Objectives
We sought to evaluate the diagnostic performance of cardiovascular magnetic resonance imaging (CMRI) for detection of cardiac amyloidosis compared with endomyocardial biopsy (EMB) in a clinical routine setting.

Background
For the clinical workup of heart failure with restrictive filling, pattern cardiac amyloidosis is an important differential diagnosis that is difficult to verify with current noninvasive techniques, especially in the presence of myocardial hypertrophy.

Methods
A total of 33 consecutive patients underwent both CMRI and EMB for workup of heart failure with restrictive filling pattern in combination with myocardial hypertrophy (n = 24) and/or clinical conditions often associated with cardiac amyloidosis (n = 18).

Results
Cardiac amyloidosis was detected by EMB in 15 of the 33 patients. In patients with biopsy-proven cardiac amyloidosis, CMRI revealed a distinct pattern of late gadolinium enhancement, which was distributed over the entire subendocardial circumference, extending in various degrees into the neighboring myocardium. This pattern was found in 12 of the 15 patients diagnosed with cardiac amyloidosis by EMB, compared with only 1 individual in the group of 18 patients diagnosed with other myocardial diseases. Consequently, using this pattern as a diagnostic criterion, the sensitivity of CMRI for diagnosing cardiac amyloidosis was 80%, yielding a specificity of 94%. The positive predictive value was 92%, and the negative predictive value was 85%.

Conclusions
In patients with biopsy-proven cardiac amyloidosis, late gadolinium enhancement frequently occurs in a peculiar pattern. On the basis of the gold standard, EMB, noninvasive CMRI can be used to diagnose or rule out cardiac amyloidosis with good sensitivity and excellent specificity in a clinical routine setting. (J Am Coll Cardiol 2008; 51:1022–30) © 2008 by the American College of Cardiology Foundation

In the clinical workup of patients with diastolic heart failure and myocardial hypertrophy, cardiac amyloidosis is an important differential diagnosis (1). Effective treatments for some forms of cardiac amyloidosis exist, but treatment options are extremely limited once severe symptoms of heart failure become clinically apparent. Consequently, the early diagnosis of cardiac amyloidosis may significantly improve the clinical outcome (1).

The gold standard for diagnosing cardiac amyloidosis is endomyocardial biopsy (EMB) (2), but this technique is invasive, limited to experienced centers, and thus not widely available. Hence, in clinical practice, the diagnosis of cardiac amyloidosis rests mainly on echocardiographic findings, supported by the clinical history, and a diagnostic noncardiac biopsy (3,4). However, diagnosis by echocardiography has limitations (5), particularly if hypertrophy from other causes is present. Other noninvasive methods also have limitations (6), including electrocardiography (7) or scintigraphic techniques (8,9).

Recent pilot data (10,11) suggest that noninvasive cardiovascular magnetic resonance imaging (CMRI) using late gadolinium enhancement (LGE) may be a valuable tool for diagnosing cardiac amyloidosis. This technique has proven clinical value for noninvasive tissue characterization in several cardiac diseases (12) and may overcome many...
limitations of other noninvasive methods in the clinical setting of suspected cardiac amyloidosis (13).

Consequently, we sought to evaluate the diagnostic performance of CMRI for detection of cardiac amyloidosis compared with the gold-standard EMB in a routine clinical setting in consecutive patients admitted for workup of heart failure with restrictive filling pattern in combination with myocardial hypertrophy and/or conditions often associated with cardiac amyloidosis.

Methods

**Patient population.** Between 2003 and 2006, 33 consecutive patients underwent both CMRI and EMBs for workup of heart failure with restrictive filling pattern in combination with myocardial hypertrophy (n = 24) and/or conditions often associated with cardiac amyloidosis (n = 18) such as systemic amyloidosis (n = 4), multiple myeloma (n = 5), lymphoma (n = 2), end-stage renal failure (n = 3), or other conditions (n = 4). To allow evaluation of the diagnostic performance of CMRI in a clinical routine setting, patients with dyspnea at rest, atrial fibrillation, ventricular arrhythmias, and other frequent cardiac disorders such as coronary artery disease were not excluded. All patients gave written informed consent and were included in the study.

