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Usefulness of microvolt T-wave alternans for predicting outcome in patients with Chagas disease with implantable cardioverter defibrillators☆

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ABSTRACT

Background: Chagas disease (ChD) may lead to life-threatening heart disease, including malignant ventricular arrhythmias. The use of implantable cardioverter defibrillators (ICDs) has become the main therapeutic strategy for secondary prevention of SCD in Chagas disease (ChD). Microvolt T-wave alternans (MTWA) is a direct measure of ventricular repolarization instability and has emerged as a potentially useful way of determining arrhythmia vulnerability. However, this methodology has not been evaluated in patients with ChD.
Objective: To evaluate the predictive value of MTWA testing for appropriate therapy or death in ChD patients with ICDs.
Methods: This prospective study included consecutive patients who received ICD implantations in a Brazilian tertiary referral center.
Results: Seventy-two patients were followed for a median time of 422 (range 294–642) days. Thirty-three patients had ChD. The MTWA was non-negative (positive or indeterminate) in 27 (81.8%) of ChD patients. The combined primary outcome (appropriate ICD therapy or death) occurred in 29 patients (40.3%); 17 out 33 ChD patients presented the primary outcome. There was a statistically significant difference in event-free survival between ChD patients with negative and non-negative MTWA results ($p = 0.02$). Non-negative MTWA tests nearly triple the risk of appropriate ICD therapy or death (HR = 2.7, 95% CI: 1.7–4.4, $p = 0.01$) in patients with ChD and was the only variable associated with outcomes. The sensitivity and the negative predictive value was 100% in ChD patients.
Conclusions: MTWA may be useful in recognizing high-risk ICD patients who may require adjunctive therapies with antiarrhythmic drugs or catheter ablation.

1. Introduction

Chagas disease (ChD) is caused by the protozoan *Trypanosoma cruzi* and was discovered and described by the Brazilian physician Carlos Chagas in 1909 [1]. It remains a serious public health problem in the Americas and affects about 10 million people in Latin America, four million of which are Brazilians [2]. Sudden cardiac death (SCD) is a typical evolution of ChD and accounts for the death of more than 50% of ChD patients [3], with reports since the first described cases [1].

The use of ICDs has become the main therapeutic strategy for preventing sudden death [4]. Considering that malignant ventricular arrhythmias are more frequent in patients with ChD than other heart diseases, and SCD is frequently observed in these patients [5], this cardiomyopathy is now an emerging indication for ICD implantation.

The ACC/AHA/HRS 2012 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities recommends ICD implantation in ChD patients for primary and secondary prevention of SCD [6]. There is no information on the effectiveness of ICD implantation for primary prevention of SCD in ChD patients without malignant ventricular arrhythmia. A clinical trial has been designed to address this issue [7]. Although high cost and clinical uncertainties limit the routine use of ICDs for primary prevention of SCD in most Latin American countries, current

Glossary of abbreviations: AF, atrial fibrillation; ATP, antitachycardia pacing; ChD, Chagas disease; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MTWA, microvolt T-wave alternans; NPV, negative predictive value; PPV, positive predictive value; NYHA, New York Heart Association; SCD, sudden cardiac death; VT, ventricular tachycardia.

☆ DisclosureThe authors declare no conflicts of interest and that the study was conducted in accordance with current ethical standards.

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evidence supports its use for secondary prevention in patients with ChD [8].

A recent report from the National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop addressing Sudden Cardiac Death Prediction and Prevention emphasizes the need to find other risk markers for SCD aside from left ventricular ejection fraction (LVEF), which could be applied to the large group of patients currently eligible for ICD therapy. This would refine prediction of SCD risk and improve ICD allocation [9].

