ORIGINAL ARTICLE

Presence of Dysautonomia as a Predictor of Structural Heart Disease in Patients with Chagas Disease

Presencia de disautonomía como predictor del desarrollo de cardiopatía estructural en pacientes con enfermedad de Chagas

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ABSTRACT

Background: Several studies have demonstrated the presence of autonomic dysfunction in early stages of Chagas disease (ChD). The Valsalva maneuver (VM) has been widely used to assess autonomic function in many conditions. The Valsalva ratio (VR), which the ratio of maximal to minimal heart during the VM, is one of the most widely used tests for assessing autonomic function. The role of dysautonomia assessed by the VR as a predictor of early development of structural heart disease in Chagas disease patients without overt heart disease has not been well studied.
Objective: The aim of this study was to evaluate whether the VR can predict early development of structural cardiac abnormalities during the follow-up of patients with ChD.
Methods: Patients with positive serology test for Chagas disease were screened. Patients with abnormal electrocardiogram (ECG), abnormal 24-hour Holter monitoring or abnormal echocardiogram were excluded. The VM was performed with continuous recording of the R-R interval on the ECG. The VR was calculated by dividing the longest RR interval after VM by the shortest RR interval during VM. A VR <1.1 was considered abnormal result.
The primary end point was the development of structural heart disease, defined as any of the following: left ventricular (LV) dilatation (LV diastolic diameter > 60 mm in men or > 55 mm in women), LV dysfunction [LV ejection fraction (EF) drop > 10 points or LVEF < 50%], complex ventricular arrhythmia or second-degree atrioventricular block type Mobitz II or greater.
Results: A total of 200 patients were included; mean age was 45 ± 8 years and 44% were female. Abnormal VR occurred in 24% (n = 48). Median follow-up was 38 months (interquartile range, IQR, 19 - 43). The primary end point occurred in 4.5% (n = 9).
On multivariate analysis, abnormal VR was an independent predictor of the primary end point (HR 3.81, 95 % CI 2.81- 5.92; p=0.011). The area under the ROC curve was 0.77 (95% CI 0.63-0.92).
Conclusions: An abnormal VR at baseline is a predictor of early development of structural heart disease in patients with ChD considered to be stage 0, with moderate discrimination capacity.

Keywords: Chagas disease - Dysautonomía - Valsalva ratio - Prognosis

RESUMEN

Introducción: Varios estudios han demostrado la presencia de disfunción autonómica en etapas tempranas de la enfermedad de Chagas (ECH). La maniobra de Valsalva (MV) ha sido ampliamente utilizada para evaluar la función autonómica en diversas patologías. El Índice de Valsalva (IV), la relación entre la máxima taquicardia y bradicardia inducidas por la MV estándar, es una de las pruebas más utilizadas para evaluar la función autonómica. El papel de la disautonomía evaluada mediante el IV como predictor temprano del desarrollo de cardiopatía estructural en pacientes con Chagas sin cardiopatía demostrable ha sido poco estudiado.
Objetivo: Evaluar si el IV es un predictor del desarrollo temprano de alteraciones estructurales cardíacas en el seguimiento de pacientes con ECH
Material y métodos: Se incluyeron prospectivamente pacientes con serología positiva de Chagas. Se excluyeron los pacientes con anormalidades en el electrocardiograma (ECG), el ECG Holter de 24 horas o el ecocardiograma. Se realizó una MV con registro continuo del intervalo R-R en el ECG. El IV se calculó dividiendo el intervalo RR más largo después de la MV por el intervalo RR más corto durante la MV. Se consideró IV anormal un valor <1,1. Fue punto final primario del estudio el desarrollo de cardiopatía estructural, definido como uno de los siguientes: dilatación del ventrículo izquierdo (VI) (diámetro diastólico > 60 mm en hombres o >55 mm en mujeres), deterioro de la función ventricular (caída > 10 puntos de la fracción de eyección -FEVI-, o FEVI <5 0%), arritmia ventricular compleja o bloqueo auriculoventricular de segundo grado Mobitz II, o mayor.

