Original Research

The Usefulness of T-wave Peak to T-wave End Interval in Identifying Malignant Arrhythmias in Patients with Chagas Disease

Luciana Armaganijan[1], Dalmo A. Moreira[1], Roberta R. Nolasco de Araújo[1], Marcelo A. Puzzi[1], Fernando P. Munhoz[1], Murilo J. Carvalho[1], Lilian N. Gallo[1], João Ítalo D. França[1] Renato D. Lopes[2]

[1]Division of Cardiac Arrhythmias and Electrophysiology, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil; [2]Duke University Medical Center, Duke Clinical Research Institute, Durham, NC, USA

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Introduction: Abnormal ventricular repolarization has been proposed as a marker of arrhythmogenesis, and cardiovascular morbidity and mortality. However, little is known about the influence of the interval between the peak and the end of the T wave (Tp-Te) on the inducibility of sustained ventricular arrhythmias (VA) in patients with Chagas disease (CD).

Methods: Using a case-control design, chagasics undergoing electrophysiological study (EPS) in the last three years were matched by age and sex. Cases represented those with positive EPS and controls those with no inducible VA. Tp-Te>100 ms was considered abnormal. Logistic regression analysis was performed to assess the association between Tp-Te and a positive EPS, after adjusting for confounders.

Results: A total of 105 patients (mean age 56 years, 52.4% male) were included: 41 (39%) had a positive EPS; 85.4% with inducible VA (n=35) had non-sustained ventricular tachycardia on the Holter monitoring, compared to 62.5% with negative EPS (n=40, p<0.001). While ventricular aneurysm (adjusted OR=5.3, 95% CI: 1.11-24.96, p=0.03) and coronary artery disease (adjusted OR=8.8, 95% CI: 1.45-53.15, p=0.01) were associated with an increased risk of malignant arrhythmias, a greater ejection fraction (adjusted OR=0.96, 95% CI: 0.93-0.99, p<0.01) was associated with a lower risk of VA. Prolonged Tp-Te trended to be associated with an increased risk of induced VA (p=0.07).

Conclusions: Ventricular aneurysm, coronary artery disease, and ejection fraction are associated with inducible VA. Prolonged TP-Te may have a modest role in the identification of patients with CD who are at high risk for VA. Further studies are warranted to validate our results and to correlate them with clinical outcomes.

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Address:
Luciana Armaganijan

Av. Dante Pazzanese, 500
Vila Mariana
CEP 04012-180
São Paulo, SP, Brazil
e-mail: luciana_ya@hotmail.com.br

First described in 1909, Chagas disease remains a major public health problem in many Latin American countries, affecting approximately 15 to 16 million people and accounting for a mortality of 20,000 individuals per year.[1] It has been estimated that 75 to 90 million people (25% of the Latin American population) are at risk of acquiring the disease.[1] Chagas disease was recognized in the United States as early as the 1950s, when the first reports of local vector-borne cases were published.[2] More recently, immigration patterns from endemic countries have changed the epidemiology of this disease in the US.

About two thirds of people with chronic symptoms develop cardiac damage, including dilatation and severe ventricular dysfunction, tachyarrhythmias (atrial fibrillation/flutter, ventricular tachycardia), bradyarrhythmias (various degrees of atrioventricular block) and, not uncommonly, sudden and unexpected death.[3]

Abnormal ventricular repolarization has been proposed as a potential marker of arrhythmogenesis, and cardiovascular morbidity and mortality.[4] Measurement of the interval between the peak and the end of the T wave (Tp-Te) has been suggested for the detection of spatial and transmural dispersion in repolarization.[5] However, its clinical value has not been fully studied in the subgroup of patients with Chagas disease. The aim of this study was to assess whether or not Tp-Te is associated with the inducibility of sustained malignant ventricular arrhythmias in this specific population.

