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Clinical predictors of inducible sustained ventricular tachycardia during electrophysiologic study in patients with chronic Chagas' heart disease

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ABSTRACT

Background: Clinical independent predictors of inducible sustained ventricular tachycardia (VT) during electrophysiologic study (EPS) are not known in patients with chronic Chagas' heart disease. The purpose of this investigation was to fill this gap.
Methods: The medical charts of 47 patients with a positive serology for Chagas' disease who had undergone EPS between September 2006 and July 2012 at our institution were reviewed. Reasons for the EPS were the presence of unexplained syncope, non-sustained ventricular tachycardia (NSVT) on either resting ECG or 24 h-Holter monitoring as well as a LVEF < 55% and >35% at echocardiography. A stepwise logistic regression analysis was performed to identify noninvasive predictors of inducible sustained VT/ventricular fibrillation during EPS.
Results: On univariate analysis, syncopal episodes ($p = 0.04$), amiodarone therapy ($p < 0.005$), diastolic blood pressure ($p = 0.03$), creatinine serum levels ($p < 0.001$), potassium serum levels ($p < 0.001$), and lengthening of the QRS complex ($p = 0.03$) were associated with inducible sustained VT during EPS. In the multivariate model, amiodarone therapy ($p = 0.03$; hazard ratio = 10; Wald coefficient = 4.5; 95% confidence interval 1.2 to 85.2) was the only variable retained as independent predictor of inducible sustained VT during EPS.
Conclusion: Amiodarone therapy was the only independent variable associated with sustained VT inducibility during EPS in patients with chronic Chagas' heart disease.

1. Introduction

Chagas' disease affects about 10 million people in Latin America, another 25 million are at risk of acquiring the disease, and about 10,000 people die of the disease annually. Chagas' disease has become global as a result of international immigration, about 750,000 people with chronic Chagas' disease are living outside South America, mainly in the United States and Europe [1]. As a result, the world economic burden of Chagas' disease is US$ 7.9 billion annually, higher than that seen in cervical or oral cancer, and affects the economy of both endemic and non-endemic countries [2].

The disease is caused by the protozoan *Trypanosoma cruzi*, it is transmitted to humans by eye mucosa or skin lesion contact with the feces of sucking-bugs. However, other sources of transmission, like oral transmission, have become important nowadays. Initial infection occurs in early infancy, but the clinical manifestations of Chagas' cardiomyopathy, which affects about 30% of infected patients, appear up to 20 years later [3]. Chagas' cardiomyopathy manifests by chronic systolic heart failure (CHF) [4], thromboembolism [3], malignant ventricular arrhythmias [5,6], and sudden cardiac death (SCD) [7].

SCD affects about 5% of the general, unselected population with chronic Chagas' disease [7]. It is the mode of death in 17 to 50% of patients with this condition [8,9], and afflicts patients with overt chronic Chagas' heart disease [10], particularly those with ventricular dysrhythmias on the 12-lead ECG and mild to moderate left ventricular systolic dysfunction [11]. In the vast majority of cases, SCD is caused by sustained ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF) or VF itself [7].

An electrophysiologic study (EPS) is useful for identifying chronic Chagas' disease patients at high risk of SCD. In fact, patients with chronic Chagas' heart disease in whom sustained VT/VF are induced during EPS have a higher risk of SCD in comparison to those in whom such malignant arrhythmias are not induced [12]. EPS is not widely available and impractical to be offered to millions of people. Nonetheless, it would be of interest to predict on clinical grounds which patients will develop sustained VT/VF during EPS. This might be used as means of selecting patients for EPS. Accordingly, the present study was undertaken in

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an attempt to determine clinical predictors of inducible sustained VT during EPS.

2. Methods

2.1. Patients

The medical charts of patients with a positive serology for Chagas' disease who had undergone EPS between September 2006 and July 2012 at our institution were considered for the study. Inclusion criteria were an EPS performed for the following reasons: unexplained syncope, non-sustained ventricular tachycardia (NSVT) on either resting ECG or 24 h-Holter monitoring as well as a LVEF < 55% and >35% at echocardiography. The diagnostic work-up, besides the EPS, consisted of history-taken and physical examination at presentation, 12-lead ECG, standard laboratory tests, and 2-D echocardiography. The New York Heart Association Functional Class, heart rate, systolic and diastolic blood pressure were noted on study admission.

