

Predictive Value of Clinical and Electrophysiological Variables in Patients with Chronic Chagasic Cardiomyopathy and Nonsustained Ventricular Tachycardia

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Objective - Risk stratification of patients with non-sustained ventricular tachycardia (NSVT) and chronic chagasic cardiomyopathy (CCC).

Methods - Seventy eight patients with CCC and NSVT were consecutively and prospectively studied. All patients underwent to 24-hour Holter monitoring, radioisotopic ventriculography, left ventricular angiography, and electrophysiologic study. With programmed ventricular stimulation.

Results - Sustained monomorphic ventricular tachycardia (SMVT) was induced in 25 patients (32%), NSVT in 20 (25.6%) and ventricular fibrillation in 4 (5.1%). In 29 patients (37.2%) no arrhythmia was inducible. During a 55.7-month-follow-up, 22 (28.2%) patients died, 16 due to sudden death, 2 due to nonsudden cardiac death and 4 due to noncardiac death. Logistic regression analysis showed that induction was the independent and main variable that predicted the occurrence of subsequent events and cardiac death (probability of 2.56 and 2.17, respectively). The Mantel-Haenszel chi-square test showed that survival probability was significantly lower in the inducible group than in the noninducible group. The percentage of patients free of events was significantly higher in the noninducible group.

Conclusion - Induction of SMVT during programmed ventricular stimulation was a predictor of arrhythmia occurrence cardiac death and general mortality in patients with CCC and NSVT.

Key words: Chagasic heart disease, nonsustained ventricular tachycardia, electrophysiologic study

Ventricular arrhythmias have been related to subsequent mortality in patients with heart disease encouraging studies on risk stratification and management of complex ventricular arrhythmias¹⁻⁴. The importance of the prognosis is influenced by specific clinical manifestations and their severity, and the impact of NSVT on valvular heart disease, congenital heart disease, cardiomyopathy and coronary disease⁵. In our environment, CCC has already been reported because of its prevalence, pathogenesis and prognosis. Studies were mostly related to conduction disturbances, syncope investigation, and efficacy of antiarrhythmic drugs in patients with sustained ventricular tachycardia⁶⁻¹⁶.

Few studies have been conducted in patients with CCC and complex ventricular arrhythmias, and hard data about this subject are lacking. The problems of the studies that have been conducted are related to population heterogeneity, different protocols related to programmed ventricular stimulation and no correlation analysis between clinical and laboratory variables¹⁷⁻²¹.

The objectives of our study are to analyze clinical variables (sex, age, presence of syncope), laboratory evaluation (conduction disturbances, complex ventricular arrhythmias, segmental abnormalities, ejection fraction) and electrophysiologic studies (induction of sustained monomorphic ventricular tachycardia - SMVT) in patients with CCC and NSVT for risk stratification, and survival study of this high risk population.

Methods

Seventy-eight patients with CCC and NSVT from the Clinical Cardiology Division, Hospital São Paulo, Escola Paulista de Medicina, of the Federal University of São Paulo were consecutively studied. Inpatients were admitted due to either syncope or near syncope or due to cardiac failure, or all of these. Nonsustained ventricular tachycardia was recorded on electrocardiogram or 24-hour Holter monitoring. Diag-

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nostic criteria for CCC included serologic tests and presence of heart disease, through history and physical examination, 12-lead electrocardiogram, chest roentgenogram and echocardiogram. Patients with decompensated congestive heart failure, coronary heart disease, cardiomyopathy of any etiology, pregnancy and serious chronic disease were excluded. We studied 45 male and 33 female patients with ages ranging from 21 to 68 years (mean 46.4 ± 10.7).

All patients underwent clinical and laboratory evaluation, including serological reactions (Machado Guerreiro immunofluorescence), 12-lead electrocardiogram, chest roentgenogram, two-channel 24-hour Holter monitoring, echocardiogram, radioisotopic ventriculography, left ventricular angiography and electrophysiologic study. All antiarrhythmic drugs were discontinued for at least 5 half-lives and for 45 days if the drug was amiodarone. Patients older than 40 years also had coronary angiography performed by either the Sones or Judkins technique.

