Assessing Autonomic Function in Hypertrophic Cardiomyopathy

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Objective

Assess the autonomic function in hypertrophic cardiomyopathy (HCM) through heart rate variability (HRV) and to correlate it to echocardiographic data.

Methods

Two groups were studied, and compared for gender, age and HR: A) Ten (10) patients reporting septal HCM (70% non-obstructive); B) ten (10) healthy volunteers. HRV was analyzed along four successive stages: at rest, under controlled breathing, while bending, and controlled breathing associated to bending. Variables means were compared between groups and intra-groups in the different stages; in Group A, variables means were correlated to echocardiographic measurements (interventricular septum and left atrial diameter).

Results

No HRV difference was reported among groups in the first 3 stages. In the fourth stage vagal activity was shown to be higher in Group A [quadratic mean log between RR intervals (RMSSD) – 1.35 ± 0.14 vs 1.17 ± 0.16; $p=0.019$; high frequency component logarithm (LogHF)- 4.89 ± 0.22 vs 4.62 ± 0.26; $p=0.032$]. Along the stages, vagal measurements [rate of pairs of consecutive RR intervals whose difference is $\geq$ 50ms (pNN50) and LogHF] also showed lower reduction in the third stage in Group A, while LogHF showed some increase in last stage ($p=0.027$), thus indicating marked parasympathetic activity in that group. Group A HRV analysis showed no difference among patients reporting larger hypertrophy or atrial diameter.

Conclusion

1) parasympathetic prevalence was shown during autonomic stimulation in HCM patients; 2) no correlation was found between HRV and echocardiographic measurements under analysis.

Key words

autonomic nervous system (ANS), hypertrophic cardiomyopathy (HCM), heart rate (HR)

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Hypertrophic cardiomyopathy (HCM) is a genetic disease where ventricular hypertrophy associated with preserved systolic function and diastolic dysfunction stand out (with changes in ventricular relaxation and compliance) under no associated conditions to produce such change. Clinical development of the condition is variable, usually family-related, heterogeneously expressed, with autosomic dominant transmission[1,2]. It has for some time been speculated that the development of myocardial hypertrophy in that condition might be related to some increase in sympathetic activity[3]. Brush and collaborators (1989) demonstrated that neuronal uptake of norepinephrine was reduced in HCM patients, thus emphasizing the assumption that sympathetic nervous system disorders might be related to phenomena found in that condition, particularly sudden death[4]. Schafers and collaborators also verified decrease in beta receptors density in that condition, in addition to reduction in norepinephrine neuronal uptake[5].

The study of the autonomic nervous system (ANS) has been gaining strength in most recent decades as an attempt to set behavior patterns for the different diseases that may be correlated to sudden death events[6-8]. Particularly for diabetics (whose evolution is disautonomic), and for those who have had acute myocardial infarction (AMI), autonomic function changes are significantly correlated to increased mortality rate[9-13].

Heart rate variability (HRV) analysis is a simple, invasive method, and aims at assessing the balance between sympatho-vagal activity on the heart; consequently, at identifying the phenomena related to ANS disorders that may contribute for the genesis of arrhythmias[14].

Some works have analyzed HRV in the last decade, with conflicting results. Those using 24-hour Holter for HRV analysis found sympathetic prevailing over parasympathetic activity. Such changes were found to be correlated to the presence of symptoms, ventricular arrhythmia, and left ventricle outflow tract obstruction (LVO)[15-19].

Such argument was contested by Fei and collaborators while studying a group of thirty-one (31) HCM patients and thirty-one (31) normal individuals through 24-hour HRV Holter analysis. HCM patients reported significantly lower low frequency (LF) component, and lower low frequency/high frequency ratio (LF/HF), and high frequency (HF) components that were higher as compared to control group individuals, thus indicating a reduction in sympathetic activity in their normal, day-to-day activities[20]. Similar results were found by Limbruno and collaborators while using autonomic short-term stimulating protocols for HRV analysis. Sympathetic activity compromising was found to be higher in individuals with obstructive HCM [21,22].

