Functional capacity and right ventricular function in patients with Chagas heart disease

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Aims
Right ventricular (RV) dysfunction is an important factor on effort tolerance in cardiopulmonary diseases. Nevertheless, the role of RV function in predicting exercise capacity in patients with Chagas disease has not been reported. This study aims to evaluate whether RV function assessed by tissue Doppler can predict functional capacity in patients with Chagas heart disease.

Methods and results
We evaluated 65 patients (48.6 ± 9.1 years, 60% men) with Chagas heart disease. Standard and tissue Doppler echocardiography were performed before maximal exercise testing. Tissue Doppler imaging (TDI) was used to measure RV peak annular systolic and diastolic velocities. Exercise testing was performed using a standard Bruce protocol. Linear regression analysis was used to determine multivariate peak oxygen consumption (VO2) predictors. All patients were in NYHA functional class I or II. Mean peak VO2 was 32.4 ± 10.2 mL/kg/min and mean LV ejection fraction was 43 ± 11%. There was correlation between TDI RV peak systolic velocity and LV ejection fraction (r = 0.5; P < 0.001). In a multivariate analysis, after adjustment for age and gender, RV function emerged as an independent predictor of functional capacity, as demonstrated in the model: peak VO2 (r = 0.71) was: 42.22 − (9.77 × female gender) − (0.29 × age) + (1.54 × RV systolic velocity).

Conclusion
In this cross-sectional study, RV function was an important, independent determinant of exercise capacity in patients with Chagas heart disease. TDI RV systolic annular velocity was most closely associated with peak VO2, regardless of the influence of age, gender, and other echocardiographic parameters.

Keywords
Right ventricular function • Exercise capacity • Tissue Doppler imaging • Chagas disease

Introduction
The year of 2009 marks the 100th anniversary of the discovery of Chagas disease by the Brazilian Carlos Chagas. After 100 years, millions of people are still chronically infected in Latin America, with high morbidity and mortality.1,2 Because of the increasing number of immigrants from endemic areas, the disease presents the potential to become a health problem also in non-endemic countries.3–6 Chronic cardiomyopathy is the most serious manifestation of Chagas disease and one of the main causes of heart failure.7

The main differential diagnosis of Chagas cardiomyopathy is idiopathic cardiomyopathy.1 However, Chagas cardiomyopathy has several peculiarities, such as high frequency of arrhythmias, early cardiac denervation, myocardial perfusion abnormalities, and a more extensive amount of myocardial destruction.8,9 Parasite persistence and immunological mechanism seem inextricably related in myocardial aggression in the chronic phase of Chagas heart disease.10

Exercise capacity, expressed as peak VO2, remains one of the best predictors of prognosis in heart failure.11,12 However, left ventricular (LV) systolic dysfunction has been shown to poorly predict exercise capacity.13,14 Instead, previous studies have shown that diastolic dysfunction is associated with a decrease in exercise capacity.15–17 Likewise, right ventricular (RV) function is a major determinant of prognosis and effort tolerance in several heart diseases.18–20 The role of RV function in predicting exercise capacity in the setting of Chagas disease has not been reported.

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Functional capacity and RV function in patients with Chagas heart disease

With recent technical advances in echocardiography, substantial progress in non-invasive methods to assess RV function has been achieved.26 Tissue Doppler imaging (TDI), which measures myocardial velocities, allows quantitative assessment of RV systolic function. Peak systolic tricuspid annular velocity (S) provides a simple, rapid, and non-invasive tool to assess RV function in patients with HF.27 Therefore, this study aims to evaluate whether RV functional parameters derived from TDI of the tricuspid annulus can independently predict functional capacity, as assessed objectively by the measurement of estimated peak \( \text{VO}_2 \) in patients with Chagas heart disease.

**Methods**

**Selection of patients**

Patients with the diagnosis of chronic Chagas heart disease routinely followed at our institution from April 2006 to August 2007 were initially considered for the study. All of these patients had been on optimized medical therapy and were clinically stable over the 3-month period preceding the study. Patients unable to exercise or who had associated heart or other diseases were excluded, and so were patients who presented with pacemakers or atrial fibrillation.

To be included in the study, patients had to have at least two positive serological tests for antibodies against *Trypanosoma cruzi*, together with the typical electrocardiographic28 or echocardiographic findings of Chagas heart disease.29

A total of 65 patients met the study criteria. The local research Ethics Committee approved the study and all patients gave informed consent to participate in it. At the time of enrolment, all patients underwent clinical examination and NYHA functional class was established. Standard laboratory tests, 12-lead ECG and a comprehensive Doppler echocardiogram with colour flow mapping were performed in all patients.

