

# Cardiopulmonary Exercise and Respiratory Function Testing and Their Association with Mortality and Heart Transplantation in Patients with Heart Failure

Alam Merchant, Jason Li, Michael Fong, Ahmet Baydur\*

Divisions of Pulmonary and Critical Care medicine and Cardiology, Keck School of Medicine, and Keck Medical Center, University of Southern California (USC), Los Angeles, CA, USA

Email: \*baydur@usc.edu

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## Abstract

**Background:** Among cardiopulmonary exercise testing (CPET) variables, maximum oxygen uptake ( $\text{VO}_2\text{max}$ ) and ventilatory efficiency ( $\text{VE}/\text{VCO}_2$  slope) are frequently used predictive indices for mortality and heart transplantation in patients with advanced heart failure. **Objective:** To identify less commonly used variables associated with mortality and eventual transplantation for heart failure patients and assess their reliability. **Methods:** Patients identified with stable advanced heart failure underwent symptom-limited CPET using the Godfrey protocol. We compared variables between eventually transplanted and non-transplanted, and, separately, between living and deceased patients. Derived variables included  $\text{Ve}/\text{VCO}_2$ ,  $\text{Ve}/\text{VCO}_2/\text{O}_2$ , chronotropic index (CI), and oxygen uptake efficiency slope (OUES). **Results:** One hundred sixty-six individuals ( $52 \pm 15.6$  y) were identified with heart failure. Left ventricular ejection fraction (LVEF) was  $38 \pm 17\%$ . Eighteen (11%) patients subsequently underwent transplantation. Two (12%) transplanted and 26 (18%) non-transplanted patients expired during the study. Expired patients exhibited significantly lower  $\text{VO}_2\text{peak}$ ,  $\text{VO}_2$  at AT,  $\text{VCO}_2\text{peak}$ , and  $\text{O}_2/\text{pulse}$ , and higher peak  $\text{Ve}/\text{VCO}_2$ ,  $\text{Ve}/\text{VCO}_2/\text{O}_2$ ,  $\text{Ve}/\text{VCO}_2$  slope, and  $\text{Ve}/\text{VCO}_2/\text{VO}_2$  than living patients. Oxygen uptake efficiency slope (OUES) was lower in the deceased group ( $p < 0.001$ ). Peak  $\text{PetCO}_2$  was 7.7% less in expired patients ( $p = 0.01$ ).  $\text{VO}_2\text{peak}$  was 28% lower in patients who subsequently underwent transplantation. These individuals also exhibited significantly lower OUES and peak  $\text{PetCO}_2$ , and 94% higher CI than the non-transplanted group. **Conclusions:** Our findings confirm the potential utility of less commonly used indices of CPET, such as  $\text{Ve}/\text{VCO}_2/\text{O}_2$ , OUES, and CI, in strengthening the identification of suitable candidates for heart transplantation

in the context of heart failure management.

## Keywords

Cardiopulmonary Exercise Testing, Heart Failure, Heart Transplantation, Oxygen Pulse, Oxygen Uptake Efficiency Slope, Ventilatory Equivalents

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## 1. Introduction

Cardiopulmonary exercise testing (CPET) has emerged as a valuable tool for predicting prognosis in heart failure (HF) patients and offers insights that guide decisions related to heart transplantation. Among the well-established CPET variables, peak oxygen uptake ( $\text{VO}_2$ ), ventilatory efficiency (expressed as the slope of  $\text{VE}/\text{VCO}_2$ ), and peak work rate (W) have demonstrated significant predictive value [1]. Current guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) acknowledge the importance of these variables in risk assessment for heart failure patients [2]. Existing literature lacks comprehensive studies that retrospectively analyze CPET variables in patients who have definitively undergone heart transplantation.

Despite the recognized significance of  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope, and peak work rate, our investigation explored whether additional CPET variables could offer further insight into prognosis and transplantation probability. We sought to address this gap by analyzing CPET variables in a broad heart failure population, providing a more comprehensive perspective on mortality risk. We aimed to identify and compare additional variables associated with mortality and transplantation for heart failure patients.