MTWA is a direct measure of ventricular repolarization instability and identifies a particular arrhythmogenic substrate [10]. There is evidence that MTWA testing may effectively risk-stratify patients at risk for arrhythmias. A recent meta-analysis of MTWA showed that patients who did not test negative for MTWA had more than a threefold risk of arrhythmic events [11], and that non-negative MTWA results predict shocks or arrhythmia in patients with ICDs [11]. Moreover, in patients with a negative test, the likelihood of arrhythmic death or of an appropriate ICD discharge is markedly reduced [12]. This has led to the hypothesis that MTWA can be used to identify patients most likely to benefit from ICD implantation. However, the value of MTWA for risk stratification has not yet been evaluated in ChD patients. A previous study from our group showed that ChD is associated with a higher frequency of abnormal MTWA tests, even in the absence of left ventricular dysfunction [12]. Accordingly, the present study was designed to prospectively test the hypothesis that MTWA is a clinically important risk stratifier for secondary prevention of SCD in ChD patients with an indication for ICD implantation.

The primary objective of this study was to determine whether MTWA predicts appropriate therapy or death in ChD patients with ICDs. The secondary objectives were to compare ChD and non-ChD patients in order to assess the association between MTWA results and appropriate therapy or death, and to evaluate the performance of the MTWA test (sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios) in patients with ChD.

2. Methods

2.1. Patient population

This is a prospective cohort of all patients, with or without ChD, who received ICD implantation for secondary prevention of SCD in a Reference Center at the Hospital das Clínicas of Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, from March 2011 until April 2013. Data from complementary tests such as electrocardiography, echocardiography, Holter monitoring and invasive electrophysiological testing were collected if available. The diagnosis of Chagas disease was confirmed by ≥2 different positive reactions against *T. cruzi*. All patients were referred for ICD implantation for secondary prevention of SCD, according to the guidelines for ICD implantation defined by the Brazilian Ministry of Health [13].

As MTWA can only be measured during a regular atrial rhythm, patients with persistent atrial fibrillation or flutter, or who required ventricular pacing at the time of MTWA testing, were excluded. Patients with NYHA class IV heart failure, or who were unable to exercise on a treadmill, were also excluded from the study.

All patients received chronic optimal medical therapy.

2.2. Study protocol

The investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki and the study protocol was approved by the Research Ethics Board of Universidade Federal de Minas Gerais. All patients provided written informed consent. Patients referred to the Pacemaker Clinic of the Hospital das Clínicas of Universidade Federal de Minas Gerais for ICD implantation were submitted to MTWA testing, and underwent submaximal treadmill exercise to achieve a heart rate of 120 bpm for at least 2 min while receiving their usual medication, including beta blockers and amiodarone [14]. MTWA was measured with the CH2000 system (Cambridge Heart, Inc., Bedford, MA), utilizing a spectral method of analysis (D10 algorithm) designed to enable the detection of alternans in the microvolt range.

MTWA was defined as positive when it was sustained for at least 1 min with an onset heart rate < 110 bpm, amplitude ≥ 1.9 μV, and alternans ratio (signal-to-noise ratio) ≥ 3 in the vector magnitude lead, any orthogonal lead or two consecutive precordial leads (MTWA+). MTWA was defined as negative if the criteria for a positive test were not met, if there was no significant alternans for 1 min while the heart rate was ≥105 bpm, and if the tracing was not obscured by noise and had <10% ectopic beats (MTWA−). When an indeterminate result was obtained, the test was repeated by the investigators [14]. In accordance with common practice, the protocol specified combining positive and indeterminate tests into a single MTWA− "non-negative" group, which was compared with MTWA negatives [15].

The surgical techniques used for device implantation were similar to those previously reported [16]. The follow-up was based on programmed control visits for the evaluation of patients' clinical conditions and device interrogation, and on hospital admissions due to the incidence of device interventions or any acute cardiac illness. Patient outcomes were assessed at three, six, 12, 18, 24 and 30 months after implantation at the Pacemaker Clinic and, when necessary, by telephone interview or chart review.

