RELATÓRIO FINAL

Projeto de Pesquisa

DISFUNÇÃO AUTONÔMICA NA DOENÇA DE CHAGAS: MECANISMOS E IMPLICAÇÕES PROGNÓSTICAS

Processo nº. CDS – 1002-04

Coordenação

ANTONIO LUIZ PINHO RIBEIRO
DISFUNÇÃO AUTONÔMICA NA DOENÇA DE CHAGAS: MECANISMOS E IMPLICAÇÕES PROGNÓSTICAS

Projeto de Pesquisa

COORDENAÇÃO

Antonio Luiz Pinho Ribeiro

Relatório final

Belo Horizonte, Brasil
junho de 08
Avaliação de marcadores de prognóstico adverso na Doença de Chagas

1.1 Validação independente do escore de Rassi para predição de risco na doença de Chagas

Sumário

Introdução: D. Chagas é condição potencialmente fatal, de importância clínica e epidemiológica. A predição de risco de morte é um desafio, já que, a tripanossomiase apresenta curso clínico bastante variado com diferentes desfechos. Recentemente, um escore de risco foi publicado por Rassi e cols (NEJM-2006). O presente trabalho tem como objetivo validar o escore de Rassi em amostra independente com 165 pacientes, sabidamente portadores de doença de Chagas.

Métodos: 165 chagásicos seguidos por, em média, 78 meses. Submetidos a exame clínico, Rx de tórax, Ecocardiograma, Holter de 24h, ECG de 12 derivações e separados de acordo com a classe funcional pela NYHA. Os paciente foram divididos em 3 grupos, segundo o escore de Rassi, baixo, médio e alto risco de morte de acordo com pontuação distribuída pelas alterações nos exames supracitados.

Realizamos análise de sobrevivência através do método de Kaplan-Meier. Resultados: Dos 165 pacientes avaliados 115 foram classificados como de baixo risco, 44 como de médio risco e 6 como de alto risco. No primeiro grupo 3 (2,6%) indivíduos faleceram, no segundo foram 6 (13,6%) e no terceiro grupo 4 (66,7).

Conclusão: O risco de morte (ver tabela abaixo) em nossa amostra foi de 2,6% para o primeiro grupo, de 13,6% para o segundo e de 66,7% para o terceiro, índices muito próximos aos encontrados por Rassi e cols. O escore de Rassi mostrou-se útil em amostra independente para predizer risco de morte e pode ser usado na prática clínica.

Publicação resultante:

Temas livres apresentados:
1.2 Valor prognóstico do ECGAR na doença de Chagas

Resumo

Introdução - O real valor do eletrocardiograma de alta resolução (ECGAR) na estratificação de risco da doença de Chagas, doença potencialmente letal e prevalente na América Latina, continua não bem definido. A proposta deste estudo foi determinar o valor prognóstico do ECGAR na doença de Chagas utilizando-se de modelos multivariados.

Métodos - O estudo selecionou 184 pacientes chagásicos em regime ambulatorial (107 homens; idade: 43+/−10 anos), que possuíam ritmo sinusal no eletrocardiograma convencional (ECG) e não apresentavam outras patologias sistêmicas. Todos os pacientes envolvidos submeteram-se avaliação clínica e através de exames complementares, tais como ECG, raio x de tórax, Holter de 24 horas, ecocardiograma, teste ergométrico e o ECGAR. O tratamento medicamentoso convencional, quando necessário, foi continuado de forma individualizada. Utilizamos o teste de Cox para análise estatística dos potenciais fatores de risco obtidos pelos métodos não invasivos descritos.

Resultados - Durante um seguimento de 74 +/-17 meses, ocorreram 13 óbitos. Três fatores prognósticos independentes foram identificados: Fração de ejeção abaixo de 50% (HR=6.1 p=0.003), taquicardia ventricular no Holter ou no teste ergométrico (HR=10 p=0.003) e o prolongamento (>133ms) do QRS filtrado (HR=7.0, p=0.002).

Conclusão - A duração do QRS filtrado, obtido no ECGAR, é fator preditor independente de morte em pacientes com doença de Chagas.

Publicações resultantes:


Apresentação de temas livres


1.3 Valor Prognóstico Independente da Disfunção Ventricular Direita na Miocardiopatia Chagásica.


Objetivos: Avaliar o valor prognóstico da função ventricular direita na MCh.

Delineamento: Estudo prospectivo.

Metodologia: Foram incluídos 160 ptes com MCh, 100 homens (63%) e 60 mulheres (37%), com idade de 48 ±12,2 anos (22 a 73), acompanhados de junho de 1999 a janeiro de 2006. História clínica, ECG e ecocardiograma foram obtidos em todos. Pacientes com outras doenças cardíacas associadas foram excluídos. Para estudo da função do VD, foram empregados vários parâmetros ao ecocardiograma, como o grau de dilatação em relação ao VE, obtido pela planimetria, a análise de sua contratilidade e o índice de Tei (IPM).

Resultados: A maioria dos ptes estava em classe funcional I ou II (79%) da NYHA. 34 ptes (21 %) estavam em classe funcional III ou IV. Durante um período de seguimento de 34±23 meses (mediana de 30), 44 ptes morreram (36% morte súbita e 52% falência cardíaca progressiva). A fração de ejeção do VE foi de 37%±12. Disfunção ventricular direita foi detectada em 39% dos ptes. Na análise multivariada pelo modelo de Cox, foram identificados 4 preditores independentes de morte: classe funcional III ou IV da NYHA, fração de ejeção do VE, tempo de desaceleração do fluxo mitral e disfunção do VD (Tab 1).

<table>
<thead>
<tr>
<th>CF (NYHA)</th>
<th>RR</th>
<th>IC (95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE do VE (%)</td>
<td>0,95</td>
<td>0,92 - 0,99</td>
<td>0,010</td>
</tr>
<tr>
<td>redo FM (ms)</td>
<td>0,99</td>
<td>0,99 - 0,99</td>
<td>0,053</td>
</tr>
<tr>
<td>Disfunção do</td>
<td>2,52</td>
<td>1,17 - 0,019</td>
<td>0,019</td>
</tr>
</tbody>
</table>

Conclusão: Este estudo demonstrou que a função do VD foi fator preditor independente de mortalidade em ptes com MCh, acrescentando informações prognósticas adicionais aos outros parâmetros já estabelecidos, como classe funcional e efeitos sistólico e diastólico do VE.

Publicação resultante:
Apresentação de temas livres:

NUNES, M.C., ROCHA, M.O., RIBEIRO, A.L., CARMO, G.A., REZENDE, R.A., BARBOSA, M.

NUNES, M.C., BARBOSA, M.M., RIBEIRO, A.L., REZENDE, R.A., ROCHA, M.O.


Avaliação da resposta ao esforço e da inervação simpática na Doença de Chagas

2.1 Avaliação da resposta cronotrópica ao esforço na Doença de Chagas

Resumo

A insuficiência cronotrópica constitui achado comum entre os pacientes chagásicos. Novas metodologias estão sendo empregadas na avaliação da resposta cronotrópica em vários grupos de pacientes. O índice cronotrópico-metabólico, um desses novos métodos, quantifica a relação entre o aumento da frequência cardíaca e o consumo máximo de oxigênio (VO2 max) durante o teste ergométrico. A resposta normal é linear, com índice em torno de 1,0. Objetivamos avaliar a resposta cronotrópica e em indivíduos saudáveis e pacientes chagásicos com e sem disfunção ventricular esquerda, utilizando-se do índice cronotrópico-metabólico. Foram avaliados 171 pacientes com doença de Chagas sem doenças associadas e 24 controles submetidos a protocolo clínico e ao teste ergométrico máximo. Os chagásicos foram divididos em dois grupos: Ch1= pacientes com fração de ejeção (FE) > 39% e Ch 2= FE<40%. A análise e o cálculo do índice cronotrópico-metabólico foram feitos pelo método de Wilkoff. Os pacientes chagásicos apresentaram maior idade e maior prevalência de bloqueio completo de ramo direito, assim como menor VO2 max ao teste ergométrico. Ambos os grupos de chagásicos apresentaram menor inclinação do índice cronotrópico-metabólico (Ch1: 0,91±0,10, Ch2: 0,89±0,08) do que os controles (1,0±0,12, p< 0,001). Pacientes com doença de Chagas com e sem disfunção ventricular esquerda podem apresentar resposta cronotrópica deprimida, manifesta por menor inclinação do índice cronotrópico-metabólico.

A resposta simpática foi ao esforço foi objeto das publicações:


Os autoanticorpos dirigidos ao sistema simpático também foram objeto de estudo:

2.2 Avaliação da inervação simpática pela metaiodobenzilguanidina na Doença de Chagas

A disfunção autonômica, uma anormalidade característica da doença de Chagas, tem sido implicada como fundamental na patogênese da doença de Chagas. A grande maioria dos estudos de função autonômica avaliou o controle parassimpático cardíaco, indicando que esta divisão do SNA é acometida intensa e precocemente na doença de Chagas. Existem dúvidas, porém, sobre a importância e a intensidade do acometimento simpático. As limitações parecem estar relacionadas a maior complexidade estrutural do SNA simpático, que dificultaria o reconhecimento precoce do acometimento e a existência de limitações metodológicas significativas, relacionadas a dificuldades na avaliação quantitativa do controle simpático cardiovascular. Adicionalmente, não está claro se as anormalidades da inervação simpática estariam relacionadas a mecanismos específicos ou as alterações inespecíficas, progressivas, que se instauram com a deterioração da função ventricular em qualquer cardiopatia. Acredita-se que a desnervação simpática cardíaca seja mais intensa na cardiopatia chagásica do que na cardiopatia dilatada idiopática.

O objetivo do estudo foi, assim, avaliar, através do estudo da inervação simpática pela técnica da cintilografia pela metaiodobenzilguanidina, a presença de comprometimento simpático em pacientes com cardiomiopatia chagásica, comparando-os a pacientes com cardiomiopatia dilatada idiopática.

Forma recrutados 20 pacientes chagásicos e 20 pacientes com miocardiopatia dilatada idiopática, em classe funcional II ou III, fração de ejeção do VE < 45% e idade entre 20 e 50 anos. Os pacientes foram avaliados através de exame clínico, eletrocardiograma, ecodopplercardiograma, Holter de 24 horas com variabilidade da frequência cardíaca, Dosagem de BNP e Cintilografia perfusional e da inervação simpática pela MIBG. As variáveis de ‘desfecho’, decorrentes dos testes de função cardiovascular, serão comparadas entre pacientes ICC de etiologia chagásica e idiopática.

Os dados, já coletados, encontram-se em fase de análise.
3  Avaliação da estratégia clínica de reconhecimento de pacientes com disfunção sistólica global do ventrículo esquerdo pela dosagem do hormônio natriurético tipo B na Doença de Chagas

Objetivo: Descrever o comportamento do peptídeo natriurético tipo B (BNP) em chagásicos com o intuito de estabelecer o seu valor no diagnóstico da disfunção sistólica do ventrículo esquerdo (VE).

Métodos: Pacientes com doença de Chagas e controles saudáveis sem patologias concomitantes foram submetidos a protocolo padronizado, incluindo ECG e ecocardiografia, sendo divididos em 3 grupos de acordo com o estado sorológico e a fração de ejeção do VE (FEVE): grupo 0 (controles, n = 26), grupo 1 (chagásicos, FEVE > 0,40) e grupo 2 (chagásicos, FEVE <= 0,40, n = 15). As concentrações plasmáticas de BNP foram medidas por radioimunoensai e comparadas entre os grupos. A performance diagnóstica do BNP no reconhecimento da disfunção sistólica global ventricular esquerda nos chagásicos foi avaliada usando-se a curva ROC.

Resultados: As concentrações de BNP estavam significativamente aumentadas no grupo 2, quando comparados ao grupo 1 e aos controles e se correlacionaram com a FEVE (rs: - 0.46, P < 0.01). A área sob a curva ROC para as diferentes concentrações de BNP no diagnóstico da disfunção ventricular esquerda global foi de 0.89± 0.04. A elevação do BNP (>210 pg/dl) teve uma sensibilidade of 80%, especificidade de 93.2%, valor preditivo (+) de 52.2% e (-) de 98.1%.

Conclusão: Pacientes chagásicos com redução significativa da fração de ejeção do ventrículo esquerdo apresentaram elevação significativa do BNP. A dosagem de BNP pode ser um método acurado de "screening" de pacientes com risco aumentado de insuficiência cardiaca e morte.

Artigo publicado:

4. Dissertação de mestrado concluída

Paulo Sergio de Oliveira Cavalcanti. Análise comparativa do eletrocardiograma de alta resolução com variáveis clínicas na doença de Chagas . 2006. Dissertação (Medicina (Medicina Tropical)) - Universidade Federal de Minas Gerais.

5. Capítulos de livros

RIBEIRO, A.L. Métodos de avaliação funcional não invasivos da cardiopatia chagásica e outras cardiopatias infecciosas In: Dinâmica das Doenças Infecciosas e Parasitárias e da Medicina Tropical. Fiocruz, 2006

DECLARAÇÃO

Declaro, para os devidos fins, que o PROF. ANTÔNIO LUIZ PINHO RIBEIRO participou, como presidente, da defesa de dissertação de mestrado de PAULO SÉRGIO DE OLIVEIRA CAVALCANTI, intitulada: “ANÁLISE COMPARATIVA DO ELETROCARDIOGRAMA DE ALTA RESOLUÇÃO COM AS VARIÁVEIS CLÍNICAS NA DOENÇA DE CHAGAS”, realizada no dia 02 de maio de 2006, pelo Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais.

Belo Horizonte, 02 de maio de 2006.

Prof. Manoel Otávio da Costa Rocha
Coordenador do Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical
Prognostic Value of Signal-Averaged Electrocardiogram in Chagas Disease

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SAECG in Chagas Disease. Background: The value of signal-averaged ECG (SAECG) in the risk stratification of Chagas disease (ChD), a potentially lethal illness prevalent in Latin America, remains controversial. The aim of this prospective longitudinal study was to determine the prognostic value of SAECG in ChD, using multivariate models with other established prognostic predictors, and to develop a simple prediction risk score.

Methods: The study enrolled 184 ambulatory ChD patients (107 men; age: 48 ± 12 years) in sinus rhythm and without other systemic diseases. All patients underwent comprehensive evaluation that included clinical examination, ECG, chest X-ray, 24-hour Holter monitoring, echocardiogram, stress testing, and time domain SAECG. Individual medical treatment was adjusted according to a standardized treatment regimen. The association of potential risk factors obtained by noninvasive evaluation and death was tested by Cox proportional-hazards analysis.

Results: During mean follow-up time of 74 ± 17 months, 13 patients died. Three independent prognostic factors were identified: left ventricular ejection fraction <50% (HR = 5.2, P = 0.048), ventricular tachycardia at either Holter monitoring or stress testing (HR = 9.9, P = 0.036), and prolonged (>150 ms) filtered QRS complex (HR = 4.3, P = 0.035). A prognostic score developed considering the number of risk factors of each patient had an excellent performance in predicting death (c statistic: 0.92).

Conclusions: Prolonged filtered QRS duration obtained by SAECG is an independent predictor of death in ChD. A prediction score including three risk factors, depressed left ventricular ejection fraction, ventricular tachycardia and prolonged filtered QRS complex, has shown to be useful for stratifying risk categories in ChD. (J Cardiovasc Electrophysiol, Vol. 19, pp. 502-509, May 2008.)

signal averaged electrocardiography, Chagas disease, prognosis

Introduction

Chagas disease (ChD) is one of the main causes of heart block, arrhythmia, heart failure, embolism, and sudden death in Latin America, where nearly 20 million people are infected. The clinical course of ChD is quite variable, and the mechanisms responsible for the progression of this potentially lethal cardiac disease are barely understood. The identification of factors that can predict high risk of deaths may result in a more intensive medical management of such patients and, eventually, in improved patient survival.

This study was partly supported by grants from Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Belo Horizonte, Brazil; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brasília, Brazil; and Consiglio Nazionale delle Ricerche (CNR), Roma, Italy.

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Death in ChD is frequently sudden, and malignant ventricular arrhythmia is the main mechanism of death. Indeed, Chagas cardiopathy, characterized by diffuse chronic inflammatory infiltration, necrotic degeneration, and substitutive fibrosis, affects the contractile myocardium, the specialized conducting tissue, and the intracardiac autonomic nervous system simultaneously. These structural abnormalities may result in unidirectional block and slow conduction in circumscribed ventricular regions, which is essential for the appearance of reentrant ventricular arrhythmias, the main trigger of sudden death in chronic Chagas heart disease. Therefore, the anatomopathological substrate of late potentials are present in ChD, and signal-averaged electrocardiogram (SAECG), its standard method of recognition, would be useful in risk stratification in ChD.

Nonetheless, there are very few reports on SAECG in ChD, and its role in risk stratification is largely controversial. The aim of this study is to determine the prognostic value of SAECG in ChD, considering other established prognostic predictors and using multivariate models. A simple risk prediction score including SAECG variables was developed and compared with an established risk score.
Methods

Patient Population

Patient recruitment was carried out at the ChD Outpatient Reference Center of Federal University of Minas Gerais, Brazil. We selected consecutive patients aged between 20 and 70 years with a definite serological ChD status (≥2 different positive reactions to Trypanosoma cruzi in patients at risk of infection). Those who agreed to participate in this study signed a written informed consent and were submitted to a standard screening protocol that included clinical and laboratorial examinations, electrocardiogram, and chest X-ray. Exclusion criteria were: (1) atrial fibrillation or flutter, artificial pacemaker rhythm or any other nonsinus cardiac rhythm; (2) any evidence of other cardiovascular disease, diabetes mellitus, thyroid dysfunction, chronic obstructive pulmonary disease, renal or hepatic failure, anemia, or any other significant systemic disease; (3) alcoholism; (4) pregnancy; (5) follow-up for less than 18 months.

Study Protocol

The investigation conforms with the principles outlined in the Declaration of Helsinki, and the Research Ethics Board of Federal University of Minas Gerais approved the study protocol. All patients were submitted to clinical examination and New York Heart Association (NYHA) functional class evaluation. Individual medical therapy was adjusted according to a standardized treatment regimen. However, at the beginning of the study, very few patients (7%) were under medication, including four subjects using amiodarone. Chest radiography by conventional technique was performed at the Radiology Unit of the University Hospital and analyzed by one observer supervised by an experienced researcher (M.O.C.R.). Cardiac silhouette and cardiotoracic ratio were assessed as previously reported, and cardiomegaly was defined as a cardiotoracic ratio higher than 0.50. Standard 12-lead ECG was recorded at paper speed of 25 mm/s with a portable Fukuda Denki Model FX-2111 electrocardiograph (Fukuda Co., Tokyo, Japan). ECG tracing was blindly analyzed by a cardiologist experienced in electrocardiography (A.L.P.R.) using the Buenos Aires code specifically designed for ChD. Variables potentially related to the prognosis, such as mean heart rate, QRS duration, and the presence of ventricular premature beats (VPB), intraventricular block, either first- or second-degree AV block, and low voltage QRS, were recorded. Patients underwent Doppler echocardiography with color flow in an ATL Philips HDI 5000 machine (Bothell, Washington, USA) operated by an experienced echocardiographer (M.V.L.B) blind to patient clinical status as described elsewhere. The left ventricular ejection fraction (LVEF) obtained by Simpson's method using the equipment software was considered abnormally reduced if inferior to 50%, according to previous studies on the same sample. Left ventricular end-dimension and the presence of apical aneurysm, evaluated by two-dimensional study, were also recorded.

Twenty-four-hour Holter monitoring was performed using a portable three-channel cassette tape recorder (Dynamis, Cardios, São Paulo, Brazil). The individuals were encouraged to continue their normal daily activities during recordings and to avoid both physical exercise and drugs that might interfere with autonomic function. The tapes were analyzed when at least 18 hours of good quality tracings were available. The recordings were analyzed on a Burdick/DMI/Cardios Hospital Holter System (Burdick, Deerfield, WI, USA/Cardios, São Paulo, Brazil) by a semi-automatic technique. Minimal, mean, and maximal heart rate, the number of ventricular and supraventricular premature beats, and the occurrence of pauses and heart blocks were recorded. The variable "number of VPBs" was dichotomized in accordance with previous studies, and "frequent VPBs" were defined as more than 1000 VPBs per 24 hours. Ventricular tachycardia was defined as three or more consecutive VPBs with a rate above 100 bpm. A maximal stress test was performed according to the standard Bruce protocol, and heart rate, blood pressure, and ECG were monitored at rest, during each stage of exercise, at peak exercise, and during recovery. Chronotropic incompetence was defined as the inability to achieve at least 85% of the predicted heart rate according to Astrand's formula (220-age) at peak exercise. Ventricular tachycardia was considered effort-induced if present during the exercise or the recovery phases.

SAECD was acquired with a Burdick SAECG system (Burdick) with XYZ Frank orthogonal leads and standard methodology. A mean of 616 ± 147 valid beats were averaged in each recording, which resulted in a final noise level lower than 1.0 µV at bandpass filter setting from 40 to 230 Hz. The following SAECG parameters were analyzed in time domain by an independent observer blind to the study protocol: (1) the filtered QRS (ms) duration, (2) the duration of the potentials at the terminal region of ventricular activation below 40 µV (low-amplitude signal duration below 40 µV, LAS40, ms), and (3) the root-mean-square voltage of the terminal 40 ms of ventricular activation (RMS40, µV). Characteristics of late potential in the absence of intraventricular block include: (1) filtered QRS complex > 114 ms; (2) signal < 0.20 mV in the last 40 ms of the filtered QRS complex; and (3) voltage < 40 mV in the terminal QRS complex for > 38 ms. Identification of at least two abnormal parameters out of three defined the presence of ventricular late potentials. In the presence of bundle branch block (BBB), ventricular late potentials were considered present if RMS40 < 14 µV, regardless of filtered QRS duration. Additionally, considering that the filtered QRS duration was the strongest SAECG predictor of death in univariate analysis and that it was an independent predictor of events in patients with either heart failure or BBB in other studies, this variable was dichotomized as either ≤ or > 150 ms, a value defined after plotting the ROC curve in search of a cut point with at least 85% of specificity.

In this prospective longitudinal study, the date of entry was defined as the date when noninvasive testing was begun. Patients were followed until death or until the last ambulatory visit in either 2005 or 2006. Death was ascertained by reviewing medical records and interviewing relatives involved in the patient's care. The mode of death (for example, sudden, cardiac, and noncardiac death) was not categorized in this study.

Statistics Analysis

Data obtained from continuous variables were expressed as either mean ± standard deviation or median with the interquartile range. Data concerning categorical variables were expressed as proportions. A P value < 0.05 was considered significant. Cumulative survival curve was plotted by
the Kaplan–Meier method and mortality rates were compared using log-rank test. SPSS version 10 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Univariate and multivariate Cox proportional-hazards models (backward method) were used to determine the contribution of independent variables. Results are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). If the Pearson’s correlation coefficient between variables was 0.60 or larger, only the variable judged clinically important was entered into the multivariate model. Proportional-hazards model and interaction assumptions were tested and no violation was observed. Since the final model was constituted by three dichotomous variables with similar β regression coefficient values (rounded to two), a prognostic score was developed considering the number of risk factors of each patient. The sample was then divided in three groups: group 1, zero or one risk factor; group 2, two risk factors, and group 3, all three risk factors present. The prediction accuracy of the scoring system was examined by calculating the c statistics, the area under the ROC curve. Finally, the prediction accuracy of this new score system was evaluated in relation to that of an established score applied to this population in a previous report by comparing the c statistics obtained with the Hanley and McNeil method. Kaplan–Meier survival curves for patients and the 5-year follow-up mortality rate in the three risk groups (new score and Rassi’s score) were generated to illustrate the partitioning of the risk of death.

Results

Baseline Characteristics of the Study Group

Our study population was constituted of 184 subjects (97%) out of 190 CHD patients enrolled from 1 February 1993 to 1 July 1999 followed for at least 24 months. Patients were followed during a mean period of 74 ± 17 months (median 78). The sample consisted of 107 male (58%) and 77 female (42%) patients with mean age of 48 ± 12 years (22–73 years old). Almost all patients were in NYHA class I (175, 95%) and only one patient was in NYHA III (none in NYHA IV), reflecting the ambulatory origin of this sample. Cardiomegaly in chest X-ray was observed in 33 patients (18%). Electrocardiograms were available in 182 patients; BBB was observed in 61 patients (34%), rarely at the left bundle (only 3 cases). From 58 patients with right BBB, 45 also had left anterior hemiblock, a typical feature of CHD. VPBs were found in 16 cases (9%). Either first- or second-degree AV block were also found in 16 (9%) and low QRS voltage in four (2%).

The mean left ventricular diastolic dimension was 52.7 ± 6.4 mm (median: 52.0 mm) and the mean ejection fraction was 57.5% ± 10.3% (median: 61%). Depressed LVEF was observed in 59 patients (21%) and ventricular aneurysms in 37 (20%). Holter monitoring was available in 181 patients and ventricular arrhythmias were frequently found: 50 patients (28%) displayed more than 1000 VPBs in 24 hours, and ventricular tachycardia was observed in 42 cases (23%).

At stress testing (available in 180 patients), chronotropic incompetence was observed in 43 cases (24%) and ventricular tachycardia at stress in 15 cases (8%). Forty-nine patients (27%) presented with ventricular tachycardia induced by effort at stress testing or registered during 24-hour Holter monitoring. SAECG was available in 171 patients and late potentials, as defined above, were observed in 70 patients (41%). Prolonged filtered QRS (>150 ms) was present in 26 patients (15%). Filtered QRS duration was, in general, longer than QRS duration in the ECG both in survivors and nonsurvivors (19 ± 9 ms vs. 15 ± 12 ms, P = 0.27).

Follow-Up and Predictors of Death

Thirteen patients (7%) died during follow-up. The baseline clinical characteristics of survivors and nonsurvivors are compared in Table 1. No patient received either cardiac-resynchronization therapy or cardiac transplant, and two patients (1%) who received cardioverter-defibrillator were censored at the time of implantation.

All the investigated variables (listed in Table 1) were examined as potential predictors of survival in univariate Cox regression models. Cardiomegaly (chest X-ray), QRS duration and BBB (ECG), LVEF, left ventricular diastolic dimension and aneurysm (echocardiogram), frequent VPB and ventricular tachycardia (Holter), effort-induced tachycardia (stress testing), and all SAECG parameters were significantly related to risk of death in univariate analysis.

After the exclusion of variables exhibiting multicollinearity, five variables found to have prognostic significance by univariate analysis were entered into the multivariate model: cardiomegaly, depressed LVEF, ventricular aneurysm, ventricular tachycardia at stress testing or 24-hour Holter, and prolonged filtered QRS. Three variables maintained prognostic significance after multivariate analysis: depressed LVEF, ventricular tachycardia at either stress testing or 24-hour Holter monitoring, and prolonged filtered QRS (Table 2 and Fig. 1).

Risk Scores

A simple model was constructed by adding the number of risk factors presented by each patient, which ranged from zero to three. The model predicted death with excellence with an area under the ROC curve (c statistic) of 0.92 (0.86–0.97, Fig. 3). When classified in three groups (group 1: either zero or one factor, group 2: two factors, group 3: all three risk factors present), the Kaplan–Meier curve demonstrated a clear distinction in risk of death among them (Fig. 2, Table 3). The performance of this model was compared with an established risk score, Rassi’s score, which displayed an area under the ROC curve (c statistic) of 0.84 (0.72–0.96) for our sample, a difference of −0.08 in relation to the new score (P = 0.13). The ability of Rassi’s and the new risk groups in stratifying risk in this CHD population is displayed in Figure 2 (Kaplan–Meier curves) and Table 3 (risk of death after 5-year follow-up).

Discussion

In the present study, we examined if SAECG, a technique previously shown to predict arrhythmic events and death in several conditions, could provide independent prognostic information in CHD. Moreover, we tested if a simple model derived from our study predicts death in this sample accurately in comparison to the presently established predicting score.

Few previous studies have addressed the predictive value of SAECG in CHD death risk. De Moraes and colleagues6
studied 192 ChD patients classified in four groups using SAECG according to either the presence or absence of BBB and sustained ventricular tachycardia. Late potentials were defined (40 Hz filter) by conventional criteria in the sample without BBB, and the presence of RMS40 < 14 μV in patients with BBB regardless of filtered QRS duration. Late potentials recognized patients with a narrow QRS complex who presented with sustained ventricular tachycardia and predicted recurrence of ventricular tachycardia during a mean follow-up of 40 months in this group accurately. Four patients died during follow-up, all of them with BBB. absence of RMS40 < 14 μV, but with long filtered QRS duration (>150 ms). Left ventricular function was not evaluated systematically in this study. More recently, Benchimol Barbosa et al followed 50 ChD patients for 84 ± 39 months; 34% presented either composite

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Univariate Predictors of Death in a Cohort of 184 Chagas Disease Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NonSurvivors (n = 133)</td>
</tr>
<tr>
<td>Clinical and Radiological Exams</td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 (34–52)</td>
</tr>
<tr>
<td>Male gender</td>
<td>10 (77)</td>
</tr>
<tr>
<td>NYHA class III-IV</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>13</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>66 (60–71)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>130 (104–150)</td>
</tr>
<tr>
<td>PVC</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>8 (62)</td>
</tr>
<tr>
<td>1st or 2nd degree AV block</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Low-QRS voltage</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>13</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>63 (56–70)</td>
</tr>
<tr>
<td>LVF% (%)</td>
<td>35 (28–48)</td>
</tr>
<tr>
<td>Ventricular aneurysm</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Ventricular aneurysm</td>
<td>7 (54)</td>
</tr>
<tr>
<td>24-hour Holter Monitoring</td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>13</td>
</tr>
<tr>
<td>Mean 24-hour heart rate (bpm)</td>
<td>72 (60–79.5)</td>
</tr>
<tr>
<td>PVR &gt; 1000/24 hour</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Stress Testing</td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>13</td>
</tr>
<tr>
<td>Chronotropic incompetence</td>
<td>5 (39)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>3 (46)</td>
</tr>
<tr>
<td>Ventricular tachycardia at stress testing</td>
<td>11 (85)</td>
</tr>
<tr>
<td>24-hour Holter</td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>10</td>
</tr>
<tr>
<td>LAS40 (ms)</td>
<td>72.5 (37.25–80)</td>
</tr>
<tr>
<td>RMS40 (μV)</td>
<td>11.5 (5–18.75)</td>
</tr>
<tr>
<td>Filtered QRS duration (ms)</td>
<td>151.5 (127–162.25)</td>
</tr>
<tr>
<td>Filtered QRS &gt; 150 ms</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Late potentials</td>
<td>8 (80)</td>
</tr>
</tbody>
</table>

LAS40 = duration of potentials below 40 μV in the terminal region until offset of ventricular activation; LVDD = left ventricular end-diastolic diameter; LVF = left ventricular ejection fraction; NYHA = New York heart Association; PVR = premature ventricular beats; RMS40 = root-mean-squared voltage of the last 40 ms of ventricular activation.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Multivariate Cox Proportional-Hazard Analysis of Risk of Death in Chagas Disease Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (n = 170)</td>
</tr>
<tr>
<td>LVF &lt; 0.50</td>
<td>34 (20)</td>
</tr>
<tr>
<td>Ventricular tachycardia at stress testing or at 24-hour Holter</td>
<td>45 (26)</td>
</tr>
<tr>
<td>Filtered QRS &gt; 150 ms</td>
<td>26 (15)</td>
</tr>
</tbody>
</table>

LVF = left ventricular ejection fraction.
Figure 1. Kaplan-Meier curves demonstrating mortality in Chagas disease patients classified according to the presence of risk factors. (A) Reduced left ventricular ejection fraction (<0.50) at the echocardiogram, (b) ventricular tachycardia either at stress testing or 24-hour Holter monitoring, and (c) prolonged filtered QRS >150 ms at SAECG.

Figure 2. Kaplan-Meier curves demonstrating cardiac mortality in patients classified according to risk scores. (a) New risk score described in this study, (b) Rassi's risk score.

end-point of death or ventricular tachycardia. Late potentials, defined as suggested by the American College of Cardiology, in patients without BBB, and in those with BBB, as suggested by De Moraes (RMS40 < 14 μV), were not predictive of risk of death in multivariate analysis.

At variance with previous studies, we found that prolonged filtered QRS duration measured by SAECG was a powerful and independent marker of risk of death in ChD. Indeed, methodological issues might explain these different results. BBB is a typical electrocardiographic feature of ChD, and its presence may hamper the value of conventional time-domain SAECG measurements in the prediction of cardiac events. Indeed, both previous studies used the same simple definition of late potentials in those patients (RMS40 < 14 μV) to avoid a false positive test result related only to prolonged QRS duration due to intraventricular conduction disturbance. However, more recent analysis performed in a subset of patients from the MUSTT study showed that filtered QRS duration alone was a more powerful predictor of death than other definitions of abnormal SAECG, and that relations were stronger for cardiac death than for arrhythmic death. Brembilla-Perrot and colleagues found that long filtered QRS and induction of ventricular tachycardia were also independent predictors...
TABLE 3
Risk of Death in Chagas Disease Patients at 5-Year Follow-Up According to Rassi’s Risk Category and the New Score

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>n = 156</th>
<th>Death at 5 Years</th>
<th>New Score (n = 149)</th>
<th>Death at 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>110 (69.6)</td>
<td>3 (1-7)</td>
<td>0 or 1</td>
<td>118 (79.2)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>42 (26.6)</td>
<td>10 (4-22)</td>
<td>2</td>
<td>25 (16.8)</td>
</tr>
<tr>
<td>High</td>
<td>6 (3.8)</td>
<td>67 (30-90)</td>
<td>3</td>
<td>6 (4.0)</td>
</tr>
</tbody>
</table>

*The risk category at Rassi’s score was calculated by adding the points of each of the following risk factors: male sex (2 points), low-QRS voltage on the electrocardiogram (2 points), nonsustained ventricular tachycardia on 24-hour Holter monitoring (3 points), segmental or global wall-motion abnormality on the echocardiogram (3 points), cardiomegaly on chest radiography (5 points), and NYHA class III or IV (5 points). The prognostic index was categorized in three groups: low risk (0 to 6 points), intermediate risk (7 to 11 points), and high risk (12 to 20 points). At the new score, each of the following factors is worth one point: ventricular tachycardia at either stress testing or Holter monitoring, left ventricular ejection fraction < 0.50, filtered QRS > 150 ms at SABCO. Low-risk group has zero or one risk factors, intermediate risk, two factors, and high risk, all three factors. CI denotes confidence interval. The number of patients differs from those in the previous tables since only patients with complete noninvasive tests and complete 5-year follow-up were included in this analysis.

of total cardiac mortality in patients with BBB syncope and history of myocardial infarction. Both studies concluded that prolonged filtered QRS duration is a simple means of detecting patients at risk of cardiac mortality. Our results strongly confirmed such previous reports for a ChD sample.

The meaning of our findings and of others’ may be related with the hypothesis that the longer the filtered QRS is, the larger the myocardial scarring is, resulting in heterogeneous propagation not only in the terminal depolarization wave front (late potentials), but perhaps also in the initial and midsegments of the depolarization wave front. Indeed, the close relation between the extent of myocardial fibrosis and the duration of filtered QRS was elegantly demonstrated by Yamada et al. who performed SABCOs in 32 patients with dilated cardiomyopathy followed by left ventricular endomyocardial biopsy. Filtered QRS duration correlated with the extent of myocardial fibrosis (r = 0.623, P < 0.001) closely, even when fibrosis was classified as intercellular (r = 0.695, P < 0.0001). As suggested by Gomes et al., prolonged filtered QRS may reflect an early stage in the development to extensive scarring later manifested by the development of intraventricular conduction defects.

The presence of a wide QRS complex in surface electrocardiogram is an established marker of high risk of death and arrhythmic events in patients with heart failure and in unscreened medical population, although the risk may vary among different populations such as in ischemic versus nonischemic heart failure groups, or considering left BBB versus right BBB. ChD studies performed more than 20 years ago showed that BBB is a marker of increased risk of death in unscreened populations. More recent longitudinal studies that evaluated left ventricular function were not able to confirm the independent prognostic value of intraventricular defects in ChD. Indeed, the QRS duration is directly related to left ventricular diastolic dimension and inversely related to the LVEF in ChD. These findings were confirmed in the present study, as BBB was a univariate predictor of risk of death that did not maintain its independent value in the multivariate model.

A main outcome of our study is the development of a simple and accurate prediction model, comparable in terms of efficiency with a more complex one, recently published and externally validated by our group. Three independent prognostic factors were identified in our study: LVEF below 50% (HR = 5.2; P = 0.048), ventricular tachycardia at either Holter monitoring or stress testing (HR = 9.9, P = 0.036), and prolonged (> 150 ms) filtered QRS complex (HR = 4.3, P = 0.035). The new score system has the advantage of simplicity: it requires only a simple addition of risk factors to classify the patients in three different risk categories. At variance, Rassi’s score has to be calculated considering numerous risk factors with different punctuations and a conversion table to classify patients in one of three risk categories. In our sample, Rassi’s categories of low and moderate risk displayed an almost identical risk profile, in contrast with the clear distinction of risk of death between the three categories with the new risk score (see Table 3 and Fig. 2). Nonetheless, we should stress that Rassi’s score, validated in two external cohorts, was developed with a larger sample, with longer follow-up, and had higher mortality rate than those of the current study, and now it stands as the standard general use prediction score of ChD.

Figure 3. ROC curves of score systems used to predict death in Chagas disease population. The area under the ROC curve for the new score was 0.92 (0.86-0.97) and for Rassi’s score was 0.84 (0.72-0.96) (difference: -0.08, P = 0.11).
An important issue of both risk prediction models is that they were developed in studies whose outcome was total death (for all causes) rather than sudden death. Sudden death, mainly due to ventricular arrhythmia, is the main Chd death mode, and selecting candidate patients for cardiac defibrillator implantation is a major decision in Chd management. Sudden death may occur in Chd patients even in the absence of left ventricular dysfunction, and it would be valuable to know if SAECG may help in the recognition of high-risk patients for whom cardiac defibrillator implantation might be effective in primary prevention.

Further limitations of our study should be pointed out. First, the new score system was not validated with an independent data set. Second, the limited number of deaths in this study sample may have restricted the number of significant risk predictors selected, and some established risk factors in Chd such as NYHA functional class III/IV and cardiomegaly were not selected in the final model. A plausible reason for the absence of these severity markers is the relative predominance of asymptomatic patients with mild disease in our clinic-based sample, similarly to the population found in the community. In this setting, a prolonged filtered QRS duration is finding more common than heart failure with NYHA class III or IV and is may be more valuable in the stratification of risk. Third, we used time domain SAECG measurements in patients with and without BBB, which, as discussed above, is rather a choice of paradigm shift than a limitation. Finally, SAECG is not frequently used nowadays, and the restricted number of SAECG equipment in South America may hamper the practical use of the proposed risk score.

