Prognostic Prediction of Cardiopulmonary Exercise Test Parameters in Heart Failure Patients with Atrial Fibrillation

António Valentim Gonçalves, Tiago Pereira-da-Silva, Rui Soares, Joana Feliciano, Rita Ilhão Moreira, Pedro Rio, Ana Abreu, Rui Cruz Ferreira
Centro Hospitalar Universitário Lisboa Central, Hospital de Santa Marta, Lisbon – Portugal

Abstract

Background: Atrial fibrillation (AF) is associated with increased mortality in heart failure (HF) patients.

Objective: To evaluate whether the risk of AF patients can be precisely stratified by relation with cardiopulmonary exercise test (CPET) cut-offs for heart transplantation (HT) selection.

Methods: Prospective evaluation of 274 consecutive HF patients with left ventricular ejection fraction ≤ 40%. The primary endpoint was a composite of cardiac death or urgent HT in 1-year follow-up. The primary endpoint was analysed by several CPET parameters for the highest area under the curve and for positive (PPV) and negative predictive value (NPV) in AF and sinus rhythm (SR) patients to detect if the current cut-offs for HT selection can precisely stratify the AF group. Statistical differences with a p-value <0.05 were considered significant.

Results: There were 51 patients in the AF group and 223 in the SR group. The primary outcome was higher in the AF group (17.6% vs 8.1%, p = 0.038). The cut-off value of pVO$_2$ for HT selection showed a PPV of 100% and an NPV of 95.5% for the primary outcome in the AF group, with a PPV of 38.5% and an NPV of 94.3% in the SR group. The cut-off value of VE/VCO$_2$ slope showed lower values of PPV (33.3%) and similar NPV (92.3%) to pVO$_2$ results in the AF group.

Conclusion: Despite the fact that AF carries a worse prognosis for HF patients, the current cut-off of pVO$_2$ for HT selection can precisely stratify this high-risk group. (Arq Bras Cardiol. 2020; 114(2):209-218)

Keywords: Atrial Fibrillation/mortality; Peak Expiratory Flow Rate; Exercise Test; Oxygen Consumption; Heart Failure; Prognosis.

Introduction

Heart failure (HF) and atrial fibrillation (AF) often coexist, with AF occurring in some reports in more than 50% of HF patients, and HF in more than one-third of AF patients. Since the burden of each is growing, they have been called the two new epidemics of cardiovascular (CV) disease.

The presence of AF in HF patients is associated with adverse hemodynamic consequences, which may exacerbate HF, increasing morbidity and mortality. The cardiopulmonary exercise test (CPET) is a powerful predictor of mortality in HF patients and is used as the criterion standard for the need for heart transplantation (HT), with peak O$_2$ consumption (pVO$_2$) and the relation between ventilation and CO$_2$ production (VE/VCO$_2$ slope) as the most used risk assessment tools. However, less information is known about whether HF patients with AF can be precisely stratified with the current CPET cut-offs for HT selection. Since the combination of HF and AF provide a worse prognosis, a timely referral for HT or mechanical circulatory support could be extraordinarily important to reduce the negative prognostic effect of AF in HF patients.

The present study seeks to compare the prognostic importance in HF patients of CPET parameters in AF versus sinus rhythm (SR) patients.

Methods

The investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the study protocol. All patients provided written informed consent.

Patient population and study protocol

The study included a single centre analysis of 274 consecutive HF patients referred to our institution with left ventricular ejection fraction (LVEF) ≤ 40% and New York Heart Association (NYHA) class II or III, from 2009 to 2016. All the patients were referred for evaluation with HF team and possible indication for HT or mechanical circulatory support. Patients with elective HT during the follow-up period (patients who had indication for HT and a heart become available in the first year of follow-up) were excluded from the analysis.
Prospective follow-up included initial evaluation within a period of one month in each patient with:

- Clinical data including etiology of HF, implanted devices, medication, comorbidities, NYHA class and Heart Failure Survival Score (HFSS);\(^8\)
  - Laboratory data;
  - Electrocardiographic data;
  - Echocardiographic data;
  - CPET data.