Electrophysiologic studies were performed with patient not sedated, by puncture of femoral right and left veins to position the electrode catheters, using the percutaneous modified Seldinger technique. A small amount of local anesthetic (2% solution of lidocaine hydrochloride) was infiltrated into the area. Catheters were inserted and positioned in the high right atrium, in contact with the septum until a His bundle potential was recorded, in the right ventricular apex and outflow tract, if it was necessary. During the study, a bolus of 2500U of heparin was administered followed by 1000U/h. After recording of A-H and H-V intervals, sinus node function, sinoatrial conduction time, sinus node recovery time and analysis of A-V conduction were performed. Programmed ventricular stimulation was performed in the right ventricular apex, during two pacing cycle lengths (600 and 450ms), beginning late in diastole and moved progressively earlier until ventricular refractoriness was reached. The extrastimulus was delivered after a train of 8 paced complexes. If a single extrastimulus (S2) did not induce SMVT, a second extrastimulus (S3) was added. Double extrastimuli were introduced starting with an S1-S2 interval 50ms greater than an effective ventricular refractory period and an S2-S3 interval equal to the S1-S2 interval. The S2-S3 coupling interval was shortened by 10ms decrements until S3 became refractory, at which time S2 was decreased by 10ms decrements until S3 evoked a response. This sequence was also repeated in the right ventricular outflow tract until both extrastimuli reached refractoriness or sustained ventricular tachyarrhythmias were induced. The induction was reproduced, except in cases of electric cardioversion. Stimulation was performed with impulses 1-2ms in duration at twice the diastolic threshold.

All patients with SMVT were treated with amiodarone or sotalol. Diuretics, digitalis, angiotensin-converting enzyme inhibitors and antihypertensive therapy were administered according to indications.

Definitions: A) Ventricular tachycardia - three or more consecutive ventricular complexes at a rate of more than 100 beats/min; sustained ventricular tachycardia: tachycardia that lasted more than 30 seconds or when cardiovas-

cular collapse was present; nonsustained ventricular tachycardia without cardiovascular collapse that ended spontaneously in less than 30 seconds; B) inducible ventricular tachycardia: six or more ventricular complexes induced by programmed electrical stimulation. If it lasted more than 30 seconds or if hemodynamic collapse occurred, it was defined as sustained; if not, it was defined as nonsustained; C) ventricular fibrillation: sustained ventricular arrhythmia with disorganized electric activity on ECG without distinct QRS complexes; D) sudden death: unexpected, nontraumatic, in patients with or without previous disease, occurring within an hour after the onset of symptoms. The victim should be well 24-hours before if death was not witnessed²²; E) cardiac death: that caused by sudden death or due to heart failure; F) events: included cardiac death, spontaneous sustained ventricular tachycardia and recurrence of syncope.

Statistical analysis - The Chi-square test with Fisher's exact proportion was used to study a possible correlation between variables; the Mann-Whitney test was used to compare two independent groups; Wilcoxon's test was used to compare nondependent groups²³ and the Mantel-Haenszel test²⁴ was used for survival analysis between patients with SMVT, induced and noninduced. A p value of <0.05 was considered significant and marked with a sign (*). The results were analyzed using a stepwise logistic regression (program SAS Institute Inc. SAS/STAT User's Guide, Version 6).

Results

According to symptoms, 37 patients (47.4%) had syncope, 57 had near syncope and 12 had chest pain. According to the functional classification of congestive heart failure (New York Heart Association), 38 patients (48.7%) were in class I, 28 (35.9%) in class II, 8 in class III and 4 in class IV. Only 2 patients had atrial fibrillation. Sixty-three patients (80.8%) had conduction disturbances, atrioventricular block, fascicular blocks or bundle branch block. Twenty-four hour Holter monitoring recorded 11 and 1355 premature ventricular complexes/hour (median 203.5) and one and 2500 NSVT (median 3.5) episodes. Ejection fraction varied from 0.10 to 0.80 (mean 0.47, median 0.48). Twenty-seven patients (34.6%) had segmental abnormalities, which were located mainly in the apex (59%). None of the patients had coronary lesions on cineangiography.

Electrophysiologic studies detected sinus node dysfunction defined by prolonged sinus node recovery time in 3 patients (3.8%); HV interval was normal in 60 patients (76.9%). These evaluations were not made in 8 patients with pacemakers.

