



## Article/Artigo

# Evaluation of the six-minute walk test in patients with chronic heart failure associated with Chagas' disease and systemic arterial hypertension

Avaliação do teste de caminhada de seis minutos em pacientes com insuficiência cardíaca crônica associada à doença de Chagas e hipertensão arterial sistêmica

Kelly Cristina Colaço Dourado<sup>1</sup>, Reinaldo Bulgarelli Bestetti<sup>1</sup>, Augusto Cardinalli-Neto<sup>1</sup> and José Antônio Cordeiro<sup>2</sup>

### ABSTRACT

**Introduction:** To evaluate physical capacity as determined by the six-minute walk test (6MWT) in patients with chronic heart failure due to Chagas' disease associated with systemic arterial hypertension (Chagas-SAH). **Methods:** A total of 98 patients routinely followed at the Cardiomyopathy Outpatient Service were recruited. Of these, 60 (61%) were diagnosed with Chagas disease and 38 (39%) with Chagas-SAH. **Results:** The distance walked during 6 min was  $357.9 \pm 98$  m for Chagas-SAH patients and  $395.8 \pm 121$  m for Chagas cardiomyopathy patients ( $p > 0.05$ ). In patients with Chagas-SAH, a negative correlation occurred between the 6MWT and the total score of the Minnesota Living with Heart Failure Questionnaire ( $r = -0.51$ ;  $p = 0.001$ ). No other correlations were determined between 6MWT values and continuous variables in patients with Chagas-SAH. **Conclusions:** The results of the 6MWT in Chagas-SAH patients are similar to those verified in Chagas cardiomyopathy patients with chronic heart failure. Coexistence of SAH does not seem to affect the functional capacity of Chagas cardiomyopathy patients with chronic heart failure.

**Key-words:** Heart failure. Chagas disease. American Trypanosomiasis. Six-minute walk test. Physical capacity. Functional capacity

### RESUMO

**Introdução:** Avaliar a capacidade física medida pelo teste de caminhada de seis minutos em pacientes com insuficiência cardíaca crônica secundária à associação de cardiomiopatia chagásica com hipertensão arterial sistêmica (Chagas-HAS). **Métodos:** Noventa e oito pacientes rotineiramente tratados no Ambulatório de Cardiomiopatia do Hospital de Base foram utilizados no estudo. Deles, 60 (61%) eram portadores de cardiomiopatia chagásica (ChCM), enquanto 38 (39%) apresentavam a associação Chagas-HAS. **Resultados:** A distância média caminhada foi de  $357,9 \pm 98$  m no grupo Chagas-SAH e  $395,8 \pm 121$  m no grupo ChCM ( $p > 0,05$ ). Nos pacientes com Chagas-SAH, houve correlação negativa entre o Teste de Caminhada de 6 Minutos e a somatória de pontos obtida no Questionário Vivendo com a Insuficiência Cardíaca. ( $r = -0,51$ ;  $p = 0,001$ ). Nenhuma outra correlação foi observada entre o teste de caminhada de seis minutos e as variáveis contínuas examinadas no grupo Chagas-SAH. **Conclusões:** Os resultados do teste de caminhada de seis minutos em pacientes com Chagas-SAH são semelhantes aos observados em pacientes com ChCM. A coexistência de HAS parece não afetar a capacidade funcional de pacientes com a associação de cardiomiopatia da doença de Chagas e HAS.

**Palavras-chaves:** Insuficiência cardíaca. Doença de Chagas. Trypanossomíase Americana. Teste de caminhada de seis minutos. Capacidade física. Capacidade funcional.

1. Department of Cardiology and Cardiovascular Surgery, Hospital de Base, School of Medicine of São José do Rio Preto, SP, Brazil. 2. Department of Statistics, Hospital de Base, School of Medicine of São José do Rio Preto, SP, Brazil.

**Address to:** Dr. Reinaldo Bulgarelli Bestetti. Hospital de Base/Setor de Eletrocardiografia/FAMERP. Av. Brigadeiro Faria Lima 5544, 15090-000 São José do Rio Preto, SP, Brazil.

Phone: 55 17 3201-5065

e-mail: rbestetti@netsite.com.br

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### INTRODUCTION

Approximately 11 million people are affected by Chagas' disease in Latin America. The disease is caused by the protozoan *Trypanosoma cruzi*, which is transmitted to humans through contact with the feces of a biting bug<sup>1</sup>. Chagas' disease can now be found throughout the world due to international immigration<sup>2</sup>.

