Ventricular Arrhythmias and Left Ventricular Hypertrophy in Hypertrophic Cardiomyopathy

Beatriz Piva e Mattos¹,², Marco Antonio Rodrigues Torres¹,², Valéria Centeno de Freitas¹, Fernando Luís Scolari², Melina Silva de Loreto²
Servço de Cardiologia do Hospital de Clínicas de Porto Alegre¹; Faculdade de Medicina - Universidade Federal do Rio Grande do Sul², Porto Alegre, RS – Brazil

Abstract

Background: In hypertrophic cardiomyopathy (HCM), the degree of left ventricular hypertrophy (LVH) could influence the development of ventricular arrhythmias.

Objective: In HCM, analyze the association between the occurrence of ventricular arrhythmias determined by Holter electrocardiogram (ECG-Holter) and the degree of LVH determined by maximum wall thickness (MWT) in echocardiography and body mass index (BMI).

Methods: Fifty-four consecutive patients with HCM underwent 24-hour ECG-Holter and echocardiography for assessment of level of LVH through MWT and BMI. Two levels were established for the occurrence of Ventricular Arrhythmias: I - alone or paired extrasystoles and II – Non- Sustained Ventricular Tachycardia (NSVT).

Results: In 13 patients (24%) with NSVT (level II), there was a higher frequency of MWT of the left ventricle (LV) ≥ 21 mm (n = 10, 77%, 25 ± 4 mm) and LLLV = 144 g/m² (n = 10, 77%, 200 ± 30 g/m²), in comparison with those presenting with extrasystole arrhythmias (level I) (n = 41, 76%), in which these measures were identified in, respectively, 37 % (n = 15, 23 ± 1 mm), p = 0.023, and 39% (n = 16, 192 ± 53 g / m²) of the cases (p = 0.026). The cut-off values mentioned were determined by the ROC curve with a confidence interval of 95%. NSVT was more common in patients with MWTLV ≥ 21 mm and LLLV ≥ 144 g/m² (8 of 13, 62%) than in those with (4 of 13, 31%) or without (1 of 13; 8%) echocardiographic variables above cut-off values (p = 0.04).

Conclusion: In HCM, occurrence of ventricular arrhythmias by Holter was associated with the degree of LVH assessed by echocardiography through MWT and BMI (Arq Bras Cardiol. 2013; [online].ahead print, PP.0-0).

Keywords: Arrhythmias, Cardiac; Hypertrophy, Left Ventricular; Cardiomyopathy, Hypertrophic.

Introduction

Hypertrophic Cardiomyopathy (HCM) is a complex genetic disease, the diagnosis of which is based on the identification of left ventricular hypertrophy (LVH) demonstrated by absence of dilatation of the chamber and any other condition that can cause an abnormality of a similar degree. In young people under 25 years of age and athletes, it is the main cause of sudden death, produced by ventricular fibrillation that may or may not be preceded by ventricular tachycardia. A characteristic histopathological pattern represented by hypertrophy and cellular disorganization, coupled with fibrosis, predisposes victims to the onset of ventricular arrhythmias, which express the abnormal electrophysiological conduction and the electric instability of the myocardium.

Records of non-sustained ventricular tachycardia on Holter electrocardiogram-(ECG-Holter) and massive LVH with a maximum parietal thickness ≥ 30 mm are considered predictors of sudden death in this disease. Studies based on necropsy or in transplanted HCM hearts identify a direct relationship between the degree of fibrosis and the maximum parietal thickness of the left ventricle (LV). Areas of fibrosis, detected in the form of late highlight by means of magnetic resonance imaging with gadolinium, relate to the risk of ventricular arrhythmias and, probably, to sudden death. However, it has not yet been clearly shown if the increase in the parietal thickness of the LV favors the occurrence of ventricular arrhythmias captured by 24-hour ECG-Holter monitoring in an outpatient cohort unreferenced with HCM.

