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ANORMALIDADES ELETROCARDIOGRÁFICAS TÍPICAS E NT-PRO BNP ELEVADO NA DOENÇA DE CHAGAS

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RESUMO

INTRODUÇÃO: Desde que foi descrita a cardiopatia chagásica, o eletrocardiograma desempenha papel essencial na avaliação dos pacientes. O diagnóstico da cardiopatia chagásica é definido pela presença de alterações típicas em indivíduos soropositivos a despeito da presença de sintomas. Ele pode ser útil para identificar os pacientes com pior prognóstico e aqueles com maior probabilidade de ter o NT-proBNP elevado. Não se conhece a relação entre as anormalidades eletrocardiográficas típicas e o NT-proBNP e seu análogo. OBJETIVOS: Descrever os eletrocardiogramas da linha de base uma grande coorte de pacientes portadores da doença de Chagas que moram em área endêmica e estabelecer associação entre o número de alterações eletrocardiográficas típicas e níveis elevados de NT-proBNP em pacientes portadores da doença de Chagas. MÉTODO: Foram selecionados 1.959 pacientes portadores da doença de Chagas atendidos pelo Programa de Saúde da Família em 21 municípios da região norte de Minas Gerais. RESULTADOS: A cardiopatia chagásica acomete 1.084 pacientes da coorte. Os níveis de NT-proBNP eram sugestivos de insuficiência cardíaca em 11,7% dessa população. Houve importante associação entre a presença de uma ou mais alterações eletrocardiográficas e NT-proBNP elevado com OR: 9,12 (IC 95% 5,62 – 14,80) em regressão logística multivariada. Considerando a associação entre o número de alterações de 1, 2 e 3 ou mais e o NT-proBNP elevado o OR foi 7,11 (4,33 –11,67); 16,04 (9,27 – 27,77) e 47,82 (17,98 – 127,20) respectivamente. CONCLUSÃO: A presença e o número de alterações eletrocardiográficas típicas da doença de Chagas foram independentemente associados à gravidade da cardiopatia chagásica.

Palavras-chave: cardiopatia chagásica; eletrocardiograma; peptídeo natriurético cerebral

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 1959 Chagas disease patients in 21 municipalities within a limited region in the northern part of the State of Minas Gerais (Brazil), 1084 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.

Key Words: Chagas cardiomyopathy; Electrocardiography; Brain Natriuretic Peptide

LISTA DE ABREVIATURAS E SIGLAS

São Paulo – Minas Gerais Tropical Medicine Research Center ..... SaMi-Trop

Eletrocardiograma e *Electrocardiogram* ..... ECG

Chagas Cardiomyopathy ..... ChCM

Organização Pan Americana de Saúde ..... OPAS

Código de Minnesota ..... CM

Polymerase chain reaction ..... PCR

Infarto agudo do miocárdio ..... IAM

Chagas disease ..... ChD

Heart failure ..... HF

N-terminal of the prohormone BNP ..... NT-proBNP

Right bundle branch block ..... RBBB

Left anterior hemiblock ..... LAH

Left ventricular ejection fraction ..... LVEF

Ventricular extra systoles ..... VES

Left bundle branch block ..... LBBB

Pacemaker rhythm ..... PM

Atrioventricular block ..... AVB

Electrical inactivity ..... EI

Ventricular repolarization ..... VR

Atrial fibrillation ..... AF

Myocardium Infarction ..... MI

Low QRS voltage LV

Rede de Telessaúde de Minas Gerais ..... RTMG

Statistical package for social sciences ..... SPSS

World Health Organization ..... WHO

Positive predictive value ..... PPV

Negative predictive value ..... NPV

SUMÁRIO

1. CONSIDERAÇÕES INICIAIS

A doença de Chagas foi descrita em 1909 pelo grande cientista e médico brasileiro Carlos Justiniano Ribeiro Chagas que, num dos maiores feitos da ciência mundial, descreveu não só os aspectos clínicos como também seu agente causal, o *Trypanosoma cruzi*, e o principal mecanismo de transmissão, a inoculação do parasita presente nas fezes dos Triatomíneos(1). Embora a transmissão sido parcialmente controlada, ainda hoje a doença acomete cerca de 6 milhões de pessoas no mundo, a cada ano se registram 30.000 novos casos e 14.000 óbitos segundo a Organização Pan Americana de Saúde (OPAS) em documento de 2016(2). Inicialmente restrita à zona rural dos países da América Latina onde morava a maioria dos pacientes, ela se urbanizou e se tornou globalizada com os movimentos migratórios(3). Ela tem grande impacto na economia mundial: dados conservadores estimam um gasto de US$ 7,19 bilhões/ano(4). Uma grande proporção dos danos se deve à morbi-mortalidade da doença que acomete os indivíduos em fase produtiva. Os gastos estimados excedem aqueles de doenças que recebem maior atenção da comunidade médica como o câncer de colo uterino(4).

A cardiopatia chagásica é uma doença heterogênea com grande variação em sua apresentação clínica e no seu prognóstico(5). A morte súbita e a insuficiência cardíaca são causas bem conhecidas de morte desses pacientes, especialmente naqueles com a função do ventrículo esquerdo deprimida(5). O acidente vascular cerebral também foi identificado como importante causa de morbi-mortalidade. A insuficiência cardíaca nos cardiopatas chagásicos quando comparada a outras cardiopatias em estágios semelhantes têm maior mortalidade (6, 7), pior qualidade de vida e maior número de hospitalizações (7).

As alterações eletrocardiográficas podem predizer o aparecimento de insuficiência cardíaca, acidente vascular cerebral isquêmico e o risco de morte nos cardiopatas chagásicos. Sendo o eletrocardiograma um exame de baixo custo e amplamente disponível, ele tem papel

primordial na avaliação desses pacientes. Entretanto, a maioria dos estudos de prognóstico foi realizada com populações de portadores de doença de Chagas, não exclusivamente com os cardiopatas. Temos até hoje uma única coorte que incluiu apenas cardiopatas chagásicos (8); o escore preditor gerado tem uma variável eletrocardiográfica corroborando a importância do eletrocardiograma (ECG) na avaliação e prognóstico dos cardiopatas chagásicos. É possível que alterações importantes para a população de chagásicos como um todo não tenham o mesmo valor prognóstico nos chagásicos já sabidamente cardiopatas.

A coorte do Estudo SaMi-Trop é composta por 1.084 portadores de alterações eletrocardiográficas maiores e permitirá avaliar a evolução eletrocardiográfica desses pacientes. Esta será a maior análise de eletrocardiogramas de cardiopatas chagásicos em uma coorte já registrada. Quando ingressei no mestrado os ECG da linha de base (2013-2014) já tinham sido revisados conforme o Código de Minnesota pelo cardiologista Jorge Sette. Coube a mim fazer a revisão dos ECG da segunda onda (2015-2016) e da terceira onda (2018-2019). Nessa dissertação de mestrado sob a orientação do Prof. Dr. Antônio Luiz Pinho Ribeiro descrevemos os eletrocardiogramas dessa população em sua linha de base e a relação das alterações eletrocardiográficas maiores com idade, sexo, fatores de risco para doença cardiovascular e o NT-proBNP. Em um segundo momento, com o acompanhamento da coorte e a repetição dos exames realizados na linha de base, poderemos avaliar a influência das alterações do ECG no prognóstico dos indivíduos.

2. REVISÃO DA LITERATURA

Title page

Article title: Electrocardiogram in Chagas disease

Running title: Brito BO - Electrocardiogram in Chagas disease

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Title: Electrocardiogram in Chagas disease

Structured Abstract:

Since the initial descriptions of Chagas Cardiomyopathy (ChCM), the electrocardiogram (ECG) has played a key role in patient evaluations. The chronic ChCM diagnosis is defined by the presence of typical ECG abnormalities in seropositive individuals, regardless of the presence of symptoms. However, these abnormalities are rarely specific and, particularly among the elderly, can be caused by other simultaneous cardiomyopathies, which can predict the occurrence of heart failure, stroke, and even death. Nevertheless, most prognostic studies have included Chagas Disease (ChD) populations, and not exclusively ChCM. Thus, more studies are needed to evaluate the efficiency of ECGs to produce reliable prognoses in established chronic ChCM.

Keywords: Chagas disease. Electrocardiogram. Heart Failure. Stroke. Death. Prognosis.

1. Introduction

Since the initial descriptions of Chagas Cardiomyopathy (ChCM), the electrocardiogram (ECG) has played a key role in patient evaluations. Chagas and Villela considered that arrhythmia constitutes the predominant symptom of such a cardiomyopathy (1). Although there are many unclear aspects of Chagas disease (ChD), the ECG is a well-known method to diagnose and define ChD prognoses. Moreover, it is a low-cost and widely used exam, even in remote areas.

The chronic ChCM diagnosis is defined by the presence of typical ECG abnormalities in seropositive individuals, regardless of the presence of symptoms (2). It is the most severe and frequent form of ChD and affects 20% to 40% of all chronic ChD patients (3). During the course of disease, the ECG presents progressive abnormalities that indicate myocardial damage and its worsening (4, 5). Maguire et al. demonstrated that in 6 years 20% of the ChD patients developed abnormalities, while it only occurred in 10% of seronegative individuals (4). A more recent study found an incidence of cardiomyopathy of 1.85 per 100 people-years. (6) Chronic ChCM appears in three basic syndromes, all of which can coexist in an individual patient: heart failure, cardiac arrhythmia, and thromboembolism. Clinical presentation varies widely according to disease duration and the extent of myocardial damage (3).