Against such conflicting results, the present paper has the purpose of: 1) assessing the behavior of the autonomic function in individuals with asymmetric septal HCM as compared to control group through HRV at rest, under respiratory stimulus, and bend tests, and 2) correlating findings to the analysis of septally hypertrophic HRV, and left atrium (LA) size.

Methods

In the period between 09/2001 and 12/2002, twenty (20) individuals were split into two groups paired by gender, age, and heart rate (HR): Group A – made up of ten (10) individuals with asymmetric, septal HCM; and Group B – made up of ten (10) normal individuals.

Among the individuals in Group A, age ranged from 27 to 55 years of age (40.3 ± 9.8), being 90% males. Among Group B individuals, age ranged from 26 to 45 years of age, (37.2 ± 6.4), being 80% males. Among Group A patients, four (4) were on propranolol and one (1) on verapamil.

Asymmetric septal HCM was diagnosed based on echocardiographic evidence of asymmetric septal hypertrophy of left ventricle (larger than 13mm), which did not present dilation, in individuals with no identifiable cause for hypertrophy[1,2,23]. Those who had been submitted to septal myectomy or to alcoholization of septal artery, those on amiodarone, or those for whom medication discontinuation was considered unacceptable were excluded from Group A. Also excluded were those reporting coronary heart disease, hypertension, aortic stenosis or any other condition that would lead to myocardial hypertrophy, nonsinosoidal rhythm, or advanced atrioventricular blockings, and those with a history of diabetes mellitus and chronic alcohol abuse.

All individuals were submitted to clinical examination (anamnesis and physical exam), 12-lead electrocardiogram at rest, echocardiogram, and laboratory exams (creatinine, total cholesterol and fractions, triglycerides, glucose and uric acid) at timepoints no longer than six months as of assessment of autonomic cardiac function. Assessment of autonomic function was carried out at rest and under non-pharmacological stimulus following protocol, as described below.

Standard, unidimensional and bidimensional representations were obtained for the echocardiogram, together with flow study through continuous, pulsed Apogee CX 200 (ATL, EUA)[24] color Doppler. Exams were carried out by the same person (who was not aware of results obtained by protocol for the assessment of autonomic function), aiming at determining cavity measures, the type of hypertrophy, analysis of systolic and diastolic function, the presence of anterior systolic movement of the mitral valve, mitral failure level, and pressure gradient in left ventricle outflow. Cavity measures were obtained following the American Society of Echocardiography protocol in use: diastolic diameter of LV (DDLV), systolic diameter of LV (SDLV), interventricular septum thickness (IVST), posterior wall thickness (PWT) and LA diameter (LAD)[25].

Assessment of autonomic function was carried out by computerized short term data collection for HRV analysis, through the use Predictor IIC (Corazonix, EUA) system. For HRV data, electrocardiographic signals were taken at 1kHz sampling rate, using a 16-Bit A/D converter, and real time analysis of MC5 lead (T wave abnormalities) after skin was cleaned with slight abrasion by using cotton wool at alcohol at 70%, with positive electrode placed on 5th or 6th intercostal space to left hemiclavicular line, and negative electrode in the left infraclavicular region. Based on continuous electrocardiographic records, RR intervals or instant heart rate (HR) (defined as RR interval inversion multiplied by 60) were calculated after normal consecutive QRS complexes were detected. The identification of trustworthy, normal complexes was carried out by cross-correlation method with a "model signal" obtained at early capturing through visual inspection, thus allowing efficient rejection of ventricular or supraventricular extrasystoles as well as artifacts during the course of protocol. After automatic analysis, RR intervals were reevaluated by two observers using a manually editing method.