Methods

Using a case-control design, medical charts were reviewed and patients undergoing electrophysiological study (EPS) in the last three years were matched by age and sex. The cases were composed of patients with a positive EPS and the controls were composed of those with no inducible sustained ventricular arrhythmias. Baseline characteristics (history of systemic hypertension, diabetes mellitus, coronary artery disease, and New York Heart Association [NYHA] functional class), resting 12-lead ECGs, two-dimensional echocardiogram, and 24-hour Holter monitoring records performed within 6 months before the EPS were assessed. The diagnosis of coronary artery disease (CAD) was defined as the presence of at least one vessel with stenosis >50% on angiography. In cases with symptoms compatible with CAD in the absence of risk factors, patients with normal exercise testing, myocardial scintigraphy, or cardiac angiotomography were considered to have no CAD.

Electrocardiogram

The Tp-Te interval was measured manually in each precordial lead and obtained from the difference between the QT interval and the QT peak interval, calculated from the beginning of the QRS until the peak of the T wave (using resting 12-lead ECGs recorded at 25 mm/s paper speed and 10 mm/mV amplitude). The end of the T wave was defined as the return to the baseline or the nadir between the T and U waves. The measurement was obtained by two independent observers as an average over three consecutive beats. In case of disagreement with a difference of 20 ms or more, a third expert was recruited. Tp-Te greater than 100 ms was considered abnormal.

24-hour Holter monitoring

The 24-hour Holter monitoring was used to obtain information about the presence of isolated premature ventricular contractions and episodes of ventricular tachycardia. Premature ventricular contractions were defined as the presence of beats originating in the ventricles, including isolated and paired beats. Sustained ventricular tachycardia was defined as a tachycardia originating in the ventricles with a heart rate of at least 100 /min, lasting at least 30 s, and/or associated with hemodynamic or clinical instability. Finally, non-sustained ventricular tachycardia was defined as the presence of at least 3 consecutive ventricular beats without meeting the criteria for sustained ventricular tachycardia.

Electrophysiological study

All patients underwent an EPS according to the following protocol: programmed ventricular stimulation with up to 3 extrastimuli and rapid ventricular pacing (up to 250 ms) in the right ventricular apex and right ventricular outflow tract.

Echocardiogram

Echocardiographic measurements included left ventricular ejection fraction, diastolic and systolic left ventricular diameters. Ejection fraction was analyzed as a continuous variable in our multivariable model.

Outcomes

The primary outcome was the inducibility of sustained ventricular arrhythmias (i.e. sustained ventricular tachycardia or fibrillation) during the EPS. The patients were divided into two groups: group A (cases) was the inducible group, and group B (controls) was the non-inducible group. Those with T waves smaller than 1.5 mm in amplitude were excluded.

Statistical analysis

Continuous data were expressed as mean ± SD or median with interquartile range, as appropriate. Categorical data were expressed as absolute and relative frequencies. Differences between groups (cases and controls) were analyzed using the 2-sample t-test (parametric data) or the Mann–Whitney test (nonparametric data) for continuous variables, and the χ^2

or Fisher's exact test for categorical variables. Missing data were treated as follows: for continuous variables with missing data, the mean and median imputation method was used; for categorical variables with missing data, we used the single imputation method, choosing one or another value. The 2-sample t-test was used to compare the Tp-Te intervals between cases and controls (considering Tp-Te interval as a continuous variable). Fisher's exact test was used to test the association of a prolonged Tp-Te interval with malignant arrhythmias (using Tp-Te interval as a categorical variable with a cutoff of 100 ms, according to previous studies).[6] Logistic regression analysis was used to adjust the main outcome for important covariates. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

One hundred five patients (age 56.51 ± 12.7 years, 52.4% male) with Chagas disease were included in the study. Forty-one patients (39%) had inducible ventricular arrhythmias, 84% of which were monomorphic ventricular tachycardia, 6% polymorphic ventricular tachycardia, 5% ventricular flutter, and 5% ventricular fibrillation.