## 2. Methods

### 2.1. Patients

This was a single-center retrospective study of patients with stable chronic heart failure who routinely underwent annual CPET to assess functional capacity and determine candidacy for heart transplantation. The study period was from December 2020 through January 2023. Patients were identified from a larger group of individuals initially referred for evaluation of exertional dyspnea and fatigue. The investigation was approved as an exempt study by the institutional review board of the University of Southern California Health Sciences Center (HS-21-00017). As policy, in our laboratory all patients are asked to study and sign a consent form prior to any CPET, including those conducted for routine clinical purposes. Heart failure was identified according to the consensus statement published by Bozkurt *et al.* [3]. Patients with pneumonia, acute heart and/or respiratory failure, cancer, COVID-19 infection, and chronic respiratory disorders such as obstructive airway, interstitial lung and neuromuscular diseases were excluded from analysis.

During the analysis, we did not separate patients with heart failure with reduced ejection fraction from those with preserved ejection fraction because there were fewer patients in the latter group. For the purpose of this study, we grouped all heart failure patients together and categorized them by mortality status and whether they received heart transplants or not (**Figure 1**). All testing was completed before any heart transplants took place.

## 2.2. Lung Function Testing

Spirometry was performed in the seated position according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [4]. Reference values for FVC and FEV<sub>1</sub> were from Crapo *et al.* [5].

## 2.3. Cardiopulmonary Exercise Testing

These studies incorporated the following details: 1) clinical and anthropometric characteristics of patients; 2) adherence to international guidelines for methods of CPET [6]; and 3) the safety of CPET, defined as reported adverse events. The CPETs were performed before any heart transplants took place.

The exercise testing equipment consisted of a stationary cycle ergometer (Med Graphics CPX Ultima system, Medical Graphics Corporation, St. Paul, MN) that was calibrated before and after each test. The mechanical dead space volume, depending on the mouthpiece and connections used, ranged from 45 to 65 mL for this system. Calibration of gas concentrations using primary standard gases and flow was performed using a 3 L syringe prior to each test. Patients were asked not to exercise on the day of the test and to refrain from consuming caffeinated beverages four hours before the test. Following the explanation of each procedure, informed consent was obtained under witness. Prior to beginning the test, subjects were familiarized with the stationary cycle ergometer and mouthpiece and cycled on the ergometer for approximately 10 minutes. They were seated and breathed through a mouthpiece with a nose clip in place. After a minimum of five minutes of resting measurements, they were exercised on the ergometer with increasing workloads at increments of 5 - 15 Watts, based on patients' tolerability, using the Godfrey protocol [7]. Data collection continued for several minutes post-exercise for gas collection and electrocardiogram monitoring purposes.

The following variables were recorded every 15 seconds: minute ventilation ( $V'_E$ ), inspired oxygen concentration ( $FiO_2$ ), end-tidal oxygen tension ( $PetO_2$ ), inspired oxygen uptake ( $VO_2$ ), and end-tidal carbon dioxide output ( $PetCO_2$ ). Peak  $VO_2$  was expressed as the highest 30-second average value recorded during the last stage of the exercise test [8]. Anaerobic threshold (AT) was determined by the V-slope method [9]. Heart rate and rhythm were monitored continuously throughout the study with the 12-lead ECG. In addition, the following variables were derived from the data: tidal volume ( $V_t$ ), respiratory rate, minute ventilation  $V_e$ /maximum voluntary ventilation ( $V_e/MVV$ ), respiratory exchange ratio (RER),  $O_2$ /pulse ( $VO_2/HR$ ), and ventilatory equivalents for carbon dioxide and oxygen ( $V_e/VCO_2$

and  $V_e/V_{O_2}$ , respectively). Peak  $V_{O_2}$  was determined as the highest 20- to 30-second average achieved during exercise and expressed as ml/kg/min. The  $V_e/V_{CO_2}$  slope was computed using least squares linear regression fitting of breath-by-breath values recorded throughout the whole exercise [8]. Normal values for these variables were derived from Sun *et al.* [9].  $V_e/V_{CO_2}$  was also corrected for  $V_{O_2}$  ( $V_e/V_{CO_2}/V_{O_2}$ ) [10]. The chronotropic index (CI) was calculated by dividing the difference between maximal and resting heart rate (in beats/min) by the difference between maximal and resting oxygen uptake (in L/min). Predicted values for CI were computed as follows:

$$CI = 106.9 + (0.16 \times \text{age}) + (14.3 \times \text{sex}) - (0.31 \times \text{height}) - (0.24 \times \text{weight}) \text{ [11].}$$

All patients with  $V_{O_2\text{max}}$  (expressed in mL/min) less than 84% predicted were considered as having functional limitation of cardiovascular, pulmonary vascular, or ventilatory limitation [12] ATS Statement on CPX]. Patients with a  $V_e/MVV$  of greater than 75% predicted were considered to have a reduced ventilatory reserve. An  $O_2/\text{pulse}$  of less than 80% predicted represented a reduced stroke volume related to circulatory limitation [13]. No patients experienced any adverse events during testing.

