertheless, some difficulties may also hamper the reliability of the determination of these VTs. Indeed, VT_1 and VT_2 cannot be determined in some patients

with heart failure.⁴⁰ However, in this study, we demonstrated that, if cardiac patients enrolled for exercise programs were well compensated, VTs can be determined in the vast majority of the patients with heart failure, even if they have a severe degree of LV dysfunction. Furthermore, a non-negligible intra- and inter-observer variability have been demonstrated in determining VTs in cardiac patients with heart failure.⁴⁰ However, in this study the rate of disagreement between the observer 1 and observer 2 was very low, demonstrating that training is essential to appropriately interpret CPET data and, when the same approach was used to prescribe exercise, the intra- and inter-observer variability dramatically decreases. Finally, a ramp cycle protocol may have also positively influenced the results of this study.

7 | CONCLUSIONS

A range-based assessment of EI for prescribing exercise could misclassify the effective EI, as assessed by VTs, particularly in cardiac patients on β -blocker therapy. The 2020 ESC guideline-based EI domains present a better correspondence with EI derived from VT₁ and VT₂, as compared to the previous recommendations. However, a shift from a “range-based” to a “ventilatory threshold-based” EI determination is advisable to prescribe an appropriate level of EI for each individual, according to individual characteristics, personal clinical history, and therapy.

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CONFLICTS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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