In conclusion, we report that SAECG may be used in risk stratification in Chd for the first time: prolonged filtered QRS duration (≥150 ms) is an independent predictor of death. Other independent prognostic factors are LVEF below 50% and ventricular tachycardia at either Holter monitoring or stress testing. The simple prediction score developed had an excellent performance in recognizing patients with low, moderate, and high risk of death.

References


LETTER TO THE EDITOR

Risk Stratification in Chagas Disease: Further Improvements are Needed

Response to the Editor:

Dear Sir,

We would like to thank Drs. Rassi and Rassi Jr. for their careful reading of, and thoughtful comments on our recent study,1 in which we described the hitherto unrecognized prognostic value of Signal-Averaged ECG (SAECG) in Chagas disease (ChD). Some of their comments have already been discussed in our article, such as the possibility of underfitting, since "the limited number of deaths in this study sample might have restricted the number of significant risk predictors selected."1 We have also acknowledged that the lack of SAECG equipments in South America1 was a practical limitation of the proposed score system. Finally, we agree that a normal ECG has a strong positive prognostic value and that risk stratification should be preferentially restricted to those patients with established cardiopathy.2 We, therefore, recalculated our estimates in a sample that included only patients with abnormal ECG or echocardiogram and confirmed that our results were quite similar to those previously obtained (see Table 1). It appears that our score performed fairly well in this subsample, with a c statistic of 0.90 (95% CI: 0.83–0.96).

There are other criticisms that are, in our opinion, unacceptable. First: ROC curve is a method of choice in the assessment of the discrimination ability of survival and logistic analysis models even with small data sets.3-5 Although it is of little help in the selection of model variables,2 indeed, we used the ROC curve only to evaluate the model performance. The same methodology was used by Rassi et al. in their own study,6 and we could not find in the literature or in the quoted reference7 any restriction related to heterogeneity of the sample (that is not significant in our study) or limited number of events. Second: Evaluation of ventricular volume by Simpson's rule is the recommended method for evaluating left ventricular function,2 rather than a time consuming option. Third: A major criticism of Rassi's refers to the possibility of overfitting in our model, that is, that some variable could be added spuriously in the model, or with an inaccurate regression coefficient. In this case, our results would fail to be replicated in other studies and the proposed score would be useless. While we could not reject a priori this hypothesis, in relation to the small number of outcomes and the absence of external validation of the proposed score, we have several reasons to believe that this is not the case. Two of the three selected variables, nonsustained ventricular tachycardia and depressed LV ejection fraction are established risk factors in Chagas cardiomyopathy.8 The third selected variable, the prolonged duration of filtered QRS, was not an irrelevant and occasional covariate selected by an automated stepwise regression procedure, as typically occurs in overfitted models. Prolonged filtered QRS duration, which has prognostic value in patients with either heart failure9 or BBB,10 was the focus of this study, and its relation to the risk of death in Chagas disease is meaningful and fully compatible with clinical and physiopathological features of the disease. If anything, in small data set, "external knowledge should be incorporated as much as possible in the modeling process."11 Finally, as a proof of the robustness of this parameter as a predictor of death in Chagas disease, we observed that QRS duration even if measured on a conventional ECG, maintained its predictive value (Table 2 and Fig. 1). If in the proposed score the prolonged filtered SAECG QRS duration was substituted by ECG QRS duration > 133 ms, the model maintained its excellent performance, with c statistics of 0.92 (95% CI: 0.87–0.97). Indeed, the QRS duration obtained by SAECG and by conventional ECG are highly correlated variables (r = 0.89, P < 0.001) and the fact that the model retains its performance after the exchange strongly suggests that its inclusion in the model was not spurious.

In conclusion, a very simple prediction model could be built using only three variables measured by routine exams performed in the clinical practice, without the need

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doi: 10.1111/j.1540-8167.2008.01173.x

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### TABLE 1
Multivariate Cox Proportional-Hazards Analysis of Risk of Death in Chagas Disease Patients with Cardiac Disease

<table>
<thead>
<tr>
<th>Prevalence (n = 136)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>β Regression Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt; 0.50</td>
<td>34 (25%)</td>
<td>4.3 (0.9–24.4)</td>
<td>0.053</td>
</tr>
<tr>
<td>Ventricular tachycardia at 24 h Holter</td>
<td>41 (39%)</td>
<td>9.3 (1.1–80.3)</td>
<td>0.040</td>
</tr>
<tr>
<td>or at 24-h Holter Filtered QRS &gt; 150 ms</td>
<td>26 (19%)</td>
<td>3.3 (1.0–14.7)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction. Results obtained from the reanalysis of the data set of the previous article,1 excluding patients without cardiopathy. Observe that the estimates are almost identical to those previously reported.

### TABLE 2
Multivariate Cox Proportional-Hazards Analysis of Risk of Death in Chagas Disease Patients Substituting the Filtered QRS > 150 ms for the ECG QRS > 133 ms

<table>
<thead>
<tr>
<th>Prevalence (n = 178)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>β Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt; 0.50</td>
<td>36 (20%)</td>
<td>7.7 (1.5–39.7)</td>
<td>0.014</td>
</tr>
<tr>
<td>Ventricular tachycardia at stress testing or at 24-h Holter Filtered QRS &gt; 133 ms</td>
<td>46 (26%)</td>
<td>5.1 (1.0–26.2)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction. Results obtained from the reanalysis of the data set of the previous article,1 substituting the filtered SAECG QRS > 150 ms for the ECG QRS > 133 ms.
of conversion tables or subjective evaluation. Much has to be done in order to validate this score in clinical practice. We have repeatedly praised Rassi and colleagues for their landmark study in this field\textsuperscript{1,2,11} and stated that their score "stands as the standard general use prediction score of Chagas disease."\textsuperscript{1} However, medicine is an ever-changing science and the pursuit of improvements in established knowledge is, more than a choice, an obligation of all clinicians and researchers.

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Right ventricular dysfunction is an independent predictor of survival in patients with dilated chronic Chagas' cardiomyopathy

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Abstract

Background: Right ventricular (RV) involvement is a typical feature of Chagas' disease. In patients with congestive heart failure of other etiologies, RV dysfunction is a strong indicator of poor prognosis. However, the prognostic value of RV dysfunction in patients with Chagas' cardiomyopathy has not been reported. This study sought to investigate the prognostic value of RV dysfunction, apart from other well-established risk factors, in patients with Chagas' cardiomyopathy.

Methods: The study enrolled 158 patients (99 men; mean age of 48±12 years) from a tertiary center for Chagas' disease. Patients were selected if found to have both the diagnosis of Chagas' disease and cardiomyopathy. All patients underwent a comprehensive Doppler echocardiogram and the global RV function was quantitatively assessed using the RV index of myocardial performance (Tei index).

Results: Most of the patients were in NYHA classes I and II (79%). During a mean follow up of 34±23 months, 44 patients (28%) died: 24 (55%) patients died of progressive heart failure and 16 (36%) of sudden death. RV Tei index emerged as an independent predictor of survival (hazard ratio 5.75, 95% confidence interval 1.69 to 19.51). Kaplan-Meier survival curves showed a higher cumulative mortality among patients in the highest quartile of RV Tei index, compared with other 3 quartiles (log-rank statistic 21.87, p<0.001). After adjustment for clinical data and LV ejection fraction, RV Tei index in the highest quartile (≥0.56) remained a significant predictor of death (hazard ratio 5.29, 95% confidence interval 2.43 to 11.52).

Conclusions: RV function assessed by the Tei index added significant prognostic information, incremental to the NYHA clinical classification and to the standard echocardiographic evaluation of LV systolic function. A simple measure of a Doppler index, which allows analysis of both systolic and diastolic function of the RV, appears to be a useful non-invasive tool for risk stratification in patients with dilated chronic Chagas' cardiomyopathy.

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Keywords: Right ventricle; Chagas' disease; Cardiomyopathy; Tei index; Echocardiography

Chagas' disease remains one of the most prevalent infectious diseases in Latin America, despite the dramatic progress in transmission control [1]. In the past decades, after urban migrations, Chagas' disease began to spread in the cities and became a health problem in non-endemic countries, where it can be transmitted vertically and by blood transfusion or organ transplantation [2]. Heart involvement is the major characteristic of the disease, because of its features, frequency and clinical impact. However, it is also a
source of controversy. Right ventricular involvement is a typical feature of Chagas' disease and it has been described in the early stages of the disease [3–5].

The prognosis of patients with chronic heart failure is poor. Chagas' heart disease, when compared to other etiologies of heart failure, was demonstrated to be associated with a higher risk of death [6,7]. The identification of factors that can predict a high risk of cardiac events may result in more intensive medical management or even heart transplantation, leading to improvement on patient's survival.

RV performance is now well established as a powerful predictor of prognosis in patients with heart failure of both ischemic and non-ischemic origin [8–10], in whom a reduced RV ejection fraction, estimated by radionuclide ventriculography or by the thermodilution method, has been shown to be an important prognostic indicator. However, these procedures are expensive, time consuming and not suitable for serial evaluations. Thus, although studies have suggested a high potential of RV systolic function parameters for the prediction of cardiac events, RV function is not routinely evaluated to stratify the risk of patients with heart failure. Echocardiographic assessment of RV function remains difficult and challenging. More recently, an easily measured non-invasive Doppler-derived myocardial performance index, also referred to as the Tei index, has been proposed to assess global RV function [11].

Although LV ejection fraction is known to provide prognostic information in patients with Chagas' cardiomyopathy [12,13], no prior study has challenged the prognostic value of the evaluation of the RV function evaluated by the index of myocardial performance versus other clinical and echocardiographic parameters in patients with Chagas' disease. The purpose of this study was to determine if RV global function evaluation adds prognostic value independently and incrementally to other prognostic indicators in patients with Chagas' cardiomyopathy.

1. Methods

1.1. Patients

The study enrolled 160 consecutive patients who were referred to a tertiary center for Chagas' disease from June 1999 until Jan 2006. Two patients were excluded because they were lost to follow up. The final study group thus consisted of 158 patients.

The diagnosis of Chagas' disease required at least two positive serologic tests for antibodies against Trypanosoma cruzi (indirect hemagglutination, indirect immunofluorescence, or enzyme-linked immunosorbent assay). Inclusion criteria were both the diagnosis of Chagas' disease and cardiomyopathy. Dilated cardiomyopathy is characterized by the echocardiographic finding of a dilated left ventricle with impaired ventricular systolic function. Patients were selected if they had a left ventricular diastolic diameter/body surface area (BSA) ≥ 31 mm and left ventricle ejection fraction (LVEF) <55% [14]. These patients are also classified as chronic Chagas' cardiomyopathy, which represents the most severe form of Chagas' heart disease [15]. Patients who had associated heart or other diseases were excluded. The protocol of the study was approved by the Research Ethics Board of the Federal University of Minas Gerais, Brazil, and an informed written consent was obtained in all cases.

All patients underwent clinical examination and NYHA functional class was established. Medical therapy was individually adjusted according to a standardized treatment regimen. Twelve-lead ECG and a comprehensive Doppler echocardiogram with color flow mapping was obtained from all patients.

1.2. Doppler echocardiography

Images were acquired using a Sonos 5500 equipment (Hewlett-Packard, Andover, MA, USA), with 2.5 to 3.5 MHz transducers. All the exams were performed by the same cardiologist who was blinded to the clinical evaluation of the patients.

Chamber dimensions and wall thickness were measured according to the recommendations of the American Society of Echocardiography. LV ejection fraction was calculated according to the modified Simpson's rule [14,16].

Diastolic function was assessed by pulsed-wave Doppler examination of mitral and pulmonary venous inflow as previously described and validated [17]. In the apical four-chamber view, mitral inflow was obtained with pulsed-wave Doppler at the tips of the mitral valve. E and A peak velocities, A wave duration and a deceleration time (DT) of the E wave were measured from the mitral inflow. Systolic, diastolic and atrial reversal (AR) peak velocities, as well as the duration of the AR, were obtained from the pulmonary venous flow at the right upper pulmonary vein [17].

The RV morphology and function was evaluated qualitatively by multiple echocardiographic views, including parasternal long- and short-axis, RV inflow, apical 4-chamber, and subcostal views. In each view, assessment of the RV included an analysis of the shape of the RV cavity and motion of the RV free wall, measurement of the chamber area and of the wall thickness [14]. Some standard measurements of the RV were also made. RV systolic function was qualitatively considered normal or reduced compared to the LV function [14,16].

Tei index, defined as the sum of the isovolumetric contraction and relaxation time divided by the ejection time of the RV, was calculated by subtracting the RV outflow velocity time (b) from the interval between cessation and onset of the tricuspid inflow velocity (a), and then dividing by the time of the RV outflow velocity (a–b/b) [11]. A Doppler-derived index of the LV was also calculated using the LV outflow velocity time and the mitral inflow to obtain LV (b) and (a) values, respectively, as described above. The presence and degree of tricuspid regurgitation (TR) was evaluated by Doppler, guided by color flow mapping [18]. The pulmonary artery systolic pressure (PASP) was estimated.
using the modified Bernoulli equation (\(TR \text{ jet velocity}^2 \times 4\)) and adding 10 mm Hg as a clinical estimation of the right atrial pressure.

1.3. Follow up and clinical outcome

The date of enrollment in the study was defined as the date in which Doppler echocardiographic exam was performed. Patients were followed until death or at the end of the study (censored). Death and the mechanism of death were identified from hospital records, telephone interviews with relatives, or examining the death certificate. Cardiac death was defined as death caused by any cardiovascular disease and non-cardiovascular death was due to any other cause. Death was classified as sudden if it occurred within 1 h after a change in symptoms, was unwitnessed in a patient whose condition had been stable, or occurred during sleep. It was due to progressive heart failure if it occurred after a documented period of symptomatic or hemodynamic deterioration.

1.4. Statistical analysis

Cardiac death was used as the clinical outcome event. Categorical data are presented as absolute value and percentages, and continuous data are expressed as mean values ± SD. The significance of baseline differences was determined by the chi-square test, Fisher's exact test, or the unpaired t-test, as appropriate.
Correlation analysis between pulmonary artery systolic pressure (PASP) and parameters of the LV and RV function was based on a Pearson's correlation coefficient. The PASP was included in the model as a continuous or as a qualitative variable, excluding the 35 patients in whom tricuspid regurgitation velocity could not be obtained.

Estimations of the risk of death were performed using Cox proportional-hazards models by univariate and multivariate analysis. If the Pearson's correlation coefficient between variables was 0.60 or more, only variables judged to be clinically more important entered the multivariable model. Variables entered the model if they were significant at a level of 0.1 in the univariate analysis.

The incremental values of RV Tei index over functional class and Doppler echocardiographic parameters of systolic function of the LV were assessed in three modeling steps. The first step consisted of clinical data used as baseline risk factors. LV ejection fraction was added in the next step. In the final step, RV Tei index was added. A significant improvement in model prediction was based on the likelihood ratio statistics, which follows a chi-square distribution, and the p value was based on the incremental value compared with the previous model.

Because multivariate analysis requires a complete set of variables for each patient, missing data from one or more parameter restricted the analysis to 145 patients (92%), with only 13 cases with missing values. There were no significant differences in baseline characteristics or survival between patients with complete data and those with missing data.

Cumulative survival curve was performed by Kaplan-Meier method, and mortality rates were compared using the log-rank test. SPSS version 13 (SPSS Inc., Chicago, Illinois) was used for all analyses.

2. Results

2.1. Baseline characteristics of the study group

The study population consisted of 99 males (63%). Mean age was 48±12 years (22–73 years). Most of the patients were in NYHA class I or II (79%). Only thirty-three patients were in NYHA classes III and IV (21%). One hundred and twenty-four patients (78%) were taking angiotensin-converting enzyme inhibitors, 96 (61%) diuretics, 70 (44%) amiodarone, 46 (29%) digoxin, 38 (24%) anticoagulants and 17 (11%) beta blocking agents.

Only six patients (4%) presented with atrial fibrillation and 15 (9%) had a pacemaker at enrollment. The proportion of patients with a pacemaker and premature ventricular contractions was higher among non-survivors (Table 1). No difference was observed in regard to other ECG variables.

The mean LV ejection fraction was 36.9±12.6% (median: 38%). There was a significant negative correlation between the RV Tei index and LV ejection fraction (r=−0.52, p<0.001). LV diastolic and systolic dimensions (r=0.38, p<0.001 and r=0.50, p<0.001, respectively). LV Tei index had a strong correlation with ejection fraction (r=−0.62, p<0.001) and also correlated with RV Tei index (r=0.35, p<0.001).

In 35 patients tricuspid regurgitation velocity could not be measured and PASP was not estimated. As expected, PASP correlated with the RV Tei index (r=−0.54, p<0.001). Other parameters used to measure RV performance, such as diameter and area at the end of diastole, also correlated with PASP (r=0.21; p=0.033, and r=0.40; p<0.001 respectively). The RV Tei index was associated with the subjectively evaluation of RV systolic function by two-dimensional imaging. In patients with normal RV, the mean value of the RV Tei index was 0.35, compared with 0.65 in those with RV dysfunction (p<0.001).

2.2. Follow up

Patients were followed for a mean of 34±23 months (median 30; range, 7 days to 6.1 years); 44 patients (28%) died: 24 (55%) patients died of progressive heart failure, 16 (36%) of sudden death and three (7%) of stroke. Only one patient (0.6%) died of a non-cardiac cause. All the patients were followed for at least 6 months, except if an end point occurred. Two patients (1%) received a cardiovascular-defibrillator and were censored at the time of implant. No patient received cardiac-resynchronization therapy or a cardiac transplant. The baseline clinical characteristics of the survivors and non-survivors are compared in Table 1.

Table 2

<table>
<thead>
<tr>
<th>Right ventricular parameters predictors of cardiac death in the univariate analyses</th>
<th>All patients (n=158)</th>
<th>Survivors (n=114)</th>
<th>Non-survivors (n=44)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV diastolic diameter (mm)</td>
<td>21.6±9.6</td>
<td>20.0±8.3</td>
<td>25.5±11.7</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV diastolic area (cm²)</td>
<td>15.9±7.1</td>
<td>14.5±6.1</td>
<td>20.1±8.2</td>
<td>1.12 (1.08–1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV Tei index*</td>
<td>0.45±0.31</td>
<td>0.39±0.25</td>
<td>0.66±0.37</td>
<td>17.7 (6.14–51.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASP (mm Hg)</td>
<td>37.2±12.5</td>
<td>33.0±11.6</td>
<td>42.0±13.3</td>
<td>1.04 (1.01–1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe TR (m²/s)</td>
<td>22 (14)</td>
<td>6 (5)</td>
<td>16 (36)</td>
<td>3.16 (2.23–4.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV dysfunction* (m²/s)</td>
<td>62 (39)</td>
<td>30 (26)</td>
<td>32 (73)</td>
<td>2.42 (1.87–3.14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RV = right ventricle; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation.

* Predictor of death in multivariate analyses.

Pulmonary artery systolic pressure could be assessed in 123 patients (79%).

Qualitatively evaluation of RV function by two-dimensional echocardiogram.
2.3. Predictors of cardiac events

All the investigated variables (listed in Table 1) were examined as potential predictors of survival in univariate Cox regression models. Clinical risk factors such as S2 gallop, systemic congestion, systolic blood pressure and syncope were associated with an adverse outcome. Medication was not predictive of subsequent mortality.

Right bundle-branch block was the most frequent ECG abnormality, but it was not associated with mortality. Premature ventricular complexes and pacemaker were correlated with LV systolic function, but in the multivariate analysis, neither appeared as predictors of death.

The differences in echocardiographic parameters between survivors and non-survivors are shown in Table 1. There was a significant difference in LV parameters of systolic and diastolic function, including Doppler mitral inflow and pulmonary venous flow between the survival and non-survivors. After each of these significant variables was entered into Cox regression model, LV ejection fraction remained associated with cardiac death (hazard ratio 0.96, 95% confidence interval 0.91 to 0.99).

Several standard Doppler echocardiographic measurements that were used to assess the RV function were associated with mortality in a univariate analysis (Table 2). However, the quantitative evaluation of global RV function by Doppler-derived Tei index had the strongest impact on cardiac mortality (hazard ratio 17.7, 95% confidence interval 6.14 to 51.02) amongst other measurements, such as RV diameter and area at the end of diastole, as shown in Table 2.

In a multivariate Cox regression, forward and backward stepwise analysis adjusted by other variables, prolonged RV Tei index remained a significant predictor of death (hazard ratio 5.75, 95% confidence interval 1.69 to 19.51), and this parameter added incremental prognostic value to the NYHA functional class (Fig. 1) and to ejection fraction ≤ 30% (Table 3, Fig. 2). Cardiac mortality was compared by Kaplan–Meier analysis according to the quartiles of RV Tei index. When RV index was

Table 3
Multivariate analyses of clinical and Doppler echocardiographic variables predicting cardiac death in patients with Chagas' cardiomyopathy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA classes III–IV</td>
<td>2.15</td>
<td>1.16–4.29</td>
<td>0.030</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.96</td>
<td>0.91–0.99</td>
<td>0.026</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>5.75</td>
<td>1.69–19.51</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Fig. 3. Kaplan–Meier demonstrating cardiac mortality in patients classified in the highest quartile of RV Tei index versus those in lower 3 quartiles. Two subgroups have different prognosis on the basis of the value of the Doppler index of 0.56. Cum = cumulative.
>0.56 (highest quartile), the hazard ratio of cardiac death was significantly increased compared with lower quartiles (hazard ratio 5.29, 95% confidence interval 2.43 to 11.52) (Fig. 3).

3. Discussion

The principal finding of the current study was that prolonged RV Tei index was an independent powerful predictor of survival in patients with impaired LV function due to Chagas’ disease. This relation is independent of other clinical and echocardiographic variables that are known to have prognostic value such as NYHA functional class and LV ejection fraction.

3.1. Predictors of death in Chagas’ disease

Patients with Chagas’ disease have been recognized to have a very limited survival rate, particularly after developing symptoms of heart failure. Similar to a previous study from a tertiary center [19,20], the mortality rate of our group of Chagas’ patients (28%) was influenced by the high proportion of patients with advanced degrees of myocardial damage and progressive cardiac failure as the principal cause of death. The association between functional status and mortality has been previously recognized [12,13,20]. Different from our findings, some investigations [21,22] have suggested that male sex is a marker of LV dilatation, which is a risk factor for death in Chagas’ disease. Ventricular arrhythmias and atrioventricular blocks have been related to underlying myocardial dysfunction [20,23], which could explain the reported prognostic value of ECG. However, in our group of patients, ECG variables were not independent prognostic factors.

3.2. Prognostic value of RV function in Chagas’ cardiomyopathy

Although early RV involvement has been shown in studies analyzing biventricular function [3,4] in asymptomatic patients with chronic Chagas’ heart disease, we have previously shown that RV dysfunction by Doppler echocardiography was evident only when it was associated with dilatation and functional impairment of the LV [5].

In the present study, the most important result of our study is the independent prognostic information derived from the determination of the RV global function by the Tei index in patients with Chagas’ cardiomyopathy. Previous studies had demonstrated a similar result in patients with advanced heart failure of other etiologies, most of whom were awaiting heart transplantation [8]. In contrast, most of our patients were mildly symptomatic outpatients (79% in classes I and II), referred for evaluation of LV dysfunction because of positive serology tests for T. cruzi. However, even when the analysis is restricted to NYHA class II or III patients, this index remains as a predictor of death. This demonstrates the usefulness of RV function in stratifying patients with higher risk of death, whatever the degree of heart failure may be. RV dysfunction was a powerful predictor of survival when it was added to the multivariate model, after previously documented prognostic parameters, such as NYHA class and LV ejection fraction, had been included. Also, the prognostic impact of the RV Tei index remained when an analysis stratifying for different causes of death was performed.

In an echocardiographic study, Viotti et al. [13] found that LV systolic dimension and ejection fraction were independent prognostic factors of mortality in patients with Chagas’ disease, but RV function and markers of diastolic dysfunction were not evaluated. In another study, Mady et al. [12] studying patients with heart failure due to Chagas’ cardiomyopathy ranging from mild to severe forms, functional class, VO2max and LV ejection fraction were identified as effective predictors of survival. However, RV function was not analyzed.

Previous studies have compared the prognosis of patients with heart failure of several etiologies, showing different survival rates. It was shown that Chagas’ patients with LV dysfunction seemed to have a poorer clinical course than patients with similar degrees of dilated cardiomyopathy due to other etiologies, but RV function was not reported [6]. In a cohort of patients with heart failure of different etiologies [7], Chagas’ heart disease was the main prognostic factor for mortality, being more important than other markers of poor prognosis, such as LV ejection fraction, LV diastolic diameter and cardiac index. We may speculate that the worse prognosis reported in Chagas’ disease may be in part related to the frequent involvement of the RV in this disease. De Groeve et al. [9] studying patients with heart failure, demonstrated that RV ejection fraction was the most powerful predictor of survival, even when the population was stratified according to the etiology. However, to the best of our knowledge, the present study is the first to show that RV function, assessed by the Tei index, predicts survival in a group of patients with Chagas’ cardiomyopathy.

3.3. Prognostic importance of the RV index of myocardial performance (Tei index)

The Tei index is easily obtained and has been reported to be clinically useful in assessing global RV function. The index combines systolic and diastolic time intervals and is independent of heart rate and ventricular geometry. Because the index has a wide numeric range, it may better assist in reflecting various degrees of dysfunction. In the present study, we showed a strong correlation between a prolonged index and mortality, supporting the hypothesis that the index correlates with the clinical severity of RV dysfunction. In fact, we found an association between the subjective analysis of the RV by two-dimensional echocardiography and high values of the index. Previous studies [24,25] demonstrated the prognostic significance of the LV performance index in patients with heart failure. Tei et al. [11] have shown that the index correlates with the symptoms and survival in patients with primary pulmonary hypertension. However, different
from our findings, the RV Tei index did not correlate with RV systolic pressure in the presence of RV myocardial dysfunction.

Our study extends the reported prognostic significance of the RV Tei index in an ischemic population to a population of patients with non-ischemic underlying cause of LV dysfunction. When a cut off value of 0.56 was used for the RV Tei, mortality curves were well separated, indicating the potential of the index to predict an adverse outcome (Fig. 3).

Therefore, measurements of RV Tei index should be routinely performed in patients with Chagas’ disease and reduced LV systolic function, not only to estimate RV function but also to assess prognosis and risk stratification.

3.4. Pulmonary artery systolic pressure and RV systolic function

RV function is determined by intrinsic RV contractile function and by preload and afterload. In the present study, we demonstrated that there was a significant but weak correlation between RV index and PASP. It has been suggested that Chagas’ cardiomyopathy is a chronic myocarditis of an inflammatory nature with a progressive fibrotic process affecting the myocardium of both ventricles. Patients with RV dysfunction presented with more extensive biventricular involvement due to the primary pathologic process. These patients had a poor prognosis, independent of the level of the PASP. In patients with idiopathic cardiomyopathy, it has been demonstrated that myocardial compromise can affect the RV, causing significant depression of function, despite normal pulmonary artery pressure [26]. Previous studies have failed to demonstrate a correlation between PASP and RV function in patients with heart failure [27,28].

Elevated PASP has been established as a predictor of death in patients with heart failure with both ischemic and non-ischemic cardiomyopathy. Cappola et al. [29] demonstrated that mean pulmonary arterial pressure is the most important baseline hemodynamic predictor of death in patients with cardiomyopathy. It was a more powerful predictor of death among patients with myocarditis than among patients with other underlying causes of cardiomyopathy. In our study, however, multivariate analyses did not select PASP as an independent predictor of survival, either when we included this parameter as a continuous or as a qualitative variable, using the tricuspid flow velocity derived right ventricular to right atrial pressure gradient. This is in agreement with previous investigations in patients with dilated cardiomyopathy that have failed to show a consistent correlation between overall survival and the level of pulmonary artery pressure [9].

3.5. Clinical implications

Cardiac transplantation has become an accepted therapy for many patients with end-stage chronic Chagas’ heart disease [31]. A fairly rigid selection process is required in order to obtain excellent results in individual patients. Although it may be easy to identify the most severely ill patients with a poor prognosis for survival, timing may be somewhat difficult. Moreover, consideration based solely on a low ejection fraction has become less reliable since the introduction of optimal medical therapy. The results of the current study are likely to have a significant impact on the management of patients with chronic Chagas’ cardiomyopathy, identifying patients who are at higher risk of dying, so that it may be used to select the proper time for heart transplantation. These chagasic patients with RV dysfunction have low cardiac output without clinical evidence of elevated filling pressure, so they may be surprisingly stable clinically and often do not present with urgent symptoms. However, this is related with an ominous prognosis.

3.6. Study limitations

The RV has a complex geometry, which makes its systolic function difficult to analyze. No perfect method to analyze this chamber has been described and the ideal tool needs to be established. Magnetic resonance imaging is emerging as a very promising technique, but its use is not yet widely available. Although echocardiogram is far from being perfect to analyze the RV, it is a good method to detect clinically significant RV failure. Some new Doppler indices to analyze RV function, such as tissue Doppler imaging [30], have been described but, although reports using these parameters show promising results, they were not used in the present study.

Invasive methods were not used to obtain pulmonary artery pressure because of ethical issues, but non-invasive methods have been validated and shown to be accurate in calculating PASP. Although the estimate of right atrial pressure based on the appearance of the inferior vena cava gives a more accurate Doppler pulmonary artery pressure estimates it was not obtained in the present study. However, the Doppler-determined right ventricular to right atrial pressure gradient was also included for statistical analysis. Calculation of the right ventricular to right atrial pressure gradient in these patients provides an accurate non-invasive estimate of PASP [32].

The study end point was cardiac mortality including sudden death. It is assumed that sudden death was caused by a cardiac arrhythmia, although this cannot be proved conclusively.

4. Conclusions

This present study has shown for the first time that RV dysfunction was a predictor of mortality in patients with dilated chronic Chagas’ cardiomyopathy. RV function assessed by the Tei index added significant prognostic information on mortality, incremental to the NYHA functional class and to the standard echocardiographic evaluation of LV systolic function. A simple measure of this Doppler index, which analyzes both systolic and diastolic function of the RV, appears to be a useful non-invasive tool for risk
stratification in patients with heart failure secondary to Chagas’ cardiomyopathy. Patients with RV dysfunction are a particularly high-risk group and should be targeted for aggressive therapy.

References


Levels of anti-M₂ and anti-β₁ autoantibodies do not correlate with the degree of heart dysfunction in Chagas’ heart disease

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Abstract

Chronic chagasic cardiomyopathy (CCC) is characterized mainly by a dilated cardiomyopathy complicated by frequent and complex ventricular arrhythmias and/or conduction defects. The aim of the present study was to evaluate functional implications of neurotransmitter receptor autoantibodies in vivo. Sera from chagasic patients were used to measure the level of autoantibodies to peptide fragments from the M₂ cholineric and β₁ adrenergic receptors. Optical density values and the frequency of anti-M₂ and anti-β₁ antibodies were significantly higher in the indeterminate form and in CCC patients than in normal individuals. There was no correlation between levels of autoantibodies and clinical parameters of ventricular dysfunction, as assessed by echocardiography. Patients presenting with chronotropic insufficiency in exercise test had higher levels of anti-M₂ but not anti-β₁ autoantibodies. Although anti-M₂ and anti-β₁ antibodies do not appear to play a role in the pathophysiology of the heart failure that accompanies severe CCC, anti-M₂ cholineric autoantibodies may contribute to the pathogenesis of Chagas’ disease dysautonomia. © 2006 Elsevier SAS. All rights reserved.

Keywords: Chagas’ disease; Cardiomyopathy; Neurotransmitter receptor; Autoantibody

1. Introduction

In Latin America, chronic chagasic cardiomyopathy (CCC) affects around 30% of individuals infected with the protozoan parasite Trypanosoma cruzi. In a significant proportion of the latter, severe heart disease occurs and is frequently the cause of death. There are several hypotheses to explain the pathogenesis of severe heart disease in infected individuals, including the role of parasite persistence [1,2], autoimmune events [3–6] and microvascular dysfunction [7].

CCC is characterized mainly by a dilated cardiomyopathy complicated by frequent and complex ventricular arrhythmias and/or conduction defects [8]. Autonomic dysfunction occurs early in the course of the disease and may be associated with poor prognosis [9–12]. It has been argued that the fixation of neurotransmitter receptors by anti-receptor antibodies contributes to the autonomic dysfunction and poor clinical evolution [12–14]. Although a strong association between circulating antipeptide M₂ muscarinic acetylcholine receptor (mACHR) autoantibodies and the presence of low heart rate variability index, bradycardia and cardiac or esophageal autonomic dysfunction in chronic chagasic patients was verified [15], it is not known whether the presence and/or titer of anti-receptor antibodies correlates with CCC severity.

Here, the presence and levels of autoantibodies against peptide sequences belonging to adrenergic (β₁) and muscarinic...
(Mγ) receptors were evaluated in sera of a group of 58 individuals. We also investigated the correlation between the titers of autoantibodies and the following aspects of clinical CCC manifestations: left ventricular systolic function and response to effort.

2. Methods

2.1. Study population and subject evaluation

We performed this study with 6 healthy individuals and 52 chagasic patients with different clinical forms of the disease. All individuals were recruited at the Referral Center for Training in Infectious and Parasitic Diseases (CTR-DIP) at the Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG) and underwent a complete clinical examination and the following laboratory workup: full blood count, free T4, thyroid-stimulating hormone, glucose, potassium, creatinine, blood urea nitrogen, electrocardiogram (ECG), chest X-ray, a 24-h Holter examination, echo Doppler cardiology (ECHO) and a treadmill exercise test. Patients with hypertension, diabetes, thyroid or renal disturbances or any other cardiac or systemic diseases and those using steroid drugs were excluded from this study, as these conditions could prevent adequate interpretation of cardiac disease severity and immune parameters. The study received ethical clearance from the Ethics Review Board of Universidade Federal de Minas Gerais. Informed consent was obtained from all patients and non-infected individuals. Human experimental guidelines of the Brazilian Ministry of Health were followed in the performance of the experiments described here.

Chagasic patients were also categorized into groups according to the degree of heart dysfunction, as previously described [8]. Briefly, patients with an indeterminate form (IND) (n = 8) or chronic chagasic cardiomyopathy grade I (CCC I) (n = 8) were those with normal ECG and radiological studies or with only minor alterations in their ECHO (e.g. regional contraction defects), respectively. Patients classified as CCC II/III (n = 7) were those with minor or moderate ECO alterations, including block of the anterosuperior division of the left branch, right bundle branch block or uniform ventricular premature contractions. Patients classified as CCC IV (n = 15) were those manifesting severe conduction defects (e.g. left bundle branch block, left anterior divisional block with right bundle branch block or total atrioventricular block) or complex ventricular arrhythmias (complex ventricular premature beats, non-sustained or sustained ventricular tachycardia). Finally, patients classified as CCC V were those with ventricular enlargement, as observed on the ECHO, irrespective of the presence of arrhythmias or conduction defects [8]. The control group was made up of non-infected (NI) healthy individuals (Table 1).

A maximal stress test was performed according to the standard Bruce protocol. Chronotropic insufficiency was arbitrarily defined as the inability to achieve at least 85% of the predicted heart rate according to Astrand's formula (220-age) at peak exercise [16]. Patients underwent echocardiography with color flow using an ATL Philips HDI 5000 apparatus operated by an experienced echocardiographer, blinded to the clinical status of the patients. The left ventricular ejection fraction (LVEF) was obtained by Simpson's method using the software provided with the equipment [17].

2.2. Measurement of antibodies against anti-M2 cholinergic and anti-β1 adrenergic receptors

Serum samples were obtained by conventional venipuncture, centrifuged and stored at −80°C until use in an immunoassay (ELISA) with M2 synthetic cholinergic peptide [18] and β1 adrenergic synthetic peptide [14] as coating antigens, as previously described [19]. The sequence H-W-W-R-A-E-S-D-E-A-R-C-Y-N-D-P-K-C-C-D-F-V-N-R-C (20 μg/ml) corresponding to the second extracellular loop of the human β1-adrenergic receptor, and the sequence V-R-T-V-E-D-G-E-C-Y-I-Q-F-F-S-N-A-A-V-T-F-G-T-A (10 μg/ml), corresponding to the second extracellular loop of the human M2 cholinergic receptor, were used in the present studies. The samples were assayed in parallel at a 1/50 dilution, and optical density (OD) values were measured with an ELISA reader (Uniskan Laboratory System). This antibody dilution was found to be optimal to separate CCC patients from the control indeterminate form of Chagas' heart disease (data not shown).

2.3. Statistical analysis

Data are expressed as means ± S.E.M. or median and interquartile range. Analysis was performed using the computer program GraphPad (GraphPad, San Diego, CA, USA).

Table 1
Clinical characteristics of non-infected individuals and patients classified with different levels of CCC

<table>
<thead>
<tr>
<th></th>
<th>NI (n = 6)</th>
<th>IND (n = 8)</th>
<th>I (n = 8)</th>
<th>II/III (n = 7)</th>
<th>IV (n = 15)</th>
<th>V (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38 ± 6.9</td>
<td>47 ± 3.4</td>
<td>48 ± 8.2</td>
<td>47 ± 4.5</td>
<td>44 ± 2.0</td>
<td>43 ± 2.3</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>67</td>
<td>38</td>
<td>30</td>
<td>29</td>
<td>47</td>
<td>79</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>68 ± 6</td>
<td>64 ± 4</td>
<td>66 ± 2</td>
<td>60 ± 3</td>
<td>61 ± 2</td>
<td>45 ± 3*</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>48 ± 1</td>
<td>48 ± 1</td>
<td>49 ± 1</td>
<td>47 ± 2</td>
<td>50 ± 1</td>
<td>62 ± 1*</td>
</tr>
<tr>
<td>NVB24 h</td>
<td>ND</td>
<td>1</td>
<td>3</td>
<td>725</td>
<td>88</td>
<td>840</td>
</tr>
</tbody>
</table>

Values are shown as mean ± S.E.M., except for number of ventricular premature beats in 24 h that are shown as median [25–75% percentile]. NI, non-infected; IND, indeterminate form; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; NVB24, number of ventricular premature beats. *p < 0.01 when compared to non-infected and chagasic individuals. Non-normally distributed data were transformed before performing ANOVA and means comparisons.
Comparison between groups was carried out by using analysis of variance (ANOVA) followed by Student–Newman–Keuls post test (parametric distribution). Probability values were considered significant when \( P < 0.05 \).

