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Prognostic Significance of Myocardial Fibrosis Quantification by Histopathology and Magnetic Resonance Imaging in Patients With Severe Aortic Valve Disease

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Objectives We sought to determine whether the quantitative assessment of myocardial fibrosis (MF), either by histopathology or by contrast-enhanced magnetic resonance imaging (ce-MRI), could help predict long-term survival after aortic valve replacement.

Background Severe aortic valve disease is characterized by progressive accumulation of interstitial MF.

Methods Fifty-four patients scheduled to undergo aortic valve replacement were examined by ce-MRI. Delayed-enhanced images were used for the quantitative assessment of MF. In addition, interstitial MF was quantified by histological analysis of myocardial samples obtained during open-heart surgery and stained with picrosirius red. The ce-MRI study was repeated 27 ± 22 months after surgery to assess left ventricular functional improvement, and all patients were followed for 52 ± 17 months to evaluate long-term survival.

Results There was a good correlation between the amount of MF measured by histopathology and by ce-MRI ($r = 0.69$, $p < 0.001$). In addition, the amount of MF demonstrated a significant inverse correlation with the degree of left ventricular functional improvement after surgery ($r = -0.42$, $p = 0.04$ for histopathology; $r = -0.47$, $p = 0.02$ for ce-MRI). Kaplan-Meier analyses revealed that higher degrees of MF accumulation were associated with worse long-term survival (chi-square = 6.32, $p = 0.01$ for histopathology; chi-square = 5.85, $p = 0.02$ for ce-MRI). On multivariate Cox regression analyses, patient age and the amount of MF were found to be independent predictors of all-cause mortality.

Conclusions The amount of MF, either by histopathology or by ce-MRI, is associated with the degree of left ventricular functional improvement and all-cause mortality late after aortic valve replacement in patients with severe aortic valve disease. (J Am Coll Cardiol 2010;56:278–87) © 2010 by the American College of Cardiology Foundation

Severe aortic valve disease is characterized by progressive accumulation of interstitial myocardial fibrosis (MF) and impairment of myocyte ultrastructure (1–4). Previous studies have shown that the amount of MF and the degree of myocyte degeneration are inversely related to both systolic (1) and diastolic (5,6) left ventricular (LV) function. Yet, the few studies that investigated the relationship between interstitial MF and LV functional recovery after aortic valve replacement have reported conflicting results (1,2). Moreover, the prognostic significance of interstitial MF in terms of long-term survival after aortic valve replacement remains to be demonstrated.

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In recent years, contrast-enhanced magnetic resonance imaging (ce-MRI) with the delayed-enhancement technique has been shown to provide an accurate assessment of myocardial necrosis and fibrosis, not only in the setting of myocardial infarction (7–10) but also in a variety of other nonischemic cardiomyopathies (11–14). Unlike histopathology, ce-MRI is not able to evaluate interstitial MF at the microscopic level due to insufficient spatial resolution. Nevertheless, although widespread and diffuse, the distribution of interstitial MF in chronic aortic valve disease can

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be regionally accentuated (4,15). Therefore, we hypothesized that there would be a relationship between the degree of diffuse interstitial MF by histopathology and the prevalence of focal regions of accentuated MF that could be identified by ce-MRI.

In the present study we sought to determine whether the amount of MF measured by ce-MRI demonstrated good correlation when compared with the gold-standard histopathological analyses. Additionally, we attempted to determine whether the quantitative assessment of MF, either by ce-MRI or by histopathology, could help predict LV functional improvement and long-term survival after aortic valve replacement surgery.

Methods

Patients. Fifty-four patients with severe aortic valve disease and indication for aortic valve replacement were prospectively enrolled between May 2001 and May 2003. All patients over 40 years old had a coronary angiography, and those with significant coronary artery disease (CAD) (luminal stenosis >50%) were excluded. Patients with concomitant mitral valve disease were also excluded. In addition, there were 2 distinct control groups: 8 subjects who died of noncardiac causes and had no previous history of cardiovascular disease served as control subjects for the quantitative histological analyses; and 10 normal volunteers served as control subjects for the quantitative ce-MRI analyses. The study was approved by the Institutional Ethics Committee, and all patients gave written informed consent.

Tissue sampling and histological analyses. During open-heart surgery, 0.8-cm-thick myectomy samples weighing 25 to 70 mg were obtained from the basal LV septum approximately 2 cm below the base of the commissure between the right and left aortic cusps. For each patient, 5 paraffin-embedded sections were stained with picrosirius red (16). The regions of interstitial MF were determined by quantitative video-morphometry with an automated image analysis system (Quantimet 520 Image Analysis System, Cambridge Instruments, Cambridge, United Kingdom). For each patient, quantification of interstitial MF was performed on 12 different fields representative of all myocardial layers sampled. Patients were categorized into 3 groups: Group 1, patients with MF ≤20%; Group 2, patients with MF between 20% and 30%; and Group 3, patients with MF ≥30%.