Patients were excluded if one of the following:

- Age < 18 years;
- Planned percutaneous coronary revascularization or cardiac surgery;
- Elective HT in the follow-up period;
- Exercise-limiting comorbidities (cerebrovascular disease, musculoskeletal impairment, or severe peripheral vascular disease);
- Previous HT.

Follow-up and endpoint

All patients were followed-up for 12 months from the date of completion of the aforementioned complementary exams.

The primary endpoint was a composite of cardiac death or urgent HT (occurring during an unplanned hospitalization with dependency of inotropes for worsening HF). Data were obtained from the outpatient clinic visits and medical charts review and was complemented with a standardized telephone interview to all patients at 12 months of follow-up. Secondary endpoints included all-cause mortality, sudden cardiac death and death for worsening HF.

Definition of atrial fibrillation

Only persistent or permanent AF was considered for the analysis. The diagnosis was made by electrocardiographic recording in the initial evaluation.

Cardiopulmonary exercise testing

A maximal symptom-limited treadmill CPET was performed using the modified Bruce protocol (GE Marquette Series 2000 treadmill). The gas analysis was preceded by the calibration of the equipment. Minute ventilation, oxygen uptake and carbon dioxide production were acquired breath-by-breath, using a SensorMedics Vmax 229 gas analyser. The pVO\(_2\) was defined as the highest 30-second average achieved during exercise and was normalized for body mass.\(^9\) The anaerobic threshold was determined by combining the standard methods (V-slope preferentially and ventilatory equivalents). The VE/VCO\(_2\) slope was calculated by least-squares linear regression, using data acquired throughout the whole exercise. Several composite parameters of CPET were also calculated. Patients were encouraged to perform exercise until the respiratory exchange ratio (RER) was ≥ 1.10.

Statistical analysis

All analyses compare AF patients with SR patients. Data were analysed using the software Statistical Package for the Social Science for Windows, version 24.0 (SPSS Inc, Chicago IL).

Baseline characteristics were summarized as frequencies (percentages) for categorical variables, as means and standard deviations for continuous variables when normality was verified and as median and interquartile range when normality was not verified by the Kolmogorov-Smirnov test. The Student’s t-test for independent samples or the Mann-Whitney test when normality was not verified were used for the analysis of the variables.

Univariable and multivariable Cox proportional-hazards models were applied, with p values for time-to-event analyses being based on log-rank tests, and hazard ratios for treatment effects and 95% confidence intervals presented to study the combined endpoint considering the follow-up time of 12 months.

For selecting patients who would benefit from early selection for HT or mechanical circulatory support, the primary endpoint was analysed by several CPET parameters for the highest area under the curve (AUC) in the 12 months’ follow-up. Hanley & McNeil test was used to compare two correlated receiver operating characteristics curves.\(^11\)

The guideline recommended cut-off value of pVO\(_2\) (pVO\(_2\) ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without beta-blockers (BB)) and VE/VCO\(_2\) slope (VE/VCO\(_2\) slope > 35 with a RER < 1.05) for HT selection were analysed (and compared for positive and negative predictive value (PPV and NPV, respectively) in our population of AF and SR patients.

Statistical differences with a p-value < 0.05 were considered significant.

Results

Overview of AF and SR groups

A total of 274 patients were enrolled in the study, with 51 patients in the AF group and 223 in the SR group. The baseline characteristics of SR and AF groups are presented and compared in Table 1.

In regard to clinical data, AF patients were older (57.96 ± 8.61 vs 52.61 ± 12.53, p < 0.001) and had a lower percentage of females. Medication with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, BB and mineralocorticoid receptor antagonists were similar and highly prevalent in both groups, and no differences were found regarding implantable cardioverter-defibrillator and cardiac resynchronization therapy between the two groups. There were no significant differences for sodium and NT-proBNP, but glomerular filtration rate (GFR) values were lower in the AF group (65.03 ± 29.05 vs 76.84 ± 30.20, p = 0.012).