**Echocardiography**

Images were acquired using a Sonos 5500 (Hewlett–Packard, Andover, MA, USA) equipment with 2.5–3.5 MHz transducers. All echocardiograms were performed by one investigator (M.C.P.N.) who was blinded to the clinical evaluation of the patients. The echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography.30 Diastolic function was assessed as previously described.31

Global RV function was quantitatively assessed using the RV index of myocardial performance (Tei index).32 RV diastolic area was measured in the apical four-chamber view. Pulmonary artery pressure was estimated by the tricuspid regurgitation velocity. Peak systolic (S), early, and late diastolic tissue Doppler velocities were acquired at the tricuspid annulus (Figure 1), as previously described.33 Three cardiac cycles were measured during complete expiration and averaged for all Doppler measurements.

**Exercise testing protocol**

After the echocardiogram was obtained, a symptom-limited exercise test was performed on a treadmill (Digistress Pulsar, Micromed, Brazil) using a standard Bruce protocol. A physician, who was unaware of the echocardiographic results, was present during all the studies to encourage maximal exertion. On the day of the treadmill test, patients received their usual cardiac medications and were requested to abstain from food, coffee, cigarettes, and vigorous physical activity for at least 3 h before. A 12-lead ECG was continuously monitored and recorded every 1 min. Cuff blood pressure was obtained manually at rest, during the last 30 s of each stage, and during the 4-min recovery period, in orthostatic position. Heart rate was determined from the electrocardiographic recording.

The primary endpoint was maximal exercise capacity defined by the estimated peak oxygen uptake (peak\(\text{VO}_2\)), expressed in mL/kg/min.34

**Statistical analysis**

Descriptive characteristics of normal continuous variables were expressed as mean and standard deviation (mean \( \pm \) SD), and categorical variables presented as absolute numbers and/or percentages. Non-normal data were presented as median and interquartile range. A two-tailed significance level of 0.05 was considered statistically significant. Correlation between peak \( \text{VO}_2 \) was assessed by the Pearson’s or Spearman correlation coefficient for categorical data; either the unpaired Student \( t \)-test or the Mann–Whitney \( U \) test was used, as appropriate. Logarithm transformation of non-normal variables was performed for subsequent analysis when necessary. Receiver–operator characteristic curve analysis identified the best cut-off value of peak RV systolic velocity for identifying RV dysfunction.

Backward multivariate linear regression models were used to estimate the relative contributions of the clinical, demographic and echocardiographic variables to exercise capacity. Multivariate models were constructed selecting variables significant in univariate analyses. Age and gender were also kept throughout the models, as they were considered to be important control variables on the basis of subject. SPSS software (version 13.0) was used for statistical analysis.

**Results**

**Baseline patient characteristics**

The study population consisted of 65 consecutive outpatients with Chagas heart disease. Mean age was 48.6 \( \pm \) 9.1 years, and 60% were men. The clinical characteristics are presented in Table 1. All patients were in NYHA functional class I or II. Twelve patients (18%) presented with systemic congestion. All patients were taking angiotensin-converting enzyme inhibitors or angiotensin II

![Figure 1](https://example.com/figure1.png)
receptor blocker, 43 (66%) diuretics, 32 (49%) amiodarone, 13 (20%) beta-blocking agents, 9 (14%) anticoagulants, and 3 (5%) digoxin. Right bundle-branch block was the most frequent ECG abnormality.

### Right ventricular function in Chagas heart disease and its relationship to left ventricular function

Echocardiographic data are listed in Table 1. Mean LV ejection fraction was 43 ± 11% and the mean peak tricuspid annular velocity was 11.6 ± 2.2 cm/s (ranged from 7.1 to 16.0). A peak RV systolic velocity value higher than 10 cm/s had a sensitivity of 82% and a specificity of 75% for predicting RV dysfunction, with area under the curve of 0.810.

A positive correlation was noted between RV systolic velocity and LV ejection fraction (r = 0.5; P < 0.001). Similarly, a correlation was also found between RV systolic velocity and RV Tei index (r = −0.3; P = 0.013). Pulmonary artery systolic pressure correlated with the RV Tei index (r = 0.32; P = 0.024), but there was no correlation with RV systolic velocity. As expected LV ejection fraction also correlated negatively with pulmonary artery systolic pressure (r = −0.33; P = 0.019).

