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Noninvasive Detection of Fibrosis Applying Contrast-Enhanced Cardiac Magnetic Resonance in Different Forms of Left Ventricular Hypertrophy

Relation to Remodeling

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Objectives We aimed to evaluate the incidence and patterns of late gadolinium enhancement (LGE) in different forms of left ventricular hypertrophy (LVH) and to determine their relation to severity of left ventricular (LV) remodeling.

Background Left ventricular hypertrophy is an independent predictor of cardiac mortality. The relationship between LVH and myocardial fibrosis as defined by LGE cardiovascular magnetic resonance (CMR) is not well understood.

Methods A total of 440 patients with aortic stenosis (AS), arterial hypertension (AH), or hypertrophic cardiomyopathy (HCM) fulfilling echo criteria of LVH underwent CMR with assessment of LV size, weight, function, and LGE. Patients with increased left ventricular mass index (LVMI) resulting in global LVH in CMR were included in the study.

Results Criteria were fulfilled by 83 patients (56 men, age 57 ± 14 years; AS, n = 21; AH, n = 26; HCM, n = 36). Late gadolinium enhancement was present in all forms of LVH (AS: 62%, AH: 50%; HCM: 72%, p = NS) and was correlated with LVMI (r = 0.237, p = 0.045). There was no significant relationship between morphological obstruction and LGE. The AS subjects with LGE showed higher LV end-diastolic volumes than those without (1.0 ± 0.2 ml/cm vs. 0.8 ± 0.2 ml/cm, p < 0.015). Typical patterns of LGE were observed in HCM but not in AS and AH.

Conclusions Fibrosis as detected by CMR is a frequent feature of LVH, regardless of its cause, and depends on the severity of LV remodeling. As LGE emerges as a useful tool for risk stratification also in nonischemic heart diseases, our findings have the potential to individualize treatment strategies. (J Am Coll Cardiol 2009;53:284–91) © 2009 by the American College of Cardiology Foundation

Left ventricular hypertrophy (LVH) is an independent predictor of cardiac mortality, regardless of its etiology (1–4). Left ventricular hypertrophy can be caused by 2 main pathophysiologically distinct categories, namely primary or secondary LVH. In hypertrophic cardiomyopathy (HCM) the LVH is mainly genetically determined (5), in contrast to aortic stenosis (AS) and arterial hypertension (AH), where LVH is a compensatory mechanism to pressure overload (6).

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Histopathologic studies have shown myocardial fibrosis in HCM, AS, and AH (7–10), and myocardial fibrosis itself is associated with increased risk of cardiac sudden death and congestive heart failure (9,11–13). Novel therapeutic strategies are expected to target fibrosis by inhibition of humoral pathways (e.g., the renin-angiotensin-aldosterone system) (14). Cardiovascular magnetic resonance (CMR) offers the unique opportunity to noninvasively quantify both LVH with high reproducibility (15) as well as myocardial fibrosis (as defined by late gadolinium enhancement [LGE]) (16) with high spatial resolution (17) and thus might provide a useful tool with which to monitor novel therapeutic strategies targeting these phenomena. Data relating the pattern and degree of fibrosis to secondary LVH are lacking, and there are no studies addressing this in LVH due to AH. Accordingly, we aimed to evaluate the incidence and patterns of LGE in different forms of LVH and to determine its relation to severity of left ventricular (LV) remodeling.

Methods

Setting. Four hundred forty inpatients and outpatients with LVH (M-mode–based measurements of LV-wall thicknesses referenced to height and corrected for sex) due to AS, AH, or HCM were screened (18). All patients

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underwent a comprehensive CMR examination, and LV mass, end-diastolic volume, ejection fraction (EF), and the amount of LGE were quantified.

Inclusion criteria. We used the following inclusion criteria: LVH defined from CMR as a left ventricular mass index (LVMI) >1.06 g/cm in men and >0.8 g/cm in women (19). Normal values were obtained from a sample of healthy volunteers (n = 147, age 19 to 74 years).