Patients who showed either ventilatory or circulatory limitation were classified based on predominant CPET features; if, for example, they exhibited resting tachycardia (heart rate > 90 beats/min), a normal  $V_e/MVV$  (<75%), a decreased  $O_2/\text{pulse}$  (<80% predicted), and ventilatory equivalents that were increased (>30) and/or failed to decrease with exercise, they were classified as having a circulatory deficit. The slope and intercept for  $V_e/V_{CO_2}$  were computed for all patients according to the relationship  $y = a + bx$ , where  $y$  was the difference between  $V_e$  at rest and peak exercise,  $x$  was the difference between  $V_{CO_2}$  at rest and peak exercise,  $a$  was the intercept and  $b$  was the slope [9]. The oxygen uptake efficiency slope (OUES) was derived from the relationship of  $V_{O_2}$  to the logarithm of  $V_e$  during exercise:  $V_{O_2} = a \log_{10} V_e + b$ , where “ $a$ ” is the OUES and “ $b$ ” is the intercept [14].

## 2.4. Statistical Analysis

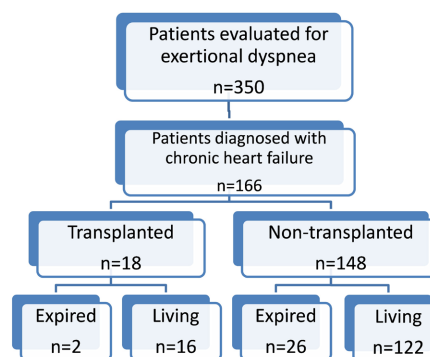
Descriptive data are shown as mean and standard deviation. Normality of the data was confirmed using the Shapiro-Wilk test. Comparisons among cohorts were conducted by multivariate analysis of variance (ANOVA), using the Bonferroni correction to account for the large number of compared variables. Associations between physiologic variables were determined by Pearson’s correlation, expressed as  $r^2$ . A p-value of <0.05 was considered statistically significant for inter-group comparisons and for inter-variable associations.

## 3. Results

### 3.1. Patient Characteristics

Of 350 patients who underwent evaluation for exertional dyspnea and were screened for heart failure, 166 were diagnosed with heart failure related to struc-

tural heart disease (**Figure 1**). The remaining patients ( $n = 184$ ) had primary diagnoses of various forms of respiratory disorders or idiopathic pulmonary hypertension. Their overall mean age and standard deviation ( $\pm$ SD) was  $52 \pm 15.6$  years with a distribution of 128 males and 38 females (**Table 1**). Their mean body mass index (BMI) was  $25.9 \pm 2.5$  kg/m<sup>2</sup>. Eighty (48%) patients were former smokers (more than 2 years previously); none were current smokers. Beta-blockers were used among 75% of study participants. The severity of cardiac dysfunction was classified as New York Heart Association Severity II and III. In 97 patients for whom echocardiographic data were available, the mean ( $\pm$ SD) left ventricular ejection fraction (LVEF) was  $38 \pm 17\%$ ; eighty percent of patients exhibited a reduced ejection fraction ( $<40\%$ ). We found no significant differences in the LVEF among survivors and expired patients, nor among those who underwent heart transplant versus those who did not (**Table 2** and **Table 3**). Seventeen percent of patients were diagnosed with ischemic etiology of heart failure, while 75% were diagnosed with non-ischemic dilated cardiomyopathy. Twenty-eight patients (17%) expired by the end of data collection. Eighteen patients (11%) underwent heart transplantation. Two (11%) of the transplanted and 26 (18%) of the non-transplanted patients expired during the study.