All individuals had been fasting for at least 4 hours, and were asked not to consume any tobacco product for 2 hours prior to signal capturing for HRV analysis. Individuals in Group A - who had been on betablockers or calcium channel blockers – had their medication discontinued for a period equivalent to 5 half-lives before protocol was carried out[18,26]. Exams took place from 1:00 p.m. to 5:00 p.m. at a silent, clear setting, at approximately 27°C temperature.

For the autonomic evaluation, electrocardiographic signals were obtained after 5-minute resting time in supine position for the stabilization of autonomic activity in compliance with four- consecutive-stage protocol requirement, as described below: a) Stage I: record of HRV at rest, in supine position at 0° during 5 minutes; b) Stage II: record of HRV under controlled breathing (see below) in dorsal decubitus at 0° during 5 minutes; c) Stage III: record of HRV for 5 minutes with individual submitted to bend tests at 60°, obtained after 10 minutes as of bending position; d) Stage IV: record of HRV under controlled breathing, with individual submitted to bending at 60° during 5 minutes.

Controlled breathing was defined as 5-second respiratory cycles monitored by investigator through the use of a chronometer and visual signs (hand raising and lowering for inspiration and expiration time points, respectively) and auditive signs (verbally). Respiratory cycle control followed physiologic ratio between inspiratory and expiratory intervals, kept at 2:3, with spontaneous thoracic expansion depth for patient's higher comfort. Individuals were trained for 30 seconds prior to Stage II before records were taken.

HRV signals were analyzed for time domain and frequency domain at all stages (Table I). In regard to time domain, variables extracted from normal, consecutive RR intervals series were: a) mean of normal RR intervals (RRm); b) SD of normal RR intervals (SDNN); c) quadratic mean between normal, consecutive RR intervals (RMSSD), and d) ratio of normal, consecutive RR intervals, whose difference is equal to or higher than 50ms as compared to record (pNN50). As for frequency domain, the series of normal, consecutive RR intervals was linearly interpolated for the calculation of power spectral density function (PSDF) through the use of fast Fourier transformation (FFT). Before FFT was calculated, mean of series was subtracted, and series processed by stapling through the use of a Hanning window to avoid artifacts due to the discontinuity of the end points. Spectral estimates have been calculated by elevating the spectrum of amplitude of normal RR intervals series to square values during the time of analysis, in compliance with Predictor IIc protocol. The two spectrum components in the short term series – calculated as area under the curve (AUC) for PSDF - were: a) high frequency (HF), defined between 0.15 to 0.40Hz frequencies; and b) low frequency (LF), defined between 0.05 - 0.15Hz frequencies[8,27].

A normality test was carried out for each variable in each group and at each stage through standard asymmetry and standard curtosis test. Null normality hypothesis was accepteded when the two tests reported values between -2 and +2. Variables where normality hypothesis was rejected were turned into their natural logarithms and reevaluated by normality test.

Intergroups and intrastages comparisons for variables reporting null, accepted normality hypothesis were carried out through the use of Student's "t" test to compare mean values for samples with equal and unequal variances. For the purpose of comparison of variances, Sinedekor's "f" test was used, when the null hypothesis for equality among variances was tested. Variables whole null hypothesis

Table I – Measures for HRV in time and frequency domain and their autonomic influences

	Definition	Autonomic influence
Time domain		
RRm	Mean of RR intervals	
SDNN	Standard Deviation of RR intervals	Sympathetic and parasympathetic
RMSSD	Quadratic mean of differences between consecutive RR intervals	Parassimpática
pNN50	Ratio of consecutive RR intervals whose difference is > a 50ms	Parassimpática
Frequency domain		
HF	High frequency component	Parasympathetic
LF	Low frequency component	Sympathetic and parasympathetic

for normality was rejected - even after logarithmic transformation – were compared through Mann-Whitney test. For intragroups, intrastage comparison of variables, paired "t" Student test was used with zero difference null hypothesis between the stages. Statistical significance was defined by $p<0.05$ for all tests.

Calculations were carried out using the software *Statgraphics Plus*, Version 5.0 (*Manugistic Inc*, Rockville, MD, EUA).