### 3. Results

There was no significant difference in the age distribution between non-infected individuals and chagasic patients (Table 1). In agreement with the clinical parameters used to classify the group, patients with CCC V had lower left ventricle ejection fraction and greater diastolic diameter than patients with the other degrees of CCC. There was great variation in the number of ventricular premature beats over 24 h, and patients with CCC I/III or worse had greater numbers of premature beats than those with the IND form or CCC 1 (Table 1).

The distribution of anti-M2 cholinergic and anti-\( \beta_1 \) adrenergic autoantibodies detected by ELISA is shown in Table 2. It can be seen that the frequency of anti-M2 cholinergic autoantibody was higher in CCC patients (mean 86%) than in subjects with the IND form (mean 38%) of Chagas' disease. The non-infected individuals were negative in the study system. When the distribution of anti-\( \beta_1 \) adrenergic autoantibodies was evaluated, no differences in the frequency between CCC patients (mean 67%) and IND (mean 77%) were observed. Table 2 also shows the distribution of both autoantibodies in the different degrees of CCC, and it can be observed that no differences existed between the different degrees of CCC.

Fig. 1 shows the levels of cholinergic (M2) and adrenergic (\( \beta_1 \)) autoantibodies in serum from non-chagasic and chagasic individuals. It can be seen that chagasic patients presented greater levels of both autoantibodies. However, when chagasic patients were grouped according to disease severity \( [8] \), there was no difference in the OD values of both M2 and \( \beta_1 \) autoantibodies among the different clinical groups (Fig. 1). The lack of correlation between levels of autoantibodies and disease severity was further reinforced when the levels of antibodies and clinical parameters of ventricular dysfunction were studied (Table 3); there was clearly no correlation with the degree of heart dysfunction, as assessed by the left ventricular diameter and ejection fraction and the number of ventricular premature beats (Table 3).

The levels of anti-M2 antibodies were higher in patients with than in those without chronotropic insufficiency (Fig. 2). The levels of anti-\( \beta_1 \) antibodies were similar in patients with or without chronotropic incompetence (Fig. 2).

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Anti-M2 cholinergic</th>
<th>Anti-( \beta_1 ) adrenergic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. positive/total</td>
<td>Percentage</td>
</tr>
<tr>
<td>NI</td>
<td>0/6</td>
<td>0</td>
</tr>
<tr>
<td>IND</td>
<td>3/8</td>
<td>37.5*</td>
</tr>
<tr>
<td>CCC I</td>
<td>7/8</td>
<td>87.5</td>
</tr>
<tr>
<td>CCC II/III</td>
<td>5/7</td>
<td>71.4</td>
</tr>
<tr>
<td>CCC IV</td>
<td>14/15</td>
<td>93.3</td>
</tr>
<tr>
<td>CCC V</td>
<td>12/14</td>
<td>85.7</td>
</tr>
</tbody>
</table>

Microtiter wells were coated with 1 \( \mu \)g peptides (anti-M2 and anti-\( \beta_1 \)) and ELISA was carried out in the presence of sera from non-infected individuals (NI), indeterminate form (IND) and infected patients with different degrees of chronic chagasic cardiomyopathy (CCC 1 to V). OD values more than 2 SD above normal mean were considered positive. Cut-off values for anti-M2 cholinergic, 0.200, and for anti-\( \beta_1 \) adrenergic, 0.100. Prevalence values of anti-M2 cholinergic autoantibodies differ with \( *P < 0.0005 \) versus CCC 1 to V.

### Table 3

<table>
<thead>
<tr>
<th>LVEF (%)</th>
<th>LVEDD (mm)</th>
<th>NVPB (in 24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-adrenergic antibodies</td>
<td>( R = 0.053 )</td>
<td>( R = 0.052 )</td>
</tr>
<tr>
<td>Anti-cholinergic antibodies</td>
<td>( P = 0.725 )</td>
<td>( P = 0.733 )</td>
</tr>
</tbody>
</table>

LVEF, left ventricle ejection fraction; LVEDD, left ventricle end-diastolic diameter; NVPB, number of ventricular premature beats.
4. Discussion

Global systolic left ventricular dysfunction is the strongest predictor of morbidity and mortality during Chagas' heart disease [20,21]. It has been argued that an autoimmune response against antigens present in heart tissue may favor the development of the more severe forms of Chagas' cardiomyopathy. Antibodies against adrenergic and cholinergic receptors are among the many autoantibodies that have been described in Chagas' disease. For example, antibodies against β1-adrenoceptors and M2 mAChR have been found in the sera of patients and experimental animals with Chagas' disease [5,12,14]. Anti-M2 and anti-β1 antibodies are also found in sera of patients with non-Chagas forms of heart disease [22–25]. In Chagas' disease, these antibodies may induce acute functional alterations of isolated hearts from experimental animals (e.g. enhance or decrease contractility) and may also interact with the respective receptor and induce sequestration and endocytosis of the receptor [25–29]. Thus, it is clear that chagasic patients have anti-M2 or anti-β1 receptor antibodies and that the binding of these autoantibodies to the receptors may have functional consequences. In non-chagasic individuals, anti-β1 receptor antibodies were previously found in association with failure of left ventricular function, serious ventricular arrhythmias and elevated incidence of sudden death [22–25]. However, it is unclear whether individuals with heart failure caused by T. cruzi infection or by idiopathic factors are able to develop these heart alterations because they possess autoantibodies or whether they develop these autoantibodies as a consequence of chronic cardiac tissue injury.

Our results showed that individuals with CCC had elevated levels of antibodies against peptide sequences of both adrenergic and cholinergic receptors when compared with non-infected controls. The frequency of anti-M2 autoantibody was higher in CCC than in the IND form of the disease, suggesting that the anti-M2 autoantibody could be used as an early marker of evolution in Chagas' cardiomyopathy. However, levels of this autoantibody were not able to differentiate the various forms of Chagas' heart disease. This was reflected in the lack of correlation between levels of autoantibodies and the left ventricular ejection fraction or the left ventricular end-diastolic diameter, both important parameters of left ventricular dysfunction. Thus, although the presence of autoantibodies is associated with the presence of Chagas' heart disease, there seems to be no association between the levels of autoantibodies and the degree of left ventricular function. The latter results suggest that left ventricular dysfunction appears not to be the cause of augmented serum levels of anti-M2 and anti-β1 autoantibodies in Chagas' disease and, on the other hand, the autoantibodies may not have a direct role in the pathogenesis of the left ventricular dysfunction that accompanies the most severe cases of Chagas' disease. One limitation of the present study is that we measured levels of the antibodies against peptide sequences present in the relevant M2 and β1 receptors and not the function of the antibodies present in serum of patients. One could argue that it is the function and not the levels of antibodies that determine their function and putative relevance in causing or worsening disease. Most studies to date have evaluated the function of these receptors using isolated cells or organs from animals, a clearly artificial situation (see for example refs. [13] and [28]). We are currently trying to address this situation by evaluating the function of these receptors using tests of autonomic function, including heart rate variability analysis, best suited for the study of vagal influences, and muscle sympathetic nerve activity (RMSA), a procedure that uses microneurography to directly record sympathetic nerve activity to muscle.

Despite the apparent lack of association between left ventricular function and the level of autoantibodies, there were significant associations between the level of anti-M2 autoantibodies and the chronotropic response to exercise. Indeed, the level of anti-M2, but not anti-β1, receptor peptide autoantibodies was greater in patients in whom the presence of chronotropic incompetence during exercise testing was detected. One possibility to explain the latter findings could be that a partial agonist action of the antibodies could potentially increase parasympathetic tone during exercise. There is experimental evidence to support the latter possibility [26]. On the other hand, chronic activation of muscarinic receptors by anti-receptor antibodies may induce their internalization and, consequently, loss of parasympathetic function [27]. Heart rate increment during exercise is dependent on both vagal withdrawal and sympathetic activation [30] and baroreflex impairment and/or parasympathetic dysfunction may be responsible for chronotropic incompetence observed in Chagas' disease [30,31] and other cardiopathies [32]. Indeed, we have shown that, in Chagas' disease, reduced exercise-induced heart rate increase is clearly associated with reduced vagal modulation evaluated by heart rate and heart rate variability parameters [31]. Moreover, we have also observed an association between higher anti-M2 receptor autoantibody levels and reduced HF power density obtained using HRV frequency-domain analysis, an almost pure vagal index [33].
So, anti-M2 receptor autoantibodies, reduced vagal modulation and chronotropic incompetence are closely related phenomena in Chagas’ disease [33]. An alternative possibility is that there is loss of parasympathetic tonus that could be accompanied by unopposed adrenergic stimulation, leading to a loss of sympathetic tonus secondary to chronic stimulation. These hypotheses were not tested in the present study, and future studies should attempt to evaluate the expression (and perhaps function) of these receptors in the heart of patients with varying degrees of Chagas’ disease. Regardless of the mechanism, our results do suggest that the presence of anti-M2 autoantibodies may play a role in the dysautonomia frequently observed in chagasic patients [8,11].

In conclusion, we showed that the levels of anti-M2 or anti-β2 receptor autoantibodies in sera of patients with Chagas’ disease seemed not to correlate with the severity of left ventricular dysfunction. Nevertheless, the levels of anti-M2 autoantibodies were greater in patients with chronotropic incompetence. Overall, these results point to an important role of anti-M2 receptor autoantibodies in the pathogenesis of the dysautonomia but question the relevance of autoantibodies in the cascade of events leading to heart failure in Chagas’ disease.

Acknowledgments

This investigation received financial support from FAPEMIG, the UNDWP World Bank/WHO Special Program for Research and Training in Tropical Diseases (970728), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-Brazil), National Research Council (CONICET) of Argentina, TDR-WHO A20771, and the University of Buenos Aires (UBACYT), Buenos Aires, Argentina.

References


predicts a long-term benefit from adjuvant chemotherapy. These findings may be useful for deciding on postoperative treatment in patients who have received preoperative chemoradiotherapy.

Curigliano et al. suggest that improving the ypT0 rate by using newer, possibly more active drugs would improve survival. We argue that the surrogacy of ypT0 — or more generally of tumor downstaging for survival — is unproved and that prognostic association is not causality. Thus, if more effective systemic treatment is needed, we think that restricting its delivery to the preoperative setting to improve pathological complete response rates (ypT0) will not suffice to control distant disease spread.

A Risk Score for Predicting Death in Chagas’ Heart Disease

To the editor: Rassi et al. (Aug. 24 issue) developed a risk score to predict death in Chagas’ disease. They used data obtained by clinical examination and routine noninvasive tests. We analyzed our own data in order to evaluate the performance of the risk score in an independent sample. In a cohort of 183 patients with Chagas’ disease and without other cardiopathies or diseases, we followed 158 patients for 5 years or more at the Federal University of Minas Gerais, in Belo Horizonte, Brazil. All patients were evaluated by means of clinical examination, electrocardiography, chest radiography, echocardiography, Holter monitorring, and exercise testing. They were classified (according to the risk score) as low-, intermediate-, or high-risk patients, and their vital status at 5 years was assessed. Although our cohort differs from that of Rassi et al., including a smaller proportion of high-risk patients, the observed 5-year risk of death for each risk stratum

| Table 1. Risk of Death at 5 Years in the Original and External Cohorts According to the Risk Categories of Rassi et al. for Patients with Chagas Disease.† |
|---------------------------------|---------------------------------|
| **Risk Category**               | **Cohort of Rassi et al. (N=331)** | **UFMG Cohort (N=158)** |
|                                 | **No. (%)** | **Risk of Death at 5 Yr.** | **No. (%)** | **Risk of Death at 5 Yr.** |
| Low                             | 203 (61.3)  | 2 (0-5)                  | 110 (69.6)  | 3 (1-7)                   |
| Intermediate                    | 62 (18.7)   | 18 (8-28)                | 42 (26.6)   | 10 (4-22)                 |
| High                            | 66 (19.9)   | 63 (51-75)               | 67 (30-90)  |                           |
| Difference in probability of death† | 0.61          |                           | 0.64          |                           |
| C statistic (95% CI)‡           | 0.84 (0.79-0.89) |                           | 0.84 (0.72-0.96) |                           |

*The risk category was calculated by adding the points for each of the following risk factors: male sex (2 points), low QRS voltage on the electrocardiogram (2 points), nonsustained ventricular tachycardia on 24-hour Holter monitoring (3 points), segmental or global wall-motion abnormality on the echocardiogram (3 points), cardiomegaly on chest radiography (5 points), and New York Heart Association class III or IV (5 points). The prognostic index was categorized as follows: low risk (0 to 6 points), intermediate risk (7 to 11 points), and high risk (12 to 20 points). UFMG denotes Federal University of Minas Gerais, and CI confidence interval.
†The difference in the probability of death between the high- and the low-risk groups was calculated with the formula (P_{high} - P_{low}) * 100.
‡The C statistic is for the overall score.
CORRESPONDENCE

in the two cohorts was similar (Table 1). The score that Rassi et al. developed was a powerful predictive tool in our sample and may be valuable in clinical practice for stratifying the risk of death among patients with Chagas’ disease.

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TO THE EDITOR: In the study by Rassi et al., the percentage of patients treated with amiodarone was high, whereas the percentage treated with angiotensin-converting-enzyme (ACE) inhibitors or beta-blockers was low. ACE inhibitors have a known effect on the prognosis of these patients. Furthermore, the exclusion of patients over 70 years of age who had sustained ventricular tachycardia or pacemakers was not justified, in our opinion, for the predictive analysis of the risk of death. Finally, the multivariate analysis excluded some measures of left ventricular function derived from the echocardiogram. Only one such variable, segmental or global wall-motion abnormality, was included. Systolic function is an important predictor of the risk of death, as illustrated in a previous score of risk derived from a cohort of 856 patients.1 The results of the Cox model and the score could have changed substantially with the inclusion of left ventricular ejection fraction or other measures of systolic function.

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TO THE EDITOR: In the article by Rassi et al. concerning Chagas’ cardiomyopathy, we were particularly intrigued by the finding that low voltage on the electrocardiogram was an independent risk factor for death. We recently reported an association between low electrocardiographic voltage and adverse outcomes in patients with systolic heart failure.2 In our experience, low electrocardiographic voltage was associated with a reduced ratio of left ventricular mass to body-surface area. We would be interested in knowing whether low electrocardiographic voltage was associated with a similar cardiac phenotype in patients with Chagas’ cardiomyopathy.

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TO THE EDITOR: Chagas’ disease is too often neglected in developed countries, as noted by Maguire in his recent Perspective article.1 DNA vaccines able to prevent Trypanosoma cruzi infection in animal models have been repeatedly created in the past decade, based on highly conserved amastigote or trypomastigote antigens.2,3 However, in searching PubMed for publications on clinical trials for Chagas’ disease, my colleagues and I were astonished by the lack of any trials of preventive vaccination.

Aside from vector control and the screening of blood donors, vaccination is a very effective strategy for reducing costs associated with health care, especially in developing countries. When dealing with life-threatening complications from such a well-defined infectious disease, I believe that more money should be focused on prevention rather than on treatments that have low therapeutic indexes (e.g., most antiprotosomial medications) or very high cost (e.g., heart transplantation). What’s more, therapeutic vaccines (i.e., those administered during the chronic phase of Chagas’ disease) have been shown to reduce the severity of cardiomyopathy in infected animal models.4 When will the time come for a field trial?

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2. Boscardin SS, Kinosita SS, Feijmani AE, Rodrigues MM. Immunization with cDNA expressed by amastigotes of Trypano-

DR. RASSI AND COLLEAGUES REPLY: The observation and the contribution of Drs. Rocha and Ribeiro confirm the accuracy of our clinical risk score in predicting death in Chagas’ heart disease in another independent cohort. Dr. Viotti and colleagues are concerned that amiodarone was frequently administered to our study population (the development cohort), whereas ACE inhibitors and beta-blockers were not. The high use of amiodarone can be explained by the presence of palpitations in 30% of our patients and by the frequent occurrence of episodes of nonsustained ventricular tachycardia (46.5%). Regarding the low use of ACE inhibitors and beta-blockers, it should be noted that our study started in 1996 and was conducted before the widespread acceptance of these agents as standard therapy for patients with heart failure. Although heart failure in Chagas’ disease is treated in a similar fashion to heart failure from other causes, the efficacy of ACE inhibitors and beta-blockers for reducing the risk of death in this population remains to be established.

Dr. Viotti and colleagues also question why we excluded patients older than 70 years of age and with sustained ventricular tachycardia or pacemakers at study entry. We excluded these patients before analyzing the data to avoid the effects of confounding conditions and to prevent the inclusion of patients who were already known to have a poor prognosis or whose prognosis had already changed owing to a specific intervention.

Finally, Dr. Viotti and colleagues suggest that other measures of systolic left ventricular function, such as ejection fraction, should have been included in our analyses. Echocardiographic left ventricular function and dimension were evaluated by visual interpretation in our study. In clinical practice, the visual estimation of ejection fraction from two-dimensional echocardiography is common and has been reported to yield results that correspond closely to those obtained by other sophisticated methods.6,7 Left ventricular diastolic diameter was not included in the multivariate analysis because it showed collinearity with wall-motion abnormalities and cardiomegaly.

Dr. Kamath and Drazner wonder whether low electrocardiographic voltage in Chagas’ heart disease could be due to a reduced ratio of left ventricular mass to body-surface area. We believe that widespread myocardial fibrosis producing electrical silence plays a major role in the reduced electrocardiographic voltage. Although our study does not allow us to determine the mechanism, it does clearly show that reduced voltage, defined as voltage in each limb lead equal to or less than 0.5 mV, is an independent predictor of death in Chagas’ heart disease.

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DR. MAGUIRE REPLIES: Formidable technical and regulatory hurdles and the lack of a commercial market in wealthy countries have stood in the way of the development of vaccines for diseases such as Chagas’ disease that affect poor people in poor countries.2,3 However, large grants from the Bill and Melinda Gates Foundation and other donors, as well as private and public partnerships of companies, governments, nonprofit entities, and international organizations, are beginning to address these obstacles.3,4 In addition, recent studies of the pathogenesis of Chagas’ disease have diminished concerns that a vaccine would trigger an autoimmune reaction against the heart.4 Although the case for a vaccine to prevent T. cruzi
infection is compelling, it is likely that regional initiatives in Latin America will succeed in interrupting vector-borne and transfusion-associated transmission before such a vaccine becomes available. Dr. Focosi correctly points out the shortcomings of current treatments, and better drugs or an effective therapeutic vaccine would indeed bring immeasurable benefit to the million or more persons already infected with T. cruzi.

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The Value of Medical Spending in the United States

TO THE EDITOR: Medical care contributed to improvements in life expectancy between 1960 and 2000, as reported by Cutler et al. (Aug. 31 issue). However, when we take a longer look, it is striking how little medical care contributed to life expectancy during the full span of the 20th century. Between 1950 and 2000 (years that coincided with the explosion in medical technology in the United States), life expectancy increased by 8.8 years; however, it increased by 20.9 years from 1900 to 1950, years when medicine often had little to offer in the way of meaningful interventions. Most of the decline in death rates for the infectious diseases that were the principal causes of death during this period occurred before a treatment or vaccine for these diseases had been discovered. A rising standard of living and the associated improvements in housing, sanitation, and nutrition account for many times more years added to our life expectancy than all aspects of medical care combined. We should keep this fact in mind when we recall that the life expectancy of a black infant born today is still 5.3 years less than that of a white infant.

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TO THE EDITOR: Cutler et al. misrepresent the relative inefficiency of the U.S. health care system. It is only in the past 10 years that “medical spending has increased at roughly the same rate in all countries,” as ranked by the Organization of Economic Cooperation and Development (OECD). This temporary phenomenon was due to the brief success of managed care in holding down costs in the mid-1990s.

During the period discussed by Cutler et al. (1960–2000), the United States ranked near the bottom internationally in terms of improving health and the relative efficiency of its health care spending. Yes, health care costs are rising everywhere. But the United States required 1.19 percentage points of the national gross domestic product (GDP) for new health care spending for every year of improved life expectancy, the highest ratio in the world. Most other countries hovered around half a percentage point of GDP per year of increased longevity.

Moreover, the United States now ranks 21st out of 30 OECD countries in longevity, despite having the highest health care costs in the world. The country was 16th among the same group in 1960. That's not what I would call value for money.

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Chronic Incompetence and Abnormal Autonomic Modulation in Ambulatory Chagas Disease Patients

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Barros, M.D.,§ Vladimir da Costa Val Barros, M.D.,‡§ Adelina Martha
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Background: Chagas disease (ChD) patients might present chronotropic incompetence during ex-
ercise, although its physiopathology remains uncertain. We evaluated the heart rate (HR) response to exercise testing in ChD patients in order to determine the role of autonomic modulation and left
ventricular dysfunction in the physiopathology of chronotropic incompetence.

Methods: ChD ambulatory patients (n = 170) and healthy controls (n = 24) underwent a stan-
dardized protocol including Doppler echocardiography, Holter monitoring, HR variability analysis,
brain natriuretic peptide (BNP) measurement, and maximal exercise testing. The chronotropic
response was calculated as the percentage of predicted HR achieved and the HR increment (ΔHR)
during exercise. ChD patients were divided according to the absence or presence of cardiopathy and
chronotropic incompetence (< 85% predicted HR).

Results: Chronotropic incompetence was present in 34 (20%) of all ChD patients. The group with
cardiopathy displayed reduced ΔHR (91 ± 19 bpm) during exercise in comparison with ChD patients
without cardiopathy (100 ± 19 bpm). Both the values observed in ChD groups were significantly
different from those of controls (112 ± 13 bpm). Exercise duration, maximal oxygen consumption, and
systolic blood pressure increment were significantly reduced in patients with abnormal chronotropic
response. ΔHR during the exercise was significantly correlated with markers of autonomic control
of sinus node, such as rest HR (r = −0.498, P ≤ 0.001), peak HR during exercise (r = 0.775, P ≤
0.001), minimal HR during Holter recording (r = −0.231, P = 0.003), and high- and low-frequency
components of short-term HR variability (r = 0.188, P = 0.042 and r = 0.203, P = 0.027). Neither
left ventricular function nor BNP levels were independently related to the presence of chronotropic
incompetence.

Conclusions: Chronotropic incompetence may be considered an early sign of autonomic dysfunc-
tion in ChD patients.

Chagas disease; exercise test; chronotropic incompetence; autonomic nervous system; heart rate
variability

Chagas disease (ChD) is caused by the protozoon Trypanosoma cruzi and represents one of the main
causes of mortality in Latin America, where nearly 15 million individuals are infected. The disease has
a high socioeconomic impact as a result of the in-
fecction of a relevant population contingent during
their most productive years. The clinical course
of ChD is quite variable; while some infected
individuals develop fatal heart disease, others remain completely asymptomatic throughout life.\textsuperscript{1,2}

In their seminal study published in 1922, Chagas and Villela described a peculiar absence of chronotropic response to atropine in Chagas cardiopathy patients.\textsuperscript{3} Further studies confirmed that ChD patients might present chronotropic incompetence during dynamic and isometric exercise\textsuperscript{4-8} or dobutamine stress.\textsuperscript{9} Nonetheless, the physiopathology of chronotropic incompetence in ChD is far from being elucidated. Left ventricular dysfunction,\textsuperscript{10} parasympathetic dysfunction,\textsuperscript{4,6,7} sympathetic denervation,\textsuperscript{11} reduced circulating norepinephrine levels,\textsuperscript{12} autoantibodies against \(\beta\)-adrenergic receptors\textsuperscript{3,13} and sinus node dysfunction\textsuperscript{13} are the factors that have been considered as possible determinants of the observed chronotropic incompetence. An additional point of interest derives from the fact that chronotropic incompetence is of negative prognostic significance in other clinical settings.\textsuperscript{14}

The objective of the present study was to assess the heart rate (HR) response to a standard treadmill exercise test in a large sample of ambulatory ChD patients in order to determine the role of autonomic heart control, studied by time and frequency-domain analysis of HR variability, and left ventricular dysfunction (evaluated by echocardiography), in the physiopathology of chronotropic incompetence.

**METHODS**

**Patient Population**

Patients were recruited at the Chagas Disease Outpatient Center of the Federal University of Minas Gerais, Brazil, to which they were referred from blood banks or primary care services for the determination of suspected or confirmed infection with \(T. cruzi\). A confirmed diagnosis of ChD on serological grounds was defined by the presence of two or more different positive reactions to \(T. cruzi\) (indirect immunofluorescence, enzyme-linked immunosorbent assay, or indirect hemagglutination). Patients who agreed to participate and signed a written informed consent were submitted to a standard screening protocol that included medical history, physical examination, ECG, laboratory examination, and chest roentgenogram. Exclusion criteria were [1] other systemic disorders, like cardiovascular disease, diabetes, thyroid dysfunction, chronic obstructive pulmonary disease, renal or hepatic failure, anemia, and high blood pressure; [2] pregnancy; [3] alcoholism; [4] use of drugs that could compromise the chronotropic response in exercise testing; [5] chronic atrial fibrillation or pacemaker rhythm at basal ECG; and [6] exercise testing interruption due to technical or medical reasons (chest pain, dizziness, arrhythmia, and abnormal increase in blood pressure). The study population consisted of 170 ambulatory patients with confirmed serological findings of ChD and absence of other systemic disorders. A control group of 24 healthy volunteers aged 20–70 years with no risk or serological evidence of ChD was also submitted to the same evaluation.

**Study Protocol**

The Research Ethical Board of the Federal University of Minas Gerais approved the study protocol. Doppler echocardiographic features,\textsuperscript{15} brain natriuretic peptide (BNP) levels,\textsuperscript{16} and HR variability indices\textsuperscript{17} of this population have been previously reported and other methodological aspects can be obtained in the cited articles. Patients underwent Doppler echocardiography with color flow using an ATL Philips HDI 5000 apparatus (Bothell, Washington, USA) operated by an experienced echocardiographer (M.V.L.B.), blinded to the clinical status of the patients.\textsuperscript{15} The left ventricular ejection fraction (LVEF) was obtained by Simpson's method using the software provided with the equipment. We measured BNP by radioimmunooassay (RIA, all samples in the same assay) using hBNP as standard, tyr\textsuperscript{0}-BNP for iodination, and a specific hBNP antibody (Peninsula Laboratories, USA), as previously described.\textsuperscript{16}

Twenty-four-hour Holter monitoring was performed using a portable three-channel cassette tape recorder (Dynamis, Cardios, São Paulo, Brazil). Subjects were encouraged to continue with their normal everyday activities during the recordings, avoiding physical exercise or drugs that could interfere with autonomic function. Analysis of the tapes was performed when at least 18 hours of good quality tracings were available. The recordings were analyzed on a Burdick/DMI/Cardios Hospital Holter System (Spacelabs Burdick, Deerfield, Wisconsin/Cardios, São Paulo, Brazil) by a semiautomatic technique. Minimal, mean, and maximal HR, the number of ectopic ventricular and supraventricular beats, and the occurrence of pauses and
heart blocks were recorded. The following time-domain HR variability indices were calculated: standard deviation of R-R intervals (SDNN) and square root of the mean of squares of differences between adjacent R-R intervals (rMSSD). Spectral analysis of HR variability was computed using Fast Fourier transformation (Burdick HRV software Space Labs, Burdick, Deerfield, Wisconsin, USA) and was expressed as total power [0.01–1.00 Hz] and low-frequency [0.04–0.15 Hz] and high-frequency [0.15–0.40 Hz] components. The low-to-high frequency component ratio (LF/FF) was also calculated. In order to minimize nonstationary oscillations of HR variability, spectral analysis was performed during sleep, in a 5-minute segment of good quality and without ectopic beats, close to the lowest HR. For technical reasons, frequency-domain analysis was performed only in the last 115 consecutive patients with ChD.

A maximal stress test was performed according to the standard Bruce protocol. Patients were encouraged to exercise until they reached their maximal effort. HR and blood pressure were measured at rest, during each stage of exercise, at peak exercise, and during recovery. Exercise capacity as estimated maximal oxygen consumption (VO2 max) was calculated based on a previously published nomogram. Subjects were not credited with achieving any given stage of exercise unless they reached the point when blood pressure was measured, namely, 2 minutes into that stage. Patients who could not achieve maximal effort due to medical or technical reasons were not included in this study since they could be erroneously classified as having chronotropic incompetence even if the stress testing was interrupted by arrhythmias or dizziness. The characteristics studied included resting HR, peak HR, peak–rest HR increment (ΔHR) during exercise test, percent of age-predicted HR achieved, peak systolic blood pressure, effort-induced systolic blood pressure increment, estimated VO2 max, double product, and the presence of arrhythmias.

ChD and control subjects were compared according to general features and HR response to exercise. For these comparisons, ChD patients were divided into two groups according to the presence (group II) or absence (group I) of at least one of the typical evidences of Chagas cardiopathy, defined as (1) NYHA functional class; (2) ECG abnormalities including 2nd or 3rd degree atrioventricular or intraventricular blocks, abnormal Q wave, ventricular ectopic beat per tracing, low voltage QRS in standard leads; (3) cardiothoracic index >0.50; and (4) LVEF <40% or presence of ventricular aneurysms.

For further analysis, ChD patients were divided into two groups according to the presence (group B) or absence (group A) of chronotropic incompetence, defined as the inability to achieve at least 85% of the predicted HR according to Astrand's formula [220-age] at peak exercise. General features, BNP levels, left ventricular function variables, HR variability indices, and exercise test features were compared between the two groups and correlated with the peak–rest ΔHR during exercise test, considered here as an index of chronotropic competence.

Statistical Analysis

Data obtained from continuous variables are expressed as mean ± standard deviation or median with the interquartile range. Pearson's or Spearman's correlation coefficients were used to measure correlation between variables. When necessary, mathematical transformation of nonnormal or heteroscedastic data was performed to allow subsequent analysis. Baseline features and transformed indices for the groups were compared by Student's t-test or Wilcoxon test, when appropriate. Since the age was significantly correlated with many indices studied in multiple linear regression models, covariance analysis (ANCOVA) was used when necessary. In the ChD group, univariate and multivariate analysis were performed considering ΔHR during exercise test as dependent variable, and age, ejection fraction, HR before stress test, Holter and HR variability indices, and BNP as independent variables. Data concerning categorical variables were expressed as proportions and were compared by the chi-square test for 2 × k contingency tables. A P value of <0.05 was considered significant.

RESULTS

ChD patients were slightly older than controls but with similar gender distribution (Table 1). ChD patients with cardiopathy (group II) achieved smaller estimated VO2 max and blood pressure increment during effort in comparison to controls. Effort-induced ventricular ectopic beats were more frequent in ChD patients than in controls. When comparing group I and group II patients, ventricular ectopies were significantly more frequent also in patients with cardiopathy.
Table 1. General Characteristics of Controls and Patients with Chagas Disease

<table>
<thead>
<tr>
<th>Variable Group</th>
<th>Controls n = 24</th>
<th>Chagas I n = 52</th>
<th>Chagas II n = 118</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.6 ± 9.3</td>
<td>39.8 ± 9.0</td>
<td>41.8 ± 9.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Female* (% )</td>
<td>7 (29)</td>
<td>21 (40)</td>
<td>52 (44)</td>
<td>0.397</td>
</tr>
<tr>
<td>LVEF% (%)</td>
<td>64 (61–66)</td>
<td>62 (60–65)</td>
<td>60 (50–64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ln BNP values (pg/mL)</td>
<td>4.6 ± 0.6</td>
<td>4.7 ± 0.4</td>
<td>4.9 ± 0.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Estimated VO₂ max ml/kg per min</td>
<td>49.4 ± 10.1</td>
<td>45.8 ± 10.6</td>
<td>44.2 ± 8.6</td>
<td>0.033c</td>
</tr>
<tr>
<td>ΔSystolic BP (mmHg)</td>
<td>55.8 ± 12.8</td>
<td>48.2 ± 16.4</td>
<td>43.0 ± 21.1</td>
<td>0.015c</td>
</tr>
<tr>
<td>Rest HR (bpm)</td>
<td>71 ± 13</td>
<td>70 ± 12</td>
<td>71 ± 12</td>
<td>0.795c</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>112 ± 13</td>
<td>100 ± 19</td>
<td>91 ± 19</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>% Maximal age-predicted HRB</td>
<td>101 (98–104)</td>
<td>96 (90–99)</td>
<td>85 (85–96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronotropic incompetencea (% )</td>
<td>0 (0–6)</td>
<td>5 (9.6)</td>
<td>29 (24.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Effort-induced VPCa (%)</td>
<td>4 (17)</td>
<td>23 (44)</td>
<td>68 (58)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values were expressed as mean ± SD when appropriate, except a when expressed as proportions, b when expressed as medians (interquartile range); c adjusted for age. HR = heart rate. bpm = beats per minute. LVEF = left ventricular ejection fraction. BNP = brain natriuretic peptide. VO2 max = maximal oxygen consumption. BP = blood pressure. Δ systolic BP = peak-rest BP. ΔHR = peak-rest HR increment. Chronotropic incompetence = inability to achieve at least 85% of the age-predicted HR. VPC = ventricular premature beats.

Although mean HR before stress testing was not different among groups, ΔHR at the end of maximal exercise was reduced in both the ChD groups and was more pronouncedly reduced in group II. Chronotropic incompetence, defined as inability to achieve at least 85% of the age-predicted HR, was detectable only in ChD patients: 5 in group I (9.6%) and 29 in group II (24.6%, P = 0.003, Table I and Fig. 1).

Among the 170 ChD patients studied, 34 (20%) failed to achieve 85% of the age-predicted maximum HR and were assigned to group B (patients with chronotropic incompetence). Group A consisted of 136 (80%) patients without chronotropic incompetence. General and echocardiographic features and BNP levels were similar between groups (Table 2). LVEF values were slightly reduced in the group with chronotropic incompetence (group B). Exercise duration, VO2 max, and systolic blood pressure increment during the exercise were significantly reduced in patients with abnormal chronotropic response (Table 2). HR and HR variability indices were not significantly different between patients with and without chronotropic incompetence (Table 3). Ventricular ectopic beats during Holter monitoring were more frequent in group B patients.

Correlation analysis showed significant correlations (Table 4) between ΔHR during exercise test and the following parameters: age (Fig. 2A), HR before the exercise (Fig. 2B), peak HR at the end of the exercise, minimal HR during 24-hour Holter recording (Fig. 2C), and both high- and low-frequency components of short-term HR variability (Fig. 2D). In multivariate analysis, HR before and at the peak of the exercise were the independent predictors of the chronotropic response. LVEF was marginally correlated to ΔHR. Ventricular premature beats number in 24 hours was well correlated with ΔHR (rs = −0.238, P = 0.002). Both parameters did not remain significant predictors of chronotropic incompetence after multivariate analysis.

Figure 1. Percent of age-predicted HR increment achieved during exercise test in controls and Chagas disease patients groups I and II.
Table 2. General and Echocardiographic Features of Chagas Disease Patients with (group B) and without (group A) Chronotropic Incompetence

<table>
<thead>
<tr>
<th>Variable Group</th>
<th>A</th>
<th>B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.7 ± 9.5</td>
<td>42.1 ± 8.2</td>
<td>0.866</td>
</tr>
<tr>
<td>Femalea (n (%))</td>
<td>59 (43)</td>
<td>14 (41)</td>
<td>0.849</td>
</tr>
<tr>
<td>Right BBBb (n (%))</td>
<td>33 (24)</td>
<td>12 (35)</td>
<td>0.278</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62 (57-65)</td>
<td>59 (50-62)</td>
<td>0.020</td>
</tr>
<tr>
<td>LV diastolic dimensionc (mm)</td>
<td>50 (48-55)</td>
<td>55 (48-56)</td>
<td>0.153</td>
</tr>
<tr>
<td>Diastolic dysfunctiond (n (%))</td>
<td>15 (11)</td>
<td>6 (17)</td>
<td>0.395</td>
</tr>
<tr>
<td>LV wall motion scoree (mm)</td>
<td>1.00 (1.00-1.31)</td>
<td>1.09 (1.00-1.86)</td>
<td>0.187</td>
</tr>
<tr>
<td>LV aneurysm (n (%))</td>
<td>25 (18)</td>
<td>8 (23)</td>
<td>0.447</td>
</tr>
<tr>
<td>BNPf (pg/mL)</td>
<td>38.7 (28.0-50.9)</td>
<td>40.7 (32.7-69.4)</td>
<td>0.280</td>
</tr>
<tr>
<td>ΔSystolic BP (mmHg)</td>
<td>47 ± 19</td>
<td>34 ± 19</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of exercise (s)</td>
<td>772 (621-886)</td>
<td>621 (570-785)</td>
<td>0.002</td>
</tr>
<tr>
<td>Estimated VO₂ maxg (ml/kg per min)</td>
<td>45 (37-51)</td>
<td>37 (35-46)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values were expressed as mean ± SD when appropriate, except a when expressed as proportions; b when expressed as medians (interquartile range); BB = right bundle branch block; LVEF = left ventricular ejection fraction; LV = left ventricular; BNP = brain natriuretic peptide; s = seconds, BP = blood pressure; Δsystolic BP = peak-rest BP; VO₂ max = maximal oxygen consumption.

DISCUSSION

Although chronotropic incompetence is a recognized feature of ChD, its pathogenesis remains uncertain.

Patients with chronotropic incompetence exhibited a significantly impaired exercise capacity, as reflected by a reduced duration of exercise and VO₂ max in comparison to ChD patients with a normal HR response. The prevalence of chronotropic incompetence was 20% in this clinic-based sample, composed of ambulatory patients referred from blood banks or primary care services, generally with normal milder forms of the disease. This prevalence, however, could underestimate the real incidence of this phenomenon, since patients who interrupted their tests because of symptoms and for medical reasons were excluded from the study.