Methods

Patient selection

Fifty-four consecutive patients were chosen from an unreferenced cohort registered at the HCM Outpatient Clinic of the Cardiology Service of the Hospital de Clínicas de Porto Alegre, UFRGS, between March 2007 and
December 2011. The HCM diagnosis was established based on the clinical condition and on identification by means of asymmetrical LVH echocardiogram with maximum parietal thickness ≥ 15 mm in any segment and septum/posterior wall ratio of > 1.3 in the absence of dilatation of the chamber and another cause. Exclusion criteria included the following: LV concentric hypertrophy, other forms of cardiomyopathy, coronary artery disease, and/or congenital valvular heart disease. Patients underwent a preliminary clinical and electrocardiographic evaluation, followed by resting echocardiography and 24-hour ECG-Holter performed in the traditional way. The echocardiogram was recorded by a single examiner. The results of the ECG-Holter were evaluated blindly, without prior knowledge of the diagnosis. The use of cardioactive medication was not a consideration for either inclusion or exclusion from the study. This study was approved by the local Research Ethics Committee. All patients signed an informed consent form.

**Echocardiogram**

Mono and two-dimensional transthoracic echocardiography with pulsed and continuous color Doppler was performed at rest to evaluate the structure and function of the heart chambers, including spectral flow analysis according to current recommendations. The evaluations were performed with Vivid 7 General Electric equipment (GE Healthcare, Milwaukee, WI, USA). The images obtained included parasternal longitudinal cuts and cross-parasternal and apical views of two, three, four and five chambers with multifrequency transducers of 2.5 to 3.5 MHz, performed in a standardized manner with the patient in the left decubitus position. The following measures were considered: left atrial diameter, final diastolic diameter of LV, end systolic diameter of LV, end diastolic thickness of the interventricular septum, end diastolic thickness of the posterior wall of the LV, LV mass indexed with body surface area and ejection fraction. The maximum parietal thickness was regarded as the one corresponding to the LV segment, which exhibited the greatest degree of thickening. The degree of LVH was evaluated by the maximum wall thickness and body mass index. The maximum gradient in the left ventricular outflow tract was measured at rest and during the Valsalva maneuver with the apical cut-off of five chambers, with continuous Doppler directed parallel to the outflow tract of this chamber according to Bernoulli’s modified equation. The presence of occlusion was defined as the mechanical impediment of the left ventricular outflow tract, resulting from contact or approximation of the mitral valve with the interventricular septum in mesosystole. The record of a maximum systolic gradient ≥ 30 mmHg at rest was considered compatible with obstructive forms. Latent obstruction was defined by a gradient <30 mm Hg at rest and ≥ 30 mmHg with Valsalva maneuver. Non-obstructive forms corresponded to a gradient at rest and with Valsalva < 30 mmHg.

**Holter electrocardiogram**

The outpatient 24-hour ECG-Holter monitor recorded three leads: VII modified V1 and V5. Recordings were analyzed using the GE Mars 8000 and the recorder was the GE Seer Light (GE Medical Systems, Milwaukee, WI, USA). Paired ventricular extrasystoles were characterized as two consecutive extrasystoles, and non-sustained ventricular tachycardia was characterized by the presence of three or more consecutive extrasystoles with a rate of ≥ 100 beats / minute. In patients with more than one Holter ECG, concurrent to the echocardiography, the one with the greatest frequency of ventricular arrhythmia was selected. Two levels were established for ventricular arrhythmias: level I - alone or paired extrasystoles and level II – non-sustained ventricular tachycardia.

**Statistical Analysis**

Quantitative data were described by mean and standard deviation, or by median (Md) and interquartile intervals (25th and 75th percentiles). The category variables were expressed by absolute and relative frequency. The differences between two groups, based on the comparison of continuous variables with symmetric and asymmetric distribution, were analyzed, respectively, using the Student t test for independent samples and the Mann-Whitney test. Category variables were compared using the chi-square test for heterogeneity and chi-square for linear trend. From the ROC curve with a confidence interval (CI) of 95%, cutoff values for echocardiographic measurements regarding the maximum parietal thickness of LV and mass index of LV were determined, in order to discriminate between patients with higher and lower frequency of ventricular arrhythmias. The data were processed using SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois, USA). The level of statistical significance adopted was p < 0.05.