Higher percentage of right ventricular dysfunction (40.0% vs 13.0%, p < 0.001) and lower values of LVEF (24.96 ± 7.44 vs 27.91 ± 7.23, p = 0.010), revealed a worse biventricular function in AF group.

CPET data showed no differences regarding heart rate parameters, but the AF group had lower baseline and maximal systolic blood pressure (SBP). Significant differences between
Table 1 – Baseline characteristics of AF and SR groups

| Clinical data – characteristics | SR - n = 223 | AF - n = 51 | p for ≠ between groups |
|--------------------------------|-------------|------------|------------------------|
| Age                           | 52.61 ± 12.53 | 57.96 ± 8.61 | < 0.001                |
| Female (%)                    | 61 (27.4%)  | 6 (11.8%)  | 0.019                  |
| BMI (kg/m²)                   | 26.80 ± 4.07 | 27.47 ± 4.78 | 0.361                  |
| Ischemic etiology (%)         | 90 (40.4%)  | 14 (27.5%) | 0.087                  |
| ACEi/ARA (%)                  | 211 (96.3%) | 50 (98.0%) | 0.544                  |
| BB (%)                        | 179 (80.3%) | 40 (78.4%) | 0.768                  |
| MRA (%)                       | 184 (72.2%) | 38 (74.5%) | 0.677                  |
| Diabetes (%)                  | 43 (21.4%)  | 10 (22.7%) | 0.846                  |
| Baseline ICD (%)              | 109 (49.8%) | 27 (52.9%) | 0.493                  |
| Baseline CRT (%)              | 48 (21.5%)  | 12 (23.5%) | 0.781                  |
| HFSS                           | 8.77 ± 0.95 | 6.22 ± 0.93 | < 0.001                |
| Laboratory data               |             |            |                        |
| Glomerular filtration rate (ml/min) | 76.84 ± 30.20 | 65.03 ± 29.05 | 0.012                 |
| Sodium (mEq/L)                | 137.8 (135.7-139.3) | 136.9 (133.6-139.3) | 0.052                |
| NT-proBNP (pg/ml)             | 2,046.79 ± 2,223.07 | 3,247.38 ± 4,578.571 | 0.097                |
| Echocardiographic data        |             |            |                        |
| LVEDD (mm/m²)                 | 38 (35-43)  | 38 (35-43) | 0.237                  |
| LVEF (%)                      | 29 (22-34)  | 26 (20-30) | 0.010                  |
| MR III-IV (%)                 | 87 (39.0%)  | 12 (23.5%) | 0.073                  |
| RV dysfunction (%)            | 29 (13.0%)  | 22 (40%)   | < 0.001                |
| CPET data                     |             |            |                        |
| Initial HR (%)                | 82 (72-92)  | 83 (70-100)| 0.232                  |
| Maximal HR                    | 137 (121-157) | 130 (115-179) | 0.747                 |
| Maximal HR predicted (%)      | 82.77 ± 12.86 | 86.88 ± 23.37 | 0.230                |
| Delta HR during exercise      | 53 (39-71)  | 52 (34-64) | 0.636                  |
| HRR1 (%)                      | 17 (12-26)  | 16 (10-25) | 0.624                  |
| Initial SBP (%)               | 115 (110-125) | 1,110 (100-120) | 0.026                |
| Maximal SBP                   | 155.30 ± 26.83 | 145.92 ± 28.98 | 0.028                |
| Duration of CPET (min)        | 10.83 ± 3.99 | 6.53 ± 4.30 | < 0.001                |
| Peak RER (%)                  | 1.10 ± 0.09 | 1.11 ± 0.09 | 0.340                  |
| pVO₂ (ml/kg/min)              | 20.27 ± 5.54 | 17.81 ± 5.55 | 0.005                 |
| pVO₂ predicted (%)            | 68.12 ± 17.65 | 63.12 ± 18.29 | 0.072                |
| VE/VO₂ slope                  | 30.64 ± 6.78 | 34.33 ± 8.88 | 0.006                  |
| OUES                          | 1.63 ± 0.58 | 1.64 ± 0.60 | 0.035                  |
| AT18 time (minutes)           | 7.49 ± 3.44 | 5.49 ± 3.63 | < 0.001                |
| pVO₂ (ml/kg/min) at AT         | 16.35 ± 4.29 | 14.29 ± 4.32 | 0.002                  |

