

Unveiling the limitations of non-metabolic thresholds in assessing maximal effort: The role of cardiopulmonary exercise testing

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ABSTRACT

Introduction: Maximal effort, defined by a respiratory exchange ratio (RER) ≥ 1.10 , is crucial for accurate interpretation of cardiopulmonary exercise testing (CPET). Standard tests rely on non-metabolic thresholds, such as peak predicted heart rate (ppHR) $\geq 85\%$, double product (DP) $\geq 20,000$ bpm*mmHg and peak metabolic equivalent of task (MET) ≥ 5.0 . This study aimed to assess the effectiveness of non-metabolic thresholds in detecting maximal effort, compared with the RER ≥ 1.10 criterion.

Methods: We retrospectively analyzed stable patients who underwent CPET from 2022 to 2023, regardless of test indication, history of heart failure (HF), or medication use. All patients also performed transthoracic echocardiography.

Results: Among 239 middle-aged patients (53 ± 14 years, 67 % male), 86 % achieved a RER ≥ 1.10 , and 65 % had a diagnosis of HF. Non-metabolic thresholds correctly identified maximal efforts (RER ≥ 1.10) in 75 % of the cases (AUC < 0.600). Misclassified cases were more likely to have a history of atrial fibrillation (AF), paced rhythm, HF, and beta-blockers or RAAS inhibitors use. These patients exhibited lower VO_2 peak and higher VE/VCO₂ slope. Multivariable analysis identified HF history (OR 4.8, CI 95 % 1.6–15.6, p: 0.005), low resting DP (≤ 7500 mmHg*bpm), and ramp protocol as independent predictors of discordant tests.

Conclusion: Non-metabolic thresholds misclassified up to 25 % of tests with RER ≥ 1.10 as non-maximal, potentially leading to inaccurate interpretation. In patients with HF, poor expected functional capacity and low DP, direct referral to CPET-equipped facilities may provide more accurate assessment than relying on non-metabolic thresholds.

1. Introduction

Exercise testing is a common diagnostic tool widely used to diagnose coronary artery disease (CAD) in patients with symptoms such as chest pain or shortness of breath, particularly those at low risk of chronic coronary syndrome [1]. It also helps predict cardiovascular events, assess exercise-induced symptoms, exercise tolerance, arrhythmias, and monitor responses to medical treatments for various cardiomyopathies [2,3].

The ideal duration for exercise tests follows a symptom-limited protocol, meaning the test continues until the patient feels unable to proceed [4]. However, the decision to stop can be patient-determined,

protocol-determined (i.e., submaximal exercise testing during cardiac rehabilitation), or physician-determined in the occurrence of specific clinical endpoints such as chest pain, arrhythmias, hypertensive/hypotensive response [5,6].

The maximal effort is crucial for the accurate interpretation of exercise tests. Performing a non-maximal effort restricts the interpretation of the results, precluding the clinician from assessing conditions like inducible ischemia or functional capacity [7]. In cardiopulmonary exercise tests (CPET), maximal effort is typically indicated by a respiratory exchange ratio (RER) ≥ 1.10 [8]. In the absence of lactate blood levels, this RER threshold is considered the gold standard indication of metabolic acidosis during CPET [9].

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Standard tests use non-metabolic thresholds, such as peak predicted heart rate (ppHR) $\geq 85\%$, double product (DP) $\geq 20,000$ bpm*mmHg, or a peak metabolic equivalent of task (MET) ≥ 5.0 [10].

To our knowledge, few studies have compared the efficiency of these non-metabolic thresholds, and very few, if any, have compared their diagnostic performance to achieving RER ≥ 1.10 .

Therefore, our study aimed to compare the effectiveness of non-metabolic thresholds in defining a maximal test with the criterion of achieving a RER ≥ 1.10 during CPET.

2. Methods

2.1. Study population

This monocentric, retrospective study enrolled all consecutive patients who underwent cardiopulmonary exercise testing (CPET) at the Italian referral center for Heart Failure (HF) and Cardiomyopathies in Trieste between 2022 and 2023. For the study proposal, patients were included regardless of the CPET indication.

