

# Detection and Quantification of Myocardial Fibrosis in Hypertrophic Cardiomyopathy by Contrast-Enhanced Cardiovascular Magnetic Resonance

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**Introduction and objectives.** Severity of hypertrophic cardiomyopathy has been associated with the amount of myocardial fibrosis in autopsy studies. Cardiovascular magnetic resonance allows, by means of the delayed contrast-enhancement technique, an in vivo detection of focal myocardial fibrosis. Our aim was to study myocardial fibrosis in patients with hypertrophic cardiomyopathy by means of contrast-enhanced cardiovascular magnetic resonance.

**Methods.** 43 patients (30 males; mean age, 47 [18] years) were studied by cardiovascular magnetic resonance. In all patients left ventricular function and mass was analyzed. Total mass of myocardial fibrosis, as identified by delayed contrast-enhancement, was also calculated.

**Results.** In 63% of patients some degree of myocardial delayed contrast-enhancement was observed, total mass of myocardial fibrosis ranging between 1 and 59 g (mean, 17 g). There was a positive correlation between the amount of myocardial fibrosis and the degree of hypertrophy. Maximal wall thickness was higher in patients with myocardial fibrosis (23 [7] vs 18 [4] mm, respectively,  $P=0.04$ ). Familial cases were also more prevalent among this group (48% vs 13%, respectively), as well as conventional clinical risk factors.

**Conclusions.** Myocardial fibrosis as detected by contrast-enhanced cardiovascular magnetic resonance is highly prevalent in hypertrophic cardiomyopathy patients, particularly in familial cases with severe hypertrophy and associated risk factors.

**Key words:** Hypertrophic cardiomyopathy. Magnetic resonance imaging. Myocardial fibrosis. Contrast enhancement.

## Detección y cuantificación de la fibrosis miocárdica en la miocardiopatía hipertrófica mediante cardi resonancia magnética con contraste

**Introducción y objetivos.** Estudios necrópsicos han asociado la severidad de la miocardiopatía hipertrófica con la cantidad de fibrosis miocárdica. La cardi resonancia magnética con contraste permite, mediante la secuencia de realce tardío, la detección in vivo de la fibrosis miocárdica focal. El objetivo del presente estudio fue cuantificar la fibrosis miocárdica mediante el realce tardío en pacientes con miocardiopatía hipertrófica.

**Métodos.** Se practicó un estudio de cardi resonancia magnética con contraste en 43 pacientes (30 varones; edad media  $47 \pm 18$  años) con miocardiopatía hipertrófica. En todos ellos se realizaron secuencias de cine-resonancia para el estudio de la función ventricular izquierda y la masa ventricular izquierda. Además, se calculó la masa total de fibrosis miocárdica mediante la identificación del realce tardío a los 10 min de la administración de contraste paramagnético.

**Resultados.** En el 63% de los pacientes se observó realce tardío con una masa total de fibrosis miocárdica media de 17 g (intervalo, 1-59 g). Se evidenció una correlación positiva entre la cantidad de fibrosis miocárdica y el grado de hipertrofia. El grosor parietal máximo era superior en pacientes con fibrosis miocárdica ( $23 \pm 7$  frente a  $18 \pm 4$  mm, respectivamente;  $p = 0,04$ ). Los casos familiares también eran más prevalentes en este grupo (el 48 frente al 13%, respectivamente), así como la presencia de factores de riesgo convencionales.

**Conclusiones.** La fibrosis miocárdica detectada por cardi resonancia magnética es altamente prevalente en pacientes con miocardiopatía hipertrófica, en particular en casos familiares con severa hipertrofia y factores de riesgo asociados.

**Palabras clave:** Miocardiopatía hipertrófica. Cardi resonancia magnética. Fibrosis miocárdica. Realce tardío.

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## ABBREVIATIONS

HCM: hypertrophic cardiomyopathy  
 MRI: magnetic resonance imaging  
 DE: delayed enhancement  
 LVM: left ventricular mass

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a progressive disease characterized by inappropriate myocardial hypertrophy and, at the microscopic level, focal myocardial fibrosis, scar tissue, myofibrillar disarray, and small-vessel disease, leading to a heterogeneous clinical, and pathological profile.<sup>1</sup> In necropsy studies, the severity of HCM has been related to the presence and amount of myocardial fibrosis.<sup>2-5</sup> However, the prognostic value of myocardial fibrosis has been difficult to determine due to the lack of diagnostic methods able to detect its presence in vivo.