Initial infection occurs in early childhood in the majority of cases and about 30% of patients will develop Chagas' cardiomyopathy up to 20 years later<sup>3</sup>. Chagas' cardiomyopathy is clinically characterized by the appearance of atrioventricular blocks<sup>4</sup>, dysrhythmias<sup>5</sup>, thromboembolism<sup>6,7</sup>, chest pain<sup>8</sup>, sudden cardiac death<sup>9</sup> and chronic heart failure<sup>10</sup>.

Systemic arterial hypertension can affect about 30% of inhabitants in areas where Chagas' disease is endemic<sup>11</sup> and it may also compromise about 33% of Chagas' disease patients<sup>12</sup>. Chronic heart failure can affect 8% of patients with both conditions<sup>12</sup>.

In patients with chronic heart failure associated with Chagas' disease-systemic arterial hypertension (Chagas-SAH), no data exist regarding functional capacity. In fact, Chagas cardiomyopathy is characterized by the presence of mononuclear cell infiltrate along with reparative fibrosis throughout the myocardium<sup>13</sup>, accompanied by myocytolysis and vasospasm of the microvasculature in a similar fashion to that observed in catecholamine cardiomyopathy<sup>14</sup>.

Therefore, the additional burden posed by systemic arterial hypertension could aggravate the appearance of myocardial fibrosis, microvasculature spasm and autonomic imbalance of Chagas' disease patients<sup>15</sup>, ultimately affecting the functional capacity of patients with this condition.

Therefore, the purpose of this study was to evaluate functional capacity in patients with chronic heart failure due to Chagas-SAH using the 6-minute walk test.

## METHODS

### Patients

A total of 98 patients routinely followed up at the Cardiomyopathy Outpatient Service of Hospital de Base from January from 2004 to January 2008 were recruited for the study. Of these, 60 (61%) were diagnosed with Chagas cardiomyopathy and 38 (39%) with Chagas-SAH. The diagnosis of Chagas' disease was based on positive serology and the diagnosis of SAH when systolic arterial pressure was >140 mmHg and/or diastolic blood pressure was > 90mmHg. Patients with normal pressure values, but with previous history of SAH who were taking antihypertensive medicine on admission were also considered to have SAH.

To be included in the study, patients had to present; 1) left ventricular ejection fraction < 55% on their echocardiograph, 2) the absence of any other disease that could induce heart disease by itself. Patients with physical incapacity that precluded clear communication with the researcher to the point of interfering in the 6-minute walk test (6MWT) performance were also excluded from the investigation.

All patients underwent clinical history, physical examination, standard laboratory tests, 12-lead ECG, chest X-Ray, and 2D Dopplerechocardiography. Patients with New York Heart Association class I/II symptoms were treated with B-blockers (carvedilol, targeted dose 50mg/day, or metoprolol succinate, targeted-dose 200mg/day) and angiotensin converting enzyme inhibitors (ACEI), [enalapril (targeted dose 20mg/day), or captopril (targeted-dose 75mg/day)], or losartan (targeted dose 50mg/day). Patients with New York Heart Association Class III/IV were treated with digoxin and furosemide to alleviate symptoms, as well as ACEI/losartan at targeted doses and spironolactone (25 to 50mg/day). The daily dose of each drug was that taken at the time of the 6MWT performance. All patients also replied to the Minnesota Living with Heart Failure Questionnaire (MLWHFQ)<sup>16</sup>, as previously described<sup>17</sup>.

### The 6-minute walk test

After written, free, informed consent was obtained from each patient, for whom information regarding the objectives, methods and potential risks was provided, the 6MWT was performed.

The 6-minute walk test was performed in a hallway surface, 30m in length, located in the Outpatient Service of the Hospital de Base. All the patients were supervised by a physiotherapist (KCCD) during the testing. Patients were allowed to stop walking if they developed either shortness of breath or fatigue; however, they were permitted to walk after the symptoms ceased if still within 6 min of initiating testing. Heart rate was measured before walking, 3 and 6 minutes after initiating walking. Blood pressure was measured before and 3 min after the test ended with a manual sphygmomanometer in the antecubital vein, with patients seated for 15 min in a comfortable chair. None of the patients presented complications related to the 6MWT.

### Statistical analysis

Unless indicated otherwise, data are expressed as mean  $\pm$  standard deviation. Continuous variables between two groups were compared by the T Test for unpaired data, whilst categorical variables between two groups were compared by the Fischer exact test. Correlation between continuous variables in each group was established by the Spearman test, in which an  $r$  value > 0.50 was considered significant. In all circumstances, differences at the level of  $p < 0.05$  were considered statistically significant.

### Ethical

The study was approved by the local ethics in research committee (Resolution 077/2006).