This review exclusively discusses the role of the 12-lead electrocardiogram in the clinical evaluation of the chronic form of ChD.

2. Search method

Data for the present review were identified through a PubMed and Lilacs search using the following MeSH terms: “Chagas Cardiomyopathy” OR “Chagas Disease” AND “Electrocard*”. The search was performed in February, 2018 and considered all studies conducted with humans. The original search identified 576 articles. However, after reading

the titles and abstracts to find any and all terms related to ECG alterations and to 12-lead ECG, only 120 were selected for a complete reading of the entire text. After having read the texts, only 49 articles met the criteria for this investigation. In order to describe the relation between ChD and stroke, a new search was conducted using the following MeSH terms: “Chagas Cardiomyopathy” OR “Chagas Disease” AND “Stroke”. This search identified 140 studies, only 7 of which met the inclusion criteria.

3. Prevalence of electrocardiographic alterations

The ECG abnormalities were more prevalent in ChD individuals than in seronegative ones, as has been consistently demonstrated in many studies (7-13). A retrospective observational study assessed 264,324 primary care patients, including 7,590 self-reported ChD patients. Only 31.45% had normal ECG versus 61.15% of the seronegative group (7). In addition to having a higher prevalence of abnormal ECG, ChD patients also presented more abnormalities per tracing, and the proportion of those with more than three alterations reached nearly 20% (7, 14). Although the number of ECG alterations increases with aging, it is more expressive in ChD individuals (7, 15). Maguire et al., upon examining a rural area population, also identified that abnormal ECG is more frequent in seropositive patients and that it is more remarkable in those between 25 and 44 years of age (10). These authors also showed that ECG abnormalities are more frequent in men than in women (26.1% x 15.3%) (10). This same research group described the progressive nature of ECG alterations during a 6 years follow-up (4), in which the incidence o ECG abnormalities proved to be higher in seropositive individuals, and no new abnormality was found in the elderly.

The progressive nature of ECG alterations in the elderly is controversial and needs to be clarified. In an elderly cohort (8), with a mean age of 68 years, 86.9% of ChD patients presented ECG abnormalities, as compared to 75.8% of the seronegative patients ($p<0.001$).

These findings indicate that only a small portion of ChD elderly patients have the indeterminate form of ChD, contrary to that reported in prior literature. The higher prevalence of ECG abnormalities in seropositive people indicates that they are not only explained by other cardiopathies, but also by the progression of ChCM. It was further demonstrated that ECG alterations and their associations are related to a higher risk of death in ChD elderly patients (8). This may be due to the continuous process of cardiac damage beginning with the infection in childhood and continuing during the patients' entire adulthood, leading to a higher frequency of ECG abnormalities, which is an established cardiomyopathy marker, in infected elderly patients, as compared to non-infected patients (8).

ChD can cause any type of ECG alteration, but a predominance of conduction disturbances and ventricular extra systoles are the most common. ChD seems to evolve from the normal ECG to those with mild alterations then to defined typical abnormalities. Thus, after the first unspecific alterations, there is a tendency for even more complex abnormalities to occur on the same ECG (4, 16, 17). The possibility of a regression in alterations in nearly 8% of all ChD patients, particularly those related to ventricular depolarization and repolarization, as well as to ventricular extra systoles (VES) (18, 19). However, the disappearance of ECG abnormalities must be viewed as a consequence of ECG mutability, not as a regression (18, 19).

The prevalence of each abnormality depends on the studied population, as shown in Table 1, which describes the results from observational studies that evaluated more than 200 ChD individuals. In Table 1, Right bundle branch block combined with Left anterior hemiblock (RBBB + LAH) cases are not included in the Right bundle branch block (RBBB) count unless they are signalized. Given that most of the studies are Brazilian and that Rosenbaum (20) was a pioneer in ChD studies, we choose to include his work in this table despite the use of a population of less than 200 ChD patients. Many studies have shown a

remarkable preponderance of the prevalence of the RBBB (7, 10, 11, 16, 20-22) and its strong association with ChD (7, 10). Marcolino et al. found an Odds Ratio of 10.73 (95% Confidence Interval (CI): 10.10 - 11.41), which improved when RBBB was combined with LAH (OR: 12.09, 95% CI 11.20-13.04) (7). The combination of RBBB to LAH was more prevalent in ChD than in other cardiomyopathies (11, 23). It must also be highlighted that the Left Bundle Branch Block (LBBB) is much less frequent in ChD (24).

ChCM patients have longer PR interval (10, 14, 15) and QRS complex duration (14, 15) when compared to seronegative patients. Moreover, as a consequence of conduction disturbances, ChCM has a strong association with Pacemaker (PM) rhythm (OR: 13.29%, 95% CI: 11.47-15.40) as well as with second degree (OR: 4.05, 95% CI: 2.47-6.63) and third degree (OR: 13.29, 95% CI: 11.47 - 15.40) Atrioventricular Block (AVB) (7).

The presence of electrical inactivity (EI), whether isolated or combined with other alterations on the ECG, was associated with ChCM (22, 25). Its prevalence ranges from 0.5% to 30% among the studies in the literature. EIs are often associated to ventricular conduction disturbances and VES (10, 22), which could show a more extensive myocardial damage and a worse survival rate (26, 27).

Ventricular repolarization (VR) abnormalities are quite frequent (13, 14), the prevalence of which ranges from 0.2% to 40% (27). These tend to occur in the early course of the disease (28) and, before the occurrence of other abnormalities, are not related to a worse prognosis (28, 29). Prata et al. considered them unspecific (13), as they could be the consequence of diffuse myocarditis (13, 28), autonomic dysfunction, or even malnourishment (13). Although VR alterations and EIs are usually associated with coronary artery disease, the ChCM patients presented normal coronary arteries (30, 31). Moreover, the ischemia shown in the scintigraphy of these patients proved not to be associated with ECG alterations or thoracic pain (30, 31) nor with severe wall motion abnormalities when at rest (31).

Atrial Fibrillation (AF) is often associated with ChD (OR: 3.15, 95% CI: 2.83-3.51) (7), and its prevalence is higher in the elderly (7, 13) and in men (7), ChCM has a similar prevalence of AF when compared to the other cardiomyopathies (23). Thus, it can be understood that this arrhythmia is more indicative of an advanced cardiac disease than of a specific alteration (14).

VES is a high frequency abnormality (13, 22, 24) and is associated with a worse prognosis (17). However, the 12-lead ECG does not recognize the transitory character of this ventricular arrhythmia nor does it allow for the evaluation of its severity (26). These alterations can also occur in the ECG of healthy people and are unable to differentiate the seropositives from the seronegatives. Although they are typical of ChCM, they should not be considered specific (26).

Table 1. Prevalence of electrocardiographic alterations in Chagas disease among the studies

Author (year)	N Sample	Mean Age	RBBB	RBBB + LAH	LBBB	VR	EI	VES	AF/Flutter	PM	AVB 1st or 2nd	AVB 3rd	LV
Rosenbaum,1955 (20)	130 (H)	47	48.4	-	2.3	37.0	-	47.0	14.6	-	6.1	3.8	13.0
Laranja, 1956 (32)	683 (P)	-	48.3	-	2.2	12.9	-	42.6	6.6	-	28.1	8.2	-
Dias e Kloetzel, 1968 (29)	387 (P)	-	11.3	-	0.5	4.9	-	17.0	1.8	-	2.8	2.6	-
Maguire, 1983 (10)	346 (P)	-	5.8	4.6	-	9.0	0.6	7.5	-	-	1.4	-	-
Arteaga, 1985 (22)	553 (H)	46	10.6	25.3	2.3	30.9	30.7	18.8	4.4	-	5.5	11.2	-
Pereira e Coura, 1986 (33)	255 (P)	-	18.4	-	-	18.0	5.5	14.5	1.2		6.6	-	2.7
Acquatella, 1987 (34)	775 (P)	47.7	16.7	-	0.7	19.6	5.9	20.1	3.8	-	4.2	0.5	-
Barretto, 1989 (27)	1004 (O)	41.5	40.7	-	2.0	40.4	38.5	29.0	4.2	-	10.4	5.6	-
Pontes Prata, 1993 (13)	2000 (O)	45.5	32.4	-	1.9	28.2	7.1	42.2	9.0	-	10.8	3.9	1.2
Garzon e Lorga, 1995 (26)	1010 (O)	-	33.3	-	3.1	26.7	25.1	40.3	2.5	-	6.0	5.6	7.0
Salles, 2004 (35)	738 (O)	46.3	14.1	24.3	3.3	7.7	3.7	14.5	-	-	6.5	-	-
Rassi, 2006 (36)	424 (H)	47	18.6	24.3	7.1	27.8	6.6	37.3	3.1	-	9.0	-	9.0
Williams-Blangero, 2007 (15)	722 (P)	41.9	15.2	5.2	-	-	-	-	0.7	-	-	-	-
Gonçalves, 2011(37)	2120 (P)	-	3.7	2.9	0.5	13.3	9.8	4.3	0.2	-	1.0	-	0.1
Ribeiro, 2013 (14)	497 (P)	48	16.1	3.6	0.6	4.6	2.4	2.4	0.4	1.0	3.0	0	3.4
Ribeiro, 2014 (8)	557 (P)	69	23.2#	9.2#	3.2	11.3	5.9	10.1	6.1	1.1	6.8	0.5	2.5
Marcolino, 2015 (7)	7590 (O)	57	22.7	13.7	3.0	0.2	1.5	5.4	5.3	3.5	5.1	0.2	-

Kind of Sample: H: Hospitalized; O: Outpatient; P: Population; # RBBB + LAH cases are included in the RBBB count

4. Eletrocardiographic alterations related to heart failure

The ECG of ChD patients can show us valuable information about a patient's evolution to heart failure (HF). The main studies which evaluated this aspect are described in Table 2. In ChD patients, there is a significant correlation between a QRS duration > 100ms and reduced left ventricle ejection fraction (LVEF) and increased dimensions of the left ventricle in diastole (38). However, the QRS duration does not correlate to regional abnormalities of left ventricle contraction nor to the presence of apical aneurisms. Hence, QRS is unable to predict a normal left ventricle (38). The importance of QRS duration in this cross-sectional study is corroborated by an 8-year follow-up cohort, which concluded that the only isolated electrocardiographic variable which correlated with a drop of 5% or more in the LVEF and with an increase in diameter of the left ventricle in diastole was the QRS duration (39). The appearance of new ECG abnormalities also correlated to a drop in the LVEF (39).