Until now, cardiac magnetic resonance imaging (MRI), with delayed enhancement (DE) following the administration of contrast material, is the only approach that allows in vivo detection of myocardial scarring caused by necrosis,<sup>6</sup> as well as focal myocardial fibrosis of nonischemic origin.<sup>7,8</sup> Several authors<sup>9</sup> have recently shown the potential value of this technique in the clinical assessment of patients with HCM. Nevertheless, only a few studies have attempted to show the clinical value of DE in HCM. Our purpose was to describe the presence and distribution of myocardial fibrosis in a series of patients with HCM, and to determine whether there is a relationship between the extent of myocardial fibrosis and the severity of the disease.

## METHODS

### Patients

The study included 43 consecutive patients (30 men; mean age, 47 [18] years) diagnosed with HCM on echocardiography, defined as left ventricular wall thickness  $\geq 15$  mm, with no known cause of ventricular hypertrophy. Contraindication for the cardiac MRI study was the only exclusion criterion. Clinical risk was assessed using already established criteria<sup>10</sup>: family history of sudden death, unexplained syncope, documented ventricular tachycardia, severe left ventricular hypertrophy  $\geq 30$  mm.

### Cardiac MRI Studies

All patients underwent cardiac MRI with contrast material using a Philips Intera 1.5T scanner. After the usual scout views were obtained, cine-MRI was

performed with a steady-state free-precession sequence in slices along the longitudinal axis of the left ventricle, as well as multiple 10-mm slices along the transverse axis from the base to the apex of the left ventricle. At least 16 phases of the cardiac cycle were acquired for each slice and reproduced as a continuous loop.

An endovenous injection of 0.1 mmol/kg of gadoteridol (Gadovist, Schering AG, Berlin, Germany) was given, and a 3D gradient-echo inversion-recovery sequence was acquired 10 minutes after injection of the contrast material<sup>11</sup> to analyze DE. The inversion time was adjusted to suppress the normal myocardium signal (200-300 ms). This sequence was programmed in multiple slices of the transversal axis of the left ventricle, using the same orientation as for cine-MRI imaging.

### Image Analysis

The cine-MRI and DE images were analyzed in a second stage with special software (Mass, MEDIS, Leiden, The Netherlands), and the endo- and epicardial borders of the left ventricle were manually traced on the systolic and diastolic cine-MRI images for each transversal section. The left ventricular mass (LVM), end-diastolic volume, and end-systolic volume were calculated for each patient.

The presence of DE in the left ventricle was visually analyzed, along with its distribution pattern, and location. Based on the images obtained from the transverse axis of the left ventricle, planimetry was used to calculate the total weight of myocardial fibrosis identified by DE.

### Statistical Analysis

Continuous quantitative variables are expressed as mean (standard deviation) and compared using the Student *t* test for independent samples. The Mann-Whitney U-test was used for variables that did not have a normal distribution. A *P* value less than .05 was considered significant.

## RESULTS

The clinical characteristics of the patients studied are shown in Table. Cardiac MRI showed left ventricular hypertrophy with a maximal wall thickness of 14-39 mm (mean, 21 [6] mm), and an LVM of 67-358 g (mean, 169 [61] g). All patients except 2 showed LVEF values on cardiac MRI  $\geq 50\%$  (mean, 71% [13%]).