All patients with left ventricular systolic dysfunction were treated with beta-blockers and angiotensin converting enzyme inhibitors/angiotensin receptor block (ACEI/ARB) at target or maximal tolerated doses. Those with systemic and pulmonary congestion received diuretics and/or digitalis when appropriated. Patients were given amiodarone at the discretion of the referral doctor. Overall, 39 (83%) patients were on ACEI/ARB, 36 (76%) on beta-blockers at target or maximal tolerated daily dose, and 24 (51%) on diuretics. Seventeen (35%) patients received treatment with spironolactone, and 14 (29%) were on amiodarone. Mean daily dose of enalapril was 18.7 ± 10.2 mg, mean daily dose of captopril 70.7 ± 19.8 mg, mean daily dose of losartan 45.4 ± 10.1 mg, mean daily dose of carvedilol 26 ± 18 mg, mean daily dose of atenolol 37.2 ± 17.7 mg, mean daily dose of digoxin 0.12 ± 0 mg, and mean daily dose of amiodarone 278.6 ± 112.2 mg. Such medications were maintained at the time of EPS.

During the EPS, ventricular stimulation was performed only in the right ventricular apex, using 3 extra-stimuli with up 200 ms interval at most. The cycle length of extra stimuli were 600, 500 and 430 ms, respectively.

2.2. Statistical analysis

Continuous variables are shown as mean ± standard deviation, whereas categorical variables are presented as percentages. Continuous variables between inducible and non-inducible SVT groups were compared using the unpaired T Test, while categorical variables between both groups were compared by the χ-square test. Differences between variables at the level of $p < 0.05$ were entered in stepwise logistic regression analysis to identify noninvasive predictors of inducible sustained VT/VF during EPS.

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3. Results

A total of 47 patients fulfilled the inclusion criteria and were entered in the study. During EPS, sustained VT was induced in 12 (25%) of 47 patients. By contrast, VF was induced in none of the patients. Table 1 lists the clinical characteristics of patients with inducible and non-inducible sustained VT during EPS. Table 2 depicts electrocardiographic and echocardiographic variables in both patients' groups. Also, the AH interval was 94.4 ± 25.8 ms in patients with and 98 ± 48.7 ms in patients with no inducible sustained VT ($p > 0.05$), while the HV interval was 55.4 ± 13.5 ms in patients with sustained VT and 57.6 ± 26.3 ms ($p > 0.05$) in patients with no inducible sustained VT. The cycle length of inducible sustained VT was 309 ± 49 ms. The episodes of sustained VT were treated with cardioversion in 4 (33%) out of 12 patients, and a burst of ventricular stimulation in 7 (58%) out of 12 patients. One episode of inducible sustained VT terminated spontaneously.

On univariate analysis, history of syncopal episodes ($p = 0.04$), amiodarone therapy ($p < 0.005$), diastolic blood pressure ($p = 0.03$), creatinine serum levels ($p < 0.001$), potassium serum levels ($p < 0.001$), and lengthening of the QRS complex during EPS ($p = 0.03$) were associated with inducible sustained VT during EPS. In the multivariate model, however, amiodarone therapy ($p = 0.03$; hazard ratio = 10; Wald coefficient = 4.5; 95% confidence interval 1.2 to 85.2) was the only variable retained as an independent predictor of inducible sustained VT during EPS.

Table 1
Clinical and laboratory characteristics of a cohort of patients with chronic Chagas' heart disease with inducible or no inducible sustained ventricular tachycardia during electrophysiologic study.

Variables	SVT (n = 12)	No SVT (n = 35)
Age (years)	57 ± 9	57 ± 12
Male	8 (67%)	21 (60%)
NYHA III/IV	1 (8%)	6 (17%)
Syncope	9 (75%)	13 (37%)*
ACEI/ARB	10 (83%)	29 (83%)
Beta-blockers	7 (58%)	29 (83%)
Digoxin	3 (25%)	9 (26%)
Diuretic	6 (50%)	18 (51%)
Spironolactone	6 (50%)	11 (31%)
Amiodarone	8 (67%)	6 (17%)**
Heart rate	66 ± 11	69 ± 13
SBP (mmHg)	113.6 ± 13.6	127.3 ± 24.9
DBP (mmHg)	70.9 ± 8.3	80.3 ± 13.1***
Sodium (mEq/L)	138.9 ± 5	140.4 ± 2.9
Potassium (mEq/L)	4.1 ± 0.2	4.3 ± 0.4
Creatinine (mg/dL)	1.1 ± 0.3	1.3 ± 0.5**
Hemoglobin (g/dL)	13.6 ± 0.8	13.6 ± 1.7

SVT = sustained ventricular tachycardia; ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor block; SBP = systolic blood pressure; DBP = diastolic blood pressure.
* p = 0.04.
** p < 0.005.
*** p = 0.03.