All patients underwent transthoracic echocardiography (TTE), performed between 0 and 10 days before or after the CPET. Both CPET and echocardiography were performed during clinical stability (i.e., at least 6 months after changes in medical therapy, invasive procedures, and HF hospitalization).

All patients received optimized medical therapy according to the guidelines in effect at the time of the enrolment [11]. All CPETs were performed on top of medical treatment without withdrawal of anti-hypertensive drugs or beta-blockers.

Informed consent was obtained from all the participants according to the policy of the institutional review board. This study complies with the Declaration of Helsinki. The ethical committee approved the study (IRB: 99-177).

A simplified dataset version has been uploaded as supplementary electronic material. Further data are available from the corresponding author on reasonable request.

2.2. Cardiopulmonary exercise test

CPET was conducted using an individualized cycle-ergometer ramp protocol. The exercise ramp protocol was individualized based on clinical considerations. In the absence of clinical events, CPET was symptom-limited and self-interrupted by the patients regardless of the peak respiratory exchange ratio (RER) achieved. A “breath-by-breath” analysis of respiratory gases and ventilation was performed. Since reaching maximal oxygen uptake (VO_2 max)—the point at which VO_2 no longer increases despite a higher workload—is challenging, we commonly refer to VO_2 peak, defined as the highest measured VO_2 rate during the last 30 s of the CPET [6]. The Wasserman equation, adjusted for age and sex, was used to calculate the percentage of predicted peak VO_2 (pp VO_2 peak) [12]. Exercise oscillatory ventilation (EOV) was defined as cyclic fluctuations in ventilation based on commonly used diagnostic criteria [13].

The VE/ VCO_2 slope was calculated as the slope of the linear relationship between ventilation (VE) and VCO_2 from 1 min after the start of exercise to the end of the isocapnic buffering period as previously outlined [6,14].

Predicted maximal heart rate (HR) was defined using the formula $220 - \text{age}$ in males and $210 - \text{age}$ in females. The ppHR peak was calculated as $(\text{HR peak}/\text{predicted maximal HR}) \times 100$ [15]. The HR reserve (HRR) was calculated following the Karvonen formula (predicted maximal HR – HR measured/HR maximal HF predicted) respectively at rest or at the peak of the exercise [16]. The delta HR represents the difference between the HR measured at the peak of the exercise and rest. The DP was calculated as the product of systolic blood pressure (SBP) and the HR, measured at both rest and the peak of the exercise (bpm*mmHg).

As 1 MET is equivalent to 3.5 ml/Kg/min of oxygen uptake at rest, METs were calculated using the following formula: $(VO_2 \text{ peak}/\text{kg})/3.5$ [17].

The achievement of maximal exercise was indicated by a RER value of 1.10 or greater.

For the study proposal, non-metabolic criteria for the maximal effort were defined as a composite of ppHR peak $\geq 85\%$ or DP peak $\geq 20,000$ bpm*mmHg or METs peak ≥ 5.0 , according to the most utilized thresholds for cardiovascular exercise testing.

For the sake of simplicity, the term “concordant” was used to indicate a case where there was a RER ≥ 1.10 and the simultaneous positivity of non-metabolic criteria (see above). Conversely, the term “discordant” was used to refer to all other conditions.

In this study, the Vyntus™ CPX Metabolic Cart (Vyaire Medical) was the equipment used.

CPET data were collected by re-analyzing the related reports by two expert independent operators (NB, TMC), who were unaware of the patients’ status at the time of reanalysis.

2.3. Echocardiography

All patients underwent complete transthoracic echocardiographic evaluation at rest. The two-dimensional, and standard Doppler variables were measured following international guidelines [18]. All echocardiographic examinations were performed and reviewed by a cardiologist with expertise in cardiovascular imaging for HF at the third-level training stage. Left ventricular (LV) volumes and ejection fraction (EF) were determined using the Simpson’s biplane method. Chamber dimensions, areas, and volumes were adjusted for body surface area (BSA) [19]. Diastolic function was assessed according to current guidelines [20,21].