**Figure 1.** Flow chart describing the study cohort.

**Table 1.** Anthropometric and physiological data of 166 patients.

Age (y)	52 $\pm$ 15.6
Sex (M/F)	128/38
BMI (kg/m <sup>2</sup> )	29.5 $\pm$ 5.9
Beta-blocker use (%)	75
LVEF (%)	38.4 $\pm$ 17
<b>Etiologies:</b>	
Ischemic (%)	17
Non-ischemic dilated cardiomyopathy (%)	75
Hypertrophic cardiomyopathy (%)	4
Congenital (%)	4
Reduced ejection fraction (%)	80

## Continued

Preserved ejection fraction (%)	20
FVC (L)	3.5 ± 1.1
FVC (% predicted)	82 ± 18
FEV1 (L)	2.7 ± 0.9
FEV1 (% predicted)	81 ± 19
FEV1/FVC (%)	78 ± 11
Vemax/MVV (%)	46 ± 14
RER	1.19 ± 0.09
VO <sub>2</sub> max (mL/kg/min)	15.5 ± 15.9
VO <sub>2</sub> max (% predicted)	54.7 ± 16.8
VO <sub>2</sub> at anaerobic threshold (mL/kg/min)	10.7 ± 3.6
VCO <sub>2</sub> max (mL/kg/min)	19.9 ± 8.7
Ve/VCO <sub>2</sub> slope	37.1 ± 14.2
Ve/VCO <sub>2</sub> intercept (L/min)	1.7 ± 3
Ve/VCO <sub>2</sub> /VO <sub>2</sub>	2.4 ± 1
ΔVO <sub>2</sub> /ΔWork (mL/kg/min/Watt)	11.3 ± 0.9
Chronotropic index (/L)	30.3 ± 3.6
OUES (mL/min/L/min)	1320 ± 535
PetCO <sub>2</sub> , rest (mm Hg)	32.5 ± 5.3
PetCO <sub>2</sub> , peak (mm Hg)	31.7 ± 5.5

Values are mean ± SD. Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; Ve, minute ventilation; MVV, maximum voluntary ventilation; RER, respiratory exchange ratio; VO<sub>2</sub>, oxygen output; VCO<sub>2</sub>, carbon dioxide output; AT, anaerobic threshold; OUES, oxygen uptake efficiency slope; PetCO<sub>2</sub>, end-tidal carbon dioxide tension; PetO<sub>2</sub>, end-tidal oxygen tension.

**Table 2.** Physiologic variables in expired and living patients.

	Expired	Living	p
n	28	138	-----
LVEF (%)	33.5 ± 16	39.5 ± 17	0.1
FVC (L)	2.9 ± 0.9	3.6 ± 1.2	<b>&lt;0.001</b>
FVC (% predicted)	71.9 ± 18.8	85.3 ± 16.9	<b>&lt;0.001</b>
FEV1 (L)	2.3 ± 0.7	2.8 ± 0.9	<b>0.002</b>
FEV1 (% predicted)	73 ± 19	83 ± 18	<b>0.001</b>
FEV1/FVC (%)	77 ± 15	78 ± 9	0.7
Vemax/MVV	0.46 ± 0.13	0.46 ± 0.14	0.83
RER	3.2 ± 0.2	3.2 ± 0.1	0.64
VO <sub>2</sub> max (mL/kg/min)	12 ± 3.8	16.5 ± 6	<b>&lt;0.001</b>
VO <sub>2</sub> max (% predicted)	45.5 ± 14.6	57.5 ± 16.5	<b>&lt;0.001</b>
VO <sub>2</sub> at AT (mL/kg/min)	8.6 ± 2.3	11.2 ± 3.7	<b>&lt;0.001</b>
VCO <sub>2</sub> max (mL/kg/min)	15.2 ± 6.8	21.3 ± 8.7	<b>&lt;0.001</b>

## Continued

Ve/VCO <sub>2</sub> slope	42.4 ± 10.9	35.5 ± 14.8	<b>0.01</b>
Ve/VCO <sub>2</sub> intercept (L/min)	0.9 ± 2.5	1.8 ± 3.4	0.16
Ve/VCO <sub>2</sub> /VO <sub>2</sub>	3.5 ± 1.2	2.2 ± 0.7	<b>0.005</b>
Ve/VO <sub>2</sub> max	51.6 ± 14.6	44.3 ± 10.8	<b>0.001</b>
Ve/VO <sub>2</sub> at AT	38.7 ± 7.9	34.5 ± 13.9	0.078
ΔVO <sub>2</sub> /ΔWork (mL/kg/min/Watt)	11.9 ± 11.6	11.1 ± 8.3	0.62
Chronotropic index (/L)	34.4 ± 47.5	29.3 ± 32	0.43
O <sub>2</sub> /pulse, max	8.6 ± 3.2	10.4 ± 3.3	0.02
OUES (mL/min/L/min)	1,049 ± 511	1,394 ± 530	<b>&lt;0.001</b>
PetCO <sub>2</sub> , rest (mm Hg)	32.3 ± 4.9	32.6 ± 5.4	0.71
PetCO <sub>2</sub> , peak (mm Hg)	29.8 ± 6.1	32.3 ± 5.2	<b>0.01</b>

Values are mean ± SD. Abbreviations are the same as in **Table 1**.

