Adrenergic Nervous System Influences on the Induction of Ventricular Tachycardia

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Background: Sudden cardiac death is a major cause of mortality in western countries and the ventricular tachyarrhythmias are mainly involved in this regard. The adrenergic autonomic nervous system has influences in provoking life-threatening arrhythmias, and the prevention of such arrhythmias with beta-blockers supports this viewpoint. To evaluate the effect of the adrenergic nervous system and some catecholamine-releasing stimuli on the induction of ventricular tachycardia, we decided to explore the occurrence of ventricular tachycardia in patients subjected to three consecutive tests, exercise testing, isoproterenol infusion, and mental stress.

Methods: Nineteen subjects who experienced exercise test-induced ventricular tachycardia were subjected to an isoproterenol infusion and mental stress. All but one patient had cardiac disease, with 70% due to Chagas' disease. Seventeen of the 19 study subjects had normal ventricular function.

Results: Exercise test-induced ventricular tachycardia was nonsustained in 17 patients and sustained in 2 cases. Isoproterenol infusion induced nonsustained ventricular tachycardia in 9 of 19 patients. Mental stress, on its own, was able to induce nonsustained ventricular tachycardia in 2 of 19 patients.

Conclusions: Among patients preselected for exercise-induced ventricular tachycardia, almost half could be induced into ventricular tachycardia by isoproterenol infusion. Mental stress was a less powerful inducer of ventricular arrhythmias in this study group. **A.N.E. 2002;7(4):281-288**

adrenergic nervous system; ventricular tachycardia; chronic Chagasic myocarditis

Sudden death still remains a major cause of mortality in western countries.¹ Causes leading to such a life-threatening condition are varied and of different nature, while ventricular tachyarrhythmias are mainly involved in this regard. The mechanisms underlying the generation of ventricular tachyarrhythmias result from a complex interaction among multiple factors, one of them being the autonomic nervous system, in particular its adrenergic limb. In fact, there is ample consensus that all cardiac arrhythmias are dependent on the adrenergic nervous system influences, as supported by an important body of experimental, clinical and therapeutic evidence.²

The adrenergic nervous system is known to modulate the function of the cardiovascular system, with different stimuli, i.e., exercise, isoproterenol infusion, or mental stress being likely to enhance its activity, resulting in ventricular tachycardia. In turn, physical exercise stimulates the adrenergic nervous system and may provoke ventricular arrhythmias in normal as well as abnormal hearts. The prevention of such arrhythmias with beta-blockers supports the view of adrenergic nervous system as playing a role in its genesis.³⁻¹² Isoproterenol, a beta-adrenergic agonist, can also induce ventricular tachycardia and it has been used to assess the efficacy of antiarrhythmic drugs.^{13,14} On

the other hand, mental stress can cause malignant ventricular arrhythmias, syncope, or sudden death, even in patients with no apparent structural heart disease.^{15,16}

Given this background, we decided to carry out a study addressed to analyze the appearance of ventricular tachycardia in persons registering no antecedents of arrhythmias that were subjected to three consecutive tests, exercise testing, isoproterenol infusion, and mental stress, each one of them known to induce such a complaint. Many of the recruited volunteers were seropositive for Chagas' disease, which offered the opportunity to assess the influence of the above proposed stimuli in persons prone to develop some form of cardiac arrhythmias.

Given this background, our aim was to evaluate the induction of ventricular arrhythmias by isoproterenol infusion and mental stress in subjects pre-selected on the basis of having exercise-induced ventricular tachycardia.

MATERIAL AND METHODS

Patients

Among 2053 patients subjected to 2464 exercise stress tests (average 1.3 test/patient), we identified 19 patients who experienced VT. These 19 patients developed three or more episodes of exercise-induced nonsustained or sustained ventricular tachycardia. Upon that, patients were explained of the purposes of the study and recruited following obtaining their informed consent to be performed an isoproterenol infusion and mental stress.¹⁷ A complete clinical evaluation, which comprised a 12-lead electrocardiogram (ECG), routine laboratory data, chest x-ray, two-dimensional echocardiogram, and *Trypanosoma cruzi* specific serology was performed. Patients with unstable angina, ST-T segment ischemic changes during exercise, ventricular preexcitation, QTc > 440 ms, or electrolyte imbalances were excluded. All antiarrhythmic drugs were discontinued at least five half lives before the exercise stress test was carried out. Ventricular tachycardia was defined as ≥ 3 sequential ventricular complexes at a rate of ≥ 100 beats/min. If such arrhythmia lasted more than 30 sec or resulted in cardiovascular collapse, it was defined as sustained ventricular tachycardia, otherwise it was considered to be nonsustained ventricular tachycardia.