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Resultados: Se incluyeron 200 pacientes, edad 45 ± 8 años, 44 % mujeres. Se encontró IV anormal en el 24% (n=48). La mediana de seguimiento fue de 38 meses (rango intercuartílico, RIC, 19-43). El punto final primario se presentó en el 4,5 % (n=9). En el análisis multivariado, el IV anormal fue un predictor independiente del punto final primario (HR 3,81, IC 95 % 2,81- 5,92; p=0,011). El área bajo la curva ROC fue de 0,77 (IC95% 0,63-0,92)
Conclusiones: La presencia de IV anormal basal es un predictor de desarrollo de cardiopatía estructural en pacientes con ECH estadio 0, con una capacidad de discriminación moderada..

Palabras claves: Enfermedad de Chagas - Disautonomía - Índice de Valsalva - Pronóstico

INTRODUCTION

Chagas disease (ChD) remains an important health issue in Latin America and in recent decades it has also spread to other regions including the United States and Europe due to migratory processes. In Argentina, it is estimated to affect between 1.5 and 2 million people, with between 350 000 and 500 000 suffering from some degree of heart disease. (1,2)

The chronic stage of ChD has a variable period in which there is no evidence of structural heart disease or involvement of other organ. This period is known as indeterminate or chronic ChD without overt structural heart disease. (3,4) However, about 30% of patients with positive serology will develop some type of structural heart disease along the course of the disease. In these patients, risk assessment represents an important challenge.

Several studies have demonstrated the presence of autonomic dysfunction in early stages of ChD. (5-8) These abnormalities could be involved in the progression of the disease.

The Valsalva maneuver (VM) has been widely used to assess autonomic function in many conditions. (9) The Valsalva ratio (VR), which is the ratio of maximal to minimal heart during the VM, is one of the most widely used tests for assessing autonomic function, because it is simple, reproducible and inexpensive. (9,10)

The role of dysautonomia assessed by the VR as a predictor of early development of structural heart disease in ChD patients without overt heart disease has not been well studied.

The aim of this study was to evaluate whether the VR, as an expression of dysautonomia, can predict early development of structural cardiac abnormalities during the follow-up of patients with ChD.

METHODS

We conducted a prospective study in a single center with a follow-up program for patients with ChD. Between July 2016 and July 2018, patients with at least two positive serology tests for Trypanosoma cruzi (indirect hemagglutination, ELISA, or indirect immunofluorescence) were included in the study. A medical record was taken to all the patients, including physical examination and electrocardiogram (ECG), Doppler echocardiography and 24-hour Holter monitoring.

To be included, patients should not have overt heart disease, defined as absence of cardiovascular symptoms or signs, normal cardiovascular physical examination, normal ECG, echocardiogram without significant abnormalities and 24-hour Holter monitoring within normal parameters. Patients with a history of hypertension, diabetes mellitus, thyroid disease, ischemic heart disease, neurologic disease or kidney failure were excluded.

Patients who met the inclusion criteria were asked to perform the standard VM. The standard procedure is as follows: the patient lies in the supine position and is asked to blow through a mouthpiece connected to a manometer until reaching an expiratory pressure of 40 mm Hg. Once this pressure is reached, the patient maintains it for 15 seconds under constant supervision. Then, the mouthpiece is released and the patient continues breathing normally. An ECG is continuously recorded throughout the procedure, starting 15 seconds before expiration and continuing for 15 seconds thereafter.

The VR was calculated by measuring (in milliseconds) the shortest RR interval during the maneuver (denominator) and the longest RR interval shortly after the maneuver (numerator). Thus, the formula is: longest RR interval shortly after the maneuver/shortest RR interval during the maneuver = VR (Valsalva ratio). A VR < 1.1 was considered an abnormal result.

Patients were monitored periodically with scheduled medical interviews according to the institutional ChD follow-up program based on medical criteria.

The primary end point was the development of structural heart disease, defined as any of the following: left ventricular (LV) dilatation (LV diastolic diameter > 60 mm in men or > 55 mm in women), LV dysfunction [LV ejection fraction (EF) drop > 10 points or LVEF < 50%), complex ventricular arrhythmia or second-degree atrioventricular block type Mobitz II or greater.

The study was approved by the institutional review board and all the patients signed an informed consent form before being included.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as percentage. Continuous variables with normal distribution were compared using the Student's t test and the Wilcoxon test was used for variables with skewed distributions. Categorical variables were compared using the chi-square test and Fisher's exact test if any of the variables had an expected frequency < 5.