Ribeiro et al. reinforced this finding in 2013 when they reported that the QRS duration > 120ms and that the QT interval > 440ms present a moderate accuracy through which to predict reduced LVEF in ChD patients (14). The same study also identified the abnormalities most frequently associated with LVEF in ChD (14), among which were: frequent supraventricular premature beats, VES, AF, RBBB, possible old MI, and major isolated ST-T abnormalities (14). These results corroborate findings from Barreto et al. who identified a higher incidence of ECG abnormalities in ChCM populations in classes III and IV (New York Heart Association), namely: VES ($p < 0.001$), ventricular conduction disturbances ($p < 0.001$), EI ($p < 0.001$) and VR alterations ($p < 0.001$) (27). The combination of ventricular conduction disturbances with VES or with sinusal bradycardia was associated with both reduced LVEF and an increased left ventricle diameter (40).

The QRS score estimates the fibrosis area, considering the alterations of amplitude, duration, and morphology of Q, R, and S waves. Each point corresponds to an area of 3%

fibrosis in the left ventricle (41). A QRS score > 2 points had the highest accuracy for predicting the presence of any late gadolinium enhancement and the reduced LVEF in cardiac resonance (41).

Table 2. Electrocardiographic alterations related to heart failure in Chagas disease

Cohort studies					
Author (year)	**N**	**Population**	**End Points**	**Follow up**	**Prognostic factors**
Pereira et al, 1985 (18)	248	ChD X Seronegatives	Progression to HF	6 years	EI, VR, VES incidence
Acquatella et al, 1987 (34)	775	With and without cardiomyopathy	Functional class (NYHA)	5 years	Abnormal ECG
Barretto et al, 1989 (27)	1004	ChD	Functional class (NYHA), Cardiothoracic index	2 years	Higher incidence of abnormal ECG in NYHA III and IV.
Ianni et al, 2001 (5)	159	ChD indeterminate form	LVEF	98.6+/-30.4 months	Incidence of new ECG alterations had no impact on LVEF
Nascimento et al., 2012 (39)	152	With and without cardiomyopathy	Drop of 5% of LVEF, Diameter of the left ventricle in diastole	6.8 years	QRS duration and appearance of new ECG alterations.
Cross-sectional studies					
Author (year)	**N**	**Population**	**End Points**	**Follow up**	**Prognostic factors**
Casado et al., 1990 (40)	44	ChCM without HF	LVEF, left ventricle volume	Cross-sectional	Association of ECG alterations in the same tracing.
Ribeiro et al., 2000 (38)	98	With and without cardiomyopathy	LVEF, Diameter of the left ventricle in diastole	Cross-sectional	QRS >100ms.
Salles et al., 2003 (42)	738	With and without cardiomyopathy	LVEF	Cross-sectional	QTd >60ms, VES >10%, LBBB
Marques et al., 2006 (25)	106	Assymptomatic chronic ChD	Diastolic and systolic dysfunction	Cross-sectional	Presence of typical ECG alterations
Strauss et al., 2011(41)	44	With and without cardiomyopathy	Late gadolinium enhancement area, reduced LVEF	Cross-sectional	QRS score
Ribeiro et al., 2013 (14)	1000	With and without cardiomyopathy	LVEF	Cross-sectional	QTc interval, QRS duration.

5. Electrocardiographic alterations related to stroke risk in Chagas disease

ChD is an independent risk factor for stroke incidence (43-45), even when compared to a population with a high risk for this outcome (44), and can reach an Odds Ratio of 7.17 (95% CI: 1.50–34.19) (44). Furthermore, the elderly ChD patients who have had a stroke have a higher risk of death than do seronegative patients (46). The Cox model to evaluate death due to a stroke in ChD identified that AF is a variable with higher HR: 3.87 (CI 95% 1.26–11.91), followed by BNP (46). Although AF is an important risk factor in the genesis of ischemic stroke related to ChD, one study showed that the occurrence of AF was not associated with strokes in ChCM patients (47), while the presence of LV thrombus and apical aneurysm were. These results could be the consequence of the study's cross-sectional character as well as the protection provided by anticoagulation.

Sousa et al. (48) elaborated a score to evaluate thromboembolic risk in ChD. These authors identified as independent risk variables: LV systolic dysfunction HR: 13.21 (CI 95%: 4.72-37), apical aneurysm HR: 2.32 (CI 95%: 1.09-4.95), and VR alterations on the 12-lead ECG HR: 2.62 (IC 95%: 1.20-5.7) (48). Another study illustrated that the incidence of stroke is higher in patients with mild LV dysfunction (mean LVEF of 48%), when compared to those with severe dysfunction (mean LVEF of 36%) (49), and that there was no association with the presence of thrombus in the left atrium. This reinforces the role of ECG abnormalities as predictors of strokes.

6. Eletrocardiographic alterations related to death risk in Chagas disease

The main causes of death in ChD are HF, sudden death and stroke with a predominance of the first (28, 50, 51). Although the majority of patients show clinical evidence of HF before sudden death, almost one-third of these events occur in asymptomatic individuals, who seldom have normal clinical and radiographic exams and who rarely have

normal ECGs (52, 53). ECG carries much important information about mortality that must be analyzed in the clinical exam. Table 3 summarizes the studies that showed ECG alterations related to the risk of death.

The patients with normal ECGs have a life expectancy compatible with their gender and age (4, 50), while those with abnormalities have a higher mortality rate (4, 53) even if there is no other sign of HF (50). The mortality rate increases when the individual with altered ECG develops HF.

Combined ECG alterations in the same patient are related to a higher mortality rate (28). The presence of three or more alterations indicates a bad prognosis. There has been a preponderance of sudden death in those who presented VES together with RBBB or primary T-wave alterations. However, when RBBB is associated with VR alterations, the death caused by HF was more common (28). The number of alterations in the ECG was also a predictor of death in one ChCM patients cohort (8). In this cohort, the combination of RBBB to LAH was the most heavily related to death (8), which is in accordance to other studies (27, 53-55).

The alterations of P, QRS, and T axes represent a risk of death HR: 1.48 (95% CI 1.16-1.88); 1.34 (95% CI 1.04-1.73) and 1.35 (95% CI 1.07-1.71) (56). T-wave axis deviations (>-15° to > -180° or >105° to < 180°) were also associated with death in another study (35). A wider QT interval was related to death possibly as a determining factor of sudden arrhythmic death (57). This same study identified that EI is a prognosis variable (57), which is in accordance with a previous study (27).

The analysis of the only cohort comprised solely of ChCM patients was published in 2006 (36). The final model indicated that only one 12-lead ECG variable increased the death risk: low QRS voltage (LV) HR=1.87 (95% CI 1.03-3.37). It must be highlighted that LV did not predict adverse outcomes in other cohorts. It is possible that the ECG alterations

important to the prognosis of ChD patients as a whole group do not have the same prognostic value in ChD patients with established cardiomyopathy.

Table 3. Electrocardiographic alterations related to death in Chagas disease

Author (year)	N	Population	Follow up	Prognostic factors
Porto, 1964 (28)	503	With and without cardiomyopathy	5 years	VES, number of ECG alterations
Espinosa et al., 1985 (50)	107	With and without cardiomyopathy	10 years	ECG alterations, HF symptoms
Acquatella et al., 1987 (34)	775	With and without cardiomyopathy	5 years	ECG alterations, Functional class
Maguire et al., 1987 (4)	1017	ChD X Seronegatives	7 years	Incidence of ECG alterations
Barretto et al., 1989 (27)	1004	ChD	2 years	Higher incidence of VES and IE
Espinosa et al., 1991 (58)	66	With and without cardiomyopathy	12 years	AF
Bestetti et al., 1993 (53)	24	ChD who had sudden death	Case control	ECG alterations (VES 79%; LAH 58%; RBBB 37%; VR alterations 41%; EI 25%, AVB 1st 16%; AF 16%
Salles et al., 2003 (57)	738	With and without cardiomyopathy	58 +/- 39 months	EI, QTd > 65ms increments; QTc Bazet >465ms
Salles et al., 2004 (35)	738	With and without cardiomyopathy	58 +/- 39 months	T-axis deviation (>-15° to >-180° or >105° to < 180°)
Viotti et al., 2005 (54)	856	ChD with cardiomyopathy without HF and ChD without cardiomyopathy	8 years	Intraventricular conduction disturbances; Ventricular tachycardia
Rassi et al., 2006 (36)	424	ChD with cardiomyopathy	7.9 +/- 3.2 years	LV of QRS
Gonçalves et al., 2010 (55)	120	ChD	24 years	RBBB + LAH, LBBB, Polymorphic ventricular tachycardia, PR interval > 0.16s.
Ribeiro et al., 2014 (8)	1462	Elderly with and without cardiomyopathy	10 years	Presence and number of major ECG alterations (Minnesota code); RBBB + LAH was the most important alteration.
Moraes et al., 2018 (56)	1426	General population (38% with ChD)	12.8 years	Abnormal axis of P, QRS and T waves.

