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Association between typical electrocardiographic abnormalities and NT-proBNP elevation in a large cohort of patients with Chagas disease from endemic area

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Abstract

Chagas cardiomyopathy is the most harmful complication of Chagas disease. The electrocardiogram is a well-studied exam and has been considered an important tool for detection and evaluation of Chagas cardiomyopathy since the first years of its description. Many of its abnormalities have been described as associated with a worse prognosis. Serum BNP levels were described as inversely related to the left ventricular ejection fraction and as an independent predictor of death. It was not reported how electrocardiographic alterations correlate to NT-proBNP and its analog. The present study aims to describe the baseline electrocardiograms of a large cohort of patients with Chagas disease from endemic area and to establish an association between the number of electrocardiogram alterations and high levels of NT-ProBNP in Chagas disease patients. This study selected 1,959 Chagas disease patients in 21 municipalities within a limited region in the northern part of the State of Minas Gerais (Brazil), 1,084 of them had Chagas cardiomyopathy. NT-proBNP levels were suggestive of heart failure in 11.7% of this population. One or more electrocardiographic alterations have an Odds Ratio of 9.12 (CI 95% 5.62 – 14.80) to have NT-proBNP elevation. Considering the association between the number of 1, 2, and 3 or more alterations in electrocardiogram and NT-proBNP elevation, the ORs were 7.11 (CI 95% 4.33–11.67); 16.04 (CI 95% 9.27–27.77) and 47.82 (CI 95% 17.98–127.20), respectively. The presence and the number of typical electrocardiographic alterations of Chagas disease are independently associated with the severity of the cardiomyopathy.

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Keywords

Chagas cardiomyopathy; Electrocardiography; Brain Natriuretic Peptide

1. Introduction

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* and remains a health problem despite the partial control of its transmission. The World Health Organization estimates that approximately 8 million people have been infected, particularly in Latin America where the disease is endemic. In recent decades, the epidemiological profile has changed due to migratory movements, which has led to both the urbanization and globalization of the disease. There are nearly 300,000 infected people in USA, and 30,000 to 45,000 of these individuals have an unrecognized form of Chagas cardiomyopathy (ChCM) according to the Centers for Disease Control and Prevention [1, 2].

ChCM is the most harmful complication of Chagas disease. Its annual incidence among the patients with indeterminate form is 1.85 per 100 people-years [3]. Many exams, which can easily be performed on outpatients, provide valuable information about both the prognosis of ChCM and the presence of left ventricular systolic dysfunction. Serum BNP levels were described as inversely related to the left ventricular ejection fraction, with a high positive predictive value of 80% and an even higher negative predictive value of 97% to identify those patients with low left ventricular ejection fraction [4]. The BNP, or its analog, NT-proBNP, was also described as a marker of ventricular arrhythmias [5], and diastolic dysfunction [6, 7], as well as an independent predictor of death [8]. Therefore, considering these results, we assumed that high BNP levels are associated with heart failure (HF) and could be considered a surrogate marker of this condition.

The electrocardiogram (ECG) is a well-studied exam and has been considered an important tool for detection and evaluation of ChCM since the first years of its description [9]. Many of its abnormalities have been described as associated with a worse prognosis in ChCM and the need of further evaluation [10–13]. However, it is not reported how electrocardiographic alterations correlate to BNP. Because the ECG has a low cost and is a widely available exam, it can be useful in identifying those patients with a higher probability for NT-ProBNP alterations. Therefore, the present study, aims to describe the baseline electrocardiograms of a large cohort of patients with Chagas disease from an endemic area, named São Paulo-Minas Gerais Tropical Medicine Research Center cohort (SaMi-Trop Study), and to establish an association between the number of ECG alterations evaluated according to the Minnesota Code and high levels of NT-ProBNP in *T. cruzi* chronically infected individuals [14].

