Evaluation of the Autonomic Function in Patients with Hypertrophic Cardiomyopathy with and without Syncope

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Abstract

Background: Several mechanisms may be involved in the trigger of syncope in patients with hypertrophic cardiomyopathy (HCM), including hemodynamic collapses that might be related to an autonomic imbalance.

Objective: To evaluate and compare the autonomic function of patients presenting HCM with unexplained syncope (US) to those without syncope.

Methods: Thirty-seven patients were included, 16 with US and 21 without syncope. Their autonomic function was assessed by spontaneous and phenylephrine induced baroreflex sensitivity (BRS), by heart rate variability (HRV) in time domain during 24-hour Holter and in frequency domain (spectral analysis), both in supine position and at 70° head-up tilt (HUT).

Results: The spontaneous BRS was similar in both groups (16,46 ± 12,99 vs. 18,31 ± 9,88 ms/mmHg, p = 0,464), as was phenylephrine-induced BRS (18,33 ± 9,31 vs. 15,83 ± 15,48 ms/mmHg, p = 0,521). No differences were observed in SDNN (137,69 ± 36,62 vs . 145,95 ± 38,07 ms, p = 0,389). The group presenting syncope had a significantly lower RMSSD (24,88 ± 10,03 vs. 35,58 ± 16,43 ms, p = 0,042) and a tendency to lower pNN50 (4,51 ± 3,78 vs . 8,83 ± 7,98%, p =0,085) and lower values of the high frequency component of HRV spectral analysis at rest (637,59 ± 1.295,53 vs. 782,65 ± 1.264,14 ms2, p = 0,075). No significant difference was observed in response to HUT (p = 0,053). HUT sensitivity, specificity and accuracy in identifying the etiology of US in HCM patients were 6%, 66% and 40%, respectively.

Conclusions: A lower parasympathetic tone was observed in HCM patients with US, but the clinical relevance of this finding remains unclear. HUT is not a valuable tool for evaluating the origin of syncope in these patients, mainly because of its poor specificity. (Arq Bras Cardiol. 2013;100(2):180-186)

Keywords: Cardiomyopathy, hypertrophic; syncope; autonomic nervous system.

Introduction

Unexplained syncope is considered a major risk factor for sudden death in patients with hypertrophic cardiomyopathy (HCM), especially in young people[1]. Nevertheless, its low sensitivity and specificity is explained by the several possible mechanisms involved in the pathogenesis of this symptom, which may or may not be associated with the underlying cardiac disease[2-7].

It has recently been demonstrated that patients with HCM may have an abnormal vascular control, presenting with hypotension during exercise[8,9] or even during daily activities[10], as a result of an exaggerated drop in systemic vascular resistance, because of an impaired forearm vasoconstriction or a paradoxical vasodilatation. This abnormality may determine syncope or near syncope[10] and is probably related to a deficiency in the afferent limb of the cardiopulmonary reflex arc[11], suggesting that an autonomic nervous system (ANS) dysfunction may play a role in the development of these symptoms.

Despite these recent reports, few studies have compared HCM patients with and without history of unexplained syncope. Considering the possible involvement of the autonomic nervous system in the pathogenesis of this disorder, the aim of this study was to evaluate and compare the autonomic nervous system function, represented by heart rate variability, baroreflex sensitivity and response to orthostatic stress, in HCM patients with and without unexplained syncope.

Methods

Patients were prospectively selected between April 2007 and August 2009. The diagnosis of HCM was based on the finding of a LV hypertrophy equal to or greater than 15 mm in the absence of either cardiac or systemic disease that

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could explain this abnormality. Exclusion criteria were an age older than 60 years (n = 4), a cardiac rhythm other than a sinus rhythm (n = 4), syncope episodes associated with atrial arrhythmias (n = 3), previous miectomy (n = 1), an outflow tract gradient greater than 70 mmHg (n = 2), contraindications for interrupting antiarrhythmic drugs (n = 1), systolic dysfunction (n = 1) and blood pressure exceeding 160/90 mmHg at the first evaluation. The patients were divided in two groups based on their history of previous syncope episodes. Therefore, the final study group involved 37 patients, 16 with and 21 without previous syncope episodes (Tables 1 and 2). In the group presenting syncope, it was not possible to identify arrhythmic causes during the 24-hour Holter monitoring, and no significant outflow tract obstruction (defined as gradient greater than 50 mmHg) had been observed by echocardiogram at rest, except in one patient who presented an outflow tract gradient of 68 mmHg. Intraventricular gradient greater than 30 mmHg was found in 5 (33,3%) patients in syncope group and in 3 (14,3%) patients without syncope (p = 0,175).

