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Results of Electrophysiologic Studies in Patients with Acute Chagasic Myocarditis

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Summary

Background: As the acute stage of Chagas' myocarditis is rarely detected, little is known about the electrophysiologic characteristics of that stage.

Hypothesis: This investigation was undertaken to conduct an electrophysiologic study of the properties of the heart during the acute phase of Chagasic myocarditis.

Methods: We studied eight patients who had positive xenodiagnosis, positive mice culture, and positive complement fixation test for Chagas' disease.

Results: Trypanosoma cruzi were identified in all of the patients' stained blood samples. Right ventricular endomyocardial biopsies were obtained, evidencing a distinct infiltrate of lymphocytes that confirmed the diagnosis of acute myocarditis. The cardiac dimensions and the ventricular systolic and diastolic function were preserved in all patients. The electrocardiogram evidenced conduction defects in two patients. The signal-averaged electrocardiogram displayed late potentials in three patients. In the electrophysiologic study, atrial fibrillation or flutter was induced in four patients. When compared with control patients, Chagasic patients were found to have greater values of atrial threshold, A-H interval, and atrioventricular (AV) nodal effective refractory period. The H-V interval was mildly prolonged in two patients, but the dynamic AV nodal conduction was preserved (1:1 conduction during right atrial stimulation at a cycle length of 400 ms) in all the Chagasic patients. The ventricular parameters were within normal limits, and no sustained ventricular arrhythmia could be induced.

Conclusions: Patients with mild acute Chagasic myocarditis may suffer from electrical abnormalities and arrhythmias that are more evident at the supraventricular level and the AV junction.

Key words: acute Chagasic myocarditis, electrophysiologic study

Introduction

Chronic Chagasic myocarditis is a widespread disease in Latin America where it has been estimated to afflict 10 to 20 million people.[1, 2] After the acute infection with the *Trypanosoma cruzi*, the natural history of the disease slowly advances from the asymptomatic stage to an arrhythmic phase. It then evolves to a final stage of dilated myocardiopathy accompanied with heart failure.[3] In most patients, the acute infection and asymptomatic phase are not diagnosed, and little is known about these phases. In the last few years, however, there has been an increase in the number of cases in which an accurate diagnosis of the acute infection has been made.[4] During that acute stage, the clinical picture can vary from a mild form with an acute febrile syndrome but without clinical signs or symptoms of heart disease, to congestive heart failure and even death.[4] To the best of our knowledge, however, the electrophysiologic properties of the heart during the acute phase of Chagasic myocarditis have not been studied by electrophysiology. This is what the present paper is concerned with.

Methods

The procedures were carefully explained to all patients. Those who accepted to participate signed a written informed consent. The study protocol was previously approved by the

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Human Research Committee of our institution and was in accordance with the Declaration of Helsinki.

Patients

Eight patients (7 men) aged 28 ± 12 years with a well-established diagnosis of acute Chagasic myocarditis were included. The inclusion criteria were the following: (1) The patient had experienced an acute febrile syndrome in the 30 days before being enrolled in the study; (2) the patient was a resident of a previously identified rural area where Chagas' disease is endemic; (3) *Trypanosoma cruzi* was identified in the patient's stained blood samples; (4) the patient had a positive xenodiagnosis, positive mice culture, and positive complement fixation test.

The electrophysiologic parameters of these Chagasic patients were compared with those of 125 patients (48 men), aged 34 ± 16 years, who were studied in our electrophysiology laboratory for the evaluation of supraventricular arrhythmias and who had neither structural heart disease nor ventricular dysfunction. Patients with Wolff-Parkinson-White syndrome were excluded from the control group because they have a short H-V interval.

Clinical Noninvasive Evaluation

All the patients underwent exhaustive medical examination, 12-lead conventional electrocardiogram (ECG), signal-averaged ECG, thoracic x-ray, and echo-Doppler evaluation.