**Results**

**Characteristics of the patients**

Mean age was 54 ± 13 years, with 48 (89%) ≥ 40 years; 33 (61%) were female. There was a predominance of cases with light or moderate impairment of functional capacity (New York Heart Association Functional Class - CFNYHA I/II, n = 40, 74%) compared with those with severe limitation (CFNYHA III/IV, n = 14, 26%). All patients were taking prescribed medication: 41 (76%) used beta-blockers, 17 (31%) used calcium channel blockers such as verapamil or diltiazem, and 5 (9%) used amiodarone (Table 1).

**Holter electrocardiogram**

Ventricular arrhythmias on ECG-Holter exam were identified in all cases. Isolated ventricular extrasystoles were seen in 46 (85%) patients, ranging from 1 to 1461, with an average of 130 ± 277. Twenty (37%) had paired ventricular extrasystoles numberling 1 to 15, and 12 (22%) and 13 (24%) experienced non-sustained ventricular tachycardia (NSVT), with 1 to 7 saved, ranging from 3 to 24 beats. Patients with NSVT presented, relative to those without this arrhythmia (n = 41, 76%), a higher number of isolated ventricular extrasystoles (Md 131, p25 = 6.25 and p75 = 316 versus Md 9, p25 and p75 = 1 and p75 = 91, p = 0.27) and paired extrasystoles (Md 2, p25 = 0, p75 = 5 versus Md 0 p25 = 0, p75 = 1, p = 0.013). Demographic and clinical data did not differ between patients with level I and II ventricular arrhythmias (Table 1).
Table 1 - Demographic and clinical characteristics of 54 consecutive patients with Hypertrophic Cardiomyopathy and Ventricular Arrhythmias in 24-hour-Electrocardiogram-Holter

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 54)</th>
<th>Level I (n = 41)</th>
<th>Level II (n = 13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 13</td>
<td>54 ± 14</td>
<td>53 ± 14</td>
<td>0.902</td>
</tr>
<tr>
<td>≥ 40 years</td>
<td>48 (89%)</td>
<td>37 (90%)</td>
<td>11 (85%)</td>
<td>0.623</td>
</tr>
<tr>
<td>Women</td>
<td>33 (61%)</td>
<td>27 (66%)</td>
<td>6 (46%)</td>
<td>0.328</td>
</tr>
<tr>
<td>CF NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I /II</td>
<td>40 (74%)</td>
<td>28 (68%)</td>
<td>12 (92%)</td>
<td>0.146</td>
</tr>
<tr>
<td>III/IV</td>
<td>14 (26%)</td>
<td>13 (32%)</td>
<td>1 (8%)</td>
<td>0.146</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>41 (76%)</td>
<td>30 (73%)</td>
<td>11 (85%)</td>
<td>0.485</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>17 (31%)</td>
<td>13 (32%)</td>
<td>4 (31%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5 (9%)</td>
<td>5 (12%)</td>
<td>0 (0%)</td>
<td>0.321</td>
</tr>
</tbody>
</table>

P values refer to the comparison of patients with Level I and II of Ventricular Arrhythmias; Level I - isolated or paired extrasystoles; Level II - non-sustained ventricular tachycardia, FC - functional class NYHA - New York Heart Association.