7. Conclusions

Electrocardiographic abnormalities are frequent in ChD and define the presence of cardiomyopathy. However, they are not specific and, particularly among the elderly, can be caused by other simultaneous cardiomyopathies.

These abnormalities can predict the occurrence of HF, stroke, and death. Nevertheless, most prognostic studies have included ChD populations, not exclusively ChCM. Thus, more studies are needed to evaluate the ECG's real prognosis in established chronic ChCM.

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3. OBJETIVOS

- Descrever os eletrocardiogramas da linha de base da coorte *São Paulo – Minas Gerais Tropical Medicine Research Center* (SaMi-Trop);

- Estabelecer associação entre o número de alterações eletrocardiográficas avaliadas conforme o Código de Minnesota e valores elevados do NT-proBNP em pacientes portadores da doença de Chagas crônica.

4. MATERIAL E MÉTODOS

4.1 Desenho do estudo SaMi-Trop

O estudo SaMi-Trop (9) consiste em uma rede de colaboração de pesquisadores dos estados de Minas Gerais e São Paulo que foi estabelecida para conduzir projetos de pesquisa relacionados à doença de Chagas financiado pelo NIH através do *grant* para Centros de Referência em Medicina Tropical. Foi delineada uma coorte prospectiva iniciada em 2013, com pelo menos 2 anos de seguimento, e posteriormente estendido até 2019.

A coorte de pacientes foi estabelecida através do Serviço de Telecardiologia da Rede de Telessaúde de Minas Gerais (RTMG) que recebe eletrocardiogramas e a história clínica de pacientes em uma central de análise. Todos os eletrocardiogramas e dados clínicos dos pacientes são encaminhados para uma central de leitura que também coleta dados clínicos sobre os pacientes como a história de doença de Chagas. Foram selecionados 21 municípios do norte de Minas Gerais onde se esperava que a prevalência de cardiopatia chagásica crônica fosse elevada (Figura 1). Os pacientes elegíveis foram selecionados através dos ECG realizados entre 2011 e 2012 que, daquele momento em diante, seriam os eletrocardiogramas índice. A Figura 2 mostra como a coorte foi constituída.

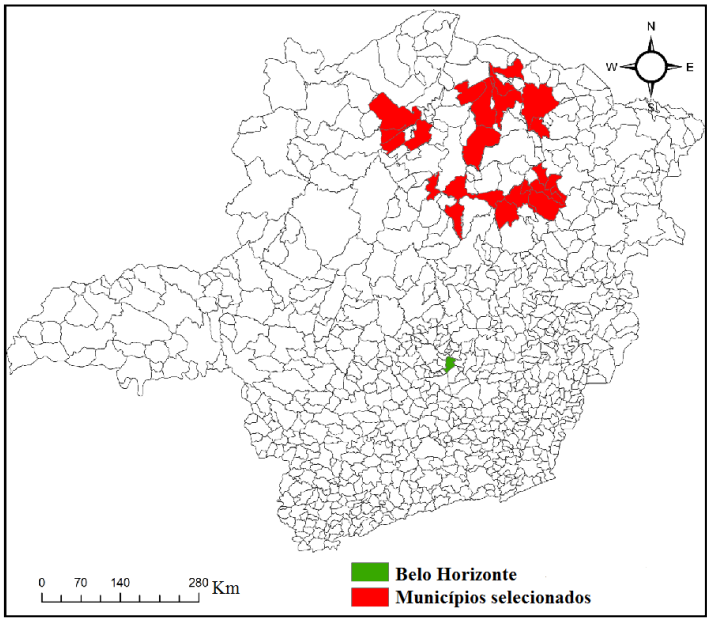
Todos os pacientes elegíveis foram recrutados pelo Programa de Saúde da Família entre 2013-2104. A visita inicial a eles foi feita na Unidade Básica de Saúde por equipe

previamente treinada. Foi utilizado um questionário padrão para entrevistá-los e os mesmos tiveram suas amostras de sangue coletadas e eletrocardiogramas realizados. Os questionários aplicados aos pacientes continham informações sociodemográficas, determinantes sociais de saúde, comportamentos relacionados à saúde (tabagismo, consumo de álcool e atividade física), comorbidades auto-relatadas, medicações em uso, história de tratamento prévio para Doença de Chagas, sinais e sintomas da doença, classe funcional, e qualidade de vida (WHO-QOL-BREF). Todos os dados foram encaminhados ao banco de dados na Universidade de São Paulo via internet.

Foi realizado um eletrocardiograma de 12 derivações basal em repouso de todos os pacientes usando um aparelho de ECG conectado a computador (TEB, São Paulo, Brasil). Os eletrocardiogramas foram enviados via rede para a RTMG e laudados por cardiologistas treinados. Os laudos foram encaminhados para os médicos dos pacientes.

Todos os participantes elegíveis foram testados para a presença de anticorpos anti- *T. cruzi* usando Imunoensaio com Micropartículas Quimioluminescentes. Os resultados negativos foram confirmados por dois outros imunoensaios enzimáticos com diferentes antígenos. A coorte final é composta de pacientes confirmados como soropositivos.

Figura 1. Localização geográfica dos municípios do Projeto SaMi- Trop (9)



4.2 Critérios de inclusão

Foram elegíveis apenas os pacientes que preencheram todos os seguintes critérios de inclusão:

1) Doença de Chagas auto-reportada;

2) Idade maior ou igual a 19 anos;

3) Presença de eletrocardiograma basal alterado na avaliação de 2012-2013.

4.3 Critérios de exclusão

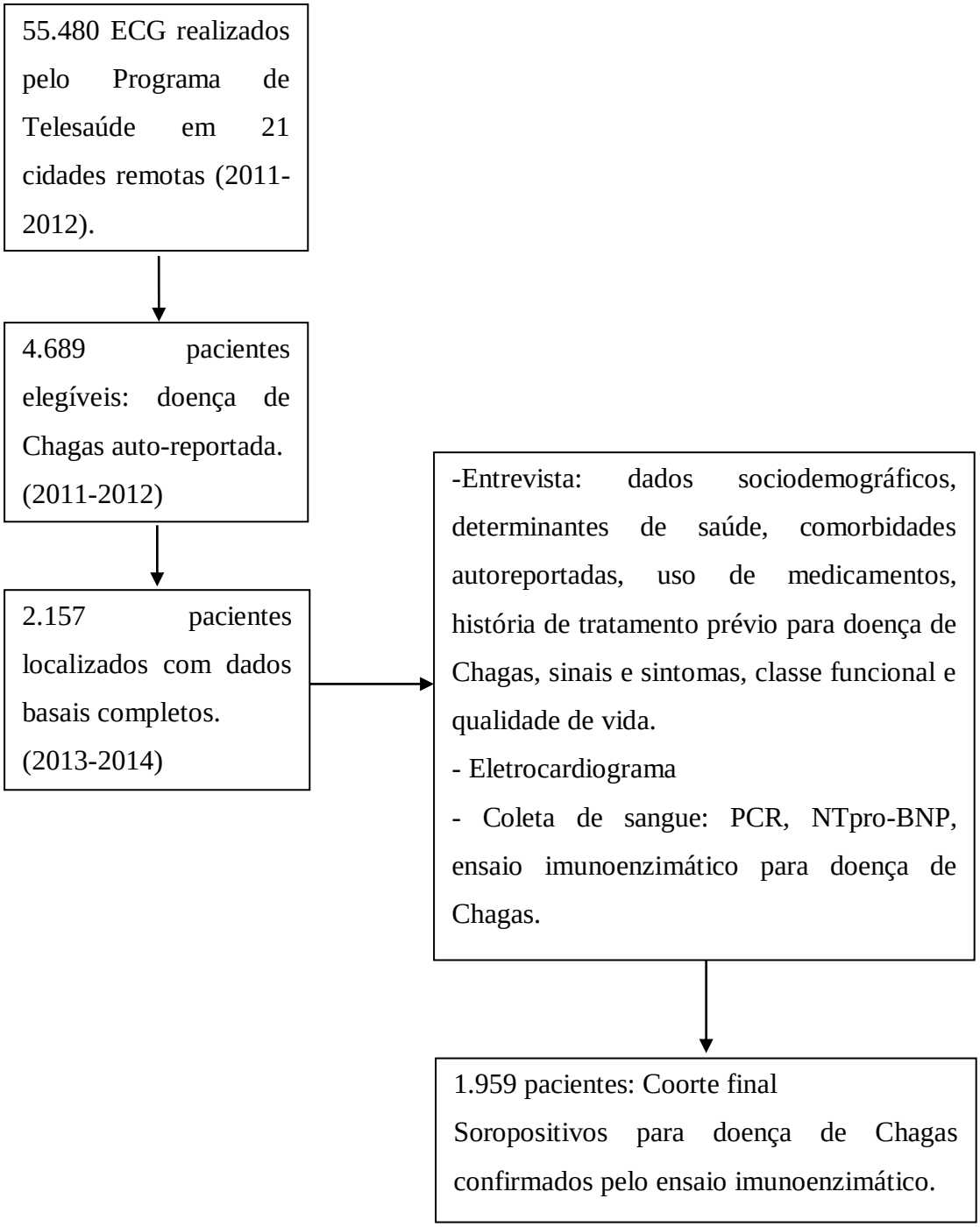
Foram excluídos os seguintes pacientes:

1) Gestantes ou mulheres que amamentavam

2) Portadores de doenças muito graves com prognóstico de sobrevida menor que dois anos.