Programmed ventricular stimulation induced SMVT in 25 patients (32%), NSVT in 20 (25.6%), ventricular fibrillation in 4 (5.1%); in 29 patients noninducible ventricular arrhythmias (37.2%) occurred. Utilization of 3 extrastimuli was necessary to induce SMVT in 17 patients (68%). Electrical cardioversion was performed in 13 patients (52%) with induced ventricular arrhythmias. Cycle length of SMVT varied from 130 to 320 ms (median 240 ms, mean 228 ms).

Male gender (48% x 12%), syncope (47% x 22%), age (54 x 45 years) conduction disturbances (40% x 7%) and lower ejection fraction were significantly associated with induction of SMVT.

Clinical evaluation - Mean clinical follow-up was 55.7±37.7 months (median 50.5), without a significant difference between inducible and noninducible groups. During follow-up 22 deaths (28.2%) occurred, 16 (72.7%) due to sudden death, 2 (9%) due to nonsudden cardiac death, one due to stroke, one due to mesenteric thromboembolism, one due to arrhythmia and one due to sepsis. Spontaneous sustained ventricular tachycardia was noticed in 6 patients from the inducible group and one from the noninducible group (p=0.005). Laboratory induction had a positive predictive value of 24% and a negative predictive value of 98% for developing clinical SMVT.

Events were observed in 24 patients (sudden death in 16, nonsudden cardiac death in 1, spontaneous SVT in 7, and syncope recurrence in 3 patients). Episodes of spontaneous SVT occurred in patients with sudden death (3 patients) or nonsudden death (one patient). Events occurred more often in patients with conduction disturbances and in the inducible group. Cardiac death occurred more frequently in patients with low ejection fraction and also in the inducible group. A significant association existed between sudden or general mortality and SMVT induction (table I). Therefore, SMVT induction had a positive predictive value of 63% and a negative predictive value of 80% for occurrence of events. Cardiac mortality had a positive predictive value of 46% and a negative predictive value of 85%.

Logistic regression analysis had higher probability of SMVT induction among men and a 2.74 higher induction probability for every 10 year increase in age. Induction was also significant, (2.58 times more frequent) for event occurrence and cardiac mortality (table II).

During a mean follow-up of 65.0±38.7 months (median

77), 4 patients with induced ventricular fibrillation to programmed ventricular stimulation did not have events.

Survival curves - Accumulated survival probability was related to general and cardiac mortality and to the proportion free of events from the whole population studied (table III).

The Mantel - Haenszel test was used to compare accumulated survival curves considering SMVT induction as a predictor of survival. Inducible and noninducible patients had significant differences related to general or cardiac death and event occurrence (table IV and figures I, II, III).

Discussion

Population characteristics - Chronic chagasic cardiomyopathy has a male predominance, with a progressive incidence from the third decade of life²⁵. Seventy-eight chagasic patients with a mean age of 46.4±10.7 years old were studied. Forty-five patients were males (57.7%).

Table III - Cumulative survival probability and percentage of patients free of cardiac events

Time (months)	Cumulated survival probability		Percent free of events
	General mortality	Cardiac mortality	
0 - 12	100	100	100
12 - 24	91.7	93.2	93.1
24 - 36	88.7	90.2	89.9
36 - 48	83.9	87.0	86.7
48 - 60	81.9	85.2	82.9
60 - 72	81.9	85.2	80.7
72 - 84	74.7	78.3	71.2
84 - 96	63.6	70.7	63.2
96 - 108	60.2	70.7	63.2
108 - 120	50.6	63.8	44.4
120 - 132	50.6	63.8	35.6

Table I - Correlation between SMVT and event occurrence, cardiac death (CD), sudden death (SD) and general mortality (GM)

Induction of SMVT	Events	CD	SD	GM
Present	15	11	10	12
Absent	9	7	6	10
χ ²	11.07*	7.74*	7.69*	6.03*

Table IV - Cumulative survival probability according general mortality, cardiac mortality and percentage of patients free of cardiac events in inducible (IND) and noninducible (NI) patients