The events recorded and stored in the ICDs were retrieved as intracardiac electrograms, including marker channel annotations, and were analyzed by three experienced cardiologists with expertise in cardiac arrhythmia. Device programming was standardized [19].

The primary composite endpoint was all-cause mortality or appropriate ICD therapy.

Appropriate therapy, defined as the incidence of appropriate shock or antitachycardia pacing (ATP), was triggered by potentially lethal ventricular arrhythmias: ventricular tachycardia (VT) or ventricular fibrillation (VF) detected by the ICDs [17].

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation or as median and interquartile range (interquartile range, from Q1 to Q3), whereas qualitative variables were described as absolute number and frequency.

Appropriate tests were applied for comparing proportions (Fisher's exact test or chi-square test), means (*t*-test) or medians (Kruskal–Wallis test). Survival curves were plotted using the Kaplan–Meier method and the rates of event-free survival and mortality were compared using the log-rank test (Mantel–Cox test). The predictive value of MTWA test and other variables was tested using Cox survival analysis. These variables included age, gender, medication (beta blockers, amiodarone and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), etiology of heart disease, LVEF (as a continuous variable, dichotomized as either < or ≥30%, or < or ≥40%), NYHA functional classification, QRS duration >120 ms, nonsustained VT on 24-hour Holter monitoring and inducibility of monomorphic VT with programmed ventricular stimulation. All statistical tests were two-sided and used an alpha level of 0.05 to reject the null hypothesis.

The sample size required for this study was calculated as follows, using the Power and Sample Size Calculations software [18]. It was assumed that 70% of the enrolled patients would have non-negative MTWA results and that the combined event rate (death or appropriate therapy) would be 50% [5]. Given these assumptions, 32 ChD patients with interpretable ICD records were required in order to achieve 90% power and a type I error rate of 0.05.

3. Results

3.1. Baseline features

The study population consisted of 72 patients, 46 men (63.9%) and 26 women (36.1%), aged between 28 and 84 years (median: 61 years). Of these, 33 (45.8%) patients had ChD and the remaining 39 subjects (non-ChD patients) had been diagnosed with ischemic cardiomyopathy ($n = 15$; 20.8%), nonischemic dilated cardiomyopathy ($n = 9$; 12.5%) or other cardiomyopathies ($n = 15$; 20.8%). Amiodarone and beta blockers were frequently used, especially after the implantation (Table 1).

Concerning indications for ICD implantation, 43 patients (59.7%) had a history of at least one episode of spontaneous VT and 25 (34.7%) had been resuscitated from sudden death. Four (5.6%) underwent ICD implantation because they had suffered syncope and VT was induced during an electrophysiology study. The MTWA test was negative in 29 (40.3%), positive in six patients (8.3%) and indeterminate in 37 (51.4%), totaling 43 (59.7%) non-negative tests. Indeterminate results were due to the inability to achieve the target heart rate of >105 bpm (52.8%), unsustained MTWA (36.1%), rapid increase in heart rate (5.6%) and frequent ectopic beats (5.6%). No indeterminate test was due to noisy recording. We observed that patients with ChD tested non-negative for MTWA ($n = 27$) at a higher rate than those without ChD (81.8% versus 41.0%, $p = 0.001$).

The MTWA-non-negative and negative patients were comparable with respect to age, LVEF, NYHA functional classification, and standard cardiac medication, except for the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (93% versus 72.4%, $p = 0.02$). The MTWA-non-negative group had a lower proportion of males (48.8% versus 86.2%, $p = 0.001$).

Table 1
Comparison of baseline demographic, clinical, electrocardiographic and echocardiographic characteristics between patients with and without Chagas disease undergoing implantable cardioverter defibrillator implantation at the HC-UFMG, between March 2011 and April 2013.