The Cox proportional hazards model was used for univariate analysis of the end point of development of structural heart disease. The VR was included as a continuous variable and as dichotomous variable (normal or abnormal). Those variables that resulted in significant differences between the groups with and without dysautonomia were also included. Predictor variables with a p value < 0.10 on the univariate analysis were included in a multivariate model. A survival analysis was performed using the Kaplan-Meier method for the VR dichotomized into normal/abnormal.

A ROC curve was constructed to establish the area under

the curve (AUC) and evaluate the discriminative capacity of the VR. A p value < 0.05 was considered statistically significant. All calculations were performed using Epi-Info 7 and Statistix 8 software packages. Epidat 3.1 was used to construct the ROC curve.

RESULTS

Of 280 patients evaluated, 80 were excluded for presenting any of the exclusion criteria. A total of 200 patients were included; mean age was 45 ± 8 years and 44% were women. Table 1 shows the baseline characteristics of the population. The VR was 1.22 ± 0.12 and was abnormal in 24% of the patients (n = 48).

The abnormal VR group had higher E/e' ratio on the Doppler echocardiogram (9.48 ± 2.5 vs. 7.1 ± 1.8, p <0.001) and lower S-wave in tissue Doppler imaging (0.08 ± 0.02 vs. 0.10 ± 0.02 cm/s, p = 0.023). In addition, there was trend at the limit of significance in baseline diastolic blood pressure (DBP) and maximum heart rate (HR) reached in the baseline 24-h Holter monitoring. The rest of the variables had no differences between the groups.

Median follow-up was 38 months (interquartile range 19 - 43) and the end point of development of structural heart disease occurred in 4.5% (n=9). Of these, 3 patients had increased diastolic diameter without ventricular dysfunction, LVEF decreased in 1, 4 had ventricular arrhythmia and 1 patient had second-degree AV block. There were no deaths during follow-up and only 1 patient was hospitalized for a scheduled pacemaker implantation.

Table 2 shows the univariate and multivariate analysis for the primary end point.

On multivariate analysis, both VR as a continuous variable (HR 1.02, 95 % CI 1.01-1.06, p = 0.042) and abnormal VR (HR 3.81, 95 % CI 2.81- 5.92; p=0.011) were independent predictors of development of heart disease. Figure 1 shows the Kaplan-Meier curve and the ROC curve. The area under the ROC curve was 0.77 (95% CI 0.62- 0.93) (Figure 2).

DISCUSSION

In our study, we found that in a population of patients with ChD without overt heart disease, an abnormal VR was associated with early development of structural heart disease at a relatively short follow-up period of 3 years. Patients with an abnormal VR had a more than 3.5-fold increased likelihood of developing early heart disease, with moderate discrimination ability (AUC 0.77).

Over 20 years ago, Olivera et al. (11) found a reduction in VR among patients with ChD without overt cardiovascular disease compared to healthy controls. In addition, during follow-up, abnormal VR was associated with the development of second-degree AV block in ChD patients. Later, Ribeiro et al. (12) published a meta-analysis of 7 studies with more than 350

Table 1. Baseline characteristics

	Total (n=200)	Normal VR (n=152)	Abnormal VR (n = 48)	p
Age (years)	47 (6)	48 (5)	46 (5)	0.176
Women, n (%)	89 (44.5)	67 (44)	22 (45)	0.655
SBP (mm Hg)	117 (14)	117 (14)	116 (15)	0.712
DBP (mm Hg)	68 (11)	69 (10)	66 (13)	0.053
Valsalva ratio	1.22 (0.12)	1.32 (0.10)	1.01 (0.02)	<0.001
24-h Holter monitoring				
Mean HR	73 (8)	73 (8)	72 (7)	0.423
Minimum HR (bpm)	52 (6)	52 (6)	53 (4)	0.825
Maximum HR (bpm)	120 (15)	121 (22)	115 (15)	0.052
Echocardiogram				
LVDD (mm)	47 (4.2)	47 (4.4)	46 (3.7)	0.721
IVS (mm)	9.2 (1.1)	9.2 (1.1)	9.5 (2.2)	0.232
LAA (cm2)	17.5 (3.9)	18.1 (3.6)	17.4 (4)	0.303
LVEF	63 (5)	63 (5)	63 (5)	0.675
E/A ratio	1.26 (0.43)	1.21 (0.4)	1.28 (0.35)	0.324
E/e' ratio	7.9 (3.1)	7.1 (1.8)	9.48 (2.5)	<0.001
S-wave TDI (m/s)	0.09 (0.02)	0.10 (0.02)	0.08 (0.02)	0.023

DBP: diastolic blood pressure; HR: heart rate; IVS: interventricular septum in diastole; LAA: left atrial area; LVEDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; TDI: Tissue Doppler imaging; VR: Valsalva ratio
Quantitative variables are presented as mean (SD).

patients (including the study by Olivera previously mentioned) and found that the VR was decreased in patients with ChD without overt structural heart disease compared to patients without ChD.