Among the patients submitted to exercise test (93,8% of syncope group patients and 90,5% of without syncope group), we found that abnormal blood pressure response to exercise was similar between the groups (26,67 vs. 21,05%, p = 0,618).

Study protocol

The evaluation was performed after the hospital's Ethical Committee approval. Written informed consent was obtained from all patients. Patients arrived between 8 and 9 AM, after a fasting period of at least 6 hours. All cardioactive medications were discontinued for at least five half-lives before the study.

Initial evaluation

Patients were asked to answer a personal and family history questionnaire. Data from a rest electrocardiogram, echocardiogram, brain natriuretic peptide dosage and blood pressure (BP) response to exercise were then collected. Blood pressure response was considered abnormal if there was a drop or if the increase in the systolic BP was lower than 20 mmHg.

Blood pressure and electrocardiogram monitoring

The electrocardiogram and beat-to-beat BP measurements were obtained and analyzed by the Task Force System (CNSystems Medizintechnik GmbH, Graz, Austria). After monitoring and with a peripheral venous access in an antecubital vein, the patient remained resting in the supine position for at least 15 minutes.

Spontaneous baroreflex sensitivity (BRS)

After the rest period, 15 consecutive minutes of continuous systolic BP and heart rate were registered. The spontaneous BRS was analyzed by the sequence method, which is based on the identification of the spontaneous occurrence of three or more beats that are characterized by a progressive increase in the systolic BP associated with prolongation of the RR interval, or by a progressive decrease in the systolic BP associated with a reduction of the RR interval. This identification was automatic and the data were considered eligible when modifications of the systolic BP and the RR interval were equal to or greater than 1 mmHg e 5ms, respectively.

Phenylephrine induced baroreflex sensitivity

Patients were maintained on continuous BP and electrocardiogram monitoring. The vasoconstrictor agent phenylephrine was administered intravenously (2 to 4 mcg/kg), at least three bolus in 10-minute intervals, to produce an increase in the systolic BP of 15 to 40 mmHg. The consecutive values of the systolic BP and the corresponding RR intervals,

Table 1 - Clinical characteristics of patients with and without previous history of syncope

Variable	With syncope n =16	Without syncope n = 21	p
Age, years, mean±sd (median)	36.31 ± 13.34 (36)	37.52 ± 13.27 (38)	0.818
Male gender, n(%)	9 (56.3)	14 (66.7)	0.517
FC II or III NYHA, n(%)	6 (37.5)	4 (19.04)	0.244
Medical Therapy, n(%)	13 (81.3)	16 (76.2)	0.711
Beta-blocker therapy, n(%)	9 (56.3)	14 (66.7)	0.335
Atrial fibrillation history, n(%)	4 (25.0)	0 (00)	0.015
Family history of SD < 50y,n(%)	11 (68.8)	8 (38.1)	0.065
Family history of HCM, n(%)	9 (56.3)	8 (38.1)	0.272
AA/hour, mean±sd (median)	5.20 ± 9.68 (0.37)	33.35 ± 127.93 (0.55)	0.854
VA/hour, mean±sd (median)	6.96 ± 20.05 (0.85)	17.80 ± 39.56 (2.41)	0.036
Isolated VA, mean± sd (median)	160.44 ± 473.72 (14.5)	412.76 ± 936.87 (53)	0.034
Pared VA, mean±sd (median)	2.00 ± 4.32 (0)	4.00 ± 7.69 (0)	0.651
NSVT, n (%)	5 (31.30)	6 (28.60)	0.860
BNP, pg/ml, mean±sd (median)	196.86 ± 181.49 (101.50)	399.22 ± 610.39 (142.50)	0.414

AA : atrial arrhythmia; BNP : brain natriuretic peptide; FC : functional class; HCM : hypertrophic cardiomyopathy; NYHA : New York Heart Association; NSTV : non-sustained ventricular tachycardia; sd : standard-deviation; SD : sudden death; VA : ventricular arrhythmia.

