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Heart Failure with Reduced Ejection Fraction and Prognostic Scales: The Impact of Exercise Modality in Cardiopulmonary Exercise Tests

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Abstract: The cardiopulmonary exercise (CPET) test is an essential tool to determine the severity, prognosis, and need for invasive treatments in heart failure with reduced ejection fraction (HFrEF) but disregards the exercise modality. The present study aimed at analyzing the differences between treadmill and cycle-ergometer exercises. This was a prospective study, involving 65 patients with HfrEF who performed treadmill exercise followed by cycle-ergometer exercise 72 h later. We enrolled 65 patients, aged 58 ± 9 years, with an ejection fraction of $29 \pm 9\%$. Peak VO_2 was 20% greater (95% CI: 18–21%; $p < 0.000$) on the treadmill, and the ventilatory efficiency estimated by the VE/VCO_2 slope (32 ± 8 vs. 34 ± 9; $p < 0.05$). The ventilatory response was greater on the treadmill: maximum ventilation (55 ± 16 vs. 46 ± 11 L/min; $p < 0.000$) and ventilatory reserve at the maximum effort (28 ± 17 vs. $41 \pm 15\%$; $p < 0.000$). These values led to a change in the functional class of 23 (51%) patients and ventilatory class of 28 (47%) patients. Differences in the main parameters, including peak VO_2 and VE/VCO_2, impact prognostic scales and possible advanced treatments; therefore, the results should be interpreted in accordance with the exercise modality.

Keywords: heart failure with reduced ejection fraction; prognostic scales; VO_2; VE/VCO_2 slope; cardiopulmonary exercise tests; treadmill; cycle ergometer

1. Introduction

Exercise intolerance in heart failure with reduced ejection fraction (HFrEF) results from changes in oxygen delivery to skeletal muscles and its utilization by myocytes [1]. Cardiopulmonary exercise tests (CPETs) demonstrate this imbalance between oxygen supply and demand, particularly decreased oxygen consumption (VO_2) and maximum workload [2].

CPET is an objective, reproducible and non-invasive test [3] for the functional capacity of patients with HFrEF, routinely used in the baseline and follow-up assessments of this disease to determine its severity, prognosis and need for invasive treatments [4]. The gold-standard quantifier of functional capacity in CPET is VO_2 [5].

The most common exercise modalities in CPET are the treadmill and cycle ergometer, but protocols vary with the objective and limitation and/or weakness of the subject being studied [6,7]. Advantages of the treadmill stress test are familiarity with the exercise modality, participation of a higher number of muscle groups and greater work against gravity, thereby increasing the stress to which the systems involved in response to exercise are subjected [7,8]. For all these factors, peak VO_2 is 5–16% higher with treadmill than

with cycle ergometer tests [9–11]. This difference in peak VO_2 may occur in diseases whose prognostic stratification is based on this parameter, among other factors [2]. Disadvantages of the treadmill are determined by difficulties in the exact quantification of the work to which the patient has been subjected and relationship between the speed–slope and the metabolic cost [7]. The other CPET modality, the cycle ergometer, minimizes artifacts, is more affordable, and requires less space compared to the treadmill, but its main advantage is to facilitate quantification of the external work to which the patient is subjected [7]. Conversely, the cycle ergometer leads to lower-limb fatigue in untrained participants and lower VO_2 compared to the treadmill, among other disadvantages [12].

The analysis of peak VO_2 for determining prognostic scale scores [13] and decision making regarding the indication of advanced therapies, such as heart transplantation [14] or left ventricular assist devices (LVADs) [4,15], disregards the exercise modality, assuming that the oxygen requirement is identical in both tests. This assumption can lead to error by underestimating the real functional class of the patient.

Recently, parameters in addition to peak VO_2 have been incorporated into the prognostic stratification of HFrEF, such as the VE/VCO_2 slope [16] and exercise oscillatory ventilation [17] (EOV). These parameters have become increasingly relevant for obtaining predictive information, regardless of the patient's effort.

To date, few studies involving a small sample size of select patients have compared the results from both exercise modalities using the parameters peak VO_2 and VE/VCO_2 slope [18–24].

The aim of the present study was to analyze differences in CPET parameters between exercise modalities (treadmill and cycle ergometer) and their impact on the functional assessment and severity stratification of patients with HFrEF.

2. Materials and Methods

We prospectively enrolled outpatients with heart failure from the Asturias Central University Hospital (Hospital Universitario Central de Asturias—HUCA). All of them were in a clinically stable condition, undergoing current optimal treatment, and were referred for CPET from July 2019 to March 2020.

Inclusion criteria were left ventricular ejection fraction (LVEF) < 40% and New York Heart Association functional classes I–III [25]. Exclusion criteria included: (a) hospitalization within the last 3 months for decompensated heart disease or uncontrolled atrial fibrillation, (b) patients suffering any severe event during the CPETs or the cooldown period as myocardial ischemia and/or severe arrhythmia (ventricular tachycardia and ventricular fibrillation), and (c) not having completed both CPETs.