Exclusion criteria. Subjects with evidence of coronary artery disease by coronary angiography (n = 64) or clinical assessment were excluded. Young patients (age <40 years) with a low pre-test probability lacking the usual risk factors (diabetes, smoking, AH, hyperlipidemia, family history of coronary artery disease) were included without invasive coronary angiography. Also excluded were patients with severe arrhythmia or general contraindications for CMR.

Ethical approval was obtained from the local Research Ethics Committee. All subjects provided written informed consent.

Definitions. Aortic stenosis was established in echocardiography by measurement of aortic valve pressure gradient and was confirmed by CMR-derived planimetry of aortic valve area (20). In accordance with American College of Cardiology guidelines, AS was graded as follows: mild: >1.5 cm^2; moderate: 1.5 to 1.0 cm^2; and severe: <1.0 cm^2 (21).

Patients were assigned to AH if blood pressure was above 139 mm Hg systolic or 89 mm Hg diastolic in multiple measurements, as recommended in European Society of Cardiology guidelines 2007 (22).

Diagnosis of HCM was established by clinical criteria, including echocardiography, according to the current guidelines (23). In this study, only patients with global LVH (increased LVMI) were included. Obstruction was verified by CMR and defined as an LV outflow tract area <2.7 cm^2 (24).

Image acquisition. CMR was performed on 3 1.5-T cardiac-dedicated clinical magnetic resonance systems (Sonata/Avanto, Siemens Medical Solutions, Erlangen, Germany, and CV/i, General Electric Health Care, Waukesha, Wisconsin). The CMR protocol consisted of a functional study, additional specific studies (planimetry of aortic valve area in AS, planimetry of LV outflow tract area in HCM), and LGE imaging.

For the functional studies, 3 standard long-axis slices and a stack of contiguous short-axis slices (slice thickness: 10 mm, no gap, 30 phases/RR-interval) were acquired with electrocardiography-gated steady-state free-precession cine-images (Sonata: repetition time 2.9 ms, echo time 1.2 ms, flip angle 80°, matrix 256 × 146, field of view typically 340 mm, bandwidth 930 Hz/pixel; CV/i: repetition time 3.8 ms, echo time 1.6 ms, flip angle 45°, matrix 256 × 192) in breath-hold technique. In HCM, the LV outflow tract area was quantified as described recently (24). Planimetry of aortic valve area was performed as established by Friedrich et al. (25,26). The LGE images covering the LV were acquired 10 min after intravenous injection of 0.2 mmol gadolinium-diethyltriaminepentaacetic acid (Magnevist, Bayer Schering Pharma, Germany) with a segmented inversion recovery sequence with an inversion time optimized to null normal myocardial signal (TI between 200 ms and 300 ms). The LGE images were acquired in same position as the functional studies and in end-systole. Questionable LGE was considered only if it could be reproduced in a second plane perpendicular to the finding or by changing the readout direction.

Abbreviations and Acronyms

- **AH** = arterial hypertension
- **AS** = aortic stenosis
- **CMR** = cardiovascular magnetic resonance
- **EF** = ejection fraction
- **HCM** = hypertrophic cardiomyopathy
- **LGE** = late gadolinium enhancement
- **LV** = left ventricle/ventricular
- **LVEDVI** = left ventricular end-diastolic volume index
- **LVH** = left ventricular hypertrophy
- **LVMI** = left ventricular mass index
- **RV** = right ventricle/ventricular

Image analysis. For quantification of LV function and volumes, the endocardial and epicardial contours were manually drawn in end-systole and -diastole with dedicated software (MASS 6, Medis, Leiden, the Netherlands). The LV mass was calculated from the total myocardial volume multiplied by the specific gravity of the myocardium (1.05 g/ml). The LV mass and LV end-diastolic volume were indexed to height in cm.

Late gadolinium enhancement was defined as myocardial areas with signal intensity above the average of apparently normal myocardium plus 2 standard deviations. Areas of LGE were manually traced, and total mass of LGE was calculated and expressed as percentage LGE. The distribution and pattern of LGE was visually analyzed in a 17-segment model (27).