Chronotropic incompetence has been recognized as a factor that limits the exercise capacity of heart failure patients. Moreover, in an asymptomatic population-based cohort, the presence of chronotropic incompetence was predicted by increased cavity size and, among men, by depressed systolic function. Since left ventricular

Table 3. Holter Monitoring and Heart Rate Variability Indices in Chagas Disease Patients with (group B) and without (group A) Chronotropic Incompetence

<table>
<thead>
<tr>
<th>Variable Group</th>
<th>A</th>
<th>B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-hour HR (bpm)</td>
<td>74 ± 9</td>
<td>71 ± 12</td>
<td>0.251</td>
</tr>
<tr>
<td>Maximal 24-hour HR (bpm)</td>
<td>135 ± 18</td>
<td>130 ± 14</td>
<td>0.203</td>
</tr>
<tr>
<td>Minimal 24-hour HR (bpm)</td>
<td>48 ± 7</td>
<td>48 ± 9</td>
<td>0.845</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>152 (120-173)</td>
<td>144 (111-200)</td>
<td>0.744</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>29 (23-40)</td>
<td>35 (21-49)</td>
<td>0.421</td>
</tr>
<tr>
<td>VPC (n/24 hour)</td>
<td>33 (5-113)</td>
<td>393 (13-3078)</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean RR (spectral analysis) (ms²)</td>
<td>1040 (965-1127)</td>
<td>990 (941-1123)</td>
<td>0.484</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>333 (150-567)</td>
<td>183 (104-561)</td>
<td>0.775</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>470 (308-968)</td>
<td>386 (203-1598)</td>
<td>0.685</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.82 (0.92-3.22)</td>
<td>1.88 (0.46-4.6)</td>
<td>0.639</td>
</tr>
</tbody>
</table>

Values were expressed as mean ± SD when appropriate, except a when expressed as medians (interquartile range); HR = heart rate; bpm = beats per minute; SDNN = standard deviation of normal R-R intervals; RMSSD = root mean square of successive differences; VPC = ventricular premature beats; HF = high frequency; ms² = milliseconds squared; LF = low frequency; LF/HF = LF/HF ratio.
Table 4. Correlation Coefficients among Peak–Rest HR Increment (ΔHR) During Exercise Test and Age, Ejection Fraction, Rest HR Before and at the Peak of the Exercise, HF and LF Components of Spectral Analysis, and Minimal, Mean, and Maximal HR During 24-hour Holter in 170 Chagas Disease Patients

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>EF</th>
<th>HR Resting</th>
<th>HR Peak</th>
<th>Minimal 24-Hour HR</th>
<th>Maximal 24-Hour RR</th>
<th>LnHF</th>
<th>LnLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHR</td>
<td>−0.315</td>
<td>0.134^a</td>
<td>−0.498</td>
<td>0.775</td>
<td>−0.231</td>
<td>0.095</td>
<td>0.188</td>
<td>0.205</td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td>0.086</td>
<td>0.000</td>
<td>0.000</td>
<td>0.003</td>
<td>0.226</td>
<td>0.042</td>
<td>0.027</td>
</tr>
</tbody>
</table>

All coefficients were calculated by Pearson's product-moment correlation, except ^a calculated by Spearman's method. All coefficients, except for age and EF, were adjusted for age. Abbreviations as in Tables 1 and 2.

dysfunction is a major feature of Chagas cardiopathy, it could be hypothesized that chronotropic incompetence might be secondary to depressed left ventricular systolic performance in ChD. In this study, we found a limited correlation between LVEF and chronotropic response which, however, was no longer significant at multivariate analysis. Moreover, BNP levels, an indirect marker of neurohumoral activation in ChD patients with depressed ventricular function, were also not

Figure 2. Scatter plots of peak–rest HR increment (ΔHR) during exercise test and age (A), HR before stress test (B), minimal HR during 24-hour Holter monitoring (C), and High-frequency component of spectral analysis (D) in 170 Chagas disease patients.
correlated with HR response to exercise. Both findings make this hypothesis unlikely.

Abnormal HR response to effort has been attributed to autonomic dysfunction in heart failure and ChD. Gallo et al. showed, in a small number of ChD patients, a lower HR increase at a 5-minute treadmill protocol, as well as abnormal HR response to atropine and Valsalva maneuver. In a subsequent study, the same authors found that Chagas cardiopathy patients had a lower HR response during the initial 10 seconds of discontinuous dynamic exercise on a bicycle ergometer in comparison with control subjects. Both findings were considered to reflect an abnormal vagal modulation, which was particularly evident during the initial phases of exercise, when vagal withdrawal is likely to occur. At variance with our findings, Gallo and coworkers did not find differences in VO2 max and other metabolic responses to long-term exercise among groups. Indeed, some discordant findings may be explained by the different designs and aims of the studies. Gallo and coworkers performed physiological studies in small groups of patients in order to evaluate the functional conditions of the two divisions of the autonomic nervous system. We performed a clinic-based study using a standard treadmill protocol with the objective of recognizing the determinants of chronotropic incompetence in ChD.

In the present study, we observed a positive correlation between HR increase induced by exercise and most of the HR and HR variability parameters that reflect vagal modulation. ΔHR was significantly correlated with HR before exercise and minimal nocturnal HR during Holter recording. Moreover, there was a correlation between ΔHR and low- and high-frequency components of HR variability measured on a nocturnal 5-minute period, when spectral components are less likely to reflect the prevailing parasympathetic modulation. Thus, patients with evidence of a preserved vagal modulation of sinus node function displayed the maximum increase of HR during exercise, whereas patients with signs of reduced vagal modulation exhibited chronotropic incompetence. The strong correlation between age and ΔHR also supported the concept that a preserved autonomic innervation was a major determinant of a physiological chronotropic response to exercise.

The significant correlation between ΔHR and peak HR at the end of exercise, as well as low-frequency component of HR variability was consistent with the hypothesis that a preserved sympathetic innervation is also likely to play a critical role. Regarding this latter point, it may be relevant to recall that, in this study, ChD patients with chronotropic incompetence also displayed blunted systolic blood pressure response, which could be related to abnormal sympathetic influence. Indeed, Losa et al. described reduced norepinephrine levels in heart failure patients with ChD compared to patients with heart failure of other etiologies, although these observations were not confirmed in a subsequent study. Regional cardiac sympathetic denervation was also observed early in the course of Chagas cardiomyopathy by iodine-123 meta-iodobenzylguanidine myocardial scans. Several studies have shown the existence of circulating antibodies that bind to β-adrenergic and muscarinic cholinergic receptors in ChD. The deposited autoantibodies behaving as agonists could induce desensitization and/or down-regulation of the receptors and lead to a progressive receptor blockade, determining a partial sympathetic and parasympathetic denervation. Indeed, postsynaptic desensitization of the β-adrenergic receptor has been proposed as a mechanism of attenuated HR response to exercise in heart failure patients and cannot be excluded in ChD patients.

The presence of an abnormal autonomic modulation in ChD patients is an established finding. In previous studies, we reported that this alteration was independent of the presence of left ventricular dysfunction. In this study, we observed that chronotropic incompetence could also be present in ChD patients without cardiomyopathy and was not directly related to the presence of LV dysfunction or indirect signs of neurohumoral activation. Indeed, most patients with and without chronotropic incompetence had normal indices of LV systolic and diastolic function and dimension. Nonetheless, chronotropic response was more profoundly depressed in patients with signs of cardiac involvement; in these subjects, a blunted systolic blood pressure response and a greater number of effort-induced ventricular ectopic beats were also observed. All these findings could be interpreted as an indirect evidence of a more extensive derangement of cardiac function and regulatory mechanisms.

Some limitations of the present study should be pointed out. Pharmacological evaluation of the sinus node function was not performed and subclinical form of sinus node syndrome cannot be
excluded. Our results cannot be generalized to ChD patients with more severe heart disease, since we excluded from this study those with atrial fibrillation, pacemaker rhythm as well as those that could not achieve maximal effort due to serious symptoms or ECG abnormalities. Chronotropic incompetence was arbitrarily defined as the inability to achieve at least 85% of the predicted HR, a criterion that has been proposed and used by others. Frequency-domain analysis of HR variability was performed using commercial equipment in a 5-minute segment close to the lowest HR during sleep to better evaluate vagal modulation and to avoid nonstationarity that could hamper spectral analysis. Additional information on autonomic control mechanisms could have been obtained by analyzing recordings collected in laboratory settings, especially during controlled breathing or tilt test.

In conclusion, 20% of ChD patients in a clinic-based sample presented chronotropic incompetence, which significantly impaired the exercise capacity, but was not directly related to LV dysfunction. Presence of a physiological autonomic modulation was a major determinant of a preserved chronotropic response to exercise. Chronotropic incompetence may be considered an early sign of autonomic dysfunction in ambulatory ChD patients.

Acknowledgments: This study was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES), from Brazil, and Consiglio Nazionale delle Ricerche (CNR), from Italy.

REFERENCES


Índice cronotrópico-metabólico na doença de Chagas

Chronotropic-metabolic index in Chagas’ disease

Ana Luiza Lunardi Rocha¹, Manoel Otávio da Costa Rocha¹, Bruno Otávio Soares Teixeira³, Federico Lombardi³, Cláudia Drumond Guimarães Abreu², Roberto José Bittencourt¹, Márcio Vinicius Lins Barros¹,⁵ e Antonio Luiz Pinho Ribeiro¹,²

RESUMO
A insuficiência cronotrópica constitui achado comum entre os pacientes chagásicos. Novas metodologias estão sendo empregadas na avaliação da resposta cronotrópica em vários grupos de pacientes. O índice cronotrópico-metabólico, um desses novos métodos, quantifica a relação entre o aumento da frequência cardíaca e o consumo máximo de oxigênio (VO₂ max) durante o teste ergométrico. A resposta normal é linear, com índice em torno de 1.0. Objetivamos avaliar a resposta cronotrópica e em indivíduos saudáveis e pacientes chagásicos com e sem disfunção ventricular esquerda, utilizando-se do índice cronotrópico-metabólico. Foram avaliados 171 pacientes com doença de Chagas sem doenças associadas e 24 controles submetidos a protocolo clínico e ao teste ergométrico máximo. Os chagásicos foram divididos em dois grupos: CH₁ = pacientes com fração de ejeção (EF) > 35% e CH₂ = EF<40%. A análise e o cálculo do índice cronotrópico-metabólico foram feitos pelo método de Wilkoff. Os pacientes chagásicos apresentaram maior idade e maior prevalência de bloqueio completo de ramo direito, assim como menor VO₂ max ao teste ergométrico. Ambos os grupos de chagásicos apresentaram menor inclinação do índice cronotrópico-metabólica (CH₁: 0.91±0.10, CH₂: 0.89±0.08) do que os controles (1.0±0.12, p < 0.001). Pacientes com doença de Chagas com e sem disfunção ventricular esquerda podem apresentar resposta cronotrópica deprimida, manifesta por menor inclinação do índice cronotrópico-metabólico.


ABSTRACT
Chronotropic incompetence is a common feature in Chagas’ disease patients. New methodologies are now available to evaluate the chronotropic response in different subsets. The chronotropic-metabolic index (CMI) is one of these new indexes and quantifies the relationship between the increment of heart rate and the maximal oxygen consumption (VO₂ max) during exercise testing. In normal subjects there is linear response and the index is around 1.0. The aim of the study was to evaluate the chronotropic response in healthy controls and Chagas’ disease patients with and without left ventricular dysfunction, using CMI. Twenty-four controls and 171 Chagas’ disease patients underwent a clinical protocol and maximal exercise testing. Chagas’ disease patients were divided into two groups: CH₁ = patients with ejection fraction (EF) > 35% and CH₂ = EF<40%. CMI was analyzed and calculated according to the Wilkoff method. Chagas’ disease patients were older than controls and showed higher prevalence of right bundle branch block, as well as lower VO₂ max during exercise. Both groups of Chagas’ disease patients showed a less steep curve in the chronotropic-metabolic index (CH₁: 0.91±0.10, CH₂: 0.89±0.08) than controls (1.0±0.12, p < 0.001). Chagas’ disease patients with and without left ventricular dysfunction chronotropic incompetence may exhibit reduced chronotropic response to exercise, expressed by a less steep chronotropic-metabolic index.

Key-words: Chagas’ disease. Autonomic nervous system. Chronotropism.


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A doença de Chagas representa uma das mais importantes causas de morte na América Latina, onde quase 20 milhões de pessoas estão infectadas. A doença causa grande impacto socioeconômico já que acarreta muitos indivíduos em idade produtiva. O curso clínico da doença é bastante variável. Enquanto muitos indivíduos podem desenvolver cardiopatia grave, às vezes fatal, outros permanecem totalmente assintomáticos sem nunca desenvolverem formas crônicas. Sendo assim, torna-se importante definir marcadores de risco de evolução desfavorável e de morte nos pacientes com doença de Chagas.

A insuficiência crônica (ICr) é caracterizada como a incapacidade de aumentar a frequência cardíaca (FC) durante o teste ergométrico (TE) e está claramente relacionada com o pior prognóstico dos pacientes com coronariopatia. Embora a ICr seja um evento relativamente comum em pacientes chagásicos, sua importância na evolução deste é ainda pouco conhecida. Novas metodologias estão sendo empregadas na avaliação da resposta cronotrópica em vários grupos de pacientes. O índice cronotrópico metabólico (ICM) é um dos novos métodos, é obtido pela análise da relação entre o aumento da frequência cardíaca (FC) e o consumo máximo de oxigênio (VO2) durante o teste ergométrico (TE). A resposta normal é linear, com índice de 1.0. Existem vantagens na avaliação da ICr pelo ICM, já que este avalia a ICr em relação ao consumo de oxigênio, mas o seu comportamento na doença de Chagas é ainda desconhecido.

Este estudo tem como objetivo avaliar a resposta cronotrópica, utilizando-se do ICM, em pacientes chagásicos e com disfunção ventricular esquerda (dVE) comparando-os com pacientes controles, sem doença de Chagas.

PACIENTES E MÉTODOS

O estudo, de desenho clínico epidemiológico transversal, faz parte de estudo prospectivo intitulado "Disfunção autonômica na doença de Chagas: mecanismos e implicações pragmáticas" e foi aprovado pelo Comitê de Ética em Pesquisa da UFMG. Pacientes foram examinados no Ambulatório de Referência em Doença de Chagas do Centro de Treinamento e Referência em Doenças Infecciosas e Parasitárias da Universidade Federal de Minas Gerais. O diagnóstico de doença de Chagas foi confirmado por sorologias positivas para T. cruzi por dois ou mais métodos diferentes (ELISA, RIFI, hemaglutinação indireta). Pacientes não selecionados, atendidos consecutivamente no Ambulatório de Referência no período entre janeiro de 1998 e julho de 1999 e que concordaram em participar do estudo, assinaram termo de consentimento e foram submetidos a anamnese, exame físico, ECG, exames laboratoriais e radiografia de tórax. Os critérios de exclusão foram: 1) presença de outra doença sistêmica, como cardiopatia, diabetes, disfunção tiroideana, doença pulmonar obstrutiva crônica, insuficiência hepática ou renal, anemia, hiper tensão arterial; 2) gravidez; 3) alcoolismo; 4) uso de drogas que comprometem a resposta cronotrópica ao TE; 5) interrupção do TE por indicação médica (fon-tórica, tontura, arritmia, aumento exagerado da pressão arterial). Foram avaliados 24 indivíduos saudáveis e 171 pacientes com doença de Chagas. Os chagásicos foram divididos em dois grupos: CH1: pacientes com fração de ejeção (FE) ≥40% e CH2: pacientes com FE <40%. Todos foram submetidos ao protocolo clínico, TE e ecocardiograma.

Os participantes do estudo foram submetidos ao ecodoppler ecardiograma colorido utilizando um equipamento ECHI 5000. As medidas foram realizadas por um experiente ecocardiografista (MV LB) de acordo com as recomendações da Sociedade Americana de Ecolcardiografia. A fração de ejeção do ventriculo esquerdo foi obtida pelo método de Simpson.

O TE foi realizado de acordo com o protocolo de Bruce, em esteira rolante. Os pacientes foram encorajados a se exercitar até atingir o pico da FC. A resposta cronotrópica foi avaliada pela porcentagem atingida da FC máxima prevista para idade, de acordo com a fórmula de Astrand (FCmax =220 idade). A análise e o cálculo do ICM foram feitos pelo método de Wilkoff que avalia a variação da frequência cardíaca com função linear do consumo de oxigênio ao esforço. Os indivíduos normais exibem uma resposta linear na porcentagem da FC em relação à porcentagem da reserva metabólica, com valores próximos de um, enquanto a insuficiência cronotrópica se manifesta por valores maiores.

Os dados foram analisados utilizando-se os softwares Episio versão 6 e SPSS versão 10. Variáveis quantitativas foram descritas pela média ou mediana e medidas de dispersão (desvio padrão e intervalo interquartil, respectivamente). A análise da normalidade e da homogeneidade da variância foi realizada antes da utilização de métodos paramétricos; transformações matemáticas foram realizadas se convenientes. Análises de variância (ANOVA) e da co-variância (ANCOVA, com ajuste para a idade) foram utilizadas para comparação entre os grupos, com comparação de médias realizada com correção de Bonferroni para comparações múltiplas. Coeficientes de correlação entre o ICM e outras variáveis quantitativas foram calculados pelos métodos de Pearson (r) e de Spearman (rs), dependendo da distribuição normal ou não das variáveis. Variáveis qualitativas foram descritas pela frequência e proporção e analisadas em tabelas 2 x k pelo teste do qui-quadrado. Em todos os testes, alfa (p) foi considerado <0,05 como um indicador de significância estatística.

RESULTADOS

Pacientes chagásicos apresentaram maior idade e maior prevalência de bloqueio completo de ramo direito, enquanto chagásicos com depressão da FE apresentaram maior prevalência de disfunção diástolica e aneurisma de VE (Tabela 1). Ambos os grupos de chagásicos apresentaram menor inclinação do ICM como menor porcentagem da frequência cardíaca máxima atingida ao esforço, além de tendência a menor consumo máximo de oxigênio (Tabela 2). O ICM não se correlacionou com a FEVE: r = 0,05, p = 0,48 (Figura 1). O ICM apresentou elevada correlação com a porcentagem atingida da frequência cardíaca.
Tabela 1 - Características gerais e ao ecocardiograma de indivíduos saudáveis (controles) e chagásicos com FE maior ou igual (Ch1) ou menor que 40% (Ch2).

<table>
<thead>
<tr>
<th></th>
<th>Controle</th>
<th>Ch1</th>
<th>Ch2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>154</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Idade (anos)</td>
<td>35,6 ± 9,3</td>
<td>41,7 ± 9,3</td>
<td>42,8 ± 9,2</td>
<td>0,01</td>
</tr>
<tr>
<td>Mulheres (%)</td>
<td>26</td>
<td>43</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>BRD (%)†</td>
<td>0</td>
<td>25,5</td>
<td>43,9</td>
<td>&lt;0,01</td>
</tr>
<tr>
<td>Fração de ejeção VE (%)</td>
<td>64 (61-66)</td>
<td>62 (58-65)</td>
<td>55 (31-39)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Disfunção diastólica (%)</td>
<td>0</td>
<td>5,8</td>
<td>51,3</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Asimetria de VE (%)*</td>
<td>0</td>
<td>15,6</td>
<td>52,9</td>
<td>&lt;0,001</td>
</tr>
</tbody>
</table>

Valores expressos em médias ± DP quando apropriado; exceção * expresso em proporções e †, como mediana (intervalo interquartil). BRD = bloco comprovado de ramo direito; VE = ventrículo esquerdo.

Tabela 2 - Características ao teste ergométrico de indivíduos saudáveis (controles) e chagásicos com FE maior ou igual (Ch1) ou menor que 40% (Ch2).

<table>
<thead>
<tr>
<th></th>
<th>Controle</th>
<th>Ch1</th>
<th>Ch2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>154</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Duração de exercício (s) †*</td>
<td>844 (780-1001)</td>
<td>719,5 (612-861)</td>
<td>649 (629-792)</td>
<td>0,13</td>
</tr>
<tr>
<td>VO₂ max (ml/kg/min) *</td>
<td>60,4 (10,1)</td>
<td>44,7 (9,4)</td>
<td>44,1 (8,3)</td>
<td>0,058</td>
</tr>
<tr>
<td>FC basal (lpm)</td>
<td>71 ± 13</td>
<td>69 ± 12</td>
<td>71 ± 12</td>
<td>0,91</td>
</tr>
<tr>
<td>FC máxima (lpm) †*</td>
<td>180,5 (161-195)</td>
<td>184,5 (152-175)</td>
<td>160 (143-173)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>△ FC (lpm)</td>
<td>10 (12)</td>
<td>91 (19)</td>
<td>86 (19)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>FC máxima atingida (%) †*</td>
<td>101 (98-104)</td>
<td>92 (87-96)</td>
<td>89 (83-101)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>ICRM †*</td>
<td>1,00 (0,12)</td>
<td>0,91 (0,10)</td>
<td>0,89 (0,08)</td>
<td>&lt;0,001</td>
</tr>
</tbody>
</table>

Valores expressos em médias ± DP quando apropriado; exceção * expresso em proporções e †, como mediana (intervalo interquartil). S: segundos, VO₂: consumo de oxigênio máximo estimado; FC: frequência cardíaca; lpm: batimentos por minuto; △ FC: diferença entre a FC de pico do esforço e a basal; ICRM: Inclinação obtida pelo gráfico da variação da frequência cardíaca ao esforço sobre a reserva metabólica. Os valores de p se referem a análises ANOVA ou ANCOVA (ajustadas para idade*) para os indicadores, com comparação de médias pelo método de Bonferroni.

prevista para a idade (r = 0,60, p < 0,001, Figura 2) e o consumo máximo de oxigênio estimado (r = 0,344, P < 0,001). A diferença entre o ICRM obtido entre os controles e chagásicos dos dois grupos persiste significativa (p = 0,002) mesmo após ajuste por análise de covariância para a idade e o consumo máximo de oxigênio estimado (controle x Ch1 p = 0,002, controle x Ch2 p = 0,018, Ch1 x Ch2 p = 1,000).

![Figura 1 - Correlação entre a fração de ejeção do ventrículo esquerdo e a resposta cronotrópica ao esforço, avaliada pela inclinação do índice cronotrópico-metabólico (ICRM) em 171 chagásicos e 24 controles.](image)

![Figura 2 - Correlação entre a porcentagem atingida da frequência cardíaca prevista para a idade e o índice cronotrópico-metabólico (ICRM) em 171 chagásicos e 24 controles.](image)

DISCUSSÃO

A regularização da frequência cardíaca pode estar prejudicada em diversas situações patológicas, sabendo-se que o pico da frequência cardíaca nos pacientes com coronariopatia é menor do que nas pessoas sadias, ao exercício máximo. Mais recentemente, Lauer e colaboradores encontraram que a insuficiência cronotrópica associa-se com aumento da
mortalidade total e do risco de doença arterial coronariana. Adicionalmente, em uma coorte de indivíduos assintomáticos, a presença de insuficiência cronotrópica foi previsível pelo aumento do tamanho da cavidade ventricular esquerda e, nos homens, pela depressão da fração de ejeção do ventrículo esquerdo. Neste estudo, o menor aumento da frequência cardíaca ao esforço foi observado em ambos os grupos de pacientes chagásicos, de forma independente da presença de disfunção ventricular esquerda. A insuficiência cronotrópica não é incomum na fase crônica da doença de Chagas que, embora de impacto prognóstico incerto, tem sido atribuída à disfunção autonômica predominantemente vagal ou à disfunção do nó sinusal.

Na verdade, diversos estudos têm demonstrado distúrbio precoce da função autonômica, em graus variáveis, em diferentes formas clínicas da doença de Chagas, com potencial papel na fisiopatogênese da morte súbita em pacientes chagásicos. Assim, é possível que a insuficiência cronotrópica observada ao teste ergométrico em pacientes com doença de Chagas sem disfunção ventricular esquerda significativa seja um marcador de disfunção autonômica precoce observada nos estudos supracitados.

Os achados do presente trabalho confirmam observações prévias de Gallo e cols demonstrando um menor aumento da frequência cardíaca em pacientes com doença de Chagas, usando protocolos experimentais tanto em esteira como em cicloergómetro, correlacionando o atraso à redução do controle autonômico vagal. Nossos resultados diferem dos estudos precedentes pelo uso de protocolo rotineiro na prática clínica (Bruce) em estudo transversal realizado em amostra representativa da população ambulatorial com a doença de Chagas.

Embora, teoricamente, o ICM pode ser mais sensível e fidedigno para avaliação da insuficiência cronotrópica, nós encontramos excelente correlação entre este novo método e a avaliação convencional na amostra em questão. Como a inclinação da reta não é o único parâmetro que pode ser analisado pelo método de Wilkoff, análises adicionais são necessárias para se avaliar se essa nova metodologia tem algum papel na avaliação da resposta ao esforço no paciente chagásico.

Algumas limitações do presente estudo merecem discussão. A resposta cronotrópica está significativamente relacionada ao consumo máximo estimado de oxigênio, embora não possamos afirmar, a partir dos dados do presente estudo, se é a insuficiência cronotrópica que provoca uma menor capacidade aeróbica ou vice-versa. Entretanto, chagásicos apresentam menor ICM mesmo após o ajuste para o consumo máximo estimado de oxigênio, o que comprova que a menor capacidade aeróbica não é a principal causa da insuficiência cronotrópica observada entre os chagásicos. Uma limitação adicional se relaciona ao fato de que o cálculo indireto do consumo máximo de oxigênio é uma medida relativamente imprecisa, que não substenta a medida direta, não realizada neste estudo. Entretanto, os objetivos do presente estudo estão voltados ao estudo do ICM e as considerações acerca da capacidade aeróbica são secundárias aos resultados principais.

Concluindo, a insuficiência cronotrópica está presente em pacientes chagásicos independentemente da presença de disfunção ventricular esquerda. O ICM pode ser aplicado no estudo da resposta ao esforço em pacientes chagásicos, embora a insuficiência cronotrópica possa ser reconhecida, de forma mais simples, pela avaliação da porcentagem da frequência cardíaca máxima atingida. O significado fisiopatológico e o impacto prognóstico do ICM na doença de Chagas permanecem obscuros e devem ser avaliados em novos estudos.

REFERÊNCIAS BIBLIOGRÁFICAS


Brain natriuretic peptide based strategy to detect left ventricular dysfunction in Chagas disease: A comparison with the conventional approach*

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Abstract

Background: Left ventricular dysfunction (LVD) is the major predictor of mortality in Chagas disease (ChD).

Aims: To compare the diagnostic performance of the conventional approach (ECC and chest X-ray) in the recognition of LVD in ChD, with a new strategy, in which BNP is measured in patients with an abnormal ECG.

Methods: Consecutive ChD patients recruited at an Outpatient Reference Center in Belo Horizonte, Brazil, without other systemic diseases, in 1998–99 (sample 1, n = 165) and in 2001–02 (sample 2, n = 62) underwent ECC, chest X-ray, BNP measurement and echocardiography.

Results: The prevalence of LVD (ejection fraction ≤ 40%) was 9.1% in the sample 1. The conventional strategy recognized all patients with LVD (sensitivity: 100%, 95% CI: 79.6–100% and negative predictive value − PV 100%, 92.1–100%), but with low specificity (30%, 95% CI: 23.2–37.8) and − PV (12.5%, 95% CI: 17.7–19.6). The BNP/ECG strategy showed significantly better specificity (96.0%, 95% CI: 91.5–98.2, p < 0.001) and + PV (66.7%, 95% CI: 43.7–83.7, p < 0.001), and non-significantly lower sensitivity (80.0%, 95% CI: 54.8–93.0, p = 0.25) and − PV (98.0%, 95% CI: 94.2–99.3, p = 0.08). Overall accuracy was improved with the new strategy, (94.5%, 95% CI: 90.0–97.1 × 36.4%, 95% CI: 29.4–43.9, p < 0.001). Similar results were obtained for the sample 2.

Conclusions: The BNP-based strategy was more accurate than the conventional approach in the detection of LVD in ChD patients and should be considered as a valid option.

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Keywords: Natriuretic peptides; Cardiomyopathy; Diagnosis; Ventricles; Sensitivity and specificity; Chagas disease

Abbreviations: LV, left ventricular; LVSD, LV systolic dysfunction; ECC, electrocardiogram; BNP, brain natriuretic peptide; +PV, positive predictive value; − PV, negative predictive value.
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1. Introduction

Chagas disease is a major health challenge in Latin America, where recent estimates indicate an infection prevalence of 13 million, with 3.0–3.3 million symptomatic cases [1]. Left ventricular (LV) systolic dysfunction, which is the main predictor of mortality in Chagas disease, [2] occurs in nearly 15% of this population [3]. In other clinical settings, treatment of LV systolic dysfunction (LVSD) may
reduce the risk of heart failure by as much as 37% in asymptomatic patients [4] and the risk of death in about one fifth [5]. Since LVSD is asymptomatic in approximately 50% of cases, [6] screening for LVSD has been considered to be highly useful by some authors, [7] although this issue is still a matter of debate [8].

Echocardiography is the best non-invasive technique used in the assessment of left ventricular function in Chagas disease. However, there are limitations for its widespread use, especially the difficulty in performing the echocardiogram in rural areas where the disease is endemic, and the need for an experienced examiner. Therefore, the development of alternative screening methods for the detection of LV dysfunction is desirable. ECG and chest X-ray are usually recommended as first-line methods in the recognition of LV dysfunction in Chagas disease [9]. Although the ECG has been recognized as a highly sensitive test, the diagnostic accuracy of a chest X-ray is considered poor [10] and the overall diagnostic performance of this strategy has not been studied. Recently, we demonstrated that an elevation of brain natriuretic peptide (BNP) concentration measured by radioimmunoassay (RIA) in blood, a reliable indicator of systolic left ventricular dysfunction, might be a promising screening method in Chagas disease [11]. This excellent diagnostic performance were confirmed in a subsequent study using a simple and reliable point-of-care commercial kit for BNP measurement, which could be easily used in such distant rural areas [12].

In the present study we compared, using the STARD initiative patterns, the diagnostic accuracy of abnormalities in ECG and/or chest X-ray in the recognition of LV dysfunction (conventional approach) with a new strategy, in which BNP is measured in patients with an abnormal ECG.

2. Methodology

The study protocol was approved by the Ethics Committee of the Federal University of Minas Gerais and was conducted at the Chagas Disease Outpatient Center of the University Hospital, a regional reference center for blood banks and primary care units in Belo Horizonte, Minas Gerais, Brazil. The study was planned before data collection (prospective design) and complies with STARD initiative [13]. All examinations were interpreted by investigators blinded to the results of the other diagnostic tests and they were generally performed within the same week. No adverse effect resulting from the diagnostic procedures occurred.

2.1. Study design

The two different strategies are described in Fig. 1 and were applied to all study subjects, with no kind of verification bias. The conventional strategy [9] consists of the simultaneous evaluation of the patient by electrocardiogram and chest X-ray (ECG/X-ray); those patients with abnormal results in one or both tests are considered to have the cardiac form of the disease and would be candidates to the echocardiographic study. In the new BNP-based strategy (ECG/BNP), a normal ECG obviates the need for further testing for global LV systolic dysfunction; those patients with an abnormal ECG and elevated BNP levels might have LV systolic dysfunction and should undergo an echocardiography study.

2.2. Patients

The study population consisted of two distinct samples: a first sample recruited in 1998–99 and a second sample studied during the 2001–2 period, both including consecutive patients (20–70 years of age) with a definite diagnosis of Chagas disease. The diagnosis of Chagas disease was based on the presence of at least two positive serological examinations using distinct techniques (ELISA, indirect hemagglutination or indirect immunofluorescence) in an individual with a relevant epidemiological history. The recruited patients signed an informed consent term and underwent a standardized protocol that included extensive clinical, ECG, laboratory and chest X-ray examinations, echocardiogram and BNP measurement. Exclusion criteria were other significant systemic diseases, alcoholism, or pregnancy.

The study design and the number of patients submitted to the diagnostic procedures are displayed in the flow diagram [13] in Fig. 2. The first sample was selected from a group of 222 consecutive Chagas disease patients without other apparent systemic diseases who underwent a routine medical visit at the Chagas Disease Outpatient Center of the University Hospital. Twenty-nine patients were excluded during the recruitment procedures due to concomitant systemic diseases (hypertension, diabetes or thyroid dysfunction, n=18), alcoholism (n=1) or impossibility of following the study protocol (n=10). For the remaining 193 patients, incomplete data precluded the analysis of 28 subjects, since 19 samples of BNP were lost, seven patients did not undergo a chest X-ray or ECG and two echocardiographic studies were not performed for technical reasons. These patients had general features similar to those of patients included in the study, with a prevalence of left ventricular dysfunction, defined by LV ejection fraction of 40% or less of 15.4% (4/26).
The second sample was selected using a similar recruitment procedure. Of 75 patients that satisfied the criteria for inclusion and did not present exclusion criteria, 62 (82.3\%) had completed all required tests. The second sample had a clinical profile similar to that of the first, with a 14.5\% prevalence of LV systolic dysfunction (nine patients). The general features of both samples patients are shown in Table 1. The 165 subjects in the first study sample were predominantly males (57\%), with a mean age of 42.4±9.7 years; the second sample was not significantly different. Most patients in both samples are asymptomatic and only few patients (six in sample 1 and five in sample 2) were in NYHA functional class III or IV.

2.3. Procedures

The reference standard of LV systolic function was the LV ejection fraction (LVEF), estimated using the Simpson rule and obtained by a standardized echocardiogram. All studies were performed by an experienced examiner (MVLB) using an ATL HDI 5000 device (Bothell, Washington, USA). Significant left ventricular systolic dysfunction is considered to be present if LV ejection fraction is ≤0.40. This cut-off point was chosen since it has been previously used in several clinical trials performed on patients with LV dysfunction [14].

In all participants, a standard 12 leads ECG was recorded at a paper speed of 25 mm/s with a portable Fukuda Denshii Model FX-2111 electrocardiograph (Fukuda Co., Tokyo, Japan). The tracing was analyzed blindly by a cardiologist experienced in electrocardiography (ALPR) using the Buenos Aires code, specifically designed to be used in Chagas disease, [15] and normal and abnormal ECG were identified. Chest radiography was performed according to the conventional technique used at the Radiological Unit of the University Hospital of UFMG and analyzed by one observer (AAP) supervised by an experienced researcher (MOCK). The cardiac silhouette and the cardio-thoracic ratio were assessed as previously reported [10]. Chest radiography with a cardiothoracic ratio greater than 0.50 or an enlarged cardiac silhouette, or both, was considered abnormal.

BNP measurement was performed in venous blood after a supine 20 min rest by different methods in both samples. In the first sample, BNP measurement was performed by a researcher experienced in the natruretic peptide field (AMR), in the Department of Physiology and Biophysics of the Federal University of Minas Gerais, as previously described [11]. Samples were placed in chilled tubes containing protease inhibitors (EDTA, PMSF and Pepstatin A, all 10⁻⁵ M, all purchased from Sigma Chemical Co., St Louis, MO, USA). After centrifugation at 1500 ×g for 15 min at 4 °C, plasma was separated and stored at -80 °C. For BNP extraction, plasma was allowed to pass slowly through a Sep-Pak C18 column (Waters Corp., USA) activated by sequential washes with acetonitrile and 0.2% ammonium acetate, pH 4, and eluted with an acetonitrile:ammonium acetate solution (60:40). The samples were dried in a Speed-Vac apparatus and redissolved in buffer for

<table>
<thead>
<tr>
<th>Features*</th>
<th>Sample 1 (n = 165)</th>
<th>Sample 2 (n = 62)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>57.0</td>
<td>50.0</td>
<td>0.37</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.4 (9.7)</td>
<td>44.1 (9.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>NYHA functional class I, %</td>
<td>60.0</td>
<td>71.0</td>
<td>0.13</td>
</tr>
<tr>
<td>Abnormal ECG, %</td>
<td>69.1</td>
<td>64.5</td>
<td>0.52</td>
</tr>
<tr>
<td>Cardiac-thoracic index</td>
<td>0.47 (0.06)</td>
<td>0.47 (0.05)</td>
<td>0.27</td>
</tr>
<tr>
<td>Enlarged cardiac silhouette, %</td>
<td>19.4</td>
<td>25.8</td>
<td>0.36</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>137 (82.8)</td>
<td>20.7 (58.3)</td>
<td>na</td>
</tr>
<tr>
<td>Elevated BNP, %</td>
<td>13.9</td>
<td>19.4</td>
<td>0.35</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>56.4 (10.4)</td>
<td>57.8 (12.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>LV systolic dysfunction, %</td>
<td>9.1</td>
<td>14.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Abnormal ECG or X-ray, %</td>
<td>72.7</td>
<td>66.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Abnormal ECG and elevated BNP, %</td>
<td>10.9</td>
<td>19.4</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Data are means (SD), unless otherwise indicated. *P value refers to the comparison between the two samples. † median (interquartile range), na = not applicable.
assay, BNP was measured by RIA using hBNP as standard, 

$\text{tyr}^*\text{-BNP}$ for iodination and specific hBNP antibody (all purchased from Peninsula Laboratories, USA). Each sample was tested in duplicate and the final result was the mean value; all samples were measured in the same assay. In the second sample, [12] a small amount of blood (5 mL) collected into tubes containing potassium EDTA (1 mg/mL of blood), were centrifuged at 3000 $\times g$ for 10 min and plasma was obtained and frozen at $-80^\circ$C until further analysis, performed at Southwestern Medical School, Dallas, Texas. BNP was measured using the Thiaze BNP test ( Biosite Inc., USA), which is a fluorescence immuno-

assay for the quantitative determination of BNP in plasma specimens. The precision, analytical sensitivity and stability characteristics of the system have been previously described [16]. Each sample was tested in triplicate to minimize variation from single observations and for internal controls and the final results were reported as the mean of the 3 samples.

The diagnostic performance of the BNP values in the diagnosis of LV systolic dysfunction in the Chagas disease population was evaluated using the receiver–operator–characteristic (ROC) curve. The area under the curve was 0.89±0.04 in the first sample [11] and 0.92±0.03 in the second sample [12]. Different cut-off points were obtained for different samples, since the BNP methods used were also different (RIA and fluorescence immunoassay) [17]. Based on the analysis of the ROC curve and aiming at obtaining specificity $\geq 80\%$, a BNP cut-off value of 210 pg/mL was chosen for the first sample and a cut-off value of 75 pg/mL was chosen for the second sample. Other cut-off values were tested considering also the ECG results without further improvements of the diagnostic performance.

3. Statistical analysis

The number of subjects needed to be examined (NNE) by echocardiography to detect one case of LV systolic dysfunction in both strategies was calculated as 1/prevalence of LV dysfunction in abnormal screening tests [18]. The sensitivity, specificity, accuracy, positive and the negative predictive values and positive and negative like-

lihood ratios (LR) were calculated for each strategy of detection of abnormal LV systolic function [19]. Confidence intervals (95%) were calculated by the method of Wilson [20] using CIA software, version 2.0.0 (Confidence Interval Analysis for Windows, London, 2000). The statistical significance of the differences in diagnostic measurement strategies was assessed by the McNemar test for paired data. All measurements of diagnostic indexes were performed for both strategies also in the sample 2 and compared to those obtained in the sample 1 by the $t$ test. A $p$-value of $<0.05$ was considered significant.