Table 2 - Echocardiographic characteristics of patients with and without previous history of syncope

Variable	With syncope (n=15)	Without syncope (n=21)	p
Gradient, mean±sd, (median)	18.42 ± 21.57 (6.8)	12.61 ± 16.74 (4.8)	0.629
Gradient > 30mmHg, n(%)	5 (33.33)	3 (14.3)	0.175
LV thickness, mm, mean±sd (median)	22.13 ± 4.81 (21)	26.19 ± 9.61 (24)	0.088
LV thickness ≥ 30mm, n(%)	2 (13.33)	4 (19.0)	0.650
LV diastolic dimension, mm, mean±sd (median)	42.8 ± 5.16 (43)	41.29 ± 6.54 (41)	0.641
LV systolic dimension, mm, mean±sd (median)	24.93 ± 3.85 (25)	23.90 ± 6.09 (25)	0.723
LA dimension, mm, mean±sd (median)	42.27 ± 6.67 (42)	41.24 ± 6.48 (41)	0.531
LVEF, %, mean±sd (median)	73.51 ± 5.84 (72)	73.00 ± 8.47 (72)	0.974
Diastolic dysfunction, n(%)	9 (60.00)	11 (52.4)	0.650

LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; sd: standard-deviation.

considered one beat later, were plotted, and then a linear regression graphic was constructed. The inclination of this line represented the quantitative measurement of the BRS. We considered only those ramps in which the correlation coefficient (r^2) was greater than 0.60. The average of these measurements was calculated for each patient.

Head-up tilting (HUT)

Patients were exposed to 70 degree tilting for 40 minutes on an electrically operated tilt table with a footboard support and two security belts, one at the level of the thorax and the other at the level of the knees. In case of a positive response to HUT, the table was immediately returned to a supine position. The European Society of Cardiology criteria were used to define the responses to HUT[12].

Heart rate variability (HRV)

The HRV was acquired in time and frequency domains. The time domain variables of HRV considered were the standard deviation of normal RR intervals (SDNN), the root mean square of successive differences (RMSSD) and the percentage of adjacent normal RR intervals that differ by at least 50 ms (pNN50) during 24 hours of electrocardiogram recording. In the frequency domain, the high (0.15–0.4Hz), low (0.04–0.15Hz) and very low (0–0.04Hz) frequency bands and the total power density of the spectrum were considered, in absolute values and in normalized units, at rest (for 15 minutes) and in the first 5 minutes of 70 degree tilting.

Data analysis

Categorical variables are expressed as absolute (n) and relative frequencies (%). The association of these variables and the previous history of syncope were evaluated by the chi-squared test, adjusted by Fisher statistics. Quantitative variables are expressed as the mean value ± standard deviation and median; the comparison between the groups was performed using the Mann-Whitney test, once not all variables studied were normally distributed. For the variables studied at two moments in time, the Mann-Whitney test was used to verify the differences between the groups at the moments studied. Then, the Wilcoxon test was applied to verify the differences between the two times of observation. A p value < 0.05 was considered significant.

Results

Spontaneous baroreflex sensitivity

No significant difference was found in the spontaneous BRS when the patients with and without syncope were compared (16.46 ± 12.99 *vs.* 18.31 ± 9.88 ms/mmHg; p = 0.464). When only the values of spontaneous BRS characterized by progressive systolic BP increases and RR interval prolongations were considered, no statistically significant difference was found between the groups (18.48 ± 17.42 *vs.* 18.95 ± 11.20 ms/mmHg; p = 0.373). A similar response was noted when the values characterized by the decrease of the systolic BP and RR interval were considered (15.17 ± 9.32 *vs.* 17.45 ± 9.77 ms/mmHg; p = 0.524). Data from one patient (without syncope) were omitted, because that patient did not fulfill the method criteria for identification of the spontaneous sequences.