	Overall cohort $n = 72$	Chagas disease $n = 33$	Non-Chagas disease $n = 39$	p-Value
Age (years)	61 (51–69)	63 (57–70)	57 (47–66)	**0.017**
Male gender (n/%)	46 (63.9)	13 (39.4)	33 (84.6)	**0.001**
Use of beta blockers (n/%)	62 (86.1)	29 (87.9)	33 (84.6)	0.750
Use of ACEI or ARB (n/%)	61 (84.7)	30 (90.9)	31 (79.5)	0.210
Use of amiodarone (n/%)	60 (83.3)	27 (81.8)	33 (84.6)	0.760
NYHA II–III (n/%)	42 (58.3)	25 (75.7)	17 (43.6)	**0.020**
QRS > 120 ms	27 (37.5)	17 (51.5)	10 (25.6)	**0.030**
RBBB (n/%)	18 (25.0)	13 (39.4)	5 (12.8)	**0.020**
LBBB (n/%)	11 (15.3)	6 (18.2)	5 (12.8)	**0.020**
LVEF (%)	39 (30–50)	38 (28–47)	40 (34–55)	0.140
Non-negative MTWA	43 (59.7)	27 (81.8)	16 (41.0)	**0.001**
Follow-up time in days	422 (294–642)	524 (271–763)	394 (294–532)	**0.040**

Data are numbers (percentages) or medians (Q_1–Q_3).
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; HC-UFMG = Hospital das Clínicas, Universidade Federal de Minas Gerais; NYHA = New York Heart Association; RBBB = right bundle branch block; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; and MTWA = microvolt T-wave alternans.

3.2. Follow-up

All patients attended the follow-up, which had a median duration of 421 (range 294–642) days. Perioperative complications were observed in four patients (5.6%); three with hematomas and one with an incision infection, which was successfully treated with oral antibiotics. During the follow-up period, four (5.6%) patients died, three with ChD and one without ChD (9.1% versus 2.6%, $p = 0.33$). In the non-ChD group, death was associated with heart failure. In ChD patients, one patient suffered sudden cardiac death and two died of non-cardiac causes.

The combined primary outcome (appropriate ICD therapy or death) occurred in 29 patients (40.3%); 17 out 33 ChD patients presented the primary outcome. Event-free survival rates with respect to MTWA results were calculated by the Kaplan–Meier method during follow-up and are shown in Fig. 1. Patients with a negative MTWA test experienced fewer events. The median event-free survival period was 750 days (95% CI: 601–899) for MTWA-negative and 498 days (95% CI: 408–589) for MTWA-non-negative patients ($p = 0.08$) in the overall cohort. In the ChD group (Fig. 2), the median event-free survival period was 509 (±165) days for MTWA-negative and 365 (±132) days for MTWA-non-negative patients ($p = 0.02$). No statistically significant difference was observed in event-free survival between MTWA-negative and non-negative patients in the non-ChD group (Fig. 3, $p = 0.34$). In this study, there was no relationship between use of medication and the outcome of MTWA testing. No significant association was found between MTWA predictions and QRS > 120 ms or LVEF <30% or <40%.

3.3. Predictors of events

Univariate analysis showed that none of the candidate variables were associated with the incidence of appropriate therapy or with event-free survival (appropriate therapy or death), although there is a trend for ChD (HR 1.7, 95% CI: 0.9–3.0, $p = 0.07$). There was a tendency toward the prediction of events for the ChD group. The only variable associated with the outcomes was the non-negative MTWA result. The MTWA hazard ratio for event-free survival was 1.6 (95% CI: 1.1–2.2; $p = 0.02$) for the overall cohort and 2.7 (95% CI: 1.7–4.4; $p = 0.01$) for ChD patients (Table 2).