Values are mean ± standard deviation or median (interquartile range); p values are calculated by Student’s T-test for independent samples or Mann-Whitney U test as appropriate. SR: sinus rhythm; AF: atrial fibrillation; BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitors; ARA: angiotensin receptor blockers; BB: beta-blockers; MRA: mineralocorticoid receptor antagonists; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; HFSS: Heart Failure Survival Score; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; RV: right ventricular; HR: heart rate; HRR1: heart rate recovery in the first minute after finishing CPET; SBP: systolic blood pressure; CPET: cardiopulmonary exercise test; RER: respiratory exchange ratio; AT: anaerobic threshold.
the two groups were also observed with prognostic measures of CPET, with a worse status in AF group revealed by a lower CPET duration, pVO₂, oxygen uptake efficiency slope (OUES), time to anaerobic threshold (AT), pVO₂ at AT and a higher VE/VCO₂ slope (Table 1).

Primary and secondary endpoints

At 1 year, the primary endpoint (cardiac death or urgent HT) had occurred in 27 (9.9%) patients as represented in Table 2. There were no patients requiring mechanical circulatory support. The AF group had more events regarding the combined endpoint (17.6% vs 8.1%, p = 0.038), with cardiac mortality alone showing a trend for a worse prognosis in the AF group (11.8% vs 5.4%, p = 0.097), with no statistical difference regarding urgent HT (5.9% vs 2.7%, p = 0.249).

Secondary endpoints showed higher all-cause mortality (17.6% vs 6.3%, p = 0.008) and a higher sudden cardiac death (7.8% vs 2.2%, p = 0.043) in the AF group, with no difference regarding death for worsening HF (3.9% vs 3.1%, p = 0.777).

Complete data of univariable Cox analysis for prediction of the primary endpoint is presented in Table 3 and Table 4.

HFSS, Sodium, NT-proBNP, right ventricular dysfunction, LVEF, CPET duration, heart rate recovery in the first minute after finishing CPET (HHR1) and initial and maximal SBP during CPET were predictors of the primary endpoint in both groups.

With the exception of HHR1, heart rate (HR) parameters during CPET were only predictors of the primary endpoint in the AF group, as seen with lower values of maximal HR, lower values of maximal (%) predicted HR and a lower variation of the HR during exercise, for patients with AF for whom the primary endpoint occurred and for those for whom it did not, respectively (Table 4).

On the other hand, the use of BB was only a predictor of the primary endpoint in the SR group (Table 3).

Relationship between CPET prognostic parameters and primary outcome

The power to predict the primary outcome by CPET parameters is represented in the supplementary index. Univariate Cox analysis shows that pVO₂, pVO₂ (%) predicted, pVO₂ at AT, VE/VCO₂ slope and OUES are all predictors of the primary outcome in both groups (p < 0.05 for all).