The speckle tracking echocardiography (STE) analysis was assessed in high-quality studies with a satisfactory frame rate. Averaged global longitudinal strain (GLS) was calculated from two-, three-, and four-chamber apical views [22]. Peak atrial longitudinal strain (PALS) was calculated from a four-chamber apical view [23].

The echocardiographic analysis was performed using TOMTEC Arena® Imaging Systems.

All measurements were averaged from either three beats (for patients with sinus rhythm) or five beats (for those with atrial fibrillation).

2.4. Statistical analysis

The summary statistics of the clinical and the instrumental variables were expressed as mean \pm standard deviation (SD), median (interquartile range, IQR), or counts and percentage, as appropriate. The T-student test was employed for continuous variables with a Gaussian distribution, whereas the Mann-Whitney test was used for continuous variables with a non-Gaussian distribution. The Chi-square test was calculated for discrete variables, and the Fisher exact test was used when necessary.

To evaluate the precision of established non-metabolic thresholds for maximal exercise, receiver operating characteristic curve (ROC) and area under the curve (AUC) analysis were employed. The AUCs were compared using the De Long test.

A univariable logistic regression analysis was conducted for the remaining parameters to identify any significant pre-test variables. Subsequently, multivariable logistic regression models were constructed using a backward-conditional stepwise algorithm to determine the most robust subset of independent predictors. The multivariable parameters were selected from the significant univariable analysis results to minimize biological collinearity.

Hazard ratios and 95% confidence intervals were calculated for each parameter.

The “optimal” thresholds for basal rest parameters were determined by maximizing the sum of sensitivity and specificity values of the

corresponding ROC curves.

All calculations were performed using IBM SPSS 30 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Characteristic of the overall population

The study cohort included 239 patients who completed at least one CPET during the pre-specified observation period. Table 1 summarizes the key clinical parameters for the overall population, comparing maximal and non-maximal tests.

Most patients were middle-aged males, with a body mass index above the normal range and sinus rhythm at electrocardiogram (ECG). A history of heart failure was detected in 65 % of the population studied.

Heart failure (HF) was evenly distributed between ischaemic (45 %) and non-ischaemic (55 %) causes. The most common clinic phenotype was HF with reduced ejection fraction (HFrEF), affecting 61 % of the patients (40 % of the overall population).

The respective proportions of patients receiving β -blockers and ACE inhibitors (ACEi)/angiotensin receptor blockers (ARBs)/angiotensin receptor neprilysin inhibitors (ARNI) were 74 % and 64 %.

The median value of left ventricular (LV) end-diastolic volume indexed (LVEDVi) was 67 ml/m² (IQR 49–94), and the median LVEF was 49 % (IQR: 32–60). The LV GLS was overall reduced, as well as the PALS.

The CPET was interrupted in most cases (74 %) due to muscular exhaustion. No adverse events were observed.

The overall population's mean aerobic capacity was mildly reduced (ppVO₂ peak: 71 %, IQR 60–86) with a mean value of VE/VCO₂ slope at the upper limit of the normal range (32 ± 6).

A total of 206 patients (86 %) in the study cohort reached maximal effort (see those with RER ≥ 1.10). No statistically significant differences were observed between maximal and non-maximal tests, except for weight and delta HR (see Table 1).

3.2. Metabolic vs non-metabolic thresholds for maximal effort

As reported in Table 2, the three non-metabolic thresholds (METs ≥5, DP peak ≥20,000 mmHg*bpm and ppHR peak ≥85 %) exhibited no statistically significant difference between the patient cohort with RER ≥ 1.10 and < 1.10. The sole parameter that approached a p-value of 0.05 was the ppHR peak (p-value: 0.056).

Neither alternative non-metabolic criteria (the presence of any one of them) nor cumulative criteria (the simultaneous occurrence of all three aforementioned criteria) were able to detect the cohort reaching RER ≥ 1.10 (respectively 154 (75 %) vs 21 (64 %), p-value: 0.180; 65 (32 %) vs 7 (21 %), p-value: 0.229). Sensitivity, specificity and derived indices have been reported in Supplementary Table 1.