4. Results

4.1. First study

ECG abnormalities and an enlarged heart silhouette were found in 69.1 and 19.4% of patients of the first sample, respectively (Table 1). The median BNP value was 137.0 pg/ml (Q1–Q3: 97.7–180.7 pg/ml); in the same original study, normal subjects had median values of 144.7 pg/ml (Q1–Q3: 103.9–163.6 pg/ml) [11]. The wide range of distribution of BNP values and the relative low number of patients with systolic dysfunction (15 patients, 9.1%) hinders the interpretation of these numbers. The median BNP value was 131.0 pg/ml (Q1–Q3: 95.4–169.7 pg/ml) in patients with LV ejection fraction $>0.40$ and 228.7 pg/ml (Q1–Q3: 176.2–360.8 pg/ml, $p<0.001$) in those with LV ejection fraction $\leq 0.40$.

An abnormal ECG or X-ray was observed in 120 patients (72.7%) while elevation of BNP in patients with abnormal ECG occurred in 41 subjects (10.9%). The NNE, calculated as 1/prevalence of LV dysfunction in the abnormal screening test subgroup, was 8.0 [1/15/120] by the conventional strategy and 2 [1/12/18] by the new strategy.

The conventional strategy (ECG/X-ray) recognized all patients with LV systolic dysfunction (sensitivity: 100%, 95% CI: 79.6–100% and negative predictive value – PV 100%, 92.1–100%), but with low specificity (30%, 95% CI: 23.2–37.8) and positive predictive value (12.5%, 95%CI 17.7–19.6), yielding an overall accuracy of 36.4% (95% CI: 29.4–43.9, see Table 2).

Table 2

<table>
<thead>
<tr>
<th>Sample 1 (n=165)</th>
<th>Sample 2 (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECG/BNP (95% CI)</td>
</tr>
<tr>
<td>Sensitivity(%)</td>
<td>80.9 (54.8–93.0)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96.0 (91.5–98.2)</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>66.7 (43.7–83.7)</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>96.0 (94.2–99.3)</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>94.5 (90.0–97.1)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>20.0 (8.77–45.58)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.21 (0.07–0.57)</td>
</tr>
</tbody>
</table>

*P value refers to the comparison of the measurements of the diagnostic performance of ECG/BNP and ECG/X-ray.
The BNP/ECG-based strategy was significantly better than the conventional approach (Table 2) in terms of specificity (96.0, 95% CI: 91.5–98.2, p < 0.001) and positive predictive value (66.7, 95% CI: 43.7–83.7, p < 0.001), displaying non-significantly lower sensitivity (80.0, 95% CI: 54.8–93.0, p = 0.25) and negative predictive value (98.0, 95% CI: 94.2–99.3, p = 0.08). The overall accuracy was much improved with the new strategy (94.5, 95% CI: 90.0–97.1, p < 0.001).

The superiority of using the new strategy can be graphically displayed using the likelihood ratios and a Fagan nomogram (Fig. 3). Considering the positive likelihood ratio obtained for the sample 1 (conventional approach, 1.4, 95% CI: 1.37–1.61; new strategy, 20.0, 95% CI: 8.77–45.58) and an estimated 10% pre-test prevalence of left ventricular dysfunction in an outpatient Chagas disease population, an elevated BNP in the presence of an abnormal ECG increases the post-test probability to 68.9%, although the post-test probability after an abnormal ECG or X-ray would be only 13.4%. The negative likelihood ratio was zero (95% CI: 0.00–0.69) in the conventional approach and 0.21 (95% CI: 0.07–0.57) in the new one, indicating that a negative test in both strategies leads to a very low post-test probability of LV dysfunction, i.e., 0% and 2.3%, respectively.

4.2. Second study

The frequency of abnormal ECG, X-ray and BNP measurement is displayed in Table 1. BNP values were significantly different, reflecting the different methodologies used for BNP measurement. The median BNP value was 11.7 pg/ml (Q1–Q3: 5.6–30.7 pg/ml) in patients with LV ejection fraction >0.40 and 93.5 pg/ml (Q1–Q3: 66.5–534.5 pg/ml, p < 0.001) in those with LV ejection fraction ≤0.40.

Both strategies were applied to the second sample and the indexes obtained, displayed in Table 2, were closely similar when compared to those of the first sample. All comparisons between measurements obtained in the two samples revealed absence of statistically significant differences, although a slight degeneration of the diagnostic performance of the new strategy is suggested by a lower positive likelihood ratio (8.24, 95% CI: 3.33–20.36).

5. Discussion

This study describes the comparison of two strategies for the detection of left ventricular systolic dysfunction in two different groups (first and second samples) of patients with positive serology for Chagas disease, showing that measuring BNP in patients with abnormal ECG is more accurate than performing ECGs and chest X-rays in all patients. To our knowledge, this is the first study that compares these two strategies in patients with Chagas disease and it is one of first reports in tropical medicine field that complies with the STARD initiative recommendations.

The electrocardiogram and chest X-ray have been used in Chagas disease since the original studies by Carlos Chagas [21] and have an established role in the management of Chagas disease patients, with both diagnostic and prognostic importance [9]. Nonetheless, major improvements in the diagnostic capabilities and therapeutic options have occurred in the last decades and it is now clear that left ventricular systolic dysfunction, evaluated non-invasively by echocardiography, is the best predictor of an elevated risk of death in Chagas disease. Moreover, it is now indisputable that pharmacological treatment may halt the progression of LV dysfunction in studies performed at other settings, indicating the urgent need to redefine strategies to recognize and treat these patients.

When the accuracy of this classical strategy was scrutinized using modern evidence-based diagnostic tools, we observed that it was able to detect all patients with significant LV systolic dysfunction, with a sensitivity and negative predictive value of 100% in both samples. However, the specificity, the positive predictive value and
the overall accuracy were relatively low, indicating that a large number of patients would need to be examined by echocardiography in order to detect one that could benefit from pharmacological treatment. We hypothesize that this relatively low accuracy can be attributed to two factors: the use of two diagnostic tests in parallel, which can lower the specificity and positive predictive values, [22] and the poor diagnostic performance of the chest X-ray [10].

Few other studies have addressed the issue of screening to recognize Chagas patients with LV systolic dysfunction [3,23]. Besetti studied a hospital cohort of 74 Chagas disease patients and found a prevalence of 59% of left ventricular systolic dysfunction, defined as ejection fraction below 55% [23]. The combination of New York Heart Association functional class (2 or more) and a systolic blood pressure below 120 mmHg predicted left ventricular dysfunction with a sensitivity of 59% and a specificity of 77%. ECG variables were not predictive of LV dysfunction and BNP measurement was not performed. Although potentially useful in the hospital setting, this strategy may not be applicable to screening of ambulatory patients, since different clinical profiles and LV dysfunction prevalence may impair the transferability of the diagnostic strategy [24]. It should also be pointed out that the sensitivity of the strategy in the latter study is relatively low, leading to the withholding of the echocardiogram in a large number of patients (41%) that would benefit from the formal evaluation of LV systolic function. More recently, Salles and colleagues, [3] after studying 738 adult outpatients in the chronic phase of Chagas disease, reported that a QT dispersion above 60 ms was associated with LV systolic dysfunction and could be used to predict asymptomatic dysfunction in chronic Chagas' disease. A model considering QT dispersion, the presence of cardiomegaly, frequent PVCs, and male sex had 90% specificity and 71% sensitivity in this population, in which LV systolic dysfunction (ejection fraction<45%) was observed in 14.7% of cases. Although the diagnostic performance of this strategy was quite good, limitations related to QT dispersion measurements may hamper its use in general practice [3,25].

We evaluated a new strategy, based on sequential tests and the use of a new and promising simple method for the diagnosis of LV systolic dysfunction, i.e., the measurement of BNP in blood samples [11,12]. In the present study, that BNP-based approach was more accurate and superior to the conventional one in terms of specificity and positive predictive value in both samples. A marked and significant increment of accuracy, odds ratio and positive likelihood ratio was detected, with a reduction of the number of patients to be examined by echocardiography from 8 to 2. Since the echocardiogram is not widely available in the public health system in many areas of the Latin America, patients candidate to the echocardiogram by the conventional approach are not actually being submitted to the exam. The marked reduction of the number of cases needed to be examined by echocardiography using this new strategy may permit that all screened patients would be examined by the echocardiogram, optimizing the use of limited resources. In fact, the association of ECG and BNP measurement was successful in the detection of LV systolic dysfunction when tested in other clinical settings [18,22,26] and was recommended by the recently released NICE guideline for Management of Chronic Heart Failure in Adults in Primary and Secondary Care [27]. Nonetheless, the use of BNP as a diagnostic tool is a recent conquest and there are unsolved issues and problems related to the implementation of its use in clinical practice [28]. Different commercial and experimental measurement techniques are available, with different cut-off points and clinical determinants [29]. In our study, a different methodology was applied to the first and second samples (RIA and fluorescence immunoassay), leading to markedly different cut-off points [17]. More than a limitation, this fact indicates that the excellent performance obtained in the first sample was transferable to the second sample, in which a commercial kit was used. The cost-effectiveness of this strategy is still controversial, although studies have suggested that screening high-risk subjects by BNP before echocardiography could reduce the cost per detected case of LV systolic dysfunction by 26% [18] and may be economically attractive for patient groups with at least 1% prevalence of moderate or greater LV systolic dysfunction [30]. Additionally, commercial BNP measurement was not yet available in many Latin America cities by the time of the writing of this paper (September 2004) and this strategy could be applied only if, as expected, measuring BNP becomes a widespread and low-cost laboratory method in the near future, what could be anticipated by the simplicity and the reliability of the point-of-care measurement system used in the second sample.

In our study, the new strategy is non-significantly less sensitive and with a lower negative predictive value than the traditional one. Indeed, three out 15 patients with LV dysfunction, in the sample 1, and two out nine, in the sample 2, would be missed by a BNP-based strategy. Since the main aim of a screening test is to be a 'rule out' test, missing target patients could be a limitation of this new strategy. Additionally, relatively wide confidence intervals for the new strategy positive likelihood ratios and predictive values should also be considered a limitation of our findings. Further analysis of the data, using ROC curves and different cut-points (data not shown), did not improve the sensitivity of this strategy without compromising the specificity. Vasan et al. [31] reported limited sensitivity of BNP measurement in recognizing LV systolic dysfunction in a community-based cohort and Tang et al. [32] found that more than 1 in 5 patients with systolic HF and chronic symptoms in specialized outpatient HF clinic had plasma BNP in the "normal" range, suggesting a more limited value of BNP measurement as a screening test in the clinical setting.
A major challenge in global diseases is "to transform new knowledge into cost-effective, equitably affordable interventions and to guarantee their access to the patients and populations of endemic countries" [1]. Effectively screening for LV systolic dysfunction is a major issue in Chagas disease, since it can significantly reduce mortality and morbidity. A BNP-based strategy proved to be accurate and should be considered as an alternative option in the detection of LV systolic dysfunction in Chagas disease. Nonetheless, further studies should be performed to define the best strategy in the management of Chagas disease cardiopathy.

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References

An update on the management of Chagas cardiomyopathy

Manoel OC Rocha, Mauro M Teixeira and Antonio L Ribeiro

Chagas disease, caused by the protozoan parasite Trypanosoma cruzi, infects nearly 18 million people in Latin America and mainly affects the heart, causing heart failure, arrhythmias, heart block, thromboembolism, stroke and death. In this review, the clinical diagnosis and management of Chagas cardiomyopathy are discussed. Particular emphasis is placed on the clinical staging of patients and the use of various diagnostic tests that may be useful in individualizing treatment of the two most relevant clinical syndromes, that is, heart failure and arrhythmias. The relevance of specific treatments are discussed, stressing the important role of parasite persistence in disease pathogenesis. We also discuss new therapy modalities that may have a role in the treatment of Chagas cardiomyopathy.


Overview of the disease

Epidemiology

Chagas disease is an illness caused by the protozoan parasite Trypanosoma cruzi that is endemic in South and Central America, where it is estimated that 16–18 million people are infected and nearly 100–120 million are at risk of contracting the disease [1]. Chronic cardiomyopathy is the most important and severe manifestation of human Chagas disease, eventually affecting approximately 20–30% of those in the chronic phase of the disease and, in this group, causing heart failure, arrhythmias, heart blocks, thromboembolism, stroke and sudden death [2,3]. Indeed, 21,000 Chagas-related deaths are thought to occur every year in Latin America [4]. Moreover, Chagas disease treatment is very costly and frequently affects patients in their most productive working years [5].

The principal mechanism of T. cruzi transmission to humans is through infected secretions from blood-sucking insects (triatomine bugs) [1]. Other important mechanisms are transfusion of blood from infected donors and transplacental transmission from an infected mother to the fetus [6]. Oral transmission has been reported in sporadic human microepidemics in Brazil [7] and other mechanisms of T. cruzi transmission, such as laboratory accidents and organ transplantation [6,9], are considered infrequent [1].

In the past 20 years, there have been major advances in the control of Chagas disease in most of the countries where this infection is endemic. At present, vector-transmitted infection by T. cruzi has been the target of several national control programs and this has led to a significant drop in the incidence of new cases in places where programs are active [10,11]. Owing to a coordinated multinational program in the Southern Cone South American countries, the transmission of Chagas disease by vectors and by blood transfusion has been interrupted in Uruguay in 1997, in Chile in 1999, and in eight of the 12 endemic states of Brazil in 2000 and so the incidence of new infections by T. cruzi in the whole continent has decreased by 70%. In June 2006, the Pan-American Health Organization/WHO certified Brazil as having eliminated Chagas disease transmission by both the principal vector (Triatoma infestans) and transfusion of blood and blood products [12]. Similar multinational control initiatives have been launched in the Andean countries and in Central America, and rapid progress has been recorded [13]. As a consequence, the prevalence of Chagas disease is
decreasing in Brazil and other Latin American countries. Owing to cohort effect, the disease might remain a public health problem for some time among older individuals. The present burden of *T. cruzi* infection for the elderly living in areas where the transmission has been interrupted has been scarcely studied (14-19) and deserves more attention from the scientific community and from policy makers.

Transmission via blood transfusion is still a matter of concern in many places, including developed regions with large immigrant populations, such as the USA and Europe (17,18). The American Red Cross conducted a clinical trial during August 2006-January 2007, screening 148,969 blood samples at three blood-collection centers in the USA, and identified 32 donations (~one in 4,655) as confirmed positive for *T. cruzi* antibodies (17). Maternal-fetal transmission can occur in 1–10% of pregnancies in infected women and may be an important mechanism in countries where vector and blood transmission has been eliminated (18).

Chagas disease can reactivate in patients with AIDS and the CNS is the most commonly involved site, followed by the heart (20,21). Early diagnosis and treatment with benznidazole or nifurtimox probably improve the survival rate (21).

**Natural history**

In endemic areas, the great majority of acute Chagas disease cases are unapparent and most symptomatic patients present slight clinical manifestations. Classical acute cases are found primarily among children up to 10 years of age and the mortality depends mainly on the presence of acute cardiomyopathy or meningitis. Untreated acute disease has a duration of approximately 4–12 weeks, with a progressive decrease of blood parasitemia (22).

Most untreated acute cases evolve into the so-called indeterminate form of chronic Chagas disease. This is defined by the presence of infection, confirmed by either serological or parasitological tests, the absence of symptoms and of electrocardiographic and radiologic abnormalities (comprising heart, esophagus and colon evaluation) (23). Patients with the indeterminate form constitute the majority of infected people in endemic areas and approximately 40% of these patients may persist forever in this clinical situation (24).

Patients classified as possessing the indeterminate form of the disease have an excellent prognosis, and deaths due to the infection are considered rare (23,24). Nevertheless, 25% of indeterminate-form patients may present significant structural and/or functional abnormalities when they are fully evaluated by more sensitive diagnostic methods, such as ergometry, dynamic ECG, autonomic tests or echocardiography (23,25-28). The exact clinical and prognostic meaning of these abnormalities is not known but a study suggested that mild segmental left ventricular wall motion abnormalities are associated with worsening of systolic function in Chagas disease patients who have normal baseline global systolic performance (29). Indeed, these findings support previous results from Espinosa et al. who observed, after a mean follow-up of 4.9 years, that 33% of patients with normal ECG but early left ventricular segmental abnormalities evolved to overt cardiac form (30). Nonetheless, we do not have sufficient data on established predictors to identify who will progress to the more severe forms of the disease and would, therefore, benefit the most from early specific treatment.

The host- and/or parasite-related factors that determine the outcome of *T. cruzi* infection in infected people have not been identified. Several hypotheses have been raised to explain the pathogenesis of Chagas heart disease (31), including an essential role of parasite persistence, a role for autoimmune processes, the participation of structural and functional lesions in the microvasculature and the role of cholinergic and adrenergic organ derangement. Recent studies using more sensitive techniques for parasite detection (PCR and immunohistochemistry) have suggested that the association of chronic Chagas disease lesions, inflammation and parasite products (DNA and protein) occurs much more often than previously thought (32,33). Indeed, there is now good evidence to indicate that parasitism of heart tissue is both necessary and sufficient to induce inflammation and tissue damage in Chagas disease (34). Thus, it is suggested that the chronic inflammatory infiltrate observed in the heart of Chagas disease patients may be the result of a continuous release of inflammatory mediators by tissue cells in response to *T. cruzi* and/or its products. In addition, there is also evidence to suggest that autoimmunity may contribute significantly to the inflammatory damage to heart cells and conduction system of the heart (35). Alternatively, autoimmunity may be mediated by living parasites hidden in the adrenal gland (36). The realization that parasites play an essential role in driving tissue inflammation in the chronic phase of the disease has obvious implications in the treatment of patients.

The evolution from the indeterminate to a ‘clinical’ form (cardiomyopathy and the megasymphdromes) of chronic Chagas disease generally occurs 10–20 years after the acute phase in a slow and progressive fashion. Epidemiological studies in the endemic area have shown that 2–5% of patients will evolve each year from the indeterminate to a clinical form of the disease (23,24). In Brazil, approximately 20–30% of patients develop a cardiac form, 5–8% chronic esophagopathy and 4–6% chronic colopathy (23,24). Geographical differences in the clinical manifestations of Chagas disease in Latin American regions may occur and digestive syndromes are not frequently reported outside Brazil (37). From the epidemiological and clinical points of view, chronic cardiomyopathy is the most important chronic form of Chagas disease, because of its associated morbidity and mortality and the consequent medical and social impact (2,19).

The main pathological finding in the hearts of infected patients is that of a chronic progressive and fibrosing myocarditis (38). Interestingly, focal myocarditis is found even in the indeterminate form of the disease and is more intense as the disease progresses to the more severe clinical stages. In the chronic stages of the disease, tissue parasitism and blood parasitemia are scant. The loss of cardiomyocytes and substitution of lost cells by fibrotic tissue appears to induce disruption of
muscle fibers and fascicles (39,40). This architectural disarrangement causes malfunctioning of the electrophysiological sinucitia and is important for the tendency of Chagas disease patients to develop heart failure and ventricular arrhythmias, the markers of adverse prognosis related to high and premature mortality rates.

Prognostic factors in patients with Chagas disease have been reviewed recently (41). From 606 potentially relevant studies, 12 met the inclusion criteria: eight clinic-based studies including 3928 patients and four hospital-based studies including 349 patients (41). Impaired left ventricular function by echocardiogram or cineventriculogram was the most common and consistent independent predictor of death (19,42-45). New York Heart Association (NYHA) functional class III/IV, cardiomegaly on the chest radiography, and nonsustained ventricular tachycardia on 24-h Holter monitoring or stress testing were also independently associated with higher mortality. The typical ECG abnormalities demonstrated limited additional prognostic value and other often-mentioned risk factors, advanced age and male sex, showed inconsistent results (41). Electrophysiological variables, obtained by invasive study (46,47) or evaluated by ECG analysis, such as QT dispersion and duration (54), may prove to have additional prognostic value in selected studies.

In any given group of patients, however strict the classification, remarkable individual functional differences among the constituents of the same clinical group will be found. Chagas disease is a notable entity not only for its clinical pleomorphism, but also for the striking individuality among Chagas disease patients. Thus, although patients with more severe disease have a worse prognosis as a group, there is much individual variation. This makes it essential that patients are stratified and followed-up carefully (21).

A potentially helpful simple score to predict death was developed to permit the stratification of risk in Chagas heart disease (48); moreover, the score was validated successfully in independent cohorts (49,49). Six independent prognostic factors were identified and each was assigned a number of points: NYHA class III or IV (5 points), evidence of cardiomegaly on radiography (5 points), left ventricular systolic dysfunction on echocardiography (3 points), nonsustained ventricular tachycardia on 24-h Holter monitoring or stress testing (3 points), low QRS voltage on electrocardiography (2 points), and male sex (2 points) (48). Patients were classified in three risk groups according to the final score: low risk (0–6 points), intermediate risk (7–11 points) and high risk (12–20 points). In the original study, the 5-year mortality rates for these three groups were 2, 18 and 63%, respectively (48) and, in an external validation sample, 3, 10 and 67% (49).

Diagnosis

In a patient with an appropriate epidemiological background, the detection of serum antibodies against T. cruzi or its components by at least two different methodologies is sufficient to support the diagnosis of Chagas disease. There are several techniques available to detect anti-T. cruzi antibodies, including indirect immunofluorescence, indirect hemagglutination and immunoenzymatic assays (28). At present, well-standardized commercial kits are available and widely employed in Latin America, mainly for screening of blood donors and for seroepidemiological surveys. The radiounprecipitation assay has been used as a confirmatory test in several ongoing and published studies of T. cruzi in blood donors in the USA and has demonstrated equivalent or superior rates of agreement, when compared with several other test formats, with the indirect immunofluorescence-positive test considered here as the gold standard (50).

The parasitologic diagnosis of Chagas disease is important in the acute phase and is based on detection of T. cruzi trypanomastigote forms by microscopic examination of fresh blood samples or by using indirect methods, such as xenodiagnosis and hemoculture. These tests are not essential during chronic Chagas disease as parasitemia is often absent and repeated parasitologic tests are usually necessary to demonstrate the parasitemia (51,52). PCR has limited use in routine diagnosis owing to the need for specific laboratory facilities, common DNA cross-contamination and high costs. At the same time, the high variability of PCR results found in different regions of Brazil raises some questions concerning its applicability for diagnosis. PCR's high specificity is indicative that it can be used as a confirmation method in inconclusive serology diagnosis (53), as well as an auxiliary method in post-therapeutic control of chronic Chagas disease (see below) (54). It can also be used in specific situations, such as in heart transplant recipients, where early diagnosis of Chagas disease relapse is necessary to initiate appropriate therapy (55,56).

Clinical findings & staging

Heart disease secondary to a progressive and frequently late chronic myocarditis is the most important clinical manifestation of Chagas disease. In the early stages of the infection, only small numbers of patients display the clinical signs of the disease. In fact, most of the infected subjects enter silently into the chronic phase. Clinical presentation varies widely according to the degree of myocardial damage and most patients present a milder form of heart disease. The adaptation and tolerance of the heart varies with the speed and quality of the pathogenetic process, especially if damage to the myocardium develops rapidly or gradually over the course of many years. On average, the heart involvement is fully developed approximately 20 years after the primary infection, although this takes place earlier in some subjects and later in others. Clinical manifestations of severe chronic Chagas heart disease comprise three basic syndromes: heart failure, cardiac arrhythmia and thromboembolism. Chest pain that resembles angina in location and character, but has no consistent relationship to effort and is not relieved by nitrates, may occur in almost a quarter of Chagas disease patients in the absence of obstructive coronary disease at the epicardial level. Although abnormal coronary flow regulation related to endothelial and nonendothelial dysfunction has been reported in Chagas disease patients with chest pain, the hypothesis of chronic myocardial
ischemia in Chagas cardiomyopathy still awaits conclusive support [31]. Acute myocardial infarction is not common in Chagas disease and may present with atypical chest pain and, eventually, with normal coronary arteries [57].

Heart failure is usually biventricular. Clinical manifestations of right ventricular failure, as increased jugular venous pressure, peripheral edema and liver enlargement, were formerly reported as more prevalent and more pronounced than those of left-sided failure. Nevertheless, it has nowadays been observed that, although early signs of right ventricular involvement have been shown before left ventricular dysfunction in studies analyzing biventricular function [58,59], right ventricular dysfunction is significant only when there is also a significant associated involvement of the left side, especially when left ventricular filling pressure and pulmonary pressure is elevated [60]. Indeed, left ventricular systolic dysfunction is the major feature of Chagas cardiomyopathy, and it is the main predictor of the risk of death [61]. Although diastolic left ventricular abnormalities have been noted in the absence of regional or global left ventricular systolic dysfunction, in general, there is a strong correlation between systolic dysfunction and impairment of left ventricular filling in Chagas disease [62].

Chronic Chagas heart disease is characterized by a wide variety of structural abnormalities that generate unidirectional block and slow conduction in circumscribed ventricular regions, essential for the appearance of re-entrant ventricular arrhythmias, which are the main triggering factor of sudden death in chronic Chagas heart disease [62]. The severity of ventricular arrhythmias tends to correlate with the degree of left ventricular dysfunction [62]. However, it is not uncommon to have patients with ventricular tachycardia who have well-preserved global ventricular performance. Virtually all patients with heart failure have frequent monomorphic or polymorphic ventricular premature beats and runs of nonsustained ventricular tachycardia. Episodes of malignant ventricular arrhythmia seem to be much more frequent in Chagas disease patients than with those with other types of underlying heart disease [63]. Although sudden death is common, it rarely occurs in asymptomatic patients [64]. The final event in these patients is presumed to be ventricular tachycardia and fibrillation but bradyarrhythmias may also occur. Atrial fibrillation typically occurs in patients with advanced heart failure and is characterized by relatively low ventricular rate, related to the coexistence of ventricular conduction disturbances.

Intraventricular and atrioventricular conduction disturbances are common manifestations of Chagas heart disease and are generally related to the presence of left ventricular dysfunction and ventricular arrhythmias. Right bundle branch block is the most frequent electrocardiographic abnormality and it is typically associated with left anterior hemiblock; left bundle branch block is relatively infrequent and is a harbinger of ominous prognosis [65]. The QRS duration is directly related to the left ventricle dimension and inversely related to the ejection fraction, although its independent prognostic value remains to be proved [66]. Chagas disease is a main cause of atrioventricular blocks in Latin American countries and, although atrioventricular node functional abnormalities may occur, they are generally caused by widespread and distal fibrosis of the conduction system. Sinus node dysfunction is also a concern and these patients are frequently candidates for the implantation of pacemakers. In comparison with pacemaker patients without Chagas disease, Chagas disease patients are significantly younger and have a lower left ventricular ejection fraction and more frequent ventricular arrhythmia during Holter monitoring [67].

Systemic and pulmonary embolism, arising from mural thrombi in cardiac chambers and from deep-venous thrombosis due to low cardiac output, is a common complication of Chagas disease. Stroke is frequent in Chagas cardiomyopathy and is associated with systolic dysfunction and with intracardiac thrombi; occurring mainly in patients with typical apical aneurysm of Chagas disease [68,69]. Chagas disease has been considered an often unrecognized cause of stroke and should be regularly included in its differential diagnosis in patients of Latin American origin [70].

To take into account the great clinical pleomorphism of Chagas disease and in order to plan clinical cohorts of patients, several classification systems were developed in Chagas cardiomyopathy. Kuschnir [71] and Los Andes University [72] classification systems have been frequently used in longitudinal studies [22,45,73,74]. We have also developed a clinical classification system displaying a spectral range of the disease, from the indeterminate form through to Chagas cardiomyopathy (Table 1) [2]. This classification system is based on the type and severity of cardiac involvement and is related to different underlying pathogenetic mechanisms, with potential prognostic value. More recently, a committee of experts proposed another staging system [19], based mainly on international heart failure guidelines (Table 2) [75,76]. The main virtue of this new classification system is that it is compatible with international standards and, in general terms, with therapeutic recommendations for each stage of heart failure. A comprehensive and comparative evaluation of all these classification systems, including their validity, reliability, sensitivity, specificity and predictive value, has not yet been performed.

The relevance of various diagnostic methods

The ECG is the single most important examination in Chagas disease patients (Tables 1 & 2). Numerous epidemiological studies have shown that patients with a normal ECG have an excellent medium-term survival rate [23,24,77]. Moreover, severe global left ventricular dysfunction, the main prognostic marker in Chagas disease, is rare in such patients. The greater the number and severity of ECG alterations registered in the same tracing, the more advanced the myocardial damage possibly is, and the worse the prognosis should be. Although rare, sudden death may occur in patients with a normal ECG as the initial manifestation of the disease [62]; however, it is generally a complication of late advanced disease [64].

Echocardiography is the best noninvasive technique used in the assessment of cardiac function and represents an important method in the evaluation of Chagas cardiomyopathy. Variables
Management of Chagas cardiomyopathy

Table 1. Clinical classification of chagasic cardiomyopathy.

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic indeterminate</td>
<td>Asymptomatic, no significant alteration on physical examination, ECG, chest x-ray, esophagogram and barium enema. No change on evaluation by sensitive techniques (echocardiogram, exercise testing and Holter)</td>
</tr>
<tr>
<td>CCC1</td>
<td>Asymptomatic, no significant alteration on physical examination, ECG, chest x-ray, esophagogram and barium enema. Sensitive techniques can detect cardiac abnormalities of variable severity</td>
</tr>
<tr>
<td>CCC2</td>
<td>Asymptomatic patients or those presenting NYHA functional class I, without clinical and radiological signs of heart enlargement, but with minor ECG alterations, such as low voltage of QRS complexes in the standard leads, block of the anterosuperior division of the left branch, minor changes in the SI segment and in the T wave</td>
</tr>
<tr>
<td>CCC3</td>
<td>Patients without manifestations of heart failure or in NYHA functional class II and without enlargement of the cardiac silhouette. These patients may display advanced intraventricular conduction disturbances, such as right bundle branch block, and usually few uniform ventricular premature contractions</td>
</tr>
<tr>
<td>CCC4</td>
<td>As in the previous group, these patients do not show signs of cardiac enlargement. However, the ECG abnormalities displayed by this group are significantly more severe and include right bundle branch block associated with left anterior hemiblock, abnormal Q waves, diffuse negative symmetric T waves, left bundle branch block, second-degree atrioventricular block Mobitz type II and complete atrioventricular block. Repetitive ventricular premature contractions are frequent</td>
</tr>
<tr>
<td>CCC5</td>
<td>Patients with clinical, radiological and, especially, echocardiographic signs of heart enlargement, with or without manifestation of cardiac insufficiency</td>
</tr>
</tbody>
</table>


usually employed in the clinical evaluation of and clinical research on Chagas disease patients are: the ejection fraction, left ventricular diastolic and systolic diameters, left atrium diameter, the estimate of right ventricular size, the evaluation of global and segmental myocardial contractility and the assessment of diastolic function. New echocardiographic methodologies, such as the tissue Doppler [25,28,31,78-80] and the strain rate [81], may help in the evaluation of the Chagas disease patient.

Global systolic left ventricular dysfunction is the strongest predictor of morbidity and mortality in Chagas disease [19,43-45] and asymptomatic left ventricular systolic dysfunction is at least as common as symptomatic heart failure, as defined by clinical criteria. Identification and treatment of patients with left ventricular global systolic dysfunction can improve survival and reduce morbidity. Since it is costly to submit all patients with Chagas disease to echocardiographic evaluation, it is desirable to develop screening methods to indicate which patients should be submitted to complete left ventricular evaluation. An enlarged heart silhouette at chest x-ray, although a specific sign of cardiac dilatation, lacks sensitivity and has a poor overall diagnostic performance [82]. Elevation of brain natriuretic peptide (BNP) levels in blood, a reliable indicator of systolic left ventricular dysfunction in different clinical and epidemiological settings, is a promising screening method [83-86]. In patients with abnormal ECG and/or chest x-ray, BNP elevation has a positive predictive value of 80% and a negative predictive value of 97% for the detection of patients with depressed left ventricular ejection fraction [84]. A diagnostic strategy including ECG and BNP performed better than the classical approach with ECG and/or chest x-ray [86]. Moreover, BNP level is also a marker of the presence of ventricular arrhythmia [88] and diastolic dysfunction [89].

One of the most interesting findings in the study of the heart in Chagas cardiomyopathy is the pattern of segmental myocardial contractility disturbance that makes this disease in some ways closer to ischemic than to idiopathic cardiomyopathy. The segments predominantly involved are the apex and the postero-inferior wall of the left ventricle [25,79]. These latter changes appear even in the indeterminate form of Chagas cardiomyopathy (~20–30% of cases) and are universally present in cases of severe heart failure [25,79]. Echocardiography allows the identification of almost all apical lesions, even small ones. It is important to note that the apical lesion in Chagas disease is not generally associated with contractile dysfunction in the anteroseptal segment of the left ventricle, which distinguishes Chagas disease from patients with coronary artery disease complicated with infarction where contractile dysfunction is observed. The involvement of other segments of the left ventricle in Chagas disease is almost impossible to differentiate from coronary artery disease and the clinical and epidemiological aspects are essential for differential diagnosis.

The use of transesophageal echocardiography allows the identification of possible cardiac sources of emboli with high accuracy [81]. As Chagas disease is frequently complicated by embolic accidents, transesophageal echocardiography can be important in deciding the benefit of anticoagulant therapy.

The assessment of left ventricular diastolic function in Chagas disease has shown that diastolic dysfunction may occur early in the disease. Studies by our group have demonstrated a
Table 2. Stages of Chagas cardiomyopathy, in accordance with the Brazilian consensus in Chagas disease.

<table>
<thead>
<tr>
<th>Stage</th>
<th>ECG</th>
<th>Echocardiogram</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>B1</td>
<td>Abnormal</td>
<td>Abnormal LVEF &gt; 45%</td>
<td>Absent</td>
</tr>
<tr>
<td>B2</td>
<td>Abnormal</td>
<td>Abnormal LVEF &lt; 45%</td>
<td>Absent</td>
</tr>
<tr>
<td>C</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Treatable</td>
</tr>
<tr>
<td>D</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Refractory</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction.
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relationship between systolic and diastolic function, so that the presence of abnormal relaxation and compliance is generally associated with poor ejection fraction of the left ventricle in Chagas disease patients [61]. Tissue Doppler imaging is an innovative technique that may help in the detection of pseudonormal pattern of diastolic dysfunction, which is harder to diagnose with conventional Doppler analysis [78].

Dynamic ECG recording is especially important in Chagas disease because of the relatively frequent occurrence of asymptomatic transient arrhythmias [89]. Identification of complex forms of ventricular arrhythmias, such as couplets, bigemism and, especially, ventricular tachycardia, is prognostically important [88,41]. The detection of potentially lethal arrhythmias, as prolonged ventricular tachycardia or transient advanced heart blocks, may indicate the necessity of specific antiarrhythmic therapy or devices. Sick sinus syndrome is also frequent in Chagas disease patients and can be recognized by Holter monitoring. The lack of significant ventricular arrhythmia in 24-h ECG does not, however, preclude risk of death due to arrhythmia. Ambulatory monitoring may also be used in the investigation of pulsitations and syncope [89,90] and to assess the efficacy of antiarrhythmic therapy [67].

Holter monitoring is also a valuable tool in the assessment of heart rate variability (HRV), an indirect measure of autonomic nervous system control of the heart [91]. Reduced indexes of HRV could be found in Chagas disease patients before the development of overt cardiac disease [27,92], indicating mainly vagal involvement [93]. Some HRV methods, such as heart rate turbulence [94,95], useful as prognostic markers in other cardiopathies [96], may be evaluated using Holter monitoring and may sometimes help in the identification of patients prone to present malignant arrhythmias, an attractive hypothesis that deserves to be tested.

In selected patients, invasive electrophysiologic study may be useful for identifying the cause of syncope (when non-invasive tests are inconclusive) [90] or to guide the use of antiarrhythmic devices, such as cardiac pacemakers and implanted defibrillators [46]. Moreover, induction of ventricular tachycardia during programmed ventricular stimulation is a predictor of arrhythmia, cardiac death and general mortality in patients with Chagas cardiomyopathy and nonsustained ventricular tachycardia [47].

Maximal exercise testing is usually assessed with the use of a standard Bruce protocol and can be conducted safely in patients with Chagas disease. Exercise testing enables the assessment of the influence of the exercise in provoking arrhythmias and also plays a role in defining the type of work a patient may perform. Exercise-induced ventricular tachycardia has the same ominous prognostic significance as that observed in Holter monitoring [97,48]. Chronotropic insufficiency and abnormal blood pressure response are more frequent in Chagas disease patients and may also hamper their effort capacity [98,99]. Autonomic impairment, sick sinus syndrome and left ventricular dysfunction are putative causes of these abnormalities, but it is also well known that some patients with advanced cardiomyopathy may retain an excellent exercise capacity. Indeed, as with many other aspects of Chagas disease physiopathology, the response to exercise cannot be predicted by other means and stress testing is an essential tool in the evaluation of Chagas cardiomyopathy patients.

Radioisotopic techniques, such as myocardial scintigraphy with Thallium-201, have been performed in combination with stress testing in order to study the myocardial perfusion pattern in the following clinical situations:

- Patients with precardial pain
- Left ventricular segmental hypocontractility
- Ischemic ECG abnormalities

Both transient and irreversible perfusion defects may be detected by myocardial perfusion scanning in these patients. This finding may represent microvascular abnormalities, disautonomia or areas of myocardial fibrosis [100,101]. In patients who complain of angina-like pain, perfusion disturbances may occur, usually in the presence of normal coronary arteries. Occasionally, cardiac and coronary catherization are required to exclude the presence of epicardial obstructive coronary artery disease [102].

Cardiac magnetic resonance may have a role in the evaluation of Chagas cardiomyopathy, since it offers a wide variety of imaging tools to evaluate, in detail, morphology, function and other tissue characterization abilities, such as detection of edema and fat [103]. Myocardial delayed enhancement by MRI could quantify myocardial fibrosis in patients with Chagas heart disease, thus helping in the definition of the severity of the disease [104].
Optimal therapy

Specific treatment

Two drugs are indicated for the specific treatment of Chagas disease, namely benznidazole and nifurtimox, although only the former is currently available in Brazil and the latter in the USA [103]. Benznidazole is administered in a daily dose of 5–10 mg/kg of bodyweight for children and in a daily dose of 5 mg/kg for adults, both to be taken twice daily. The recommended duration of therapy is 60 days. Nifurtimox is prescribed in a total daily dose of 15 mg/kg for children and 8–10 mg/kg for adults, both taken three-times daily, for a period of 90 days. Benznidazole may provoke an allergic rash of variable intensity, usually appearing approximately on day 9 of treatment, which is the most common side effect and is usually a reversible disorder [106]. Nevertheless, treatment should be interrupted when the eruption is intense or followed by fever and lymphadenopathy. Neutropenia and agranulocytosis may occur sometimes, whereas the occurrence of severe thrombocytopenia is rare. Hematologic alterations tend to occur early and require the interruption of treatment. A complete hematologic evaluation should be performed in the first 3 weeks of treatment. A sensory neuropathy is a rare, toxic, dose-related manifestation that can be prevented by not exceeding the recommended dose of the drug, especially for adults. The most frequent adverse effects observed in the use of nifurtimox are anorexia, loss of weight, psychic alterations, excitability, sleeplessness, digestive manifestations such as nausea or vomiting and, occasionally, intestinal colic and diarrhea [106].