2. Material and Methods

2.1 Study Design

This report is a cross-sectional descriptive study of ECGs and serum NT-proBNP obtained from the baseline of a large cohort of patients with Chagas disease from endemic area named SaMi-Trop Study [14]. The SaMi-Trop consists of a network of collaborating

scientists in the States of Minas Gerais and São Paulo and has been established to develop and conduct research projects on Chagas disease. The SaMi-Trop study is a prospective cohort begun in 2013 with at least two years of follow-up. The baseline visit (2013 to 2014) was performed at public health primary care units by previously trained staff. The patients were interviewed using a standardized questionnaire, had a blood sample collected, and underwent an ECG evaluation [14]. Participants with missing or bad quality ECG were excluded from the analysis.

This study selected 1,959 Chagas disease patients who received medical care through the family health program team in 21 municipalities within a limited region in the northern part of the State of Minas Gerais, where the prevalence of patients with chronic ChCM was expected to be high [14]. All participants in the study provided written informed consent. The protocol was approved by the Brazilian National Institutional Review Board (CONEP), number 179.685/2012.

2.2 Electrocardiogram

A resting 12-lead ECG was recorded using an ECG PC machine (TEB, São Paulo, Brazil). The ECG recordings were sent electronically to the Telehealth system. ECG's measures were automatically analyzed using the University of Glasgow ECG analysis program (release 28.5, issued on January 2014), and the abnormalities were classified by a trained cardiologist using the Minnesota Code (MC) criteria [14].

Electrocardiograms were analyzed considering the typical abnormalities of Chagas disease described in the II Brazilian Consensus on Chagas disease [15]. ECG abnormalities included old myocardial infarction (major Q-waves abnormalities [MC 1.1.x or 1.2.x]) or possible myocardial infarction (minor Q-waves abnormalities with ST segment or T-wave abnormalities [MC 1.3.x and 4.1.x, 4.2, 5.1, or 5.2]), complete intraventricular blocks (MC 7.1, 7.2, 7.4, or 7.8), major isolated ST segment or T-wave abnormalities (MC 4.1.x, 4.2, 5.1 or 5.2), atrial fibrillation or flutter (MC 8.3.x.), major atrioventricular conduction abnormalities or pacemaker use (MC 6.1, 6.2.x, 6.8, 8.6.1 or 8.6.2), and heart rate lower than 40 bpm.

2.3 *Trypanosoma cruzi* infection status and NT-ProBNP Assay

All eligible participants were tested for the presence of anti-*T. cruzi* antibodies using chemiluminescent microparticle immunoassay. Negative results were confirmed by two other enzyme immunoassays presenting different antigens. The final cohort was comprised only by seropositive patients [14].

We measured the N-terminal of the prohormone BNP (NT-ProBNP) in every participant of this cohort at the baseline [14]. The obtained NT-proBNP values were considered high for the age range according to the established cut-off points [16, 17]:

- age < 50 years: NT-proBNP > 450 pg/mL;
- age 50–75 years: NT-proBNP > 900 pg/mL;
- age > 75 years: NT-proBNP > 1,800 pg/mL.

2.4 Statistical analysis

A descriptive analysis of the data with frequencies, means, medians of electrocardiographic variables, and major abnormalities were obtained. The groups were stratified according to sex and high NT-ProBNP levels, and were compared through conventional statistical methods. The groups were stratified by sex considering Pinto-Filho et al.'s results in a large cohort of Brazilian adults [18], which demonstrated a higher prevalence of major ECG abnormalities in men.

The Kolmogorov-Smirnov test was performed to evaluate normality. The variables with normal distribution were described as means and standard deviation, while those with asymmetric distribution were described as medians and the first to third interquartile range. The Mann-Whitney test was applied to compare the medians. To compare categorical variables, the chi-squared and the Fisher tests were used.

Logistic regression was applied to test the association of typical electrocardiographic abnormalities with high NT-ProBNP levels. Our model was first adjusted to age and sex, and in a more complete model, it was adjusted to the presence of 1, 2, 3, or more than 3 classical cardiovascular risk factors, including: hypertension, diabetes mellitus, current smoking, chronic kidney disease, previous myocardium infarction and high cholesterol. All analyses were made using SPSS Statistics 20 (Chicago, Illinois). A 2-sided p-value<0.05 was considered statistically significant.