Time (months)	Cumulated survival probability				Percent free of events	
	General mortality		Cardiac mortality		IND	NI
0 - 12	IND	NI	IND	NI	IND	NI
12 - 24	100	100	100	100	100	100
12 - 24	82.9	95.6	87.2	95.6	86.9	95.6
24 - 36	78.4	93.2	82.6	93.2	82.1	93.2
36 - 48	68.6	90.6	72.9	93.2	71.9	93.2
48 - 60	62.9	90.6	67.3	93.2	60.4	93.2
60 - 72	62.9	90.6	67.3	93.2	54.3	93.2
72 - 84	62.9	78.8	67.3	81.5	47.9	81.0
84 - 96	35.9	74.4	42.1	81.5	27.4	81.0
96 - 108	35.9	69.1	42.1	81.5	27.4	81.0
108 - 120	23.9	61.8	31.6	75.0	11.7	64.8
120 - 132		61.8		75.0		50.4
χ ²	7.41*		7.41*		15.37*	

Table II - Regression analysis according to dependent variables: SMVT induction, presence of events and cardiac mortality (CM), confidence interval (CI) 95%

Variable	Dependent	Independent	Odds ratio	CI 95%
		Age	1.14	1.06 - 1.23
Events		SMVT induction	2.58	1.51 - 4.43
CM		SMVT induction	2.17	1.23 - 3.83

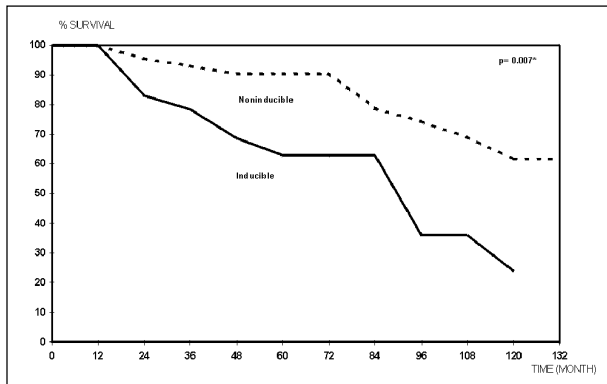


Fig. 1 - Total Mortality.

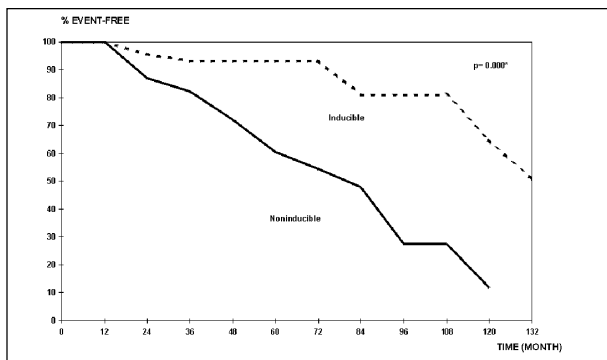


Fig. 2 - Events.

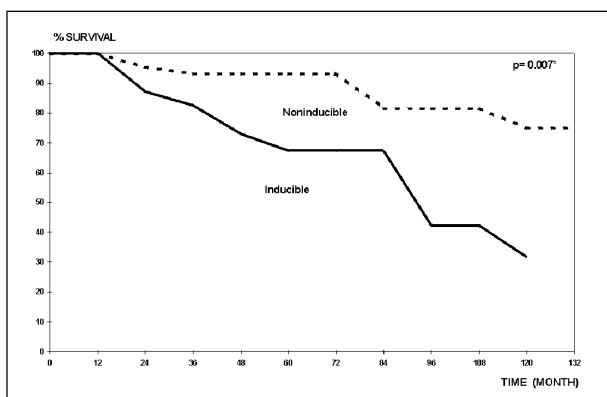


Fig. 3 - Cardiac Mortality.

Conduction disturbances are present in 60 to 87% of patients with Chagas disease, and right bundle branch block with left anterior fascicular block is present in 16 to 39% of patients²⁶⁻²⁸. Our study population showed similar findings with 80.8% of conduction disturbances with predominance of right bundle branch block associated with left anterior fascicular block in 32% of patients. Sinus node dysfunction occurred in 3 patients (3.8%). These data differ from that in the literature that reported an incidence ranging from 18 to 45% among patients with decompensated heart failure. His-Purkinje system dysfunction, corresponding to an increase in HV interval was found in 10 patients (12.8%),

and this finding was similar to the 13.5% reported by Ben-chimol²⁹.