## RESULTS

Patient demographics are presented in **Table 1**.

Mean sodium serum levels were  $140.8 \pm 4.0$  mEq/L in Chagas' disease patients and  $141.3 \pm 5.0$  mEq/L in Chagas-SAH ( $p > 0.05$ ), whereas mean potassium serum levels were  $4.4 \pm 0.3$  mEq/L in Chagas' disease patients and  $4.3 \pm 0.6$  mEq/L in Chagas-SAH. Mean creatinine serum levels were  $1.2 \pm 0.3$  mg/dL in Chagas' disease patients and  $1.3 \pm 0.4$  in Chagas-SAH ( $p > 0.05$ ), and the hemoglobin levels were  $13.3 \pm 1.4$  g/L in Chagas' disease patients and  $12.9 \pm 1.5$  in Chagas-SAH ( $p > 0.05$ ).

**TABLE 1 - Demographics among Chagas disease (n=60) and Chagas-SAH (n=38) patients.**

|                   | Chagas-SAH      | Chagas disease  | P value |
|-------------------|-----------------|-----------------|---------|
| Age (years)       | 63 $\pm$ 10     | 55 $\pm$ 14     | ns      |
| Male              | 26 (88%)        | 41 (68%)        | ns      |
| NYHA Class III/IV | 8 (21%)         | 15 (25%)        | ns      |
| Heart Rate (bpm)  | 73 $\pm$ 9      | 74 $\pm$ 8      | ns      |
| SAP (mmHg)        | 128 $\pm$ 15.3  | 112.2 13.6      | 0.02    |
| ACEI/ARB          | 14 (37%)        | 49 (82%)        | <0.0005 |
| Beta-Blockers     | 11 (29%)        | 15 (25%)        | ns      |
| Diuretics         | 14 (37%)        | 49 (82%)        | <0.0005 |
| Amiodarone        | 9 (24%)         | 39 (65%)        | <0.0005 |
| LWHF score        | 41.3 $\pm$ 20.6 | 37.7 $\pm$ 21.4 | ns      |

NYHA: New York heart Association Class; bpm=beats per minute; SAP: systolic anterior pressure; converting enzyme inhibitor/angiotensin receptor of bradykinin.

Cardiomegaly verified in the chest X-ray was observed in 16 (27%) of Chagas' disease patients and in 16 (43%) Chagas-SAH patients ( $p=0.003$ ). Pulmonary venous congestion was detected in none of the Chagas' disease patients, but in 5 (13%) Chagas-SAH patients ( $p=0.007$ ).

**Table 2** depicts electrocardiographic variables observed in Chagas' disease and in Chagas-SAH. The echocardiographic variables obtained in this study are presented in **Table 3**.

**TABLE 2 - Comparison of electrocardiographic findings in Chagas (n=60) and Chagas-SAH (n=38) cardiomyopathy groups.**

|                     | Chagas-SAH<br>n(%) | Chagas disease<br>n(%) | P value |
|---------------------|--------------------|------------------------|---------|
| Non-sinus rhythm    | 10 (26.0)          | 31 (52.0)              | 0.02    |
| Pacemaker           | 9 (24.0)           | 19 (32.0)              | ns      |
| Atrial fibrillation | 1 (3.0)            | 12 (20.0)              | 0,01    |
| RBBB                | 1 (3.0)            | 24 (40.0)              | <0.0005 |
| LBBB                | 4 (10.0)           | 3 (5.0)                | ns      |
| LAFB                | 3 (8.0)            | 3 (7.0)                | ns      |
| PVC                 | 13 (34.0)          | 19 (32.0)              | ns      |
| LVH                 | 16 (42.0)          | 5 (8.0)                | 0.007   |
| Necrosis            | 3 (8.0)            | 8 (13.0)               | ns      |
| Ischemia            | 4 (10.0)           | 6 (10.0)               | ns      |
| Low Voltage QRS     | 6 (16.0)           | 23 (38.0)              | 0.01    |

RBBB: right bundle branch block, LBBB: left bundle branch block, LAFB: left anterior fascicular block, PVC: premature ventricular contractions, LVH: left ventricular hypertrophy.