Statistical analysis. Statistical analyses were performed with SPSS version 13.0 for windows (SPSS Inc., Chicago, Illinois). Data are presented as mean ± SD. Continuous variables were compared with the unpaired *t* test. Noncontinuous variables were compared with the chi-square test. We tested for data normality with the Kolmogorov-Smirnov test. Group comparisons were performed with analysis of variance with Bonferroni post hoc test for normally distributed data and the Kruskal-Wallis H test when data were not normally distributed. All correlations were performed with the Spearman correlation coefficient. Differences were considered significant when $p < 0.05$.

Results

Study population. Of the 440 screened patients, 83 (56 men, age 57 ± 14 years) fulfilled our inclusion criteria. A large proportion of the screened patients were excluded due to the lack of global LVH (as defined by increased LVMI in CMR). All CMR images were of diagnostic quality.

In the entire study population the LVMI was 1.34 ± 0.37 g/cm (men: 1.43 ± 0.36 g/cm, women: 1.15 ± 0.31 g/cm,

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$p < 0.001$). The left ventricular end-diastolic volume index (LVEDVI) was 0.95 ± 0.26 ml/cm (men: 1.00 ± 0.26 ml/cm, women: 0.84 ± 0.22 ml/cm, $p = 0.003$). There was no difference in LVMI and LVEDVI between groups. The EF was within normal range (mean: 69 ± 12%, men: 67 ± 12%, women: 73 ± 10%, $p = 0.025$), but significant differences ($p < 0.05$) between AH and HCM or AS were noted (Table 1).

LGE in entire population. The incidence of LGE was 63% (men: 66%, women: 56%, p = NS) for the entire population and was the highest in HCM but was not significantly different among the subgroups. This remained the case when AS and AH were combined together as "secondary" LVH and compared with HCM as primary LVH.

The amount of LGE was 19 ± 22 g (men: 20 ± 25 g, women: 17 ± 13 g, p = NS). The percentage LGE was significantly higher in HCM than in the other groups ($p < 0.05$). The LVMI correlated significantly to the amount of LGE ($r = 0.237$, $p = 0.045$) (Fig. 1) in the entire population and HCM but not in AS or AH. In general, patients with positive LGE had higher LVMI and higher maximum end-diastolic wall thickness than patients with negative LGE (Fig. 2). The LVEDVI and EF did not correlate to LGE.

LGE in AS. The LGE in AS (n = 21) was present in 62% (n = 13). Generally the lesions were small and focal with an average amount of 8 ± 8 g (3 ± 3% of the total LV mass). The degree of stenosis was not related to the presence of LGE. The incidence of LGE in severe AS (n = 11) was not significantly different from intermediate or mild AS (55% vs. 70%, p = 0.466). Aortic stenosis with LGE had a higher LVMI (1.4 ± 0.2 g/cm vs. 1.1 ± 0.3 g/cm, p = 0.028) (Fig. 2) and a higher LVEDVI (1.0 ± 0.2 ml/cm vs. 0.8 ± 0.2 ml/cm, p = 0.015) compared with AS without LGE. The amount of LGE was not significantly correlated with LVMI ($r = 0.261$, p = 0.194) (Fig. 1). No specific pattern of LGE could be identified, but lesions were usually non-subendocardial. The cumulative segmental involvement for each segment is shown in Figure 3. There was no significant relationship between the presence of LGE and EF (Table 2).

LGE in AH. All patients in this group (n = 26) had primary AH and were under routine medical treatment (beta-blockers: 70%, angiotensin-converting enzyme inhibitors: 50%, angiotensin II receptor type 1 blockers: 15%, calcium channel blockers: 40%, diuretics: 50%, aldosterone antagonists: 0%). There was no significant influence of medication on LVMI or LGE.

Late gadolinium enhancement was present in 50% of the patients (n = 13). In the subgroup with LGE the amount of LGE was 11 ± 9 g (5 ± 4% of the total LV mass). There was no significant relationship between LVMI, LVEDVI, or EF and presence of fibrosis (Fig. 2, Table 2). However, we observed a trend toward higher LVMI in the LGE positive patients (Fig. 2). There were no age differences between subgroups with and without LGE. No specific pattern of LGE could be identified, but lesions were predominantly nonsubendocardial (95%). The cumulative segmental involvement is shown in Figure 3.