Demographic, anthropometric, comorbidity, and treatment data for all patients included in the study were recorded.

The study protocol was approved by the Research Ethics Committee of the Principality of Asturias (registration number 174/19). All patients included in the study received a patient information sheet and signed the informed consent form for participation in the study.

2.1. CPET

Each patient performed two CPETs up to their maximum tolerance. The first CPET was performed on a treadmill (HP Cosmos Pulsar 2002, Nußdorf, Germany), using a modified version of the protocol developed by Bruce [26], comprising 1 min stages with increasing speeds ranging from 2.7 to 6 km/h and progressive incline from 0% to 16%. The second CPET was performed 72 h later on a cycle ergometer (Corival Lode BV, Groninga, Netherlands) with 5–20 W/min increments adjusted to the functional limitation of each patient. Before the second test, the patients were evaluated to ensure the absence of changes in symptoms, physical findings, weight, and medication.

In addition to performing the breath-by-breath gas analysis (Ergocard, Medisoft Exp'Air 1.25, Breeze, Belgium) averaging the data every 10 s, the oxygen saturation and heart rate (HR) were continuously monitored by pulse oximetry and 12-lead electrocardiog-

raphy, respectively. Every 2 min, blood pressure (BP) was manually recorded, and degrees of dyspnea and lower-limb fatigue were assessed using the modified Borg scale (0–10) [27]. The ergospirometer was calibrated before each test [12].

HR (bpm), oxygen saturation (%), VO_2 (mL/min), CO_2 production (VCO_2; mL/min) and minute ventilation (VE; L/min) were recorded continuously. The following values were calculated: respiratory quotient (RQ), ventilatory equivalents for O_2 and CO_2 (EqO_2 and $EqCO_2$), VE/VCO_2 slope, ventilatory threshold (VT) using the system of ventilatory equivalents [6], breathing reserve (BR = $(1 - [VE/\text{maximal voluntary ventilation}]) \times 100$) [6], end-tidal CO_2 and O_2 pressures ($PetCO_2$ and $PetO_2$; mmHg), O_2 pulse (VO_2/HR; mL/bpm), and the presence of EOV, which was measured as cyclic oscillations in ventilation during $\geq 60\%$ of exercise with an amplitude $\geq 15\%$ of the mean value at rest [6]. Maximum values were recorded as those averaged over the last 20 s of the test. The HR recovery index (HRR-1; bpm) calculated the difference between the maximum HR during exercise and the HR 1 min after completing the test [28].

The criteria used to end the test were the maximum effort perceived by the supervised patient, serious cardiovascular events, and presence of limiting symptoms. In the recovery phase, monitoring was maintained for 3 min [6].

Functional limitation was rated using the Weber classification [29]. This classification divides patients with HFrEF as functions of the peak VO_2/kg and prognosis: class A, peak $VO_2/kg \geq 20$ min/mL/kg; class B, peak VO_2/kg = 16–20 min/mL/kg; class C, peak VO_2/kg = 10–15 min/mL/kg; and class D, peak $VO_2/kg \leq 10$ min/mL/kg. Patients in class A have the best prognosis.

The ventilatory classification was proposed by Arena et al. [30], which divides patients into four classes as functions of the VE/VCO_2 slope and prognosis: class I, VE/VCO_2 slope < 30; class II, ≥ 30 VE/VCO_2 slope < 36; class III, ≥ 36 VE/VCO_2 slope < 45; and class IV, VE/VCO_2 slope ≥ 45. Patients with ventilatory class I have the best prognosis.

2.2. Spirometry

Prior to CPET, spirometry was performed in a seated position to record the forced expiratory volume in the first second (FEV1), the forced vital capacity (FVC), and FEV1/FVC ratio. These parameters were interpreted using the theoretical reference values of the Global Lung Initiative [31]. Obstruction was defined as having a post-bronchodilator FEV1/FVC ratio lower than the lower limit of normal (LLN) [32]. The diagnosis of chronic obstructive pulmonary disease (COPD) was conducted following the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [33]. Maximal voluntary ventilation (MVV) was estimated using the formula FEV1 $\times$ 40 [6].

2.3. Statistical Analysis

Data analysis was conducted using the statistical program Stata (Version 15.4.2, StataCorp, College Station, TX, USA). A descriptive analysis was initially performed. Numerical data are expressed as numbers and percentages. The quantitative variables are expressed as the mean and standard deviation. The paired t-test was used to compare continuous data. Differences between proportions were analyzed using the Pearson chi-squared test. Correlations between peak VO_2 in each exercise modality were evaluated by calculating the Pearson correlation. A *p*-value of ≤ 0.05 was considered as statistically significant.

3. Results

From the 80 patients initially referred for the study, 15 were excluded; 10 did not fulfill the inclusion criteria and the other 5 did not complete the two CPETs previously described. Finally, we enrolled a total of 65 patients, including 49 (75%) men and 16 (25%) women, with a mean age of 57.8 $\pm$ 9.3 years. The mean LVEF was 29.5% $\pm$ 8.6%. Table 1 outlines the characteristics of the participants.