Table 2
Electrocardiographic findings and echocardiographic features in patients with chronic Chagas' heart disease with inducible or no inducible malignant arrhythmias during electrophysiologic study.

Variables	SVT (n = 12)	No SVT (n = 35)
Atrial fibrillation	1 (8%)	7 (20%)
Pacemaker	3 (25%)	6 (17%)
Left bundle branch block	0 (0%)	5 (14%)
LAFB	3 (25%)	13 (37%)
RBBB	3 (25%)	16 (46%)
Low QRS voltage	0 (0%)	1 (3%)
VPC	4 (33%)	4 (11%)
NSVT	10 (83%)	21 (60%)
QRS duration (ms)	142 ± 37.1	137.9 ± 28***
LVDD (mm)	60.1 ± 9.2	58.1 ± 9
LVSD (mm)	46.2 ± 10.3	43.4 ± 12.4
Right ventricle (mm)	21.1 ± 5.2	23.8 ± 6.7
SWMA	2 (17%)	4 (11%)
LVEF (%)	45.8 ± 13.2	53.1 ± 15.7

SVT = sustained ventricular tachycardia; LFAB = left anterior fascicular block; RBBB = right bundle branch block; VPC = ventricular premature contractions; NSVT = non-sustained ventricular tachycardia; LVDD = left ventricular diastolic diameter; LVSD = left ventricular systolic diameter; SWMA = systolic wall motion abnormalities; LVEF = left ventricular ejection fraction.
*** p = 0.03.

4. Discussion

This study clearly shows that one quarter of patients with chronic Chagas' heart disease with mild left ventricular systolic dysfunction and/or syncope/NSVT has inducible sustained VT during EPS, and that the vast majority of them need electric intervention to terminate the arrhythmia. Furthermore, only amiodarone therapy in this setting was independently associated with an inducible sustained VT during EPS in the multivariable model.

The prevalence of sustained VT induced during EPS observed in this cross-sectional investigation is somewhat lower than that found by Silva et al. [12]. In fact, Silva et al. were able to induce sustained VT and VF during EPS in 25 (32%) and 4 (5%), respectively, of 78 patients with chronic Chagas' heart disease with mild left ventricular systolic dysfunction and NSVT. Twenty-two (78%) of the patients died, 16 of them suddenly, in a 56 ± 38 months follow-up [12]. It is conceivable that the high frequency with which beta-blockers were used in or investigation in comparison with the study by Silva et al. [12] can account, at least in part, for the difference among studies. In fact, in the Silva et al. study [12], beta-blockers were not used. On the other hand, beta-blocker therapy has been found to have a beneficial effect experimentally and in patients with chronic Chagas' heart disease [13–16], similarly to what happens in an experimental model of catecholamine cardiomyopathy [17]. In patients with chronic Chagas' heart disease, beta-blocker therapy parallels the beneficial effect observed in non-Chagas' disease patients regarding the appearance of malignant ventricular arrhythmias [18]. Collectively, these findings suggest that beta-blocker therapy can be useful for reducing inducibility of sustained VT during EPS in patients with mild to moderate left ventricular systolic dysfunction and NSVT during EPS.

The prevalence of inducible sustained VT during EPS is consistent with the high frequency of syncopal episodes experienced by Chagas' disease patients with left ventricular systolic impairment in our study, and probably reflects the underlying mechanism behind malignant ventricular arrhythmias in patients with this condition. In patients with chronic Chagas' heart disease, there are areas of normal myocardium intermingled with areas of reparative fibrosis. Moreover, a mononuclear cell infiltration coexists with such areas of fibrosis. This can lead to areas of slow conduction electric stimulus close to scar areas, thus triggering many foci of re-entry throughout the myocardium, mainly in the epicardial layer [6,19]. Furthermore, parasympathetic denervation [20,21] can lead to intracardiac autonomic imbalance, thus aggravating the arrhythmic threshold and provoking malignant arrhythmia appearance even in patients with mild left ventricular systolic dysfunction. Collectively, such findings can explain, at least in part, the prevalence of 25% of sustained VT induced at EPS in Chagas' disease patients without severe left ventricular systolic dysfunction.

