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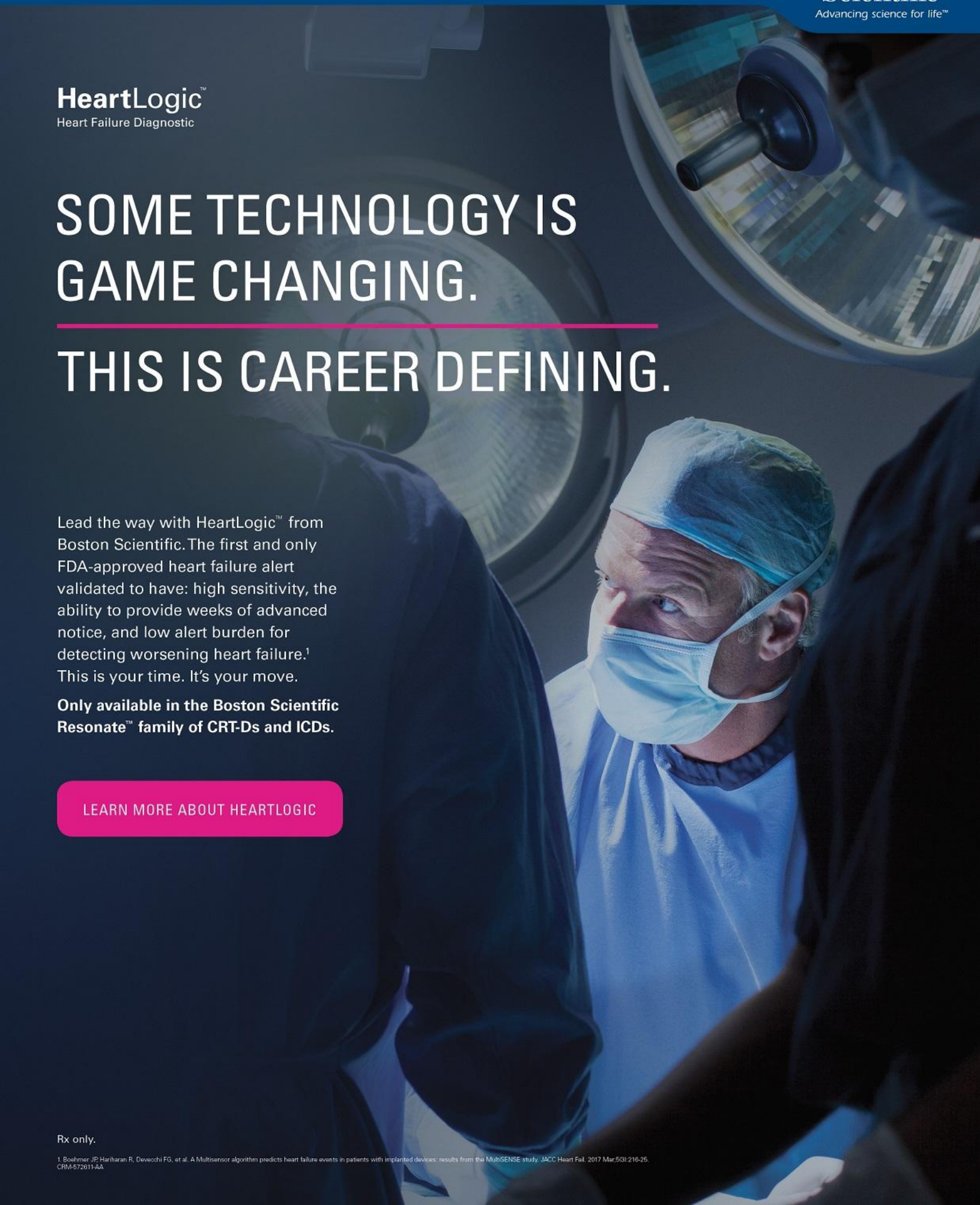

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1. Boehmer JP, Hariharan R, Devecchi FG, et al. A Multisensor algorithm predicts heart failure events in patients with implanted devices: results from the MultiSENSE study. JACC Heart Fail. 2017 Mar;5(3):216-25.

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Electrocardiographic Ventricular Repolarization Parameters in Chronic Chagas' Disease as Predictors of Asymptomatic Left Ventricular Systolic Dysfunction

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SALLES, G.F., ET AL.: Electrocardiographic Ventricular Repolarization Parameters in Chronic Chagas' Disease as Predictors of Asymptomatic Left Ventricular Systolic Dysfunction. *Electrocardiographic repolarization parameters are potential markers of arrhythmogenic risk and have not been evaluated in Chagas' disease. The aim of this report was to investigate their associations with LV systolic function assessed by two-dimensional echocardiography. In a cross-sectional study involving 738 adult outpatients in the chronic phase of Chagas' disease, maximal QTc and T wave peak-to-end (TpTe) intervals, and QT, QTapex (QTa), JT and TpTe interval dispersions, and variation coefficients were measured and calculated from 12-lead standard ECGs. Clinical, radiological, ECG, and echocardiographic data were recorded. In bivariate statistical analysis, all repolarization parameters were significantly increased in patients with moderate or severe LV systolic dysfunction, and these patients showed more clinical, radiologic, and ECG abnormalities. Receiver operating characteristic curve analysis demonstrated that isolatedly QTd had the best predictive performance for LV dysfunction, with an 80% specificity and 67% sensitivity for values >60 ms in the subgroup of chagasic patients with abnormal ECGs and no heart failure. Multivariate logistic regression selected, as the best predictive model for LV dysfunction in this subgroup of patients, the presence of cardiomegaly on chest X ray (OR 14.06, 95% CI, 5.54–35.71), QTd > 60 ms (OR 9.35, 95% CI, 4.01–21.81), male gender (OR 7.70, 95% CI, 2.98–19.91) and the presence of frequent premature ventricular contractions (PVCs) on ECG (OR 4.06, 95% CI, 1.65–9.97). This model showed 90% specificity and 71% sensitivity. In conclusion, QTd was associated to LV systolic function and could be used to predict asymptomatic dysfunction in chronic Chagas' disease. The presence of cardiomegaly, frequent PVCs, and male sex refined LV function stratification in these patients. (PACE 2003; 26:1326–1335)*

Chagas' disease, QT intervals, QT dispersion, systolic dysfunction, ventricular repolarization, electrocardiology

Introduction

Chagas' heart disease remains an important public health problem in Latin American countries, where it is estimated that nearly 20 million are infected and 25–30% will develop symptoms of congestive heart failure, ventricular arrhythmias, or thromboembolism.[1] It is the leading cause of cardiovascular death in endemic areas[2] from sudden arrhythmic or progressive heart failure.