**Table 3.** Physiologic variables in transplanted (obtained pre-transplant) and non-transplanted patients.

	Pre-transplant	Non-transplanted	p
n	18	148	-----
LVEF (%)	31.6 ± 16.8	39.3 ± 17	0.09
FVC (L)	3.1 ± 0.8	3.5 ± 1.2	0.12
FVC (% predicted)	74.7 ± 13.9	83.1 ± 18.5	0.07
FEV1 (L)	2.3 ± 0.6	2.8 ± 0.9	<b>0.033</b>
FEV1 (% predicted)	70 ± 15	82.3 ± 18.8	<b>0.011</b>
FEV1/FVC (%)	74.5 ± 33.3	77.9 ± 30.4	0.21
V <sub>max</sub> /MVV	0.46 ± 0.13	0.46 ± 0.14	0.83
RER	1.2 ± 0.2	1.2 ± 0.1	0.3
VO <sub>2</sub> max (mL/kg/min)	11.4 ± 2.4	15.9 ± 5.9	<b>0.002</b>
VO <sub>2</sub> max (% predicted)	40.8 ± 9.6	56.4 ± 16.8	<b>&lt;0.001</b>
VO <sub>2</sub> at AT (mL/kg/min)	8.2 ± 2.3	10.9 ± 3.6	<b>0.001</b>
VCO <sub>2</sub> max (mL/kg/min)	13.4 ± 3.3	20.6 ± 8.9	<b>0.001</b>
Ve/VCO <sub>2</sub> slope	42.9 ± 11.1	36.4 ± 14.4	<b>0.02</b>
Ve/VCO <sub>2</sub> intercept (L/min)	0.5 ± 2.4	1.7 ± 3.2	0.14
Ve/VCO <sub>2</sub> /VO <sub>2</sub>	3.8 ± 1	2.3 ± 0.6	<b>0.001</b>
Ve/VO <sub>2</sub> max	50.2 ± 30.8	45.5 ± 12.2	0.13
Ve/VO <sub>2</sub> at AT	40.1 ± 14.3	34.9 ± 12.7	0.12
ΔVO <sub>2</sub> /ΔWork (mL/kg/min/Watt)	9.7 ± 3.6	11.5 ± 9.3	0.45
Chronotropic index (/L)	53.6 ± 63.7	27.6 ± 30.9	<b>0.005</b>
O <sub>2</sub> /pulse, max	8.6 ± 2.2	10.1 ± 3.2	0.06
OUES (mL/min/L/min)	912 ± 295	1364 ± 537	<b>&lt;0.001</b>
PetCO <sub>2</sub> , resting (mm Hg)	33.4 ± 5.1	32.6 ± 5.3	0.35
PetCO <sub>2</sub> , peak (mm Hg)	28.3 ± 5.6	32.1 ± 5.3	<b>0.007</b>

Values are mean ± SD. Abbreviations are the same as in **Table 1**.

### 3.2. Expired and Living Patients

**Table 2** compares expired and living patients based on cardiopulmonary exercise testing (CPET) results. Expired patients had 19% lower forced vital capacity (FVC) and 18% lower forced expiratory volume in one second (FEV1) compared to living patients ( $p < 0.001$  and  $p = 0.002$ , respectively). However, there were no significant differences among % predicted FVC, FEV1/FVC, and  $V_e/VCO_2$  intercept values.

