Myocardial Fibrosis in Patients with Hypertrophic Cardiomyopathy and High Risk for Sudden Death

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Abstract

Background: The stratification of risk for sudden death in hypertrophic cardiomyopathy (HCM) continues to be a true challenge due to the great heterogeneity of this disease’s presentation, as most individuals remain asymptomatic during their entire lives and others present sudden death as first symptom. Recent studies have suggested that myocardial fibrosis may represent an important substrate for the malignant ventricular arrhythmias, that are responsible for the cases of sudden death related to this disease.

Objective: To assess the prevalence and quantification of myocardial fibrosis (MF) in hypertrophic cardiomyopathy (HCM) patients with implantable cardioverter - defibrillator (ICD) indicated due to their high risk or recovered from cardiac sudden death.

Methods: Twenty-eight HCM patients with ICD were submitted to multidetector computed tomography to assess myocardial fibrosis by delayed enhancement technique.

Results: Myocardial fibrosis was present in 96% of these HCM patients with (20.38 ± 15.55 g) comprising 15.96 ± 10.20% of the total myocardial mass. MF was observed in a significantly higher prevalence as compared to other classical risk factors for sudden death.

Conclusion: It is possible to conclude that there is a high prevalence of myocardial fibrosis in hypertrophic cardiomyopathy patients with high-risk or recovered from cardiac sudden death, like those with clinical indication to implantable cardioverter - defibrillator. The higher prevalence of myocardial fibrosis in comparison to classical risk factors of worse prognosis raise the hypothesis that the myocardial fibrosis may be an important substrate in the genesis of life-threatening arrhythmias in these high risk HCM population. (Arq Bras Cardiol 2010; 94(4):502-506)

Key words: Hypertrophic cardiomyopathy; myocardial fibrosis; multidetector computed tomography.

Introduction

Hypertrophic cardiomyopathy is considered to be the major cause of sudden cardiac death (SCD) among young adults1,2,14. Despite the traditional clinical criteria of worse prognosis5,11 and the genetic advances with regard to the discovery of over 200 mutations that are responsible for the disease13,18, the stratification of sudden death risk in hypertrophic cardiomyopathy (HCM) continues to be a true challenge due to the great heterogeneity of its presentation, as most individuals remain asymptomatic during their entire lives and some others present sudden death as first symptom.

The histopathological analysis of the hearts of HCM patients who died of sudden death demonstrated considerable presence of myocardial fibrosis19 (MF). This fibrosis may be diagnosed by the non-invasive delayed enhancement technique by magnetic resonance20, which may constitute an important substrate for malignant ventricular arrhythmias, as suggested by studies that correlated the presence of non-sustained ventricular tachycardia and the presence of MF diagnosed by magnetic resonance19,21-24.

In this manner, although the delayed enhancement magnetic resonance technique has showed to be an important tool for the assessment of MF in HCM20,23, it presents some limitations, like in the assessment of patients who carry pacemakers and implantable cardioverter-defibrillator (ICD), because in such cases there are formal contraindications regarding the employment of magnetic resonance26.

Recently, the detection of MF in ischemic cardiomyopathy by multidetector computed tomography (MDCT) delayed enhancement technique was demonstrated27-28. Moreover, our
group was the first to demonstrate the MF can be assessment by MDCT delayed enhancement using a technique similar to that employed in ischemic patients, as the areas of MF evaluated by tomography presented an excellent correlation to the resonance²⁹.

Thus, the objective of this paper was to investigate the prevalence of myocardial fibrosis in high risk HCM patients with ICD due to clinical indication by MDCT delayed enhancement technique.

Methods

Between October 2006 and December 2007, 30 hypertrophic patients with ICD by clinical indication, followed-up in the Unit of Cardiomyopathies and Artificial Cardiac Stimulation of Instituto do Coração (InCor-HC, FMUSP, São Paulo, Brazil), were consecutively referred to the assessment of myocardial fibrosis by MDCT. Of this sample, a patient with renal insufficiency and another one who refused to participate in the study were excluded. The 28 remaining patients who signed the informed consent were submitted to the analyses after approval by the institutional ethics committee.