Since the original description of Day et al.,[3] QT dispersion (QTd), defined as the greatest interlead variability of QT intervals, is presumed to represent a noninvasive measurement of ventricular repolarization inhomogeneity and a potential marker of arrhythmogenic risk. Within the last decade, various repolarization parameters have been evaluated in several clinical conditions like long QT syndromes,[4] coronary artery disease,[5,6] heart failure of different etiologies,[7,8] other cardiopathies,[9] and in primary noncardiac diseases like diabetes mellitus[10] or in population-based studies,[11] with rather inconsistent results.[12]

Although Chagas' heart disease, because of its main characteristics (a chronically evolving myocarditis with fibrosis, hypertrophy, and dilatation, accompanying autonomic dysfunction, and a high prevalence of serious ventricular arrhythmias and sudden arrhythmic death),[13] seems a perfect candidate for assessment of ventricular repolarization dispersion parameters; however, such a study has never been reported. As left ventricular

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(LV) systolic function has been demonstrated to be one of the most important prognostic factors in Chagas' cardiopathy,[14–17] the aim of the present study was to investigate the associations between several electrocardiographic (ECG) repolarization parameters and two-dimensional echocardiographically assessed LV function in a large group of patients in the chronic phase of Chagas' disease.

Patients and Methods

Patients

The study included 814 patients attending the Chagas' disease outpatient clinic of Evandro Chagas Hospital (Oswaldo Cruz Foundation, Rio de Janeiro, Brazil) from January 1989 to December 1999. All patients had at least two positive anti-*trypanossoma cruzi* serological reactions by three distinct techniques (indirect hemaglutination, indirect immunofluorescence, and enzyme linked immunosorbent assay). All were submitted to a thorough clinical examination by the same physician on their first visit, with special attention to signs and symptoms of cardiovascular disease: syncope or near-syncope, palpitations, thoracic pain, and heart failure (diagnosed by Framingham criteria[18]). Patients with evidence of other cardiopathies, serum electrolyte potassium or calcium abnormalities, use of any antiarrhythmic drug, or severe renal dysfunction were excluded. The presence of systemic arterial hypertension was not an exclusion criterion unless there was LV hypertrophy on echocardiogram. The study complies with the Declaration of Helsinki, the local ethics committee approved its protocol and all patients gave written, informed consent.

ECG and Repolarization Parameters

Standard resting 12-lead ECGs were recorded at 25 mm/s paper speed and 10 mm/mV amplitude on the same day of the first medical interview. ECG exclusion criteria were the impossibility of measuring the intervals in at least eight leads and four precordial leads (n = 51), atrial fibrillation (n = 5), artificially paced rhythm (n = 13), total or 2:1 second atrioventricular (AV) block (n = 3), and poor recording quality (n = 4), leaving a total of 738 patients with measured ECGs. Two independent observers with no knowledge of the clinical or echocardiographic data performed ECG analysis and measurements. ECG abnormalities were classified according to the modified Minnesota code for Chagas' disease.[19] The presence of supraventricular premature contractions, monomorphic, nonrepetitive, and rare (<10% of all cycles) premature ventricular contractions (PVCs), nonspecific ST-T wave abnormalities, asymptomatic sinus bradycardia, and incomplete intraventricular conduction disturbances were not considered alterations that defined chagasic heart disease.[15] For repolarization parameter measurements, the ECGs were digitized in a flatbed scanner, 100% amplified (corresponding to 50 mm/s paper speed) and manually measured on screen with a commercial image software (resolution 0.25 mm). QRS duration, QT apex (QTa), and total QT intervals were measured in each lead and JT and Tpeak-to-Tend (TpTe) intervals calculated. The end of the T wave was defined as the visual return to the TP baseline; when U waves were present, the QT was measured to the nadir between T and U waves. When the end of the QRS complex was difficult to define, it was considered at the intersection of the S wave with the isoelectric baseline. Whenever the offset of the QRS or T wave could not be identified, the lead was discarded from analysis. The extrasystolic and postextrasystolic cycles were also excluded. The precedent RR interval to the measured cycle was used to calculate the heart rate-corrected QT (QTc) interval using Bazzet's formula.[20] Whenever possible three consecutive cycles were measured and the mean values approximated to the nearest 5 ms. Maximal QTc (QTcmax) and TpTe (TpTemax) intervals were recorded. Interval dispersions were defined for QT (QTd), QTa (QTad), JT (JTd), and TpTe (TpTed) as the difference between maximum and minimum values obtained in any of the 12 leads. QTd was also adjusted to the number of measured leads (adjQTd) according to the formula: $\text{adjQTd} = \text{QTd}/(\text{number of measured leads})^{1/2}$, previously described.[21] No attempt was made to correct any dispersion measurement for heart rate, as it has been consistently showed that QTd is not cycle length dependent.[22] Variation coefficient for each interval (QT-VC, QTa-VC, JT-VC, and TpTe-VC) was calculated according to the formula: $\text{VC} = (\text{SD}/\text{mean}) \times 100$. Forty-five randomly chosen ECGs were analyzed again at least 6 months after the first measurement to assess reproducibility.

Radiological Examination

Chest X rays on posteroanterior and left lateral views with contrasted esophagus were obtained on the same day, and cardiomegaly was defined as a cardiothoracic index > 0.5, properly measured by an independent observer unaware of other patient data.