When considered continuous variables, METs, DP peak, and ppHR peak demonstrated an AUC below 0.600 and no significant p-values in all three cases, indicating their inability to detect maximal metabolic effort accurately (see Fig. 1).

3.3. Concordant vs discordant CPETs

As reported in Table 3, 154 (75 %) of the 206 tests with RER ≥ 1.10 were classified as “concordant”, and 54 (25 %) were classified as “discordant”.

The two groups exhibited comparable characteristics for age, sex, and weight. Patients who performed the discordant test were more likely to have a history of atrial fibrillation (AF) or previous pacemaker (PM) implantation. Furthermore, a significantly higher incidence of HF was observed in the discordant group (92 % vs 58 %, p < 0.001), irrespective of whether the HF was caused by ischemic or non-ischemic factors, or its clinical presentation (HFpEF vs. HFmrEF, HFrEF).

In considering drug medical therapy, the discordant class was more

Table 1

Characteristics of the overall population, compared between maximal and non-maximal tests.

Variable	Overall (n = 239)	RER ≥ 1.10 (n = 206)	RER < 1.10 (n = 33)	p-value
Clinical characteristics				
Age, years	53 ± 14	53 ± 13	51 ± 16	0.570
Male sex, n (%)	162 (67)	142 (69)	20 (61)	0.342
Height, cm	172 ± 9	173 ± 9	170 ± 8	0.093
Weight, kg	78 ± 16	77 ± 16	84 ± 15	0.046
BMI, kg/m ²	26 ± 5	26 ± 4	29 ± 4	<0.001
Sinus rhythm, n (%)	205 (85)	175 (85)	30 (91)	0.363
Hypertension, n (%)	72 (30)	59 (29)	13 (39)	0.225
Heart failure, n (%)	158 (65)	138 (68)	20 (61)	0.426
HFpEF, n (%)	49 (20)	43 (31)	6 (30)	0.933
HFmrEF, n (%)	13 (5)	12 (9)	1 (5)	0.579
HFrEF, n (%)	97 (40)	84 (60)	13 (65)	0.695
Non-ischaemic aetiology, n (%)	132 (55)	115 (83)	17 (81)	0.841
Medical therapy				
Beta-blockers, n (%)	179 (74 %)	153 (75 %)	26 (79)	0.639
ARNI/ACEi/ARBs, n (%)	155 (64 %)	131 (64 %)	24 (73)	0.340
Echo characteristics				
LVEF, %	49 [32–60]	49 [32–60]	50 [32–66]	1.000
LVEDVi, ml/m ²	67 [49–94]	68 [50–94]	61 [47–86]	0.979
GLS LV, %	−14.9 [−17.5 to −10.7]	−15 [−17.6 to −10.5]	−13.5 [−17 to −10.9]	0.486
PALS, %	22 [15–32]	21 [15–32]	26 [17–32]	0.196
CPET parameters				
SBP peak, mmHg	163 ± 32	163 ± 32	163 ± 34	0.955
DBP peak, mmHg	85 ± 13	85 ± 13	82 ± 13	0.163
HR peak, bpm	133 ± 26	134 ± 25	128 ± 31	0.220
Delta HR, bpm	60 ± 26	62 ± 24	52 ± 26	0.034
ppHR peak, %	80 ± 15	81 ± 14	76 ± 13	0.111
HRR peak, %	32 ± 23	33 ± 23	39 ± 27	0.149
DP peak, mmHg*bpm	21,856 ± 7669	22,258 ± 7176	21,335 ± 8182	0.502
MET peak	5.5 [4.2–7]	5.6 [4.3–7]	5.1 [4.1–6.2]	0.140
Ramp protocol	12 ± 5	13 ± 6	11 ± 4	0.096
RER peak	1.23 ± 0.1	1.23 ± 0.1	1.04 ± 0.05	<0.001
VO ₂ peak/kg, ml/kg/min	19.2 [15.1–24.6]	19.5 [15.2–24.6]	17.8 [14.5–21.8]	0.140
ppVO ₂ peak, %	71 [60–86]	71 [60–86]	78 [58–88]	0.325
Watt peak, watt	112 [82–150]	113 [83–154]	112 [65–139]	0.979
VE/VCO ₂ slope	32 ± 6	32 ± 6	33 ± 8	0.274
Interruption for muscular exhaustion, n (%)	179 (74)	156 (76)	23 (72)	0.489