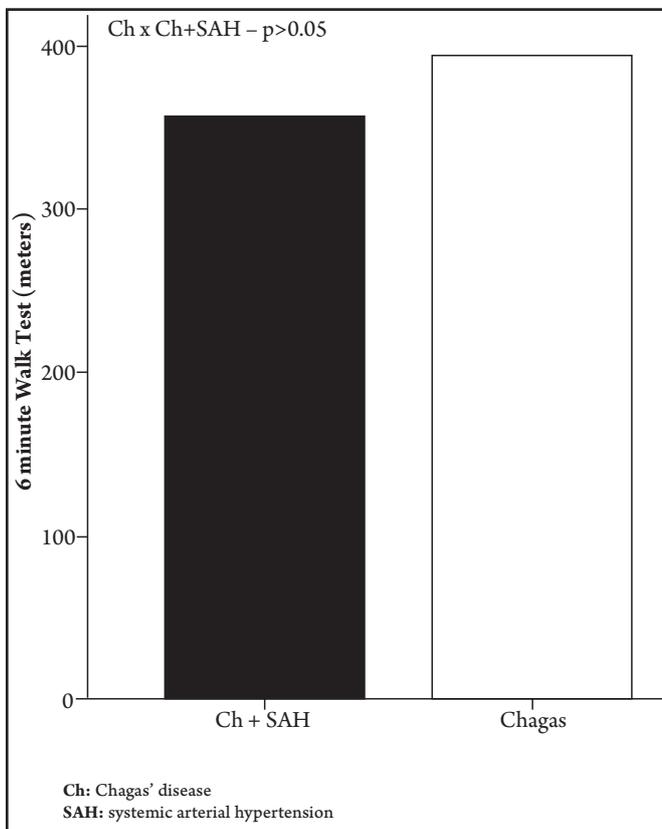
**TABLE 3 - Comparison of echocardiographic variables in Chagas (n=60) and Chagas-SAH (n=38) groups.**

|             | Chagas-SAH  | Chagas disease | p value |
|-------------|-------------|----------------|---------|
| LVEF (%)    | 51.8 ± 12.9 | 44.9 ± 13.8    | 0.001   |
| LAD (mm)    | 43.9 ± 7.7  | 46.5 ± 8.5     | 0.01    |
| LVDD (mm)   | 52.7 ± 10.9 | 61.6 ± 9       | <0.0005 |
| LV Mass (g) | 261 ± 72    | 317.6 ± 77.5   | <0.0005 |
| LVAA        | 3 (8%)      | 8 (13%)        | ns      |
| MR          | 10 (23%)    | 53 (88%)       | <0.0005 |
| Akinesia    | 0 (0%)      | 12 (20%)       | 0.03    |
| Hypokinesia | 9 (24%)     | 27 (45%)       | 0.03    |

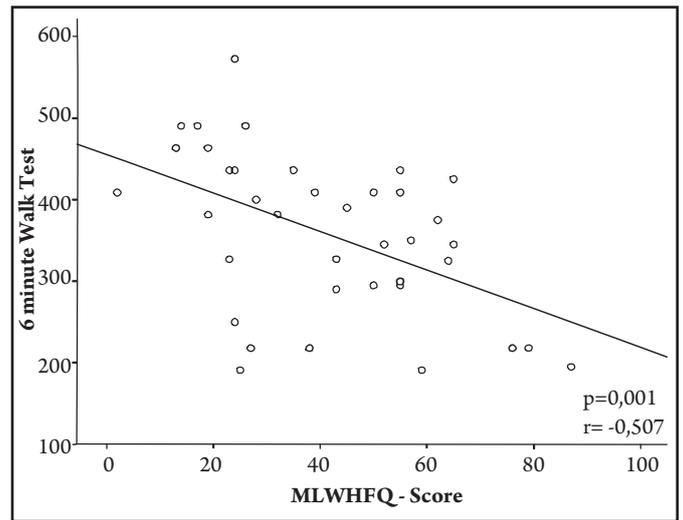
LVEF: left ventricular ejection fraction, LAD: left atrium dimension, LVDD: left ventricular diastolic dimension, LV: left ventricle, MR: mitral regurgitation.

The mean distance walked during 6 min was 357.9 ± 98 m for Chagas-SAH patients and 395 ± 121m for Chagas disease patients (p >0.05). **Figure 1** illustrates the results of the 6MWT. The proportion of patients who walked less than 300 m was 11 out of 38 (29%) individuals among Chagas-SAH patients and 9 out of 60 (15%) individuals among Chagas' disease patients (p>0.05).

In patients with Chagas-SAH, a negative correlation was determined between the 6MWT and the total score of the MLWHFQ (r= -0.51; p=0.001), as illustrated in **Figure 2**. No other correlations were determined between the 6MWT and continuous variables in patients with Chagas-SAH. A tendency toward a correlation was determined between the 6MWT and hemoglobin levels (r=0.34; p=0.007) and the total score of the MLWHFQ (r= -0.38; p=0.003) in the Chagas disease group.