In general, the baseline characteristics were similar in patients with a positive and negative EPS (Table 1). The majority of patients in both groups were in NYHA functional class I. Around 50% of the overall population had hypertension. CAD was more commonly seen in the group with a positive EPS than in patients with a negative EPS. Subjects with inducible ventricular arrhythmias were more often on amiodarone, had a lower ejection fraction and a more frequent history of non-sustained ventricular tachycardia compared to those without arrhythmias. There were no significant correlations between symptoms of syncope and presyncope and/or sudden cardiac death and inducibility of ventricular arrhythmias. Three patients (7.3%) in the group with a positive EPS had a history of aborted sudden death, compared to 5 (7.8%) in the negative EPS group (p=0.16).

Concomitant medications

About 47% of patients with no inducible ventricular arrhythmias were on amiodarone compared to 82.9% of the positive EPS group ($p<0.01$). The use of other antiarrhythmics, such as beta-blockers, calcium channel blockers, and sotalol, did not differ between the groups (Table 2).

Electrocardiographic and echocardiographic findings

The commonest ECG abnormality in both groups was right bundle brunch block, followed by left anterior fascicular block. The presence of first-degree AV block, Q wave, and low QRS voltage did not differ between the groups. The mean ejection fraction in the negative EPS group was 50.17%, compared to 41.69% in the positive EPS group. Left ventricular end-diastolic and systolic diameters were greater in those with a positive EPS (p=0.07 and 0.05, respectively). The majority of patients (85.4%) in the group with inducible ventricular arrhythmias (n=35)

Table 1. Baseline characteristics of patients with and without inducible ventricular arrhythmias during electrophysiological study.

	VT/VF on electrophysiological study				p
	No	(n=64)	Yes	(n=41)	
Age	56.11±14.11		57.15±10.26		0.71
Male	30	(46.9%)	20	(48.8%)	1.00
Systemic hypertension	33	(51.6%)	23	(56.1%)	0.69
Diabetes mellitus	7	(11%)	2	(4.9%)	0.47
Hyperlipidemia	16	(25.0%)	7	(17.1%)	0.46
Coronary artery disease	2	(3.1%)	6	(14.6%)	0.05
Syncope/presyncope	34	(53.1%)	16	(39.0%)	0.16
NYHA class:					
I	48	(75%)	25	(61%)	0.13
II	13	(20.3%)	11	(26.8%)	0.48
III	2	(3.1%)	5	(12.2%)	0.10
IV	1	(1.6%)	0	(0%)	1.00

VF – ventricular fibrillation; VT – ventricular tachycardia.

Table 2. Concomitant medications in patients with and without inducible ventricular arrhythmias during electrophysiological study.

	VT/VF on electrophysiological study				p
	No	(n=64)	Yes	(n=41)	
Beta-blocker	31	(48.4%)	25	(60.9%)	0.23
Calcium channel blocker	3	(4.7%)	0	(0%)	0.27
Amiodarone	30	(46.9%)	34	(82.9%)	<0.01
Sotalol	1	(1.6%)	0	(0%)	1.00
Propafenone	0	(0%)	0	(0%)	-

VF – ventricular fibrillation; VT – ventricular tachycardia.

had non-sustained ventricular tachycardia on 24-hour Holter monitoring, compared to 62.5% in those with a negative EPS (n=40, p<0.001) (Table 3).

Factors associated with ventricular arrhythmias

While the presence of left ventricular aneurysm (adjusted odds ratio, OR=5.3, 95% confidence interval, CI: 1.11-24.96, p=0.03) and CAD (adjusted OR=8.8, 95% CI: 1.45-53.15, p=0.01) were associated with an increased risk of inducible ventricular arrhythmias, a greater ejection fraction (adjusted OR per 1% increase=0.96, 95%: CI 0.93-0.99, p<0.01) was associated with a lower risk of inducible malignant arrhythmias. Prolonged Tp-Te tended to be associated with an increased risk of induced ventricular arrhythmias (p=0.07) (Table 4).

Discussion

This study has two main findings. First, patients with Chagas disease undergoing EPS had a positive test 39% of the time. Second, ventricular aneurysm, coronary artery disease, and ejection fraction were associated with inducible ventricular arrhythmias. Prolonged Tp-Te tended to be associated with an increased risk of induced ventricular arrhythmias; it may therefore still have a role in identifying patients with Chagas disease who are at risk for malignant arrhythmias.