Table 1. Baseline characteristics of the included patients (*n* = 65).

	Mean (SD)/No (%)
Age (years)	57.8 ± 9.3
Sex (male)	49 (75%)
Body mass index (kg/m^2)	29.2 ± 4.4
Comorbidity	
- Atrial fibrillation	12 (18%)
- COPD	18 (28%)
• Mild	8 (44%)
• Moderate	9 (50%)
• Severe	1 (6%)
• Very severe	0 (0%)
Functional class	
- NYHA class I	13 (20%)
- NYHA class II	41 (63%)
- NYHA class III	11 (17%)
- NYHA class IV	0 (0%)
Cause of HFrEF	
- Ischemic	28 (44%)
- Idiopathic	27 (42%)
- Hereditary	6 (9%)
- Other	4 (5%)
LVEF (%)	29.5 ± 8.6
Laboratory values	
- Hemoglobin (g/dL)	14.05 ± 1.78
- Creatinine (mg/dL)	1.19 ± 0.8
- Glomerular filtration rate (mL/min/1.73 m^2)	71.6 ± 19.09
Spirometry (mL/% theoretical)	
- FEV$_1$	2701 ± 757 (84 ± 16%)
- FVC	3762 ± 1020 (90 ± 16%)
- FEV$_1$/FVC ratio	71 ± 7%
Chronic treatment	
- Beta-blocker	63 (97%)
- ACE-I	37 (57%)
- ARB	27 (41%)
- Mineralocorticoid receptor antagonist	37 (57%)
- Angiotensin receptor-neprilysin inhibitor	22 (34%)
- Loop diuretic	45 (69%)
- Thiazides	2 (3%)
- Ivabradine	7 (11%)
- Digoxin	1 (2%)
- Amiodarone	4 (6%)
Implantable cardioverter defibrillator	34 (52%)
- Single chamber	11 (32%)
- Cardiac resynchronization therapy	23 (68%)

COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; HFrEF: heart failure with reduced left ventricular ejection fraction; LVEF: left ventricular ejection fraction; FEV$_1$: maximum expiratory volume in the first second; FVC: forced vital capacity; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin AT$_1$-receptor blocker.

Comorbidities included atrial fibrillation with controlled ventricular response in 12 (18%) patients and COPD in 18 (28%) patients. COPD was mild and moderate in 44% and 50% of the patients, respectively.

3.1. CPET

The time interval between the two CPETs was 3.0 ± 1.9 days. Table 2 shows the detailed results of both CPETs.

Table 2. Cardiopulmonary exercise testing parameters.

CPET Variable	Treadmill	Cycle Ergometer	*p* Value
Test Duration (minutes)	10.5 ± 2.7	10.2 ± 3.1	NS
Reached VT (%)	93.8%	76.9%	$p < 0.05$
RQ Max	1.04 ± 0.05	1.03 ± 0.06	NS
HR at Rest (bpm)	69.6 ± 10.9	68.8 ± 11.0	NS
HR at Maximum Effort (bpm)	117.3 ± 15.7	107.5 ± 15.2	$p < 0.000$
HR Recovery Index (bpm)	22.4 ± 12.8	16.4 ± 8.8	$p < 0.000$
SBP at Rest (mmHg)	123.3 ± 21.6	125.3 ± 21.8	NS
SBP at the End of Exercise (mmHg)	158.7 ± 33.5	161.4 ± 30.9	NS
DBP at Rest (mmHg)	75.8 ± 10.8	78.9 ± 12.2	$p < 0.05$
DBP at the End of Exercise (mmHg)	81.5 ± 16.6	87.4 ± 16.2	$p < 0.000$
Initial O_2 Saturation (%)	97.0 ± 1.3	97.2 ± 1.2	NS
Final O_2 Saturation (%)	96.4 ± 1.8	97.2 ± 1.4	$p < 0.000$
Resting VO_2 (mL/min)	412.7 ± 162.2	416.6 ± 166.1	NS
Peak VO_2 (mL/min)	1734.9 ± 549.9	1390.5 ± 427.0	$p < 0.000$
Peak VO_2/kg (mL/min/kg)	21.0 ± 5.1	16.9 ± 4.1	$p < 0.000$
VO_2 at VT (mL/min)	1612.5 ± 382.5	1274.0 ± 361.8	$p < 0.000$
VCO_2 at VT (mL/min)	1587.7 ± 376.2	1259.0 ± 354.3	$p < 0.000$
O_2 pulse at VT (mL/bpm)	14.6 ± 3.6	12.5 ± 3.3	$p < 0.000$
VE/VCO_2 Slope	32.2 ± 7.9	33.9 ± 8.8	$p < 0.05$
VE Max (L/min)	54.7 ± 16.3	45.8 ± 11.4	$p < 0.000$
RR Max (rpm)	30.5 ± 5.6	27.3 ± 5.0	$p < 0.000$
EqO_2 at VT	35.6 ± 4.9	37.0 ± 5.5	$p < 0.05$
$EQCO_2$ at VT	36.3 ± 5.0	37.4 ± 5.4	$p < 0.05$
$P_{ET}CO_2$ at Rest (mmHg)	32.0 ± 4.4	32.8 ± 4.9	NS
$P_{ET}CO_2$ at VT (mmHg)	36.2 ± 4.2	36.1 ± 4.5	NS
$\Delta P_{ET}CO_2$ (mmHg)	3.8 ± 4.0	2.3 ± 4.7	$p < 0.05$
BR at Maximum Effort (%)	28.4 ± 17.1	41.1 ± 15.2	$p < 0.000$
Exercise Oscillatory Ventilation(%)	29.6	36.5	NS
Final Borg Dyspnea (1–10)	5.4 ± 2.4	3.7 ± 2.3	$p < 0.000$
Final Borg Lower Limbs (1–10)	3.8 ± 3.1	4.8 ± 2.4	$p < 0.05$

