Cardiopulmonary exercise and 6-min walk tests as predictors of quality of life and long-term mortality among patients with heart failure due to Chagas disease☆

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The cardiopulmonary exercise test (CPET) is an established tool to assess prognosis in patients with heart failure (HF) [1–3]. However, little is known about the prognostic value of CPET in patients with HF due to Chagas disease. We assessed the performance of functional variables from 1) the CPET; 2) echocardiograms; and 3) the 6-min walk test (6MWT) in predicting quality of life and long-term mortality among patients with HF due to Chagas disease.

We studied 55 patients with HF due to Chagas disease with left ventricular dysfunction (ejection fraction [EF] <45%) and symptoms who were identified from participants in 2 randomized clinical trials [4] and followed for all-cause mortality. A detailed description of the study procedures was previously published [5]. This study was approved by the institutional review board of the Santa Izabel Hospital, Bahia, Brazil. All patients gave informed consent to participate in the trials.

Continuous variables were described as mean ± SD. The Student *t* test and Chi-square test were used as appropriate. Correlations with quality of life were assessed by univariable and multivariable linear regression analyses (backward stepwise protocol). C statistic and receiver operating characteristic (ROC) curves were used to determine the best thresholds for mortality prediction. Kaplan–Meier survival curves were constructed based on these thresholds, and multivariable Cox proportional hazard analysis (backward stepwise protocol) was used to determine associations with survival. A p value <0.05 was considered significant.

There was no loss to follow-up, and the mean follow-up was 32 ± 19 months. Patients were distributed among New York Heart Association classes II to IV as follows: class II, 41 patients (74%); class III, 12 patients (22%); and class IV, 2 patients (4%). Sinus rhythm was present in 40 patients (73%), 6 (11%) patients were on atrial fibrillation, and 9 (16%) had a pacemaker. The mean heart rate was 68 ± 8 bpm.

In general, patients were well treated for HF: 89% took an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 62% used beta-blockers, 86% a diuretic, and 74% an aldosterone blocker. A complete description of the baseline population characteristics was previously published [5].

By echocardiogram, mean EF was 27.6% ± 6.6%, and mean left atrial diameter was 44 ± 7 mm. The mean distance during the 6MWT was 399 ± 102 m, and the mean Chagas score [6] was 13 ± 2.5, which is compatible with the higher risk group for this score. The CPET results showed a mean peak oxygen consumption (VO_2) of 17.3 ± 6.2 mL/kg/min, an exchange ratio of 1.08 ± 0.18, a ventilation efficiency (VE/VCO_2) slope of 36 ± 10, an O_2 pulse of 9.4 ± 3.5 mL/beat, and an oxygen uptake efficiency slope of 0.66 ± 0.27 L/min.

Mean Minnesota Living with Heart Failure Questionnaire (MLHFQ) score was 38 ± 18. There were significant correlations between better quality of life and higher peak VO_2 ($r = -0.301$, $p = 0.02$), higher 6MWT distance ($r = -0.375$, $p = 0.007$), and higher EF ($r = -0.282$, $p = 0.03$). Together, these variables explained 30% of the variation in the MLHFQ. The 6MWT distance was the only factor independently associated with higher MLHFQ score. Each 10-m increase in the distance walked in the 6MWT was associated with a reduction of 0.7 points in the MLHFQ score.

At the final follow-up, 39 patients (71%) were dead. Non-survivors had significantly lower EF and higher Chagas scores. From the CPET, only peak VO_2 and VE/VCO_2 slope were significantly different between survivors and non-survivors (Table 1).

The C statistics for the relationship between peak VO_2 and VE/VCO_2 slope and mortality were 0.70 (95% confidence interval [CI]: 0.55 to 0.85, $p = 0.02$) and 0.73 (95% CI: 0.59 to 0.87, $p = 0.007$), respectively. Based on ROC curve analysis, the best cut point for mortality discrimination was ≤18 mL/kg/min for peak VO_2

Table 1
Functional capacity and quality of life in survivors and non-survivors.

	Survivors	Non-survivors	p value
N	16	39	
Age (yrs)	51 ± 9	51 ± 9	0.96
Peak VO_2 (mL/kg/min)	20 ± 6	16.2 ± 6	0.03
VO_2 at AT (mL/kg/min)	12.3 ± 3	11.3 ± 3.6	0.32
VE/VCO_2 slope	30 ± 7	38 ± 11	0.01
OUES (L/min)	0.71 ± 0.22	0.65 ± 0.28	0.47
O_2 pulse (mL/beat)	10 ± 4.4	8.8 ± 3.0	0.10
HRR1 < 16	53%	65%	0.43
EF (%)	30 ± 6	26 ± 6	0.04
LA diameter (mm)	43 ± 6	45 ± 7	0.39
LVESD (mm)	56 ± 8	61 ± 9	0.49
LVEDD (mm)	66 ± 7	69 ± 9	0.14
6MWT (m)	443 ± 123	382 ± 89	0.05
MLHFQ	32 ± 19	41 ± 17	0.11
NSVT	68%	82%	0.27
Serum sodium (mg/dL)	138 ± 4	138 ± 4	0.81
Chagas score	11 ± 2	14 ± 2	0.01

Results are presented as mean ± SD, except for NSVT and HRR1, which are presented as proportions.
AT, anaerobic threshold; EF, ejection fraction; HRR1, heart rate recovery at the first minute; LA, left atrial; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NSVT, non-sustained ventricular tachycardia; O_2, oxygen; OUES, oxygen uptake exercise slope; 6MWT, 6-min walk test; VCO_2, carbon dioxide production; VE, ventilation; VO_2, oxygen consumption.