Echocardiography

Comprehensive two-dimensional echocardiography was performed on all patients within 1 week of first examination by the same observer, without knowledge of clinical or ECG data.

Systolic and diastolic LV dimensions were measured according to the recommendations of the American Society of Echocardiography.[23] Global systolic LV function was evaluated objectively by calculating ejection fraction on M-mode with the Teicholz and Kreulen method[24] and subjectively on two-dimensional echocardiography, being classified as normal, slight, moderate, or severely compromised.[25] Patients considered having moderate or severe LV systolic dysfunction presented an ejection fraction <0.45, besides two-dimensional classification.

Statistical Analysis

All statistics were carried out by using the STATA statistical package. Continuous data were described as means and standard deviations. Reproducibility of repolarization measurements was evaluated by intraclass variation coefficients and by the graphic method of Bland and Altman.[26] Associations between LV systolic dysfunction and other variables, including repolarization parameters, were tested bivariately by nonparametric Mann-Whitney *U* test, chi-square test, or Spearman's rank coefficient of correlation, when appropriated. Individual predictive performance of repolarization parameters for the presence of moderate or severe LV systolic dysfunction was assessed by receiver operating characteristic (ROC) curve analysis, describing areas under curve with their 95% confidence intervals (95% CI) and comparing them to an area of 0.5 under nonparametric assumptions. Finally, a multivariate regressive analysis using logistic models was fitted in a backward stepwise procedure with moderate or severe LV dysfunction as the dependent variable. All clinical, ECG, and radiological variables were submitted to the logistic models. Different models were constructed for all patients and for those with abnormal ECGs, excluding or including those with clinical overt heart failure. Odds ratio (OR) and 95% CI were calculated for each independent predictive variable. The quality of the model fitnesses was evaluated by their sensitivity and specificity using cut values, which maximized them. A two-tailed P value <0.05 was considered statistically significant.

Results

Baseline Characteristics

Table I shows the baseline characteristics of all 738 patients for whom repolarization parameters were obtained, and of subgroups with and without moderate or severe LV systolic dysfunction. As all variation coefficients of ECG intervals were intimately associated with their respective interval dispersions, only the results of QT-VC were presented. Patients with systolic dysfunction had significantly increased repolarization parameters, and a greater prevalence of symptoms, radiological cardiomegaly, and ECG abnormalities.

Reproducibility of Repolarization Parameter Measurements

Intraclass variation coefficient for ECG intervals ranged from 0.75 (for TpTe interval) to 0.99 (for QT and QTa intervals), all statistically significant ($P < 0.001$). For dispersions it varied from 0.75 (for QTd) to 0.84 (for JTd), also statistically significant at $P < 0.001$. Figure 1 shows the graphic method of Bland and Altman applied to intraobserver QTd reproducibility. The mean difference was 1.74 ms (SD 7.39 ms, range −15–5 ms), corresponding to a mean relative error of 11%.

Relation Between Repolarization Parameters and LV Function

Table II shows simple linear correlations between repolarization parameters and echocardiographic measurements of LV function. All parameters were significantly, though modestly, related to echocardiographic variables and stronger associations were found for QTd (and its correlated adjQTd) than for other parameters. Table III shows the areas under ROC curves and their 95% CI of repolarization parameters for prediction of echocardiographic moderate or severe LV systolic dysfunction in all patients and in those with ECG abnormalities. All areas were significantly different ($P < 0.001$) from the diagonal, and greatest for QTd and adjQTd. Figure 2 shows the ROC curves of QTd for prediction of moderate or severe LV dysfunction in both groups. In isolation, a QTd > 60 ms had a sensitivity and specificity of 67% and 89%, respectively, for prediction of moderate or severe LV dysfunction in all patients, and of 67% and 80% in patients with abnormal ECGs, both excluding patients with clinical overt heart failure. For comparison, the presence of cardiomegaly on chest X ray had a sensitivity of 55% and 59% and a specificity of 90% and 89%, respectively, for the same subgroups of patients (thus a slightly better specificity but a worse sensitivity than QTd).

Logistic Regressive Analysis for Prediction of LV Dysfunction

Tables IV and V show the best predictive logistic models for echocardiographically diagnosed LV systolic dysfunction in all subjects and in patients with abnormal ECGs, including or not those with clinical heart failure. All models selected QTd as an independent predictor. Other selected variables were cardiomegaly on chest X ray, frequent PVCs on ECG, male sex, and clinical heart failure in

Table I.

Baseline Characteristics of all Chagas' Disease Patients and Those with and Without Moderate or Severe Left Ventricular Systolic Dysfunction

	All Patients (n = 738)	Patients Without LV Systolic Dysfunction (n = 629)	Patients with LV Systolic Dysfunction (n = 109)
Clinical variables			
Age, years	46.33 (11.65)	45.75 (11.65)	49.71 (11.13)†
Male sex	46.2%	44.4%	56.9%‡
Syncope	3.9%	1.4%	18.3%*
Heart failure	9.8%	1.7%	56.0%*
Thoracic pain	13.4%	11.8%	22.9%†
Palpitation	22.6%	19.6%	40.4%*
Arterial hypertension	23.0%	24.2%	16.5%
Diabetes mellitus	2.4%	2.4%	2.8%
Radiologic variables			
Cardiomegaly	17.2%	9.5%	61.5%*
Electrocardiographic variables			
Abnormal ECG	54.6%	47.2%	97.2%*
Isolated RBBB	14.1%	15.1%	8.3%
Isolated LAFB	3.5%	2.5%	9.2%†
RBBB + LAFB	24.3%	20.0%	48.6%*
LBBB	3.3%	1.6%	12.8%*
EIA	3.7%	1.3%	17.4%*
Ischemia	7.7%	5.1%	22.9%*
PVCs	14.5%	8.7%	47.7%*
Heart rate, beats/min	69.26 (11.92)	68.92 (11.19)	71.20 (15.35)
Echocardiographic variables			
Diastolic LV, mm	52.75 (7.36)	50.56 (4.55)	65.18 (7.91)*
Systolic LV, mm	35.42 (9.78)	32.08 (4.78)	54.37 (9.28)*
LV ejection fraction %	61.09 (14.10)	65.89 (7.68)	33.97 (11.05)*
LV aneurysm	15.0%	8.3%	54.1%*
ECG repolarization parameters			
QTc max, $ms^{-1/2}$	441.54 (37.49)	434.81 (32.32)	480.37 (41.59)*
TpTe max, ms	101.27 (15.00)	99.61 (13.45)	110.83 (19.37)*
QTd, ms	52.23 (17.08)	48.61 (13.09)	73.12 (21.86)*
QT-VC	4.49 (1.24)	4.27 (1.03)	5.76 (1.54)*
adjQTd, ms	16.56 (5.72)	15.30 (4.18)	23.82 (7.68)*
JTd, ms	59.40 (19.89)	56.67 (17.29)	74.54 (26.28)*
QTad, ms	49.28 (20.07)	45.83 (16.27)	69.17 (27.21)*
TpTed, ms	50.76 (14.94)	48.82 (13.45)	61.93 (18.00)*