In addition to the Cox analysis, these CPET parameters were analysed for the highest AUC in the 12 months’ follow-up period. In the SR group, VE/VCO₂ slope had the highest

| Table 2 – Adverse events at 12 months follow-up |
|-----------------------------------------------|
| **Adverse events at 12 months follow-up**    |
| **SR - n (%)** | **AF - n (%)** | **p** |
| Combined endpoint | 18 (8.1%) | 9 (17.6%) | 0.038 |
| Total mortality   | 14 (6.3%) | 9 (17.6%) | 0.006 |
| Cardiac mortality | 12 (5.4%) | 6 (11.8%) | 0.097 |
| Sudden cardiac death | 5 (2.2%) | 4 (7.8%) | 0.043 |
| Death for worsening HF | 7 (3.1%) | 2 (3.9%) | 0.777 |
| Urgent HT         | 6 (2.7%) | 3 (5.9%) | 0.249 |
| Mechanical circulatory support | 0 (0%) | 0 (0%) | 1.000 |

AF: atrial fibrillation; HF: heart failure; HT: transplantation; SR: sinus rhythm.

| Table 3 – Univariate Cox proportional-hazards analysis (non-CPET parameters) |
|-----------------------------------------------|
| **Characteristics** | **All** | **SR** | **AF** |
| | **Wald** | **Hazard ratio** | **95% CI** | **p** | **Wald** | **Hazard ratio** | **95% CI** | **p** | **Wald** | **Hazard ratio** | **95% CI** | **p** |
| Age | 0.092 | 0.995 | 0.936-1.062 | 0.762 | 0.768 | 0.984 | 0.950-1.020 | 0.381 | 0.057 | 1.010 | 0.933-1.093 | 0.811 |
| Gender | 0.524 | 0.699 | 0.265-1.845 | 0.469 | 1.041 | 0.525 | 0.152-1.812 | 0.308 | 1.188 | 2.397 | 0.498-11.547 | 0.276 |
| BMI | 1.175 | 0.947 | 0.859-1.045 | 0.278 | 0.183 | 0.974 | 0.863-1.099 | 0.669 | 1.906 | 0.887 | 0.748-1.052 | 0.167 |
| Beta-Blocker | 5.139 | 2.469 | 1.130-5.393 | 0.023 | 4.259 | 2.713 | 1.051-6.998 | 0.039 | 0.877 | 1.941 | 0.484-7.797 | 0.349 |
| Diabetes | 0.130 | 1.197 | 0.451-3.174 | 0.718 | 0.027 | 0.910 | 0.297-2.792 | 0.869 | 0.691 | 2.416 | 0.302-16.326 | 0.406 |
| Baseline CRT | 1.614 | 1.995 | 0.687-5.790 | 0.204 | 1.047 | 2.160 | 0.494-10.223 | 0.010 | 8.600 | 0.244 | 0.095-0.628 | 0.003 |
| HFSS | 34.893 | 0.233 | 0.144-0.378 | < 0.001 | 22.674 | 0.233 | 0.128-0.424 | < 0.001 | 8.600 | 0.244 | 0.095-0.628 | 0.003 |
| Glomerular filtration rate | 3.520 | 0.586 | 0.971-1.101 | 0.061 | 2.578 | 0.985 | 0.967-1.003 | 0.108 | 0.205 | 0.994 | 0.969-1.020 | 0.650 |
| Sodium | 27.303 | 0.787 | 0.720-0.861 | < 0.001 | 14.635 | 0.766 | 0.668-0.878 | < 0.001 | 7.668 | 0.839 | 0.726-0.947 | 0.006 |
| NT-proBNP | 20.456 | 8.212 | 2.234-12.367 | < 0.001 | 15.171 | 6.263 | 1.894-10.223 | < 0.001 | 3.187 | 2.335 | 1.285-5.343 | 0.004 |
| LVEDD | 5.670 | 1.072 | 1.012-1.135 | 0.017 | 3.001 | 1.077 | 0.990-1.171 | 0.083 | 1.433 | 1.049 | 0.970-1.135 | 0.230 |
| LVEF | 18.934 | 0.887 | 0.840-0.906 | < 0.001 | 13.810 | 0.884 | 0.828-0.943 | < 0.001 | 3.351 | 0.912 | 0.826-0.998 | 0.049 |
| RV dysfunction | 21.377 | 3.758 | 2.144-6.588 | < 0.001 | 6.160 | 2.846 | 1.246-6.459 | 0.013 | 8.346 | 4.267 | 1.584-11.419 | 0.004 |

SR: sinus rhythm; AF: atrial fibrillation; CI: confidence interval; BMI: body mass index; CRT: cardiac resynchronization therapy; HFSS: Heart Failure Survival Score; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; RV: right ventricular.
AUC value (0.906) followed by predicted pVO₂ (%) (0.903), with OUES with the lower AUC value (0.798). Despite these numerical differences, no statistically significant difference was found when the Hanley & McNeil test was applied to compare the different AUC values of the CPET parameters.