Multidetector computed tomography

The assessment of MF by delayed enhancement MDCT was obtained using a tomograph with 64 columns of detector (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). The images were acquired seven minutes after infusion of 150 ml of iodine contrast (Iopamiron 370, Shering AG, Germany), using the following protocol retrospectively synchronized with electrocardiogram: gantry rotation of 350 to 500 ms adjusted by cardiac frequency, as to allow a multisegmented reconstruction, collimation of 64 x 0.5 mm, tube voltage of 120kV, tube current of 500mA, helical-pitch 14.4 (or pitch factor of 0.225), and scanning field of view of 220 mm.

Clinical characteristics

The assessment of risk factors for sudden cardiac death was registered in compliance with a previously described guidance⁴, thus being considered: syncope, like episodes of loss of consciousness of uncertain etiology occurred within a 12-month period before implantation of ICD⁵⁰; recovery from sudden death¹¹; family history of sudden cardiac death in first grade relatives younger than 40 years old¹²,³³, record of non-sustained ventricular tachycardia (NSVT) at Holter exam⁷,⁸,⁴,³⁵, defined as three or more consecutive ventricular extrasystoles with frequency equal or higher than 120 beats per minute during less than 30 seconds; maximal end diastolic wall thickness higher than 30 mm³⁶, verified at the echocardiogram. Moreover, other criteria were also analyzed: dilation of left ventricle was considered as end-diastolic diameter higher than 50 mm; left ventricle ejection fraction lower than 60%³⁷; obstruction of left ventricle outflow tract was considered as intraventricular gradient higher than 30 mmHg and, finally, atrial fibrillation was considered as clinical characteristics that could be associated with a worse prognosis. Symptoms of cardiac heart failure were assorted in compliance with NYHA, and the use of antiarrhythmic drugs was also registered.

Images analyses

Data from images acquired by the tomography were reconstructed using a multisegmented image reconstruction algorithm, with a 1 mm thickness during diastolic phase (in the 75% phase of R-R interval). Axial images were processed using multiplanar reformation as to generate contiguous slices in short axis covering the whole extension of the left ventricle, from apex to basis, with a 10 mm thickness average reformation, a technique capable of reflecting the mean of all the pixels of the slice as to avoid the loss of any pixel that could represent myocardial fibrosis. Habitually, 12 slices in short axis were enough to cover the entire LV. All the segments involved by the artifacts caused by the ICD cables were excluded of all patients (Figure 1)⁴⁰. The myocardial fibrosis areas were defined aided by dedicated software (Image J, NIH, USA). Using the density of pixels in a histogram that comprised the graphical representation of the myocardial fibrosis areas as well as the myocardial without fibrosis areas, a semi-automatic threshold technique, that was able to distinguish the densities of the areas visually defined as presenting or not myocardial fibrosis, was applied.

Statistical analysis

Data were shown as mean ± standard deviation. The Shapiro-Wilk test was applied in order to confirm the normality distribution. The prevalence of traditionally accepted risk factors for sudden death and the presence of myocardial fibrosis was expressed in percentage and compared through chi-square or Fisher’s Exact test. Moreover, the prevalence of cardiac heart failure (CHF) functional class based on NYHA, intraventricular obstruction and atrial fibrillation of the sample was registered.

Results

Mean age was 38.5 ± 16.6 years old, and males constituted 46.4% of the studied population.

Among the criteria of classic sudden death risk, 18% of the patients recovered from sudden death, 68% presented history of syncope of uncertain etiology, 78% presented family history of sudden death, 32% presented NSVT, and 21% of the patients presented septal hypertrophy larger than 30 mm.

Besides, the presence of intraventricular obstruction was observed in 50% of the sample, atrial fibrillation in 32%, functional class II CHF in 39%, functional class III in only one patient, and functional class IV was not present in the studied population. The mean LV ejection fraction was 70.9 ± 12.4%, the diastolic diameter of the LV was 4.1 ± 0.5cm, and the mean size of the left atrium was 4.3 ± 0.6cm, as measured by the echocardiogram.

At the moment of tomography, 86% of the individuals were in use of beta blockers, 53% of antiarrhythmic agents, 28% of...
calcium channel antagonists, 39% of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonists, 14% were in use of spironolactone and 28% of acetylsalicylic acid or oral anticoagulation drugs.