Magnetic resonance imaging (MRI) protocol. Patients underwent cardiac MRI with a 1.5-T clinical scanner (Signa CV/I, GE Medical Systems, Waukesha, Wisconsin). After localization of the heart, 8 to 12 contiguous short-axis slices encompassing the entire LV and 4 long-axis slices were prescribed. Cine images were acquired with a steady-state free precession pulse sequence. Delayed-enhancement images were acquired 5 to 15 min after a bolus injection of 0.2 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Aulnay-sous-Bois, France), with an inversion recovery fast gradient-echo pulse sequence (8). The inversion time was adjusted on the basis of the visual inspection of the images by an experienced investigator to null the signal of the normal myocardium (8,17). Additionally, to evaluate the effect that the interval between contrast administration and image acquisition could have on MF quantification, a second set of delayed-enhancement images was acquired in a subgroup of 20 patients. The first and second sets of delayed-enhancement images were acquired 12 ± 4 min and 21 ± 9 min after contrast administration, respectively.

Abbreviations and Acronyms

CAD = coronary artery disease
ce-MRI = contrast-enhanced magnetic resonance imaging
CI = confidence interval
EF = ejection fraction
HR = hazard ratio
LV = left ventricle/ventricular
MF = myocardial fibrosis
MRI = magnetic resonance imaging
NYHA = New York Heart Association
SI = signal intensity

MRI data analyses. All MRI image analyses were performed with the custom software package Cinetool (GE Medical Systems, Waukesha, Wisconsin). Cine images were used for the assessment of LV volumes, mass, and function (17). Quantification of MF by ce-MRI was based on the assessment of the short-axis delayed-enhanced images. The regions of MF were defined as the sum of pixels with signal intensity (SI) above a pre-determined threshold. The definition of this threshold was based on 3 parameters: 1) the mean SI of total myocardium; 2) the SI variability from an area of nondiseased myocardium free of focal regions of MF, which was calculated as 2 SDs of mean SI of a remote area; and 3) the SI variability that could be introduced by the image noise of the delayed-enhancement dataset, which was calculated as 2 SDs of mean SI of air. More specifically, the threshold was calculated as: mean SI of total myocardium + 2 SDs of mean SI of a remote area + 2 SDs of mean SI of air.

First, the endocardial and epicardial LV borders were manually contoured, and the mean SI of total myocardium was automatically calculated by the software. Then, the investigator delineated a remote area in a myocardial region free of any hyperenhancement and a region of interest in the air outside the patient. After these steps, the threshold value was determined, and the software automatically calculated the area of all pixels within the myocardium with SI above this cutoff value. The amount of MF was expressed as a percentage of LV mass, and patients were categorized into 3 groups: Group 1, patients with MF ≤2.5%; Group 2, patients with MF between 2.5% and 5.0%; and Group 3, patients with MF ≥5.0%. Additionally, interobserver and intraobserver variability were measured in a subgroup of 20 patients. The delayed-enhancement dataset was also qualitatively evaluated for the presence of MF by the visual inspection of the images as previously described (17).

Statistical analysis. Student *t* tests were used to compare continuous variables, which were expressed as mean ± SD.

Fisher exact test was used to compare categorical variables. Linear regression analyses were used to assess: 1) the correlation between the values of MF measured by histopathology and by ce-MRI; and 2) the relationship between the amount of MF and the degree of LV functional improvement after surgery. The Kaplan-Meier technique was used to evaluate survival times after surgery, and the log-rank test was used to compare survival curves. Cox regression was used to examine the effects of several continuous and categorical predictors of patient mortality. All tests were 2-tailed, and a value of $p < 0.05$ was considered indicative of statistical significance.

Results

Baseline characteristics. Patient baseline characteristics are summarized in Table 1. All patients were symptomatic, complaining of exertional dyspnea (94%), angina (24%), and/or syncope (9%). Among patients with predominant aortic stenosis (n = 28), 6 also exhibited moderate aortic regurgitation, and among patients with predominant aortic insufficiency (n = 26), 2 also exhibited moderate aortic stenosis. All patients underwent surgical aortic valve replacement. Due to difficulty in achieving an adequate monitoring of anticoagulant therapy in our population, all patients received biological prosthetic valves. The baseline characteristics of the control groups are summarized in Table 2.

Interstitial MF by histopathology. The amount of interstitial MF determined by histopathology was higher in patients with aortic valve disease than in control subjects (24.6 ± 9.8% vs. 6.0 ± 1.8%, $p < 0.001$). Patients with aortic regurgitation and aortic stenosis exhibited similar degrees of interstitial MF accumulation (25.8 ± 10.3% vs. 23.4 ± 9.3%, $p = 0.37$).

MF by ce-MRI. The amount of MF measured by ce-MRI was also higher in patients with aortic valve disease than in control subjects (3.72 ± 2.17% vs. 0.57 ± 0.55%, $p < 0.001$). Patients with aortic regurgitation exhibited higher MF accumulation than those with aortic stenosis (4.35 ± 2.32% vs. 3.15 ± 1.87%, $p = 0.04$). There was good