Concerning exercise capacity, expired patients exhibited 27% lower  $VO_2$  max ( $p < 0.01$ ), 20.7% lower  $VO_2$ max % predicted ( $p < 0.001$ ), and 23% lower values in  $VO_2$  at AT ( $p < 0.001$ ) compared to living patients. Deceased patients also exhibited a 29% lower  $VCO_2$  max ( $p < 0.001$ ), 14% higher peak  $V_e/VCO_2$  ( $p = 0.003$ ), 59% higher  $V_e/VCO_2/O_2$  ( $p = 0.005$ ), and 19% higher  $V_e/VCO_2$  slope ( $p = 0.009$ ). The deceased group had a 17% lower  $O_2$ /pulse than the surviving group ( $p = 0.02$ ). The oxygen uptake efficiency slope (OUES) was 25% lower in the deceased group ( $p < 0.001$ ). While  $PetCO_2$  at rest showed no significant difference among subgroups ( $p = 0.71$ ), expired patients exhibited a  $PetCO_2$  at peak exercise that was 7.7% less than in living patients ( $p = 0.01$ ). No statistically significant differences were found between expired and living patients for  $V_e/VCO_2$  at AT,  $V_e/VO_2$  at AT, and  $\Delta VO_2/\Delta Work$ .

### 3.3. Transplanted versus Non-Transplanted Patients

**Table 3** compares physiologic variables in patients who were eventually transplanted with those who were not. Patients who underwent transplantation exhibited 18% lower FEV1 (L) values compared to those who did not receive a transplant ( $p = 0.033$ ). No statistically significant differences were found between the two groups for FVC, FVC % predicted, FEV1/FVC,  $V_e/VCO_2$  intercept, and  $V_e/VO_2$  at AT.

With respect to cardiopulmonary exercise capacity, the to-be transplanted group exhibited a  $VO_2$  max that was 28% less than that of the non-transplant group ( $p = 0.002$ ). Similarly, the  $VO_2$  at anaerobic threshold ( $VO_2$  at AT) was 25% lower in the transplant group than in the non-transplanted group ( $p = 0.003$ ). Additionally, the transplant group demonstrated a 35% lower value in peak carbon dioxide production ( $VCO_2$  max) compared to the non-transplanted group ( $p = 0.001$ ).  $V_e/VCO_2/VO_2$  in the expired group was 65% higher than in living patients ( $p = 0.001$ ).

Transplanted patients exhibited an oxygen uptake efficiency slope (OUES) that was 33% lower ( $p < 0.001$ ) than in the non-transplanted group. While  $PetCO_2$  at rest exhibited no significant differences ( $p = 0.35$ ), the transplant group demonstrated a relative decrease in  $PetCO_2$  at peak exercise, 11% lower ( $p = 0.007$ ) than in the non-transplanted group. Transplanted patients exhibited a chronotropic index that was 94% higher than those who did not undergo transplant ( $p = 0.005$ ), indicating a notable decrease in heart rate response during exercise. This difference was not observed between deceased and living patients. The  $O_2$ /pulse in the

to-be transplanted group was 15% less than in the non-transplanted group, a non-significant difference ( $p = 0.06$ ).

## 4. Discussion

### 4.1. General Findings

Our findings highlight differences in exercise capacity, gas exchange, and circulatory response associated with heart transplantation compared to patients who did not receive a transplant. Key findings in deceased and transplanted patients (recorded prior to transplant) included reduced lung function,  $\text{VO}_2\text{max}$ ,  $\text{O}_2/\text{pulse}$ , OUES, and increased  $\text{Ve}/\text{VCO}_2\text{max}$  and  $\text{Ve}/\text{VO}_2$  as compared to living and non-transplanted patients, respectively.

The chronotropic index among deceased patients and in those who later underwent heart transplant was increased as compared to survivors and patients who did not undergo transplant. The index considers age, resting heart rate, and functional capacity and is independent of the stage of exercise or the protocol used [15] [16]. After adjusting for a number of demographic and physiological factors, Robbins *et al.* [17] found that a high  $\text{Ve}/\text{VCO}_2$  and a low chronotropic index remained independent predictors of death due to any cause. Others have described the  $\text{Ve}/\text{VCO}_2$  slope as a key determinant of mortality [8] [18]-[22]. Lin *et al.* [23] found that patients with heart failure and with an OUES  $< 1.3$  and  $\text{Ve}/\text{VCO}_2 > 38$  exhibited a higher risk for cardiac events, particularly those with COPD. We also found lower mean OUES values in patients who underwent transplant, indicating a higher degree of dead space breathing contributing to the decrease in cardiopulmonary reserve. In this connection, the peak  $\text{PetCO}_2$  in patients who underwent transplant was reduced, a reflection of the inability of cardiac output to keep up with ventilation, resulting in the overall ventilation/perfusion ratio exceeding 1.