*$P < 0.001$, †$P < 0.01$, ‡$P < 0.05$ for comparisons between groups with and without LV systolic dysfunction. Values are mean (SD) or frequency percentiles. adjQTd = adjusted QTd; ECG = electrocardiogram; EIA = electrically inactive area; JTd = JT dispersion; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LV = left ventricular; PVC = premature ventricular contraction; QTad = QTa dispersion; QTc_{max} = maximum corrected QT interval; QTd = QT dispersion; QT-VC = QT variation coefficient; RBBB = right bundle branch block; $TpTe_{max}$ = maximum T wave peak-to-end interval; TpTed = T wave peak-to-end interval dispersion.

the analysis where this characteristic was not excluded. The presence of left bundle branch block and electrically inactive areas on the ECG were also selected once. The general sensitivity and specificity of the predictive models ranged from 71 to 85% and 90 to 93%, respectively. No other repolarization parameter could substitute QTd in the models with equivalent performance or add predictive information to the models.

Discussion

The aim of the study was to report ECG ventricular repolarization parameters in patients with chronic Chagas' disease and their association with

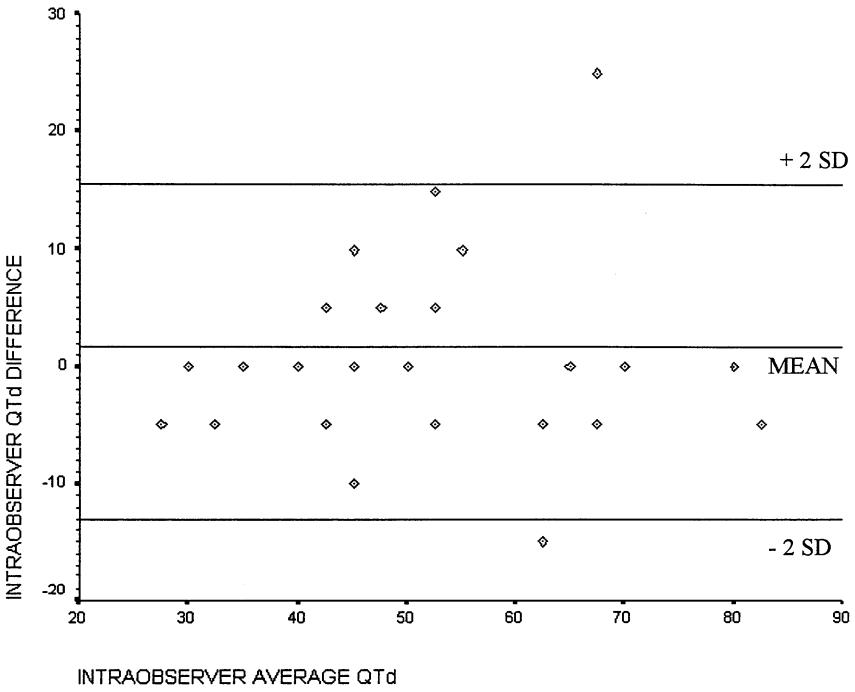


Figure 1. *Graphic method of Bland and Altman for assessing reproducibility of intraobserver QT dispersion measurement.*

LV systolic function. Its main findings were that all repolarization parameters were increased in patients with LV systolic dysfunction, and that QTd was an independent predictor of asymptomatic moderate or severe systolic dysfunction echocardiographically established. The presence of cardiomegaly on chest X ray, frequent PVCs on ECG, and male sex improved LV function stratification in these patients, irrespective of the presence or absence of clinical overt heart failure.

Table II.

Spearman's Rank Coefficient of Correlation Between Repolarization Parameters and Echocardiographic Measurements of Left Ventricular Function

	LVEF	Diastolic LV Diameter	Systolic LV Diameter
QTcmax	−0.33*	0.22*	0.29*
TpTemax	−0.17*	0.15*	0.18*
QTd	−0.34*	0.33*	0.35*
QT-VC	−0.30*	0.26*	0.29*
AdjQTd	−0.37*	0.34*	0.37*
JTd	−0.22*	0.22*	0.22*
QTad	−0.30*	0.33*	0.34*
TpTed	−0.24*	0.21*	0.23*

*$P < 0.001$. AdjQTd = adjusted QTd; JTd = JT dispersion; LV = left ventricular; LVEF = left ventricular ejection fraction; QTad = QTa dispersion; QTcmax = maximum corrected QT interval; QTd = QT dispersion; QT-VC = QT variation coefficient; TpTemax = maximum T wave peak-to-end interval; TpTed = T wave peak-to-end interval dispersion.