Todos os participantes do estudo assinaram o termo de consentimento livre esclarecido. O protocolo do estudo foi aprovado pelo CONEP, número 179.685/2012.

Figura 2. Diagrama de constituição da coorte do Projeto SaMi-Trop



4.4 Amostras de Sangue

As amostras de sangue foram coletadas em tubos separadores de plasma e deixadas para coagular em temperatura ambiente por 30 minutos. As amostras de plasma foram centrifugadas a 1300g por 10 minutos. Após, elas foram armazenadas a – 20ºC e depois encaminhadas em gelo seco para laboratório central em São Paulo.

As amostras de sangue foram analisadas para PCR do T. cruzi e NT- proBNP. Os valores do NT-proBNP obtidos foram considerados altos para as faixas de idade conforme pontos de corte estabelecidos (10, 11):

- Idade < 50 anos: NT-proBNP> 450 pg/mL;
- Idade 50-75 anos: NT-proBNP> 900 pg/mL;
- Idade > 75 anos: NT-proBNP> 1.800pg/mL.

4.5 Eletrocardiogramas

Foram obtidos eletrocardiogramas índices dos pacientes no momento de sua inclusão no estudo e dois anos após no seguimento. Os ECG de repouso de 12 derivações foram gravados através da máquina ECG PC (TEB, São Paulo, Brasil) e enviados por meio de rede para a RTMG e analisados por Cardiologistas treinados. Para fins de pesquisa, o *software* de análise desenvolvido pelo Prof. Peter MacFarlane da Universidade de Glasgow (28.5, janeiro 2014) analisou e codificou os ECG pelo Código de Minnesota. A codificação pelo CM dos ECG da Onda 1 foi revisada por cardiologista experiente.

4.5.1 Código de Minnesota

A avaliação de eletrocardiogramas como ocorre habitualmente na prática médica traz em si certa subjetividade e falta de padronização. Importantes diferenças são encontradas mesmo na análise do mesmo médico em momentos diferentes. Considerando o importante

valor do eletrocardiograma em estudos epidemiológicos da Cardiologia e a necessidade de critérios objetivos e claros de análise foi desenvolvido o Código de Minnesota (CM). (12) Este código se tornou difundido internacionalmente e amplamente utilizado desde que foi incluído pela Organização Mundial de Saúde na série *Cardiovascular Survey Methods* publicada em 1968. Entretanto, seus autores advertem que apesar de classificar a morfologia dos traçados eletrocardiográficos baseado em critérios bem definidos, ele não produz a interpretação do ECG nem o diagnóstico de doenças cardiovasculares. (12)

A classificação das alterações eletrocardiográficas pelo CM encontra-se resumida na tabela 1. Considerando-se os padrões de onda Q e QS temos, por exemplo, o CM 1-1-4. O primeiro número do código define a anormalidade considerada, sendo no caso o número 1, ele se refere a padrões de onda Q e QS. Ele define presença simultânea de onda Q nas derivações aVF e DIII. A duração de Q deve ser ≥ 0,05 segundos na maioria dos batimentos gravados em DIII associado a onda Q de amplitude ≥ 1mm na maioria dos batimentos gravados em aVF. As ondas Q em aVF não precisam ter duração ≥ 0,02 segundos nesse código. Os códigos iniciados por 1-, 4-, 5-, e o 9-2 (elevação do segmento ST) são agrupados por derivações, resultando em três subclassificações de acordo com a parede analisada: anterolateral, posterior e anterior. (12)

A tabela 2 mostra os códigos de supressão. Uma vez definido um código principal, como o 7-2-1 (Bloqueio Completo do Ramo Direito), não se admite o acréscimo dos seguintes códigos associados àquele: 1-3-8, todos os códigos 2-, 3-, 4-, e 5-, 9-2, 9-4, 9-5.

Tabela 1. Classificação das anormalidades do ECG pelo Código de Minnesota

Código	Anormalidade do ECG
1-1-1.....1-3-6	Padrões de onda Q e QS
2-1.....2-5	Desvio do eixo QRS
3-1.....3-4	Ondas R de elevada amplitude
4-1-1.....4-4	Depressão da junção (J) e do segmento ST
5-1.....5-4	Itens da onda T
6-1.....6-8	Defeitos da condução átrio-ventricular
7-1-1.....7-8	Defeitos de condução ventricular
8-1-1.....8-9	Arritmias
9-1.....9-8-2	Miscelânea incluindo elevação do segmento ST (9-2)

Tabela 2. Códigos de supressão do Código de Minnesota

Código	Código Suprimido
Todos os códigos Q e QS	7-6
Q > 0.03 na derivação D I	7-7
3-1	1-3-2
3-2	1-3-8, 7-3
6-1	Todos os códigos exceto 8-2
6-4-1	Todos os códigos
6-8	Todos os códigos
7-1-1	1-2-3, 1-2-7, 1-3-2, 1-3-4, 1-3-8, todos os códigos 2-, 3-, 4-, e 5-, 7-7, 9-2, 9-4, 9-5.
7-2-1	1-3-8, todos os códigos 2-, 3-, 4-, e 5-, 9-2, 9-4, 9-5
7-3	1-3-8
7-4	Todos os códigos 2-, 3-, 4-, e 5-, 9-2, 9-4, 9-5
8-1-2	8-2-4
8-1-4	8-1-1, 9-3
8-2-1	Todos os códigos
8-2-2	Todos os códigos
8-2-3	8-1-2
8-3-1	8-1-1, 8-1-2
8-3-2	6-2-2, 8-1-1, 8-1-2
8-3-3	8-1-1, 8-1-2
8-3-4	6-2-2

8-4-1	6-5
8-4-1 + Frequência cardíaca ≥140bpm	Todos os outros códigos exceto 7-4 ou 6-2
Frequência cardíaca>100bpm	6-5
8-4-2	8-1-1
9-1	Todos os códigos 2-

4.5.2 Análise dos eletrocardiogramas do estudo SaMi-Trop

Os ECG foram analisados considerando-se as alterações maiores do Código de Minnesota (CM) descritas como típicas no II Consenso Brasileiro de doença de Chagas. (13) As alterações maiores do CM, embora com pequenas variações entre os trabalhos, foram associadas a piores desfechos cardiovasculares em estudos epidemiológicos e são amplamente consideradas em sua metodologia. (14-18) Além da codificação, também foram feitas as medidas das ondas e dos intervalos do ECG pelo *software* de análise da Universidade de Glasgow (28.5, janeiro 2014). As alterações típicas avaliadas pelo CM são as seguintes:

- Infarto miocárdico (IAM) prévio (ondas Q maiores [CM 1.1.x ou 1.2.x]);

- Possível IAM (ondas Q menores associadas a alterações maiores de ST-T [CM 1.3.x mais 4.1.x, 4.2, 5.1, ou 5.2]);

-Bloqueio completo de ramo esquerdo (CM 7.1);

-Bloqueio completo de ramo direito (CM 7.2);

-Bloqueio intraventricular (CM 7.4);

-Bloqueio completo de ramo direito mais Hemibloqueio Anterior-esquerdo (CM 7.8);

-Alterações maiores de ST-T isoladas (CM 4.1.x, 4.2, 5.1 ou 5.2);

-Fibrilação ou flutter atrial (CM 8.3.x.);

-Bloqueio atrioventricular total (CM 6.1)

-Bloqueios atrioventriculares de segundo grau (CM 6.2.x);

-Marca-passo artificial (CM 6.8);

- Frequência cardíaca menor que 40bpm.

5. RESULTADO E DISCUSSÃO

Title: 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 1959 Chagas disease patients in 21 municipalities within a limited region in the northern part of the State of Minas Gerais (Brazil), 1084 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.

Key Words: Chagas cardiomyopathy; Electrocardiography; Brain Natriuretic Peptide

1. Introduction

Chagas disease (ChD) is caused by the protozoan parasite *Trypanosoma cruzi*. The World Health Organization (WHO) 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 ChD. 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 (PPV) of 80% and an even higher negative predictive value (NPV) of 97% to identify those patients with low 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). Several ECG abnormalities have been described in population-based studies as associated with a worse prognosis in ChCM and the need of further evaluation (10-13). However, the value of ECG abnormalities in predicting heart failure expressed by elevated NT-proBNP

levels has not been reported. 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 a 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 ChD. 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 as illustrated in Figure 1 (14). Participants with missing or undiagnosed quality ECG were excluded from the analysis.

This study selected 1,959 ChD 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 criteria (14).

Electrocardiograms were analyzed considering the typical abnormalities of ChD described in the II Brazilian Consensus on Chagas disease (15). ECG abnormalities included old myocardial infarction (MI) (major Q-waves abnormalities [MC 1.1.x or 1.2.x]) or possible MI (minor Q-waves abnormalities with ST segment or T-wave abnormalities [1.3.x and 4.1.x, 4.2, 5.1, or 5.2]), complete intraventricular blocks (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 40bpm.

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 (EIA) 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> 1.800pg/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 ChD. NT-proBNP levels were indicative 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- proBNP group has a different median QRS duration, PR interval, QTc interval (Hodges), QRS, and T-axis than the normal NT- proBNP group.