Electrophysiological Study

The electrophysiologic study was performed in a fasting antiarrhythmic drug-free state under mild sedation with diazepam. Three recording multipolar catheters (USCI, Div. of C.R. Bard, Inc., Billerica, Mass., and Mansfield Boston SC Corp., Watertown, Mass., U.S.) were placed in the right atrial appendage, His recording position, right ventricular apex, and outflow tract. The sinus node function, intra-atrial conduction, atrioventricular (AV) nodal conduction, and supraventricular arrhythmia inducibility were tested as described elsewhere.[5] Right ventricular programmed stimulation was performed with a Medtronic 5326 programmable stimulator (Medtronic, Inc., Minneapolis, Minn, U.S.) using square-wave stimuli lasting 1.5 ms with an intensity twice that of the diastolic threshold. For right ventricular programmed stimulation, two cycle lengths (600, 500 ms) were routinely used, with up to three extrastimuli delivered in the apex and outflow tract. Neither left ventricular programmed stimulation nor isoproterenol infusion was used.

When sustained arrhythmia (i.e., one lasting more than 30 s or one that produced hemodynamic collapse) could be induced, the stimulation protocol was repeated to confirm the reproducibility of arrhythmia induction. If a sustained arrhythmia could be induced and reproduced, then the patient was classified as *inducible*; if not, the patient was classified as *noninducible*.

Endomyocardial Biopsy

For electrophysiologic study, a 9 French venous introducer was put in place in the right internal jugular vein. A Stanford (Stanford University, Stanford, Calif., U.S.) bioptome was advanced into the right ventricle, and five tissue samples were obtained for microscopic analysis. The bioptome and the venous introducer were then withdrawn. The tissue samples were stained with hematoxylin-eosin and examined with a high-resolution light microscope.

Statistical Analyses

Alpha value was set at 0.05 and confidence intervals at 95%. The analyses were performed with the Excel® (Microsoft Corp., Redmond, Wash., U.S.) and Graphpad® (Graphpad Software, San Diego, Calif., U.S.) computer programs by means of Student *t*-test, chi-square test, or Fisher's test. Results are expressed as the mean ± the standard deviation.

Results

Clinical and Noninvasive Evaluations

No complication arose from the procedures. The age of the Chagasic patients and that of the controls was not significantly different, but the gender distribution was ($p = 0.008$). However, a comparative analysis between the electrophysiologic parameters of the male and those of the female patients of the control group revealed no statistically significant differences. Clinical cardiovascular examination and chest x-ray were normal in all patients, as were cardiac systolic and diastolic function, cardiac volumes, and ejection fraction (end-diastolic volume = 98 ± 14 cc; end-systolic volume = 34 ± 12 cc; ejection fraction = 0.60 ± 0.06). The 12-lead ECG displayed abnormalities in two patients (see Table I and below) and the signal-averaged ECG evidenced late potentials (filtered QRS

TABLE I Some clinical and electrophysiologic characteristics of the patient with acute Chagasic myocarditis

Patient No.	ECG	SAECG	EF	Induced arrhythmia
1	Normal	+	0.63	Atrial fibrillation
2	RBBB+LAFB	−	0.58	RVR
3	Normal	−	0.58	None
4	Normal	−	0.55	None
5	Normal	−	0.70	Atrial flutter
6	Normal	−	0.60	Atrial fibrillation
7	1° AVB	+	0.60	Atrial flutter
8	Normal	+	0.53	None

Abbreviations: ECG = electrocardiographic findings, SAECG = signal-averaged electrocardiogram, EF = left ventricular ejection fraction, RBBB + LAFB = right bundle-branch block and left anterior fascicular block, RVR = repetitive ventricular responses, 1° AVB = first degree atrioventricular block.

duration > 140 ms, root mean square voltage < 20 μV, and low amplitude signal duration filtered at 40–250 Hz > 0.38 ms) in three patients.