In our study segmental abnormalities occurred in 27 patients (34.6%), 59% in the apex. Reports of this finding in Chagas disease range between 30 to 93%³⁰⁻³³.

Finally, like previous studies³⁴⁻³⁶, coronary disease was not detected by coronary angiography in any of the patients studied.

Correlation between clinical and laboratory variables - In Brazil¹⁷⁻²¹, the induction rate of sustained ventricular arrhythmias in these patients' ranges from 0 to 32%. This wide variation is probably due to population heterogeneity, which includes patients with isolated premature ventricular beats, NSVT, ejection fraction ranging from 0.34 to 0.62 and use of different ventricular stimulation protocols. Studies with chagasic patients including only patients with NSVT on 24-hour Holter monitoring were only reported from our institution^{18,20}. In the current study the induction rate was 32%. Contrary to data in the literature^{37,38}, in our study left ventricular dysfunction was not associated with male gender.

The influence of left ventricular dysfunction on ventricular arrhythmias has been thoroughly studied in coronary disease^{39,40} and in cardiac valve disease⁴¹ but not in dilated cardiomyopathy^{42,43}. In our study, ventricular dysfunction was not related to premature ventricular beats, age or conduction disturbances of surface ECG. Santana⁴⁴ reported that complex premature ventricular beats, especially NSVT, were associated with an increase in cardiothoracic index and functional class II. Carrasco³⁷ studied 556 chronic chagasic patients using left ventricular angiography that showed that ventricular dysfunction and age were related to the presence of complex ventricular arrhythmias. Garzon⁴⁵ reported that in 901 chagasic patients electrocardiographic abnormalities were associated with the presence of low ejection fraction.

In our results global left ventricular dysfunction was not associated with the presence of segmental abnormalities. Apical aneurysms were more common in patients with preserved left ventricular function than in dilated ventricles with global dysfunction^{46,47}.

Sustained monomorphic ventricular tachycardia induction was predominant in males. The intensity of immunologic reaction leading to fibrosis may have been higher in males, intensively compromising the myocardium locally with a greater number of arrhythmogenic circuits as a consequence.

Logistic regression analysis has also shown greater probability of SMVT induction with age and an increase of more than two times for each 10 years of age.

Syncope was also a predictor of SMVT induction. Electrophysiological studies for syncope investigation in chagasic individuals found SMVT induction of 47% and 55%^{12a,13}.

Results in the literature⁴⁸ have reported a controversial association between ventricular complexity and SMVT induction due to programmed ventricular stimulation. However, among chagasic patients, Mendonça¹⁴ reported lack of association between ventricular arrhythmias or NSVT with SMVT induction. These results are similar to ours.

Correlation between ventricular dysfunction and SMVT induction was documented by Da Silva's study¹⁷ with 26 chagasic patients with frequent premature ventricular beats; by De Paola¹⁸ with 27 chagasic patients with NSVT with an induction rate of 19%; and by Mendonça¹⁴ with 60 patients with NSVT, and 20% inducibility. The present study has also found significant correlation between ventricular dysfunction and SMVT induction.

Evidence suggests that in CCC spontaneous SVT uses as a reentrant circuit left ventricular areas of fibrosis or aneurysms, mainly in the inferolateral wall followed by the septum and apex^{49,50}. Spielman⁵¹ reported induction of ventricular tachycardia and ventricular fibrillation among patients with ventricular arrhythmias who had at least one akinetic or dyskinetic zone revealed by radioisotopic ventriculography. Buxton⁵² has also reported that in patients with coronary artery disease, ventricular tachycardia was induced more frequently in the presence of left ventricular aneurysm. In our study, no significant association existed between SMVT induction and segmental abnormalities. De Paola⁵³ found a significant association between the presence of left ventricular aneurysms and spontaneous SVT in chagasic patients; but in that study none of the chagasic patients with NSVT had left ventricular aneurysms.