Table 1 Pre-Operative Characteristics of the 54 Patients

	All (n = 54)	Aortic Regurgitation (n = 26)	Aortic Stenosis (n = 28)	p Value
Sex				
Male	42 (78%)	24 (92%)	18 (64%)	0.02
Female	12 (22%)	2 (8%)	10 (36%)	
Age (yrs)	46.8 ± 13.7	46.5 ± 14.2	47.2 ± 13.5	0.85
Etiology				
Rheumatic disease	27 (50%)	20 (77%)	7 (25%)	<0.001
Bicuspid aortic valve	18 (33%)	3 (11.5%)	15 (54%)	
Degenerative/calcification	6 (11%)	0	6 (21%)	
Other	3 (6%)	3 (11.5%)	0	
NYHA functional class				
I	3 (5%)	2 (8%)	1 (4%)	0.79
II	22 (41%)	10 (38%)	12 (43%)	
III	29 (54%)	14 (54%)	15 (53%)	
Angina	13 (24%)	3 (12%)	10 (36%)	0.04
Syncope	5 (9%)	1 (4%)	4 (14%)	0.18
Pressure gradient (mm Hg)				
Peak	—	—	97 ± 27	—
Mean	—	—	63 ± 20	—
Hypertension	0	0	0	—
Diabetes	0	0	0	—
Hypercholesterolemia	0	0	0	—
Smoking	2 (4%)	1 (4%)	1 (4%)	1.0
Family history of CAD	0	0	0	—
LV EDV (ml)	244 ± 92	318 ± 68	175 ± 43	<0.001
LV ESV (ml)	124 ± 67	169 ± 67	83 ± 30	<0.001
LV mass (g)	272 ± 47	280 ± 44	266 ± 50	0.27
LVEF (%)	51 ± 11	48 ± 11	53 ± 9	0.09
MF by histopathology (%)	24.6 ± 9.8	25.8 ± 10.3	23.4 ± 9.3	0.37
MF by ce-MRI (%)	3.72 ± 2.17	4.35 ± 2.32	3.15 ± 1.87	0.04
MF by qualitative analysis				
Present	35 (65%)	18 (69%)	17 (61%)	0.51
Absent	19 (35%)	8 (31%)	11 (39%)	

CAD = coronary artery disease; ce-MRI = contrast-enhanced magnetic resonance imaging; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; MF = myocardial fibrosis; NYHA = New York Heart Association.

Table 2 Baseline Characteristics of Control Groups and Comparison With Study Population

	Patients (n = 54)	Control Groups: Histopathology (n = 8)	p Value	Control Groups: Ce-MRI (n = 10)	p Value
Sex					
Male	42 (78%)	4 (50%)	0.09	7 (70%)	0.59
Female	12 (22%)	4 (50%)		3 (30%)	
Age (yrs)	46.8 ± 13.7	33.5 ± 10.0	0.01	43.1 ± 11.8	0.42
MF by histopathology (%)	24.6 ± 9.8	6.0 ± 1.8	<0.001	—	
MF by ce-MRI (%)	3.72 ± 2.17	—		0.57 ± 0.55	<0.001
MF by qualitative analysis					
Present	35 (65%)	—		0 (0%)	<0.001
Absent	19 (35%)	—		10 (100%)	

Eight subjects who died of noncardiac causes and had no previous history of cardiovascular disease served as control subjects for the quantitative histological analyses. Ten normal volunteers served as control subjects for the contrast-enhanced magnetic resonance imaging (ce-MRI) analyses. p values are for control subjects versus patients.

MF = myocardial fibrosis.

agreement of MF measurements in the 20 patients in whom a second set of delayed-enhancement images was acquired, with a mean difference of 0.10% (95% confidence interval [CI]: −0.29% to 0.49%, limits of agreement −1.55% to 1.75%). In addition, interobserver and intraobserver reproducibility was very good, with a mean difference of −0.02% (95% CI: −0.23% to 0.19%, limits of agreement −0.91% to 0.88%) and 0.03% (95% CI: −0.15% to 0.21%, limits of agreement −0.74% to 0.79%), respectively.

Most patients exhibited a pattern of delayed-enhancement that was multifocal (3 or more foci of MF) and widespread: 21 patients (81%) with aortic regurgitation, and 20 (72%) with aortic stenosis (Fig. 1). The LV sites of myocardial involvement were highly variable. In general, any portion of the LV walls could be affected by the focal accumulation of MF. The pattern and location of MF accumulation was similar in patients with aortic regurgitation and aortic stenosis.

We were able to identify regions of MF by the qualitative visual assessment of the delayed-enhanced images in 35 patients (64%). In 17 patients, the quantitative semi-automatic analysis revealed small regions of focal MF that could not be detected by the visual assessment. Patients with visually identified regions of MF demonstrated higher amounts of MF on the quantitative analyses, both by histopathology (29.1 ± 8.0% vs. 16.2 ± 6.9%, $p < 0.0001$) and by ce-MRI (4.6 ± 2.0% vs. 2.2 ± 1.6%, $p < 0.0001$).

Relationship between histopathology and ce-MRI. Quantification of MF by ce-MRI with the technique described in the present study showed good correlation with the measurements obtained by histopathology ($r = 0.69$, $y = 3.10x + 13.0$, $p < 0.001$) (Figs. 2 and 3). Correlation was also good if considering only the subgroup of patients with aortic regurgitation ($r = 0.70$, $y = 3.09x + 12.3$, $p < 0.001$) or aortic stenosis ($r = 0.67$, $y = 3.34x + 12.9$, $p < 0.001$).

LV functional changes over time. All analyses performed to evaluate LV changes over time included only the 25 patients that underwent a second MRI study 27 ± 22 months after aortic valve replacement. The reasons for the remaining patients to not undergo the follow-up MRI included patient refusal, contact loss, place of residence too distant, death, and placement of a definitive pacemaker.

There was a significant reduction of LV mass between both studies (261 ± 54 g vs. 179 ± 52 g, $p < 0.0001$). Although the amount of MF measured by ce-MRI did not show a significant change when expressed as a percentage of LV mass (3.13 ± 2.18% vs. 3.10 ± 2.63%, $p = 0.93$), it exhibited a significant reduction when expressed as total LV fibrous content in grams (8.9 ± 8.0 g vs. 5.8 ± 6.7 g, $p = 0.005$).