Electrophysiologic Study

In the electrophysiologic study, a sustained, reproducible, supraventricular arrhythmia (atrial fibrillation and/or atrial flutter) could be induced in half of the patients by means of programmed atrial stimulation using one extrastimulus. Atrial flutters were terminated by means of overdrive stimulation. Atrial fibrillation had to be converted to sinus rhythm with electrical cardioversion. The percentage of inducibility (50%) of these arrhythmias is significantly greater than that observed in the control group (3%) ($p = 0.00001$).

The atrial stimulation threshold was significantly higher in the Chagasic patients than in the control group (Table II). The atrial effective refractory period, the mean right atrial conduction time (measured from the onset of atrial activation recorded with the high right atrial catheter to the atrial activation recorded with the His catheter), and the mean corrected sinus node recovery time were within the normal range and did not differ from the control group values. The A-H interval and the AV nodal effective refractory period were significantly longer in the Chagasic patients, but their values were still within normal limits. One Chagasic patient had a prolonged corrected sinus node recovery time. Two other patients exhibited a prolonged H-V interval (60 ms) and one of these also had an abnormal A-H interval. The ECG of these two patients displayed a right bundle-branch block associated with a left anterior fascicular block and a first-degree AV block, respectively. However, the dynamic AV node conduction was preserved in all the patients, and all of them were capable of 1:1 AV nodal conduction when submitted to atrial stimulation with a cycle length of 400 ms.

TABLE II Some of the electrophysiologically measured parameters in the Chagasic patients compared with patients without structural heart disease

Parameter	Chagasic patients	Control patients	p Value
Atrial threshold (mA)	0.90 ± 0.45	0.64 ± 0.25	0.0294
AERF (ms)	218.57 ± 21.93	208.00 ± 38.40	0.4663
RACT (ms)	25.00 ± 4.62	27.50 ± 11.98	0.5723
CSNRT (ms)	353.75 ± 167.24	274.16 ± 110.68	0.1292
A-H (ms)	103.75 ± 24.79	78.3 ± 23.9	0.0091
H-V (ms)	50.62 ± 8.21	45.29 ± 9.45	0.1491
A-V ERP (ms)	322.50 ± 72.65	250.68 ± 52.83	0.0006
RVT (mA)	0.48 ± 0.18	0.43 ± 0.18	0.4779
RVERP (ms)	231.25 ± 19.59	230.58 ± 22.21	0.9425

Abbreviations: mA = milliamperes, ms = milliseconds, AERF = atrial effective refractory period, RACT = right atrial conduction time measured from the right atrial appendage to the His-positioned catheter, CSNRT = corrected sinus node recovery time, A-V ERP = atrioventricular nodal effective refractory period, RVT = right ventricular threshold, RVERP = right ventricular effective refractory period.

The right ventricular threshold and effective refractory periods were within normal limits and did not differ from the control group values. Besides, no sustained ventricular arrhythmia could be induced by programmed stimulation.

Endomyocardial Biopsy

In seven patients, the biopsy showed a distinct infiltrate of lymphocytes that confirmed the diagnosis of acute myocarditis (Fig. 1). In the remaining patient, the biopsy specimen displayed considerable interstitial fibrosis.