LGE in HCM (n = 36). In 72% of the patients (n = 26) LGE could be detected. In the subgroup with LGE the amount of LGE was 30 ± 26 g (12 ± 9% of the total LV mass). Obstruction in HCM was not related to presence of LGE (LGE in hypertrophic obstructive cardiomyopathy: 79%, LGE in hypertrophic nonobstructive cardiomyopathy: 65%, p = 0.341). The presence of LGE was associated with higher LVMI (1.5 ± 0.5 g/cm in HCM with LGE vs. 1.2 ± 0.2 g/cm in HCM without LGE, p = 0.018) (Fig. 2). The amount of LGE was significantly correlated with LVMI ($r = 0.354$, $p = 0.038$) (Fig. 1) and the maximum end diastolic wall thickness ($r = 0.441$, $p = 0.012$). There was no relationship between LGE and LVEDVI (Table 1). The LGE in HCM was predominantly located in the anteroseptal and inferoseptal segments, at the insertion points of the right ventricle (RV) and was typically non-subendocardial. The cumulative segmental involvement is presented in Figure 3. Eighty-four percent of the patients with positive LGE had their lesion in the segment of maximum wall thickness. There was no significant relationship between the presence of LGE and EF (Table 2).

Table 1 Comparison of Patient Groups

	AS (n = 21)	AH (n = 26)	HCM (n = 36)	Intergroup Differences (p Value)
AVA (cm^2)	1.0 ± 0.3	—	—	
LVOT obstruction (n)	—	—	19	
EF (%)	70 ± 9	59 ± 10*	75 ± 9	<0.001
LVMI (g/cm)	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.4	0.490
LVEDVI (ml/cm)	0.9 ± 0.2	1.0 ± 0.3	0.9 ± 0.2	0.206
LGE (%)	62	50	72	0.203
%LGE	3 ± 3	5 ± 4	12 ± 9†	<0.001

*Ejection fraction (EF) was significantly lower in arterial hypertension (AH) compared with the other 2 groups ($p < 0.01$). †Amount of fibrosis was significantly higher in hypertrophic cardiomyopathy (HCM) compared with the other 2 groups ($p < 0.01$).

AS = aortic stenosis; AVA = aortic valve area; LGE = late gadolinium enhancement; LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular mass index; LVOT = left ventricular outflow tract; %LGE = total mass of late gadolinium enhancement calculated and expressed as percentage late gadolinium enhancement.

Discussion

Although LVH is a well-established independent risk factor for cardiac mortality, only very few studies have attempted to explore the underlying myocardial tissue alterations, particularly with respect to fibrosis. This is reflected in part by the lack of noninvasive imaging modalities with the ability to simultaneously assess both LVH and scarring. Therefore, we designed our study to assess the capability of CMR to study fibrosis over the wide spectrum of LVH comprising both the primary, genetically determined HCM as well as the secondary adaptive pattern of LVH.