CPET: Cardiopulmonary exercise test; VT: ventilatory threshold; RQ: respiratory quotient; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2: oxygen consumption; VCO_2: CO_2 production; VE: ventilation; RR: respiratory rate; EqO_2: oxygen equivalent; $EqCO_2$: carbon dioxide equivalent; $P_{ET}CO_2$: partial pressure end-tidal carbon dioxide; $\Delta P_{ET}CO_2$: $P_{ET}CO_2$ increase from start of test to VT; BR: breathing reserve; NS: not significant.

3.2. Effort Level

The exercise duration and maximum RQ were similar in both exercise modalities. RQ reached 1.04 ± 0.05 and 1.03 ± 0.06 with the treadmill and cycle ergometer, respectively ($p = 0.43$), without significant differences, suggesting a similar degree of effort.

The treadmill exercise was suspended by four (6%) patients, because of dyspnea in two patients and hypertensive crisis in the other two patients. The cycle ergometer test was suspended by 15 (23%) patients because of lower-limb fatigue in five (33%) patients, hypertensive crisis in three (20%) patients, dyspnea in three (20%) patients, and other reasons in four (27%) patients.

3.3. VO$_2$

Regarding variations in VO$_2$ during CPET, baseline VO$_2$ (subject at rest) did not differ significantly between the two modalities. However, VT and peak VO$_2$ reached during exercise differed significantly between the two modalities ($p < 0.000$); Table 3; Figure 1.

Table 3. VO$_2$ variation during CPET.

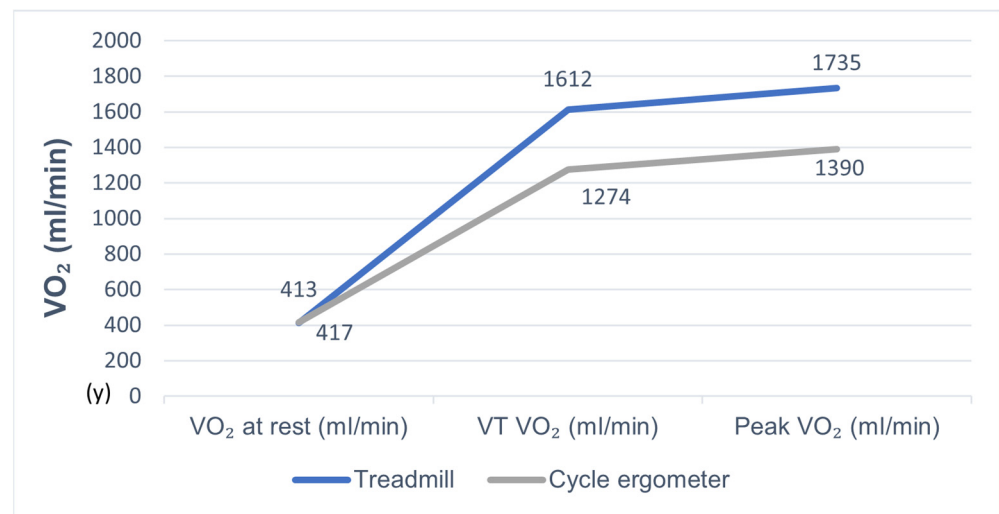|	Treadmill	Cycle Ergometer	*p*-Value
VO$_2$ at rest	412.7 ± 162.2	416.6 ± 166.1	NS
VT VO$_2$	1612.5 ± 382.5	1274.0 ± 361.8	<0.000
Peak VO$_2$	1734.9 ± 549.9	1390.5 ± 427.0	<0.000

Figure 1. VO$_2$ variation during CPET.

The peak VO$_2$/kg in treadmill and cycle ergometer exercises was 21.0 ± 5.1 and 16.9 ± 4.1 mL/min/kg, respectively, showing a significant difference ($p < 0.000$).