Study Protocol was submitted to the Ethics Committee at Pedro Ernesto University Hospital at Rio de Janeiro Federal University -Hospital Universitário Pedro Ernesto – UERJ), where it was approved. All individuals presented a written informed consent to be enrolled in the study.

Results

From the twenty (20) individuals enrolled in the study, two (2) – one (1) in each group – did not complete the protocol for autonomic evaluation. Patients' withdrawal at Stage III – as a result of a dizziness condition - did not allow exam completion. However, those patients were not excluded from the sudy. Their records were incorporated to the analysis for autonomic function in the 3 first stages. Relevant clinical and echocardiographic data are shown in Table II.

Comparison of intergroup HRV analysis at each stage - Table III shows at rest HRV in the 2 groups. No statistically significant difference was reported for RRm between HCM patients and control group individuals at rest [(mean+ SD) 950.6+78.3 vs 881.2+ 82.3]. No difference was reported, either, for any of the other measures in the time domain and in the frequency domain between the 2 groups.

When the 2 groups were compared for Stages I and II (under control breathing and bend test, respectively), no difference was reported for the measures under study – either in the time domain or in the frequency domain (Table IV and V).

However, when analyzing Stage IV (bend test associated to controlled breathing) authors observed that parameters modulated by vagal activity (LogRMSSD and LogHF) reported values significantly higher in the HCM group as compared to control groups, as shown in Table VI.

Progressive behavior of autonomic function measures during protocol - while analyzing group behavior in the two groups during stages - both groups reported similar tendency for RRm during stages, showing some increase (although not significant at that point) in mean values during controlled breathing when Stage II was compared to Stage I; significant reduction at tend test (reported when comparing Stage III to Stage I), thus revealing strong influence of controlled breathing and of bend maneuvre on vagal and sympathetic activities respectively (figure 1).

While evaluating those measures under vagal influence (LogRMSSD, pNN50 and LogHF), some differences were reported between groups, since the bend test showed significant decrease in pNN50 and in LogHF in Group B. Group A, in its turn, did not report such significant decrease. RMSSD reported significant, similar decrease in both groups. In the last stage, when controlled breathing was associated to the bend test, significant increase in HCM patients' LogHF in regard to Stage III, thus reinforcing marked parasympathetic activity in this group of patients (figure 2).

Parameters under both sympathetic and parasympathetic influence (LogDPNN and LogLF) did not report significant changes between stages in either group, except for LogLF in the transition from Stage I to Stage II, when excpected significant decrease was reported by the control group (figure 3).

How drugs affect HR - Considering the results obtained

Table II – Data on population under study

	Group A (HCM)	Group B (Control)
Number of cases	10	10
Males (%)	90	80
Age (years)	40.3 ± 9.8	37.2 ± 6.4
RRm (ms)	950.6 ± 78.3	881.2 ± 82.3
Family history of sudden death (%)*	40	10
Symptomatic (%)	80	0
Chest pain (%)	70	0
Dyspnea (%)	60	0
Syncope (%)	10	0
Palpitation (%)	10	0
Echocardiogram		
LVDD (mm)	4.3 ± 0.4	4.6 ± 0.3
SDLV (mm)	2.7 ± 1.2	2.8 ± 0.2
IVS (mm)	2.2 ± 0.6	0.8 ± 0.1
LA (mm)	4.1 ± 0.4	3.5 ± 0.3
Moderate to severe mitral failure (%)	10	0
Obstructive** (%)	30	0
Non-obstructive (%)	70	0

*RR m – mean of RR intervals; LVDD- left ventricle diastolic diameter; SDLV- systolic diameter of left ventricle; IVS- interventricular septum thickness; LA- left atrium diameter. *Unexpected death of first degree family members under 45 years old[28]. ** Gradient on left ventricle outflow higher than 30mmHg at rest[29]*

Table III – Measures for HRV during Stage I (at rest) in patients with HCM and in control group