**FIGURE 1 - Results of the 6-minute walk test according to the groups studied.**



**FIGURE 2 - Correlation between the 6-minute walk test and the Minnesota living with heart failure questionnaire in patients with Chagas-SAH patients with chronic heart failure.**

## DISCUSSION

This study shows that patients with Chagas-SAH walked a similar distance to Chagas' disease patients during the 6-minute walk test. Thus, in contrast to what might have been expected, the presence of SAH does not seem to adversely impact on physical capacity in Chagas' disease patients with chronic heart failure.

A negative correlation was determined between the score of the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and the 6MWT in patients with Chagas-SAH in this study. The questionnaire measures the self-perception of well-being in physical and emotional dimensions in patients with chronic heart failure. The physical dimension is closely related to physical capacity, so that the higher the score of well being, the lower the physical status<sup>16</sup>. Not surprisingly, therefore, in patients with Chagas-SAH, a similar negative correlation was determined between well-being self-perception and physical capacity, as detected by the 6MWT.

No difference was verified in the distance walked by Chagas' disease and Chagas-SAH patients with chronic heart failure. Nonetheless, it is necessary to bear in mind that the distance walked by Chagas' disease patients in this study was shorter than that walked in the study by Souza et al<sup>18</sup>. In this regard, it is important to note that the left ventricular ejection fraction, which correlates well with the 6MWT results, was similar in both studies. In the study by Souza et al<sup>18</sup>, however, patients were not permitted to take B-blockers. In contrast, B-blockers were an integral component of the treatment of Chagas' disease patients in the present study. Therefore, this disparity in treatment approach may account for the difference in the distance walked in the 6MWT in both studies.

Another interesting finding of this investigation was the similarity in the resting heart rate in Chagas-SAH and Chagas' disease patients. In the context of chronic heart failure, the resting heart rate has long been recognized as a reflex of peripheral sympathetic activity. In patients with Chagas disease-SAH with no chronic heart failure, parasympathetic impairment has been observed in basal conditions and in response to orthostatic stress<sup>19</sup>. In patients with chronic heart failure secondary to Chagas-SAH, however, such autonomic

derangement does not seem to affect the resting heart rate more than in Chagas cardiomyopathy patients.

Another point that deserves further consideration is related to the clinical aspects of patients with Chagas-SAH chronic heart failure. Gurgel and Almeida<sup>20</sup> performed a clinical-pathological correlation in 103 autopsied patients with chronic Chagas' heart disease, 33% of them presenting SAH. The authors observed no difference in Chagas' disease patients with or without SAH regarding the proportion of right bundle branch block or left anterior fascicular block on the 12-lead electrocardiogram. Bertanha *et al*<sup>21</sup> studied 125 patients with Chagas' disease with no manifest chronic heart failure, 55% with SAH. The authors observed no difference regarding the proportion of electrocardiographic abnormalities in patients with and without SAH. In this study, however, Chagas' disease patients showed a higher proportion of right bundle branch block than Chagas-SAH patients. This discrepancy between these studies may be accounted for by the fact that in the study by Gurgel and Almeida<sup>20</sup>, only 6% of patients had chronic heart failure and none had chronic heart failure in the study by Bertanha *et al*<sup>21</sup>, thus suggesting that intraventricular conduction delay is more prevalent in the presence of overt chronic heart failure.

Patients with Chagas-SAH used amiodarone less frequently than patients with Chagas' disease heart failure. Since amiodarone use increases the physical dimension score of the MLWHFQ, denoting decreased functional capacity in Chagas' disease patients<sup>17</sup>, it might be expected to see an adverse effect of this drug on the 6MWT of Chagas-SAH patients; however, this was not the case. Such a finding, therefore, suggests that drugs which provoke changes in the self-perception of the patient's well-being do not necessarily have an adverse effect on the 6MWT as well.

The proportion of patients who walked a distance of less than 300 meters was similar in Chagas' disease and Chagas-SAH patients. This is an important point, since non-Chagas' disease patients with similar physical incapacity have a poor 6-month prognosis<sup>22</sup>. Although this study was not powered to evaluate mortality, the results of this investigation also suggest that the presence of SAH does not impact on markers of mortality, at least not those detected by the 6-minute walk test.

In conclusion, the results of the 6-minute walk test in Chagas-SAH patients are similar to those verified in Chagas' disease with chronic heart failure. A negative correlation was determined between the 6-minute walk test and the total score of the Minnesota Living with Heart Failure Questionnaire. The coexistence of systemic arterial hypertension does not seem to affect the functional capacity of Chagas' disease patients with chronic heart failure.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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