The peak VO$_2$ and peak VO$_2$/kg were 20% (95% confidence interval: 18–21%) higher value in the treadmill exercise than in the cycle ergometer exercise ($p < 0.000$). The correlation between peak VO$_2$ and peak VO$_2$/kg was excellent (r = 0.93 vs. 0.89, $p < 0.000$) in both ergometers.

3.4. Cardiovascular Response

The maximum HR was higher in the treadmill exercise than in the cycle ergometer exercise (117.3 ± 15.7 vs. 107.5 ± 15.2 bpm; $p < 0.000$), with a better HRR-1 (22.4 ± 12.8 vs. 16.4 ± 8.8 bpm; $p < 0.000$) in patients with a sinus rhythm ($n = 53$).

The O$_2$ pulse (VO$_2$/HR) in VT was 14.6 ± 3.6 and 12.5 ± 3.3 mL/bpm in the treadmill and cycle ergometer exercises, respectively, showing a significant difference ($p < 0.000$).

In the BP response throughout the test, systolic BP did not differ at the maximum exercise capacity, but diastolic BP at the maximum effort was significantly lower in the treadmill exercise than in the cycle ergometer exercise (81.5 ± 16.6 vs. 87.4 ± 16.2 mmHg; $p < 0.000$). In both tests, patients showed a hypertensive response to exercise, with systolic BP > 220 mmHg or diastolic BP > 120 mmHg in four patients (p = NS).

Figure 2 shows a comparison of the results of cardiovascular variables by ergometer.
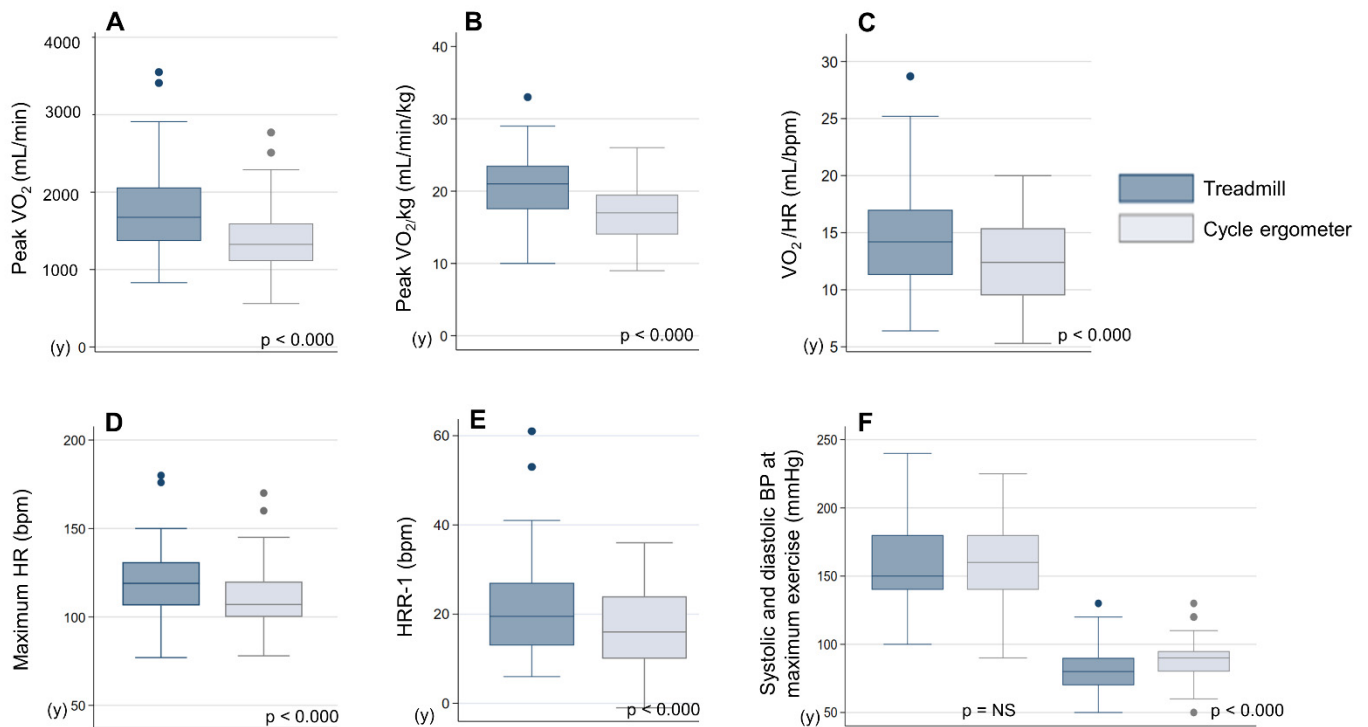
Figure 2. Boxplot of cardiovascular variables and VO_2 on the treadmill and cycle ergometer. (**A**) Peak VO_2 (mL/min), (**B**) peak VO_2/kg (mL/min/kg), (**C**) VO_2/HR at VT (mL/bpm), (**D**) maximum HR (bpm), (**E**) HRR-1 (bpm), (**F**) systolic and diastolic BP at the maximum exercise (mmHg). VO_2: oxygen consumption; HR: heart rate; HRR-1: HR recovery index; BP: blood pressure; NS: not significant.