Phenylephrine induced baroreflex sensitivity

When comparing patients with syncope and without syncope there was no significant difference in the phenylephrine-induced BRS (18.33 ± 9.31 *vs.* 15.48 ± 15.48 ms/mmHg; p = 0.521). Data from three patients (two without syncope and one with syncope) were excluded because the r^2 was lower than 0.60.

Head-up tilting (HUT)

HUT was positive in eight patients (40%), who presented hypotension and referred near syncope, one of them (6%) with previous history of syncope and seven without previous syncope (33.33%), p = 0.053. This finding attributed to HUT the following characteristics for detection of syncope etiology in this population: a sensitivity of 6%, a specificity of 66%, a positive predictive value of 12.5%, a negative predictive value of 48% and an accuracy of 40%. Among the positive responses, two were vasodepressive and six were mixed.

Heart rate variability

Analyses in time domain

The mean duration of the electrocardiographic monitoring was 23 h 55 min. During analysis, 2.8% of the data were lost due to interferences or artifacts. We did not find statistically significant differences in the mean heart rate between the groups (77.75 ± 10.33 vs. 80.48 ± 12.36 bpm; p = 0.701). For the analyses of HRV, data from two patients were excluded, both without syncope, because of a significant percentage of artifacts during the recording. When the values of SDNN were considered, no significant difference was found between the groups (137.69 ± 36.62 vs. 145.95 ± 38.07 ms; p = 0.389). The group with syncope had significantly lower values of RMSSD than the group without syncope (24.88 ± 10.03 vs. 35.58 ± 16.43 ms; p = 0,042) and we observed a tendency toward higher values of pNN50 in patients without syncope (4.51 ± 3.78 vs. 8.83 ± 7.98 %; p = 0.085).

Analyses in frequency domain

As shown in Table 3, we did not find any statistically significant differences between the groups when considering the frequency domain variables of the HRV studied. Note that the syncope group presented a tendency to lower values of the high frequency component in the supine position (p = 0.075). When the influences of postural changes on the referred parameters were studied, orthostatic posture caused a similar significant increase in the LF/HF ratio in both groups (p = 0.010 for the group with syncope; p = 0.021 for the group without syncope).

Discussion

To identify the origin of syncope in HCM patients is still a challenge. It may be caused by several mechanisms, like arrhythmias or ventricular outflow tract obstruction, but in the majority of cases it may result of a combination of factors influencing the circulatory balance. It is well known that the ANS plays a major role in cardiovascular homeostasis, once the vagal and sympathetic modulation and balance represents the main mechanism of an adequate brain perfusion maintenance.

The prognostic value of an adequate ANS function is already well established in some cardiac diseases[13,14]. Many years ago, Gilligan et al[15] observed that patients with HCM had lower parasympathetic activity (measured by HR variation during deep breathing and by Valsalva maneuver) than normal individuals, compatible with an afferent parasympathetic limb alteration. Other studies have demonstrated that HCM patients may present an altered hemodynamic behavior during exercise characterized by a drop in systemic vascular resistance and hypotension[8,9], and suggested that this could be a consequence of the activation of ventricular mechanoreceptors leading to a sympathetic withdrawal to resistance vessels. Prasad et al[10] have demonstrated that this phenomenon of hypotension occurs also during routine activities and even at rest, when they studied a group of patients presenting frequent syncope or near syncope and noted that patients with these symptoms and hypotensive episodes during BP monitoring had a lower spontaneous BRS.