Table 3 summarizes the prevalence of major typical abnormalities among men and women and among normal and elevated NT-proBNP groups. The most frequent abnormalities in the cohort were right bundle branch block, followed by major isolated ST segment abnormalities; right bundle branch block plus antero superior hemiblock; and major Q wave abnormalities. It was observed that men have more major ECG abnormalities than women. Those with elevated NT-proBNP levels had more major abnormalities, with atrial fibrilation, major Q waves and complete right bundle branch block plus antero superior hemiblock 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 ratio of association between any ECG alteration 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 proBNP 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 2.

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 ChD(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- proBNP 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-proBNP

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-proBNP 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-proBNP 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 eletrocardiographic 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 the literature in ChD patients (28). Nevertheless, sex had no significant impact on the final model.

As observed in previous studies, the most frequent abnormalities were right bundle branch block (RBBB), major isolated ST segment abnormalities, RBBB + LAH and major Q wave abnormalities(10, 29). 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, many of these patients may not have heart failure yet.

The natriuretic peptides (BNP or NT-proBNP) are important severity markers of heart failure and LVEF reduction in ChD (4-8). These were also associated with diffuse myocardial fibrosis in asymptomatic individuals (30), 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 ChD patients (21, 31). 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 ChD 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. The analysis of the only cohort comprised solely of Chagas cardiomyopathy patients was published in 2006 (21). The final model indicated that only one 12-lead ECG variable increased the death risk: LV. It must be highlighted that LV did not predict adverse outcomes in other cohorts. It is possible that the ECG alterations important to the prognosis of ChD patients as a whole group do not have the same prognostic value in ChD patients with established cardiomyopathy.

The present study has limitations. Left ventricular systolic function, the main prognostic risk factor in most cardiopathies, has not been directly evaluated in this work. The NT-proBNP was used as a surrogate marker of heart failure because its analog BNP has been described as inversely related to the left ventricular ejection fraction (4) and to worse outcomes in Chagas disease (5, 7, 8). There are few studies about NT-proBNP in Chagas disease and none of them establishes cut-off points for heart failure identification. Therefore, values obtained from heart failure general population studies were used (32, 33). Dividing patients into three age groups (of <50, 50–75, and > 75 years) yielded the optimal diagnostic accuracy. Positive predictive values for heart failure categorized by age were 76, 83 and 92 for the groups of <50, 50–75, and > 75 years respectively (33). NT-proBNP levels are also influenced by obesity, glomerular filtration rate and atrial fibrillation (16, 17). It is also important to consider that the cardiovascular risk factors included to adjust the logistic regression model were self-reported. Thus, they are influenced by the patients memory and comprehension of their health condition.

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-proBNP 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 ChD 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

Typical eletrocardiographic alterations of ChD are related to greater odds of NT-proBNP elevation, which is a marker of cardiomyopathy's severity. This association presents no major changes even if we consider other cardiovascular risk factors, such as gender and age. Men had more major ECG abnormalities than women. This study also found a longer PR interval, QTc and QRS duration, as well as altered QRS axis in the group with elevated NT-proBNP. The ECG is a simple and accurate method to predict ChD prognosis and should be performed periodically in all patients suffering from this condition in order to guide their clinical management.

Figure 1 - The SaMi-Trop Project diagram

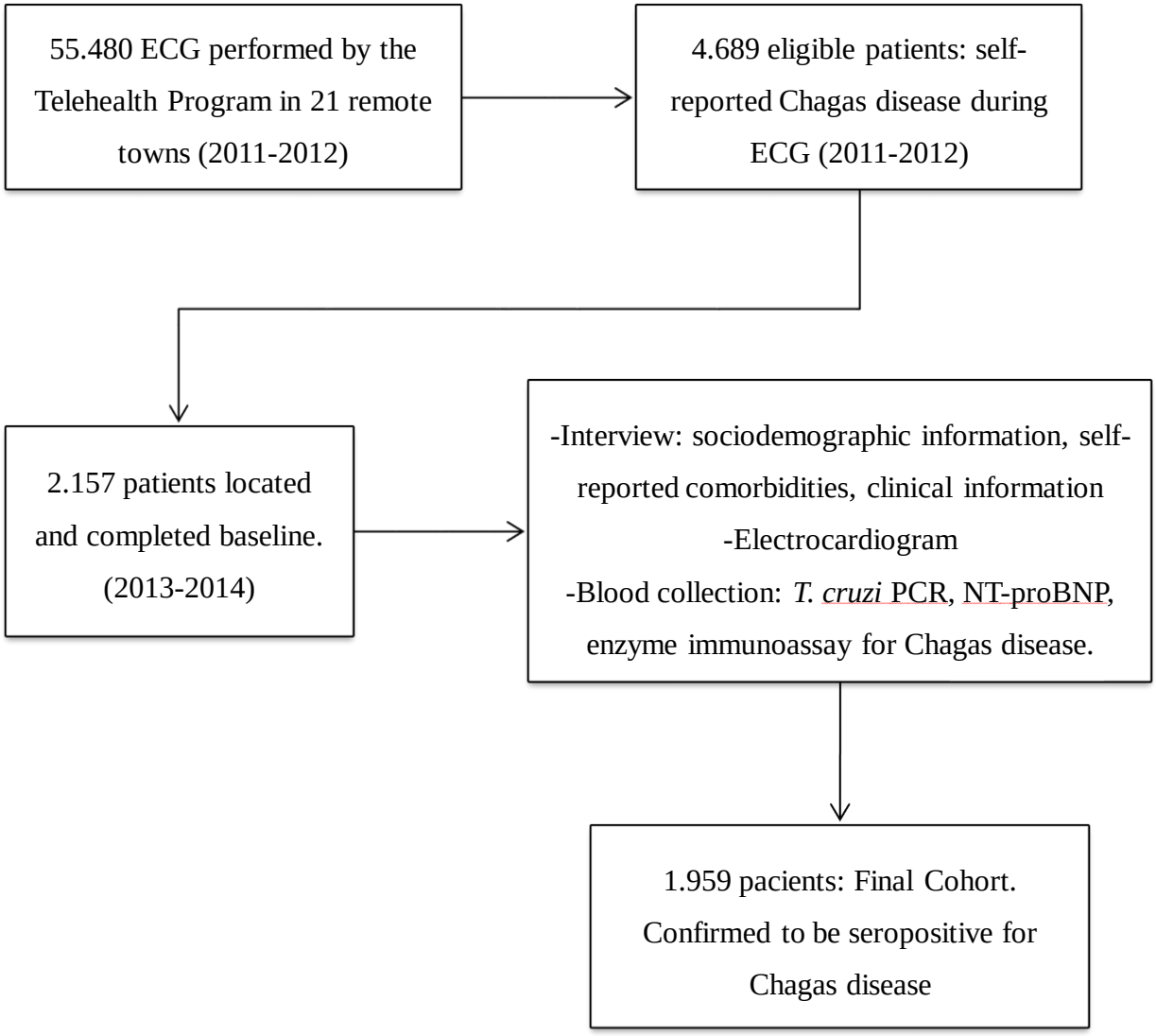


Table 1 – Clinical characteristics of the cohort population in baseline

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 capta 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
Amiodarona use[#]	22.0	22.6	21.7
Previous use of Benzonidazol[#]	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 capta income, NT-proBNP and heart rate, which are expressed by medians and quartiles. # Self-reported data.

Table 2 – Eletrocardiographic interval and measurements in SaMi-Trop according to sex and NT-proBNP levels

Variables *	**Men (n=623)**	**Women (n=1.287)**	**P**	**Normal NT-proBNP (n=1.680)**	**Elevated NT-proBNP (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

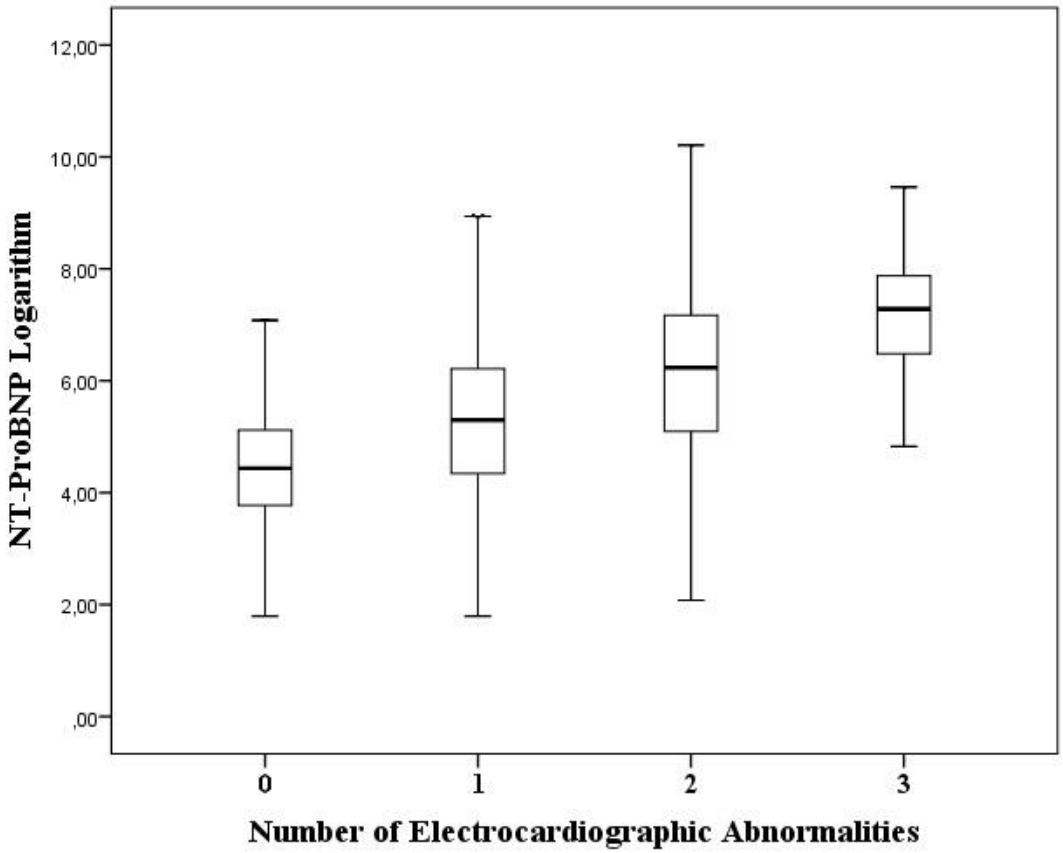
Table 3 – Major eletrocardiographic alterations present in SaMi – Trop evaluated according to the Minnesota Code criteria