	Group A (HCM)	Group B (Control)	p
Time domain			
RRm (ms)	950.6±78.3	881.2 ± 82.3	0.069
Log SDNN [log (ms)]	1.63± 0.18	1.66 ± 0.18	0.833
LogRMSSD [log(ms²)]	1.50± 0.25	1.44 ± 0.16	0.496
pNN50	5.95	6.30	0.470*
Frequency domain			
LogHF [log(ms²)]	4.66± 0.54	4.81± 0.33	0.490
LogLF [log(ms²)]	5.11 ±0.41	5.31± 0.27	0.231
** Mann-Whitney Test*			

Table IV – Measures for HRV during Stage II (controlled breathing) in patients with HCM and in control group

	Group A (HCM)	Group B (Control)	p
Time domain			
Log SDNN [log(ms)]	1.66 ±0.18	1.65±0.10	0.837
LogRMSSD [log(ms²)]	1.55 ± 0.24	1.52 ± 0.12	0.661
pNN50	9.25	8.80	0.740*
Frequency domain			
LogHF [log(ms²)]	4.98 ± 0.57	5.04 ± 0.35	0.765
LogLF [log(ms²)]	4.78 ± 0.45	4.92 ± 0.31	0.429
** Mann-Whitney Test*			

Table V – Measures for HRV during Stage III (bend test) in patients with HCM and in control group

	Group A (HCM)	Group B (Control)	p
Time domain			
Log SDNN [log(ms)]	1.60 ± 0.16	1.63 ± 0.16	0.699
LogRMSSD [log(ms²)]	1.35 ± 0.21	1.27 ± 0.14	0.302
pNN50	5.70	1.55	0.076*
Frequency domain			
LogHF [log(ms²)]	4.51 ±0.46	4.56 ± 0.30	0.778
LogLF [log(ms²)]	5.06 ± 0.36	5.21 ± 0.43	0.410
** Mann-Whitney Test*			

Table VI – Measures for HRV during Stage IV (bend test associated to controlled breathing) in patients with HCM and in control group

	Group A (HCM)	Group B (Control)	p
Time domain			
Log SDNN [log(ms)]	1.66±0.11	1.61 ±0.12	0.366
LogRMSSD [log(ms²)])	1.35±0.14	1.17± 0.16	0.019
pNN50	4.20	0.20	0.069*
Frequency domain			
LogHF [log(ms²)]	4.89±0.22	4.62±0.26	0.032
LogLF [log(ms²)]	4.98± 0.29	4.91± 0.45	0.732
** Mann-Whitney Test*			

in the previous sections in this paper showing the predominance of parasympathetic activity at 4th stage for HCM patients, the authors evaluated HR (RRm expressed) at rest in Group A for patients on negative chronotropic drugs (betabloquers and calcium antagonists), and those off drugs. No significant difference was found in results obtained (on drugs = 925.8 + 105.6, off drugs = 975.6 + 33.5; p=0.301).

HRV and echocardiographic measures - When comparing within the HCM group those patients reporting interventricular septum values (IVS) >2 and <2, no difference was found in the analysis of LogHF, LogLF and LogRMSSD at any of the 4 stages.

The same happened when the HCM group was split into 2 subgroups following LA size, and using 4.4cm as the cut point.

Discussion

Although HRV in HCM has been the focus of a number

of research papers in the last decade, controversies are still pending. It should be pointed out that literature has not reported – up to this point in time – any experiment pursuing the same objectives in this country.