Delayed enhancement was observed in 63% (27/43) of patients, with the following distribution patterns: *a*) unifocal, affecting different regions of the left ventricular myocardium (4 patients; 15%); *b*) bifocal, affecting the areas where the LV and RV join (10

**TABLE 1. Clinical Characteristics of the Patients**

	N=43
Age, y	47 (18)
Sex, M/F	30/13
LVH distribution	
Asymmetric, n (%)	36 (84)
Concentric, n (%)	5 (12)
Apical, n (%)	2 (4)
NYHA functional class, I/II/III/IV	28/14/1/0
Family history of HCM, n (%)	13 (30)
Family history of sudden death, n (%)	8 (19)
Unexplained syncope, n (%)	4 (9)
Documented sustained VT, n (%)	0
Nonsustained VT on Holter monitoring, n (%)	1 (2)
Abnormal BP response to exercise, n (%)	1 (2)
Maximal LV wall thickness $\geq 30$ mm, n (%)	5 (12)

BP: blood pressure; F: female; HCM: hypertrophic cardiomyopathy; LV: left ventricular; LVH: left ventricular hypertrophy; M: male; NYHA: New York Heart Association; VT: ventricular tachycardia; y: years.

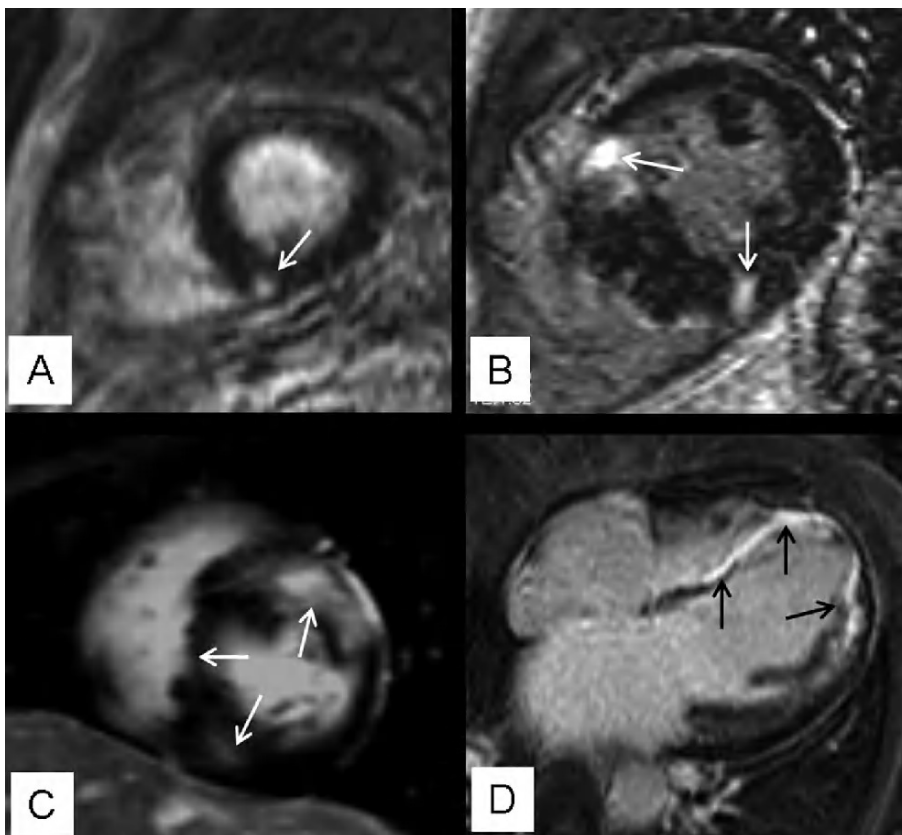
patients; 37%); *c*) multifocal (10 patients; 37%); and *d*) diffuse (3 patients; 11%) (Figure 1). The total calculated mass of myocardial fibrosis was between 1 and 59 g (mean, 17 g).

A good correlation was observed between the amount of myocardial fibrosis and the degree of hypertrophy in terms of maximal wall thickness ( $r=0.58$ ;  $P=.002$ ), as well as with the LVM ( $r=0.60$ ;  $P=.001$ ) (Figure 2). When considering the patient group with and without DE, we found significant differences in maximal wall thickness (23 [7] vs 18 [4] mm, respectively,  $P=.045$ ). However, there were no significant differences in LVM (176 [71] vs 158 [38] g,  $P=.55$ ), or end-diastolic volume (133 [46] vs 116 [27] mL;  $P=.38$ ), or end-systolic volume (43 [35] vs 30% [10%];  $P=.22$ ).