3.5. Ventilatory Response and Gas Exchange

The ventilatory response was greater on the treadmill than on the cycle ergometer, at both the maximum respiratory rate (30.5 ± 5.6 vs. 27.3 ± 5.0 rpm; $p < 0.000$) and maximum VE (54.7 ± 16.3 vs. 45.8 ± 11.4 L/min; $p < 0.000$). Lower EqO_2 (35.6 ± 4.9 vs. 37.0 ± 5.5; $p < 0.05$) and $EqCO_2$ (36.3 ± 5.0 vs. 37.4 ± 5.4; $p < 0.05$), higher $\Delta PetCO_2$ (3.8 ± 4.0 vs. 2.3 ± 4.7; $p < 0.05$), and lower VE/VCO_2 slope (32.2 ± 7.9 vs. 33.9 ± 8.8; $p < 0.05$) were also observed, reflecting a better ventilatory efficiency on the treadmill than on the cycle ergometer.

BR at the maximum effort was significantly lower on the treadmill than on the cycle ergometer (28.4 ± 17.1 vs. $41.1 \pm 15.2\%$; $p < 0.000$).

Finally, EOV was present in 19 (30%) patients during the treadmill exercise and in 23 (36%) patients during the cycle ergometer exercise, with no significant differences (p = NS).

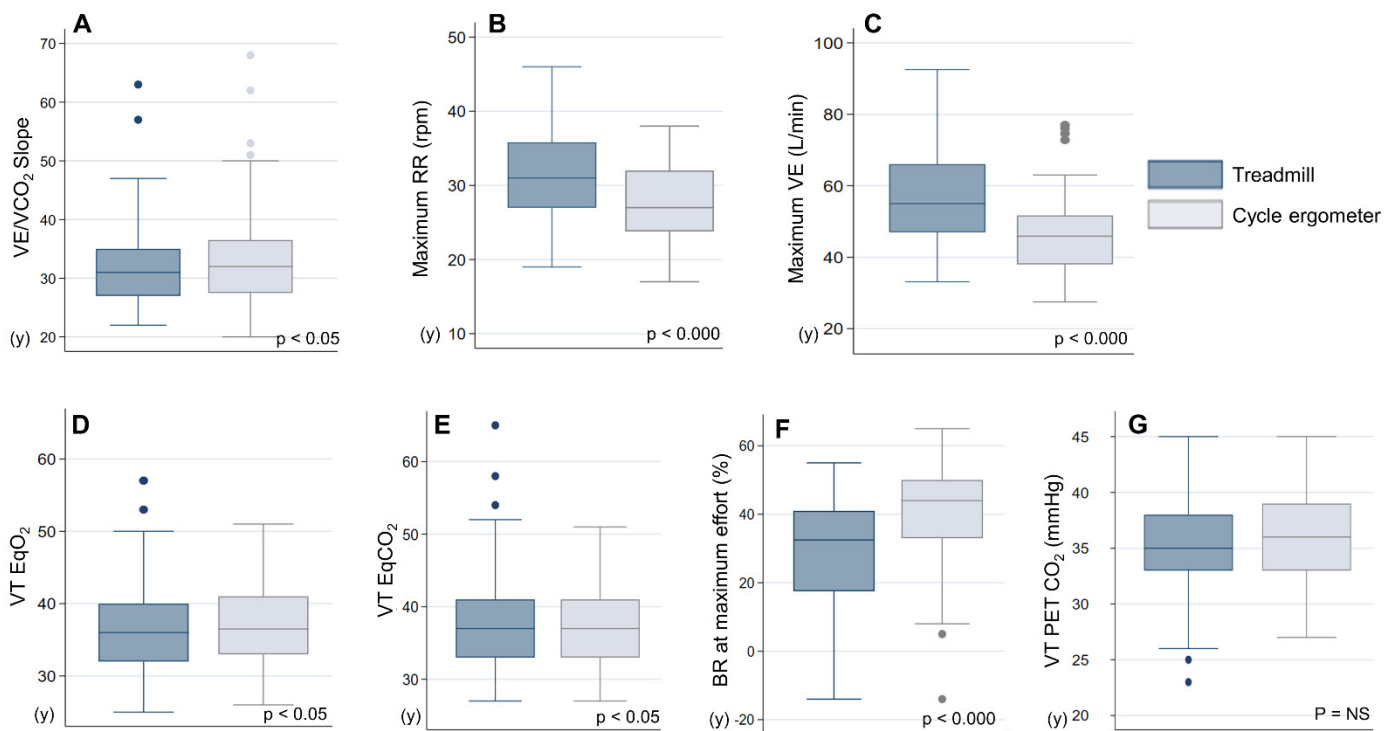Figure 3 shows a comparison of the results of respiratory variables by ergometer.