Exercise Stress Test

Exercise testing was performed by employing an ergometric bicycle according to the standard Bruce protocol. Twelve-lead ECGs were performed before and after exercise. Leads II as well as V1 or V5 were continuously recorded during exercise and for 9 min afterwards. Criteria for terminating the exercise were occurrence of sustained ventricular tachycardia, ischemic ST segment changes, angina, dyspnea, or fatigue.

Isoproterenol Test

During continuous ECG recording an isoproterenol infusion was started at 1 $\mu\text{g}/\text{m}$ or up to a maximum heart rate of 130 beats/min. The infusion was stopped when the maximum dose (5 $\mu\text{g}/\text{m}$) was achieved, or when the patient attained the maximum heart rate or developed ventricular tachycardia.

Mental Stress

An arithmetic stress¹⁷ was induced by subtracting a 2 digit number from one comprising 3 digits. If this proved to be too difficult, then the patient had to subtract 1 digit number from one containing 2 digits. The physician asked the patient to concentrate on the calculations and to blame himself/herself for lack of effort if the answers were wrong. The test lasted for 2 minutes. During that time, ECG monitoring was performed and stopped if ventricular tachycardia appeared.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD. Differences in the occurrence of ventricular tachycardia upon the inducing tests were analyzed by the McNemar and Cochran Q tests.

RESULTS

The clinical characteristics of patients are presented in Table 1. Before conducting the present investigation, 2464 exercise stress tests were carried out in 2053 patients (average 1.3 test/patient). Among this population, 19 patients had ventricular tachycardia during or shortly after exercise. Their average age was 48.3 ± 8 years (range 31-63 years). Reasons by which these persons underwent an exercise-testing were due to a previous antecedent

Table 1. Clinical Characteristics of Patients with Ventricular Tachycardia

Case	Sex Age	Cardiopathy	Indication of Study	LV Function	Induced VT Mode			VT	
					EX.	ISP	M.S	Ns	S
1	52 F	CCM	Palpitations	N	+	+		+	
2	42 F	MVP	Palpitations	N	+	+		+	
3	40 M	CCM	Palpitations	N	+	+	+	+	
4	48 M	RV A.D.	Palpitations	N	+			+	
5	31 M	CCM	Evaluation	N	+	+		+	
6	35 F	CCM	Palpitations	↓	+	+		+	
7	40 M	CCM	Palpitations	N	+	+		+	
8	58 F	Normal	Palpitations	N	+	+	+	+	
9	56 M	CCM	Palpitations	N	+	+		+	
10	50 M	AMI	Evaluation	N	+				+
11	54 M	AMI	Evaluation	↓ ↓	+				+
12	52 M	CCM	Palpitations	N	+			+	
13	43 M	CCM	Palpitations	↓ ↓	+			+	
14	63 F	CCM	Presyncope. SB	N	+			+	
15	40 M	CCM	Evaluation	N	+	+		+	
16	43 M	CCM	Evaluation	N	+			+	
17	63 F	CCM	Syncope. SB	N	+			+	
18	58 M	AHT	Evaluation	N	+			+	
19	49 F	CCM	Presyncope. SB.	N	+			+	

AHT = arterial hypertension; AMI = acute myocardial infarction; CCM = chronic chagasic myocardiopathy; EX. = exercise stress test; ISP = isoproterenol; LV = left ventricular; M.S = mental stress; MVP = mitral valve prolapse; RVAD = right ventricular arrhythmogenic dysplasia; SB = sinus bradycardia; N = normal; ↓ = mild; ↓ ↓ = moderate; Ns = nonsustained; S = sustained. Intragroup comparisons for the occurrence of ventricular tachycardia upon each one of the inducing stimuli were significant in all cases, Exercise stress test and isoproterenol tests $P < 0.001$, mental stress $P < 0.05$ (McNemar test).

of exercise-related palpitations in 10 patients, a routine cardiovascular evaluation in 6, and a presyncope plus sinus bradycardia in 1 patient. Thirteen patients were diagnosed as having chronic Chagasic myocardiopathy, 2 patients reported to have had a myocardial infarction, 1 patient presented arterial hypertension, one had mitral valve prolapse, one showed arrhythmogenic right ventricular dysplasia, and one showed no apparent structural heart disease. Two-dimensional echocardiography showed normal ventricular function in 16 patients, mildly diminished in 1 patient, and moderately diminished in 2 patients. Data dealing with variables analyzed during exercise stress test, isoproterenol infusion, and mental stress are shown in Table 2.