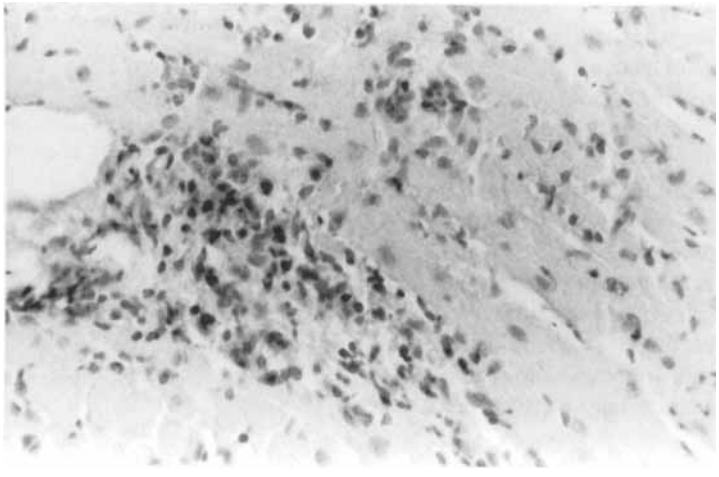

FIG. 1 Right ventricular endomyocardial biopsy specimen stained with hematoxylin-eosin. The biopsy showed a distinct infiltrate of lymphocytes that confirmed the diagnosis of acute myocarditis.

Discussion

This small group of patients had evidence of acute Chagasic myocarditis without either left ventricular systolic, diastolic dysfunction or cardiac enlargement. Thus, this group represents a mild form of acute Chagasic myocarditis that was observed in 21% of the acute Chagasic patients recently reported in our country.[4] Although these patients had the less severe form of the acute disease, in the majority the electrophysiologically measured parameters at the atrial level and the AV junction demonstrated significant differences when compared with the control group. Moreover, half of our patients also had inducible atrial flutter or atrial fibrillation.

The possibility of suffering from atrial fibrillation and/or flutter should encourage us to consider that these arrhythmias could be a significant morbid factor that could contribute to the more severe evolution seen in some patients. In fact, paroxysmal atrial fibrillation was recorded in 12 of 58 acute Chagasic patients.[4] It is then possible that these arrhythmias can produce myocardial dysfunction or embolic events and can be responsible for the more severe picture that has been reported in other patients affected by acute Chagasic myocarditis.

In a recent publication, Campos de Carvalho *et al.*[6] reported that in rat cardiac myocytes cultures infected with *Trypanosoma cruzi*, the intracellular presence of amastigotes was clearly associated with a marked decrease in junctional conductance. These authors also reported a significant reduction in sinus node firing rate and third-degree AV block in isolated rabbit hearts perfused with sera obtained from chronically infected rabbits. Therefore, it is possible that during the acute phase of Chagasic myocarditis, the presence of the parasite or the multiple humoral factors associated with it could be responsible for the delay in conduction that could in turn favor the appearance of reentrant arrhythmias such as atrial flutter or atrial fibrillation.

The only electrical abnormality that could be detected at the ventricular level was the capability of inducing repetitive ventricular response in one of the patients. However, this finding is difficult to interpret because it has been considered not to be a specific response.[7] Along the same line, three patients had late potentials, but in none of them a ventricular arrhythmia could be induced. It is possible that the late potentials in these patients were the results of conduction delay at the ventricular level.

The right ventricular biopsy results (i.e., an intense lymphocytic infiltrate suggesting a widespread acute inflammatory response at the ventricular level) indicate that the ventricles are severely affected during the acute stage of Chagas' heart disease. Our results cannot explain why the functional electrical abnormalities are more evident at the supraventricular level. It is possible that during the acute myocardial insult, the parasites or the humoral and tissular responses to their presence have a predominant atrial localization. Indeed, in an autopsy examination of patients who died with acute Chagasic myocarditis, Andrade and Miziara[8] found more marked alterations in the atria. It is also possible that the atria—being thinner and with less myocardial mass—are more susceptible to acute infection derangement.

The number of patients studied was very small and they had a mild form of acute Chagasic myocarditis. Consequently, there is an inherent limitation in using these data for characterizing the acute stage of the disease in all patients affected by acute Chagasic myocarditis. However, even though our group was small, by using the tests available today to evaluate cardiac function, we found electrical abnormalities without systolic or diastolic dysfunction. This leads us to think that in Chagasic myocarditis there are direct factors that alter the electrical function of the heart, and that cardiac arrhythmias and conduction disturbances are not a secondary expression of functional mechanical damage.

We conclude that, in mild acute Chagasic myocarditis, electrical abnormalities and arrhythmias that are more evident at the supraventricular level and at the AV junction can be present.

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