Figure 3. Boxplot of respiratory variables on the treadmill and cycle ergometer. (**A**) VE/VCO$_2$ Slope, (**B**) maximum RR (rpm), (**C**) maximum VE (L/min), (**D**) VT Eq O$_2$, (**E**) VT Eq CO$_2$, (**F**) BR at maximum effort (%), (**G**) VT PET CO$_2$ (mmHg). RR: respiratory rate; VE: ventilation; VT: ventilatory threshold; EqO$_2$: oxygen equivalent; EqCO$_2$: carbon dioxide equivalent; BR: breathing reserve; P$_{ET}$CO$_2$: partial pressure end-tidal carbon dioxide; NS: not significant.

3.6. Prognostic Classification

The Weber functional [29] and ventilatory [30] classifications were used for prognostic purposes. The Weber functional class varied as a function of peak VO$_2$/kg. The ergometer showed a change in functional class in 36 (55%) participants, with a descent on the scale during the cycle ergometer exercise (Figure 4A).
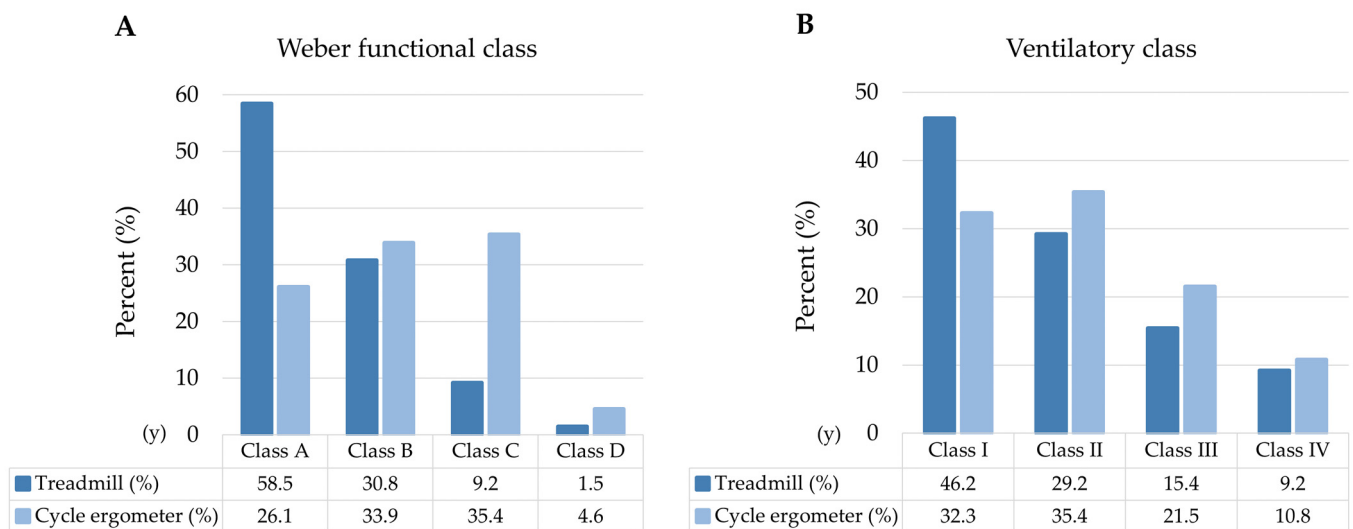

A Weber functional class	Class A	Class B	Class C	Class D
Treadmill (%)	58.5	30.8	9.2	1.5
Cycle ergometer (%)	26.1	33.9	35.4	4.6

B Ventilatory class	Class I	Class II	Class III	Class IV
Treadmill (%)	46.2	29.2	15.4	9.2
Cycle ergometer (%)	32.3	35.4	21.5	10.8

Figure 4. (**A**) Analysis of the Weber functional class as a function of peak VO$_2$/kg and ergometer. (**B**) Ventilatory class according to VE/VCO$_2$ slope and ergometer.

The ventilatory class as a function of VE/VCO$_2$ slope and ergometer changed in 31 (48%) patients, with 10 (15%) patients displaying a worse ventilatory efficiency on the treadmill and 21 (32%) on the cycle ergometer (Figure 4B).

3.7. Symptomatology and Preferences

The symptomatology of the patients according to the Borg questionnaire [27] throughout the test showed higher dyspnea values on the treadmill than on the cycle ergometer (5.4 ± 2.4 vs. 3.7 ± 2.3; *p* < 0.000) and higher lower-limb fatigue values on the cycle ergometer than on the treadmill (3.8 ± 3.1 vs. 4.8 ± 2.4; *p* < 0.05).

Regarding ergometer preference, 32 (50%) patients opted for the cycle ergometer, 26 (41%) opted for the treadmill, and six (9%) were indifferent to the type of ergometer (*p* = NS). The reasons for preferring the cycle ergometer were the greater sense of security and less dyspnea at the end of the test. The reason for preferring the treadmill was the greater familiarity with the type of exercise.