**CMRI protocol.** Electrocardiographically gated CMRI was performed in breath-hold using a 1.5-T Magnetom Sonata (Siemens Medical Systems, Erlangen, Germany). Both cine and LGE short-axis CMRI were prescribed every 10 mm (slice thickness 6 mm) from base to apex. In-plane resolution was typically 1.2 × 1.8 mm. Cine CMRI was performed using a steady-state free-precession sequence. The LGE images were acquired on average 5 min (10) after administrating gadodiamide 0.1 mmol/kg (Omniscan, Amersham-Health, Braunschweig, Germany) using a segmented inversion recovery gradient echo technique, constantly adjusting the inversion time to null normal myocardium (14). In addition, fat-saturated and T2-weighted images were obtained to allow differentiation among subepicardial LGE, epicardial fat, and pericardial effusion.

In cardiac amyloidosis, however, it may be difficult to determine the optimal inversion time that will null normal myocardium, as it may be unclear which myocardial areas are normal (10). Thus, we first acquired multiple images of the same view using different inversion times. If a large portion of left ventricular myocardium (i.e., >50%) goes through the null point earlier than the left ventricular cavity and this region is not in an obvious coronary artery distribution territory, this area is highly likely to represent myocardial disease such as cardiac amyloid. Consequently, the inversion time was then adjusted to null the remaining myocardial areas (Fig. 1).

**Figure 1** Multiple Contrast CMRI of the Same Short-Axis View Using Different TI Acquired Beginning at 4 Min After Contrast Injection

At inversion time (TI) = 80 ms, all structures are below the null point and appear gray on the image. At TI = 120 ms, a large portion of the subendocardial left ventricular (LV) myocardium (white arrows) goes through the null point earlier than the LV cavity, which crosses the null point at a TI of 200 ms (white circle). Because this region (subendocardial circumference and right ventricle) is obviously not a coronary artery distribution territory, this area is highly likely to represent myocardial disease such as cardiac amyloid (high signal at 240 ms). The myocardium surrounding this region is likely to be normal, as it is nulled at a TI of 240 ms (white arrows in black framed image). CMRI = cardiovascular magnetic resonance imaging.
CMRI analysis. Cine and contrast images were evaluated separately by 2 blinded observers as described elsewhere (15,16). In brief, endocardial and epicardial borders were outlined on the short-axis cine images. Volumes, myocardial mass, and ejection fraction were derived by summation of epicardial and endocardial contours.

Regional parameters were assessed, dividing each short axis into 12 circumferential segments (Fig. 2). For each segment, the extent of LGE was analyzed using the NIH image analysis software package (National Institutes of Health, Bethesda, Maryland), and the results were expressed as a percentage of the area of the outer, middle, and inner third of each segment.

Myocardial biopsy protocol. At least 5 endomyocardial biopsies were taken from the region showing LGE, as described elsewhere (16). In patients without the presence of LGE, at least 4 biopsies were taken from the right ventricle (septum) and usually another 4 biopsies from left ventricular lateral wall to minimize sampling errors.

Histopathological analysis. The EMBs were stained with Masson’s trichrome and examined by light microscopy. Cardiac amyloidosis was diagnosed using Congo red staining by demonstration of the typical green birefringence under cross-polarized light. Additionally, electron microscopy for visualization of amyloid deposits was performed to rule out Congo red negative amyloidosis (Fig. 2).

To diagnose/exclude inflammatory heart disease, paraffin tissue sections were treated with an avidin–biotin immunoperoxidase method (Vectastain-Elite ABC Kit, Vector, Burlingame, California) with application of the following monoclonal antibodies: CD3 (T-cells, Novocastra Laboratories, Newcastle, United Kingdom), CD68 (macrophages, natural killer cells, DAKO, Hamburg, Germany), and HLA-DR-alpha (DAKO). Myocardial inflammation indicative of myocarditis was defined as the detection of ≥14 infiltrating leukocytes/mm² (CD3+ T lymphocytes and/or CD68+ macrophages) (17).