There was a significant increase of LV ejection fraction (EF) between both studies (54 ± 10% vs. 59 ± 14%, $p = 0.02$). The amount of MF, either by histopathology or by ce-MRI, exhibited a moderate inverse correlation with the magnitude of LVEF change over time ($r = −0.42$, $p = 0.04$ for histopathology; $r = −0.47$, $p = 0.02$ for ce-MRI). In other words, the higher the amount of MF, the worse was the improvement of global LV systolic function after aortic valve replacement (Figs. 4A and 4B).

Prognostic significance. Patients were followed for 52 ± 17 months after aortic valve replacement (range 10 to 72 months). Two patients (3.7%) were lost during follow-up. Sixteen patients died 21 ± 21 months after surgery (ranging from 4 days to 62 months). There were 4 deaths in the early (<30 days) and 12 deaths in the late (>30 days) post-operative period. Deaths were due to progressive heart failure (n = 6), sudden death (n = 5), post-operative complications (n = 3), infective endocarditis (n = 1), and hemorrhagic cerebrovascular accident (n = 1). There were no deaths during the surgical procedure. Two patients required reoperation for replacement of the prosthetic valve due to infective endocarditis. Clinical and laboratory data comparing patients that died or survived are summarized in Table 3.

Kaplan-Meier analyses. The amount of interstitial MF by histopathology was significantly higher in the subgroup of

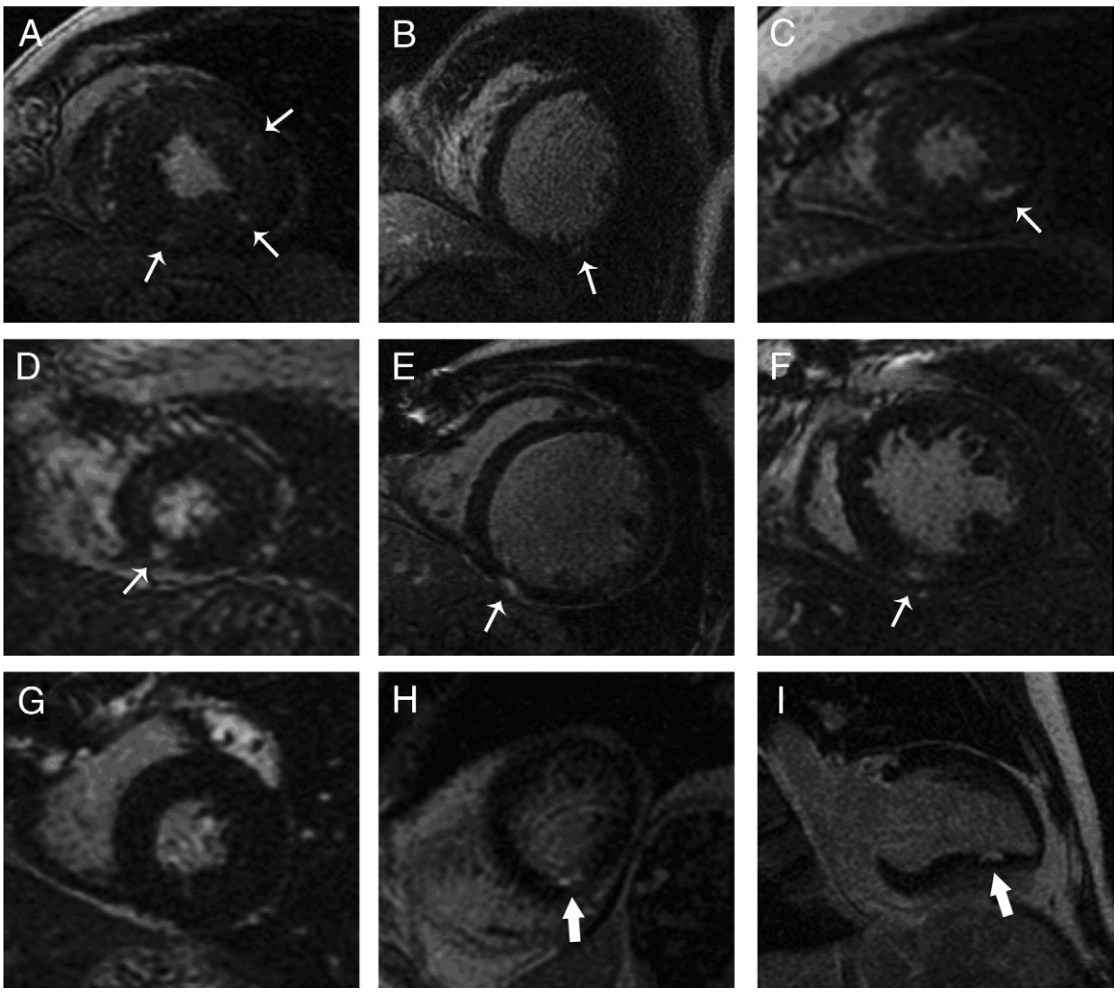

Figure 1 **Delayed-Enhanced MRI From Different Patients With Severe Aortic Valve Disease**