In the AF group, predicted pVO₂ (%) (0.878) and pVO₂ (0.869) had the highest AUC values. Similarly to the SR group, OUES had the lowest AUC value (0.833), but no statistically significant difference was found when the Hanley & McNeil test was applied to compare these parameters.

The Hanley & McNeil test was applied for comparing each CPET AUC parameter in the AF versus SR groups as well, with no statistically significant difference found.

Multivariate Cox analysis (Table 5) showed that when pVO₂ and the VE/VCO₂ slope are analysed together, significant differences were found between SR and AF groups. In the SR group, pVO₂ lost its predictive power (p = 0.280) while the VE/VCO₂ slope remained predictive of the primary outcome (p = 0.001). In the AF group, the VE/VCO₂ slope lost its predictive power (p = 0.398) and pVO₂ showed a trend towards the prediction of the primary outcome (p = 0.091).

Similar results were found in the multivariate Cox analysis of predicted pVO₂ (%) and the VE/VCO₂ slope in the AF group (p = 0.094 and p = 0.145, respectively), while in the SR group there was a difference, since predicted (%) pVO₂ (p = 0.006) and VE/VCO₂ slope (p = 0.033) kept their predictive power (p = 0.006), while pVO₂ had not (p = 0.280).

OUES lost its predictive power in the multivariate Cox analysis in both SR and AF groups when compared with pVO₂ (p = 0.948 and p = 0.539, for SR and AF group respectively)
and when compared with the VE/VCO₂ slope (p = 0.503 and p = 0.701, for SR and AF group respectively).

**Cut-off value for HT selection: PPV and NPV for the primary outcome**

The univariate Cox analysis for the primary outcome of the two recommended CPET cut-offs for HT selection⁷ (pVO₂ ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without BB and VE/VCO₂ slope ≤ 35) is represented in Table 6, showing that in the two groups, both cut-offs remained predictors of the outcome.

In pVO₂ ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without BB, the PPV for the primary outcome was 100% in the AF group and 38.5% in the SR group (Table 7), with a NPV of 95.5% and 94.3% in the AF and SR groups, respectively. Higher values were found when the analysis excluded patients not doing BB, with a PPV of 100% and 75%, and a NPV of 97.1% and 95.3% for the AF and RS groups respectively.

In VE/VCO₂ slope > 35 (Table 7), lower values of PPV were reported (33.3% and 29.8% for AF and SR groups, respectively), with similar NPV to pVO₂ (92.3% and 98.3% for AF and SR groups, respectively).

**Discussion**

The presence of AF is associated with a negative prognostic effect in HF, with 50-90% increased mortality and HF progression in the Framingham Heart Study.¹² Our population revealed some baseline differences between SR and AF groups, with some of that in previously described prognostic markers of HF, as AF patients were older,¹³,¹⁴ with lower GFR,¹⁵-¹⁷ with worse right ventricular function¹⁸ and a lower LVEF.¹⁹,²⁰ In regard to CPET parameters, our AF patients revealed a lower exercise capacity than SR patients since they had a higher VE/VCO₂ slope and a lower CPET duration, HR,²⁶ and initial and maximal SBP during CPET,²³-²⁵ right ventricular dysfunction,¹⁸ lower LVEF,¹⁹,²⁰ CPET duration, HHR,¹⁹ and initial and maximal SBP during CPET were included in this group, with all of them being formerly described as prognostic markers in HF patients.