In the present work authors have observed that: a) the HRV analysis – both in the time domain and in frequency domain – has brought similar information in regard to autonomic influences in patients with HCM and normal individuals while at rest, under controlled breathing, and during bend test; b) measures taken by higher vagal influence were higher in patients with HCM at the last stage (where controlled breathing took place with patient

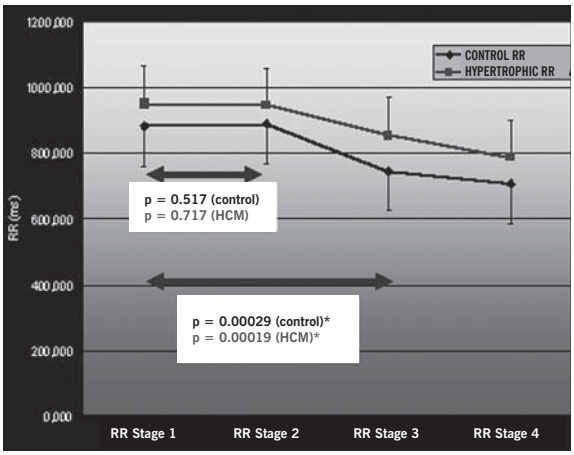

Fig. 1 *- Behavior of RRm during stages in both groups*

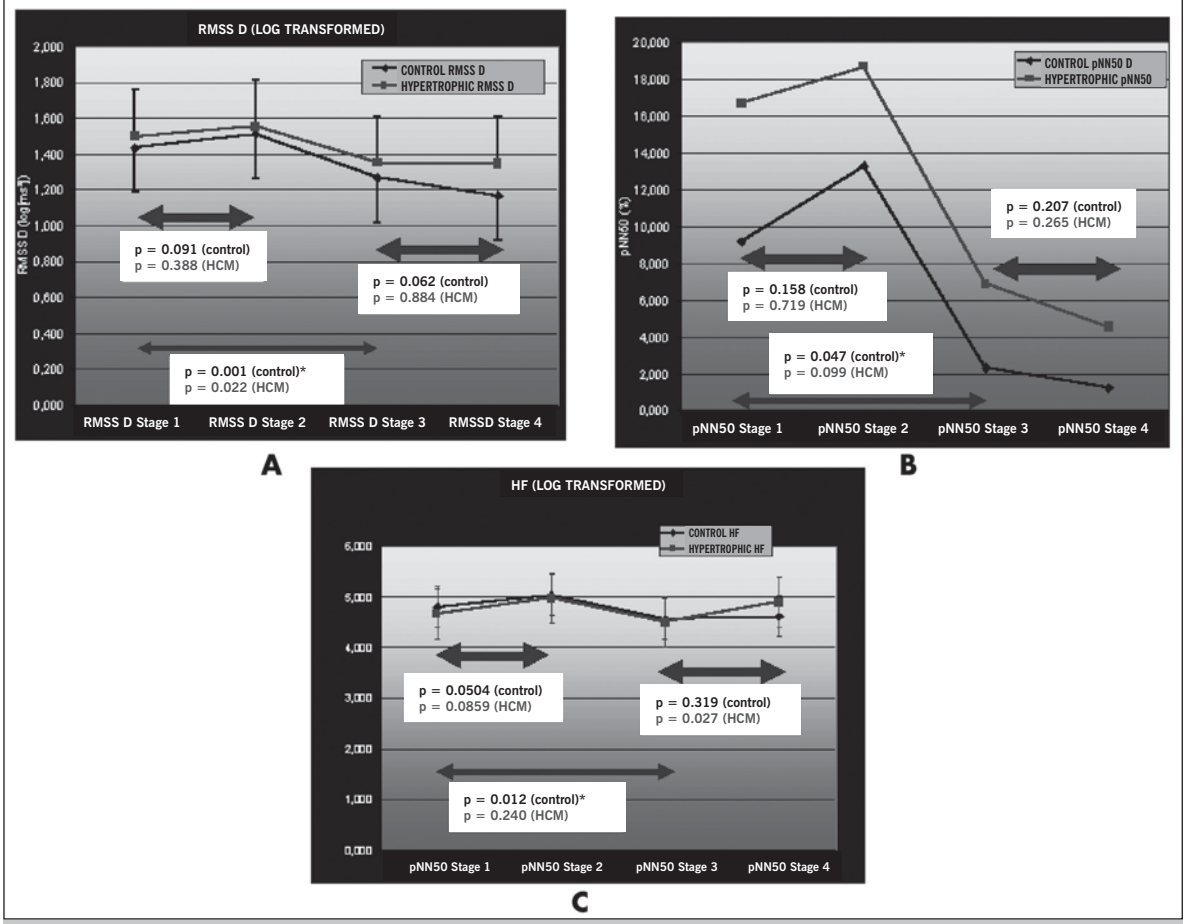

Fig. 2 *- Behavior of LogRMSSD (A), pNN50 (B) and LogHF (C) during stages in both groups*

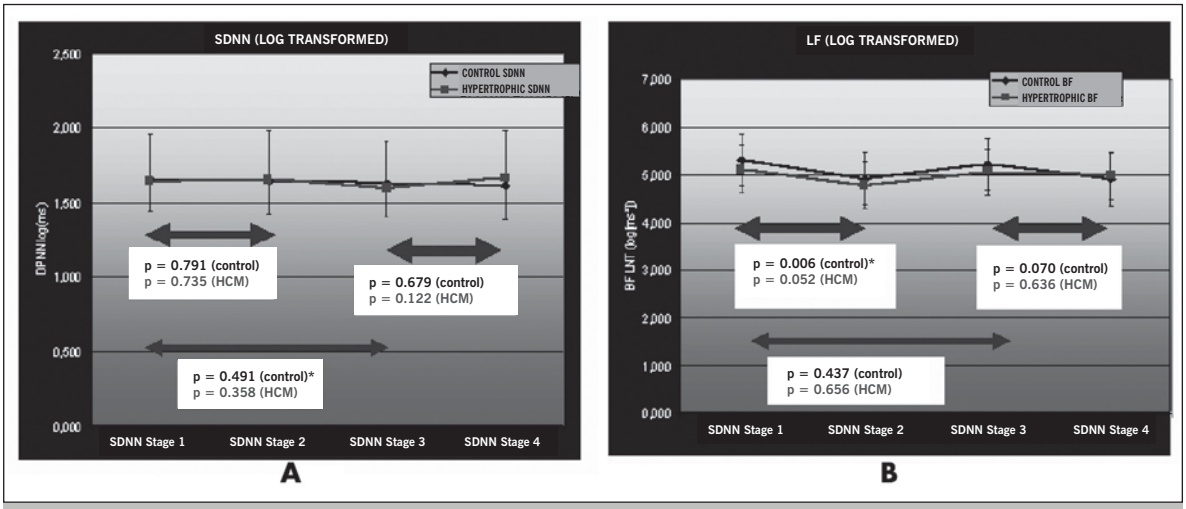

Fig. 3 *- Behavior of LogSDNN (A) and LogLF (B) during stages in both groups*

bent at 60º); c) along the two stages, measures of vagal activity – such as pNN50 and LogHF – reported less marked increase in the HCM group at bend test; when in transition to the last stage, LogHF showed significant increase, pointing towards a tendency to report higher parasympathetic activity in that group.

Contrarily to what was observed by a number of studies already cited that have analyzed HRV through the use of 24 hours Holter[16-19,30-32], no significant compromising of the autonomic function was observed in HCM patients. In the present paper, the most observed differences were those in the last stage of autonomic evaluation, with parasympathetic activity predominating, while as previously referred to in this paper, that arm of the autonomic response was compromised. However, Fei and collaborators questioned the increase in sympathetic activity reported by patients with HCM in a study published in 1995, when spectral analysis through 24-hour Holter was also used[20].

It should also be pointed out that the reliability of measures from the 24-hour recording and corresponding interpretation – particularly spectral components – are questionable, since they may hide information on the autonomic modulation of RR intervals[7]. The explanation is simple, since physiologic mechanisms responsible for HR modulation are not stationary in the 24-hour period.