Examples from patients with aortic stenosis **(A, C, D)** and aortic regurgitation **(B, E, F)** showing several foci of myocardial fibrosis (MF) accumulation **(thin arrows)**. **(G)** Example from a patient with aortic stenosis that did not have any region of identifiable MF by contrast-enhanced magnetic resonance imaging (MRI). Illustrative images showing that the regions of MF identified on the short-axis images **(H)** could also be visualized on the orthogonal long-axis views **(I) (thick arrows)**.

patients that died during follow-up than in those that survived (29.5 ± 7.6% vs. 22.5 ± 9.9%, p = 0.01). Kaplan-Meier analyses revealed that patients with a higher amount of interstitial MF by histopathology demonstrated significantly lower survival probabilities (log-rank test chi-square = 6.32, p = 0.01) (Fig. 4C). Similarly, the amount of MF by ce-MRI was higher in the subgroup that died than in those that survived (4.93 ± 2.16% vs. 3.22 ± 1.98%, p < 0.01). Patients with higher amount of MF by ce-MRI also demonstrated significantly lower survival probabilities (log-rank test chi-square = 5.85, p = 0.02) (Fig. 4D).

When we considered the qualitative assessment, 13 patients (37%) with visually identified MF and 3 patients (16%) without any MF on the visual assessment died during follow-up. Although the difference between the survival curves was not statistically significant, there was a trend toward higher mortality in the subgroup with visually identified regions of MF (log-rank test chi-square = 1.89, p = 0.17).

Cox regression analyses. In addition to the amount of MF, several well-established predictors of all-cause mortality after aortic valve replacement surgery—namely, patient age, resting LVEF, New York Heart Association (NYHA) functional class, and patient diagnosis (aortic regurgitation or aortic stenosis)—were evaluated by Cox proportional hazards regression analyses (Table 4). Two distinct multivariable analyses were performed; the first included the amount of interstitial MF by histopathology, and the second included the amount of MF by ce-MRI. When all of the aforementioned variables were considered in the first multivariable model with stepwise backward selection, MF by histopathology (hazard ratio [HR]: 1.07; p = 0.017) and patient age (HR: 1.04, p = 0.045) emerged as the 2 strongest independent predictors of all-cause mortality. If

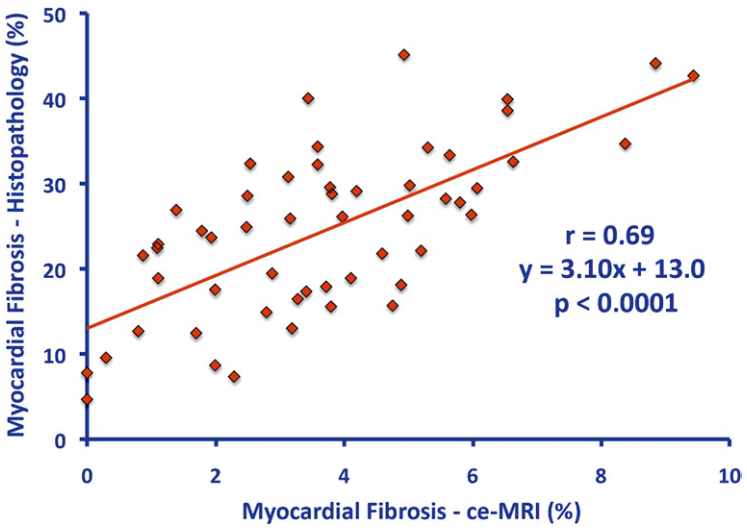

Figure 2 **Linear Regression Graph**

Note that there was a good correlation between the amount of myocardial fibrosis measured by histopathology and by contrast-enhanced magnetic resonance imaging (ce-MRI).

we considered only patients with late mortality (>30 days), MF by histopathology remained as an independent predictor of mortality (HR: 1.06, p = 0.04), but patient age was of borderline significance (HR: 1.04, p = 0.06). When we applied stepwise backward selection on the second multivariable model, the amount of MF by ce-MRI stood as an

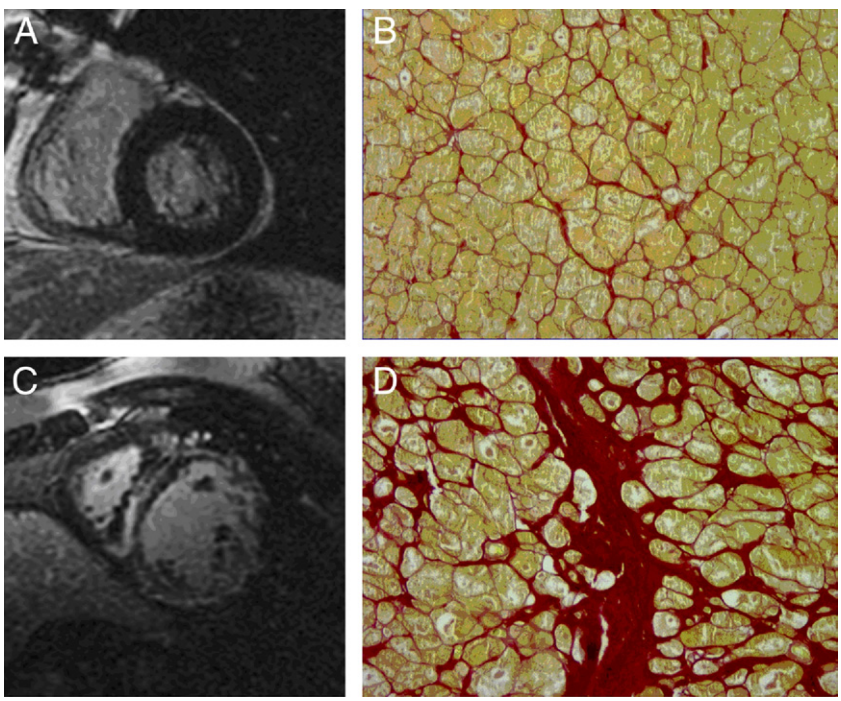

Figure 3 **Selected Examples Illustrating the Correlation Between MF by Histopathology and by ce-MRI**