Differences were found regarding maximal HR and variation of HR during the exercise, with lower values in AF patients predicting the primary outcome only in that group.

Patients not using BB were solely predictive of the primary outcome in the SR group, but not in the AF group. Whether this is in agreement with other studies that failed to reveal prognostic benefit from BB in the AF group of HF patients or to a underpowered analysis since only 11 patients in the AF group were not doing BB cannot be guaranteed.

**Cut-off value for HT selection: PPV and NPV for the primary outcome**

Whether HF patients with AF can be precisely stratified with the current CPET cut-offs for HT selection have not been specifically studied before. The cut-off value for pVO₂ showed a PPV for the primary outcome of 100% in the AF group and 38.5% in the SR group, with a NPV of 95.5% and 94.3% in the AF and SR groups, respectively. Hence, despite AF carries a worse prognosis in HF patients, the current cut-off of pVO₂ for HT selection can precisely stratified these high-risk patients, with no patients under the cut-off misdiagnosed as high risk patients and less than 5% of patients above the cut-off having the primary outcome in the 1-year follow-up (Figure 1). These results suggest that patients under the cut-off of pVO₂ should be managed accordingly, considering quickly referring for HT or mechanical circulatory support, since medical treatment is associated with negative outcomes in a 1-year period, and that we can be relatively safe in regard to 1-year outcomes of patients above the cut-off.

**Table 6 – Univariate Cox analysis for the primary outcome of the two recommended cardiopulmonary exercise test cut-offs for Heart Transplantation selection**

|                  | SR     | AF     |
|------------------|--------|--------|
| Hazard ratio     |        |        |
| pVO₂ ≤ 12 ml/kg/min | 8.673  | 44.220 |
| VE/VCO₂ slope > 35 | 20.858 | 5.613  |

SR: sinus rhythm; AF: atrial fibrillation; CI: confidence interval; pVO₂: peak O₂ consumption; BB: beta-blockers.

**Table 7 – Proportion of patients correctly classified at 12 months of follow up**

|                | AF         | SR         |
|----------------|------------|------------|
| pVO₂ ≤ 12 ml/kg/min or ≤ 14 ml/kg/min without BB | 7/7 - 100% | 5/13 - 38.5% |
| pVO₂ > 12 ml/kg/min or > 14 ml/kg/min without BB | 42/44 - 95.5% | 198/210 - 94.3% |
| pVO₂ ≤ 12 ml/kg/min only in patients doing BB | 5/5 - 100% | 6/8 - 75% |
| pVO₂ > 12 ml/kg/min only in patients doing BB | 34/35 - 97.1% | 161/169 - 95.3% |
| VE/VCO₂ slope > 35 | 7/21 - 33.3% | 14/47 - 29.8% |
| VE/VCO₂ slope ≤ 35 | 28/30 - 92.3% | 173/176 - 98.3% |

SR: sinus rhythm; AF: atrial fibrillation; pVO₂: peak O₂ consumption; BB: beta-blockers.
In regard to SR patients, the lower risks associated are responsible for a lower value of PPV above the pVO2 cutoff. The PPV was raised from 38.5% to 75% when the analysis excluded patients not doing BB. The NPV remains high in this group (94.3%).

During exercise, both CO2 output and ventilation increase steadily, but in patients with HF, the slope of the relationship is increased.31 Previous studies have confirmed the prognostic impact of VE/VCO2 in patients with HF, with higher values being associated with worse outcomes.32-35 However, the value of VE/VCO2 in AF patients with HF is not so well established, with differences in results in some trials.36,37

In our study, with a VE/VCO2 slope > 35, lower values of PPV were reported (33.3% and 29.8% for AF and SR groups, respectively), with similar NPV compared to pVO2 results (92.3% and 98.3% for AF and SR groups, respectively, figure 1). The power to predict the primary outcome by the VE/VCO2 slope, revealed an AUC of 0.906 for the SR group (the highest of all the CPET parameters analysed) and 0.844 in the AF group, with no statistically significant difference found when comparing the different AUC values of the CPET parameters. These differences in PPV may suggest that despite the fact that VE/VCO2 slope could be at least as good for prognostic assessment in HF patients as pVO2, the cut-off to use with the VE/VCO2 slope is not so well established as the cut-off for pVO2 in AF patients.