The VR assesses the integrity of cardiac autonomic function based on heart rate responses associated with the baroreflex mechanism which is responsible for stabilizing blood pressure. (9) It is a simple, reproducible, inexpensive method that does not require major equipment. However, it is important to note that the VM involves a complex mechanism of autonomic regulation which encompasses the sympathetic and parasympathetic nervous systems. During the maneuver, blood pressure and bradycardia occur simultaneously, while at the end of the test blood pressure decreases and heart rate increases. Thus, a normal VR reflects an adequate baroreceptor response to the rise and fall of blood pressure, while a reduced VR reflects vasovagal dysfunction. (13,14)

Traditionally, a VR > 1.5 has been considered normal. (10) However, some studies have considered an abnormal VR when it is ≤ 1.1. (15-17) We decided to use this latter cut-off point because it is more specific of autonomic dysfunction. (17)

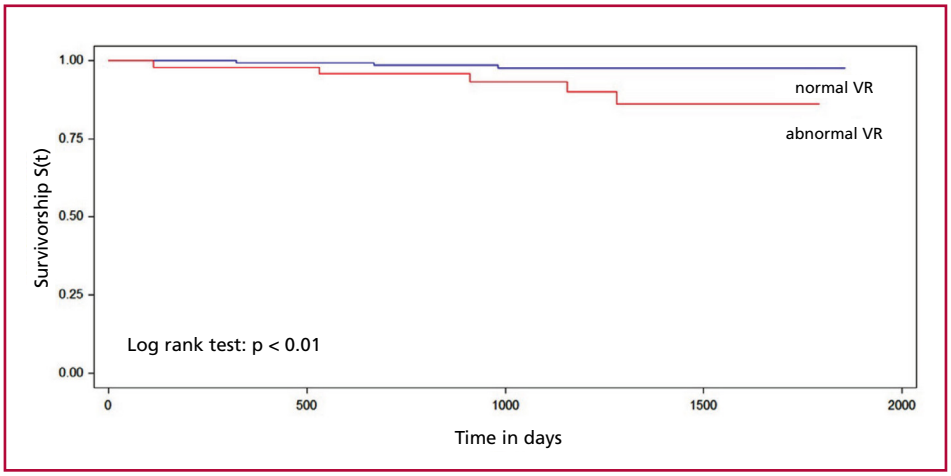
Impaired autonomic function has also been demonstrated in early stages of ChD compared to controls using other methods, such as heart rate variability, respiratory sinus arrhythmia magnitude (18,19) or chronotropic incompetence during exercise stress test. (19) These abnormalities occur early in the course of the disease and before the development of left ventricular dysfunction. (20) However, these tests have not evaluated whether the presence of dysautonomia predicts progression to ChD. Recently, a small study found a higher rate of exercise-induced ventricular arrhythmias and autonomic dysfunction in ChD patients without overt heart disease compared to controls without ChD. (21) Moraes et al. analyzed a cohort of 550 elderly patients with positive serology for ChD in Brazil, followed-up for 14years and found that the presence of dysautonomia was not independently associated with sudden death after adjusting for age and cardiovascular risk factors. (22)

The pathogenesis of vagal dysfunction remains unclear. Some authors have described denervation related to parasympathetic neuroganglionar lesions probably due to inflammation. (23) The role of circulating autoantibodies against muscarinic receptors that could cause desensitization and/or downregulation of these receptors has also been studied. (8) Several studies have shown increased activity of anti-M2 and anti-β1 antibodies in ChD patients with evidence

Table 2. Univariate and multivariate analysis for the primary end point

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
VR (continuous)	1.03	1.01 – 1.04	0.042	1.02	1.01-1.06	0.042
Abnormal VR	4.31	2.76 – 6.22	0.012	3.81	2.81 – 5.92	0.011
E/e' ratio	1.03	0.99-1.04	0.074	1.01	0.93-1.06	0.212
S-wave TDI	1.01	0.93-1.02	0.224	--	--	--

95% CI: 95% confidence interval: HR: hazard ratio: TDI: VR: Valsalva ratio: TDI: Tissue Doppler imaging



VR: Valsalva ratio

Fig. 1. Kaplan-Meier curve: normal/abnormal VR for the primary end point of development of structural heart disease.