Chronotropic incompetence may be considered a major limiting factor in the exercise capacity of patients with heart failure. It is an important cause of exercise intolerance and an independent predictor of adverse cardiovascular events and mortality [24]. Although the underlying mechanisms for chronotropic incompetence in HF are not fully understood, the imbalance of the autonomic nervous system that is shifted toward the sympathetic pathway decreases  $\beta$ -adrenergic responsiveness, resulting in a reduced heart rate response to exercise [25]. Witte *et al.* [26] found a linear correlation between change in HR and peak  $\text{VO}_2$ . CI may be considered a limiting factor in the exercise capacity of patients with HF, but it has not been a consistent finding. In a study of 195 patients, of whom 90 had severe left ventricular systolic dysfunction, Jamil *et al.* [27] showed that increasing heart rate in unselected patients with heart failure did not improve exercise tolerance or improve symptoms, and conversely, that lowering HR did not worsen exercise tolerance or exercise-related symptoms. There has been a lack of a standardized approach to diagnosing the disease, further complicated by changes in HR dynamics in the HF population, which render reference values derived from a normal population invalid.

## 4.2. Expired versus Living Patients

Deceased patients exhibited lower  $O_2$ /pulse, OUES,  $VO_2$ max,  $VO_2$  at AT,  $VCO_2$ max, and  $PETCO_2$  at peak exercise, and higher  $VE/VCO_2$ max and  $VE/VCO_2$  slope (as well corrected for  $VO_2$ ) compared to living patients. The mean  $Ve/VCO_2$  in our deceased patients is virtually the same as that reported by Sarullo *et al.* (41.8) [18]. In general, our findings align with those of Brawner's study [1], suggesting that even when cardiac transplantation is removed as an endpoint, these values still exhibit a high association with heart failure prognosis.

The difference in the  $O_2$ /pulse between deceased and surviving patients indicate a similar predictive feature of outcome [1] [10].

We found that the OUES in surviving patients was 1.05 L/min/L/min and, on average, 33% higher than in individuals who expired. Guazzi *et al.* [10] reported an OUES cutoff of 1.05 for high-risk cardiac outcomes, similar to the findings of Lin *et al.* [23] who reported a threshold of 1.3. OUES is influenced by the onset of lactic acid production and therefore incorporates circulatory, ventilatory, and musculoskeletal function. The log transformation of  $Ve$  creates high linearity in relation to  $VO_2$  [14], thus making the OUES theoretically effort-independent, enabling its calculation also in the case of a submaximal CPET. Yet, OUES has not been considered a necessary variable to be described in a CPET report. In a study of over 2000 patients with heart failure with reduced ejection fraction, Gordon *et al.* [28] concluded that while OUES was associated with clinical outcomes independent of the  $VE/VCO_2$  slope, its prognostic utility was inferior to that of peak  $VO_2$ , even when measured at submaximal effort.

Deceased patients exhibited a mean  $Ve/VCO_2/VO_2$  of 3.5, 59% higher than in surviving individuals. Using multivariate analysis, Guazzi *et al.* [10] showed that the  $Ve/VCO_2/VO_2$  index retained a prognostic power greater than that of both  $VE/VCO_2$  slope and peak  $VO_2$ . A  $Ve/VCO_2/VO_2 \geq 2.4$  indicated a higher risk for cardiac mortality.

The mean CI among deceased patients was 17% higher than in survivors (34.4/L vs 29.3/L), although this was not a statistically significant difference due to variability. An increase in the CI has been associated with decreased exercise tolerance and worse outcomes in individuals with heart failure [11]. Spiro *et al.* [29] have suggested reference values for CI for healthy men (42 - 43/L) and women (63 - 71/L). Given that 77% of our subjects were men, a mean CI of 53.6/L is well above the normal range (for men). This finding indicates a steep relationship between change in heart rate vs change in  $VO_2$  from rest to peak exercise and is typical in patients with heart failure, ischemic heart disease and valvular heart disease, severe deconditioning and certain myopathies [11].

Deceased patients had lower values for FVC and FEV1. These findings can be attributed to several factors associated with heart failure, including pulmonary congestion, pleural effusion, and/or respiratory muscle weakness.