Exercise Stress Test

Nineteen subjects experienced VT during the screening exercise test. The average heart rate at which ventricular tachycardia developed was 118.8 ± 38.10 beats/min (range 80-150 beats/min). The average load was 421.87 ± 231.66 kilopond/

meters/min (KPD/m/m) (range 150-900 KPD/m/m). In 3 patients ventricular tachycardia was induced during the maximum exercise and during the recovery period (cases 7, 13, and 16); in another 3 patients ventricular tachycardia was only induced during the recovery phase (cases 3, 11, and 17); whereas in the remaining cases during the maximum effort. In the 2 patients with an old myocardial infarction (cases 10 and 11), the exercise stress test did not induce myocardial ischemia.

The exercise-induced ventricular tachycardia showed the following characteristics: nonsustained in 17 patients and sustained in 2 patients (one reverted with intravenous lidocaine and the other one ceased spontaneously after 60 sec), average cycle length 388.94 ± 75.63 ms (range 260-520 ms). Ventricular tachycardia appeared regular in 11 patients and irregular in 8 patients, monomorphic in 18 patients, and polymorphic in 1 patient. Thirteen of 19 patients had right bundle branch block morphology (suggesting left ventricular origin), while the six additional cases showed left bundle branch block morphology (suggesting right ventricular origin).

Table 2. Variables Used in the Analysis of Ventricular Tachycardia Induced by Exercise, Isoproterenol, and Mental Stress

Variables	Exercise (n = 19)	Isoproterenol (n = 9)	M. Stress (n = 2)
HR "trigger" (bpm)	118,89 ± 38,10	113,55 ± 9,48	117,50 ± 24,69
Nonsustained VT	17	9	2
Beat numbers	5 ± 1.6	6.7 ± 1.8	4 ± 2
Sustained VT	2		
C.L. (msec)	388,94 ± 75,63	371,11 ± 95,58	290 ± 42,42
Regular	11	5	2
Irregular	8	4	
Monomorphic	18	8	2
Polymorphic	1	1	
RBBB		8	
left superior axis	10		
right inferior axis	3		
LBBB			
Left superior axis	4	1	
Right inferior axis	2		2

CL = cycle length; HR = heart rate; LBBB = left bundle branch block; RBBB = right bundle branch block; VT = ventricular tachycardia.

Isoproterenol Infusion

This test induced ventricular tachycardia in 9 of 19 patients who experienced VT during exercise testing. The average heart rate at which ventricular tachycardia developed was 113.55 ± 9.48 beats/min (range 100-125 beats/min). The average doses was $3.3 \pm 0.53 \mu\text{g/m}$ (range 1-4 $\mu\text{g/m}$). Ventricular tachycardia was nonsustained in 9 patients, showing an average cycle length of 371.11 ± 95.58 ms (range 270-520 ms). As regard to its characteristics, ventricular tachycardia was regular in 4 patients, irregular in 5 patients, monomorphic in 8 patients, and polymorphic in 1 patient. A right bundle branch block morphology was seen in 8 patients, with another patient presenting a left bundle branch block morphology.

Mental Stress

Mental stress induced ventricular tachycardia in 2 of 19 pts who experienced VT during exercise testing. One of them had chronic Chagasic myocardopathy, whereas the other one presented no apparent structural heart disease. The average heart rate at the time of detecting ventricular tachycardia was 117.50 ± 24.69 beats/min (range 100-135 beats/min). Ventricular tachycardia was nonsustained, regular, monomorphic, showing a average cycle length of 290 ± 42.42 ms (range 260-320 ms)

with a left bundle branch block morphology in the ECG tracings. The patient without apparent structural heart disease had right ventricular outflow tract ventricular tachycardia.

To get a better insight into the prior clinical status of patients and the adrenergic state that patients achieve when presenting VT, heart rate results before intervention and at the time that VT was induced are presented in Figure 1. It can be seen that patients had an statistically significant raise of their heart rate, irrespective of the stimulus employed for inducing VT. Further comparisons on the relative increase of heart rate with respect to the baseline values revealed no significant differences among the three groups.

DISCUSSION

The influence of adrenergic nervous system on the cardiac muscle can be exerted through the nerve endings, neurogenic origin, or via epinephrine release from the adrenals to circulation, humoral origin. Exercise stress test, isoproterenol infusion, and mental stress are known to stimulate such activity and may lead, therefore, to ventricular tachycardia.