RER: Respiratory Exchange Ratio; BMI: Body Mass Index; HF: Heart Failure; HFpEF: HF with preserved Ejection Fraction; HFmrEF: HF with mildly reduced Ejection Fraction; HFrEF: HF with reduced Ejection Fraction; ARNI: Angiotensin Receptor Neprilysin Inhibitor; ACEi: Angiotensin-converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; LVEF: Left Ventricular Ejection Fraction; LVEDVi: Left Ventricular End-Diastolic Volume indexed; GLS LV: Global Longitudinal Strain of Left Ventricle; PALS: Peak Atrial Longitudinal Strain; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; ppHR: percentage of predicted HR; HRR: Heart Rate Reserve; DP: Double Product; MET: Metabolic Equivalent of Task; VO₂: Oxygen uptake; ppVO₂ peak: percentage of predicted of VO₂ peak; VE: Ventilation; VCO₂: carbon dioxide production.

likely to be prescribed with beta-blockers and RAASi (90 % vs 70 %, p = 0.003; 77 % vs 60 %, p = 0.027, respectively), which resulted in lower systolic blood pressure levels (110 ± 17 vs 120 ± 19 mmHg, p = 0.001, respectively).

The discordant group exhibited lower LVEF and PALS, whereas the LV EDVi and GLS were significantly higher.

Table 2

The limits of non-metabolic thresholds in distinguishing maximal from non-maximal exercise.

Variable	Overall (n = 239)	RER ≥ 1.10 (n = 206)	RER < 1.10 (n = 33)	p-value
METs ≥5, n (%)	142 (59)	124 (60)	18 (55)	0.540
DP peak ≥20,000, n (%)	136 (57)	121 (59)	15 (46)	0.153
ppHR peak ≥85 %, n (%)	94 (39)	86 (42)	8 (24)	0.056
Alternative non-metabolic criteria, n (%)	175 (72)	154 (75)	21 (64)	0.180
Cumulative non-metabolic criteria, n (%)	72 (30)	65 (32)	7 (21)	0.229

RER: Respiratory Exchange Ratio; MET: Metabolic Equivalent of Task; DP: Double Product; ppHR: percentage of predicted HR.

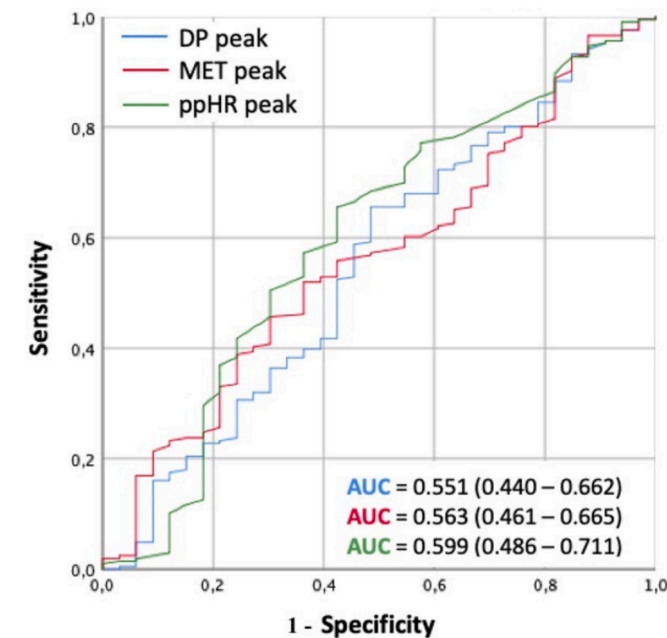


Fig. 1. ROC curve illustrating the accuracy of non-metabolic thresholds in identifying RER ≥ 1.10.