The indications for specific treatment are shown in Box 1. The relevance of specific treatment for the control of Chagas disease has recently gained interest since findings suggest that chronic parasitism is essential for disease to occur. Moreover, it is clear that specific treatment is beneficial in acute or recently infected Chagas disease patients. It is estimated that treatment with benznidazole can lead to more than 70% parasitological cure if Chagas disease patients are treated during the acute infection [107]. There is now a consensus that patients with recent infection, especially children [108,109] and adolescents [110], should be treated [108]. Indeed, parasitological cure was observed in more than 50% of the treated cases in these randomized trials [108-110]. The indication for treatment in patients with chronic Chagas disease is still a matter of controversy. After performing a systematic review published in 2002, Villar and coauthors concluded that "antitrypanocidal therapy for chronic asymptomatic T. cruzi infection has been tested in few, small size randomized controlled trials, which were designed to assess parasitic-related, but not clinical outcomes. Therefore, the potential of trypanocidal therapy to prevent Chagas disease among asymptomatic, chronically infected subjects is promising but remains to be evaluated" [111]. More recently, Viotti et al. selected infected patients 30–50 years of age and without heart failure and compared, in an observational study, clinical outcomes of 283 patients treated with benznidazole with 283 patients who did not receive any specific treatment [73]. Fewer treated patients presented progression of the disease (4 vs 14%; hazard ratio [HR]: 0.24; p = 0.002) or developed abnormalities in electrocardiography (5 vs 16%; HR: 0.27; p = 0.001) compared with untreated patients. Median time to follow-up was 9.8 years and 20% of patients from both intervention groups were lost to follow-up during the study. Although these results are a strong indication that specific treatment of chronic Chagas disease can hamper the evolution to severe chronic cardiomyopathy, the need for a randomized controlled trial, with clinical end points and long-term follow-up, is stressed expressly [6,73]. In fact, investigators in several centers in Latin America are conducting a 5-year randomized, controlled trial (the Benefit Multicentric Project; ClinicalTrials.gov Identifier: NCT00123916 [201]) to examine the effects of benznidazole on cardiac outcomes in patients with chronic infection. These potential benefits apparently do not apply to those patients with advanced chronic Chagas disease cardiomyopathy, since there is insufficient evidence to support the efficacy of specific drugs in this clinical situation [112].

However, there are important issues that need to be addressed if therapy is to be of true benefit. First, there are important and unsolved concerns regarding the long-term safety (especially a possible risk of treatment-associated malignancies) of the medication currently available [113]. Second, the early detection and proper management of the common side effects associated with the use of imidazole-containing compounds are rarely performed in endemic areas without close medical supervision. Third, in the face of the low efficacy of currently available medication for specific treatment (nifurtimox and benznidazole), it

Box 1. Recommendations for specific treatment in Chagas disease.

- Acute phase of the disease, whatever the mechanism of transmission — vectorial, transfusional, congenital, laboratory accidents or organ transplant
- As a preventive measure in cases of organ transplantation, both to the donor and to the receptor
- Cases of reactivation of the disease, as can occur in immunosuppressed patients
- Patients with recent chronic infections (5-12 years from the initial infection), specifically all children infected by Trypanosoma cruzi
- Patients with the indeterminate form or with slight heart damage, provided the treatment is performed under an investigative protocol, with systematic clinical, parasitological, immunological and laboratorial evaluation
- Young patients already displaying significant conduction disturbance or arrhythmia, also under an investigative protocol, in the hope of preventing a possible clinical deterioration
- Patients showing a tendency to clinical worsening, also under an investigative protocol

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would be useful to define those patients who show a tendency to clinical worsening and those at greatest risk of developing severe disease, as the latter could be targeted in clinical trials. Fourth, researchers are convinced that benznidazole is not the ideal drug for chronic-stage disease, but it is the only one available at present. It is valid to use it and to experiment with new formulations, schedules and indications, but it is necessary to continue to search for a safer and more efficient and safer drug [8]. In addition, the definition of simple but effective criteria of cure would be very useful, not only in larger epidemiological studies evaluating the effect of mass treatment but also in case of individual specific treatment.

The criteria of cure in Chagas disease are a matter of greater controversy. Clinical criteria are of limited value either in the acute or chronic phase of Chagas disease. Even in the absence of any treatment, symptoms usually subside within 1–2 months in the acute phase. In the chronic phase, these criteria are even less important. Chronic patients are usually symptomless and visceral lesions already present are not reversible. In long-term longitudinal studies, suitable, specific markers for the development or worsening of the pathological picture of Chagas disease need to be chosen but this has proven a very difficult task. For instance, the development of ECG signs of left anterior hemiblock in a given treated or untreated patient may result from Chagas disease-related pathogenetic mechanisms, but may also be related to other morbid processes, such as arterial hypertension. Indicators of cardiac normality or enlargement, such as the cardiothoracic ratio measured using a chest x-ray, have similar pitfalls. Nevertheless, such unspecific and variable markers have been employed as morbidity indicators in some recent studies of specific treatment of Chagas disease. As a consequence, the meaning of these alterations in long-term prospective studies is of doubtful nature.

Serological tests should demonstrate a fall in titers or negativation of the test in cases where treatment was successful. Most studies show that negativation of serological tests is uncommon but a drop in titers may occur [18,19]. One of the hypotheses raised to explain the lack of seroconversion to negative of these tests, even after the confirmed elimination of parasitemia, stems from the experimental work of Andrade and coworkers [114], who demonstrated the persistence of parasite antigens in dendritic cells of the lymphoid follicles of the spleen. The actual meaning of the drop in titers commonly observed in many treated patients has not been fully appreciated.

Lyric antibodies and trypomastigote glyconjugates have been used as alternatives to serological tests, which mainly use parasite lysates. The overall impression is that the use of certain specific antigens or a small group of specific antigens results in maintained specificity and sensitivity but with a more pronounced and detectable fall of titers after specific treatment [115]. PCR-based strategies and flow cytometry analysis offer the possibility of a high degree of sensitivity and specificity [116,117]. In addition, the results of PCR correlate well with studies evaluating lyric antibodies, again suggesting the possible use of this methodology as a criterion of cure [118].

Although parasitological techniques (hemoculture and xenodiagnosis) are essential for isolation of parasite strains, these tests are often negative owing to the low number of circulating parasites in chronic Chagas disease [118].

Thus, it is clear that the definition of cure in chronic Chagas disease is not simple as there is no single laboratory test that unequivocally diagnoses cure in treated patients. However, if we are to compare the effects of specific treatment on immune responses of treated Chagas disease patients, proper criteria of cure must be devised. In addition, a simple method to evaluate cure must be devised if we are to conduct large-scale trials to demonstrate the clinical efficacy of specific treatments.

Treatment of heart failure

Heart failure in Chagas disease patients is associated with higher rates of morbidity and mortality compared with other cardiomyopathies [119]. In a Brazilian cohort of 1220 outpatients with heart failure in functional classes III and IV (NYHA) of different etiologies, Chagas heart disease was the main prognostic factor for mortality [120]. As most patients in endemic regions are from the hinterland and from poor economic backgrounds, cost is a very important limiting factor in the management of Chagas disease patients with heart failure. In Brazil, most drugs used in the pharmacological therapy of Chagas disease — namely enalapril, captopril, digoxin, furosemide, thiazides and amiodarone — have been provided by the Brazilian Ministry of Health and distributed to the National Health Service, although heart failure-specific β-blockers, spironolactone and coumarins are generally not available.

Very few clinical trials have been carried out with patients with Chagas heart failure and some of them are short-term, nonrandomized studies [121–124]. Nonetheless, guidelines for the treatment of heart failure due to other conditions [75] are generally used to guide the treatment of the condition in the Chagas disease population. This direct transposition of recommendations derived from studies performed in patients with heart failure from other etiologies, generally in Europe and North America, to the Latin American Chagas disease patient is potentially misleading. Chagas disease has many peculiarities and the response of patients to the usual drugs prescribed in heart failure could be different [125]. Moreover, the physician’s perception that Chagas disease is a different condition may lead to suboptimal dosing or lack of initiation of medications that are of proven efficacy in patients with other etiologies of heart failure. Although many of these drugs (β-blockers, angiotensin-converting enzyme inhibitors and spironolactone) prolonged survival in heart failure patients elsewhere [75], their ability to change the prognosis of patients with Chagas cardiomyopathy is largely unknown and remains to be determined.

In order to determine the safety and efficacy of renin–angiotensin system (SAS) inhibitors and β-blockers in chronic Chagas cardiomyopathy, we conducted a double-blind, placebo-controlled randomized trial in 42 patients with T. cruzi infection and cardiomyopathy [126]. All patients received enalapril, uptitrated to 20 mg twice daily, and spironolactone 25 mg once
Management of Chagas cardiomyopathy

daily. Subsequently, 20 patients were randomly assigned to placebo and 19 to carvedilol uptitrated to 25 mg twice daily. Optimization of RAS inhibition was safe, hemodynamically well tolerated and associated with improvements in left ventricular ejection fraction (IF ≤ 45% at baseline), Framingham score, quality of life, and reductions in the cardiothoracic index and biomarkers BNP and RANTES. The addition of carvedilol, associated with a trend towards an increase in left ventricular ejection fraction, was safe, hemodynamically well tolerated and not associated with symptomatic bradycardia [123].

Our findings reinforce previous studies that have suggested a beneficial effect of angiotensin-converting enzyme inhibitors (e.g., enalapril and captopril) [121,122] and β-blockers [124] for the treatment of Chagas disease-associated cardiomyopathy. It also indicates that spironolactone, an aldosterone receptor blocker that reduces the risk of both morbidity and death among patients with severe heart failure of other etiologies [125], appears to be safe in Chagas disease [123]. Nonetheless, larger trials are needed to show effects on mortality and/or hospitalization. Indeed, the Chagas Cardiomyopathy Bioprolol Intervention Study (CHARITY), a long-term, prospective, randomized study started July 2003, is being conducted to document the potential effect of β-blockers in the morbidity and mortality of Chagas disease heart failure patients (ClinicalTrials.gov Identifier NCT00323973 [202]) [126].

The use of digitalis in the Chagas disease population may be cumbersome and only small studies have evaluated the use of this drug in this group of patients [121]. Patients with heart failure commonly have associated sinus node disease, intraventricular conduction defects and heart blocks. Moreover, Chagas heart disease is characterized by a great degree of excitability and digitalis, theoretically, may enhance ventricular arrhythmias in these patients. Thus, it is our opinion that digitalis should only be used cautiously in Chagas disease, mainly in asymptomatic patients despite optimal with vasodilators and diuretics, with careful follow-up. Both digitalis and β-blockers can aggravate bradyarrhythmias and atrioventricular conduction defects and a pacemaker implantation is frequently needed to ensure that the patient will receive the necessary dosage safely.

Pacemaker biventricular resynchronization, which benefits mainly patients with left bundle branch block and severe systolic left ventricular dysfunction, has been used in Chagas disease patients with success [127]. The high cost of such treatment, as well as the unknown efficacy in those patients with right bundle branch block (which is much more common in Chagas disease), limits its use in this setting. Again, specific studies are urgently needed, since ventricular resynchronization is now a therapeutic option for a group of heart failure patients of different etiologies.

Heart transplantation for advanced Chagas heart disease should be regarded as a valuable treatment option for selected patients [128]. The survival results after heart transplantation are paradoxically good, considering the usually high expected death rates for Chagas disease. Nonetheless, heart transplantation is a very expensive treatment, available only in a few centers, generally far from the hinterland where many Chagas disease patients live, and should be restricted to a few selected patients. The identification and treatment of the reactivation of the T. cruzi infection pose additional challenges in the post-transplantation follow-up, although early diagnosis and specific treatment of reactivation did not leave functional sequelae in the myocardium [129]. It is important to stress that the risk of reactivation does not constitute a contraindication against heart transplantation in Chagas disease patients. Partial left ventriculotomy, although conducted with success in some patients, [130], has been largely abandoned in recent years owing to considerable postoperative mortality and lack of long-term improvement of cardiac performance [131].

Cellular therapy, using bone marrow stem cells and/or skeletal myoblasts, has been used in experimental models of Chagas disease, with beneficial effects on ventricular function [132-134], and one successful treatment in human Chagas disease has been reported recently [135]. This therapeutic option, although promising, is currently experimental and needs to be evaluated more comprehensively in prospective studies. Indeed, a multicenter randomized study (Multicenter Randomized Study Of Cell Therapy In Cardiopathies – Chagas Cardiomyopathy [CMRCC-CHG]), sponsored by the Brazilian Health Ministry, is being conducted to determine the effect of cell therapy in Chagas heart failure patients, aiming to detect significant increase in the ejection fraction of the left ventricle after bone marrow-derived stem cell implants (ClinicalTrials.gov Identifier NCT00349271 [205]).

Immunoadsorption is another novel therapy that has been advocated for patients with dilated cardiomyopathy and severe congestive heart failure, leading to acute and prolonged hemodynamic improvement in initial studies [136]. Since Chagas heart disease is characterized by high antibody levels against β1-adrenergic receptors, a beneficial response is expected in Chagas disease [137]. However, clinical studies using immunoadsorption in Chagas disease are not yet available.

Treatment of arrhythmias

Treatment of ventricular arrhythmia in Chagas disease patients is essentially empirical and not supported by large randomized controlled trials. That is to say that there are no properly designed prospective trials in larger groups of Chagas disease patients to ascertain whether pharmacological or device therapy of ventricular arrhythmias prevents sudden cardiac death. Thus, clinical management may be subject to large variations in different settings and our recommendations are mainly empirical. Patients with asymptomatic ventricular premature beats or a few episodes of nonsustained ventricular tachycardia, without significant ventricular dysfunction, usually do not require any antiarrhythmic therapy [138,139]. At the other end of the spectrum, those patients with sustained ventricular tachycardia and those resuscitated from sudden death may benefit from an implantable cardioverter-defibrillator, especially in the presence of depressed left ventricular function [127,140]. Patients with chronic Chagas heart disease recovered from cardiac arrest have a peculiar arrhythmogenic profile characterized by a high
frequency of ventricular fibrillation and a short period of time for first shock [140]. Nonetheless, the widespread use of this life-saving procedure is also hindered by socioeconomics factors in Latin American countries.

The main uncertainties are observed between two poles: what to do with Chagas cardiomyopathy patients, with complex ventricular arrhythmias or nonsustained ventricular tachycardia registered on Holter monitoring tracings or elicited by effort during stress testing, in the presence of abnormal left ventricular function? In those with significant arrhythmic symptoms, such as syncope and near-syncope, the electrophysiological study [90,141] may help to distinguish patients with malignant ventricular tachycardia, in whom an implantable cardioverter-debrillator should be implanted, from those with paroxysmal atrioventricular block, with better prognosis and candidates for a conventional pacemaker. Asymptomatic or oligosymptomatic patients represent a more complex challenge. Indirect evidence, such as the subgroup analysis from the Argentinean Gencsa trial [142], suggested (but did not prove) that amiodarone may reduce death in patients with nonischemic heart failure and nonsustained ventricular tachycardia, although this prophylactic efficacy was not observed in ischemic heart failure [143]. Considering this and other studies in heart failure populations, some authors believe that administration of amiodarone to Chagas disease patients with complex ventricular arrhythmias is justified, particularly when the arrhythmia in question is nonsustained ventricular tachycardia accompanied by ventricular dysfunction [62].

Indeed, amiodarone has been reported to be the best and safest antiarrhythmic drug in Chagas disease patients, and has a low incidence of ventricular arrhythmogenic side effects [144]. Sinus node dysfunction, atrioventricular nodal delay and intra-ventricular conduction delay frequently complicate the use of amiodarone, as severe bradyarrhythmias may occur. In these situations, a permanent pacemaker may be implanted (see later). Extracardiac toxicity, such as thyroid dysfunction, corneal deposits and dermatological abnormalities, are not uncommon, although life-threatening pulmonary toxicity appears to be rare. Alternative therapies, such as catheter ablation, are restricted to selected refractory cases and tertiary referral centers [145].

Treatment of symptomatic bradyarrhythmias does not differ from that recommended for other cardiomyopathies and is usually performed by permanent pacemaker insertion [146]. Main indications for pacing are atrioventricular block and sinus node dysfunction (TABLE 3). A very important situation commonly observed in chronic Chagas disease patients is the association of atrioventricular disturbances and frequent, complex ventricular arrhythmia. In these cases, an effective pharmacological antiarrhythmic therapy may require a ‘prophylactic’ artificial pacemaker implantation in order to prevent the harmful consequences of an eventual complete atrio-ventricular block. Nonetheless, right ventricular apical pacing may generate ventricular desynchronization and increased risk of heart failure in other cardiopathies [147], a possibility that should be balanced against the risk of abrupt heart block.

**Anticoagulation**

Although the importance of systemic and pulmonary embolic phenomena has been recognized for several decades [148], specific studies about the efficacy and safety of anticoagulation in Chagas disease are not available and management should be adapted from international guidelines [149]. In general, oral anticoagulation is recommended in situations in which there is a high risk of embolic events, such as atrial fibrillation, recent intracardiac thrombi and previous embolic ischemic stroke, peripheral arterial or pulmonary embolism. The initiation of oral anticoagulation therapy may be achieved with doses of warfarin between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response [150]. Considering that many Chagas disease patients continue to live in the hinterland, long-term systematic INR testing, tracking and follow-up may be a challenge and, eventually, a limitation to oral anticoagulant therapy.

**Summary & conclusions**

Almost 100 years after its discovery, Chagas disease remains a major health challenge in Latin American countries and also in Europe and North America, if one considers the large number of immigrants who now live in the developed world. Major advances in the control of Chagas disease transmission have led to a progressive decrease in its prevalence in Brazil and other Latin American countries. Owing to cohort effect, the disease might remain a public health problem for some time among older individuals.

The host- and/or parasite-related factors that determine the outcome of T. cruzi infection in infected people have not been elucidated fully, but continuous parasite persistence, autoimmunity, microvascular lesions and disautonomia may have pathogenetic roles. Chagas disease is a notable entity not only for its clinical pleomorphism, but also for the striking individuality among Chagas disease patients. This great individual variation makes it essential that patients are stratified and followed-up carefully. A simple score developed recently may be useful in recognizing patients at high risk of death.

Heart disease secondary to a progressive and frequently late chronic myocarditis is the most important clinical manifestation of Chagas disease. The clinical manifestations of severe chronic Chagas heart disease comprise three basic syndromes: heart failure, cardiac arrhythmia and thromboembolism. Clinical staging of Chagas disease may consider its great clinical pleomorphism and the need to stratify the risk of death and orient therapeutic measures. Many non-invasive methods may help in the evaluation of these patients, but the ECG and the echocardiogram are the most important tests.

Treatment of Chagas chronic cardiomyopathy comprises specific therapy and treatment of heart failure and arrhythmias. Specific treatment with benznidazole or nifurtimox is indicated in acute cases, in children and adolescents, and in those in special situations, such as transplantation donors and recipients.
### Table 3. Indication for the use of pacemaker in Chagas disease cardiomyopathy.

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permanent pacing in acquired AV block</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Third-degree and advanced second-degree AV block with any one of the following conditions:</td>
</tr>
<tr>
<td></td>
<td>• Bradycardia with symptoms, including heart failure, presumed to be due to AV block</td>
</tr>
<tr>
<td></td>
<td>• Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia (such as amiodarone)</td>
</tr>
<tr>
<td></td>
<td>• Documented periods of asystole of at least 3.0 s or any escape rate of less than 40 beats/min in awake, symptom-free patients</td>
</tr>
<tr>
<td></td>
<td><strong>Second-degree AV block, regardless of the type or site of block, with associated symptomatic bradycardia</strong></td>
</tr>
<tr>
<td>IIa</td>
<td>Asymptomatic third-degree AV block at any anatomical site with average awake ventricular rates of 40 beats/min or faster, especially if cardiomegaly or LV dysfunction is present</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic type II second-degree AV block with narrow QRS</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic type I second-degree AV block at the infra- or infra-His levels found at electrophysiological study</td>
</tr>
<tr>
<td></td>
<td>First- or second-degree AV block with symptoms similar to pacemaker syndrome</td>
</tr>
<tr>
<td>IIb</td>
<td>Marked first-degree AV block (&gt;0.30 s) in patients with LV dysfunction and symptoms of congestive heart failure in whom a shorter AV interval results in hemodynamic improvement, presumably by decreasing left atrial filling pressure</td>
</tr>
<tr>
<td><strong>Permanent pacing in chronic bifascicular and trifascicular block</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Intermittent third-degree AV block</td>
</tr>
<tr>
<td></td>
<td>Type II second-degree AV block</td>
</tr>
<tr>
<td></td>
<td>Alternating bundle branch block</td>
</tr>
<tr>
<td>IIa</td>
<td>Syncope not demonstrated to be due to AV block when other probable causes have been excluded, specifically VT</td>
</tr>
<tr>
<td></td>
<td>Incidental finding at electrophysiological study in asymptomatic patients of markedly prolonged His-ventricular interval (&gt;100 ms) or of a pacing-induced infra-His block that is not physiological</td>
</tr>
<tr>
<td><strong>Permanent pacing in sinus node dysfunction</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Sinus node dysfunction with documented symptomatic bradycardia (including frequent sinus pauses)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic chronotropic incompetence</td>
</tr>
<tr>
<td>IIa</td>
<td>Sinus node dysfunction occurring spontaneously or as a result of necessary drug therapy, with a heart rate of less than 40 beats/min when a clear association between typical significant symptoms and the actual presence of bradycardia has not been documented</td>
</tr>
<tr>
<td></td>
<td>Syncope of unexplained origin when major abnormalities of sinus node function are discovered or provoked in electrophysiologic studies</td>
</tr>
<tr>
<td>IIb</td>
<td>In minimally symptomatic patients, chronic heart rate of less than 30 beats/min while awake</td>
</tr>
</tbody>
</table>

Class I means general agreement that the device or therapy is indicated. Class II indicates a divergence of opinion with respect to their usefulness, with Class IIa favoring and Class IIb not favoring usefulness.

AV: Atrioventricular; LV: Left ventricular; VT: Ventricular tachycardia.
Adapted from [146].

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**Expert commentary**

Although the number of new cases of Chagas disease has dropped markedly in the last few years, owing to effective control programs, there is a large population of individuals who will clearly benefit from adequate clinical management. The identification of early markers of worse prognosis would be an important advancement, as these markers may identify a group of patients who would benefit the most from early and, perhaps, more aggressive intervention. It is essential that we define whether specific treatment with currently...
available or new drugs will modify the ominous evolution of the disease observed in a significant proportion of individuals. However, in order to evaluate the effectiveness of specific treatments, it is imperative that we define adequate criteria of cure. Moreover, large multicenter trials are needed if we are to demonstrate the clinical benefit to Chagas disease patients of the drugs and devices currently used for the treatment of arrhythmias and heart failure due to other causes. β-blockers, such as metoprolol, bisoprolol and carvedilol, now stand as the cornerstone of the treatment of heart failure, but they seem to be underused in Chagas disease, owing to the absence of long-term controlled studies and the fear of complications, such as clinical deterioration and bradycardia. Innovative therapies, such as cellular implantation, should be scrutinized carefully before being incorporated in the clinical practice.

Five-year view
The forthcoming years will probably show us some important improvements in the Chagas disease field. Multinational transmission-control initiatives will produce a more pronounced reduction in new cases by elimination or diminution of vectorial and transfusional transmission. Other forms of transmission, such as congenital or oral, will have a proportionally stronger role in the maintenance of the disease cycle. Transmission via blood will continue to occur in countries where the disease is not endemic and a rigid surveillance is not maintained.

More data will be available on epidemiology and specific clinical features of the disease in the elderly, as well as on the mechanisms involved in the evolution from the indeterminate form to clinical syndromes. Screening methods, such as BNP measurement, may help in the detection of patients with left ventricular dysfunction and worse prognosis, selecting those for more intensive treatment.

Much progress is expected in the field of specific treatment, including a standardization of the control of cure and the results of international randomized trial with benznidazole. Moreover, multicenter randomized trials on the effects of bisoprolol and stem cell therapy will be also be completed and their results will help to elucidate the role of these measures in the treatment of heart failure patients. A decrease in the price of implantable cardioverter-defibrillators would make this life-saving device therapy available to a much larger population, improving the survival rate in patients with malignant ventricular arrhythmias.

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Key issues

- Chagas disease is an illness caused by the protozoan parasite *Trypanosoma cruzi* that is endemic in South and Central America, where it is estimated that 18 million people are infected.

- The principal mechanisms of *T. cruzi* transmission to humans are through infected secretions from blood-sucking insects and transfusion of blood from infected donors.

- The incidence of new infections by *T. cruzi* in the whole of South America has decreased by 70% owing to transmission-control measures.

- The host- and/or parasite-related factors that determine the outcome of *T. cruzi* infection in infected people have not been fully elucidated, but continuous parasite persistence, autoimmunity, microvascular lesions and disautonomia may have pathogenetic roles.

- Chagas disease is a notable entity for its clinical pleomorphism and great individual variation that make it essential for patients to be stratified and followed-up carefully. A simple score developed recently may be useful in recognizing patients with high risk of death.

- Heart disease secondary to a progressive and frequently late chronic myocarditis is the most important clinical manifestation of Chagas disease. Clinical manifestations of severe chronic Chagas heart disease comprise three basic syndromes: heart failure, cardiac arrhythmia and thromboembolism.

- Specific treatment with benznidazole or nifurtimox is indicated in acute cases, in children and adolescents, and in those in special situations, such as transplantation donors and recipients and after laboratory accidents. Treatment of chronic cases is a matter of controversy and a prospective randomized study is underway.

- Treatments of heart failure and arrhythmias are not different from other cardiopathies, although many peculiarities may make the management of individual cases difficult.
Management of Chagas cardiomyopathy

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Métodos de Avaliação Funcional Não-Invasivos da Cardiopatia Chagásica e outras Cardiopatias Infecciosas

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Introdução

As miocardiopatias infecciosas, também chamadas miocardiites infecciosas podem ser causadas por uma gama de agentes (vírus, riquetíases, bactérias, fungos, protozoários e helmintos). Na maioria das vezes o agente causador não é definido. Sua real incidência é desconhecida, pois a maioria dos casos é subclínica, assintomática e autolimitada (Mancini & Benjaminovitz 2001). Além disso, existe grande dificuldade diagnóstica, já que os testes não-invasivos são pouco específicos e a biópsia endomioácárdica, considerada como método padrão-ouro, é invasiva e possui sensibilidade de 35% e especificidade de 79% (Narula et al. 1996). Uma parte destas infecções evolui para miocardiopatia dilatada, provavelmente associada a mecanismos auto-imunes.

As técnicas não-invasivas de propedêutica complementar cardiovascular encontram-se disponíveis, em nosso país, na maior parte das cidades de porte médio, tendo sido incorporadas à abordagem dos pacientes com miocardiopatia em ambulatórios de referência, centros de pesquisa e, em alguns casos especiais, pelo Sistema Unico de Saúde e pela Previdência Social. Constituem técnicas de grande importância na avaliação clínica evolutiva, terapêutica, médico-trabalhista e prognóstica.

A relevância das informações, que podem ser obtidas pelo emprego de teste ergométrico, eletrocardiografias convencionais e dinâmica (Holter), ecocardiografia, cintilografia miocárdica e ressonância magnética, torna necessária a divulgação das características fundamentais dos métodos principais, os parâmetros que podem ser analisados e sua indicação na avaliação das miocardiopatias infecciosas. Por outro lado, torna sua utilização mais frequente uma necessidade concreta, quando se pretende aferir adequadamente um número significativo de cardiopatias, especialmente aqueles sintomáticos, com suspeita de comprometimento funcional ou que exerçam atividade laborativa que requeira esforço físico demasiado ou contínuo.

Avaliação ergométrica

A ergometria é técnica amplamente utilizada em cardiologia, tendo sido desenvolvida a partir do princípio de que limitações funcionais do sistema cardiovascular não demonstráveis em repouso, podem ser expostas pelo esforço. Trata-se de método fundamental, com valor diagnóstico e prognóstico bem definidos na insuficiência coronariana, mas útil também na abordagem de pacientes com miocardiopatias e valvulopatias, permitindo determinação precisa da capacidade funcional e avaliação objetiva da resposta terapêutica. Aplica-se ainda ao diagnóstico e controle do tratamento de arritmias cardíacas, à avaliação de indivíduos aparentemente sadios e à prescrição de exercícios em programas de reabilitação (Gibbons et al. 2002).

O exercício isotônico é o preferido para a avaliação ergométrica, visto que determina aumento gradativo do débito cardíaco, proporcional ao consumo de oxigênio corporal (Chaikin 1992), podendo a carga de trabalho ser medida com precisão. A resposta orgânica fisiológica ao exercício isotônico envolve ajustes cardiocirculatórios que visam manter fluxo sanguíneo adequado para a musculatura esquelética, sem comprometer a perfusão cerebral e coronariana. Inmediatamente antes do esforço, mecanismos neurogênicos reflexos determinam aumento do tônus adrenérgico e redução do tônus parassimpático. Estas alterações se tornam mais marcantes à medida que é executado o exercício, determinando aumento do débito cardíaco, decorrente do aumento do volume sistólico, incremento da frequência cardíaca e redução da resistência vascular periférica (Ellestad 1980, Duarte 1988).

A ergometria é considerada técnica segura quando executada por médicos experientes e bem treinados. O respeito às contra-indicações e aos critérios de interrupção são fundamentais para a segurança dos pacientes, assim como é obrigatória a disponibilidade de desfibrilador e material completo de reanimação cardiorrespiratória na sala de exames. Dentre as contra-indicações absolutas à realização da avaliação ergométrica estão: infarto agudo do miocárdio (nos primeiros dois dias), angina instável de alto risco, arritmias cardíacas malignas causando sintomas ou repercussão hemodinâmica, estenose aórtica grave sintomática, insuficiência cardíaca descompensada, tromboembolismo ou infarto pulmonar agudo, miocardite ou pericardite aguda, dissecção aórtica aguda. As contra-indicações relativas são: estenose do tronco da coronária esquerda, estenose valvular moderada, distúrbio hidroeletrólítico, hipertensão arterial grave (PA sistólica > 200 mmHg e/ou diastólica > 110 mmHg), taquiarritmias ou bradiarritmias, cardiomiopatia hipertrófica e outras formas de obstrução de fluxo, alteração mental ou física que impeça o exercício adequado, bloqueio atrioventricular de alto grau (Detrano & Froelicher 1988, Gibbons et al. 2002).

O teste ergométrico avalia parâmetros clínicos, hemodinâmicos e eletrocardiográficos. Sintomas e sinais que surgem durante o esforço podem ter notável valor diagnóstico.
co, devendo ser valorizados e anotados pelo médico que realiza o teste.

A resposta pressórica fisiológica ao esforço implica elevação progressiva da pressão arterial sistólica até o estabelecimento de um pátato, enquanto a pressão diastólica permanece estável ou varia em torno de 10 mmHg. A incapacidade de elevação da pressão arterial sistólica, assim como sua redução abaixo dos níveis de repouso durante o esforço, pode refletir elevação inadequada do débito cardíaco por disfunção ventricular esquerda, obstrução da via de saída do ventriculo esquerdo ou redução excessiva da resistência vascular periférica.

A frequência cardíaca aumenta progressivamente com o exercício. Pacientes hipovolêmicos, anêmicos, anissos e sem condicionamento físico podem ter resposta cronotrópica exagerada nas fases iniciais do exercício, embora a normalidade mais importante seja a incompetência cronotrópica, ou seja, a elevação inadequada da frequência cardíaca, inferior a 95% do limite do intervalo de confiança para idade e sexo. A incompetência cronotrópica pode indicar disfunção do nó sinusal, insuficiência ventricular esquerda, isquemia miocárdica e uso de drogas com efeito cronotrópico negativo (Froelicher 1987).

O duplo produto, ou índice de tensão-tempo, é obtido pela multiplicação da pressão arterial sistólica e frequência cardíaca máximas atingidas durante o teste e fornece estimativa do consumo de oxigênio miocárdico, podendo ser utiliza-do como índice de função cardiovascular (Duarte 1988, Froelicher 1987).

A análise do registro eletrocardiográfico obtido durante o esforço tem como parâmetros fundamentais o comportamento do segmento ST e da onda T e o estudo dos distúrbios do ritmo cardíaco. As anormalidades do segmento ST e da onda T induzidas por esforço podem indicar isquemia miocárdica. A capacidade funcional ou capacidade máxima de esforço, apesar de sofrer interferências das condições ambientais e de fatores como treinamento, motivação e familiaridade do examinando com o teste, é uma das variáveis mais importantes do procedimento, tendo grande valor prognóstico. A capacidade de esforço é medida através do consumo de oxigênio corporal (VO₂), que reflete a quantidade de oxigênio que é retirada do ar e é realizada no exercício. A determinação de VO₂ e a produção de dióxido de carbono (VCO₂) durante o esforço são feitas por procedimento específico, denominado ergoespirometria, que avalia a quantidade de O₂ consumido (resultante da diferença entre O₂ inspirado, constante na atmosfera e a quantidade de CO₂ expirado) e que pode ser captado e analisado por um aparelhamento sensível (Alfieri & Duarte 1993), o que torna o procedimento oneroso e complexo. Entretanto, no teste ergométrico convencional, pode-se estimar o consumo máximo de oxigênio para uma determinada carga de esforço. A ergoespirometria deve ser reservada para casos específicos, como na diferenciação da dispneia induzida pelo esforço de causa cardiogênica ou pulmonar e na avaliação objetiva da capacidade de esforço e da resposta terapêutica em possíveis candidatos ao transplante cardíaco (Ellestad 1980, Froelicher 1987, Dextrano & Froelicher 1988, Gibbons et al. 2002).

**Eletrocardiografia dinâmica**

A eletrocardiografia dinâmica, ou simplesmente Holter, foi desenvolvida de forma original por Norman Holter e adotada como método propedêutico partir da década de 1960. O Holter cresceu e tornou-se um importante campo de estudo dentro da eletrocardiografia, permitindo que o registro eletrocardiográfico fosse feito por períodos prolongados e durante as atividades habituais dos pacientes, com impacto imediato no diagnóstico das arritmias e da isquemia miocárdica. Desde então, o método se aprimorou, principalmente pela automação e miniaturização dos sistemas, e foi incorporado à prática clínica, com definição tanto de suas aplicações, como as limitações técnicas e operacionais. Novas técnicas surgiram com a introdução do uso dos computadores na cardiologia, como o estudo da variabilidade da frequência cardíaca (VFC), que permite o estudo do controle autonômico cardíaco, além de formas diferentes de registro e novos recursos de análise, como por exemplo, para os portadores de marca-passo. Deste modo, o método é hoje uma ferramenta muito importante no manejo dos pacientes cardiopatias (Crawford et al. 1999).

**Avaliação da função autonômica**

A importância do acompanhamento do sistema nervoso autônomo (SNA) nas doenças cardiovasculares tem sido objeto de intensas investigações nas últimas décadas. A regulação rápida e precisa da resposta cardiovascular às modificações ambientais e a estímulos fisiológicos, como esforço e emoção, é realizada predominantemente através do balanço entre atividade vagal e simpática. Embora estas duas divisões do SNA sejam habitualmente antagonistas, sabe-se que, em situações específicas, elas podem atuar de forma independente ou mesmo sinérgica, dificultando a avaliação específica da contribuição dos componentes simpático e parassimpático.

A avaliação funcional do controle do SNA sobre o coração pode ser feita através de testes autonômicos, nos quais se observa a resposta reflexa fisiológica à aplicação de um estímulo quantificável, fisiológico ou farmacológico, como a respiраção, o exercício e a injeção de atropina e fenilefrina. Alternativamente, informações sobre o controle autonômico cardíaco podem ser obtidas pela observação da variação intrínseca da frequência cardíaca, tanto em registros curtos, de 2 a 5 minutos de repouso, como em traçados prolongados, de 24 horas, durante as atividades habituais. A análise da VFC parte do princípio que, em condições normais, a frequência cardíaca se modifica em resposta a estímulos diversos, como exercício e estresse mental, ou mesmo em condições de repouso, fluctuando em torno de uma média. Tal variabilidade se relata, predominantemente, às alterações continuas do balanço simpático-vagal, em resposta a mecanismos de controle cardiovascular. A VFC pode ser estudada por técnicas matemáticas que abordam as características estatísticas desta variação (domínio do tempo), que decomponem os diferentes ritmos envolvidos (domínio da frequência) ou por métodos não-lineares, que utilizam métodos matemáticos avançados para descrever o comportamento da VFC (Task Force 1996, Lombardi 2003).

Os métodos estatísticos fornecem índices práticos de cálculo simples, que avaliam a dispersão dos intervalos entre os batimentos cardíacos em torno da média (como o SDNN, ou desvio-padrão dos intervalos cardíacos normais) ou compara a duração de ciclos adjacentes (como o RMSSD, que é a média dos valores absolutos das diferenças sucessivas, ou o PNN50, a porcentagem de intervalos cardíacos normais sucessivos com variação maior que 50 ms). Enquanto o SDNN é produto de todas as influências autonômicas (principalmente parassimpáticas) e neuro-humorais sobre a VFC, o RMSSD e o PNN50 são resultado direto da influência vagal sobre o
coração. Em modelos experimentais, a retirada do tônus vagal diminui o limiar fibrilatório e predispõe à morte súbita. O valor prognóstico da redução dos índices do domínio do tempo da VFC está validado em diversos estudos retrospetivos e prospectivos, principalmente após o infarto agudo do miocárdio e na insuficiência cardíaca.