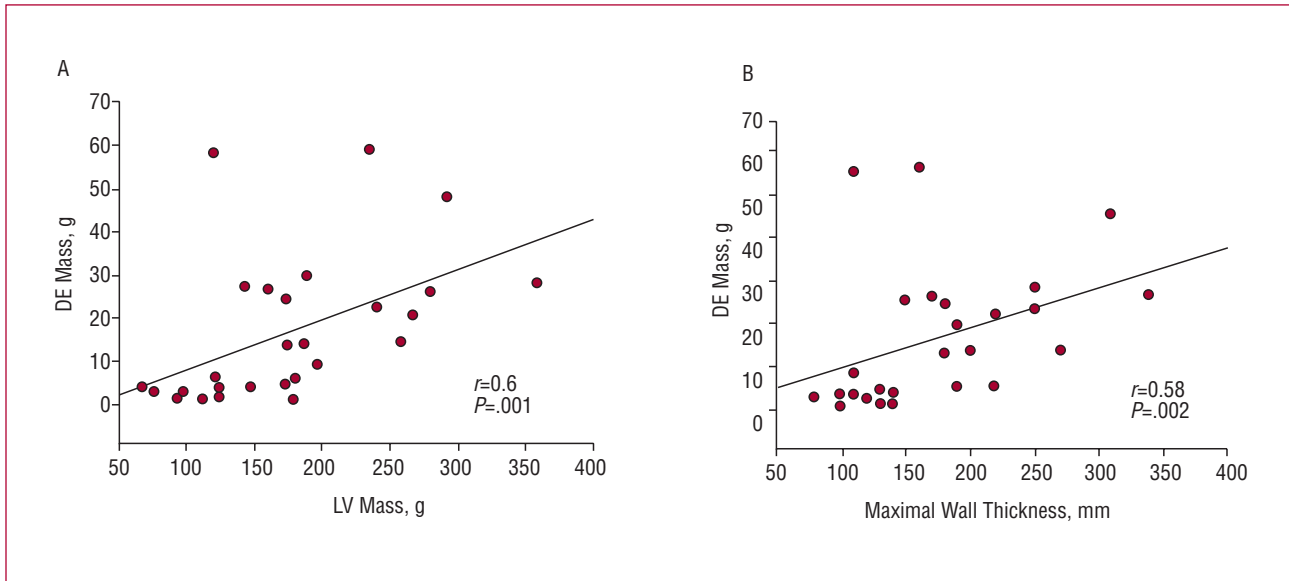
A higher prevalence of familial cases was found among patients with myocardial fibrosis compared to patients without myocardial fibrosis (48% vs 13%, respectively;  $P=.08$ ). Differences were also found when comparing the presence of conventional risk factors in both groups: 13 patients (48%) with myocardial fibrosis proven by DE presented at least 1 risk factor, whereas only 2 (13%) patients without myocardial fibrosis had one of these risk factors ( $P=.04$ ) (Figure 3).

**DISCUSSION**

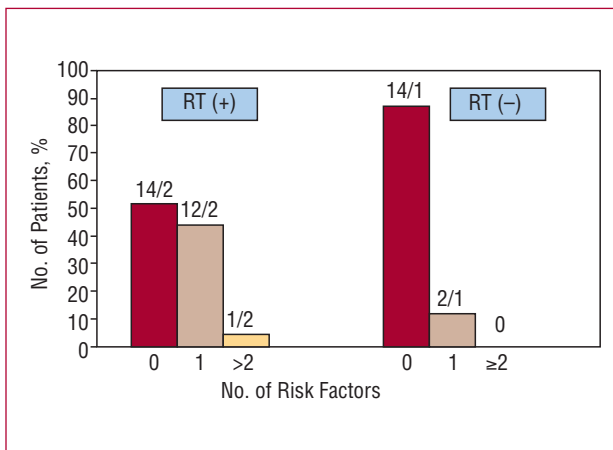
This study shows that on cardiac MRI, most patients with HCM present DE indicative of focal myocardial fibrosis. In keeping with reports recently published in



**Figure 1.** Distribution patterns of focal myocardial fibrosis detected by DE. A: corresponds to a unifocal pattern which, in this case, affects the inferior septum (arrow); B: shows the characteristic bifocal pattern affecting the area where both ventricles join (arrows); C: corresponds to a multifocal patterns that includes segments other than the left ventricle (arrows); D: illustrates an example of a diffuse pattern with a long extension of DE (arrows).