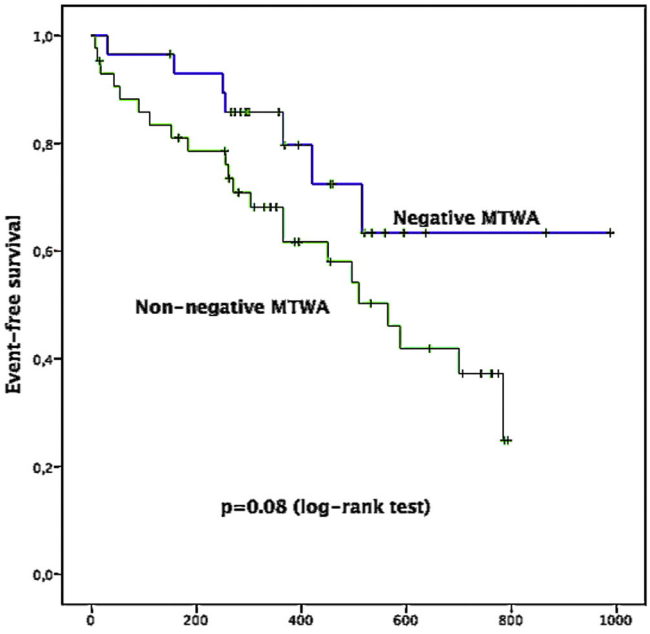

Fig. 1. Time to first event (appropriate therapy or death) in days.

3.4. Test performance

Summary estimates of sensitivity, specificity, positive predictive value, negative predictive values, positive likelihood ratio and negative likelihood ratio are detailed in Table 3. The sensitivity and the negative predictive value for the prediction of events was 100% in ChD patients.

4. Discussion

Given the challenge of risk stratification for life-threatening arrhythmic events that faces today's cardiologists and the economic

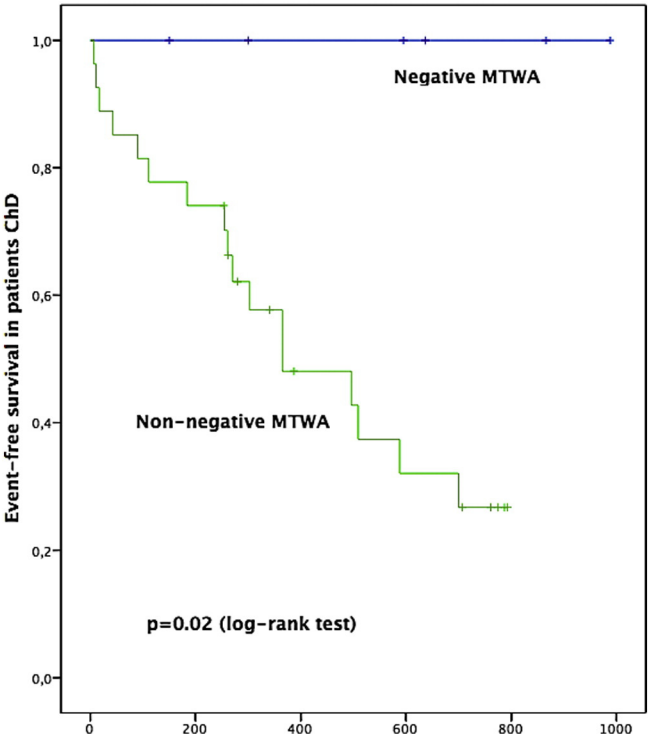

Fig. 2. Time to first event (appropriate therapy or death) in days.