Echocardiogram

The mean maximum LV parietal thickness observed was 20 ± 4 mm, with a variation of 15 to 34 mm. There was a predominance of light or moderate hypertrophy of the left ventricle: 26 (48%) had measurements between 15 and 19 mm, 21 (39%) measured between 20 and 24 mm, six (11%) measured between 25 and 29 mm and only one (2%) measured ≥ 30 mm. The LV mass index showed a variation from 97 to 248 g/m², with a mean of 158 ± 18 g/m². Obstructive forms of hypertrophy occurred in 21 (39%) patients, obstructive latent form in 6 (11%) and non-obstructive form in 27 (50%) (Table 2).

Ventricular Arrhythmias and left ventricular hypertrophy

The maximum LV wall thickness was significantly higher in patients with non-sustained ventricular tachycardia (level II) compared with those who only experienced extrasystoles (level I) (23 ± 5 mm versus 19 ± 4 mm, p = 0.001). The mass index of the LV was significantly higher in level II patients (182 ± 45 g/m² versus 151 ± 48 g/m²; p = 0.049). The other echocardiographic variables did not differ among the groups (Table 2).

Through the ROC curve with a CI of 95%, it was demonstrated that maximum parietal thickness of the LV of ≥ 21 mm and an LV mass index ≥ 144 g/m² (8 of 13, 62%) than in those with one (4 of 13; 31%) or no (1 of 13; 8%) echocardiographic variable above the cutoff values (p = 0.04). The predominance of non-sustained ventricular tachycardia on ECG-Holter rose directly and progressively with the number of echocardiographic descriptors of LVH considered for analysis (chi-square for linear tendency, p = 0.04) (Figure 2). The ROC curve showed that maximum wall thickness of the LV ≥ 21 mm had a sensitivity of 77% and a specificity of 64%, with positive and negative predictive values of 40% and 90%, respectively, for detection of non-sustained ventricular tachycardia on Holter ECG (area under the ROC curve 0.767; CI95% 0.614 – 0.920). Mass index of the LV ≥ 144 g/m² showed a sensitivity of 77% and a specificity of 61%, with a positive predictive value of 39% and a negative predictive value of 89% (area under the ROC curve 0.713; CI95% 0.530 – 0.900) (Figure 3).

Discussion

This study demonstrated that the more severe the LVH, the more conducive it is to arrhythmogenesis in HCM. The occurrence of non-sustained ventricular tachycardia was associated with greater impairment of the LV, when assessed by maximal wall thickness and body mass index. The record of non-sustained ventricular tachycardia was more frequent in patients where both echocardiographic descriptors of LVH were higher. The asymmetrical character of the hypertrophy and its heterogeneous distribution, shown by echocardiography, were the measurements of LV mass index that were less reliable in HCM. Even though LV mass index is frequently high, it shows a weak correlation with the maximum parietal thickness of the LV when evaluated by means of magnetic resonance imaging. However, in this analysis, it is noted that the record of non-sustained ventricular tachycardia, in addition to its association with a higher mass index, was more frequent in the cases where the maximum parietal thickness was high.
Table 2 - Echocardiographic measurements of 54 consecutive patients with Hypertrophic Cardiomyopathy and Ventricular Arrhythmias in 24-hour Holter electrocardiogram