## 4.3. Transplanted versus Non-Transplanted Patients

Overall, transplanted patients showed significantly lower FEV1 values, peak

$VO_{2max}$ ,  $VO_2$  at AT, and  $VCO_2$  max compared to non-transplanted individuals. Our findings are similar to those of Mancini *et al.* [30] who reported that patients listed for heart transplant were more likely to have a  $VO_{2max} < 14$  ml/kg/min. Our study's  $VO_{2max}$  range of 11.4 to 15.9 ml/kg/min aligns with this observation. Similarly, Garcia Bras *et al.* [31] identified a  $Ve/VCO_2$  slope closer to 40 as indicative of a higher likelihood of transplantation. Our study aligns with this observation and deviates slightly from the traditional  $Ve/VCO_2$  slope of 35 as defined by the ACC/AHA guidelines [2]. There has been controversy over how the slope is computed; we computed the  $Ve/VCO_2$  slope from the very beginning to the end of the  $Ve$  vs  $VCO_2$  plot, which results in a higher value than when computing the slope from the beginning up to the respiratory compensation point (RT), as the slope increases from RT to  $VO_{2max}$  [22] [32]-[36]. The overall slope also has a greater association with mortality [8] [9] [22] [33] [36] [37].

Of the ventilatory equivalents, only  $Ve/VCO_2$  discriminated between transplanted and non-transplanted patients. The finding that  $Ve/VO_2$  did not may be related to less variability in  $Ve/VCO_2$  than  $Ve/VO_2$  during moderate intensity exercise because of the sensitivity of ventilatory control to  $PaCO_2$  and pH in the physiologic ranges [9] [32]. Transplanted patients may also have reduced sensitivity to blood chemical changes from renal and neural effects of immunosuppressive agents. In addition, the OUES in patients who eventually underwent heart transplantation was, on average, 35% lower than in those who did not undergo transplant ( $p < 0.001$ ), findings similar to those of Guazzi *et al.* [10] and Lin *et al.* [23], and predictive of worse clinical outcomes (had they not undergone transplant). In addition, patients who eventually underwent heart transplant exhibited a CI that was 94% greater ( $p < 0.005$ ) than those who did not undergo transplant, with similar implications regarding their potential outcomes.

## 5. Strengths and Limitations

Our study has strengths: We describe changes in chronotropic index, OUES, and  $Ve/VCO_2/VO_2$  amongst survivors and transplanted patients, supporting a handful of other investigations [10] [22]-[28]. Other findings were similar to prior studies regarding  $VO_{2max}$  and  $VE/VCO_2$  max and its slope [1], which adds to the validity of our data. In addition, we also describe differences in the chronotropic index amongst cohorts not previously reported.

Our study also has limitations. This was a single-center retrospective study with a relatively small cohort of patients with advanced heart failure. Its retrospective nature may introduce selection and information biases. However, the changes in commonly used variables of CPET in survivors and deceased patients were similar to those of others described. Second, we did not include as covariates beta-blocker dose, device therapy or other medications; many patients were receiving combinations of medications whose timing and dose changed over time. Third, there was also a preponderance of male subjects that limits generalizability of findings to both sexes. Finally, a larger population study may reveal additional significant differences among cohorts.

We pooled patients with both reduced and preserved EF when performing the comparisons amongst subgroups in part because of uneven numbers of the subgroups. In any case, we found no statistically significant differences in LVEF between patients with HFpEF and those with HFrEF across studied variables. In addition, recent studies have shown that individuals with HFpEF have similar outcomes as those with HFrEF [37]-[40]. Shah *et al.* [38] found in a 5-year outcomes study that risk-adjusted analyses exhibited a similar mortality and rehospitalization for both HFrEF and HFpEF. Their findings were similar to results from the JCARE-CARD study [39], which showed that patients with HFpEF had a mortality risk and re-hospitalization rate similar to those with HFrEF. In addition, Triposkiadis *et al.* [40], when adjusting for risk factors, found that among patients hospitalized with HF, there was no mortality difference among patients with reduced and preserved EF.

## 6. Conclusions

Our findings confirm the potential utility of specific cardiopulmonary exercise testing (CPET) variables in informing prognostic assessments and aiding in the identification of suitable candidates for heart transplantation in the context of heart failure management. In general, the differences in variables among deceased and living patients reflect similar differences between patients eventually undergoing heart transplant and those who did not. The addition to the analysis of the chronotropic index, OUES, and  $V_e/VCO_2/VO_2$  further highlights metabolic differences among cohorts.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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