A análise do domínio da frequência, através da análise espectral da VFC, permite o estudo das diferentes divisões do SNA. Em registros de curta duração, reconhece-se que a variabilidade de alta frequência (entre 0,15 e 0,40 Hz) está relacionada quase que exclusivamente ao vago e à arritmia sinusal respiratória. A variabilidade concentrada entre 0,04 e 0,15 Hz, de baixa frequência, relacionada ao barorreflexo, tem origem simpática e/ou vagal, enquanto a relação baixa/alta frequência seria um indicador do equilíbrio simpático-vagal.

Apesar de vantagens teóricas e do potencial fisiopatológico da análise espectral da VFC, inexistem estudos clínicos demonstrando sua vantagem sobre índices convencionais do domínio do tempo.

Entre as técnicas mais novas, a mais promissora é o estudo da turbulência da frequência cardíaca (Bathel et al. 2003, Ribeiro et al. 2003), método que avalia as modificações da frequência cardíaca provocadas pelas extra-sistoles ventriculares. Após uma extra-sistle, ocorre habitualmente uma pausa compensatória e uma contração forçada subsequente, ativando o barorreflexo e oscilações da frequência cardíaca, fenômeno conhecido como turbulência da frequência cardíaca. Esta oscilação, fisiologicamente, se reduz numa série de condições psicológicas, como a doença de Chagas e após o infarto do miocárdio, situação na qual tem elevado valor prognóstico.

**Ecocardiograma**

A ecocardiografia representa atualmente um valioso método diagnóstico não-invasivo cuja aplicação na cardiologia encontra-se amplamente estabelecida. É particularmente útil no estudo das cardiopatias infecciosas, ao trazer a possibilidade de diagnosticar e acompanhar o acometimento cardíaco, permitindo melhor compreensão da história natural da doença e dos mecanismos fisiopatológicos envolvidos. As três modalações do método – Modo M, Bidimensional e Doppler – se completam, possibilitando avaliar aspectos anatômicos, funcionais e hemodinâmicos da patologia cardíaca. A ecocardiografia permite identificar dilatação das câmaras, espessura das paredes, alterações da contratilidade global e segmentar, presença de lesão de ponta (na miocardiopatia chagásica) e trombos intracavitários, além de estimar as alterações funcionais decorrentes do acometimento cardíaco.

A capacidade de o ecocardiograma fornecer informações importantes com mínimo desconforto ou risco, sem o uso de contraste ou radiação, associada à grande disponibilidade do método, faz com que seu uso seja tão difundido. Porém, o uso indiscriminado ou para triagem em pacientes hígidos não se justifica por dois motivos: o custo não é tão baixo, e, como em qualquer exame, pode haver falsos-positivos e alterações sem maior importância clínica, gerando ansiedade para o paciente, investigação adicional e até tratamentos desnecessários (Chelitlin et al. 1997).

**Cintilografia miocárdica**

As diferentes técnicas aplicadas na aquisição e processamento de imagens em cardiologia nuclear já estão bem estabelecidas. Fruto de desenvolvimento progressivo ao longo das últimas quatro décadas.

A ventriculografia radioisotópica e a angiógrafia radioisotópica têm como objetivo a avaliação funcional das câmaras ventriculares, através da marcação das hemácias circulantes com isótopo radioativo (99mTc). As imagens cardíacas são adquiridas sincronizadas ao eletrocardiograma. Os parâmetros analisados são relacionados a aspectos funcionais do coração, incluindo a motilidade global e regional das paredes, os volumes ventriculares e as mudanças fisiológicas ocorridas nas cavidades ventriculares ao longo do ciclo cardíaco. Os dados volumétricos permitem cálculo preciso e altamente reprodutível da fração de ejeção ventricular. Parâmetros da fase de enchimento rápido e lento do ventrículo esquerdo também podem ser estudados, com implicações importantes para a avaliação da função diastólica. O papel da ventriculografia e da angiógrafia radioisotópica vem diminuindo com o incremento das técnicas de ecocardiografia, mas, para pacientes selecionados, ainda guardam o seu valor, já que o ecocardiograma possui limitações, como o fato da avaliação da parede inferior do ventrículo esquerdo ser difícil, de portadores de pneumopatias terem seu exame prejudicado devido à má qualidade da imagem, e de ser um método examinador-dependente, com variabilidade inter-observador de 11% na fração de ejeção (Pennell & Pruvolich 1995).

A cintilografia miocárdica de perfusão com imagens tomográficas (SPECT) veio substituir os métodos de imagens planares, facilitando a separação de regiões vizinhas, melhorando a resolução de contraste e permitindo melhor detecção das diferenças nas concentrações de atividade no miocárdio. Em nosso meio, os principais traçadores disponíveis para imagens do miocárdio incluem o tâlio-201 e os traçadores marcados com tecnetio, entre eles principalmente o 99mTc-sestamibi e o 99mTc-tetrofosmin.

A cintilografia miocárdica de perfusão com imagens tomográficas sincronizadas pelo ECG (Gated-SPECT) permite a análise da função ventricular adicionalmente e de forma simultânea à análise da perfusão miocárdica, contribuindo para diagnóstico e avaliação prognóstica mais precisos, além de aumentar a especificidade de alguns achados do estudo da perfusão. Em situações em que haja dúvida entre um defeito perfusional persistente e um artefato por atenuação mamária ou diafragmática, a análise da motilidade e do espressamento das paredes ventriculares pode contribuir para a diferenciação destas duas causas. Quando a hipoconcentração se deve a um artefato, a motilidade dessa parede é normal, assim como o espressamento sistólico.

A tomografia por emissão de pósitrons (PET) permite estudar, de forma quantitativa, além da viabilidade miocárdica, também a perfusão regional. Os traçadores de fluxo mais utilizados são o amônia (N-13) e o rubídio (Rb-82), mas a água, marcada com oxigênio-15, também pode ser utilizada.

Nas miocardiopatias infecciosas, a presença de inflamação miocárdica pode ser detectada por radionuclides captados no miocárdio. Os mais utilizados são o 99mTc-prositosfato, citrat de gálio-67 e 99mTc ou 111In-anticorpos antimiosina. Quando há necrose miocárdica, a membrana dos miócitos é perdida, expondo as cadeias pesadas de miosina intracelular. O 111In-antimiosina, detecta, portanto, essas áreas de necrose, podendo ser usada no diagnóstico do infarto agudo do miocárdico, da miocardite e da rejeição cardíaca pós-transplante (Wackers et al. 2001). Outros traçadores, como o tâlio-
201 e os traçadores marcados com tecnécio permitem verificar alterações de perfusão, enquanto o \( ^{123} \) I-metaidodo-benzilguanida \( \left( ^{123} \text{I-MIBG} \right) \) avalia a inervação autonômica simpática do miocárdio. Para verificar o estado funcional das câmaras cardíacas, utiliza-se a angiocardiografia ou ventriculografia isotópica, que permite medir a fração de ejeção, motilidade miocárdica regional e volumes ventriculares.

**Doença de Chagas**

A miocardite mais comum em todo o mundo é aquela causada pelo *Trypanosoma cruzi*, protozoário causador da doença de Chagas, endêmico em áreas rurais das Américas do Sul e Central. A doença de Chagas permanece como um grande problema de saúde nos países da América Latina, onde se estima que haja aproximadamente 20 milhões de pacientes infectados (Marin-Neto et al. 1999), dos quais 25-35% desenvolverão alterações cardiovasculares (Maguire 1987). Sabe-se, ainda, que a disfunção ventricular esquerda representa o maior preditor de mortalidade na doença de Chagas (Mady et al. 1994), e que a disfunção assintomática é, no mínimo, tão frequente quanto a sintomática.

A infecção inicial geralmente é assintomática, porém pode haver manifestações na fase aguda, inclusive com acometimento cardíaco (miocardite aguda), sendo porém escassos os relatos de estudos por exames complementares nesta fase.

A fração crônica da doença de Chagas pode ser subdividida em forma crônica indeterminada (FCI) e em formas crônicas ditas determinadas (cardíaca, digestiva, cardiodigestiva e nervosa). Cerca de 30% dos pacientes infectados em áreas endêmicas encontram-se na FCI e, embora a característica principal destes pacientes seja a ausência de anormalidades clínicas, electrocardiográficas e radiológicas significativas, tem-se observado alterações morfofuncionais cardíacas quando se utilizam métodos complementares mais sofisticados, tais como ergometria, electrocardiografia dinâmica, provas autonômicas não-invasivas, ventriculografia radioisotópica e ecocardiografia (Ribeiro & Rocha 1998). Embora vários estudos longitudinais tenham demonstrado o bom prognóstico dos pacientes na FCI, cerca de 2 a 3% destes pacientes evoluem para uma das outras formas crônicas da doença, geralmente com padrão benigno, eventualmente progressando para formas graves e potencialmente letais. Estima-se que, dentro de 5 a 10 anos, cerca de 30% destes pacientes evoluam para cardiopatia crônica. Além disso, tem-se relatado a presença de morte súbita em chagásicos como a primeira manifestação clínica da doença. Portanto, a identificação de marcareadores precoces de dano miocárdico na doença de Chagas é importante na estratificação do risco, para que se possam estabelecer condutas individualizadas, melhorar a qualidade de vida e longevidade nesses pacientes (Rocha et al. 2003).

**Electrocardiografia convencional**

O electrocardiograma é método mais sensível e específico no diagnóstico do acometimento miocárdico na doença de Chagas do que outros métodos de avaliação de acesso fácil, como a anamnese, o exame físico e a radiografia do tórax. Entretanto, a sensibilidade do método na detecção do dano miocárdico não é elevada. A ausência de alterações electrocardiográficas não é indicador fidedigno da ausência de acometimento cardíaco. Quando estudados por métodos propedêuticos mais sofisticados, a proporção variável dos pacientes com electrocardiograma normal mostra alterações estruturais ou funcionais do coração. Adicionalmente, entre 20 e 50% desses pacientes desenvolverão alteração electrocardiográfica sugestiva de cardiopatia chagásica quando acompanhados por cerca de 10 anos. Independentemente destas considerações, entretanto, o prognóstico a médio prazo do chagásico com electrocardiograma normal é excelente: em um estudo longitudinal com seguimento de 7 anos, em uma comunidade rural, Maguire et al. (1987) não encontraram diferenças com relação à mortalidade entre indivíduos com ECG normal seropositivos e seronegativos.

Embora existam algumas alterações electrocardiográficas mais sugestivas de que o acometimento cardíaco seja, em determinado caso, secundário à etiologia chagásica, quase todas as anormalidades electrocardiográficas existentes podem ser encontradas, com predominância das anormalidades da formação e condução do ritmo cardíaco (Rosenbaum & Alvarez 1955). A combinação de alterações electrocardiográficas diferentes em um mesmo traçado pode ocorrer, sendo mais frequente naqueles com cardiopatia mais avançada e de pior prognóstico. Na vigência de cardiopatia hipertensiva ou de outra etiologia, alterações electrocardiográficas características destas condições podem se superpor aquelas típicas da cardiopatia chagásica. Alterações electrocardiográficas sugestivas de dano miocárdico pelo *T. cruzi* ocorrem também em outros processos patológicos, de modo que o electrocardiograma não é, em absoluto, método com alta especificidade na detecção da cardiopatia chagásica.

O bloqueio do ramo direito do feixe de His, completo ou incompleto, é o distúrbio de condução mais frequente na cardiopatia chagásica, sendo encontrado em 10 a 50% dos pacientes infectados, dependendo da amostra estudada. Freqüentemente está associado ao bloqueio do fascículo antero-superior do ramo esquerdo do feixe de His (hemibloqueio anterior esquerdo), combinação característica do chagásico cardiopata. Outras vezes, se associa ao bloqueio infero-posterior esquerdo (hemibloqueio posterior esquerdo), a bloqueios atrioventriculares incompletos, extra-sístoles ventriculares ou a outras alterações menos frequentes. Por motivos não completamente esclarecidos, o bloqueio de ramo esquerdo é pelo menos 10 vezes menos frequente do que o bloqueio de ramo direito na doença de Chagas.

A duração do complexo QRS se relaciona de forma direta com as dimensões do ventriculo esquerdo e, inversamente, com a função sistólica do VE, de forma que chagásicos com distúrbios de condução intraventricular apresentem, com maior frequência, depressão da função ventricular esquerda (Ribeiro et al. 2000). Adicionalmente, sabe-se que a presença de bloqueios intraventriculares, em especial do ramo direito, aumenta significativamente o risco de evolução fatal entre os infectados (Maguire et al. 1987). Não existem dados, porém, que informem se a presença de bloqueios intraventriculares constitui um fator prognóstico independente da função ventricular na evolução da cardiopatia chagásica.

A extra-sístole ventricular é também um achado muito frequente na cardiopatia chagásica, acometendo de 6 a 55% dos indivíduos sorologicamente positivos. Caracteristicamente, as extra-sístoles são frequentes, polimorfas e complexas, sendo que, ocasionalmente, formas repetidas (pares) ou sustentadas (taquicardia ventricular) de arritmia ventricular são registradas em curtos traçados de rotina. O caráter paroxístico da arritmia faz com que o electrocardiograma convencional não seja o método ideal para sua detecção. Assim, quando
pacientes com alterações no eletrocardiograma em repouso e insuficiência cardíaca são estudados através da eletrocardiografia dinâmica, extra-sistóles ventriculares são encontradas em 99% dos casos, sendo que em 87% são encontradas extra-sistóles multiformes ou formas repetidas (Carrasco et al. 1990).

As arritmias ventriculares são mais frequentes, complexas e sustentadas nos pacientes com pior função ventricular esquerda. A presença de extra-sistóles complexas no ECG se relaciona a risco aumentado de evolução fatal (Maguire et al. 1987). Adicionalmente, sabe-se que pacientes com bloqueios intraventriculares e arritmia ventricular no ECG são os que apresentam maior dilatação ventricular esquerda e depressão mais acentuada da contratilidade cardíaca (Casado et al. 1990). Em populações de chagásicos com função ventricular deprimida ao ecocardiograma, a presença de extra-sistóla ventricular complexa constitui preditor independente do risco de evolução para o óbito (Guerrero et al. 1991).

No acompanhamento do tratamento das arritmias ventriculares, o eletrocardiograma é útil principalmente para a monitorização dos efeitos eletrofisiológicos do uso de drogas antiamricínicas. Podem ocorrer prolongamento do intervalo PR, alargamento do complexo QRS, bloqueios atrioventriculares e intraventriculares e prolongamento do intervalo QTc. Este último efeito está relacionado à síndrome do QT prolongado e arritmias ventriculares potencialmente fatais, como a taquicardia ventricular do tipo “tordes de pointes”. O desaparecimento de extra-sistóles ventriculares após um ECG de rotina realizado após o uso de antiamricínicos não é evidência suficiente de que a droga foi capaz de suprimir a arritmia, pelo que é mais aconselhável fazer um carriar paroxístico das arritmias ventriculares.

O acometimento do nó sinusal pela cardiopatia chagásica foi postulado inicialmente por Brasil (1955) ao descrever a ausência de resposta do nó sinusal a estímulos físicos ou farmacológicos em 19% dos chagásicos estudados. Posteriormente, demonstrou-se o acometimento estrutural e funcional do nó sinusal em elevada proporção dos pacientes com doença de Chagas. Entretanto, apenas uma minoria apresenta manifestações de disfunção sinusal ao ECG de superfície (1 a 16% dos pacientes). As principais manifestações eletrocardiográficas da disfunção do nó sinusal são a bradicardia sinusal, especialmente se a frequência sinusal é menor que 40 bpm, a parada sinusal, o bloqueio sinoatrial de 2º grau e a existência de ritmos de suplência que denotem a inibição do marca-passos sinusal normal: os ritmos junclonais e idioventricular acelerados.

O acometimento do sistema de condução se estende ao nó atrioventricular, ao feixe de His e a seus ramos. Embora as alterações funcionais do nó AV ao estudo eletrofisiológico invasivo estejam presentes em grande número dos cardiopatas, a maioria dos bloqueios atrioventriculares (BAV) ocorre por lesão distal ao tronco do feixe de His. Podem ocorrer BAVs de primeiro grau, segundo grau (tipos I, II, 2:1 ou avançado) e terceiro grau ou completo. BAVs de primeiro e segundo podem se associar, entre outras alterações eletrocardiográficas, aos distúrbios da condução intraventricular. Quando concomitantes ao bloqueio completo do ramo direito associado a um hemibloqueio esquerdo, denotam geralmente lesão avançada e difusa do sistema de condução e, provavelmente, maior probabilidade de evolução para o bloqueio completo. No BAVT, os ventriculos são despolarizados por marca-passo subsidiários, geralmen-te localizados distalmente à divisão do feixe de His, gerando ritmos idioventriculares lentos (frequência menor que 40 bpm) e complexos QRS aflatados.

A fibrilação atrial, é a arritmia supraventricular mais frequente entre os chagásicos, sendo encontrada em 4 a 12% dos traçados eletrocardiográficos. Na maioria das vezes, a fibrilação atrial se apresenta sob a forma crônica, estando associada a pronunciado dano miocárdico, acometimento difuso do sistema de condução, arritmias ventriculares e, consequentemente, a um prognóstico sombrio (Rosenbaum & Alvarez 1955, Dias & Klotetz 1968), sendo negativamente relacionada à sobrevida, independentemente de outras variáveis, em modelo de regressão múltipla (Espinoso et al. 1991). As extra-sistóles supraventriculares são menos frequentes e importantes do que as ventriculares, ocorrendo entre 1,5 e 12% dos chagásicos.

Outras alterações significativas encontradas na cardiopatia chagásica incluem as zonas electricamente inativas, (simulando infarto agudo do miocárdio), a baixa voltagem periférica e as alterações primárias da onda T. Embora sabidamente frequentes, a prevalência dessas alterações varia muito entre as diversas séries, em parte pela utilização de critérios diagnósticos diferentes. As zonas electricamente inativas e as alterações de repolarização foram relacionadas à pior função ventricular esquerda, sendo que Salles et al. (2004) relataram aumento de risco de morte em três vezes e de morte súbita em seis vezes na presença de eixo de onda T anômalo, mesmo após correção para co-variaíves como a fração de ejeção do ventriculo esquerdo. O aumento da dispersão do intervalo QT também foi associada à disfunção ventricular esquerda e ao risco aumentado de morte (Salles et al. 2003 a, b).

Ergometria


O teste ergométrico permite a quantificação da capacidade de esforço dos indivíduos, além de fornecer informações sobre o comportamento do ritmo cardíaco durante a atividade física. Indubitavelmente, é método de fundamental importância na avaliação da capacidade laborativa dos chagásicos, devendo ser utilizado como parâmetro para o estabelecimento de critérios de admissão no trabalho e aposentadoria, principalmente naqueles que apresentam evidências clínicas ou eletrocardiográficas de comprometimento cardíaco. Preconiza-se seu uso naqueles indivíduos que pretendem exercer atividades de alto risco, como trabalho físico pesado ou profissões que colorem em risco da vida de terceiros, como motoristas, pilotos, etc. (Rocha 1997).

Embora vários estudos tenham mostrado que alterações como respostas pressórica e cronotrópica anormais, baixas taxas de consumo de oxigênio corporal e arritmias ventriculares relacionadas com o esforço sejam prevalentes na avaliação de chagásicos cardiopatas (Faria 1985, Molina et al. 1981), não se encontrou correlação direta entre o grau de disfunção ventricular e tais anormalidades (Vaz-Tostes 1993). Sugere-se que a resposta orgânica ao esforço em pacientes com cardiopatia chagásica sofra influências de outros fatores, além da função ventricular esquerda. A denervação
autonômica e as lesões estruturais e funcionais no sistema de condução e geração de estímulos podem estar relacionadas com as respostas hemodinâmicas anormais ao esforço.

O esforço pode provocar arritmias cardíacas supraventriculares e ventriculares, tanto em cardiopatas quanto em indivíduos com o sistema cardiovascular normal. O aumento do tônus adrenérgico e a modulação do tônus parasimpático determinam alterações eletrofisiológicas que favorecem o estabelecimento de importantes mecanismos arritmogênicos, tais como: aumento do automatismo, potenciais tardios e circuitos de reentrada (Podrid et al. 1987).

Os cardiopatas chagásicos, por apresentarem áreas fônicas de fibrose entremeadadas a miofibras íntegras, possuem vasto substrato anatômico para os distúrbios do ritmo cardíaco, sendo particularmente suscetíveis aos mecanismos arritmogênicos desencadeados pelo esforço (Rassi et al. 1983). As arritmias ventriculares estão entre as anormalidades mais prevalentes na avaliação ergométrica dos pacientes chagásicos e a maioria dos estudos associa o achado de arritmias ventriculares complexas durante o esforço com a presença de disfunção ventricular ou de arritmia ventricular no traçado electrocardiográfico de repouso (Faria 1985, Molina et al. 1981). A presença de taquicardia ventricular ao esforço constitui predictor independente do risco de morte na cardiopatia chagásica (Paola et al. 1994).

A ergometria pode ser utilizada como método de avaliação terapêutica tanto em pacientes com insuficiência cardíaca quanto naqueles que se submetem a terapia antiarrítmica. Sabe-se que a capacidade funcional tem grande importância prognóstica em chagásicos. Foi demonstrada sobrevida de 97% nos pacientes em classe funcional II, de 58% naqueles em classe funcional III e de 16% naqueles em classe funcional IV da New York Heart Association (NYHA) (Mady et al. 1994).

**Eletrocardiografia ambulatorial (Holter)**

Na cardiopatia chagásica, o ECG ambulatorial tem sido utilizado primariamente para avaliação das arritmias cardíacas com objetivos diagnósticos, prognósticos e terapêuticos.

Uma das principais utilizações do ECG ambulatorial é o diagnóstico de arritmias cardíacas em pacientes com sintomas cardiovasculares inexplicados, especialmente aqueles atribuídos a arritmias: palpações, tonturas e sincopes. Embora o método seja de grande valor em muitos destes pacientes, existem várias limitações a sua utilização com este objetivo. Para que se atribua um sintoma a uma determinada alteração do ritmo, é necessário que se faça a correlação temporal entre o sintoma apresentado, anotado no diário pelo paciente com ou sem utilização do marcador de eventos do gravador, e a presença de arritmias significativas no traçado electrocardiográfico simultâneo.

Como os sintomas geralmente são ocasionais, na maioria dos exames os pacientes não apresentam manifestação durante agravamento. Entre aqueles que apresentam os sintomas durante o exame, pelo menos a metade não mostra alterações eletrocardiográficas simultâneas. Assim, em apenas cerca de um quarto dos pacientes sintomáticos, o método revelará uma arritmia causadora da manifestação. Por outro lado, a ausência da arritmia ao traçado electrocardiográfico em paciente que apresentou sintomas durante o registro, auxilia na sua exclusão como causa do sintoma em questão.

Entre os pacientes que, apesar de sintomáticos, não apresentam sintomas durante a gravura, arritmias silenciosas são encontradas em 4 a 30% dos casos. Não se conhece o valor diagnóstico da presença destas arritmias silenciosas nestes pacientes. É possível que o limiar de percepção destes sintomas varie e que, em determinadas situações, o evento arrítmico provoque sintomas e que, em outras, seja silencioso. Entretanto, algumas arritmias silenciosas podem ter valor prognóstico e indicar a necessidade de medidas terapêuticas, como taquicardias ventriculares sustentadas e bloqueios atroventriculares completos com escapes ventriculares lentos.


A utilização do ECG ambulatorial na avaliação prognóstica tem valor estabelecido em pacientes após infarto agudo do miocárdio e com miocardite hipertrofica, em que a detecção de extra-sistólicas ventriculares frequentes, polimorfas e de formas repetitivas, como pares e episódios de taquicardia ventricular, se relacionam à mortalidade aumentada. Na cardiopatia chagásica, a presença de arritmias ventriculares complexas e/ou sustentadas é mais frequente naqueles pacientes com dano miocárdico mais pronunciado (Carrasco et al. 1990), sendo marcadora independente de risco aumentado de morte naqueles com depressão da função ventricular (Guerrero et al. 1991).

Entretanto, como não se conhece o valor do tratamento antiarrítmico nestas situações, o método não tem indicação universal nos chagásicos cardiopatas assintomáticos, já que existem outros indicadores prognósticos, clínicos ou através de métodos complementares mais simples, de acesso mais fácil e custo menor.

Os pacientes submetidos a intervenções terapêuticas, como a utilização de antiarrítmico para arritmia supraventricular ou ventricular, o ECG ambulatorial pode ser utilizado para controle da eficácia terapêutica, desde que se considere o já citado fenômeno da variabilidade espontânea. No tratamento da arritmia ventricular, considera-se que o tratamento está sendo eficaz quando há redução de 60 a 80% na frequência de extra-sistólicas ventriculares e supressão completa das formas repetitivas. No paciente com marca-passo cardíaco, indicado para tratamento de bloqueio atroventricular ou doença do nó sinusal, gravadores especiais podem ser usados para a detecção de disfunção do marca-passo e na avaliação da resposta do ritmo intrínseco ao esforço e ao estresse habitual diário do paciente.

**Provas autonômicas**

A existência de acometimento do SNA na doença de Chagas foi postulada já por Carlos Chagas, em 1913, sendo que atribuíu-se a Möckemberg, em 1924, a primeira descrição de lesões em gânglios e fibras nervosas autonômicas cardíacas, durante infecção experimental em cães. Mas foi Fritz Köberle, associado a colaboradores, em estudos anatomo-patológicos fundamentais realizados nas décadas de 1930 e 1960, que demonstrou a existência de comprometimento importante do SNA na doença de Chagas, em especial do parasimpático. Já no final da década de 1960, estudos do grupo de Amorim,
Marin-Neto, Gallo Junior, Manço et al., em Ribeirão Preto, confirmaram a existência de acometimento funcional da SNA na cardiopatia chagásica humana. Desde então, muito se tem escrito sobre o possível papel da disfunção autonômica na doença de Chagas. As seções a seguir sumarizam o estado atual da literatura.


Todos estes dados mostram que muitos pacientes chagásicos são privados da ação vagal inibitória tônica sobre o nodo sinusal, presente em indivíduos normais, além de não apresentarem mecanismo bradi-cardizante rápido, vago-dependente, responsável pela modulação reflexa rápida às elevações transitórias da pressão arterial, encontradas em condições fisiológicas e patológicas (Amorim & Marin-Neto 1994).


Quando se estudam pacientes com diversas formas da doença de Chagas, reconhece-se que, na maioria das vezes, os índices autonômicos se alteram gradualmente, à medida em que se agrava a cardiopatia. Assim, as alterações dos parâmetros funcionais autonômicos, encontra-dos na forma indeterminada ou na ausência de cardiopatia, são, quase sempre, menos intensas do que as encontradas em pacientes com cardiopatia evidente, sendo mais pronunciadas naqueles com insuficiência cardíaca e formas cardiogestivas (Iosa 1994, Marin-Neto et al. 1998). Entretanto, trabalhos do nosso grupo mostram que há disfunção vagal significativa mesmo em pacientes sem cardiopatia aparente, indicando também que a disautonomia é independente da deterioração da função ventricular esquerda (Ribeiro et al. 2001-2004, Oliveira 2002).

Embora o mecanismo da disfunção autonômica não tenha sido esclarecido, evidências derivadas de correlações anatomo-patológicas (Amorim et al. 1973) e experimentais (Junqueira et al. 1992) indicam que, em fração substancial dos casos, a alteração do controle vagal sobre o coração está relacionada à presença de lesões morfológicas do sistema nervoso autônomo parassimpático intracardíaco. Por outro lado, Iosa et al. (1994) atribuem as alterações funcionais do SNA a um bloqueio progressivo dos receptores adrenérgicos e muscarínicos, seguido de denervação, relacionado a mecanismos auto-imunes, principalmente a presença de anticorpos contra receptores autonômicos e de anticorpos antigan-gliosídeos (Iosa 1994).


Ecocardiograma

A ecocardiografia tornou-se exame complementar essencial não só para localização precisa das alterações patológicas, mas também para determinar o estádio evolutivo e a gravidade do comprometimento cardíaco, fornecendo excelentes índices para a orientação terapêutica e prognóstica (Rocha et al. 2003). A ecocardiografia, aliada às técnicas Doppler, permite abordagem morfofuncional do coração de forma não-invasiva e inócuca. Além de ter custo relativamente baixo, apresenta elevado grau de confiabilidade diagnóstica, sendo, portanto, elemento propedêutico de elevado valor na abordagem do paciente chagásico.

Os estudos iniciais utilizando a ecocardiografia modo M demonstravam alterações nas diversas formas clínicas da cardiopatia chagásica, Monti et al. (1979) detectaram alterações em 40% dos pacientes com cardiopatia chagásica subclínica e em 100% dos casos nos pacientes sintomáticos e Finaret et al. (1981), analisando 152 pacientes com infecção chagásica crônica assintomática, sem evidências de alterações ao ECG, radiografia de tórax e ergometria, evidenciaram
anormalidades ecocardiográficas em 21,3% dos casos, sendo o aumento da cavidade ventricular esquerda o achado mais comumente encontrado. Em nosso meio, Friedman et al. (1981) foram os primeiros a publicar acerca do ecocardiograma na doença de Chagas. Entretanto, a ecocardiografia modo M apresenta diversas limitações na avaliação do coração. Por determinar apenas a visibilização de segmentos do septo interventricular e parede posterior, a análise da contratilidade dos demais segmentos não é possível, incluindo o estudo do ápex cardíaco, segmento de importância na avaliação da cardiopatia chagásica, pela frequência e peculiaridades do comprometimento desta região, nesta patologia. Além disso, a análise das cavidades direitas, a avaliação quantitativa das valvulopatias, detecção de trombos intracavitários, determinação da função diastólica (FD) e pressão arterial pulmonar, dados de elevada importância na avaliação global cardíaca, não podem ser mensurados por esta técnica. A introdução das técnicas bidimensional e Doppler veio acrescentar informações importantes na avaliação dos pacientes chagásicos.


Diversos estudos refletem a importância do estudo da contratilidade ventricular esquerda na avaliação prognóstica dos pacientes chagásicos, independentemente de seu estágio clínico, sendo que a realização de pelo menos um estudo ecocardiográfico em um paciente chagásico pode trazer informações valiosas quanto à estratificação do risco deste indivíduo (Mady et al. 1994, Bestetti & Muccillo 1997, Rodrigues-Salas et al. 1998, Xavier 1999). Xavier (1999), após acompanhamento ecocardiográfico de uma coorte constituída de 604 pacientes, durante um período de nove anos, demonstrou que a avaliação do diâmetro sístolico do ventrículo esquerdo pela ecocardiografia foi uma das variáveis que melhor explicou a evolução para óbito de causa cardíaca em pacientes chagásicos. Mady et al. (1994) e Bestetti e Muccillo (1997) demonstraram o pior prognóstico nos pacientes chagásicos que apresentavam diminuição da fração de ejeção através da ecocardiografia bidimensional. Maciel et al. (1998) demonstraram dano miocárdico maior nos pacientes chagásicos que apresentavam anormalidades contráteis comparativamente àqueles que apresentavam apenas alterações eletrocardiográficas. Almeida Filho et al. (2002) demonstraram deteriorização da função ventricular em 69,2% dos pacientes que se apresentaram com anormalidades contráteis segmentares e função global normal, enquanto observaram piora em apenas 22,2% dos pacientes que não apresentavam anormalidades contráteis no início do seguimento clínico.

A avaliação de parâmetros da função diastólica na doença de Chagas tem demonstrado a anormalidade precoce do relaxamento ventricular esquerdo em pacientes chagásicos (Caeiro et al. 1985, Martinez Filho et al. 1986, Sousa et al. 1988). A cardiopatia chagásica pode levar a comprometimento de ambas as fases da diastole, inicialmente determinando alterações no relaxamento ventricular e, progressivamente, distúrbios relacionados com a complacência. A análise Doppler da função diastólica foi especialmente analisada no estudo de Cunha (1997), no qual embora se tenham demonstrado sinais de alteração de relaxamento no grupo de pacientes chagásicos, ao longo do período estudado, em nenhum caso foram detectados padrões de fluxo pseudonormal e restritivo, os quais se relacionam com distúrbios mais graves de relaxamento e da complacência ventricular. A caracterização dos diversos padrões de enchimento ventricular na doença de Chagas crônica, utilizando a ecocardiografia Doppler, foi demonstrada por Barros et al. (2004), os quais demonstraram que 73,6% dos pacientes com fração de ejeção (FE) ventricular esquerda inferior a 50% apresentavam algum grau de disfunção diastólica, enquanto pacientes com FE, diâmetro ventricular e escote de motilidade parietal normal mais apresentavam função diastólica normal em 92,6, 93,8 e 94,7% dos casos, respectivamente.

O caráter fibrosante da miocardite chagásica contribui para o enrijeecimento progressivo do coração, determinando padrões diversos de disfunção diastólica durante a evolução da cardiopatia. A evidência de elevação da pressão de enchimento ventricular pela análise Doppler de fluxo (padrões pseudonormal e restritivo) correlaciona-se com presença de disfunção sistólica ventricular esquerda na quase totalidade dos pacientes estudados. Portanto, na cardiopatia chagásica crônica, a presença de padrões de enchimento ventricular com sinais de elevação das pressões diastólicas parece estar relacionada ao grau de fibrose miocárdica, com posterior comprometimento contrátil da massa muscular e consequente disfunção sistólica. O acompanhamento destes pacientes torna-se relevante pela possibilidade de a disfunção diastólica representar um marcador prognóstico importante na evolução da doença de Chagas. Nunes (2003) demonstrou, em seguimento longitudinal de 93 pacientes durante três anos, que o padrão de enchimento restritivo ao Doppler, indicando disfunção sistólica, foi preditor importante de mortalidade cardíaca nos pacientes com miocardite dilatada chagásica. Aspecto de relevância a ser observado foi a identificação da presença de disfunção diastólica regional na doença de Chagas. Este conceito, introduzido recentemente com o uso do Doppler tecidual, demonstrou que pacientes chagásicos podem apresentar, precocemente, heterogeneidade no relaxamento ventricular segmentar, envolvendo particularmente o septo interventricular e a parede pós-terno inferior do VE (Barros et al. 2001).

A disfunção miocárdica grave também favorece a formação de trombos intracavitários e fenômenos tromboembólicos, que constituem a terceira causa de morte na doença de Chagas. Destaca-se a grande importância da lesão apical como sede frequente de trombos, apresentando prevalência variável, dependendo do grau de disfunção ventricular (Oliveira et al. 1988, Nunes 2003). A ecocardiografia bidimensional é o procedimento de escolha para detecção de trombo mural, sen-
do usada em vários estudos sobre miocardiopatia dilatada como "prądno-ouro" para identificação da incidência e desenvolvimento de índices sistêmicos (Combellas et al. 1985).

A análise da função ventricular utilizando a ecocardiografia bidimensional, seja na avaliação da motilidade e/ou espessamento das paredes, seja na determinação dos volumes e fração de ejeção, requerendo a delinear da interface músculo/cavidade, envolve observações de caráter subjetividade e sujeitas a variações inter e intra-observador, sendo que a experiência requerida na quantificação subjetiva da motilidade miocárdica demanda longo tempo de experiência com o método. Portanto, é importante que se utilizem técnicas que possam analisar quantitativamente a dinâmica cardíaca, especialmente quando é necessária a avaliação destes órgãos em estudos longitudinais. Dentre estas técnicas, o Doppler tecidual representa um novo método que permite a análise quantitativa e regional da função sistólica e diastólica do coração, sendo que estudos têm demonstrado sua utilidade na avaliação quantitativa de anormalidades contráteis segmentares e disfunção diastólica regional precocemente em ambas as cavidades ventriculares na doença de Chagas, podendo ser fornecido útil na estratificação de risco destes pacientes (Barros et al. 2001, 2004).

Cintilografia miocárdica

Diversos estudos demonstraram a aplicabilidade da cintilografia miocárdica na avaliação do acometimento orgânico funcional na cardiopatia chagásica. A cintilografia com tálio-201, associada ao teste ergométrico, permite verificar a existência de zonas de isquemia transitória (induzidas pelo esforço e que desaparecem com o repouso) ou definitiva (compatíveis com a presença de necrose e/ou fibrose miocárdica). A hipocaptação radiossóptica apical pode ser demonstrada em pacientes chagásicos mesmo sem cardiopatia aparente (Thom & Martins 1982), permitindo o diagnóstico precoce da doença de Chagas. É possível observar a hipocaptação radiossóptica apical também em indivíduos normais, devendo a mesma, assim, ser interpretada com cautela.

A ventriculografia radiossóptica fornece informações confiáveis sobre a função ventricular esquerda global e anormalidades da movimentação parietal em pacientes com cardiopatia chagásica. Arreaza et al. (1983) verificaram boa correlação entre a FE medida pela cineventriculografia e pela radioventriculografia. Ao compararem as duas técnicas quanto à análise da contratilidade parietal, verificaram concordância dos resultados em 77% dos casos, maior ainda quando a análise se referia à região infero-apical. Cinquenta e seis por cento dos pacientes com movimentação anormal das paredes do VE apresentavam alterações regionais, sendo que a gravidade do acometimento provavelmente do grupo de pacientes assintomáticos para aqueles com insuficiência cardíaca. As alterações da fração de ejeção guardavam proporção com o número de regiões parietais afetadas pela doença, sendo normal em pacientes assintomáticos e abruptamente deprimida em pacientes com insuficiência cardíaca.

A miocardiopatia chagásica apresenta alterações difusas de contratilidade somente em estádios avançados da doença, com grande dilatação e insuficiência cardíaca. Nas formas menos avançadas, observa-se predominio de alterações segmentares em ambos os ventrículos. A hipocinesia segmentar parece relacionar-se com os achados anatomopatológicos de adelgaçamento da parede ventricular, com fibrose e miocítose em focos sistematizados. O ápice ventricular é o segmento mais frequentemente acometido e o que apresenta graus mais intensos de hipocinesia, o que também guarda relação com os dados anatomopatológicos conhecidos na doença de Chagas (Kuschin et al. 1985).


Número expressivo de pacientes chagásicos apresenta queixa de dor torácica atípica ou algumas vezes se assemelhando à angina do peito. Maria-Neto et al. (1992 a,b) realizaram estudo cintiagramográfico cinemecradioangiográfico em 23 pacientes chagásicos que se queixavam de dor precordial, a fim de avaliar a possibilidade de causa isquêmica para esta anormalidade. Consideram que isquemia miocárdica, possivelmente de natureza microvascular, possa contribuir para a gênese do sintoma. Julgam que os defeitos de captatação definitivos, encontrados em regiões da parede ventricular com alterações pronunciadas da movimentação, provavelmente correspondem a áreas de necrose ou fibrose evidenciadas na necropsia de pacientes em vários estádios da doença de Chagas. Também em suacasuística, a maior parte destes defeitos de perfusão envolvia a região apical, sede sabidamente preferencial de lesões aneurismáticas na doença de Chagas.