Variables with significant prognosis - Some variables have negatively influenced CCC prognosis: male gender, cardiac failure, complex ventricular arrhythmias, flutter and atrial fibrillation, ventricular tachycardia, total AV - block and presence of an inactive electrical zone^{14,38,44,54-56}

Our results have not shown a higher frequency of events or cardiac death in male patients. Dias' study⁵⁶ in Bambuí has not shown gender predominance in CCC deaths either in 8.3% of total death in 268 cases.

Atrioventricular block, sinus node dysfunction, neurological mechanism and SVT can be the cause of syncope among chagasic patients¹³. In our study, syncope was not found to be a predictor of events or cardiac death.

No correlation existed between age and occurrence of events or cardiac death in our study. Laranja⁵⁷ analyzed 200 deaths caused by Chagas' disease and found that more than half (55%) of the patients died when they were 21 to 40 years old. In another study Mady⁵⁸ analyzed the survival predictors in a total of 104 chagasic men and did not find a relationship between age and death. Our results were similar to those and can be explained by the fact that NSVT was found in all patients, and the prognosis was linked to the occurrence of sustained ventricular arrhythmias.

We found a significant association between ECG conduction disturbance and clinical events, but not between ECG and death. This fact may be the result of the impact of drugs for treatment of heart failure like angiotensin-converting enzyme inhibitors, with a decrease of in mortality^{59,60}.

The prognostic value of ventricular dysfunction in CCC is well known^{14,44,58}. In our patients the mean ejection fraction was significantly lower in those who died, but this association was not observed for total cardiac events.

The use of ventricular-programmed simulation for risk

stratification in patients with dilated cardiomyopathy is controversial. In patients with CCC and complex ventricular arrhythmias, only 2^{18,20} of 5^{17,21} reports published in the literature, demonstrate a relationship between inducible ventricular arrhythmias with a prognosis during clinical follow-up.

Mendonça¹⁴ determined that in 60 chagasic patients with NSVT with mean ejection fraction of 41%, the inducible rate was 20%. During a mean follow-up time of 49 months, cardiac events and death were higher among the inducible patients. Our results have shown a significant association between event occurrence and SMVT induction, cardiac death and induction, sudden death (SD) and induction and finally between induction and death. Also, logistic rejection showed higher probability of event occurrence and cardiac death among inducible patients, with an odds ratio of 2.58 and 2.17, respectively. The four patients in whom ventricular fibrillation was induced had no cardiac events during a mean follow-up of 65 months. Induction of VF in these patients was considered a nonspecific response to programmed ventricular stimulation⁶¹.

Clinical follow-up - Mortality rates in a heterogeneous population of chagasic patients ranged between 2.8 and 31.1%^{54,57,62-66}. In our study during a mean follow-up of 55.7 months 22 deaths (28.2%) occurred. Our high mortality rate was due to our high risk patients, all with cardiac disease and NSVT.

During clinical follow-up 7 patients needed a permanent pacemaker; 4 patients had complete AV block and 3 patients had sinus node dysfunction. Patients with CCC and AV block have a progressive risk of complete AV block⁶⁷.

Occurrence of spontaneous SMVT during follow-up was also observed in 6 inducible patients and in one noninducible patient. Patients with inducible SMVT have a reentrant circuit and a higher probability of experiencing clinically sustained arrhythmias than noninducible patients do⁶⁸.

Life expectancy - Despite the social, economic and clinical importance of CCC and its morbidity and mortality, few studies about the survival of these patients have been conducted.

Mady⁵⁸ studied chagasic patients with heart failure and found survival expectancy rates of 66% in the first year, 56% in 3 years, and 48% in 5 years. Santana (44) has found a survival rate of 48% in patients with NSVT, and 100% in those with normal ECG in 7 years of follow-up. In our study, the survival rates were 91.7% in the first year; 83.8% in 3 years; 81.9% in 5 years and 50.6% in 10 years and induction was the most relevant predictor of survival and occurrence of events in our patients. Differences in survival rates were probably due to noninclusion in our study of patients with decompensated congestive heart failure.

Clinical Implications - Patients with CCC and NSVT with induction of sustained ventricular arrhythmia have a higher incidence of spontaneous SMVT, cardiac events and mortality, sudden death and total mortality than the noninducible group. Careful clinical evaluation and prospective studies may select therapeutic interventions that may benefit patients who are more prone to cardiac events.

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