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 + LAH	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 < 40bpm	0.7	1.1	0.5	0.13	0.4	2.7	< 0.001
Any major abnormality	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 eletrocardiographic alterations and NT-proBNP elevation

Number of ECG abnormalities	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 abnormalities	9.50 (5.94 – 15.18)	8.45 (5.52 - 14.18)	9.12 (5.62 – 14.80)

Figure 2- Association between the number of eletrocardiographic alterations and NT-proBNP



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6. CONSIDERAÇÕES FINAIS E CONCLUSÃO

O eletrocardiograma, essencial para o estabelecimento do diagnóstico da cardiopatia chagásica, é um exame amplamente disponível e de baixo custo. Ele agrega importantes informações sobre a evolução da doença e suas alterações podem predizer o aparecimento de insuficiência cardíaca, acidente vascular cerebral e o risco de morte.

A coorte do estudo SaMi-Trop é composta por 1.959 pacientes portadores da doença de Chagas, sendo 1.084 indivíduos portadores de alterações eletrocardiográficas maiores. Trata-se de uma grande coorte populacional de portadores da doença de Chagas acompanhada em área endêmica com um número expressivo de cardiopatas chagásicos. Identificou-se que os pacientes com NT-proBNP elevado têm mais alterações eletrocardiográficas típicas que aqueles com NT-proBNP normal, e que os homens apresentam maior proporção de alterações que as mulheres. A presença de qualquer anormalidade eletrocardiográfica típica aumenta a chance do paciente apresentar insuficiência cardíaca em 8,12 vezes em relação àqueles que não apresentam as alterações. Essa chance aumenta à medida que se associam alterações típicas num mesmo traçado independente de outras covariáveis. Os pacientes com NT-proBNP elevado também apresentam maiores medianas de intervalos PR e QTc (Hodges) e maior mediana de duração do complexo QRS, além de eixo do QRS mais desviado; essas alterações foram associadas em outros estudos à maior mortalidade, e à prevalência e incidência de insuficiência cardíaca.

Essa é a primeira vez na literatura em que se estabelece a associação do ECG com o NT-proBNP e que se estratifica a força da associação do número anormalidades com marcador de gravidade da cardiopatia chagásica. Isso fortalece a necessidade de sua realização periódica no acompanhamento dos pacientes, principalmente naqueles que moram em áreas remotas, onde o acesso ao ecocardiograma, ao NT-proBNP e aos serviços médicos é muito restrito.

Em um segundo momento, com o acompanhamento da coorte e a repetição dos exames realizados na linha de base, poder-se-á avaliar a influência das alterações do eletrocardiograma no prognóstico dos cardiopatas chagásicos. Com a descrição dessa população em sua linha de base realizada nesta dissertação, pudemos compreender melhor a relação das alterações eletrocardiográficas típicas com idade, sexo, fatores de risco para doença cardiovascular e o NT-proBNP. A metodologia de análise dos eletrocardiogramas é objetiva e reprodutível tornando possível a comparação com outros estudos e a aplicação dos resultados na prática clínica. A amostra de cardiopatas chagásicos obtida tem tamanho expressivo, sendo superior à da maioria das coortes estudadas. Dessa forma, a coorte do estudo SaMi-Trop poderá ser referência no estudo da cardiopatia chagásica.

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ANEXO A

MEDICINA
USP
COMITÊ DE ÉTICA EM PESQUISA

APROVAÇÃO

O Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, em sessão de **07/03/2012, APROVOU** o Protocolo de Pesquisa nº **042/12** intitulado**: "CENTRO DE PESQUISA DE BIOMARCADORES EM DOENÇAS TROPICAIS NEGLIGENCIADAS DE SÃO PAULO/MINAS GERAIS"** apresentado pelo **Departamento de MOLÉSTIAS INFECCIOSAS E PARASITÁRIAS**

Cabe ao pesquisador elaborar e apresentar ao CEP-FMUSP, os relatórios parciais e final sobre a pesquisa (Resolução do Conselho Nacional de Saúde nº 196, de 10/10/1996, inciso IX.2, letra "c").

O pesquisador deverá aguardar a aprovação da CONEP para iniciar a pesquisa.

Pesquisador (a) Responsável: Ester Cerdeira Sabino
Pesquisador (a) Executante: Antonio Luiz Pinho Ribeiro

CEP-FMUSP, 08 de Março de 2012.

Prof. Dr.Roger Chammas
Coordenador
Comitê de Ética em Pesquisa

Comitê de Ética em Pesquisa da Faculdade de Medicina
e-mail: cep.fmusp@hcnet.usp.br

ANEXO B

Version 24_01_2012

STUDY ID: [__][__][__][__][__][__][__][__][__]

Patient's Initials: [__][__][__][__][__]

SAMI TROP PROJECT

"Markers of prognostic in cronic Chagas cardiopathy"

Questionnaire I - Visit

University of São Paulo – Medical Tropical Institute
Telehealth Program: Federal University of Minas Gerais.

1.) City _____

2.) Date of interview: [__][__]/[__][__]/[__][__][__][__]
(day/month/year)

3.)Interviewer's ID number (RG):: [__][__][__][__][__][__][__][__][__]

3.a)Interviewer's Name:
[__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__]
[__][__][__][__][__][__][__][__][__][__][__]

Tópico I- Demographic information:

1.) Study ID:[__][__][__][__][__][__][__][__][__][__][__][__][__]

2.) Age: [__][__][__](years)

3.) Sex: [__] Male [__] Female

4.) Date of Birth: [__][__]/[__][__]/[__][__][__][__]

5.) Place of birth – City:

[__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__]

[__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__]

6.) State of Birth : [__][__]

[__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__]

[__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__][__]

Version 24_01_2012

STUDY ID: [__][__][__][__][__][__][__][__][__]

Patient's Initials: [__][__][__][__][__]

Topic II – Subject characteristics

Now we are going to ask you some general questions:

1.) What is your color?
[__] Caucasian
[__] Black
[__] Yellow (Asian)
[__] Mulatto
[__] Indian
[__] Refused to answer

2.) What is your educational level?
[__] Adult alphabetizing
[__] Never been to school
[__] I have been to school but I did not complete Elementary school
[__] Elementary school
[__] High school
[__] College or technical school
[__] Graduate school
[__] Master degree
[__] Doctor degree
[__] Refused to answer

3.) What is your total family income? R$_____,00.
(Must be included all monthly income of all people that live in the same house of the participant)
.
[__] **Refused to answer** [__] **I do not know**

3.a) How many people live in your house including you?

_____

FOR ALL PARTICIPANTS

Topic III- Lifestyle and Health

Now we are going to ask you some questions about your lifestyle and your current health. Please answer each question as completely as possible.

4.) Which of the following statements best describes your use of cigarettes?

[__] Never smoked (Skip to question 18)
[__] Used to smoke but don't anymore
[__] Currently smoke cigarettes
[__] Refused to answer

5.) If you currently smoke or when you used to smoke:

[__] Smoked no more than 100 cigarettes in my entire life
[__] Smoked some days, but not every day
[__] Smoked less than a pack of cigarettes every day
[__] Smoked about one to two packs of cigarettes every day
[__] Smoked at least two packs of cigarettes every day
[__] Refused to answer

6.) How many times in the last 30 days have you drunk?

[__] Every day or almost every day
[__] 3 to 5 times a week
[__] 1 to 2 times a week
[__] Less than one time a week
[__] Didn't drink in the last 30 days (skip to question 20)
[__] Refused to answer

7.) How many drinks, in average, do you use to drink? (Obs: a drink is equal to a dose of distilled drink, a glass of beer or a glass of wine)

[__] 1 to 2
[__] 3 to 5
[__] more than 5 less than 10
[__] more than 10
[__] Don't Know
[__] Refused to answer

Physical Activity

8.) Do you participate in exercise or any physical activity where you exert yourself, such as sport? (eg.: football, tennis, running, swimming, etc..)

[__] Yes
[__] No (go to question 23)
[_ _] Refused to answer

8.a) How many days per week do you exercise or practice this activities)?

[__] 1 time per week
[__] 2 to 3 times per week
[__] 4 to 6 times per week
[__] Every day
[__] Refused to answer

8.b) How long does this activity take each time you do it?

[__] Less than 15 minutes
[__] 15 to 30 minutes
[__] 30 minutes to 1 hour
[__] 1 hour to 2 hours
[__] More than 2 hours
[__] Refused to answer

9.) Are you able to do the following each of the following physical activities:

9.1) Can you walk down a flight of 8 steps or more without stopping?

[__] Yes
[__] No
(If Yes go to 9.2, if No go to 9.4)

9.2a) Can you carry anything up a flight of 8 steps or more without stopping?