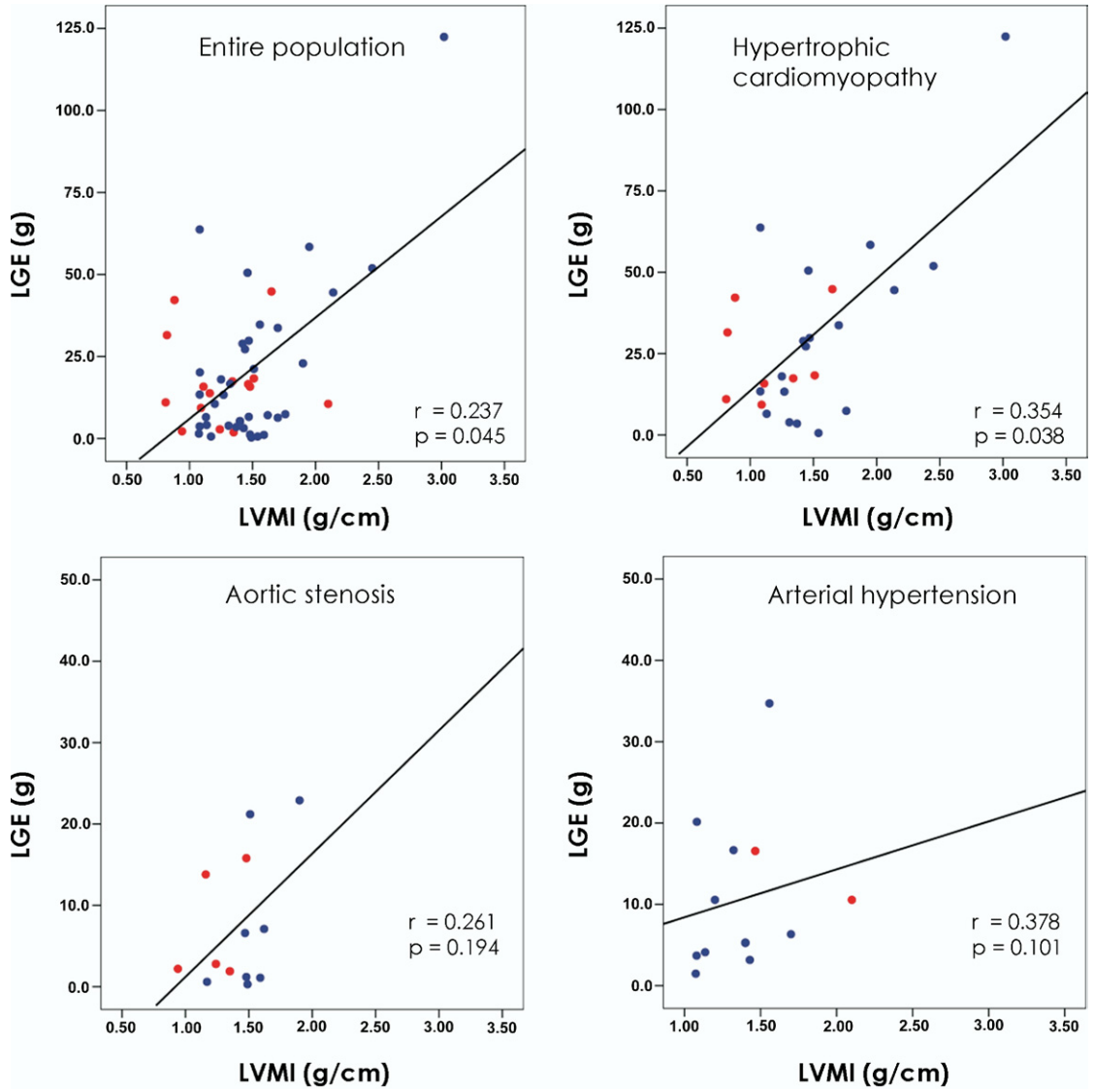

Figure 1 **Relation Between LGE and LV Mass**

Correlation between left ventricular mass index (LVMI) and the amount of late gadolinium enhancement (LGE) in the entire LGE(+) population as well as the different subgroups of left ventricular (LV) hypertrophy in both sexes (**red** = women, **blue** = men).

LGE in secondary LVH. Late gadolinium enhancement seems to be a frequent finding in adaptive LVH due to pressure overload. This is probably due to focal scarring caused by ischemic necrosis. According to the "ischemic core" hypothesis, irreversible myocardial injury occurs secondary to a mismatch between LVH and blood supply, resulting in myocardial ischemia (28). Additionally, LVH is associated with relative reduction of capillary density, because capillary angiogenesis does not occur in parallel with hypertrophying myocytes (29). These notions are supported by earlier studies observing myocyte degeneration and replacement fibrosis in response to pressure overload (30). Experience with LGE in secondary LVH is limited to a single study in which Debl et al. (31) assessed LGE in AS and compared it with findings in HCM. Our findings extend those of Debl et al. (31) to the novel setting of hypertension-related LVH. Interestingly, however, we could not reproduce the tight relationship between pressure overload and LVH and the presence of LGE in AS that they observed. The main difference between both populations was the better EF in the AS patients in the present study, and this might partially explain this discrepancy. Our findings thus underline that the state of affairs among pressure overload, LVH, and focal fibrosis is complex and seems to extend beyond a simple causality. In AS the LV mass predicts the development of heart failure independent of the severity of AS (32). Our data show the tight relationship between LV mass and myo-