ROC: receiver operating characteristic; AUC: area under the curve; MET: Metabolic Equivalent of Task; DP: Double Product; ppHR: percentage of predicted HR.

Moreover, the breath-by-breath analysis of CPET parameters revealed that the discordant group of patients was more likely to exhibit chronotropic incompetence despite the mean normal HR at rest. Similarly, systolic blood pressure demonstrated a comparatively lower increase at the peak of the effort (134 ± 22 vs 173 ± 29 mmHg, $p < 0.001$).

Patients with discordant CPET showed reduced functional capacity and signs of pulmonary vascular limitation.

This resulted in a notable decline in functional capacity with signs of pulmonary vascular limitation in patients who performed a discordant CPET (VO_2 peak/Kg $14.7 [12.8-15.6]$ vs $21.8 [18.1-26.2]$ ml/Kg/min, $p < 0.001$; VE/VCO_2 slope 35 ± 8 vs 30 ± 5 , $p < 0.001$).

3.4. Univariable and multivariable analysis

The non-metabolic criteria, whether considered as alternative or cumulative, demonstrated low effectiveness in predicting maximal effort in correlation and logistic regression analysis (see **Supplementary Table 2, 3**).

Univariable and multivariable logistic regression analyses to identify

Table 3

The comparison of concordant and discordant tests in maximal exercise tests (RER ≥ 1.10).

Variable	Concordant (n = 154)	Discordant (n = 52)	p-value
Clinical characteristics			
Age, years	52 ± 14	56 ± 10	0.080
Male sex, n (%)	108 (70)	34 (65)	0.523
BMI, kg/m ²	25 ± 4	27 ± 5	0.082
Sinus rhythm, n (%)	136 (88)	39 (75)	0.036
Hypertension, n (%)	46 (30)	13 (25)	0.470
Heart failure, n (%)	90 (58)	48 (92)	<0.001
HFpEF, n (%)	31 (34)	12 (25)	0.272
HFmrEF, n (%)	10 (6)	2 (4)	0.173
HFrEF, n (%)	50 (55)	34 (71)	0.069
Non-Ischaemic aetiology, n (%)	78 (51)	37 (71)	0.201
Medical therapy			
Beta-blockers, n (%)	106 (70)	47 (90)	0.003
ARNI/ACEi/ARBs, n (%)	91 (60)	40 (77)	0.027
Echo characteristics			
LVEF, %	55 [34-60]	38 [29-53]	0.003
LVEDVi, ml/m ²	63 [49-94]	76 [58-96]	0.006
GLS LV, %	-15.7 (-18.4; -10.9)	-12.9 (-14.9; -9.0)	<0.001
PALS, %	27 ± 15	16 ± 8	<0.001
CPET parameters			
Basal SBP, mmHg	120 ± 19	110 ± 17	0.001
SBP peak, mmHg	173 ± 29	134 ± 22	<0.001
Basal HR, bpm	73 ± 13	69 ± 13	0.080
HR peak, bpm	143 ± 20	108 ± 18	<0.001
Delta HR, bpm	70 ± 21	38 ± 15	<0.001
ppHR peak, %	86 ± 11	65 ± 11	<0.001
HRR peak, %	24 ± 17	57 ± 19	<0.001
Basal DP, mmHg*bpm	8727 ± 2346	7511 ± 1935	0.001
DP peak, mmHg*bpm	24,901 ± 6122	14,430 ± 3315	<0.001
MET peak	6.2 [5.2-7.5]	4.2 [3.7-4.4]	0.001
Ramp protocol	14 ± 6	10 ± 3	<0.001
VO ₂ peak/gg, ml/kg/min	21.8 [18.1-26.2]	14.7 [12.8-15.6]	<0.001
ppVO ₂ peak, %	76.5 [66-93]	56.5 [46-65]	<0.001
Watt peak, watt	126 [97-166]	83 [68-103]	<0.001
VE/VCO ₂ slope	30 ± 5	35 ± 8	<0.001