3. Results

The clinical characteristics of the participants are listed in Table 1. Most of this population consisted of women and low- income participants. Almost 25% have used Benzonidazol to treat Chagas disease. NT-proBNP levels were suggestive of HF in 11.7% of this population.

The electrocardiographic parameters and measurements stratified by sex and by NT-proBNP levels are described in Table 2. The elevated NT- pro BNP group has a different median QRS duration, PR interval, QTc interval (Hodges), QRS, and T-axis than the normal NT- pro BNP group.

Table 3 summarizes the prevalence of major typical abnormalities among men and women and among normal and elevated NT-pro BNP groups. The most frequent abnormalities in the cohort were right bundle branch block (RBBB), followed by major isolated ST segment abnormalities; right bundle branch block associated with anterior fascicle block (RBBB + AFB); and major Q wave abnormalities. It was observed that men have more major ECG abnormalities than women. Those with elevated NT-pro BNP levels had more major abnormalities, with atrial fibrillation, major Q waves and RBBB + AFB being the most frequent and in that order.

The number of ECG abnormalities was distributed as follows: 845 (44.2%) patients had 1 abnormality, 216 (11.3%) patients had 2 abnormalities, and 23 (1.2%) patients had 3 abnormalities. The odds of association between one or more ECG alterations and NT-proBNP elevation was 9.12 (95% CI 5.62–14.80) in multivariate regression (Hosmer and

Lemeshow test 0.42) (Table 4). Considering the association between the number of 1, 2 and 3 or more alterations in electrocardiogram and NT pro BNP elevation the odds were 7.11 (95% CI 4.33–11.67); 16.04 (95% CI 9.27–27.77) and 47.82 (95% CI 17.98–127.20) respectively (Hosmer and Lemeshow test 0.64) (Table 4). No major difference was observed between the unadjusted and the adjusted models. The impact of the number of electrocardiogram alterations on NT- proBNP is illustrated in Figure 1.

4. Discussion

This cross-sectional population-based study showed that men have more frequent electrocardiographic abnormalities than women, and that these alterations occur more often in the group with high NT-proBNP levels. The presence of major ECG abnormalities increases the odds of NT-proBNP elevation, and this relation becomes stronger if more than one abnormality coexists. Those who showed any major abnormality on the electrocardiogram had a risk of 8.12 times higher to NT-proBNP elevation. This analysis suggests that, in addition to what other studies have shown, electrocardiogram abnormalities could be useful as a marker of heart failure [10, 11, 19, 20].

For the sake of higher specificity, we the present analysis included only the major typical abnormalities associated with Chagas disease [15]. Some alterations, which may well be important for this population, have been excluded, such as low QRS voltage [21] and frequent supraventricular and ventricular premature beats [22, 23]. The electrocardiograms were analyzed by the Minnesota Criteria, which is an international standard that makes our analysis objective and reproducible in other studies as well as in clinical settings.

Although not adjusted to covariates, our analysis suggests that the elevated NT- pro BNP group has a longer QRS duration, PR and QTc intervals (Hodges), and more deviated QRS axis. These alterations were demonstrated in previous studies as related to a worse prognosis. The median QRS duration in the elevated NT- pro BNP group was 144 ms (116–162). This abnormal value is consistent with other studies that showed an association of a long QRS interval to disease evolution, HF and death [11, 24–26]. The elevated NT-pro BNP group also presented a longer mean QTc interval which has been reported in other studies as being associated with death [12] and HF [25].

Patients with high NT-pro BNP levels also had deviation of the QRS axis with a median of –52 degrees. The abnormal QRS axis was associated with the risk of increased mortality [13]. Although the elevated NT-pro BNP group has a normal T-axis median, it is different from the normal group, which may indicate a worse prognosis as shown in other studies [13, 27].

There is no typical distribution of electrocardiographic variables between the genders that could have clinical significance. In this cohort, men had more major ECG abnormalities than women, which was observed in a Brazilian healthy population [18] and was described in Chagas disease patients [28]. Nevertheless, sex had no significant impact on the final model.