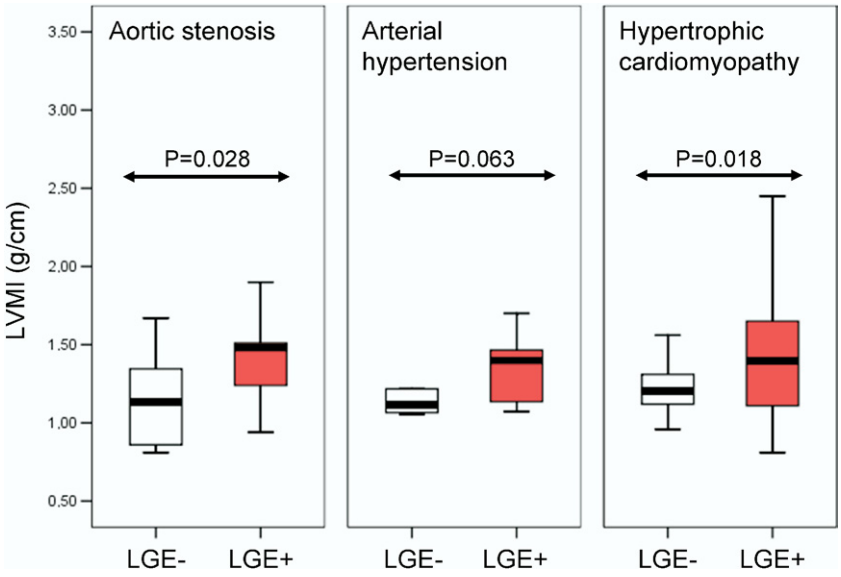

Figure 2 LV Mass in Patients With and Without LGE

Box plots showing the relation between LVMI and LGE. The LGE positive patients had higher LVMI. Abbreviations as in Figure 1

cardial fibrosis, and it seems conceivable that fibrosis is the underlying cause for a worse clinical outcome in AS with increased LV mass.

In our AH cohort the systolic LV function was preserved and unrelated to the presence of LGE. There is a known relationship between myocardial fibrosis and diastolic heart failure (33). Diastolic heart failure is a common feature in hypertensive heart disease and is caused by abnormalities in myocardial relaxation and ventricular compliance. Approximately 50% of patients hospitalized for heart failure have preserved systolic function. Although the in-hospital mortality risk is lower in these patients, the duration of hospitalization is similar to that of heart failure patients with systolic dysfunction (34). The PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) Trial has shown a prognostic impact of diastolic heart failure regarding cardiovascular events (35). Contrast-enhanced CMR might help to determine the individual risk of diastolic heart failure and might impact upon therapeutic decision-making.

LGE in primary LVH. In agreement with previous studies, we observed LGE in approximately 70% of HCM patients. We and others have observed a tight correlation between LVH and fibrosis (31,36). The exact pathophysiological grounds of LGE in HCM are not clear, but focal fibrosis, particularly collagen, seems to play a major role. Moon et al. (37) and Papavassiliu et al. (38) showed a strong correlation between LGE and increased collagen in 2 histologic case reports. The lack of correlation between fibrosis and obstruction is interesting in many aspects. First, it supports the hypothesis that fibrosis in HCM is genetically determined rather than being a response to obstruction in HCM. Indeed, Moon et al. (36) suggested a close link between LGE and certain troponin mutations in HCM. Second, because fibrosis is independent of obstruction, one might speculate that identifying focal fibrosis by CMR would provide additional complementary risk stratification means in HCM. Data from Moon et al. (36) seem to support this premise, although prospective data are not yet reported. The lack of dependency of LGE on pressure overload is supported by the fact that fibrosis is a common histopathological finding in apical HCM (39) and the weak relationship between severity of obstruction and outcome (40,41).