**Figure 2.** Plots showing the correlation between myocardial fibrosis, detected by DE, with LVM (A) and with maximal wall thickness (B).



**Figure 3.** Comparison of the number of clinical risk factors between the group with and the group without DE. Most patients without DE did not present any clinical risk factor, whereas almost half the patients with DE presented at least one clinical risk factor.

the literature,<sup>9,12</sup> this study found a correlation between the amount of myocardial fibrosis and the degree of hypertrophy by cardiac MRI. However, despite the relationship between the extension of DE and LVM, or maximal wall thickness, it is worth noting the possible absence of myocardial fibrosis even in cases with an obvious increase in LVM.

Varnava et al<sup>2</sup> demonstrated in a histological study of patients with HCM, whether deceased or subject to heart transplantation, that the presence of myocardial fibrosis in HCM is related to the degree of hypertrophy. Although these observations are based on a group of patients with much more advanced disease,

the findings of our study show myocardial fibrosis is also observed in an unselected population of patients with HCM, as found in other studies.<sup>9,12</sup> Additionally, myocardial fibrosis was present in segments with greater hypertrophy.

The importance of detecting myocardial fibrosis in unselected patients with HCM lies in the potential prognostic implication of this finding. A combination of the different clinical risk factors is currently used to stratify the risk of patients with HCM. However, the identification of patients with HCM and a high-risk profile continues to be a challenge. Moon et al<sup>9</sup> observed that the extension of the DE helped identify patients with a high-risk profile. Moreover, a greater extension of DE was observed in patients with dilation and progressive left ventricular dysfunction. In our study, the consecutive inclusion of patients resulted in a population with a relatively benign profile, since all patients except for one had none, or one risk factor for sudden death. When comparing these 2 groups, we observed that the absence of DE is more commonly associated with patients with no risk factors than those with a risk factor. This finding is of particular interest, especially when considering that there is still some debate in primary prevention about automatic implantable defibrillators for patients with only one risk factor.<sup>13</sup> Based on the literature published to date, however, the prognostic significance of DE in these patients is still not determined. Studies with long-term follow-up and large populations are still required to establish if DE in patients with only one risk factor for sudden death will change the therapeutic approach in primary prevention.



It is important to mention that the 2 patients in our series who had progressive HCM with severe left ventricular dysfunction presented greater myocardial fibrosis (Figure 1D). In these 2 patients, the total myocardial fibrosis mass was 58 and 59 g, whereas in the remaining patients it was from 1 to 48 g. This observation also correlates with the anatomical pathology findings, which showed that patients with HCM who evolved rapidly to progressive heart failure presented extensive myocardial scarring of the left ventricle at the time of heart transplantation or autopsy.<sup>14</sup>

In this study, the more frequent distribution pattern for DE was bifocal, affecting the areas where the 2 ventricles were joined, and multifocal. The bifocal pattern has been previously related to a benign profile.<sup>9,12</sup> However, the size of our sample is not sufficient to draw conclusions regarding the potential prognostic implications for the various distribution patterns of DE.

This study is limited by its cross-sectional design, which makes it impossible to establish a relationship between myocardial fibrosis and HCM prognosis. Studies with long-term follow-up are needed to draw conclusions, as well as to assess the potential prognostic value of the various distribution patterns for myocardial fibrosis.

In conclusion, this study shows that focal myocardial fibrosis, identified by DE in the cardiac MRI, is a common finding in patients with HCM. Although myocardial fibrosis is not necessarily observed in all patients with more hypertrophied ventricles, when present there is a correlation between the amount of myocardial fibrosis and the degree of hypertrophy. In addition, DE in HCM tends to be more prevalent among familial cases, as well as among those with a potentially higher risk profile. Confirmation of this in future studies may confirm the value of DE as a risk factor in HCM.

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