Na análise causal da hipocinesia segmentar e aneurismas ventriculares encontrados em pacientes com epidemiologia positiva para a doença de Chagas, deve-se considerar esta possibilidade etiológica e inclui-la no diagnóstico diferencial com a doença coronariana.

O emprego de técnicas radioisotópicas adquire relevo especial em pacientes com doenças pulmonares crônicas e com anormalidades da conformação torácica, nos quais a realizações de estudo ecocardiográfico pode estar dificultada ou mesmo impossibilitada. Realizando análise comparativa entre estes dois métodos propedêuticos, Arreaza et al. (1983) consideram que a ecocardiografia bidimensional e o estudo cintiagramético se complementam, sendo que o primeiro parece possuir deteção mais precoce da lesão apical, enquanto o segundo aparenta fornecer informações mais confiáveis e reprodutíveis com relação à função ventricular. Ressalta-se que a cintilografia radioisotópica permite o estudo morfofuncional de ambos os ventrículos.

As técnicas de medicina nuclear podem ser muito úteis ainda no esclarecimento da fisiotopatologia da doença. Simões et al. (2000) estudaram as relações entre alterações da perfusão miocárdica pelo tál-201 e da inervação simpática, usando o I-123 meta-iodobenzilguanidina, constatando associação topográfica marcada entre os defeitos de perfusão e inervação e as anormalidades contráteis regionais. Assim, a ocorrência de alterações precoces da perfusão simpática pode se relacionar, de forma causal, a alterações da perfusão e da contratilidade regional, assim como as precursoras da disfunção ventricular esquerda global.

A cardiologia nuclear compreende, assim, métodos propedêuticos não-invasivos de fácil realização, que fornecem informações valiosas para a avaliação, diagnóstico e tratamento de pacientes chagásicos. O seu emprego criterioso, como o das demais técnicas não-invasivas aqui estudadas,
deve ser considerado no diagnóstico complementar de casos selecionados em que se buscam informações mais precisas sobre a morfologia e função cardíacas, não constituindo, porém, substituto para as técnicas tradicionais de diagnóstico cardiológico.

Peptídio natriurético cerebral - BNP

Este hormônio cardíaco é um indicador confiável de disfunção ventricular esquerda (McDonagh et al. 1998). Demonstramos, recentemente, (Ribeiro et al. 2002) que esta alteração também se aplica para paciente com cardiopatia chagásica apresentando disfunção ventricular esquerda, revelando um alto valor preditivo negativo, podendo ser usado, portanto, como método de triagem, especialmente se houver alterações no ECG ou à radiografia de tórax. Portanto, diante de uma concentração normal de BNP, a probabilidade de haver disfunção global do ventrículo esquerdo é muito baixa. Já naqueles com níveis elevados de BNP, há necessidade de investigação ecocardiográfica para confirmar a disfunção.

Miocardiite viral

Nos Estados Unidos e na Europa Ocidental, a maior parte das miocardiites infecciosas é causada por vírus, sendo, historicamente, os enterovírus os agentes mais comuns, em especial os coxsackievírus do grupo B. Porém, um estudo multicêntrico recente demonstrou maior incidência de miocardiite causada pelo adeno vírus, em relação ao enterovírus, quando utilizada a PCR (reação em cadeia da polimerase) na biópsia endomiocárdica, sabidamente mais sensível que os outros métodos diagnósticos (Bowles et al. 2003).

Eletrocardiograma convencional

As alterações eletrocardiográficas na miocardiite viral aguda geralmente são transitórias e muito mais frequentes que as manifestações clínicas. A alteração mais comum é a taquicardia sínmus. Podem ser observadas anormalidades no segmento ST e na onda T, arritmias atriais e ventriculares, defeitos de condução atrioventricular e intraventricular e, raramente, ondas Q (Wynne & Braunwald 2001). Alguns pacientes podem apresentar quadro semelhante ao do infarto agudo do miocárdio, com supradesnivelamento do segmento ST, dor torácica e elevação das enzimas cardíacas (Sarda et al. 2001). O bloqueio atrioventricular total geralmente é transitório. As anormalidades na condução intraventricular estão associadas a dano miocárdico mais grave e, conseqüentemente, a pior prognóstico (Wynne & Braunwald 2001).

Enzimas cardíacas


Ecoardiograma


Cintilografia miocárdica

A cintilografia miocárdica, utilizando 111In-antimiosina, detecta áreas de necrose presentes, dentre outras patologias, na miocardiite aguda. Na miocardiite, ela representa exame de alta sensibilidade (91-100%) e com alto valor preditivo negativo (93-100%), mas de baixa especificidade e baixa valor preditivo positivo (Narula et al. 1996, Klocke et al. 2003). O 201Tl, usado em associação com o 111In-antimiosina, pode ser usado na diferenciação entre infarto agudo do miocárdico e miocardiite. Outro radiofármaco menos utilizado é o 67Ga, que detecta inflamação tecidual, possuindo as mesmas características de alta sensibilidade e baixa especificidade. Devido a baixa especificidade, à exposição à radiação e ao grande custo do método, a cintilografia não é considerada como um exame de rotina nos pacientes com suspeita de miocardiite (Friedrich et al. 1998).

Ressonância magnética

Alguns trabalhos na miocardiite aguda e subaguda mostram alterações à ressonância magnética, detectando o local, a gravidade e a extensão da inflamação (Friedrich et al. 1997, Mahrholdt 2004). A extensão do acometimento se correlaciona com o estado clínico e a função ventricular esquerda. Mas ainda são necessários novos estudos para avaliar a real aplicabilidade do método na miocardiite aguda.

Cardiopatia associada à síndrome da imunodeficiência adquirida

Outra cardiopatia que merece destaque é aquela associada à síndrome da imunodeficiência adquirida (Sida). A infecção pelo vírus da imunodeficiência humana (HIV) é uma das maiores causas de cardiopatia adquirida (Fisher & Lipshultz 2001). O acometimento cardíaco tende a ocorrer tardivamente no curso da doença, e tem sido mais prevalente diante da melhora da terapia específica, devido ao aumento da sobrevida. Análises retrospectivas e séries de necrópsias antes da introdução da terapia anti-retroviral de alta potência mostram alterações cardíacas em 25 a 75% dos pacientes com Sida (Barbaro 2001). Como é estimado que 36,1 milhões de adultos e crianças estavam vivendo com HIV/Sida e que durante o ano 2000 5,3 milhões tinham sido infectados pelo HIV (Temesgen 1999), a disfunção cardíaca associada ao HIV deve se tornar uma das principais causas de insuiciência cardíaca em todo o mundo (Barbaro 2001). As manifestações cardíacas mais comuns nos pacientes com Sida são: derrame pericárdico, miocardiite, miocardiopatia dilatada, endocardiite, hipertensão pulmonar, neoplasias malignas e cardiototoxicidade medicamentosas (Rerkpattanapipat et al. 2000). Em um estudo realizado com 440 necrópsias de portadores do HIV observou-se incidência de 18,6% (82 casos) de envolvimento card-
diaco. Por ordem de frequência, as alterações foram: derrame pericárdico, miocárdite intersticial linfocítica, miocardiopatia dilatada (frequentemente com miocardite associada), endocárdite infecciosa, linfoma e sarcoma de Kaposi (Fisher & Lipshultz 2001).


Infecções oportunistas, como aquelas causadas por Toxoplasma gondii, Mycobacterium tuberculosis e Cryptococcus neoformans estão relacionadas à miocárdite no portador do HIV. O próprio HIV tem sido descrito como causa de miocárdite (Rerkpattanapipat et al. 2000). Reilly et al. (1988) demonstraram a presença de miocárdite em todos os pacientes estudados com insuficiência cardíaca congestiva, disfunção do ventriculo esquerdo e taquicardia ventricular.

A endocárdite ocorre, aproximadamente, em 3 a 5% dos pacientes com Sida. Geralmente, está relacionada aos usuários de droga parenteral e acometem, frequentemente, a valva tricúspide, sendo o Staphylococcus aureus e o Streptococcus viridans os principais agentes.

A miocardiopatia dilatada está fortemente associada com CD4 menor que 100 células/mL. A disfunção ventricular esquerda tem valor prognóstico no paciente com Sida, já que esta reduz significativamente sua sobrevida (Currie et al. 1994).

O ecocardiograma também é útil na avaliação da função sistólica do ventriculo esquerdo, podendo, ainda, revelar adegacamento ou espessamento e dilatação ventricular esquerda. Na disfunção sistólica do ventriculo esquerdo, o elettrocardiograma convencional revela alterações inespecíficas de alteração na condução e na repolarização ventriculares. A radiografia de tórax possui baixas sensibilidade e especificidade na detecção de insuficiência cardíaca congestiva nos portadores do HIV. A incidência média anual em pacientes assintomáticos é de 15,9 casos de miocardiopatia dilatada por 1.000 pacientes (Fisher & Lipshultz 2001).

Sintomas iniciais de disfunção autonômica, frequentes nos pacientes portadores do HIV, incluem sincope, pré-sincope, redução da sudorese, diarreia, disfunção vesical e impotência. Exames como a variabilidade da frequência cardíaca, resposta hemodinâmica ao exercício isométrico e teste de iniciação podem ser realizados para o diagnóstico funcional.

A avaliação cardiológica sistemática rotineira é essencial no cuidado do paciente portador do HIV. Indivíduos assintomáticos devem ser submetidos a avaliação complementar inicial, constando de exames elettrocardiográfico e elettrocardiográfico convencional e dinâmico, repetidos conforme as características e evolução de cada caso. Pacientes com grave comprometimento orgânico, extra-cardíaco, devem ser seguidos com avaliação elettrocardiográfica mais frequente. Pacientes evidenciando manifestações clínicas de comprometimento cardíaco devem iniciar tratamento sintomático e otimização do tratamento antiretrovirial concomitantemente à avaliação complementar cardiovascular.

O advento da epidemia pelo HIV no início dos anos 1980 trouxe a possibilidade de ocorrência de reativação da infecção chagásica em pacientes co-parasitados pelo HIV e pelo Trypanosoma cruzi. Cerca de 80% dos reativados da doença de Chagas em pacientes com Sida estão documentados na literatura, a maioria destes procedentes do Brasil e da Argentina (Ferreira & Borges 2002). Praticamente todos os pacientes co-infectados, apresentando reativação, da infecção chagásica, apresentam contagem de linfócitos T CD4 inferior a 200 células/mm³. O envolvimento do sistema nervoso central caracteriza-se por uma meningoencefalite aguda, uni ou multifocal, e pela presença de imagens hipodensas, predominantemente subcorticais, à tomografia computadorizada. O envolvimento do coração geralmente é discreto, sendo poucas vezes percebido clínicamente ou radiologicamente. As manifestações clínicas, quando presentes, incluem aquelas da insuficiência cardíaca congestiva, além de arritmias cardíacas. Aumento do volume cardíaco e derrame pericárdico podem ser evidenciados ao ecocardiograma. A presença do T. cruzi pode ser evidenciada no exame direto do líquido pericárdico. No miocárdio, a presença do T. cruzi, constatada à biópsia endomiocárdica, deve ser confirmada pela imuno-histoquímica ou pela microscopia eletrônica, devido a possibilidade de infecção simultânea por outros patógenos, especialmente o Trypanosoma gambiense (Ferreira et al. 1997, Sartori et al. 1998, Ferreira & Borges 2002). O diagnóstico de reativação deve ser feito o mais precocemente possível, devido à gravidade do quadro e à possibilidade de melhorar com o tratamento tripanossomíaco. O benzonidazol é a droga de escolha, na dose de 5 mg/kg/dia, para adultos, por 60 dias (Ferreira & Borges 2002). A profilaxia secundária deve ser feita com a mesma droga, na dose de 2,5 mg/kg/dia, três vezes por semana, até a recuperação de níveis adequados de CD4.

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Arq Bras Cardiol 50: 293-299.


INTRODUÇÃO

A eletrocardiografia dinâmica, ou simplesmente Holter, foi desenvolvida de forma original por Norman Holter e introduzida comercialmente a partir da década de 1960. O Holter acrescentou uma nova dimensão à eletrocardiografia, o tempo, permitindo que o registro eletrocardiográfico fosse feito por períodos prolongados e durante as atividades habituais dos pacientes, com impacto imediato no diagnóstico das arritmias e da isquemia miocárdica. Desde então, o método foi aprimorado, principalmente pela automação e miniaturização dos sistemas, e incorporado à prática clínica, com definição tanto de suas aplicações como das limitações técnicas e operacionais. Novas técnicas surgiram com a introdução do uso dos computadores na cardiologia, como o estudo da variabilidade da frequência cardíaca (VFC), que permite o estudo do controle autonômico cardíaco, além de formas diferentes de registro e novos recursos de análise, como, por exemplo, para os portadores de marcapasso. Desse modo, o método é hoje ferramenta fundamental no diagnóstico e na estratificação de risco dos pacientes cardiopatas.

ASPECTOS METODOLÓGICOS E TÉCNICOS

O equipamento necessário à realização do Holter ambulatorial inclui os gravadores e a central de análise. Os gravadores são geralmente compactos, leves e de pequeno volume, podendo ser transportados pelo paciente em pequenas bolsas ao lado do corpo, de modo a permitir o registro dos sinais eletrocardiográficos durante todas as atividades rotineiras do indivíduo. O eletrocardiograma, em geral obtido em três derivações, é amplificado e registrado, através de gravador analógico, em fitas cassetes que rodam em velocidade muito lenta, ou gravador digital, em memória sólida, permitindo gravações contínuas de 24 ou 48 horas. Os sistemas digitais apresentam vantagens teóricas, eliminando as partes mecânicas do gravador e diminuindo o nível de ruído, mas bons registros podem ser obtidos de ambas as maneiras.

Os gravadores são usados pelo paciente atados a um cinto, como um telefone celular ou aparelho de som portátil. Durante a instalação do aparelho, o preparo da pele é fundamental: após a tricotomia, a pele deve ser limpa com álcool e abrasada levemente com tecido áspero. O paciente deve ser instruído a preencher um diário com os horários das atividades e sintomas apresentados durante o período de gravação, para permitir a correlação com possíveis alterações eletrocardiográficas presentes no traçado. Caso o paciente apresente algum sintoma, deverá acionar o marcador de eventos, que é um botão externo ao gravador e que produz um artefato na gravação que é reconhecido durante a análise do traçado, permitindo a detecção de possíveis alterações eletrocardiográficas associadas aos sintomas referidos.

A central de análise é um sistema computadorizado que adquire o registro a partir da fita gravada ou cartão digital, realizando análise semi-automática do traçado e classificando cada complexo QRS em formas, agrupados como normais, ventriculares, artefatos, entre outras. A maioria dos sistemas atuais requer um operador, médico ou técnico qualificado para rever e corrigir a classificação realizada pelo sistema, mas alguns modelos permitem a análise interativa durante a própria fase de classificação. O exame é analisado quanto às arritmias registradas, que são revistas, selecionadas e analisadas pelo operador, assim como as pausas, as taquicardias e bradicardias e as alterações da repolarização ventricular. Artefatos relacionados à movimentação dos pacientes ou interferências eletromagnéticas podem dificultar a análise do registro e devem ser eliminados. O sistema gera relatórios impressos contendo dados referentes à frequência cardíaca média, máxima e mínima horária, a distribuição de eventos.
arritmicos e isquemicos no periodo de registro e os tracados electrocardiograficos selecionados.

Novos recursos e modalidades de analise estao disponiveis nos sistemas modernos. Softwares especiais permitem a identificacao e a ampliacao das espicas de marcapasso, ja que a curta duracao e a alta frequencia do artefato produzido pelo gerador de pulso podem fazer com que este nao seja reconhecido pelos sistemas convencionais, que trabalham com taxa de amostragem e faixa de frequencia menor que os electrocardiogramas convencionais. A variabilidade dos intervalos R-R normais, ou VFC (ver adiante), e outro recurso frequentemente disponivel. Avaliacao da alternancia de onda T, dispersao do intervalo QT e electrocardiograma de alta resolucao sao outras metodologias que podem ser incorpoadas aos sistemas de Holter comercialmente disponiveis.

Como as arritmias sao eventos paroxisticos e episodicos, podendo nao ocorrer no periodo de registro de 24 a 48 horas do Holter convencional, foram desenvolvidos gravaores de registros descontinuos, adaptados a monitorizacao prolongada. Alguns modelos podem ser aplicados sobre o teorx quando o paciente apresenta o sintooma, registrando o tracao electrocardiografico no momento de sua ocorrrencia. Mais frequentemente, utiliza-se o Holter de eventos, ou loop recorder, que sao gravaores de registro incesante em circuito de memoria circular (memory loop circuit). Quando o paciente apresenta o sintooma e aperta o bocio de eventos, ocorre a gravao do tracao electrocardiografico de alguns minutos imediatamente anteriores ao inicio do sintooma e do periodo subsequente. Os registros sao transferidos para a central de analise após o periodo de monitorizacao, em geral de 2 a 4 semanas, ou sao periodicamente enviados por telefone. Existe ainda o loop recorder implantavel, que registra o sinal a partir de um pequeno (< 5cm) dipolo subcutaneo. Ao apresentar o sintooma, o paciente aciona um controle remoto que guarda na memoria do dispositivo o tracao imediatamente anterior e subsequente ao evento. O tracao, habitualmente fidedigno e de boa qualidade, e recuperado por telemetria através de um programador de marcapasso especifico. O procedimento, invasivo, apresenta excelente performance diagnosticica em pacientes bem seleccionados, especialmente na sincope de origem indeterminada.

INDICACOES

As principais indicacoes do Holter estao descritas no quadro 8.1, conforme diretriz internacional recente. De forma genetica, o Holter pode ser usado para detecao de arritmias cardiacas, avaliação do risco de eventos adversos em cardiopatas, detecao de isquemia miocardiaca e seguimento de pacientes submetidos a tratamento antiarritmico com drogas ou dispositivos (marcapasso e cardioestimulator implanteavel - CDI).

Detecao de Arritmias Cardiacas

Uma das principais utilizaes do Holter e o diag nostico de arritmias cardiacas em pacientes com sintomas cardiovasculares inexplicados, especialmente aqueles atribuidos as arritmias: palpitations, tonturas, pre-sincopes e sincopes. O metodo e de grande valor em muitos desses pacientes, embora existam limitacoes a sua utilizacao com esse objetivo. Para que se atribua um sintooma a determinada alteracao do ritmo, e necessario que se faça a correlacao temporal entre o sintooma apresentado, anotado no diapeo pelo paciente, com ou sem utilizacao do marcador de eventos do gravador, e a presenca de arritmias significativas no tracao electrocardiografico simultaneo. Como os sintomas geralmente sao ocaesioes, muitos pacientes podem nao apresentar a manifestacao durante a gravacao. Entre os pacientes que apresentam os sintomas durante o exame, pelo menos a metade nao mostra alteracoes electrocardiograficas simultaneas. Assim, o metodo revelara uma arritmia causadora da manifestacao em cerca de um quarto dos pacientes sintomaticos. Por outro lado, a ausencia da arritmia ao tracao electrocardiografico num paciente que apresentou sintomas durante o registro auxilia a exclusao desta como causa do sintooma em questao.

Entre os pacientes que, apesar de sintomaticos, nao apresentam sintomas durante a gravacao, arritmias silenciosas sao encontradas em cerca de um terço dos casos. Na maioria das vezes, tais arritmias sao coadjuvantes inoentes, sem nexo causal com o sintooma apresentado. Porém, e possivel que o limiar de percepcao desses sintomas varie e que, em determinadas situaes, o evento arritmico provoque sintomas, enquanto seja silencioso em outras. Adicionalmente, algumas arritmias silenciosas podem ter valor prog nostico e indicar a necessidade de medidas terapeuticas, com taquicardias ventriculares sustentadas e bloqueios atrioventriculares completos com escapes ventriculares lentos. O significado das diferentes arritmias especificas encontradas casualmente ao Holter estao descrito no quadro 8.2, enquanto alguns exemplos podem ser vistos no fig. 8.1.

A palpitation e um sintooma frequente, muitas vezes negligenciado, e que tem origem nas arritmias cardiacas em cerca de 40% das vezes. Como o termo e usado de forma imprecisa por pacientes e medicos, a avaliação clinica cuidadosa, com amnese e examen fisico detalhados, pode evidenciar uma causa nao-cardiaca evidente para o sintooma, abreviando a necessidade de propedutica adicional. Por outro lado, a documentacao do ritmo sinusal concomitante ao sintooma e uma excelente evidencia de que a causa do sintooma não e cardica. Embora um ou dois registros de Holter de 24 horas sejam eficazes quando o sintooma e diario ou frequente, o metodo tem baixo valor quando os sintomas são episodicos, e o Holter de eventos tem melhor performance diagnóstica nesses casos. Pacientes nao-cardiopatas com palpitations sustentadas raras, sem repercussao hemodinamica, podem apresentar arritmias significativas (p. ex., taquicardia por reentrada nodal): em alguns desses pacientes, pode ser mais pratico evitar a realizacao de multiplos exames sem arritmias e aguardar o retorno do sintooma para registro durante o episodio arritmico.

A avaliação do paciente com sincope (ou tontura e prem-sincope) e outra indicação frequente da electrocardiografia
### Quadro 8.1 Indicações da Eletrocardiografia Ambulatorial (Holter)

<table>
<thead>
<tr>
<th>Indicações</th>
<th>Classe I</th>
<th>Classe IIa</th>
<th>Classe IIb</th>
<th>Classe III</th>
</tr>
</thead>
</table>
| Avaliação de sintomas potencialmente relacionados a arritmias             | • Síncope, pré-síncope ou tontea sem outra causa aparente  
• Palpitações recorrentes inexplicadas                                                                                                           | • Dispneia, dor torácica ou fadiga sem outra causa aparente  
• Eventos neurológicos quando se suspeita de fibrilação/flutter atrial  
• Síncope, pré-síncope, tontea ou palpitações com causa identificada mas resistente ao tratamento | • Pós-IAM com disfunção de VE  
• Insuficiência cardíaca  
• Miocardiopatia hipertrófica idiopática                                                                                                     | • Acidente vascular cerebral sem outras evidências de arritmia  
• Síncope, pré-síncope, tontea ou palpitações com causa não-arritmica identificada                                                                                                           |
| Avaliação do risco de eventos futuros na ausência de sintomas arrítmicos (por detecção de arritmias e análise da VFC) |                                                                                                                                                                                                           | • Na avaliação do controle da FC na fibrilação atrial  
• Para documentar arritmias não-sustentadas recorrentes                                                                                       |                                                                                                                                                                                                           |                                                                                                                                                                                                           |
| Avaliação da eficácia antiarrítmica                                        | • Arritmia frequente e reprodutível nos traçados basais                                                                                                                                                   | • Na avaliação da pró-arritmia em pacientes de alto risco                                                                                                                      |                                                                                                                                                                                                           |                                                                                                                                                                                                           |
| Avaliação da função do marcapasso (MP) e do cardioversor implantável (CDI) | • Síncope, pré-síncope ou palpitações (suspeita de disfunção do MP)  
• Auxílio à programação de funções especiais, como resposta de FC  
• Avaliação da resposta à terapia farmacológica adjunta ao CDI                                                                                  | • Pós-operatório imediato após implante de MP ou CDI  
• Avaliação da frequência de taquicardias supraventriculares em pacientes com CDI                                                              | • Na avaliação rotineira de pacientes assintomáticos ou quando outros métodos são suficientes para o diagnóstico (ECG, telemetria, radiografia de tórax etc.) |                                                                                                                                                                                                           |

(continua)
Quadro 8.1 Indicações da Eletrocardiografia Ambulatorial (Holter) (continuação)

<table>
<thead>
<tr>
<th>Indicações</th>
<th>Classe I</th>
<th>Classe IIa</th>
<th>Classe IIb</th>
<th>Classe III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitorização de isquemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Suspeita de angina variante</td>
<td></td>
<td></td>
<td>• Dor torácica ou pré-operatório de cirurgia vascular daqueles que não podem se exercitar</td>
<td></td>
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<tr>
<td>Pacientes pediátricos</td>
<td></td>
<td></td>
<td></td>
<td>• Avaliação inicial de paciente com dor torácica que pode se exercitar</td>
</tr>
<tr>
<td>• Sincope, pré-sincope, tontura em cardiopatias</td>
<td></td>
<td></td>
<td></td>
<td>• Rastreamento de indivíduos assintomáticos</td>
</tr>
<tr>
<td>• Sincope ou pré-sincope ao esforço quando a causanção não é esclarecida</td>
<td></td>
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<tr>
<td>• Miocardiopatia hipertrofica/dilatada</td>
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<tr>
<td>• Síndrome do QT longo</td>
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<tr>
<td>• Palpitações na presença de cardiopatia</td>
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<td></td>
</tr>
<tr>
<td>• Avaliação de eficácia antiarrítmica no desenvolvimento somático rápido</td>
<td></td>
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<tr>
<td>• BAV total conatório assintomático</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Sincope, pré-sincope, palpações sustentadas sem causa aparente em pacientes não cardiopatias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Avaliação inicial de terapia antiarrítmica</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Após BAV transitório por cirurgia cardíaca ou ablação por caráter</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Avaliação do MP em pacientes sintomáticos</td>
<td></td>
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</tr>
<tr>
<td>• Pós-operatório de cirurgia para cardiopatia congênita com anormalidade hemodinâmica residual ou alto risco de arritmias</td>
<td></td>
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</tr>
<tr>
<td>• Paciente jovem (&lt; 3 anos) com taquiarritmia prévia</td>
<td></td>
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<tr>
<td>• Suspeita de taquicardia atrial incessante</td>
<td></td>
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<td></td>
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<tr>
<td>• Ectopia ventricular complexa ao ECG ou à ergometria</td>
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<td></td>
</tr>
<tr>
<td>• Sincope, pré-sincope, tontura ou palpitações com outra causa definida</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dor torácica sem evidência de cardiopatia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Avaliação rotineira de assintomáticos para atividades atléticas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Palpitações breves na ausência de cardiopatia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wolff-Parkinson-White assintomático</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fonte: Crawford et al., 1999. Considera-se a indicação como classe I, caso existam evidências suficientes ou concordância geral de que o procedimento é útil e eficaz, classe II, se existe discordância ou divergência de opinião, sendo considerada IIIa se o peso da evidência ou das opiniões indica utilidade ou eficácia e IIIb se a utilidade ou eficácia do método está menos bem estabelecida, e classe III, quando existe consenso de que o procedimento não é útil ou eficaz e pode mesmo ser lesivo. BAV = bloqueio atrioventricular; CDI = cardíodesfrizer implantável; FC = frequência cardíaca; HAS = hiperterópico arterial sistêmico; HVE = hiperreflexia ventricular esquerda; IAM = infarto agudo do miocárdio; MP = marcapasso; VE = ventriculograma; VFC = variabilidade da frequência cardíaca.</td>
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</tbody>
</table>

**Dinâmica.** Como o sintoma é usualmente esporádico e com frequência não relacionado a arritmias cardíacas, o Holter é diagnóstico em menos de 10% dos casos. Apesar disso, o método é imprescindível na maioria dos casos nos quais o diagnóstico não é evidente, já que condições graves (p. ex., TV sustentada) podem ser documentadas, além de arritmias assintomáticas que prenunciam outras de maior gravidade (p. ex., BAV avançados). O Holter de eventos aumenta a acurácia diagnóstica para um quarto a um terço dos casos, e o loop implantável é uma alternativa eficaz em casos selecionados.

### MONITORIZAÇÃO DE ISQUEMIA MIOCÁRDICA

Ao permitir a monitorização do paciente durante suas atividades habituais, o Holter fornece boa oportunidade para a avaliação da presença de isquemia miocárdica enquanto o paciente está exposto ao estresse físico e emocional da vida cotidiana. Entretanto, para que a análise do segmento ST obtida através do Holter seja confiável, deve-se observar uma série de pré-requisitos: o ritmo ser sinusal; o QRS estreito (até 0,10 segundo), com ondas R amplas nas precordiais laterais (≥ 15mm) e paredes inferiores (≥ 10mm); não deve haver super ou infradesnívelamento do segmento ST ≥ 1,0mm no registro de
base, assim como segmentos ST descendentes ou côncavos; mudanças posturais não devem provocar desnivelamentos do segmento ST ≥ 1,0mm. As seguintes condições impedem a interpretação das modificações do segmento ST ao Holter de 24 horas: hipertrofia ventricular esquerda ao ECG de 12 derivações; onda q ≥ 0,04 na derivação em estudo; fibrilção ou flutter atrial; uso de digoxina ou outras medicação que afetem o segmento ST, bloqueio de ramo esquerdo e, apenas nas precordiais direitas, bloqueio de ramo direito.

Durante a monitorização pelo Holter, a isquemia é definida pela presença do infradesnivelamento horizontalizado ou descendente do segmento ST de 1,0mm ou mais, com início e término graduais, durando o mínimo de 1 minuto. Cada episódio de isquemia transitória deve ser separado do seguinte por pelo menos 1 minuto, durante o qual o segmento ST retorna à linha de base (regra 1 × 1 × 1).

A maior parte dos estudos com o Holter na monitorização da isquemia miocárdica foi realizada em pacientes já sabidamente coronariopatas ou vasculopatas. Assim, não existem evidências atuais de que o Holter forneça informações diagnósticas sobre pacientes assintomáticos sem doença coronariana ou arterial periférica definida, e o método não deve ser usado rotineiramente para o rastreamento ou diagnóstico de doença coronariana em populações não selecionadas. Adicionalmente, embora o Holter forneça informações complementares à ergometria, a acurácia desta última é superior na avaliação diagnóstica da doença arterial coronariana. A indicação do Holter está restrita a casos de pacientes com dor torácica ou no pré-operatório de cirurgia vascular no qual o paciente não possa caminhar, como alternativa ao método de imagem (cintilografia de perfusão miocárdica ou eco de estresse, métodos de escolha nesta situação). Uma indicação
### Quadro 8.2: Significado das Arritmias Assintomáticas em Pacientes Submetidos ao Holter

<table>
<thead>
<tr>
<th>Arritmia Assintomática</th>
<th>Significado</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Noturna</td>
</tr>
<tr>
<td>Parada sinusal</td>
<td>Nenhum se &lt; 3,5 segundos</td>
</tr>
<tr>
<td>Pausas durante a fibrilação atrial</td>
<td>Nenhum</td>
</tr>
<tr>
<td>Bloqueio AV de segundo grau Mobitz tipo I</td>
<td>Pouca importância</td>
</tr>
<tr>
<td>Bloqueio AV de segundo grau Mobitz tipo II e de terceiro grau</td>
<td>Requer avaliação adicional imediata</td>
</tr>
<tr>
<td>Extra-sístoles isoladas (supraventriculares ou ventriculares) e em pares</td>
<td>Não significativa na ausência de cardiopatia estrutural</td>
</tr>
<tr>
<td>Curtos episódios de arritmia atrial</td>
<td>Não significativos; pesquisa causa se apropriado</td>
</tr>
<tr>
<td>Taquicardia ventricular não-sustentada</td>
<td>Provavelmente não importante na ausência de cardiopatia, mas avaliação adicional está indicada</td>
</tr>
<tr>
<td>Taquiarritmias frequentes e incessantes</td>
<td>Sempre importantes. Pacientes em risco de taquicardiomioptasia ou outras complicações (p. ex., acidente vascular cerebral na presença de fibrilação atrial)</td>
</tr>
</tbody>
</table>


específica do Holter para este fim é a detecção da angina variante de Prinzmetal, quando o teste ergométrico é negativo (ver Quadro 8.1).

Isquemia miocárdica pode ser registrada ao Holter em 20 a 45% dos pacientes com angina de peito estável e em 30 a 40% dos que com angina instável, embora 60 a 80% destes episódios sejam assintomáticos. Apesar da presença de isquemia silenciosa ter impacto prognóstico nessas situações clínicas, o método não está indicado rotineiramente nessas pacientes.

**Estratificação de Risco**

Como as medidas terapêuticas em cardiologia têm frequentemente custo e riscos específicos, uma das tarefas primordiais do médico é definir, por meio de marcadores clínicos e laboratoriais, os pacientes com risco mais alto de morte ou complicações graves, candidatos a tratamentos medicamentosos ou por intervenção. O Holter é sabidamente útil na estratificação de risco de arritmias cardíacas e morte numa série de condições clínicas, já que fornece informações sobre a frequência e a complexidade de arritmias ventriculares, sobre a presença de isquemia miocárdica em pacientes coroanopatas e sobre o controle autônomo cardíaco, através da variabilidade da frequência cardíaca (VFC).

A análise da VFC parte do princípio de que, em condições normais, a frequência cardíaca modifica-se em resposta a estímulos diversos, como exercício e estresse mental, ou mesmo em condições de repouso, flutuando em torno de uma média. Tal variabilidade relaciona-se, predominantemente, às alterações contínuas do balanço simpático-vagal, em resposta
a mecanismos de controle cardiovascular. A VFC pode ser estudada por técnicas matemáticas que abordam as características estatísticas desta variação (domínio do tempo), que decompos os diferentes ritmos envolvidos (domínio da frequência) ou por métodos não-lineares, que utilizam métodos matemáticos avançados para descrever o comportamento da variabilidade da FC.

Os métodos estatísticos fornecem índices práticos de cálculo simples, que avaliam a dispersão dosintervalos entre os batimentos cardíacos em torno da média (como o SDNN – desvio padrão dos intervalos cardíacos normais) ou comparam a duração de ciclos adjacentes (como o RMSSD, que é a média dos valores absolutos das diferenças sucessivas, e o PNN50 – a porcentagem de intervalos cardíacos normais sucessivos com variação maior que 50ms). Enquanto o SDNN é produto de todas as influências autonômicas (principalmente parassimpáticas) e neuro-humorais sobre a VFC, o RMSSD e o PNN50 são resultado direto da influência vagal sobre o coração. Em modelos experimentais, a retirada do tono vagal diminui o limiar fibrilatório e predispõe a morte súbita. O valor prognóstico da redução dos índices do domínio do tempo da VFC está validado em diversos estudos retrospectivos e prospectivos, principalmente após o infarto agudo do miocárdio e na insuficiência cardíaca.

A análise do domínio do tempo, por meio da análise espectral da VFC, permite o estudo das diferentes divisões do sistema nervoso autônomo. Em registros de curta duração, reconhece-se que a variabilidade de alta frequência (entre 0,15 e 0,40Hz) está relacionada quase que exclusivamente ao vago e à arritmia sinusal respiratória. A variabilidade concentrada entre 0,04 e 0,15Hz, de baixa frequência, relacionada ao barorrelexo, tem origem simpática e/ou vagal, enquanto a relação baixa/alta frequência seria um indicador do equilíbrio simpático-vagal. Apesar das vantagens teóricas e do potencial fisiopatológico da análise espectral da VFC, inexistem estudos clínicos demonstrando sua vantagem sobre índices convencionais do domínio do tempo.

Entre as técnicas mais novas, a mais promissora é o estudo da turbulência da frequência cardíaca, método que avalia as modificações da frequência cardíaca provocadas pelas extra-sistóles ventriculares. Após uma extra-sísiole ocorrerem, habitualmente, uma pausa compensatória e uma contração forçada subsequente, ativando o barorrelexo e oscilações da frequência cardíaca, fenômeno conhecido como turbulência da frequência cardíaca. Esta oscilação, fisiológica, reduz-se numa série de condições patológicas, como na doença de Chagas e após o infarto, situação na qual tem elevado valor prognóstico.

Apesar do valor prognóstico comprovado da VFC, sua utilização não é indicada rotineiramente. O método depende do tratamento técnico cuidadoso do registro do Holter, com eliminação dos artefatos. Os índices só podem ser obtidos se o ritmo for sinusal e batimentos normais predominarem em pelo menos 85% do registro, excluindo-se pacientes com marcapasso ou arritmias persistentes, como a fibrilação atrial. O valor preditivo positivo do método (isto é, a probabilidade de eventos caso a VFC esteja alterada) isoladamente é baixo, o que pode ser melhorado associando-o a outros preditores de risco, como a presença de taquicardia ventricular não-sustentada, depressão da fração de ejeção do VE e potenciais tardios ao ECG de alta resolução. Mesmo assim, o impacto da estratificação do risco arrítmico pelo Holter não está estabelecido, de modo que a estratificação de risco após o infarto (com disfunção do VE), na insuficiência cardíaca e na miocardiopatia hipertrófica é uma indicação classe IIb pelas diretrizes atuais (ver Quadro 8.1).

Avaliação da Resposta ao Tratamento Antiarrítmico por Drogas ou Dispositivos

A avaliação da resposta dos pacientes com arritmia ventricular aos antiarrítmicos convencionais foi uma indicação frequente do Holter na década de 1980. Entretanto, algumas limitações importantes se impõem: (a) as arritmias apresentam substancial variabilidade diária, de forma que uma redução significativa do número de extra-sístoles deve ocorrer para que se possa dizer que tal variação não foi devida ao acaso; (b) vários estudos mostraram que a supressão da ectopia ventricular não é garantia de melhor prognóstico; (c) muitos pacientes podem apresentar arritmias potencialmente fatais sem apresentar arritmias assintomáticas em número significativo ao Holter de 24 horas. Assim, o Holter deve ser usado para avaliação da resposta terapêutica apenas naqueles pacientes que apresentam arritmia ventricular, frequente e reproduzível, mas que necessitem de tratamento antiarrítmico medicamento. Na prática, muitos desses pacientes são na verdade candidatos ao desfibrilador implantável, que tem funções de memória e frequentemente prescinde do Holter convencional para avaliar sua eficácia. São também indicações do Holter de 24 horas nos pacientes em tratamento antiarrítmico: a pesquisa de pró-arritmia, a documentação de arritmias sustentadas ou não-sustentadas assintomáticas e a avaliação da resposta da frequência cardíaca nos pacientes com fibrilação atrial (ver Quadro 8.1).

O Holter é uma poderosa ferramenta auxiliar na avaliação do paciente portador de marcapasso ou de desfibrilador, especialmente quando este apresenta sintomas ou suspeita de disfunção (ver Quadro 8.1). Auxilia a programação de recursos fundamentais, como a resposta de frequência cardíaca ao esforço e os mecanismos de resposta do dispositivo às arritmias espontâneas do paciente. Adicionalmente, documenta arritmias concomitantes ou o efeito de terapias medicamentosas adjuvantes. Embora muitos dos dispositivos modernos apresentem memórias internas e sejam capazes de armazenar eventos (registrados pelo paciente ou a partir de parâmetros pré-selecionados), o Holter ainda mantém um importante papel no manejo dos pacientes com marcapasso ou desfibrilador implantável.
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