Our study also contrasts with Silva et al. [12] regarding the association of male patients and age with higher probability of induction of sustained VT during EPS in the logistic regression analysis. In fact, in our study, such variables were not associated with sustained VT during EPS either on univariate or multivariate analysis. However, it must be considered that the mean age in Silva et al. study was lower than observed in ours, this might explain the difference found in both study populations [12]. Another difference between our study and Silva et al. is that we did not observe an increase in the proportion of sustained VT inducibility in male patients sex. Since being male is an independent predictor of left ventricular remodeling [22], and the prevalence of male patients was similar to that found in the Silva et al. study [12], it would be reasonable to expect its association with sustained VT inducibility. Nonetheless, we have no explanation for the difference observed in our study as compared with that of Silva et al. [12].

The results of this investigation are in contrast to other studies in which several clinical and laboratorial variables were associated with SCD, a condition which can be predicted by sustained VT inducibility during EPS [11]. Such clinical characteristics are represented by electrocardiographic changes (left anterior fascicular block, QT dispersion, and premature ventricular contractions) [23] as well echocardiographic abnormalities (left ventricular diastolic diameter > 70 mm and apical aneurysm) [9], which have independently been associated with SCD in patients with Chagas' cardiomyopathy. However, our sample size was smaller than that enrolled such studies. Also, the severity of left ventricular systolic impairment observed in our investigation was lesser than these other studies. Therefore, such differences can explain the discrepancies between our study and those reported previously.

The striking feature of this investigation was the independent association between amiodarone therapy and inducible sustained VT during EPS. Amiodarone has long been used in the treatment of ventricular arrhythmias, particularly sustained VT, in patients with chronic Chagas' heart disease [24]. As expected, however, there is no evidence-based medicine to support the use of amiodarone because no randomized, placebo controlled trial have been performed because this disease is largely neglected. Amiodarone use has been associated with several types of complications in Chagas' disease patients probably due to the chronically high dose. The complications include thyroid disease (hypo or hyperthyroidism) in 21% to 39% of cases [25,26], restrictive pulmonary disease [27], ocular disease and gray-skin discoloration. A pro-arrhythmic effect secondary to chronic amiodarone use is supposed to have been occurred in one patient with chronic Chagas' heart disease [28].

Apart from the side-effects associated with amiodarone use, amiodarone therapy has been found to increase mortality in non-Chagas' disease patients with CHF. In fact, a multivariable study of patients in COMET trial has shown that amiodarone therapy increased the risk of death independently of the New York Heart Association classification, including milder forms (Class II) of the CHF syndrome, which was driven by circulatory death, as the drug did not interfere with the risk of SCD [29]. A similar finding has been observed in the SCD-HF trial in non-Chagas' disease patients with more advanced forms (Class III) of the syndrome. It must be emphasized, however, that in such studies neither syncopal episodes nor NSVT were inclusion criteria [30].

In a population comprised of patients with Chagas' and non-Chagas' cardiomyopathy, amiodarone therapy has been associated with all-cause mortality driven by death from progressive heart failure, but no effect has been observed on sudden cardiac death [31]. It should be noted, nonetheless, that NSVT is very frequently found in patients with chronic Chagas' heart disease, this may suggest a different effect of amiodarone in Chagas' disease heart failure.

One possibility of the independent association between amiodarone use and sustained VT inducibility during EPS is that amiodarone is a marker, not a cause, of patients more prone to develop malignant arrhythmia. For this reason, some authors do not recommend using treatment modality in multivariable models [32]. Another possibility is that amiodarone may have facilitated the appearance of sustained VT because its effects on myocardium with multiple areas of scarring, as observed in patients with chronic Chagas' heart disease [19]. Under such circumstances, amiodarone can produce different degrees of dromotropism in different areas of ventricular myocardial tissue, thus allowing multiple areas of reentrant circuits to occur, culminating in inducible sustained VT [28]. Finally, it is conceivable that amiodarone can slow stimulus conduction in pre-existent circuits, in line with the cycle length of the sustained VT induced at EPS in our study, thus becoming the ventricular arrhythmia more sustainable.

In conclusion, amiodarone therapy is independently associated with sustained VT inducibility at EPS in patients with chronic Chagas' disease. Further studies are necessary to establish other clinical predictors of malignant ventricular arrhythmias induced by EPS, and confirm (or discard) a causal relationship between amiodarone use and sustained VT induced by EPS, as observed in our study.

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