As observed in previous studies, the most frequent abnormalities were RBBB, major isolated ST segment abnormalities, RBBB + AFB and major Q wave abnormalities [10, 29, 30]. It is

important to notice that RBBB and major ventricular repolarization abnormalities have a similar prevalence between the groups with normal and elevated NT-proBNP. They happen in the early course of the disease; therefore, these patients may not have heart failure yet.

The natriuretic peptides (BNP or NT-proBNP) are important severity markers of heart failure and left ventricular ejection fraction reduction in Chagas disease [4–8]. These were also associated with diffuse myocardial fibrosis in asymptomatic individuals [31], which could indicate their potential to be an early marker of the disease. These have a great significance in the clinical setting when considering that, in post-beta-blocker era, the end stage of heart failure is the main cause of death in Chagas disease patients [21, 32]. Once the association of typical electrocardiographic abnormalities to this death marker has been established, the ECG is also strengthened as a disease severity marker. Considering these results, a close follow-up of Chagas disease patients should be recommended in the indeterminate form, since the appearance of a first typical ECG abnormality is a marker of the development of cardiomyopathy and heart failure. Even those who have established cardiomyopathy would benefit from a closer monitoring when presenting an increase in the number of typical alterations.

This is a cross-sectional study, so it must be viewed as a first step in the evaluation of electrocardiographic abnormalities in the SaMi-Trop cohort. Although our analysis suggests that they are related to higher NT-pro BNP levels, and these results are consistent with other studies, one should take caution to establish prognostic relations. The present study measured only prevalence of elevated NT-proBNP levels, not their incidence, which will be conducted if we can gather further data from this cohort. This study main hypothesis is that Chagas disease itself causes the myocardial damage and leads to ECG alterations and NT-proBNP elevation. Nevertheless, we should take into account that the remodeling effects of heart failure on the myocardium can produce and increase the number of ECG alterations.

5. Conclusion

The most frequent abnormalities identified in the patients who had the Chagas cardiomyopathy are in accordance to other important populational studies. Men had more major ECG abnormalities than women. Typical electrocardiographic alterations of Chagas disease are related to greater odds of NT-proBNP elevation, which is a marker of the severity of the cardiomyopathy. This association presents no major changes even if we consider other cardiovascular risk factors, gender and age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1-

Association between the number of electrocardiographic alterations and NT-proBNP

Table 1 –

Clinical characteristics of the cohort population in baseline

Characteristics	Total (n=1.959)	Men (n=636)	Women (n=1.323)
Age (years)	59 (49– 69)	59 (49 – 68)	59 (50 – 69)
Ethnicity			
White	21.7	21.5	22.0
Mixed	58.4	58.9	58.4
Black	17.8	17.9	17.8
Asian	1.4	1.3	1.4
Indigenous	0.3	0.5	0.2
Literacy	55.7	57.1	55.4
Per capita income	300 (160–500)		
Never smoked [#]	66.9	42.7	78.6
Stopped smoking [#]	25.8	44.9	16.6
Present smoker [#]	7.3	12.5	4.9
High Cholesterol [#]	40.1	30.8	44.6
Diabetes [#]	10.1	7.5	11.3
Kidney disease [#]	7.3	6.9	7.5
Arterial Hypertension [#]	36.0	42.8	32.8
Previous myocardial infarction [#]	4.7	6.4	3.9
Without comorbidities [#]	29.3	36.0	26.1
Beta blocker use [#]	7.2	4.6	8.5
Amiodarone use [#]	22.0	22.6	21.7
Previous use of Benzimidazol [#]	25.2	24.6	25.5
Permanent pacemaker	6.2	8.2	5.3
High NT-proBNP levels adjusted for age	11.7	18.6	8.4
NT- proBNP	137 (60 – 384)	140 (50 – 603)	136 (64 – 325)
Heart rate	65 (58 – 73)	63 (56 –71)	66 (59 – 74)

* Data are expressed by percentage except Age, Per capita income, NT-proBNP and heart rate, which are expressed by medians and quartiles.