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 54)</th>
<th>Level I (n = 41)</th>
<th>Level II (n = 13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial diameter (mm)</td>
<td>45 ± 7</td>
<td>45 ± 8</td>
<td>44 ± 4</td>
<td>0.573</td>
</tr>
<tr>
<td>LV diastolic diameter (mm)</td>
<td>43 ± 6</td>
<td>43 ± 6</td>
<td>44 ± 5</td>
<td>0.381</td>
</tr>
<tr>
<td>LV systolic diameter (mm)</td>
<td>26 ± 6</td>
<td>26 ± 6</td>
<td>27 ± 4</td>
<td>0.576</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>72 ± 6</td>
<td>73 ± 7</td>
<td>71 ± 4</td>
<td>0.145</td>
</tr>
<tr>
<td>LV maximum wall thickness (mm)</td>
<td>20 ± 4</td>
<td>19 ± 4</td>
<td>23 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>158 ± 48</td>
<td>151 ± 48</td>
<td>182 ± 45</td>
<td>0.049</td>
</tr>
<tr>
<td>Obstructive forms</td>
<td>21 (39%)</td>
<td>18 (44%)</td>
<td>3 (23%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Gradient at rest (mm Hg)*</td>
<td>59 (37;79)</td>
<td>54 (32;81)</td>
<td>64 (38;-)</td>
<td>0.802</td>
</tr>
<tr>
<td>Latent obstructive forms</td>
<td>6 (11%)</td>
<td>2 (5%)</td>
<td>4 (31%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Gradient at rest (mm Hg)*</td>
<td>23 (8;25)</td>
<td>13 (0;-)</td>
<td>23 (13;25)</td>
<td>0.623</td>
</tr>
<tr>
<td>Non-obstructive forms</td>
<td>27 (50%)</td>
<td>21 (51%)</td>
<td>6 (46%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gradient at rest (mm Hg)*</td>
<td>0 (0;10)</td>
<td>0 (0;21)</td>
<td>0 (0;9)</td>
<td>0.451</td>
</tr>
</tbody>
</table>

*P values refer to the comparison of patients with Level I and II of Ventricular Arrhythmias; Level I: isolated or paired extrasystoles; Level II: non-sustained ventricular tachycardia, FC: functional class; analysis by Mann-Whitney test.

Ventricular arrhythmias are the characteristic manifestation of HCM, a disease that is considered unpredictable in its development due to its arrhythmogenic potential, with annual rates of sudden death estimated at 1%26. Studies based on 24- to 48-hour ECG-Holter analysis in populations based in the community20 and in reference centers27-29 identified ventricular extrasystoles in 80% to 95% of the cases, with numbers of extrasystoles varying from 1 to 5,000. Paired ventricular extrasystolic beats were found in 30% to 40% of the recordings, and non-sustained ventricular tachycardia was found in 20% to 30%, in brief savings with a frequency ranging from 3 to 36 beats. In this study, paired ventricular extrasystoles were observed in 37% of the patients and non-sustained ventricular tachycardia in 24%, with savings of 3-24 beats. Compared with previous studies, we observed a similar prevalence of ventricular arrhythmias, despite the lowest degree of sample selection and the prevalence of patients aged ≥ 40 years with light or moderate degree of LVH.

The record of non-sustained ventricular tachycardia on Holter ECG would seem to increase the susceptibility to sudden death, but has a low positive predictive value27-30. Ventricular arrhythmias in HCM originate from re-entry and arise from an electrophysiological substrate characterized by slow conduction routes and late ventricular activation4,7. In electrograms, the registration of small amplitude and late
inscription potentials, called subdivisions, would reflect abnormal ventricular activation and would predispose to sudden death. Most of the ventricular tachycardia episodes observed here were monomorphic, preceded by extrasystoles, and would possibly be abolished by antitachycardia pacing.

Support for the hypothesis that the degree of LVH would influence arrhythmogenesis in HCM is considerable, although it has not been properly confirmed. Early investigation showed the extent of the relationship between LVH and registration of ventricular tachycardia on ECG-Holter. Subsequent studies that assessed the relationship between the maximum parietal thickness of the LV and the occurrence of non-sustained ventricular tachycardia showed conflicting results, even when carried out in the same institution, with some presumable degree of sample superposition. In one of these analyses, it was shown that the registration of non-sustained ventricular tachycardia would proportionately influence the level of LVH, afflicting 50% of those with a maximum parietal thickness ≥ 30 mm. Divergent conclusions...
could be attributed to the level of sample selection, to the methodology used and to the heterogeneous character of the disease. Unlike our study, none of the mentioned studies included isolated or paired extrasystolic beats. However, the prevalence of multifocal or paired ventricular extrasystoles and of non-sustained ventricular tachycardia was previously described in patients with extensive septal or free anterolateral wall LVH, in comparison with cases with involvement restricted to the septum. In models with human mutations of HCM, an association between the level of hypertrophy and induced ventricular arrhythmias was seen. In the presence of mutation of the α-tropomyosin gene, ventricular arrhythmias were induced in one-third of the cases; a correlation was also observed with the maximum parietal thickness of the LV and the number of risk factors for sudden death.