One previous study has shown that in a multivariate Cox analysis, pVO2 was identified as a sole significant predictor of cardiac events in HF patients in SR and the VE/VCO2 slope in AF patients.38 Our results, however, do not concur with the previous results. In fact, our multivariate Cox analysis (Table 5) showed that when pVO2 and the VE/VCO2 slope are analysed together, pVO2 lost its predictive power (p = 0.280) while the VE/VCO2 slope remained predictive of the primary outcome (p = 0.001) in the SR group. In the AF group, the VE/VCO2 slope lost its predictive power (p = 0.398) while pVO2 showed a trend for the prediction of the primary outcome (p = 0.091).

The predicted pVO2 (%) has been demonstrated as a useful prognostic marker in previous HF studies.39 In the multivariate Cox analysis of predicted pVO2 (%) and the VE/VCO2 slope, predicted pVO2 (%) kept his predictive power in the SR group (p = 0.006) in contrast to pVO2 while in the AF group, it showed a trend towards prediction of the primary outcome (p = 0.094) and had the highest AUC predictive value (0.878).

OUES is derived by plotting VO2 as a function of log10VE, which is an approximately linear relation, indicating how effectively O2 is extracted and taken into the body.40 In HF patients, OUES is reduced in proportion to disease severity and linked to outcome.41,42 In our population, OUES had the numerically lower AUC for predicting the primary outcome in both AF and SR groups and lost its predictive power in the multivariate Cox analysis when compared with pVO2 and when compared with the VE/VCO2 slope, which is in accordance with other previous study.43

**Study limitations**

There are limitations to our study that should be referenced. Even though data was obtained from the outpatient clinic visits, medical charts were reviewed and complemented with a standardized telephone interview to all patients at 12 months of follow-up to collect data for the primary and secondary outcomes. Information pertaining to the selection or not of rhythm control for the treatment of AF was not gathered. Despite this, the goal of the trial was to define, during the initial evaluation, which patients needed early indication for HT or mechanical circulatory support, reducing the importance of the aforementioned information.

Despite being a seven-year follow-up of patients evaluated for HT in one advanced HF centre, the analysed cohort was not larger than other studies of the relation between HF and AF.2,36,38 However, the sample size is similar to other studies that highlighted the value of CPET parameters, including for the selection of patients for HT.3,32,33,35,44,45

Since patients were referred for a tertiary hospital for the purpose of evaluation with HF team and possible indication
for HT or mechanical circulatory support, these patients may not be representative of the older or with higher comorbidities HF community, who are not candidate for advanced HF treatment.

Conclusions

Despite AF carries a worse prognosis for the HF patients, the current cut-off of $pVO_2$ for HT selection can precisely stratify this group of high-risk patients. The findings from the present study suggest that HF patients with AF and a CPET under the current cut-off of $pVO_2$ for HT selection should be quickly referred for HT or mechanical circulatory support, since medical treatment is associated with negative outcomes in a 1-year period, with a higher PPV than patients in SR. In addition, $pVO_2$ cut-off seems to have higher PPV than VE/VCO2 slope cut-off for the prediction of the primary outcome in HF patients with AF.

Author contributions

Conception and design of the research: Gonçalves AV, Pereira-da-Silva T, Soares R; Acquisition of data: Pereira-da-Silva T, Soares R, Feliciano J, Moreira RI, Río P; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Gonçalves AV; Critical revision of the manuscript for intellectual content: Pereira-da-Silva T, Soares R, Abreu A, Ferreira RC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro Hospitalar Lisboa Central under the protocol number CA2257. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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