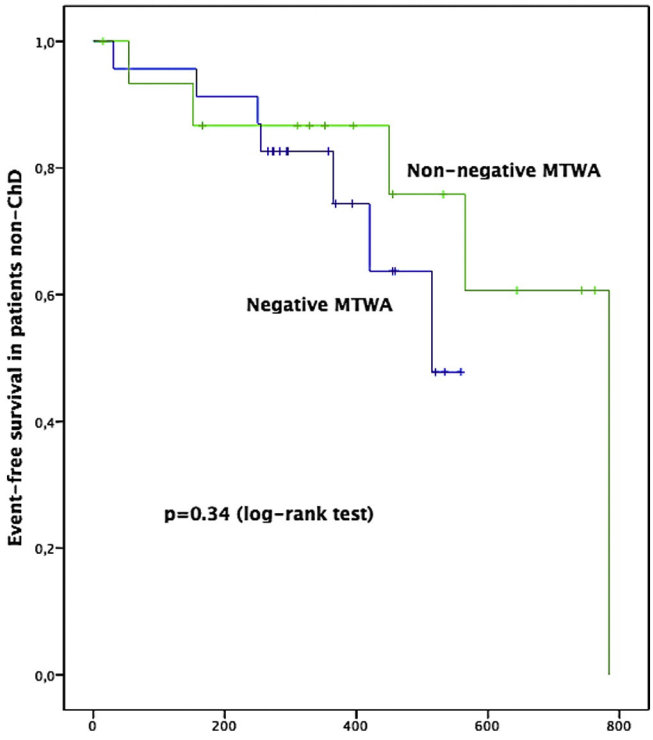

Fig. 3. Time to first event (appropriate therapy or death) in days.

implications for today's society, our study provides information on the value of MTWA testing in ChD patients with ICDs. MTWA was independently associated with the risk of appropriate therapy or death in ChD. Specifically, the event rate was significantly lower in the MTWA-negative than in the MTWA-non-negative group. Additionally, Kaplan–Meier analysis showed differences between curves for MTWA-negative and non-negative groups at any time during the follow-up. Our findings confirm a high negative predictive value of MTWA tests in a population that had never been previously studied.

ChD is a potentially lethal disease in which SCD is a major complication and most deaths are due to malignant ventricular arrhythmia [1,3].

Table 2
Predictors of the combined outcome (appropriate therapy or death), in univariate analysis in 33 Chagas disease patients undergoing implantable cardioverter defibrillator implantation at the HC-UFMG between March 2011 and April 2013.

	Appropriate therapy or death $n = 17$	Without appropriate therapy or death $n = 16$	Hazard ratio (CI 95%)
Age (years)	63 (55–71.5)	65.5 (57–70)	1.0 (0.9–1.0)
Male gender (*n*/%)	5 (29.4)	8 (50)	1.6 (0.7–3.4)
Chagas disease (*n*/%)	17 (58.6)	16 (37.2)	1.7 (0.9–3.0)
NYHA I–II (*n*/%)	15 (88.2)	14 (87.5)	1.0 (0.3–2.7)
NYHA III (*n*/%)	2 (11.8)	2 (12.5)	1.0 (0.4–2.9)
Beta blockers (*n*/%)	15 (88.2)	14 (87.5)	1.1 (0.3–2.7)
Amiodarone (*n*/%)	14 (82.4)	13 (81.2)	1.0 (0.4–2.3)
ACEI or ARB (*n*/%)	16 (94.1)	14 (87.5)	0.8 (0.6–3.2)
QRS > 120 ms (*n*/%)	9 (52.9)	8 (50)	1.0 (0.5–1.8)
LVEF (%)	38 (31–45)	36 (27–53)	0.9 (0.9–1.0)
LVEF ≤40% (*n*/%)	12 (70.6)	9 (56.2)	0.7 (0.4.1.6)
LVEF ≤30% (*n*/%)	4 (23.5)	7 (43.8)	1.0 (0.7–3.8)
Non-negative MTWA (*n*/%)	17 (100)	10 (62.5)	2.7 (1.7–4.4)
Follow-up time in days	502 (237–732)	616 (307–784)	

Data are numbers (percentages) or medians (Q_1–Q_3).
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CI = confidence interval; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; HC-UFMG = Hospital das Clínicas, Universidade Federal de Minas Gerais; MTWA = microvolt T-wave alternans.

Table 3
Microvolt T-wave alternans test performance.