Patients with a maximum wall thickness of the LV ≥ 30 mm, particularly the young and elderly, are at increased risk of cardiovascular mortality and sudden death. LVH, when increasing parietal stress and oxygen consumption, would lead to myocardial infarction, an important stimulus for the development of arrhythmias. The role of myocardial hypertrophy in arrhythmogenesis in HCM was questioned before the description of sudden death in carriers of troponin T gene mutations with normal or slightly increased LV parietal thicknesses. Ventricular fibrillation is also reported in patients with mutations of the cardiac β-myosin heavy chain with absent or late LVH.

The anomalous architecture of the myocardium, represented by cellular disorganization and fibrosis, interferes with the conduction of the stimulus, producing unidirectional block and favoring a reentry mechanism. Reparative fibrosis probably develops, induced by silent myocardial ischemia and cellular death as a consequence of myocyte hypertrophy and microcirculatory disease. Prefibrotic conditions indicative of the increase in collagen synthesis would precede LVH development in HCM. The deposition of collagen in the form of reparative fibrosis is identified at an early age and tends to worsen with age. In carriers of HCM who are victims of sudden death, when the disease is caused by other genes than the troponin T gene the presence of extensive areas of fibrosis is one of the determining factors. However, it is unclear whether the increase in LV wall thickness is dependent on fibrosis, reflecting the consequences of a process of chronic myocardial ischemia influenced by cellular hypertrophy and disease of the microcirculation, or whether it results from activation or genetic factors not yet understood or discovered.

The association demonstrated here between the occurrence of ventricular arrhythmias and the degree of LVH could contribute to individualization of factors that predispose to arrhythmogenesis in HCM. The present study showed that the maximum wall thickness of LV ≥ 21 mm and the mass index ≥ 144 g/m² are characteristics that may lead to greater myocardial electrical instability in these patients.

Limitations of the study

The possibility that our results reflect, to some degree, the very characteristics of the sample cannot be ruled out. The predominant inclusion of individuals in an older age group with the lowest degree of selection, although probably less risky, could limit the inferences to populations with this profile. However, it must also be noted that the study population may also be representative of the disease, as well as those treated at referral centers.

Conclusions

In this study based on a cohort of unreferenced ambulatory patients with HCM, of a predominant age group above 40 years, there was an association between the occurrence of ventricular arrhythmias found on ECG-Holter exam and the degree of LVH evaluated by echocardiography and in a recent meta-analysis, the fibrosis detected by magnetic resonance proved to be an independent predictor of mortality. However, for this to be considered a marker of prognosis and sudden death, additional confirmation is required. The association of fibrosis identified by magnetic resonance imaging or computer tomography with multiple detectors and fatal or non-fatal ventricular arrhythmias suggests the existence of a physiopathological link between arrhythmogenesis and fibrosis in HCM. This fact justifies the association observed between the higher frequency of ventricular arrhythmias and LV wall thickening, of which fibrosis is one of the determining factors. However, it is unclear whether the increase in LV wall thickness is dependent on fibrosis, reflecting the consequences of a process of chronic myocardial ischemia influenced by cellular hypertrophy and disease of the microcirculation, or whether it results from activation or genetic factors not yet understood or discovered.

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Conclusions

In this study based on a cohort of unreferenced ambulatory patients with HCM, of a predominant age group above 40 years, there was an association between the occurrence of ventricular arrhythmias found on ECG-Holter exam and the degree of LVH evaluated by echocardiography and determined by maximal wall thickness index and mass index. A higher prevalence of non-sustained ventricular tachycardia was evidenced when both echocardiographic descriptors of LVH were higher.
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