### Determinants of exercise capacity

All patients completed the study protocol. No patient had angina, severe arrhythmias, or significant ischaemic ST-abnormalities in the electrocardiogram during the exercise test. As expected, age was negatively correlated with peak VO₂ (r = −0.38, P = 0.002). Simple linear regression analysis revealed that peak VO₂ was significantly correlated with e', El/e' and with some parameters of RV systolic function (Table 2). Traditional measurements of mitral inflow, such as E/A and E deceleration time, did not correlate with exercise capacity. The same was true for measurements of LV ejection fraction (r = 0.21, P = 0.09), and left atrial volume index (r = −0.20, P = 0.12). There was no correlation with other LV filling parameters.

Among all measured echocardiographic parameters, the one that best correlated with exercise performance was RV annular systolic velocity (r = 0.45; P < 0.001) (Table 2 and Figure 2). We also analysed the group of patients according to the distribution of peak RV systolic velocity and we found that a peak RV systolic velocity higher than 10 cm/s identified individuals (48 patients, mean age 47 ± 9 years) with peak VO₂ higher than 33.9 mL/kg/min. In contrast, patients (17 patients, mean age 52.5 ± 9 years) with peak RV systolic velocity lower than 10 cm/s had a lower peak VO₂ (27.6 mL/kg/min) (Figure 3).

When echocardiographic parameters were entered into a backward multivariate linear regression analysis obtained from all significant univariate variables, RV peak systolic velocity emerged as the only significant and independent predictor of peak VO₂. Other independent variables that correlated to reduced exercise tolerance were increasing age and female sex, as shown by the standardized β coefficients in Table 3. To further define the role of RV function on exercise tolerance, a model based upon RV function was developed. Predicted peak VO₂ (r = 0.71) was: 42.22 − (9.77 × female gender) − (0.29 × age) + (1.54 × peak RV systolic velocity).

### Discussion

The main finding of this study was the role of RV function in predicting functional capacity in patients with Chagas heart disease. In addition, a simple to obtain measurement of RV systolic function...
(5) correlated with peak VO₂, independent of the influence of age, gender, or other echocardiographic parameters.

Although many patients with reduced LV systolic function have impaired exercise capacity, similar to previous studies, we found no correlation between LV ejection fraction and exercise parameters. Several studies have been published emphasizing the role of diastolic function as an important determinant of exercise intolerance. In patients with dilated cardiomyopathy, peak VO₂ may better correlate to diastolic filling pressures than LV function. In contrast, in our study, abnormalities of LV diastolic function were not independently associated with exercise capacity. A possible explanation may be the fact that all of our patients were clinically stable without elevated LV filling pressures (median E/e’ ratio = 8).

### Exercise capacity and right ventricular function

Previous studies have suggested that exercise capacity appears to be more closely related to RV function than to LV function. Nevertheless, only a few studies have addressed the role of RV function in predicting exercise capacity in patients with heart failure. Baker et al. found that RV ejection fraction at rest is more predictive of exercise capacity than LV ejection fraction in patients with chronic heart failure. Another study showed that, in a homogenous group of patients with advanced heart failure, RV function at rest or during exercise predicts both survival and functional capacity. Similarly, Tinoco et al. demonstrated that RV systolic dysfunction during exercise is associated with worse functional capacity. On the other hand, Clark et al. did not demonstrate this association, highlighting the multifactorial nature of exercise capacity. As in these previous studies, the present study also found RV function, assessed by TDI, to be predictor of functional capacity in compensated heart failure due to Chagas disease.

The mechanism through which RV dysfunction affects exercise capacity seems to be related to the elevation of pulmonary wedge pressure during exercise. Because right ventricle is very sensitive to load, an elevation of the pulmonary wedge pressure acts to increase pulmonary resistance, and thereby resistance to RV ejection. Indeed, exercise tolerance is related to the level of pulmonary wedge pressure at rest. However, abnormalities in central haemodynamics are not enough to fully explain exercise intolerance in heart failure and this may be influenced by several factors.

Evaluation of RV function in patients with HF is essential in clinical practice. Although there has been significant improvement in cardiac imaging, RV evaluation remains challenging due to many factors. The recent introduction of TDI has proved to be an objective mean to quantify RV function with improved accuracy and

### Table 2 Correlation of echocardiographic measurements with exercise capacity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient (r)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDd/BSA (mm/m²)</td>
<td>-0.38</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.21</td>
<td>0.089</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>-0.02</td>
<td>0.916</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>0.18</td>
<td>0.157</td>
</tr>
<tr>
<td>e’ (cm/s)</td>
<td>0.40</td>
<td>0.001</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>-0.37</td>
<td>0.003</td>
</tr>
<tr>
<td>LA volume index (mL/m²)</td>
<td>-0.20</td>
<td>0.120</td>
</tr>
<tr>
<td>E/Vp</td>
<td>-0.23</td>
<td>0.142</td>
</tr>
<tr>
<td>RV e’ (cm/s)</td>
<td>0.29</td>
<td>0.025</td>
</tr>
<tr>
<td>RV e’/A’ ratio</td>
<td>0.41</td>
<td>0.001</td>
</tr>
<tr>
<td>RV systolic velocity—S (cm/s)</td>
<td>0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>-0.28</td>
<td>0.029</td>
</tr>
<tr>
<td>PASP* (mmHg)</td>
<td>-0.36</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Pulmonary artery systolic pressure (PASP) could be calculated in 52 patients (80%).