	Overall cohort	ChD	Non-ChD
SE (%)	75.9 (CI:60.3–91.4)	100 (CI: 100–100)	41.7 (CI: 13.8–69.6)
SP (%)	51.2 (CI: 36.2–66.1)	37.5 (CI: 13.8–61.2)	59.3 (CI: 40.7–77.8)
PPV (%)	51.2 (CI: 36.2–66.1)	63 (CI: 44.7–81.2)	31.3 (CI: 8.5–54)
NPV (%)	75.9 (CI: 60.3–91.4)	100 (CI: 100–100)	69.6 (CI: 50.8–88.4)
LR+	1.5 (1.1–2.2)	1.6 (1.1–2.3)	1.0 (0.5–2.3)
LR−	0.5 (0.2–1.0)	0	1.0 (0.5–1.7)

CI = confidence interval; ChD = Chagas disease; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value; Non-ChD = non-Chagas disease; SE = sensitivity; SP = specificity.

We found that MTWA was associated with the risk of appropriate ICD therapy or death, a finding that may contribute to a better understanding of the mechanisms causing SCD in ChD and may improve risk stratification in this patient population.

The magnitude of repolarization instability, manifested by MTWA and beat-to-beat oscillations of T-wave amplitudes at other frequencies, increased before the onset of ventricular arrhythmias [19]. MTWA is a direct measure of ventricular repolarization instability and identifies a particular arrhythmogenic substrate in which hemodynamically well tolerated VT may degenerate into terminal VF [10].

Our results corroborate previous studies demonstrating that repolarization abnormalities are common and may have clinical and prognostic significance in ChD. T-wave axis deviation [20], increased QT interval dispersion or duration [21], T-wave amplitude variability [22] and spatial repolarization heterogeneity [23] were identified as independent predictors of mortality in chronic ChD patients.

The high prevalence of non-negative MTWA tests in ChD patients in our study could indeed reflect the proarrhythmic role of the two main characteristics of this cardiomyopathy. First are the alterations in the electrophysiological substrate, where multiple re-entry circuits affect fibrotic areas or aneurysms in the left ventricle [24]. The second is the presence of alterations of autonomic control mechanisms that may further alter cardiac electrical properties [25]. Indeed, the electrophysiological alterations that may account for increased MTWA in ChD patients are likely to reflect the presence of extensive myocardial fibrosis, a well-known manifestation of the disease as a result of focal myocarditis [26]. The loss of cardiomyocytes and replacement of lost cells with fibrotic tissue cause architectural derangement of muscle fibers and fascicles [27] and may lead to intercellular uncoupling, an established mechanism of spatially discordant alternans.

MTWA and, more specifically, spatially discordant repolarization alternans produce a substrate that can lead to a variety of ventricular arrhythmias [10]. T-wave alternans is directly related to alternans of the cellular action potential. Discordant alternans is linked to a mechanism of arrhythmogenesis because when ventricular action potentials from neighboring cells are alternating out of phase, repolarization gradients are amplified and produce conduction block and reentrant excitation.

An important issue in ChD is the occurrence of sudden cardiac death in patients with normal or near normal LV function [5,28,29]. ChD is associated with a higher frequency (18%) of abnormal MTWA tests, even in the absence of left ventricular dysfunction [12]. This suggests that the arrhythmogenic substrate of Chagas disease may be multifactorial, including participation factors such as electrical instability of the myocardium, microvascular ischemia, reentrant circuits, contractility alterations segment, including apical aneurysm, and not just the global systolic left ventricular dysfunction.

Regarding the prediction of arrhythmic events and mortality in patients with ICDs, our results are similar to those reported by Chow et al. [30,31], Shan et al. [32] and Sredniawa et al. [33], who studied patients with ischemic heart disease. The above results were not confirmed by Chow et al. [34] in post-myocardial infarction patients with left ventricular ejection fraction (LVEF) < 30% and prophylactic ICDs. Nevertheless, although non-negative MTWA test results were not

associated with ventricular tachyarrhythmic events, total mortality was significantly increased in this group.