Delayed-enhanced image from a patient with severe aortic stenosis that exhibited a small amount of myocardial fibrosis (MF) by contrast-enhanced magnetic resonance imaging (ce-MRI) (0.80%) **(A)** and the histopathological specimen from the same patient stained with picrosirius red showing a small amount of interstitial fibrosis by histopathology (12.6%) **(B)**. Delayed-enhanced image from a patient with severe aortic regurgitation that exhibited extensive regions of MF by ce-MRI (9.44%) **(C)**, and the histopathological specimen from the same patient showing a large amount of interstitial MF by histopathology (42.7%) **(D)**.

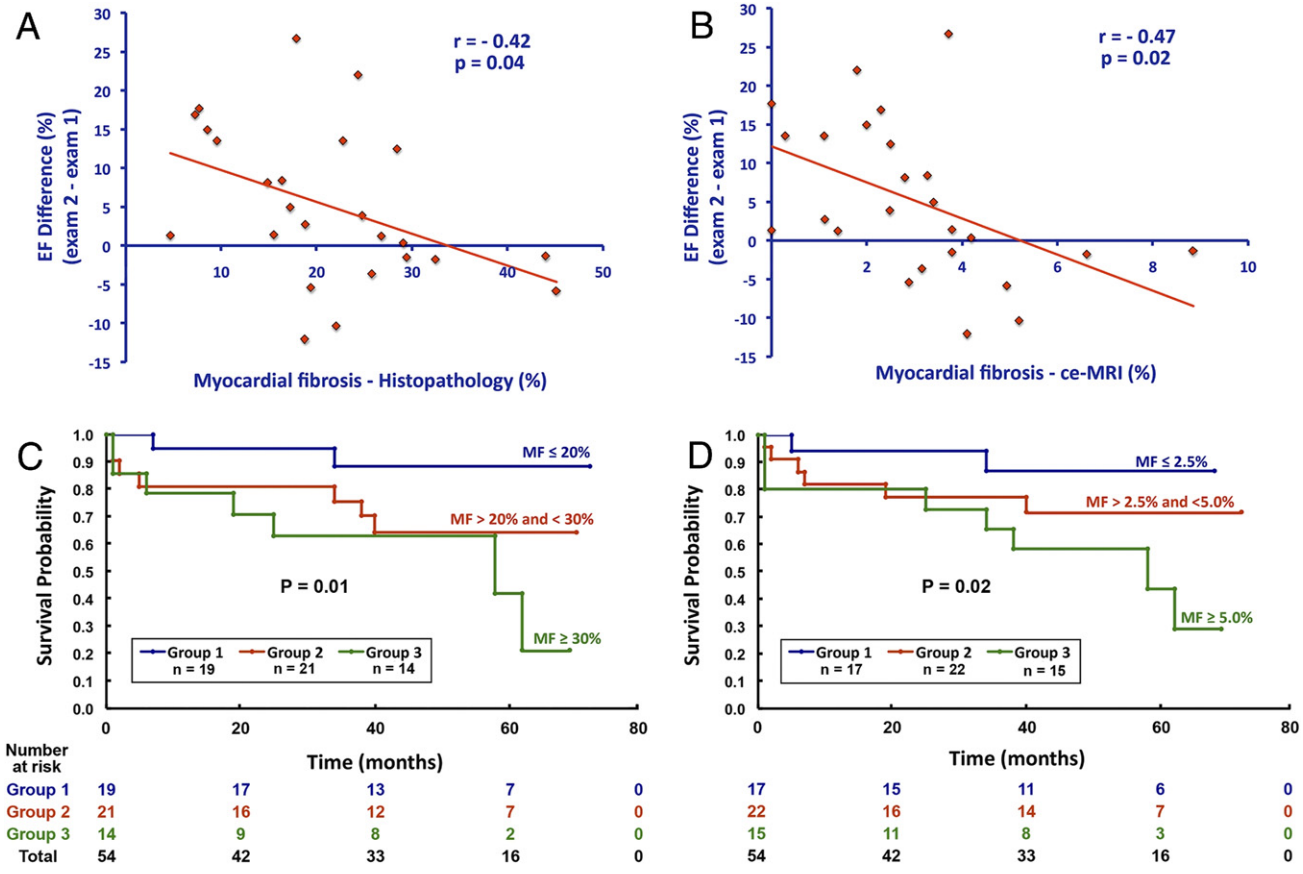

Figure 4 **Relationship Between the Amount of MF and LV Functional Improvement and Long-Term Survival After Aortic Valve Replacement Surgery**