The sympathetic stimulation caused by exercise stress test can produce different effects on the cardiac tissues, depending on the way by which is

Figure 1. Heart rate before applying the stimuli (basal) and at the time that ventricular tachycardia developed. Each point represent an individual result. (A) exercise testing; (B) ● isoproterenol; ○ mental stress. * $P < 0.001$ (Wilcoxon test for two-tailed samples).

transmitted. The neurogenic-mediated activity is characterized by sudden appearance, short duration, and the effects are unequally distributed in the cardiac tissues. The humoral origin behaves in a more progressive way, has a longer duration, and its effects are homogeneous.¹⁴ Thus, exercise can cause ventricular tachyarrhythmia in either diseased or even structurally normal hearts. Some evidence also indicates that changes in the adrenergic tone can be crucial in its induction and maintenance.¹⁸⁻²¹ The fact that ventricular tachycardia in our patient series was induced by exercise adds support to the view of adrenergic stimulation as being essential in the elicitation of such a conduction defect.¹²

Isoproterenol, a beta-adrenergic stimulant, has been used to induce ventricular tachycardia in different situations so as to simulate the effects of a high adrenergic tone.^{8,13,14,22,23} Recently, Brodsky, et al.²⁴ studied a group of 35 patients with ventric-

ular tachycardia unrelated to coronary artery disease or ventricular dysfunction. In that series, exercise stress test induced ventricular tachycardia in 69% of patients and isoproterenol infusion in half of them (33%). In our study isoproterenol-induced ventricular tachycardia was found in 9 (47.36%) of 19 patients which shows a certain degree of sensitivity of these arrhythmias to the adrenergic stimulus. The larger proportion of isoproterenol-induced ventricular tachycardia in our group, compared to that reported by Brodsky, et al, may be due to the fact that most our patients had chronic Chagasic myocardiopathy.

Mental stress is regarded as a risk factor able by itself to cause malignant ventricular tachyarrhythmia and sudden death, specially in the QT long syndrome.^{25,26} Within this setting, mental stress is a very effective way to obtain a pure adrenergic stimulation.¹⁶ In our patient series mental stress induced ventricular tachycardia in 2 cases, one of

Figure 2. Case 3. Patient with chronic Chagasic myocarditis. (A) exercise testing: in recovery phase induced monomorphic nonsustained ventricular tachycardia episodes. (B) Isoproterenol infusion induced the same ventricular arrhythmia. (C) Mental stress caused sinus tachycardia and the appearance of frequent ventricular premature contractions as well as nonsustained ventricular tachycardia, as the preceding ones.

them with a seemingly normal heart and right ventricular outflow tract VT, whereas the other patient had chronic Chagasic myocardiopathy.

During the exercise stress test, there is an increased myocardial oxygen demand. In the presence of coronary artery disease, the result is myocardial ischemia, which can induce ventricular arrhythmia. In our study, no patient showed signs or symptoms of ischemia, although the great majority showed an arrhythmogenic substrate. From these, it may be speculated that ventricular tachycardia were in some way due to changes in the myocardial refractory period along with an accel-

erated impulse conduction velocity by the adrenergic nervous system, the latter being stimulated by the exercise stress test, isoproterenol infusion or mental stress (Fig. 2).

In an experimental model, Inoue and Zipes²⁷ demonstrated that transmural myocardial infarction produced sympathetic denervation in a heterogeneous fashion resulting in catecholamine hypersensitivity.

Chronic Chagasic myocardiopathy (13 cases in our patient series), is an important consequence of *T.cruzi* infection occurring in approximately 30% of previously asymptomatic individuals.²⁸ Chronic

Chagasic myocardopathy is generally symptomless at the beginning, although this picture may further progress to an intermediate stage characterized by mild to moderate heart enlargement, which finally results in a marked cardiomegaly, cardiac failure, and severe arrhythmia.^{29,30} The basic mechanisms underlying the establishment of chronic chagasic lesions are not properly understood. Köberle³¹ has suggested that the neuronal damage occurring during the acute disease constitutes a fundamental pathogenic insult, whereas others have implicated autoimmune reactions^{32,33} and microvascular abnormalities leading to transient and local ischemia³⁴ as being also involved in the generation of myocardial injury. Whatever the case, the chronic inflammatory process and the ensuing chronic healing is likely to mimic changes caused by the ischemic etiology. In this way, it may be speculated that catecholamine-hypersensitivity is partly accounting for the ventricular tachycardia seen in these patients.^{35,36}

The adrenergic nervous system is thought to play a central role in the development of arrhythmias in many patients with heart failure.³⁷ Most of our patients had a normal ventricular function, except three patients in whom the ventricular function was depressed (mild to moderate), but they had no symptoms nor signs of heart failure. Thus, the ventricular arrhythmias detected in our study would not be related to a left ventricular dysfunction but rather to adrenergic nervous system stimulation.

There are several limitations associated with this study. The 19 subjects with exercise induced VT were selected from a large population of subjects who underwent exercise-testing, and thus the problem of selection bias. The mixed etiology of the heart disease and the small sample size limits extrapolation of the findings to other patient groups.

In conclusion, exercise-induced ventricular tachycardia in this group of patients suggests an adrenergic mechanism. In these patients, isoproterenol infusion is a more powerful trigger of VT than mental stress.

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