There are some possible explanations for focal fibrosis in HCM. Maron et al. (42) found, particularly in the septum, lumen loss and wall-thickening of the intramural coronary arteries. Recent studies described microvascular dysfunction with hypoperfusion particularly in regions with severe hypertrophy (43,44). Ischemia results from microvascular disease, and increased end diastolic pressure together with the increased demand of LVH might initiate the processes of ischemic scarring. It remains unclear why we and other investigators observed a typical pattern of LGE with frequent involvement of the septum, particularly the RV insertion points (45). It could be that wall stress is particularly high at the insertion points or that LGE in these locations represents plexiform fibrosis containing the crossing-fibers of LV and RV (46–48) or crossing-fibers within the LV (49).

Clinical implications. The identification of fibrosis in primary and secondary LVH has several potential clinical implications. The emerging link between LGE-identified fibrosis and ventricular arrhythmia in HCM (50) indicates that this approach might provide novel additional

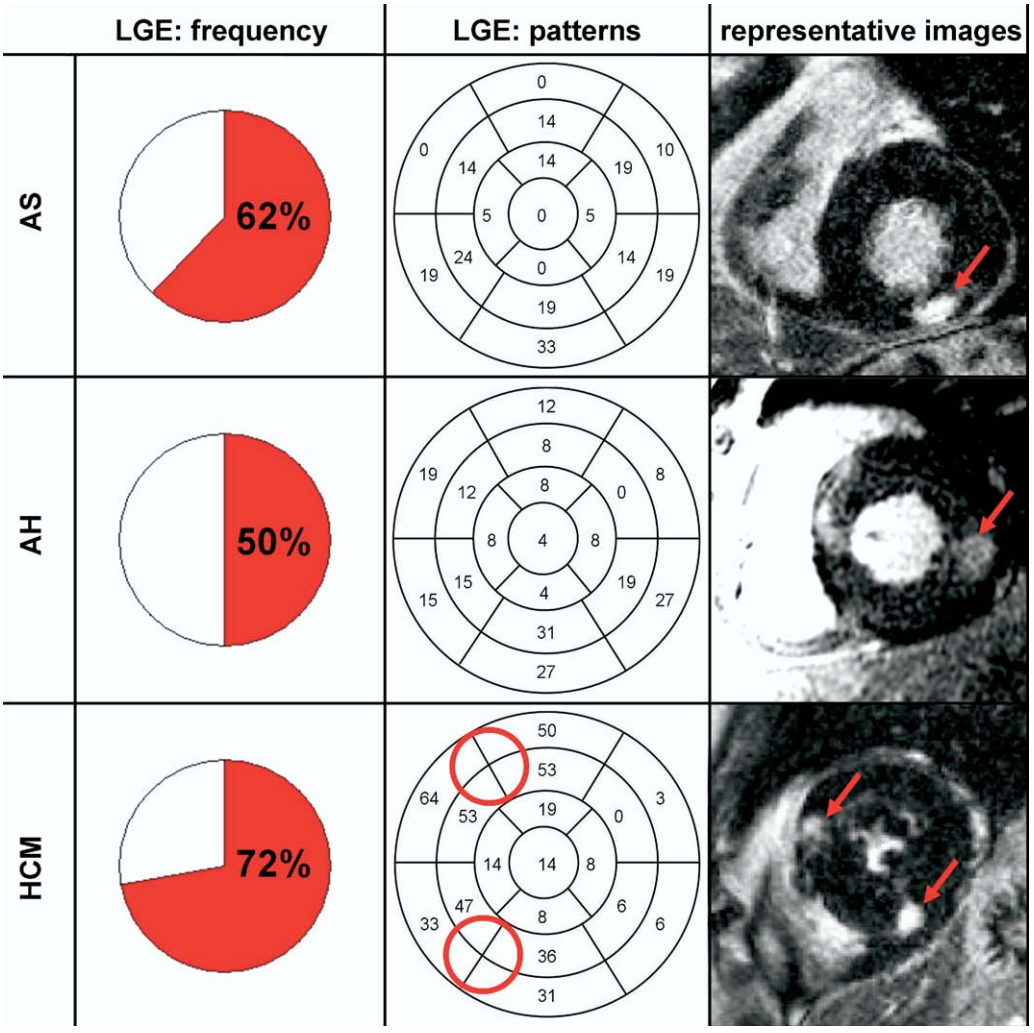

Figure 3 **Incidence and Patterns of LGE**

(Left) Incidence of late gadolinium enhancement (LGE) in patients with aortic stenosis (AS), arterial hypertension (AH), and hypertrophic cardiomyopathy (HCM). **(Middle)** Incidence of LGE within each segment (percentage) of all patients, including those with and without LGE. In HCM the late enhancement was predominantly anteroseptal and inferoseptal. In AS and AH no specific pattern of fibrosis could be identified. **(Right)** Representative short-axis slice images showing location of LGE **(red arrows)**.

risk stratification measures supplementary to the traditional risk factors.

An association among hypertensive blood pressure regulation, LVH, cardiac fibrosis, and the development of heart failure is commonly accepted (51). The renin-angiotensin-aldosterone system seems to play an important role in the pathways of adverse remodeling, including LVH and fibrosis (52). Magnetic resonance imaging might offer a unique opportunity to simultaneously monitor the fibrosis-reducing and anti-remodeling effects of novel treatment strategies. However, we did not find a relation between medical therapy and either the presence of LGE or the LV mass.