BMI: Body Mass Index; HF: Heart Failure; HFpEF: HF with preserved Ejection Fraction; HFmrEF: HF with mildly reduced Ejection Fraction; HFrEF: HF with reduced Ejection Fraction; ARNI: Angiotensin Receptor Neprilysin Inhibitor; ACEi: Angiotensin-converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; LVEF: Left Ventricular Ejection Fraction; LVEDVi: Left Ventricular End-Diastolic Volume indexed; GLS LV: Global Longitudinal Strain of Left Ventricle; PALS: Peak Atrial Longitudinal Strain; CPET: Cardiopulmonary exercise test; SBP: Systolic Blood Pressure; HR: Heart Rate; ppHR: percentage of predicted HR; HRR: Heart Rate Reserve; DP: Double Product; MET: Metabolic Equivalent of Task; VO₂: Oxygen uptake; ppVO₂ peak: percentage of predicted of VO₂ peak; VE: Ventilation; VCO₂: carbon dioxide production.

“**Concordant**” indicate tests with RER ≥ 1.10 with the simultaneous positivity of non-metabolic criteria (see above).

“**Discordant**” was used to refer to all other conditions.

pre-test predictors of discordant CPET are reported in **Table 4**. At the univariable analysis, history of AF, presence of a paced rhythm, lower BP, and assumption of beta-blockers and/or RAASi drugs were identified as predictors of a discordant CPET. Higher values of LVEF and PALS were identified as protective factors against discordant CPET.

Finally, the history of HF (irrespective of its aetiology and clinical phenotype), lower DP and higher ramp protocol were the only parameters that remained independent predictors for identifying tests misclassified as maximal according to non-metabolic thresholds, even when the RER was ≥ 1.10.

4. Discussion

The assessment of maximal effort is paramount, as it serves as a quality indicator for exercise testing [24]. Performing a non-maximal

Table 4
Predictors of a discordant test in univariable and multivariable analysis.

Variable	Univariable analysis			Multivariable analysis				
	OR	CI 95 %	p-value	OR	CI 95 %	p-value		
Rest SBP	0.971	0.952	0.990			0.003		
Rest DBP	0.965	0.934	0.998			0.037		
Rest HR < 60 bpm	1.326	0.565	3.111			0.517		
Rest DP ≤ 7500	2.536	1.331	4.829	2.345	1.161	4.736	0.017	
Ramp protocol	0.830	0.759	0.908	<0.001	0.855	0.773	0.946	0.002
HF	8.267	2.835	24.102	<0.001	4.807	1.587	14.563	0.005
Ischaemic aetiology of HF	1.784	0.730	4.358	0.204				
HFpEF	0.645	0.295	1.413	0.273				
HFmrEF	1.991	0.944	4.203	0.071				
LVEF	0.963	0.943	0.984	<0.001				
LVEDVi	1.007	0.994	1.020	0.306				
PALS	0.943	0.893	0.995	0.033				
GLS LV	0.979	0.934	1.025	0.360				
AF or PM	2.519	1.135	5.590	0.023				
Hypertension	0.768	0.375	1.573	0.471				
Beta-blockers	4.886	1.435	16.639	0.011				
ACEi/ARBs/ARNI	2.234	1.085	4.600	0.029				
BB + RAASI	2.846	1.408	5.753	0.004				

BMI: Body Mass Index; HF: Heart Failure; HFpEF: HF with preserved Ejection Fraction; HFmrEF: HF with mildly reduced Ejection Fraction; HFrfEF: HF with reduced Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; LVEDVi: Left Ventricular End-Diastolic Volume indexed; GLS LV: Global Longitudinal Strain of Left Ventricle; PALS: Peak Atrial Longitudinal Strain; ARNI: Angiotensin Receptor Neprilysin Inhibitor; ACEi: Angiotensin-converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; HRR: Heart Rate Reserve; DP: Double Product; MET: Metabolic Equivalent of Task; RER: Respiratory Exchange Ratio; VO₂: Oxygen uptake; ppVO₂ peak: percentage of predicted of VO₂ peak; VE: Ventilation; VCO₂: carbon dioxide production; IQR: Inter-Quartile Ratio.