Recognizing high-risk patients who may require specific therapies, especially invasive procedures such as ablative approaches, is a major challenge in clinical practice.

It is worth noting that MTWA testing may influence the therapeutic strategy even after ICD implantation, as the MTWA test had a sensitivity of 100% and a NPV of 100%. One possibility would be to treat MTWA-non-negative patients more aggressively, with antiarrhythmic drugs or catheter ablation. Decreasing the number of shocks triggered by the device is an important treatment goal for various reasons. A high number of shocks can contribute to mortality by causing myocardial necrosis and promoting or exacerbating ventricular dysfunction [35]. Moreover, frequent shocks lead to more demand for health care and decreased device longevity and negatively affect quality of life [36,37] and decreasing the burden of receiving ICD therapy can improve quality of life. The combined use of amiodarone and beta-blockers was effective in reducing the number of therapies in other cardiomyopathies [38,39]. Ablation decreases the burden of ICD therapy delivered and can improve the quality of life. MTWA can help you recognize which patients have benefited from these therapies.

The implantation rate in some countries is below this average [40–42]. It therefore seems important from the clinical point of view to improve the waiting lists by identifying patients at the lowest risk of SCD who can safely wait for ICD implantation, while higher-risk patients undergo the procedure before them. This is particularly important in countries like Brazil with limited funding sources. The extremely high NPV of MTWA testing suggests that patients who were scored as negative on this test are unlikely to experience SCD, and this finding supports the use of MTWA as a diagnostic parameter when scheduling ICD implantation [43].

A normal MTWA test identifies patients who generally have a good prognosis, even in a high-risk group. Numerous studies highlighted a very high NPV of negative MTWA results, in the range of 94–100% [44]. Our study findings also indicate a high NPV of MTWA in patients with ChD.

A screening test with a high NPV could be clinically useful in a population with a greater a priori risk (e.g., low ejection fraction). This finding is very important, as one of the most relevant questions from a clinical and economic perspective is “who may benefit from ICDs?” To confirm this hypothesis, further observational studies should be carried out in well-defined representative populations with ChD. In these studies, multivariable models should be carefully designed to test the incremental prognostic value of established predictors such as ejection fraction. It should be stressed that ejection fraction is not an independent predictor of ventricular arrhythmias in patients with ChD, as shown in other studies [5,28,29] and sudden cardiac death can occur in patients with normal or near-normal left ventricular function [5,28,29]. The possibility that the high NPV of MTWA could be used in combination with other markers as part of a risk-stratification algorithm should also be explored. A carefully designed trial of MTWA-guided ICD therapy in primary prevention would provide the most robust evidence. This is certainly conceivable, given that not all patients who meet current indication criteria receive an ICD at present.

4.1. Limitations

Some limitations of the present study must be outlined, as this was an observational trial reporting the experience of a single reference center. The main limitation is the use of ICD therapies for ventricular tachycardia/ventricular fibrillation as a surrogate for SCD. An analysis of previous trials by Ellenbogen et al. [45] showed that ICD shocks overestimated arrhythmic mortality by a factor of two. This limitation is inherent to most ICD trials. It is possible that the lack of specificity of ICD therapies to lethal arrhythmias could mask the true relationship between MTWA and arrhythmic mortality. Therefore, these findings might not be applicable to a non-ICD-treated population.

5. Conclusion

In conclusion, we found that ChD patients who tested non-negative for MTWA tests were 2.7 times as likely to either receive appropriate ICD therapy or evolve to death. The MTWA test emerges as a good predictor of ventricular malignant arrhythmias in ChD patients with an ICD, with its high negative predictive value MTWA. It may therefore be considered useful in determining patients that are candidates to adjunctive therapy and ventricular ablation. Finally, the usefulness of MTWA testing for the primary prevention of sudden death in ChD patients is also worthy of evaluation.

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