Relationship between the amount of myocardial fibrosis (MF) and left ventricular (LV) functional improvement **(A and B)** and long-term survival **(C and D)** after aortic valve replacement surgery. Linear regression graphs illustrating the relationship between the amount of MF, either by histopathology **(A)** or by contrast-enhanced magnetic resonance imaging (ce-MRI) **(B)**, and the degree of LV functional improvement 27 ± 22 months after aortic valve replacement. Kaplan-Meier graphs comparing the survival probabilities of the subgroups with increasing amounts of MF. Note that patients with higher degrees of MF accumulation, either by histopathology **(C)** or by ce-MRI **(D)**, demonstrated significantly lower survival probabilities after aortic valve replacement. EF = ejection fraction.

independent predictor of all-cause mortality (HR: 1.26, p = 0.027), and patient age was of borderline significance (HR: 1.04, p = 0.054). If we considered only patients with late mortality (>30 days), the results were similar: MF by ce-MRI remained as an independent predictor of mortality (HR: 1.25, p = 0.05), and patient age was of borderline significance (HR: 1.04, p = 0.07). It is important to highlight that, due to the relatively small number of events (16 deaths), there is a degree of overfitting in our multivariate Cox regression models.

Discussion

In the present study we were able to demonstrate that ce-MRI allows for the noninvasive quantification of MF in patients with severe aortic valve disease. The amount of MF measured by ce-MRI demonstrated good correlation with the values of interstitial MF obtained by the gold-standard histopathological analyses. Most importantly, this was the first study to demonstrate that the quantitative assessment of MF, either by histopathology or by ce-MRI, provides important and independent prognostic information in this patient population.

MF in severe aortic valve disease. Previous studies that used histopathology to investigate the process of chronic myocardial injury in patients with severe aortic valve disease have demonstrated that it is characterized by a significant increase of interstitial MF and by variable degrees of myocyte degeneration (1–4). The pathophysiological mechanisms involved include the excessive activation of the cardiac renin-angiotensin system (18), the over-expression of myocardial neutral endopeptidase with inhibition of the kallikrein-kinin system (19) and the increased expression of tissue inhibitor of metalloproteinase 1 and 2 (5). Our finding that the amount of interstitial MF by histopathology was significantly higher in patients with severe aortic valve disease than in control subjects (24.6% vs. 6.0%) is in

Table 3 Characteristics of Subgroups That Died or Survived During Follow-Up

	Deceased (n = 16)	Survivors (n = 38)	p Value
Sex			
Male	10 (62%)	32 (84%)	0.15
Female	6 (38%)	6 (16%)	
Age (yrs)	51.1 ± 14.9	45.0 ± 13.0	0.14
Diagnosis			
Aortic regurgitation	10 (62%)	16 (42%)	0.23
Aortic stenosis	6 (38%)	22 (58%)	
NYHA functional class			
I	1 (6%)	2 (5%)	0.02
II	2 (13%)	20 (53%)	
III	13 (81%)	16 (42%)	
LV EDV (ml)	280 ± 92	229 ± 88	0.06
LV ESV (ml)	156 ± 76	111 ± 59	0.02
LV mass (g)	285 ± 45	267 ± 48	0.20
LV EF (%)	46 ± 12	53 ± 9	0.01
MF by histopathology (%)	29.5 ± 7.6	22.5 ± 9.9	0.01
MF by ce-MRI (%)	4.93 ± 2.16	3.22 ± 1.98	<0.01
MF by qualitative analysis			
Present	13 (81%)	22 (58%)	0.10
Absent	3 (19%)	16 (42%)	

Abbreviations as in Table 1.

agreement with previous reports by Hein et al. (1) (31% vs. 11%) and by Heymans et al. (5) (16% vs. 7%).

The assessment of MF by ce-MRI. In addition to histopathology, in the present study we also used ce-MRI to quantify the regions of MF. A previous study by Moon et al. (12) also compared ce-MRI and histopathology regarding the quantitative assessment of MF. In that study, they evaluated the entire heart of a single patient with hypertrophic cardiomyopathy that had to undergo heart transplantation. One of their main findings was that LV segments with >15% interstitial MF by histopathology demonstrated a higher likelihood of exhibiting regions of MF by ce-MRI on a visual subjective analysis. Moreover, their quantitative analyses revealed a significant correlation between interstitial MF by histopathology and the amount of MF by ce-MRI (r = 0.70) (12). In agreement with Moon et al. (12), we also found a significant correlation between histopathology and ce-MRI (r = 0.69).

Previous studies by our group (17) and others (15,20,21) have demonstrated that it is possible to identify focal regions of MF in patients with severe aortic valve disease with ce-MRI. However, in these studies the assessment of MF was based on the visual subjective inspection of the delayed-enhanced images, whereas in the present study we employed a semiautomatic algorithm that allowed for the objective quantification of MF. In addition, whereas the former were observational studies, the present is a longitudinal study that followed patients for 4.3 ± 1.4 years and was able to demonstrate an association between MF and long-term survival in this population. Previous prospective trials have also demonstrated the prognostic significance of delayed-enhancement in patients with nonischemic cardiomyopathy (22,23). Our results are in agreement with these previous reports and indicate that it is possible that the prognostic significance of MF assessment by ce-MRI might be broadly applicable to other nonischemic cardiomyopathies characterized by chronic myocardial injury.