It has been consistently demonstrated that, as with other cardiopathies, LV systolic function is the main prognostic factor in Chagas' heart disease,[14–17] emphasizing the importance of its noninvasive stratification. Unfortunately, in most Chagas' disease endemic areas, two-dimensional echocardiographic examination is not available at all, and the prediction of LV dysfunction must rest on clinical, radiological, and ECG grounds, pointing out the relevance of this study's findings.

Although it has been demonstrated that even Chagas' disease patients with normal ECGs can have subtle minor LV wall-motion abnormalities when adequately investigated by echocardiography,[27] radionuclide ventriculography,[28] or angiography,[29] confirming the presence of Chagas' cardiomyopathy; their outcome is identical to nonchagasic individuals, that is, chagasic patients with normal ECGs have an uniformly good prognosis.[2,17,30] In addition, as shown in the patients in the present study, a normal ECG virtually excludes the possibility of moderate or severe LV systolic dysfunction (in fact only three patients had normal ECGs and LV systolic impairment, corresponding to a negative predictive value of 99%).

Table III.

Areas Under ROC Curves of Repolarization Parameters for Prediction of Moderate or Severe LV Systolic Dysfunction

	All Patients (n = 738)		Patients with Abnormal ECGs (n = 408)	
	Area	**95% CI**	**Area**	**95% CI**
QTcmax	0.81	0.76–0.85*	0.72	0.66–0.77*
TpTemax	0.68	0.62–0.73*	0.64	0.58–0.71*
QTd	0.87	0.83–0.91*	0.80	0.75–0.85*
QT-VC	0.80	0.75–0.85*	0.74	0.68–0.80*
AdjQTd	0.89	0.85–0.92*	0.82	0.77–0.87*
JTd	0.73	0.68–0.78*	0.67	0.61–0.72*
QTad	0.78	0.73–0.83*	0.73	0.67–0.79*
TpTed	0.73	0.67–0.78*	0.68	0.63–0.74*

P values refer to comparisons with the null hypothesis that area = 0.5. *P < 0.001. AdjQTd = adjusted QTd; CI = confidence interval; ECG = electrocardiogram; JTd = JT dispersion; LV = left ventricular; QTad = QTa dispersion; QTcmax = maximum corrected QT interval; QTd = QT dispersion; QT-VC = QT variation coefficient; ROC = receiver operating characteristic; TpTemax = maximum T wave peak-to-end interval; TpTed = T wave peak-to-end interval dispersion.

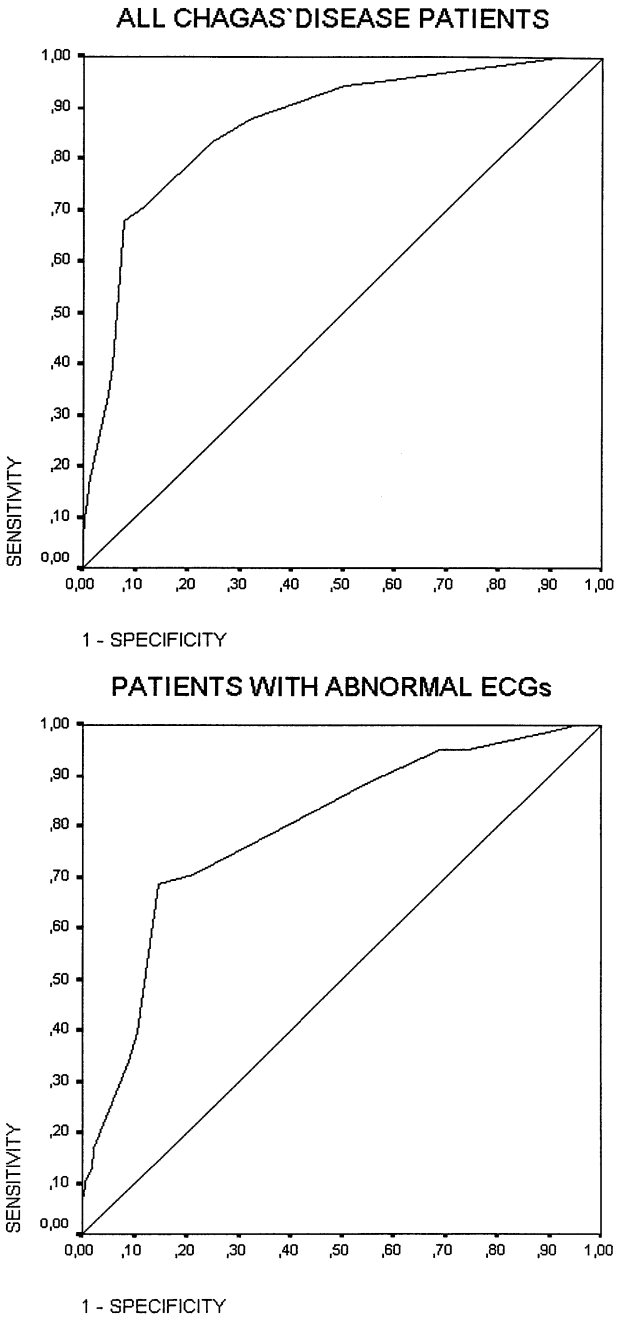


Figure 2. *Receiver operating characteristic curves of QT interval dispersion for prediction of moderate or severe left ventricular systolic dysfunction in all Chagas' disease patients (top) and in those with abnormal electrocardiograms (bottom).*

However, Chagas' disease patients with clinical overt congestive heart failure have the worst prognosis, with survival rates <50% after 3 years.[14,16,17,30] Thus, the subgroup of patients in which it is most relevant to stratify LV systolic function is that with abnormal ECGs and no clinical heart failure. In this particular group, the predictive logistic model, which included the QTd, the presence of cardiomegaly on chest X-ray, PVCs on ECG, and male sex, had a sensitivity of 71% and a specificity of 90%, constituting a relatively simple, noninvasive, inexpensive, and readily available (in endemic areas) way of assessing the possibility of asymptomatic LV dysfunction.