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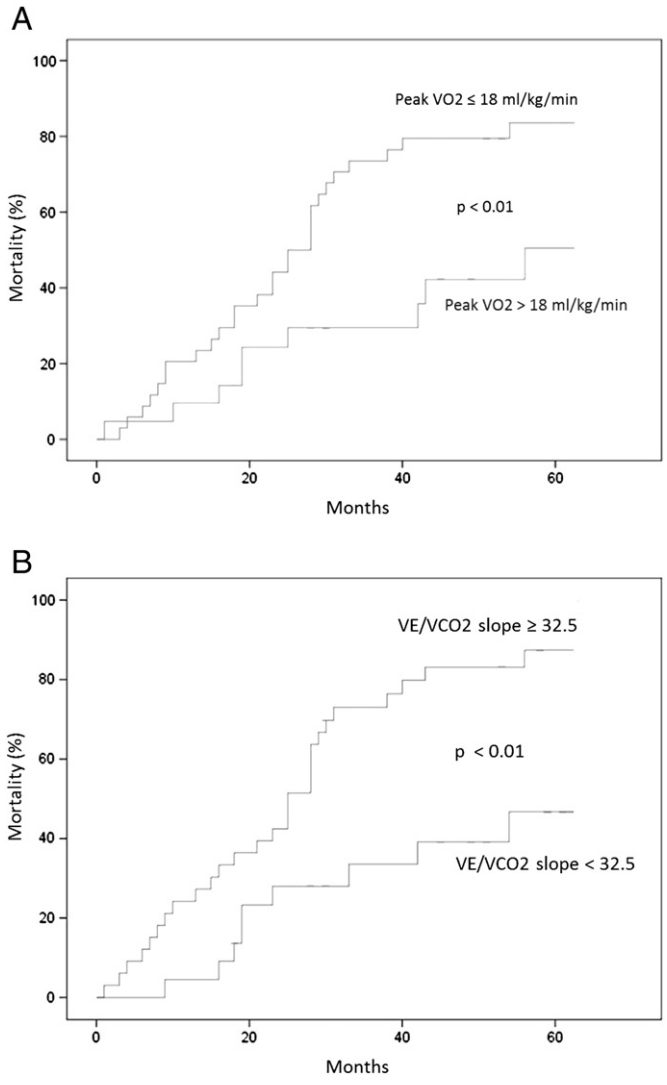

Fig. 1. Kaplan–Meier mortality curves for peak VO_2 (A) and VE/VCO_2 slope (B) according to ROC-derived thresholds.

(sensitivity 74% and specificity 69%) and ≥32.5 for VE/VCO_2 slope (sensitivity 72% and specificity 69%).

Fig. 1 shows the Kaplan–Meier curves for mortality according to the thresholds of peak VO_2 and VE/VCO_2. Patients with peak VO_2 ≤18 mL/kg/min had a mean survival of 29 ± 3 months versus 46 ± 5 months for those with peak VO_2 >18 mL/kg/min ($p = 0.013$). Patients with a VE/VCO_2 slope ≥32.5 had a mean survival of 28 ± 3 months versus 47 ± 5 months for those with a VE/VCO_2 slope <32.5 ($p = 0.006$).

After adjustment for age, EF, and Chagas score, peak VO_2 was no longer significantly associated with mortality (adjusted hazard ratio [HR]: 0.97, 95% CI: 0.91 to 1.04, $p = 0.44$); VE/VCO_2 slope remained an independent predictor of long-term mortality (adjusted HR: 2.80, 95% CI: 1.30 to 5.80, $p = 0.001$, for those with VE/VCO_2 slope ≥32.5; or adjusted HR: 1.04, 95% CI: 1.01 to 1.07, $p = 0.01$, per unit increase in VE/VCO_2 slope). Chagas score was also an independent predictor of mortality (adjusted HR: 1.28, 95% CI: 1.10 to 1.48, $p = 0.001$).

We demonstrated that better performance in the 6MWT was independently related to better quality of life as assessed by the MLHFQ. Also, we showed that higher VE/VCO_2 slope was the only CPET variable associated with greater long-term mortality in this population. Finally, we observed that the thresholds that discriminated mortality among Chagas patients with HF were less extreme than those used for assessment of patients with HF of other etiologies [7,8]. This finding may reflect a more severe disease stage despite less functional limitation and the possible need for earlier intervention among patients with HF due to Chagas.

In conclusion, among patients with HF due to Chagas disease, longer distance walked in 6 min was independently associated with better quality of life. VE/VCO_2 slope was an independent predictor of long-term mortality. If validated, our results may have implications for assessment of prognosis and clinical decision making for patients with HF due to Chagas disease.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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