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**Figure 2** Correlation between right ventricular (RV) systolic velocity and peak VO₂.

**Figure 3** Value of peak VO₂ according to right ventricular (RV) systolic velocity. Box plot are displaying median and interquartile range.
greater reproducibility than conventional echocardiography. Tricuspid annular systolic velocity derived from TDI allows quantitative assessment of RV function. Vinereanu et al. have demonstrated good reproducibility in acquiring and measuring tricuspid annular velocities, especially for the peak systolic velocity, which appears to be the most clinically useful parameter.

There are potential advantages to TDI assessment over conventional parameters of RV function. Depressed RV TDI velocities could precede global impairment, as assessed by RV fractional area change or visual assessment. In a previous investigation, Dokainish et al. showed that TDI RV systolic annular velocity could detect mild degrees of RV dysfunction that were not evident by visual assessment. Similarly, a previous study has demonstrated that TDI is useful in early detection of RV dysfunction in the setting of Chagas disease. The present study showed that quantitative assessment of longitudinal RV function can be used to predict exercise capacity and appears to be superior to conventional two-dimensional parameters of RV function in patients with Chagas heart disease.

The prognostic importance of TDI of the tricuspid annular motion has been previously demonstrated. Dokainish et al. showed that RV tissue Doppler systolic velocity is an independent predictor of outcome in patients with HF. Patients with a lower $S$ ($<9$ cm/s) exhibited worse survival than those having $S > 9$ cm/s. In our study, patients with a peak $S < 10$ cm/s also had a lower peak VO$_2$.

RV involvement in Chagas disease seems to be related to a chronic myocarditis of inflammatory nature which progresses to fibrosis and affects the myocardial of both ventricles. In fact, we found correlation between LV ejection fraction and RV TDI systolic velocity. Although previous study in chronic Chagas cardiomyopathy has demonstrated an inverse relationship between the degree of heart disease and patients’ functional capacity, in the present study, peak VO$_2$ correlated better to RV than to LV systolic function. In contrast, asymptomatic patients with chronic Chagas heart disease have been shown to have reduced functional capacity compared with controls. The results of our study suggest that RV function is an important and independent determinant of exercise tolerance in patients with Chagas heart disease. Our finding is in agreement with previous studies and emphasizes the role of RV systolic function in predicting exercise capacity. Even in patients with qualitatively preserved RV contractility, TDI was able to detect small decreases in longitudinal systolic velocity that affected exercise capacity. Whereas previous studies limited their evaluation to LV systolic and diastolic echocardiographic predictors of exercise capacity, the present study added information on the value of RV function in predicting exercise capacity.

### Study limitations

The evaluation of exercise capacity was indirect, by estimated VO$_2$, and cardiopulmonary exercise test was not performed. However, it has been established that the indirect assessment of the VO$_2$ is highly correlated with the direct measurement. Also, treadmill exercise time may be of value as an initial prognostic screening tool in patients with systolic LV dysfunction. TDI is dependent on the angle difference between the direction of myocardial motion and the sampling Doppler beam. Technologies using two-dimensional echocardiographic based velocities and strain imaging (speckle tracking or velocity vector imaging) may overcome the angle-dependency limitations intrinsic to tissue Doppler-based measurements, but these techniques were not used.

### Clinical implications

Despite the potential discrepancies between estimated and direct measurement of peak/maximal VO$_2$, both methods aid in the prediction of cardiovascular risk in asymptomatic subjects. Therefore, the assessment of functional capacity provides an opportunity to evaluate early cardiac dysfunction in patients with Chagas heart disease and also to determine the appropriate treatment.

### Conclusions

In this cross-sectional study, RV function was an important and independent determinant of exercise capacity in patients with Chagas heart disease. RV tissue Doppler systolic velocity associated the best with the estimated peak VO$_2$ in these patients. The findings of this study indicate that quantitative assessment of RV function using TDI may be more sensitive in detecting mild degrees of RV dysfunction and can be used to predict functional capacity.

### Conflict of interest

None declared.

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### References