To simplify the clinical use of this predictive model, the authors propose a scoring system based on the logistic regression coefficients, ranging from zero to seven points (Fig. 3). A score greater than three points had the same predictive performance of the logistic model. The area under the score ROC curve for prediction of LV systolic dysfunction was 0.88, therefore showing a good clinical relevance. For practical applications, the authors suggest that all Chagas' disease patients on first medical workup have a complete clinical examination and an ECG. Those with overt decompensated heart failure who have obvious LV dysfunction should be treated accordingly, and those with normal ECGs should be considered without LV systolic impairment and only be followed with annual ECGs. Those patients without clinical decompensated heart failure and with abnormal ECGs should have their QT intervals measured and QTd calculated. If the QTd is ≤60 ms, they should be considered low risk for the presence of moderate or

Table IV.

Logistic Regression Models for Prediction of Moderate or Severe Left Ventricular Systolic Dysfunction in all Chagas' Disease Patients Including or Not Those with Clinical Heart Failure

All Chagas' Disease Patients (n = 738)			Patients Without Clinical Heart Failure (n = 666)		
Variable	**Odds Ratio**	**95% CI**	**Variable**	**Odds Ratio**	**95% CI**
Heart failure (y/n)	29.42	11.66–74.20*	QTd > 60 ms (y/n)	15.47	6.85–34.97*
QTd > 60 ms (y/n)	13.22	6.37–27.42*	Cardiomegaly (y/n)	9.98	4.22–23.60*
Cardiomegaly (y/n)	10.10	4.67–21.84*	Sex (male)	6.86	2.81–16.73*
PVCs (y/n)	5.74	2.56–12.85*	PVCs (y/n)	6.89	2.78–17.11*
Sex (male)	4.91	2.27–10.63*	LBBB (y/n)	4.18	1.04–16.75‡
EIA (y/n)	8.29	2.10–32.69†			
LBBB (y/n)	4.45	1.14–17.44‡			
Sensitivity 85% (cut value: 0.2) Specificity 93%			Sensitivity 85% (cut value: 0.1) Specificity 90%		

y/n means present versus absent. *P < 0.001, †P < 0.01, ‡P < 0.05. EIA = electrically inactive area; LBBB = left bundle branch block; PVC = premature ventricular contraction; QTd = QT dispersion.

severe LV systolic dysfunction and thus be followed semestrally (a QTd $\leq$ 60 ms has a negative predictive value of 94% for detection of LV malfunction). If the QTd is >60 ms, a chest X ray should be performed and the stratification scoring system applied. If the score is greater than three points, the probability of asymptomatic LV systolic impairment is significant and the patient should be treated with an angiotensin-converting enzyme inhibitor and/or a β-blocker, and followed closely. In the patients in the present study, this approach would result in only 20 (2.7%) patients with echocardiographically proven moderate or severe LV systolic dysfunction not receiving treatment, and 22 (3%) patients without LV impairment would be treated unnecessarily. It is clear that these numbers depend on the prevalence of LV dysfunction on the studied population. Although our patients constitute an urban cohort of Chagas' disease, the prevalence of LV systolic impairment (15%) is similar to that reported in endemic areas,[31] suggesting that the current results could be generalized to the entire Chagas' disease population. More studies evaluating QTd in other Chagas' disease cohorts, specially from endemic areas, are needed to confirm the clinical use of this approach.

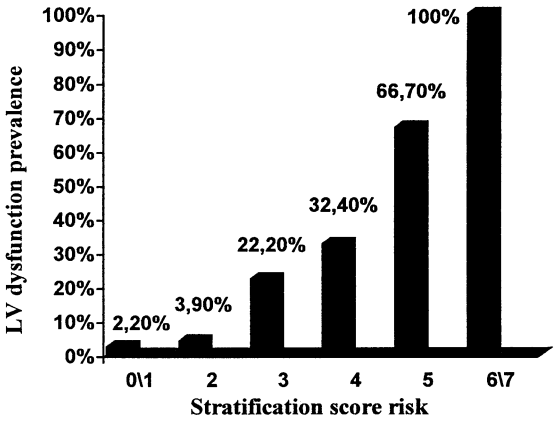
Table V.

Logistic Regression Models for Prediction of Moderate or Severe Left Ventricular Systolic Dysfunction in Chagas' Disease Patients with Abnormal ECGs Including or not Those with Clinical Heart Failure

All Patients With Abnormal ECGs (n = 403)			Patients with Abnormal ECGs and Without Clinical Heart Failure (n = 333)		
Variable	**Odds Ratio**	**95% CI**	**Variable**	**Odds Ratio**	**95% CI**
Heart failure (y/n)	25.87	9.78–68.42*	Cardiomegaly (y/n)	14.06	5.54–35.71*
Cardiomegaly (y/n)	12.42	5.49–28.12*	QTd > 60 ms (y/n)	9.35	4.01–21.81*
QTd > 60 ms (y/n)	7.97	3.78–16.81*	Gender (male)	7.70	2.98–19.91*
Sex (male)	5.47	2.41–12.42*	PVCs (y/n)	4.06	1.65–9.97†
PVCs (y/n)	3.53	1.59–7.83†			
EIA (y/n)	4.15	1.13–15.22‡			
Sensitivity 84% (cut value: 0.3) Specificity 91%			Sensitivity 71% (cut value: 0.25) Specificity 90%		

*P < 0.001, †P < 0.01, ‡P < 0.05. CI = confidence interval; ECG = electrocardiogram; EIA = electrically inactive area; PVC = premature ventricular contraction; QTd = QT dispersion.