Interestingly, 96.4% of individuals presented myocardial fibrosis by multidetector computed tomography delayed enhancement technique. There were no significantly static difference between the presence or absence of myocardial fibrosis analyses performed by two blind independent observers.

Myocardial fibrosis was present in all patients, except one, of the selected population, which presented high risk for sudden cardiac death, and appears to be more prevalent, even individually, than the other traditional risk factors of worse prognosis in this disease (Figure 2).

The model of delayed enhancement by MDCT was peculiar, characterized by its diffuse pattern in multiple focuses not respecting the coronary territory distribution, saving the subendocardium (Figure 1).

The mean mass of myocardial fibrosis was 20.38 ± 15.55 g, and the mean myocardial fibrosis percentage was 15.96 ± 10.20% of the left ventricle mass.

### Discussion

This is the first study that demonstrates myocardial fibrosis by delayed enhancement MDCT in hypertrophic cardiomyopathy patients with ICD who present high risk for sudden death.
cardiomyopathy patients with ICD.

This kind of non-invasive analysis of myocardial fibrosis, performed exclusively by magnetic resonance up till now, could not be accomplished due to its formal contraindication to patients with ICD.

In this manner, tomography may be an important method for the diagnosis and assessment of myocardial fibrosis in patients to whom magnetic resonance is contraindicated.

Besides, the presence of myocardial fibrosis in all patients, except one, of this hypertrophic population of high risk for sudden death, or even recovered from sudden death, suggests that such fibrosis may be an important substrate for the genesis of complex ventricular arrhythmias which are responsible for sudden death, as also suggested by a study that demonstrated the presence of myocardial fibrosis in the hearts of hypertrophic cardiomyopathy patients who suddenly died. Additionally, studies on magnetic resonance in hypertrophic patients also demonstrated a higher prevalence of NSVT in patients with fibrosis as compared to those without myocardial fibrosis.

The high prevalence of myocardial fibrosis in relation to all other classic criteria of worse prognosis observed in this paper may also suggest that fibrosis is a risk factor of higher sensitivity in comparison to the remaining criteria traditionally correlated to sudden death.

Apparently, evidence have been showing that myocardial fibrosis in HCM patients constitutes an important substrate for the arrhythmias responsible for sudden death in this disease. It is possible that, in the future, the non-invasive assessment of myocardial fibrosis - by resonance or tomography - be an important prognostic criteria in the complex determination of risk stratification in these patients, improving the indication of a more or less aggressive therapy, such as ICD implantation, and, at the same time, optimizing costs and avoiding the occurrence of obits secondary to this disease.

Limitations

The size of the studied sample is small. However, in this period, we recruited all HCM patients with ICD by clinical indication that were in follow-up in our ambulatory.

In this study, we did not use a control group due to HCM patients without ICD can be submitted to myocardial fibrosis investigation by magnetic resonance without ionizing radiation. Furthermore, the MDCT method for fibrosis was previously validated against magnetic resonance in ischemic diseases and in another published study carried out by our group.

Thus, the assessed group was only submitted to MDCT with the purpose of assessing myocardial fibrosis because magnetic resonance is absolutely contraindicated when there is the presence of ICD.

The artifacts caused by ICD cables induced the exclusion of inferoseptal segments in majority of patients, and due to MF frequently occurs in these areas, probably we can underestimate the size of myocardial fibrosis.

Conclusion

This is a pioneer study with regard to the detection of myocardial fibrosis in hypertrophic cardiomyopathy patients with ICD.

We conclude that there is a high prevalence of myocardial fibrosis in high risk for cardiac sudden death hypertrophic cardiomyopathy patients with ICD. The higher prevalence of myocardial fibrosis in comparison to risk factors of worse prognosis, or even to recovery from sudden death, raise the hypothesis that myocardial fibrosis may be an important and potentially necessary substrate in the genesis of the arrhythmias that unleash sudden death.

Further studies with bigger samples and longer follow-up period could confirm if there is a direct association between malignant ventricular arrhythmias and myocardial fibrosis.

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Potential Conflict of Interest

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

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Study Association

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