[__] Yes
[__] No

9.2b) Can you have sexual intercourse without stopping?

[__] Yes
[__] No
[__] Refused to answer

9.2c) Can you do outdoor work such as garden, rake, or weed?
[__] Yes
[__] No

9.2d) Can you slow dance?
[__] Yes
[__] No

9.2e) Can you walk at a normal pace on level ground?
[__] Yes
[__] No
(If Yes to any 9.2 question go to 9.3, if No go to question 10)

9.3a) Can you carry at least 11 kilograms (24 pounds) up a flight of 8 steps or more without stopping?
[__] Yes
[__] No

9.3b) Can you lift objects that weigh at least 36 kilograms (80 pounds)?
[__] Yes
[__] No
9.3c) Can you do outdoor work such as shovel or spade dirt?
[__] Yes
[__] No

9.3d) Can you do recreational activities such as soccer, basketball or volleyball?
[__] Yes
[__] No

9.3e) Can you walk at a face pace or jog slowly on level ground?
[__] Yes
[__] No

(Go to question 10)

9.4a) Can you stand and take a shower without stopping or sitting down?
[__] Yes

[__] No

9.4b) Can you change the sheets or remake a bed?
[__] Yes
[__] No

9.4c) Can you hang washed clothes out to dry?
[__] Yes
[__] No

9.4d) Can you clean windows, or mop floors?
[__] Yes
[__] No

(If No to any 9.4 question go to 9.5, if Yes for all the 9.4 questions go to question 10)

10.5) Can you dress yourself alone without stopping or receiving help?
[__] Yes
[__] No

11.) How do you feel physically when performing any of the following physical activities: climbing stairs, sweeping the sidewalk or home, car washing or other activities such as these?

[__] Do not feel fatigue, shortness of breath on exertion and palpitation;
[__] I feel sometimes, fatigue, shortness of breath on exertion and palpitation, but if I stop to rest or stop the activity, everything returns to normal;
[__] I feel good when at rest, but when doing any physical activity I feel shortness of breath on exertion, fatigue or palpitations;
[__] I'm uncomfortable even at rest and any physical activity makes me feel worse of shortness of breath on exertion, fatigue or palpitations.

12.) Use these codes to answer the following questions:

FOR THE INTERVIEW: SHOW TO THE PARTICIPANT THE RESPONSE CARD NUMBER 1

0 = I am not able to do
1 = I am able to do without help
2 = I am able to do with someone helping me
9 = I do not want to answer

[__] Are you able to perform heavy work in your home, such as: sweep across the yard, wash windows, wash bathrooms?

[__] Are you able to go up and down two flights of stairs without help?

[__] Are you able to walk one kilometer without getting tired? (10 blocks)

[__] Would you be able to do all the housework alone? Do all washing and cleaning?

[__] Could you cook?

[__] Would you be able to shop at the market and supermarket?

Topic IV - ANAMNESIS (Basic Medical History)

13.) Have you been told by a doctor or health professional that you have high cholesterol or cholesterol problems?
[__] Yes
[__] No (Skip to question 27)
[__] Don't Know
[__] Refused to answer

14.) If yes, have you been under medical treatment (taking medicine) for high cholesterol?
[__] Yes
[__] No
[__] Don't Know
[__] Refused to answer

15.) Have you been told by a doctor or health professional that you have tegumentar or visceral leishmaniasis, generally known as KALAZAR?

[__] Yes
[__] No (go to question 16)
[__] Don't Know
[__] Refused to answer

15.a) If YES, how long did you have this disease?

_____ Months/Years (mark the correct option according the time the patient informed)

16.) Have you been told by a doctor or health professional that you have Chagas disease?

[__] Yes
[__] No
[__] Don't know
[__] Refused to answer

16.a) If YES, how long have ago were you diagnosed with Chagas disease?

[__] Less than 1 year
[__] 1 to 5 years
[__] 5 to 10 years
[__] More than 10 years ago
[__] Don't know
[__] Refused to answer

17.) Are you under medical care for Chagas disease at this time?

[__] Yes
[__] No
[__] Don't know
[__] Refused to answer

17.a) If YES, can you tell us where?

[__] In this Health Unit (the same Unit Health where the interview is been conducted)
[__] Another place
[__] Refused to answer

17.b) Name of place _____

TOPIC V. TREATMENT

18.) Have you ever take the medicine called ROCHAGAN OR BENZONIDAZOL?

[__] Yes
[__] No (go to question 25)
[__] Don't know
[__] Refused to answer

If YES, please answer the following questions.

19.) How long ago did you take this medicine for the FIRST TIME?

[__] days (go to question 20)
[__] months (go to question 20)
[__] years (go to question 20)
[__] I do not know (go to question 20)
[__] Refused to answer (go to question 20)
[__] I am taking this medicine actually (go to question 19a.)

19.a) I have been taking this medicine since ___/___/_____.

20.) What was the duration of your first treatment?
[__] days
[__] months
[__] years
[__] I do not know
[__] Refused to answer (go to question 21)

21.) What was the dose of the first treatment?

FOR THE INTERVIEWER: We need to know this information as detailed as possible. If the patient knows the number of tablets and the dose in milligrams, fill up both information.

[__] tablets per day
[__] mg per day
[__] I do not know
[__] Refused to answer

22.) How long after the diagnostic did you take this medicine?

[__] Immediately or less than one month
[__] months
[__] years
[__] I do not know
[__] Refused to answer

23.) Did you take this medicine more than one time?

FOR THE INTERVIWER: THIS QUESTION REFERS TO ANOTHER TREATMENT BESIDES THE FIRST ONE.

[__] Yes
[__] No (go to question 24b)
[__] Don't know
[__] Refused to answer

24.a) If YES, how many times did you take this medicine?

_____ times.

24.b) When was the last time that you took this medicine?
[__] months ago
[__] years ago
[__] I do not know
[__] refused to answer

25.) Have you ever taken the medicine called AMIODARONE or ATLANSIL?
[__] Yes
[__] No (go to question 28)
[__] Don't know
[__] Refused to answer (go to question 28)

If YES, please answer the following questions.

26.) How long did you take this medicine?
[__] days
[__] months
[__] years
[__] I do not know (go to question 27)

[__] Refused to answer (go to question 27)

27.) What was the dose of this medicine that you took?

FOR THE INTERVIEWER: We need to know this information as detailed as possible. If the patient knows the number of tablets and the dose in milligrams, fill both information.

[__] tablets per day
[__] mg per day
[__] I do not know
[__] Refused to answer

28.) Have you been told by a doctor or health professional that you have some of these health problems listed below?

CODES	1=Yes 2=No 3=do not know 4= Refused to answer
Diabetes	
Kidney problems	
Problems with blood clotting	
Myocardial infarction	
High blood pressure	
Thyroid disease	

29.) Identify from the below signs or symptoms the one or ones you have or have had:

	YES	NO
29.a) Do you feel pain when you swallow food?		
29.b) Do you have trouble swallowing or have the sensation of "food grasping" in your esophagus?		
29.c) Has a doctor, based on a chest X-Ray, told you that you have a big esophagus?		
29.d) Is it usual for you to have no bowel movement for 3 or more days? How many times has this happened to you in the last month? _____		
29.e) Has a doctor, based on a abdominal X-Ray, told you that you have a big colon?		

29.f) Do you feel unable to climb 2 flights of stairs without resting?		
29.g) Do you have heart palpitations?		
29.h) Do you have difficulty breathing when lying down?		
29.i) Have you ever felt prolonged faintness or dizzy?		
29.j) Have you experienced swelling or puffiness in your feet in the morning?		
29.k) Does your heartbeat sometimes race when resting?		
29.l) Have you noticed any visible neck veins in the mirror when standing up or sitting?		
29.m) Has your doctor told you that you have heart abnormalities or rhythm problems on electrocardiogram?		
29.n). Have you been told that your heartbeat is not regular?		
28.o) Do you have permanent pace maker insertion?		
29.p) Have you ever noticed your heartbeat racing or beating abnormally?		
29.q) Have you ever awaked during the night short breathed or not being able to breath?		
29.r) Do you feel short breath when you have to use physical strength, for example: climbing stairs or hills?		

30.) Do you take any of these drugs?

Medicine	YES	NO	Time of use (years)
Digoxina			
Furosemida			
Hidroclorotiazida			
Captopril			
Enalapril			
Losartan			
Espironolactona			
Carvedilol			

Hydralazine			
Mononitrato de isosorbide amlodipina			
Warfarin			
AAS			
Atenolol			
Propanolol			

31.) Have you ever had or have fainting or loss of consciousness?
[__] Yes
[__] No (go to question 32)
[__] I do not know
[__] Refused to answer

31.a) If YES, how many times it happened in the last two years?
[__][__][__] times
[__] I do not remember
[__] Refused to answer

31.b) Do you remember how long in average did each episode take?
[_____] minutes
[__] I do not remember
[__] Refused to answer

32.) Do you monitor your health in another service for other medical illness?
[__] Yes, just once
[__] Yes, more than one time
[__] No
[__] Refused to answer

33.) How do you rate your health condition today?
[__] Very good
[__] Good
[__] Average
[__] Bad
[__] Very bad
[__] I do not know
[__] Refused to answer

8. DECLARAÇÃO DE APROVAÇÃO

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FOLHA DE APROVAÇÃO

"Anormalidades Eletrocardiográficas Típicas e NT PRO BNP Elevado na Doença de Chagas"

BRUNO OLIVEIRA DE FIGUEIREDO BRITO

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