		SCORE
QTd > 60ms	Absent	0
	present	2
Cardiomegaly	absent	0
	present	2
Gender	female	0
	male	2
Frequent PVCs	absent	0
	present	1



Number of Patients	117	127	27	37	15	10
%	35.1	38.1	8.1	11.1	4.5	3.1

Figure 3. *Simple scoring system for risk stratification of left ventricular systolic dysfunction in Chagas' disease patients with abnormal electrocardiograms and no overt heart failure (top) and the prevalence of left ventricular dysfunction for each summed score point (bottom).*

Although it has been recognized that QTd is increased in heart failure and LV dysfunction of various etiologies,[7,8] few studies reported direct relations between ventricular repolarization dispersion measurements and LV systolic function[5,7,32,33] or extension of damaged myocardium,[6] as found in the present study. This aspect should raise some conjectures. First, the mechanical overload associated with LV systolic dysfunction can alter myocardial electrophysiological properties and increase repolarization abnormalities and inhomogeneity.[34,35] Second, it has been demonstrated that in Chagas' disease patients, a greater prevalence of several ECG abnormalities, like PVCs, complete bundle branch blocks, electrically inactive areas, atrial fibrillation and total AV block implied a greater extension of compromised myocardium and hence worse LV systolic function.[36,37] So, it is reasonable to speculate that greater global ventricular repolarization abnormalities, reflected by increased ECG parameters of repolarization as suggested by Kors et al.,[38] can parallel greater ECG alterations and thus LV dysfunction. Finally, ECG ventricular repolarization parameters can follow the development and progression of cardiac autonomic dysfunction, as demonstrated in primary[39] or diabetic[40] dysautonomia. Chagas' disease patients have long been considered natural models for studying cardiac autonomic function,[41] since their autonomic impairments are generally precocious and parallel the progression of myocarditis and hence of ventricular damage and dysfunction.[42] This point needs to be addressed in future studies involving Chagas' disease and ventricular repolarization measurements.

In this study several ECG ventricular repolarization parameters were measured and all showed associations with echocardiographic measurements of LV function. Meanwhile, QTd and its correlated adjQTd and QT-VC showed the best predictive performance. So the authors do not recommend using ventricular repolarization parameters in Chagas' disease other than QTd for LV function stratification. Calculating QT-VC and adjusting QTd to the number of measured leads also did not improve QTd predictive performance, so the authors suggest that they should not be used as well. The maximum Tpeak-to-Tend (TpTe max) interval has been reported recently as a new indicator of transmural dispersion of repolarization,[43] and confirmed in a clinical report as a potential marker of arrhythmogenicity risk.[44] In this study this interval showed a predictive performance for LV dysfunction worse than that of QTd and maximum QTc interval in chagasic patients with abnormal ECGs. Further prospective, long-term follow-up studies are needed to determine if it will become a predictor of arrhythmic events and sudden death in Chagas' disease.

Study Limitations

The main limitation of the present study is its cross-sectional design with its well-known drawbacks, like the survival effect, for instance. The most serious patients with greater myocardium damage and worse LV function possibly did not survive long enough to be included. So, the present findings may not be applied to this particular subgroup of seriously ill, generally in-hospital, chagasic patients. In addition, the proposed

approach to stratify the risk of asymptomatic LV systolic impairment could not be applied to those patients that present with conditions that preclude the measurement of QTd, like atrial fibrillation, artificially paced rhythm, advanced AV block, or in those ECGs in which the QT interval in at least eight leads (including four precordial ones) could not be measured. In the present study these patients correspond to nearly 10% of the whole group of patients. Another limitation is inherent to repolarization parameter measurements with its known lack of standardization and poor reproducibility. The intraobserver reproducibility is similar to the best-reported indexes,[12] and surely did not affect the results.

Conclusions

The present study demonstrated that ECG ventricular repolarization parameters were associated with LV systolic function in patients in chronic phase of Chagas' disease and that QTd could be used to predict asymptomatic LV dysfunction in these patients. The data also showed that QTd was an independent predictor for moderate or severe LV systolic dysfunction in all subgroups of Chagas' disease patients investigated, and that the presence of cardiomegaly on chest X ray, frequent PVCs on the ECG, and male sex refined LV function stratification. A scoring system was proposed based on these findings to simplify LV systolic dysfunction prediction. Hence, ECG ventricular repolarization parameters, and QTd in particular, could constitute potential prognostic factors in chronic Chagas' disease and this must be addressed in future prospective long-term follow-up studies.