Spontaneous BRS measurements

In this study, we did not find a significant difference in the spontaneous BRS between HCM patients with and without syncope. These conflicting results may be explained by the inclusion criteria of the two studies. Patients with syncope of our study had less episodes of syncope and we did not include patients with near syncope. On the other hand, patients from Prasad's study had more episodes and had at least one in the previous month. Another possible explanation for the difference in our findings is that, in our study, the measurements of spontaneous BRS were obtained during rest and in a supine position. In contrast, the other study's data were acquired on different occasions during 24 hours of monitoring. For this reason, one may suggest that the BRS might have more variations in its adaptation capacity over the course of the day.

Phenylephrine induced baroreflex sensitivity

The reflex response of HR to phenylephrine – a vasoselective pressor agent – has been extensively used to evaluate BRS since its initial description in 1969[16], although it has been poorly studied in HCM patients. In our study, no differences were observed in the phenylephrine induced BRS between patients with and without syncope. In the unique report published previously that used this method, Thomson et al[11] compared HCM patients to normal people and observed similar results between the groups.

Head-up tilting (HUT)

We found no statistical difference in positive responses to HUT in HCM patients with and without unexplained syncope, but with a trend toward more positive tests in the non-syncope group. Other authors have published comparable findings, suggesting that HUT is not a good tool to evaluate the etiology of syncope in HCM patients[10,17,18]. Only Gilligan et al[19] found a greater frequency of positive responses in patients with a previous history of syncope. It is important to emphasize that these authors used isoproterenol infusion in cases with an initial negative response to passive tilting and it is supposed that HCM patients are more susceptible to mechanoreceptor activation and Bezold-Jarisch reflex deflagration when submitted to excessive adrenergic stimulation.

HUT had poor sensitivity, specificity and accuracy in identifying the etiology of syncope in this sample. We must remember that patients with unexplained syncope may have many reasons for a hemodynamic collapse, including arrhythmias. Finally, it has already been demonstrated that neurally mediated syncope corresponds to a small percentage of cases among individuals suffering from structural heart disease. This differs completely from what is found among patients with normal hearts, in whom neurally mediated syncope represents the most common cause of hemodynamic collapses.

Heart rate variability

HRV has been extensively studied in cardiovascular diseases, and its prognostic value is well established in most of these disorders, especially in ischemic heart disease[13,20]. In this study, we observed that SDNN, an estimative of total HRV, was similar between the groups. However, RMSSD values were significantly lower in patients with a history of syncope ($p = 0.042$); pNN50 values tended to be lower in the same group ($p = 0.085$). When considering the parameters analyzed in the frequency domain, we observed a tendency to lower values of the high frequency component during a supine position in the syncope group. RMSSD, pNN50 and the high frequency component of spectral analyses are measures that represent especially the parasympathetic activity.

A decrease in vagal activity has been previously related in patients with HCM when compared to normal people[21-23]. This decrease in parasympathetic function was correlated to more severe clinical presentations. Döven et al[22] observed lower values of SDNN, RMSSD and pNN50 in patients in the functional class III e IV and in those with a greater degree of outflow tract obstruction. A lower vagal activity was noted in HCM patients, especially in those with a history of syncope, thoracic pain during effort, dyspnea and mitral regurgitation[21].

Counhihan et al[24] observed that specific parameters of vagal activity, including pNN50 and the high frequency component of spectral analyses, were lower in patients presenting atrial arrhythmias on ambulatory ECG recordings. The same authors also found lower measures of HRV, global and specific to vagal activity (pNN50 and high frequency component), in patients with non-sustained ventricular tachycardia on 24h Holter monitoring. The decrease in the high frequency component of the spectral analyses was the only component of the HRV related to greater chances of cardiac events (death or hospitalization because of heart failure), after 28 months of follow-up, in the study published by Kawasaki et al[25].

On the other hand, Bittencourt et al[26] compared HCM patients with normal volunteers and did not find significant differences in HRV between the groups, when considering short electrocardiographic recordings.

We did not find, after a literature review, any study that has specifically compared the HRV in HCM patients with and without previous syncope episodes. Nevertheless, Bonaduce et al[21] have already identified a lower vagal activity in symptomatic HCM patients, including the ones presenting syncope.