4. Discussion

The exercise modality in the CPET may affect the final VO$_2$, changing the functional class and, accordingly, the therapeutic approach [13,34]. In our study, the peak VO$_2$ and peak VO$_2$/kg of patients with HFrEF were significantly higher when performing the CPET on the treadmill than on the cycle ergometer, with a 20% difference in both parameters, despite using protocols with a similar workload, as shown by no significant differences in RQ or test duration between the two ergometers.

The impact of this difference on VO$_2$ was determined by prognostic scales [13,34], such as the Weber functional classification [29], as these functional classes changed in more than half of the patients, depending on the ergometer; and by current treatment guidelines for HFrEF because the most extended cutoff peak VO$_2$/kg for considering the use of advanced therapies, such as LVAD or heart transplantation [4,14,15], is 12 mL/kg/min, without indicating the exercise modality of the CPET. In our study, peak VO$_2$/kg was lower than 12 mL/kg/min in 1 (1.5%) patient on the treadmill and in 11 (17%) patients on the cycle ergometer. The same patient may show different values depending on the ergometer. Therapeutic recommendations are based on these values, irrespective of the ergometer used in the CPET.

The VE/VCO$_2$ slope was lower, indicating a higher ventilatory efficiency when performing the test on the treadmill. In addition, the ventilatory class [30] changed in half of the patients as a function of the ergometer used in the CPET.

Regarding the ventilatory response, VE, RR, and BR reflected the higher ventilatory demand of the treadmill, although with a better ventilatory efficiency when analyzing PetCO$_2$ and EqO$_2$/EqCO$_2$. Of these parameters, only PetCO$_2$ had been studied in HFrEF by Mazaheri et al. [24], although in a small sample of exclusively male patients (*n* = 30) with significantly lower effort on the treadmill. These results highlight the importance of the exercise modality in ventilatory demand because the ventilatory response varies with the type of ergometer.

EOV may be a prognostic factor of HFrEF [13], in addition to VO$_2$ and VE/VCO$_2$ slope. However, no studies have assessed whether its presence varies as a function of exercise modality in HFrEF or not. In our study, the prevalence of EOV did not differ significantly, despite a non-significant tendency towards a higher prevalence with the cycle ergometer, which must be verified in future research.

The hemodynamic response in different exercise modalities was described by Kim et al. [20], in a study involving 18 patients with heart failure showing a higher cardiac output and a greater A–V difference in oxygen in treadmill tests as explanatory variables of the differences in VO$_2$. In our study, the higher O$_2$ pulse, as an indirect measure of the systolic volume and higher HR on the treadmill, corroborated the findings of Kim et al. [20] Using a higher number of muscle groups increases the metabolic requirement during exercise, and, consequently, the cardiac output and peak VO$_2$. This phenomenon, together

with the increase in catecholamines during the treadmill exercise and changes in blood flow distribution in HFrEF [20], may explain the higher HR on the treadmill and higher diastolic BP on the cycle ergometer. Regarding HRR-1, previous studies [22–24] reported disparate results. In our study, HRR-1 was better on the treadmill.

Finally, the patients' preference for the ergometer did not differ significantly, but they felt more secure on the cycle ergometer and more familiar with the type of exercise on the treadmill.

A few studies compared the two ergometers in the 1990s [18–20], with a small sample size of select patients, as in Witte et al. [21] ($n = 11$), Maeder et al. [22] ($n = 21$), Beckers et al. [23] ($n = 55$) and Mazaheri et al. [24] ($n = 30$). VO_2 differences ranged from 10% to 23% [18–24] and with considerable variability in VE/VCO_2 slope [21–24]. These differences may be related to the characteristics of the selected patients, small sample size, and differences between protocols, in addition to the respiratory behavior and its repercussion on related parameters, such as BR, $PetCO_2$, EqO_2, $EqCO_2$, and EOV. The patient's preference for the exercise modality was also overlooked in those studies.

The strengths of the present study are its broader population sample than those published earlier and analysis of a higher number of parameters than those published in other studies, including ventilatory parameters, such as BR, EqO_2, $EqCO_2$, and the presence of EOV, which had not been previously compared in HFrEF. Similarly, another strength of this study was the level of effort achieved with both exercise modalities, which was similar. This study was limited by its single-center setting. Future multicenter studies should be performed to corroborate the results. The lack of randomization could be considered a limitation, although the symptoms, weight, or medication did not change when performing the CPET according to the usual practice of our center: first on a treadmill and after 72 h on a cycle ergometer. Finally, our sample represented as many patients treated in routine practice as possible and included patients with chronic obstructive pulmonary disease, which could serve as a reference for new studies performing subgroup analyses.

5. Conclusions

Treadmill exercise produces a higher peak VO_2, with a higher ventilatory and cardiovascular response. In diseases whose prognostic classification partly depends on CPET parameters, such as HFrEF, the results of this test should be interpreted considering not only sex, age, disease, and comorbidity but also the ergometer used in the CPET.

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