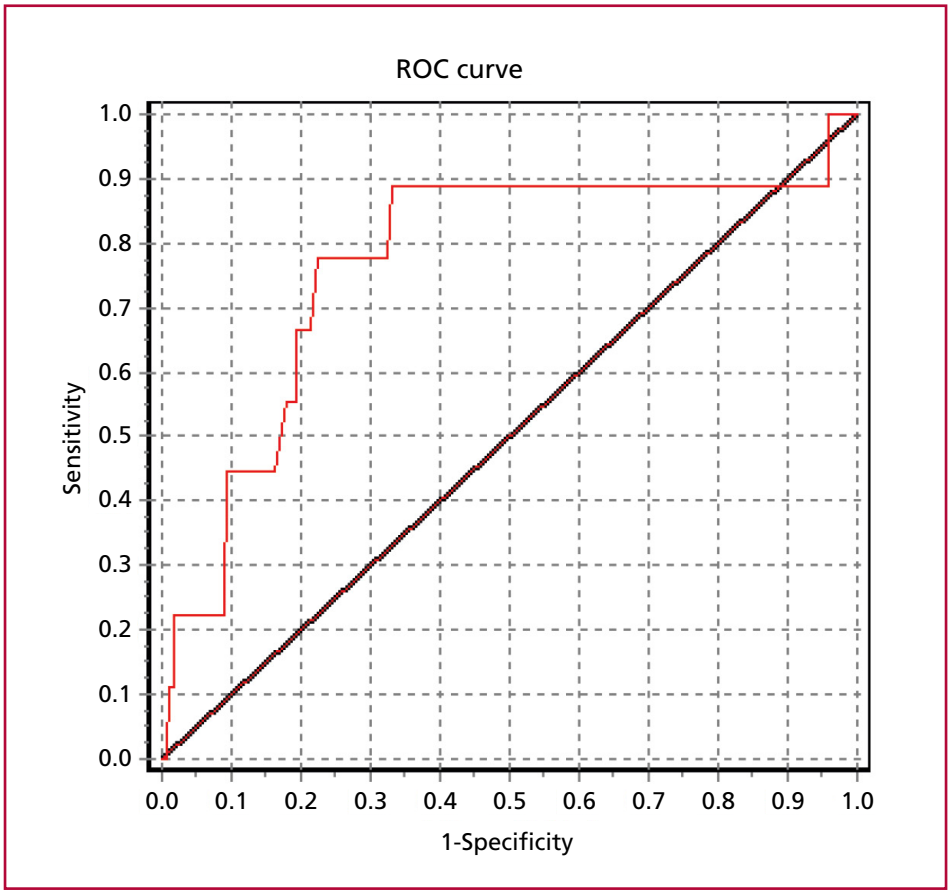


Fig. 2. ROC curve. VR as a continuous variable for the primary end point of development of structural heart disease.

AUC: 0.77 (95% CI: 0.62-0.93)
VR: Valsalva ratio

of dysautonomia but with preserved ventricular function. (5)

In the present study, we found that progression to structural heart disease was 4.5% in slightly more than 3 years, which is about 1.4% per year. A recently published meta-analysis that included 23 studies found an average progression rate of 1.9% per year in patients with indeterminate ChD. This review included studies conducted in Argentina and Brazil more than 10 years ago. (24) More recently, a cohort of patients with indeterminate ChD showed a progression rate of 1.48% per year. (25) Notably, the events were mild, and no patients died during follow-up. This is similar to the systematic review by Gonzalez et al. , which revealed a remarkably low incidence of sudden cardiac death in patients with ChD without overt disease. (26)

Study limitations

Our study has some limitations. First, it is a single-center study, with a relatively short follow-up period for the type of disease. Although the progression rate was similar to the one reported, the small number of events limits the analysis. Dysautonomia was assessed using a single method, the VR. Most studies used more than one method to assess dysautonomia. We decided to use the VR because it is inexpensive, easy to perform and quite feasible to use in daily practice.

CONCLUSION

An abnormal baseline VR is a predictor of early development of structural heart disease in patients with ChD considered to be stage 0, with moderate discrimination ability.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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