It is still speculative how a decrease in the parasympathetic activity could be associated with syncope in these patients. It is possible that it acts modulating the onset of atrial and ventricular arrhythmias. Maybe it could be considered a marker of a more severe presentation of the disease, as it has been demonstrated in other cardiomyopathies.

Study limitations

It is important to consider the small number of patients enrolled in the study. Despite being in a tertiary center, with a specialized HCM outpatients unit, it is a rare disease and unexplained syncope was not a very frequent symptom presented by our population of patients. Additionally, we cannot rule out an arrhythmic cause of syncope in

Table 3 - Indexes of heart rate variability, in frequency domain, acquired in supine position and at 60 º of tilting in syncope and without syncope groups

Variable	Syncope group (n=16)	Without syncope group (n=21)	p
VLF, ms^2, (supine), mean±sd (median)	495.44 ± 449.73 (330.50)	517.48 ± 632.66 (330.00)	0.830
VLF, ms^2, (60 º), mean±sd (median)	365.13 ± 301.97 (262.50)	466.48 ± 416.21 (301.00)	0.374
LF, ms^2, (supine), mean±sd (median)	566.59 ± 811.31 (272.25)	614.71 ± 575.98 (334.00)	0.312
LF, ms^2, (60 º), mean±sd (median)	566.95 ± 467.66 (515.00)	704.68 ± 657.05 (528.00)	0.759
HF, ms^2, (supine), mean±sd (median)	637.59 ± 1.295.53 (158.00)	782.65 ± 1.264.14 (356.00)	0.075
HF, ms^2, (60 º), mean±sd (median)	247.44 ± 280.56 (94.50)	351.20 ± 528.22 (185.00)	0.736
TPD, ms^2, (supine), mean±sd (median)	1697.64 ± 2294.01 (756.00)	1916.57 ± 2098.51 (970.00)	0.297
TPD, ms^2, (60 º), mean±sd (median)	1179.44 ± 740.73 (943.00)	1510.57 ± 1170.38 (1.148.00)	0.646
LF (nu), %, (supine), mean±sd (median)	61.37 ± 15.76 (60.40)	55.79 ± 18.17(53.30)	0.276
LF (nu), %, (60 º), mean±sd (median)	72.66 ± 15.51 (70.60)	70.30 ± 18.89 (78.30)	0.690
HF (nu), %, (supine), mean±sd (median)	38.63 ± 15.76 (39.60)	44.17 ± 18.16 (46.70)	0.276
HF (nu), %, (60 º), mean±sd (median)	27.34 ± 15.51 (29.40)	29.68 ± 18.90 (21.30)	0.713
LF/HF (supine), mean±sd (median)	2.83 ± 3.06 (1.70)	4.52 ± 10.95 (1.30)	0.381
LF/HF (60 º), mean±sd (median)	8.40 ± 10.18 (3.90)	5.81 ± 4.94 (4.50)	0.713

HF: high frequency component; LF: low frequency component; sd: standard deviation; TPD: total power density of the spectrum; VLF: very low frequency component.

this population. Continuous, prospective prolonged electrocardiographic monitoring is strongly recommended to confirm or exclude arrhythmic events during the follow-up. Concerning this issue, we must note that previous episodes of atrial fibrillation were more frequent in patients presenting syncope in our sample.

Conclusions

Our study suggests that HCM patients presenting unexplained syncope have lower vagal activity than those without syncope.

We also concluded that HUT is not a good tool in diagnosing syncope in these patients. This finding supports the idea that this method should not be recommended for routine evaluation of unexplained syncope in this specific population, mainly because of the low specificity of the test.

Author contributions

Conception and design of the research: Macatrão-Costa MF, Arteaga-Fernandez E, Hachul D; Acquisition of data: Macatrão-Costa MF, Arteaga-Fernandez E, Brito FS, Hachul D; Analysis and interpretation of the data: Macatrão-Costa MF, Brito FS, Hachul D; Statistical analysis and Writing of the manuscript: Macatrão-Costa MF; Critical revision of the manuscript for intellectual content: Arteaga-Fernandez E, Darrieux F, Melo SL, Scanavacca M, Sosa E, Hachul D.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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