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References

1. Hagar JM, Rahimtoola SH. Chagas' heart disease. Curr Prob Cardiol 1995; 20:827–924.
2. Maguire JH, Hoff R, Sherlock I, et al. Cardiac morbidity and mortality due to Chagas' disease: Prospective electrocardiographic study of a Brazilian community. Circulation 1987; 75:1140–1145.
3. Day CP, McComb JM, Campbell RWF. QT dispersion: An indication of arrhythmia risk in patients with long QT intervals. Br Heart J 1990; 63:342–344.
4. Priori SG, Napolitano C, Diehl L, et al. Dispersion of QT interval: A marker of therapeutic efficacy in the idiopathic long QT syndrome. Circulation 1994; 89:1681–1689.
5. Puljevic D, Smalcelj A, Durakovic Z, et al. Effects of postmyocardial infarction scar size, cardiac function and severity of coronary artery disease on QT interval dispersion as a risk factor for complex ventricular arrhythmias. PACE 1998; 21:1508–1516.
6. Schneider CA, Voth E, Baer FM, et al. QT dispersion is determined by the extent of viable myocardium in patients with chronic Q-wave myocardial infarction. Circulation 1997; 96:3913–3920.
7. Fu GS, Meissner A, Simon R. Repolarization dispersion and sudden cardiac death in patients with impaired left ventricular function. Eur Heart J 1997; 18:281–289.
8. Brendorp B, Elming H, Jun L, et al. QT dispersion has no prognostic information for patients with advanced congestive heart failure and reduced left ventricular systolic function. Circulation 2001; 103:831–835.
9. Turrini P, Corrado D, Basso C, et al. Dispersion of ventricular depolarization-repolarization: A noninvasive marker for risk stratification in arrhythmogenic right ventricular cardiomyopathy. Circulation 2001; 103:3075–3080.
10. Cardoso C, Salles G, Bloch K, et al. Clinical determinants of increased QT dispersion in patients with diabetes mellitus. Int J Cardiol 2001; 79:253–262.
11. Okin PM, Devereux RB, Howard BV, et al. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians. The Strong Heart Study. Circulation 2000; 101:61–66.
12. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000; 36:1749–1766.
13. Marin-Neto JA, Simões MV, Sarabanda AVL. Chagasic cardiopathy. Arq Bras Cardiol 1999; 72:247–263.
14. Mady C, Cardoso RHA, Barretto ACP, et al. Survival and predictors of survival in patients with congestive heart failure due to Chagas' cardiomyopathy. Circulation 1994; 90:3098–3102.
15. Carrasco HA, Parada H, Guerrero L, et al. Prognostic implications of clinical, electrocardiographic and hemodynamic findings in chronic Chagas' disease. Int J Cardiol 1994; 43:27–38.
16. Hagar JM, Rahimtoola SH. Chagas' heart disease in the United States. N Engl J Med 1991; 325:763–768.
17. Acquatella H, Catalioti F, Gomez-Mancebo JR, et al. Long-term control of Chagas' disease in Venezuela: Effects on serologic findings, electrocardiographic abnormalities and clinical outcome. Circulation 1987; 76:556–562.
18. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure, the Framingham study. N Engl J Med 1971; 285:1441–1449.
19. Maguire JH, Mott KE, Souza JAA, et al. Electrocardiographic classification and abbreviated lead system for population-based studies of Chagas' disease. Bull Pan Am Health Organ 1982; 16:47–58.
20. Bazzet HD. An analysis of the time relations of electrocardiograms. Heart 1920; 7:353–370.
21. Day CP, McComb JM, Matthews J, et al. Reduction in QT dispersion by sotalol following myocardial infarction. Eur Heart J 1991; 12:423–427.
22. Zabel M, Franz MR, Klingenheben T, et al. Rate-dependence of QT dispersion and the QT interval: Comparison of atrial pacing and exercise testing. J Am Coll Cardiol 2000; 36:1654–1658.
23. Sahn DJ, DeMaria A, Kisslo J, et al. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978; 58:1072–1083.
24. Teicholz LE, Kreulen T. Problems in echocardiographic volume determinations: Echocardiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976; 37:7–11.
25. Amico AF, Lichtenberg GS, Reisner SA, et al. Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction. Am Heart J 1989; 118:1259–1265.
26. Bland JM, Altman DG. Statistical methods for assessing agreements between two methods of clinical measurement. Lancet 1986; 1:307–310.
27. Acquatella H, Schiller NB, Puigbó JJ, et al. M-mode and two-dimensional echocardiography in chronic Chagas' heart disease. Circulation 1980; 62:787–798.
28. Marin-Neto JA, Marzullo P, Souza ACS, et al. Radionuclide angiographic evidence of early predominant right ventricular involvement in patients with Chagas' disease. Can J Cardiol 1988; 4:231–236.
29. Carrasco HA, Barboza JS, Inglessis G, et al. Left ventricular cineangiography in Chagas' disease: Detection of early myocardial damage. Am Heart J 1982; 104:595–602.
30. Espinoza RA, Pericchi LR, Carrasco HA, et al. Prognostic indicators of chronic chagasic cardiomyopathy. Int J Cardiol 1991; 30:195–202.
31. Borges-Pereira J, Xavier SS, Pirmez C, et al. Chagas' disease in Virgem da Lapa County, Minas Gerais State, Brazil. IV. Clinical and epidemiological aspects of the left ventricle aneurysm. Rev Soc Bras Med Trop 1998; 31:457–463.

32. Pye M, Quinn AC, Cobbe SM. QT interval dispersion: A noninvasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? Br Heart J 1994; 71:511–514.
33. Bonnar CE, Davie AP, Caruana L, et al. QT dispersion in patients with chronic heart failure: β Blockers are associated with a reduction in QT dispersion. Heart 1999; 81:297–302.
34. Dean JW, Lab MJ. Arrhythmia in heart failure: Role of mechanically induced changes in electrophysiology. Lancet 1989; 10:1309–1311.
35. James PR, Hardman SM, Taggart P. Physiological changes in ventricular filling alter cardiac electrophysiology in patients with abnormal ventricular function. Heart 2002; 88:149–152.
36. Casado J, Davila DF, Donis JH, et al. Electrocardiographic abnormalities and left ventricular systolic function in Chagas' heart disease. Int J Cardiol 1990; 27:55–62.
37. Garzon SAC, Lorga AM, Nicolau JC. Electrocardiography in Chagas' heart disease. São Paulo Med J 1995; 113:802–813.
38. Kors JA, van Herpen G, van Bemmel JH. QT dispersion as an attribute of T-loop morphology. Circulation 1999; 99:1458–1463.
39. Choy AMJ, Lang CC, Roden DM, et al. Abnormalities of the QT interval in primary disorders of autonomic failure. Am Heart J 1998; 136:664–671.
40. Wei K, Dorian P, Newman D, et al. Association between QT dispersion and autonomic dysfunction in patients with diabetes mellitus. J Am Coll Cardiol 1995; 26:859–863.
41. Amorim DS, Manço JC, Gallo L Jr, et al. Chagas' heart disease as an experimental model for studies of cardiac autonomic function in man. Mayo Clin Proc 1982; 57:48–60.
42. Simões MV, Pintya AO, Bromberg-Marin G, et al. Relation of regional sympathetic denervation and myocardial perfusion disturbance to wall motion impairment in Chagas' cardiomyopathy. Am J Cardiol 2000; 86:975–981.
43. Antzelevitch C, Shimizu W, Yan GX, et al. The M cell: Its contribution to the ECG and to normal and abnormal electrical function of the heart. J Cardiovasc Electrophysiol 1999; 10:1124–1152.
44. Lubinski A, Kornacewicz-Jach Z, Wnuk-Wojnar AM, et al. The terminal portion of the T wave: A new electrocardiographic marker of risk of ventricular arrhythmias. PACE 2000; 23: 1957–1959.