Taking that inco account, the authors have chosen to use a protocol with short-term records, which allowed better control over stimuli in the two groups, which in its turn led to easer interpretation, as done by Limbruno and collaborators in their work[21,22]. They did not find any compromising in parasympathetic activity, either; quite the opposite, they confirmed sympathetic activity reduction at rest and at bend test in obstructive HCM. However, for those patients with non-obstructive HCM – 70% of our patients – Limbruno and collaborators have not found significant difference in HRV spectral analysis either while comparing with normal individuals. The same was observed by Uemura and collaborators[17,22].

Such findings reflect a contradiction with studies that have addressed the kinetics of catecholamines in HCM. When detecting a reduction of neuronal uptake in nervous terminations, those studies suggest that the disease would be characterized by the increase in sympathetic activity due to the longer presence of norepinephrine in the synaptic gap[3-5].

Our hypothesis is that low availability of norepinephrine in sympathetic terminations may induce the opposite, which means to say, to sympathetic activity reduction, particularly in patients with higher level of intraventricular obstruction.

Additionally, the fact that patients with HCM report higher values of LogRMSSD, pNN50 and LogHF at Stage IV (characterized by controlled breathing while at 60º bend) deserves special attention, since none of the research works mentioned earlier has tested that kind of stimulus. If one follows the evolution of those measures across the stages (Illustrations 1, 2 and 3), a tendency towards amortizing decrease for LogRMSSD and pNN50, and the return to higher levels as compared to previous LogHF stage both groups will be observed, thus reflecting increased parasympathetic activity triggered by controlled breathing, which is opposed to a factor that promotes sympathetic activity – the 60º bend position. However, such response can be seen to be more intense in the HCM groups, which suggests not only the preservation of parasympathetic modulation, but the possibility that exacerbated vagal reflexes may be triggered in response to the stimulus generated by the bend test, as suggested by Gilligan and collaborators in their research work to investigate syncope in HCM[33].

In regard to the form of stimulation used in Stage IV in our work, it could be suggested that controlled breathing exacerbated vagal reflexes even more, thus resulting in

a pattern of autonomic response that differed from the control group.

It should be reminded, at this point, that while analysing RRm in HCM, and comparing those on negative chronotropic drugs and those off those drugs, no difference was found to justify the delayed action of those drugs (even though withheld for a period of 5 half-lives at least) in findings.

From the sample of patients with HCM used for the study, 80% was symptomatic, which does not agree with findings by Bonaduce[18] and Counihan[30], who observed higher HRV reduction in those patients. But those works, as already discussed previously, were based on 24-hour electrocardiographic records.

Considering the correlation between HRV and echocardiographic measures such as LA and IVS thickness while analyzing HCM patients, such data were not seen to be independent variables to interfere in autonomic function behavior. Opinions are controversial in that area, too, with some authors in defense of the relevance of such for autonomic modulation[22,26] and other opposing that assumption[16]. The fact is that even those who did find the correlation of such data (particularly septal thickness) with autonomic function disorders did not report uniform results. Gillian and collaborators found correlation in parasympathetic activity compromising while Limbruno and collaborators observed sympathetic activity compromising[22,26].

It should also be pointed out that the significant differences found in the variables - that evaluate autonomic function - allow the identification of autonomic modulation patterns typical of HCM. However, due to the small number of samples under study, those conclusions must be validated by larger samples so as to reinforce statistical power for the differences found.

So, we have concluded that: 1) the study showed that autonomic function of patients with HCM evaluated by non-pharmacologic stimulation did not differ from that observed in a control group adjusted for age, gender, and HR at rest, under controlled breathing, and at bend test; 2) significant increase in parasympathetic modulation was observed during controlled breathing when associated to bed test in patients with HCM; 3) no correlation was found between changes in HRV and IVS and LA measures.

The statistically significant differences found in the variables that evaluate autonomic function allow the identification of autonomic modulation patterns typical of HCM. However, due to the small number of samples under study, those conclusions must be validated by larger samples so as to reinforce statistical power for the differences found.

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