[#] Self-reported data

Table 2 –
Electrocardiographic interval and measurements in SaMi-Trop according to sex and NT-pro BNP levels

Variables *	Men (n=623)	Women (n=1,287)	P	Normal NT-pro BNP (n=1,680)	Elevated NT-pro BNP (n=226)	P
Heart Rate (bpm)	63 (56 – 71)	66 (59 – 74)	< 0.001	65 (58 – 73)	65 (58 – 77)	0.23
PR interval (ms)	168 (148 – 196)	158 (140 – 180)	< 0.001	160 (140 – 182)	180 (154 – 212)	< 0.001
QRS duration (ms)	116 (96 – 146)	102 (90 – 134)	< 0.001	102 (90 – 134)	144 (119 – 162)	< 0.001
P axis (degrees)	56 (29 – 70)	54 (31 – 66)	0.06	55 (32 – 66)	55 (3.7 – 76)	0.57
QRS axis (degrees)	-10 (-63 – 40)	5 (-33 – 37)	< 0.001	4 (-36 – 39)	-52 (-80 – 10)	< 0.001
T axis (degrees)	39 (7 – 65)	37 (13 – 60)	0.66	36 (12 – 59)	57 (-1 – 100)	< 0.001
P duration (ms)	114 (104 – 124)	110 (100 – 122)	0.001	112 (102 – 122)	112 (90 – 126)	0.82
QTc interval (Hodges) (ms)	436 (417 – 460)	443 (424 – 463)	< 0.001	437 (420 – 459)	461 (442 – 475)	< 0.001

Bpm = beats per minute; ms = milliseconds.

* Represented by the median and the first to third interquartile range

Table 3 – Major electrocardiographic alterations present in SaMi – Trop evaluated according to the Minnesota Code criteria

Alterations	Total (n=1,910)	Men (n=623)	Women (n=1,287)	P	Normal NT- proBNP (n=1,680)	High NT- proBNP (n=226)	P
Major Q-wave abnormalities	10.5	14.1	8.8	<0.001	9.1	21.2	<0.001
Minor Q-wave plus ST- T abnormalities	1.4	1.0	1.6	0.29	1.4	1.3	1.00
Major isolated ST-T abnormalities	11.9	9.5	13.1	0.02	12.0	11.9	1.00
LBBB	4.0	4.7	3.7	0.33	2.9	12.4	<0.001
RBBB	19.9	19.1	20.3	0.54	19.8	20.8	0.71
Intraventricular block	2.5	3.9	1.8	0.006	2.1	4.9	0.01
RBBB + AFB	11.3	15.2	9.6	<0.001	10.1	20.4	<0.001
Atrial fibrillation	4.5	6.7	3.3	0.001	2.0	22.6	<0.001
Atrial flutter	0.3	0.5	0.2	0.36	0.2	0.9	0.15
Pacemaker	3.6	5.6	2.6	0.001	2.1	14.6	<0.001
2 nd AV block	0.4	0.8	0.2	0.04	0.4	0.4	0.58
3 rd AV block	0.2	0.2	0.2	1.00	0.1	0.9	0.07
Heart rate < 40 bpm	0.7	1.1	0.5	0.10	0.4	2.7	<0.001
Any major alteration	56.8	62.4	54.0	0.001	52.0	91.2	<0.001

Table 4 –

Logistic regression analysis testing the association between the number of electrocardiographic alterations and NT-pro BNP elevation

Number of ECG alterations	Odds Ratio (95% CI)		
	Unadjusted	Adjusted by age and sex	Adjusted by age, sex and number of risk factors (1, 2, 3 or more)
1	7.23 (4.47 – 11.71)	6.91 (4.26 – 11.21)	7.11 (4.33 – 11.67)
2	16.97 (9.97 – 28.86)	15.58 (9.11 – 26.66)	16.04 (9.27 – 27.77)
3	62.70 (24.30 – 161.71)	45.46 (17.26 – 119.67)	47.82 (17.98 – 127.20)
One or more alterations	9.50 (5.94 – 15.18)	8.45 (5.52 – 14.18)	9.12 (5.62 – 14.80)