Only basal pre-exercise (rest) data were selected to detect a significant pre-test variable. See Table 1 for definitions of “Concordant and “Discordant”.

effort limits the interpretation of the test results, precluding the clinician from offering robust conclusions regarding functional capacity, inducible ischemia or arrhythmias [25].

To the best of our knowledge, this study is the first to investigate the effectiveness of commonly used thresholds for detecting maximal exercise testing in cases where breath-by-breath gas analysis is unavailable.

Although CPET is widely regarded as the most effective tool for exercise testing, particularly in the cases of HF or suspected poor functional capacity, it remains underused, primarily due to the lack of availability of the necessary technologies in all laboratories and the complexity in the interpretation of the results, requiring specific training and expertise [26,27]. Consequently, many clinicians must rely on non-metabolic criteria to identify maximal effort (ppHR peak ≥85 %, DP peak ≥20,000 mmHg*bpm, METs ≥5).

In our study we found that non-metabolic criteria were only able to identify maximal metabolic efforts in up to 75 % of the cases, with no significant difference observed between the RER ≥ 1.10 and RER < 1.10 groups. This finding indicated that up to 25 % of tests with RER ≥ 1.10 were misclassified as non-maximal (referred to as “discordant”), resulting in a fallacious interpretation of this data. Furthermore, the non-metabolic criteria presented poor diagnostic accuracy, as evidenced by AUC values consistently below 0.600 in all three cases.

Patients classified as discordant were more likely to have a history of AF, paced rhythm, HF, with higher use of beta-blockers or RAASI. They also exhibited greater echocardiographic signs of systolic and diastolic dysfunction, significantly reduced functional capacity, and heightened pulmonary vascular limitation. Multivariable analysis confirmed HF history, low rest DP (≤ 7500 mmHg*bpm), and ramp protocol as independent rest predictors, with HF linked to a five-fold higher risk of discordant test results. This latter result is also consistent with data currently available for the role of CPET in heart failure [28].

4.1. Limitations

The intrinsic limitations of a retrospective, single-center study preclude the drawing of definitive conclusions. However, this study should be considered as hypothesis-generating. Further prospective studies are required to validate our results.

The choice of the threshold of 7500 mmHg*bpm for the rest DP was mostly arbitrary, based on a value that, in clinical practice, represents a low HR and/or SBP. However, it should be noted that this cut-off demonstrated an acceptable specificity (0.700) in predicting discordant tests.

All CPETs were performed with no discontinuation of antihypertensive drugs or beta-blockers. This may have limited the assessment of ppHR and peak DP. Nevertheless, no significant difference was observed in the use of beta-blockers and antihypertensives between tests with RER ≥ 1.10 and < 1.10.

Despite submaximal CPETs (those with RER between 1.00 and 1.10) maintaining a known limited diagnostic and prognostic role, they were excluded from the study.

5. Conclusions

Currently used non-metabolic thresholds may be insufficient for accurately assessing maximal effort in a non-selected population undergoing exercise testing. Pre-test indicators such as the history of HF, the expected poor functional capacity, low DP, AF, paced rhythm and beta-blockers or RAASI are potential “red flags” for discordant tests. In such cases, physicians should prioritize direct referral to CPET to properly assess maximum effort.

CRedit authorship contribution statement

Nikita Baracchini: Writing – original draft, Methodology, Conceptualization. **Teresa Maria Capovilla:** Writing – original draft, Data curation. **Maddalena Rossi:** Writing – review & editing. **Cosimo Carriere:** Writing – review & editing, Project administration. **Antonio De Luca:** Writing – review & editing, Investigation. **Irena Tavcar:** Writing – review & editing. **Giulia Barbati:** Software, Formal analysis. **Marco Merlo:** Writing – review & editing, Supervision. **Gianfranco Sinagra:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

All authors declare no conflict of interest.

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All the authors take responsibility for the reliability and freedom from bias of the data presented and their discussed interpretation

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2025.133292>.

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