The classical definition of HCM necessitated the absence of other disorders that could explain LVH (23). It is, however, increasingly recognized that HCM, especially in elderly patients (53), might coexist with other disorders such as hypertension that might also result in LVH. On the basis of the results of this study, one can cautiously speculate that the pattern of fibrosis in HCM with predilection to involve the RV insertion points could provide a means with which to elucidate the underlying cause of LVH (46).

Recent reports showed that the presence and amount of LGE is associated with worse outcome in ischemic heart disease (54) and in both dilated and HCM (55,56). In the present study we showed that LGE is a frequent finding in different forms of LVH. Therefore, LGE might be a valuable tool for better risk stratification in these patients.

Technical considerations and limitations. A small fraction of our patients did not undergo coronary angiography to exclude coronary artery disease. However, their clinical profile rendered coronary artery disease unlikely. Moreover,

Table 2 LGE Relationship to Left Ventricular Parameters

	LGE	No LGE	p Value
Relationship Between LVEDVI (ml/cm) and Presence of LGE			
Entire population	1.0 ± 0.2	0.9 ± 0.3	0.25
AS	1.0 ± 0.2	0.8 ± 0.2	0.02
AH	1.0 ± 0.4	1.0 ± 0.3	0.50
HCM	0.9 ± 0.2	0.9 ± 0.2	0.81
Relationship Between EF (%) and Presence of LGE			
Entire population	70 ± 12	67 ± 12	0.35
AS	69 ± 10	71 ± 9	0.57
AH	61 ± 12	58 ± 9	0.25
HCM	75 ± 10	76 ± 6	0.72
Relationship Between Maximum End-Diastolic Wall Thickness (mm) and Presence of LGE			
Entire population	19 ± 5	16 ± 3	<0.001
AS	16 ± 3	16 ± 3	0.37
AH	16 ± 2	14 ± 3	0.08
HCM	23 ± 5	18 ± 2	0.005

Abbreviations as in Table 1.

none of these patients exhibited an infarct-typical pattern of LGE with subendocardial enhancement, as would be expected on the basis of the wave-front concept characteristic of coronary artery disease (57). The limited sample size in the LVH subgroups we studied did not allow us to explore several other factors (e.g., medications and sex) that could theoretically affect LGE in LVH. This likely resulted from the strict inclusion criteria we used to define LVH. Future studies with larger patient populations are definitely warranted.

Conclusions

Fibrosis as detected by CMR is a frequent feature of LVH regardless of its cause and depends on the severity of LV remodeling. As LGE emerges as a useful tool for risk-stratification also in nonischemic heart diseases, our findings have the potential to influence therapeutic strategies and to amplify the characterization of disease progress by noninvasive imaging.

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Key Words: cardiac magnetic resonance imaging ■ cardiomyopathy ■ late gadolinium enhancement ■ left ventricular hypertrophy.