Sudden death accounts for approximately 55-65% of causes of death in patients with Chagas disease, surpassing deaths from heart failure.[7] It affects patients between 30 and 50 years of age, especially males.[8] The arrhythmogenic nature of Chagas disease

Table 3. Electrocardiographic and echocardiographic parameters in patients with and without inducible ventricular arrhythmias during electrophysiological study.

	VT/VF on electrophysiological study				p
	No	(n=64)	Yes	(n=41)	
Electrocardiogram:					
RBBB	43	(67.2%)	22	(53.7%)	0.21
LAFB	29	(45.3%)	18	(43.9%)	1.00
LBBB	4	(6.3%)	4	(9.8%)	0.70
1st degree AVB	14	(21.9%)	13	(31.7%)	0.36
Q wave	3	(4.7%)	3	(7.3%)	0.67
Low QRS voltage	14	(21.9%)	5	(12.2%)	0.29
Echocardiogram:					
LV aneurysm	3	(4.7%)	6	(14.3%)	0.08
EF (%)	50.17 ± 14.9%		41.69 ± 14.19%		<0.01
LVDD (mm)	57.97 ± 8.29%		60.54 ± 7.77%		0.07
LVSD (mm)	42.58 ± 10.20%		46.27 ± 11.72%		0.05
24h-Holter:					
>30 PVCs/hour	41	(64.1%)	24	(58.5%)	1.00
NSVT	40	(62.5%)	35	(85.4%)	<0.01

AVB – atrioventricular block; EF – ejection fraction; LAFB – left anterior fascicular block; LBBB – left bundle branch block; LV – left ventricular; LVDD – left ventricular diastolic diameter; LVSD – left ventricular systolic diameter; NSVT – non-sustained ventricular tachycardia; PVC – premature ventricular contraction; RBBB – right bundle branch block.

Table 4. Factors associated with inducible ventricular arrhythmias during electrophysiological study.

	OR	95% CI	p
Left ventricular aneurysm	5.3	1.11 - 24.97	0.03
Coronary artery disease	8.8	1.45 - 53.15	0.01
Ejection fraction (per 1% increase)	0.96	0.93 - 0.99	<0.01
Tp-Te >100 ms	2.67	0.92 - 7.74	0.07

OR – odds ratio; CI – confidence interval.

is related to the presence of fibrotic tissue intermingled with preserved myocardial areas and dyskinetic regions generating an area with a high propensity for complex ventricular arrhythmias. The risk of sudden death is not uniform for all patients and the predictors of inducibility of complex arrhythmias remain a major challenge in identifying patients who have a higher risk of a fatal event.

The action potential of myocardial contractile cells depends on the electrophysiological profile of cells of the endocardium, epicardium, and M cells; thus, the differences in the time of repolarization of these three cell types are responsible for the registration of the T wave on the electrocardiogram.[9,10] It has been shown that the peak of the T wave coincides with the epicardial repolarization and the end of the T wave with the repolarization of M cells, so that T peak to T end provides a measure of the transmural dispersion of repolarization.[11] The Tp-Te interval has been suggested as a reflection of total dispersion repolarization secondary to the loss of the action potential dome in epicardium and the development of an epicardial dispersion of repolarization;[12] this, in turn, results in phase 2 re-entry, thus precipitating episodes of ventricular arrhythmias.

The dispersion of ventricular repolarization has been the subject of studies involving various diseases. A prolonged Tp-Te interval has been reported as a predictor of the risk of arrhythmia in long-QT syndrome.[13] A significant correlation between prolonged QTc, Tp-Te, Tp-Te dispersion, and the occurrence of life-threatening arrhythmic events has been suggested in patients with Brugada syndrome.[14]

An advanced NYHA functional class (III or IV), evidence of cardiomegaly on radiography, left ventricular systolic dysfunction, non-sustained ventricular tachycardia, low QRS voltage, and male sex have been demonstrated to be associated with a poorer prognosis in chagasic patients.[15] In our study, left ventricular aneurysm, the presence of CAD, and a low ejection fraction were factors associated with inducible ventricular arrhythmias. Additionally, 46.7% of patients with non-sustained ventricular tachycardia on 24-hour Holter had a positive EPS, compared to none with a negative EPS. We found no correlation between low QRS voltage and induced ventricular arrhythmias. To the best of our knowledge, this is the first study to demonstrate that the interval between the peak and the end of the T wave may have some role in stratifying patients with Chagas disease who are at high risk for arrhythmias.