As previously mentioned, the present study has a limitation regarding the spatial resolution of ce-MRI. With a typical voxel dimension of approximately 1.4 × 1.9 × 8.0 mm, ce-MRI is not currently able to evaluate interstitial MF at the microscopic level as histopathology does. Therefore, even though both methods are evaluating the same pathophysiological process (i.e., the pathological accumulation of MF), they are actually measuring 2 distinct parameters. Although histopathology directly measures the fraction of myocardial tissue occupied by interstitial fibrosis (reactive fibrosis), ce-MRI only quantifies the LV regions in which there is a focal accumulation of MF (replacement fibrosis). It is important to note, however, that histopathology is limited to the assessment of small myocardial samples obtained through surgical myectomy or endomyocardial biopsy, whereas ce-MRI enables the complete assessment of the entire LV. Newer MRI techniques especially designed for the assessment of diffuse interstitial fibrosis accumulation, such as myocardium T1 mapping (15,24), were not employed in the

Table 4 Univariable and Multivariable Associations With All-Cause Mortality

	Univariable Analysis		Multivariable Analysis 1		Multivariable Analysis 2	
Variable	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age	1.03 (0.99–1.07)	0.07	1.04 (1.00–1.08)	0.04	1.04 (1.00–1.07)	0.05
Patient diagnosis	1.82 (0.66–5.02)	0.25	—	—	—	—
LVEF	0.95 (0.91–0.99)	0.02	—	—	—	—
NYHA functional class	2.76 (0.95–8.05)	0.06	—	—	—	—
MF by histopathology	1.06 (1.01–1.11)	0.02	1.07 (1.01–1.12)	0.02	—	—
MF by ce-MRI	1.24 (1.02–1.50)	0.03	—	—	1.26 (1.03–1.54)	0.02

Both multivariable models included age, LVEF, and NYHA functional class. The first multivariable model included the amount of MF by histopathology, and the second multivariable model included the amount of MF by ce-MRI.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

present study. Moreover, we did not perform adjustments for coil location relative to the different myocardial regions being measured. Nevertheless, despite these factors, we were able to demonstrate a good correlation between the amount of MF measured by both methods and that their results are significantly related to patient prognosis after surgery.

MF and LV functional improvement. Successful replacement of the aortic valve results in substantial clinical and hemodynamic improvement in patients with severe aortic valve disease (25,26). However, not all patients respond the same way after surgery. Even after a successful procedure, some patients will not show any clinical or hemodynamic improvement and, not surprisingly, will have a poorer prognosis. Previous studies have shown that the best predictor of persistent LV dysfunction after aortic valve replacement is the presence of prolonged LV dysfunction before surgery (1,27). As mentioned, there is an inverse correlation between the amount of interstitial MF and resting LV systolic function (1). Nevertheless, the few studies that investigated the relationship between the magnitude of MF accumulation and LV functional recovery after aortic valve replacement have reported conflicting results. According to Krayenbuehl et al. (2), the presence of reduced LVEF before valve replacement but not the amount of interstitial MF was predictive of post-operative LV systolic dysfunction. In contrast, according to Hein et al. (1), patients with persistent LV dysfunction after surgery also exhibited significantly higher degrees of MF accumulation. In the present study, the follow-up MRI was performed over a wide interval after aortic valve replacement (27 ± 22 months). It is possible that this limitation could have influenced the results regarding LV functional changes over time. Nevertheless, in agreement with Hein et al. (1), we were able to demonstrate a moderate inverse correlation between the amount of MF, either by histopathology or by ce-MRI, and the degree of LV functional improvement after aortic valve replacement.

Prognostic significance. According to previous registries, among patients with aortic stenosis and preserved LV function, the operative risk during aortic valve replacement ranges from 2% to 5% in most centers (28). In addition, the 10-year actuarial survival rate of hospital survivors in surgically treated patients is approximately 85% (29). In the case of patients with aortic regurgitation, surgical mortality rates range from 3% to 8% (28,30), and a late mortality of approximately 5% to 10%/year is observed in hospital survivors who had prolonged LV dysfunction preoperatively (29,31). In the present study, the operative mortality rate of patients with aortic stenosis was 7%, and the survival rate of hospital survivors 4.4 ± 1.3 years after surgery was 85%. Among patients with aortic regurgitation, surgical mortality rate was 4% and the survival rate of hospital survivors 4.3 ± 1.5 years after surgery was 64%. As we can notice, the mortality rates observed in the present study are in agreement with these previous registries, especially if we take into consideration that all patients were symptomatic and many also exhibited LV systolic dysfunction at rest.

Previous studies have shown that the risk factors associated with higher mortality rates in this patient population include a high NYHA functional class, pre-operative impaired LV function, advanced age, and concomitant untreated CAD (28–31). This is the first study to demonstrate that the amount of MF, either by histopathology or by ce-MRI, is also a predictor of long-term survival after aortic valve replacement. Indeed, when all the aforementioned factors (with the exception of concomitant CAD, which was an exclusion criteria in the present study) were included in a multivariate model, only patient age and the amount of MF remained as independent predictors of late mortality. At this point, it is important to remember that the number of events in the present study was relatively small, resulting in overfitted multivariate models. Therefore, further studies with larger cohorts will be necessary to examine in greater detail the importance of each of these factors as predictors of late mortality. Nevertheless, our results indicate that the quantitative assessment of MF has the potential to provide additional prognostic information in the evaluation of patients with severe aortic valve disease. In the future, this marker of chronic myocardial injury, which can be noninvasively quantified by ce-MRI, might have the potential to be useful in the difficult decision-making process regarding the best moment to indicate a valve replacement surgery in patients with severe aortic valve disease.

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