Limitations

This study has limitations. First, owing to the observational nature of the study and despite the multivariable adjustments, one cannot account for unmeasured confounders. Second, the retrospective nature of the study has the major disadvantage of increased susceptibility to bias. The choice of a case-control design relied on the long latent period between the Chagas contamination and the occurrence of ventricular arrhythmias. A prospective design in this case would require an enormous sample size and years of follow up. The case-control model gave us the opportunity to use a less expensive and more feasible design. The retrospective approach to measuring the predictor variables could also result in bias due to measurement errors. In order to reduce the differential bias in measuring the predictor variables, the data used were recorded before the outcome. Additionally, the ECG analysis was performed in a blind fashion. Third, our study had a small sample size. It is also likely that there was a survival bias in our study, which we were not able to address. The sample may not be representative of all patients with Chagas disease who have inducible sustained ventricular arrhythmias, especially because those who died and were more likely to have a positive EPS were also less likely to be included in the study.

Finally, this was a single-center study and any generalization of our findings should be made with

caution. Nonetheless, this was the first time that Tp-Te was studied in patients with Chagas disease.

Conclusions

In our study, 39% of patients with Chagas disease undergoing an EPS had inducible ventricular arrhythmias. Ventricular aneurysm, CAD, and ejection fraction were associated with inducible ventricular arrhythmias. Prolonged Tp-Te may have a modest role in the identification of patients with Chagas disease who are at high risk for ventricular arrhythmias. Further studies are warranted to validate our results as well as to correlate them with clinical outcomes.

References

1. Coura JR, Dias JC. Epidemiology, control and surveillance of Chagas disease: 100 years after its discovery. Mem Inst Oswaldo Cruz. 2009; 104 Suppl 1: 31-40.
2. Tanowitz HB, Weiss LM, Montgomery SP. Chagas disease has now gone global. PLoS Negl Trop Dis. 2011; 5: e1136-1137.
3. 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.
4. Salles G, Xavier S, Sousa A, Hasslocher-Moreno A, Cardoso C. Prognostic value of QT interval parameters for mortality risk stratification in Chagas' disease: results of a long-term follow-up study. Circulation. 2003; 108: 305-312.
5. Watanabe N, Kobayashi Y, Tanno K, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. J Electrocardiol. 2004; 37: 191-200.
6. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006; 47: 1828-1834.
7. de Menezes M, Rocha A, da Silva AC, da Silva AM. [Basic causes of death in elderly patients with Chagas' disease]. Arq Bras Cardiol. 1989; 52: 75-78.
8. Bestetti RB, Freitas OC, Muccillo G, Oliveira JS. Clinical and morphological characteristics associated with sudden cardiac death in patients with Chagas' disease. Eur Heart J. 1993; 14: 1610-1614.
9. 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.
10. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation. 1998; 98: 1928-1936.
11. Fish JM, Di Diego JM, Nesterenko V, Antzelevitch C. Epicardial activation of left ventricular wall prolongs QT interval and transmural dispersion of repolarization: implications for biventricular pacing. Circulation. 2004; 109: 2136-2142.
12. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006; 47: 1828-1834.
13. Milberg P, Reinsch N, Wasmer K, et al. Transmural dispersion of repolarization as a key factor of arrhythmogenicity in a novel intact heart model of LQT3. Cardiovasc Res. 2005; 65: 397-404.
14. Castro Hevia J, Antzelevitch C, Tornıs Bárzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006; 47: 1828-1834.
15. Rassi A Jr, Rassi A, Little WC, et al. Development and validation of a risk score for predicting death in Chagas' heart disease. N Engl J Med. 2006; 355: 799-808.