Statistical analysis. Data for continuous variables are expressed as mean value ± SD, whereas data for categorical variables are expressed as the number and the percentage of patients. Comparisons between groups were done using a 2-tailed unpaired Student t test for normally distributed and Mann-Whitney U test for non-normally distributed continuous variables. For categorical variables, we used the chi-square test and Fisher exact test where appropriate. The difference between 2 groups was defined to be statistically significant if the 2-tailed p value was <0.05.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient characteristics. All patients presented with various degrees of dyspnea limiting their exercise tolerance (n = 29) or experienced dyspnea at rest (n = 4). Three patients reported atypical chest pain, and 3 other patients had atrial fibrillation. Most patients did not have evidence for systemic amyloidosis upon presentation, except 4 in whom systemic amyloidosis was demonstrated by noncardiac biopsy. Nine patients had significant coronary artery disease, defined as coronary artery stenosis >50% in diameter. All patients with coronary artery disease had already been revascularized if possible and were receiving appropriate medication. On the basis of coronary angiography at the time point of EMB, additional coronary intervention was not indicated in any of

Figure 2  Contrast Short-Axis CMRI and EMB Work Up Of Patient #17

(Top row) Contrast short-axis CMRI of Patient #17 (basal slice on the left with subsequent 6-mm slices toward the apex shown to the right; there is a 4-mm gap between slices; TI = 220 ms). For contrast CMRI analysis, each short-axis image was divided into 12 circumferential segments by applying a grid, as demonstrated in the upper row. (Bottom row) Histopathological workup of endomyocardial biopsy (EMB) samples for cardiac amyloidosis included Masson’s trichrome staining with amyloid deposits (arrows) between myocytes (A), Congo red staining (B) with demonstration of typical red/green birefringence (+) under cross-polarized light (C), as well as electron microscopy visualizing amyloid deposits between myocytes expanding the extracellular volume (D and E). LGE = late gadolinium enhancement; other abbreviations as in Figure 1.
these patients. Other clinical characteristics of all patients can be viewed in Table 1.

**Histopathological results.** The EMB was performed without complications in all 33 patients. In 15 patients, cardiac amyloidosis was identified by histopathological workup as described earlier. In the remaining 18 patients, EMB revealed myocarditis (n = 11), secondary left ventricular hypertrophy (n = 5), hypertrophic cardiomyopathy (n = 4), or combinations of those entities, as displayed in Table 1. In 1 patient (Patient #18), small amounts of nonspecific interstitial myocardial fibrosis were detected, but no definitive diagnosis could be made.

In the group of patients with significant coronary artery disease (n = 9), cardiac amyloidosis was detected in 3 patients, which was not significantly different from all patients without coronary artery disease (p = 0.5). All 4 patients with known systemic amyloidosis also had evidence of cardiac amyloidosis by EMB.

**CMRI results.** We performed CMRI in all 33 patients, including 4 patients with dyspnea at rest and 3 patients with atrial fibrillation. Although breathing and trigger artifacts occurred more frequently in those 7 patients, image quality was sufficient for analysis in all 33 patients. Late gadolinium enhancement was present in 26 of the 33 patients (79%). Baseline CMRI characteristics such as ejection fraction, end-diastolic volume, ventricular mass, and maximum ventricular wall thickness can be viewed in Table 1.

Several different patterns of LGE were present in this patient population. In 13 patients, LGE was distributed over the entire subendocardial circumference, extending in various degrees into the neighboring myocardium (Fig. 3). In 6 other patients, we found focal intramural LGE in

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<th>Patient Characteristics</th>
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<td><strong>Table 1</strong> Patient Characteristics</td>
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All = average or percentage; AMYLO = amyloidosis; Amyloid LGE Pattern = diffuse subendocardial late gadolinium enhancement distribution, as displayed in Figure 4; EDV = end-diastolic volume; EF = ejection fraction; EMB = endomyocardial biopsy; HCM = hypertrophic cardiomyopathy; IVS = interventricular septum; LGE = late gadolinium enhancement; LV = left ventricular; LVH = secondary left ventricular hypertrophy; Max = maximum; MYO = myocarditis; N/A = not applicable; PAP LGE = late gadolinium enhancement in papillary muscles.
the left interventricular septum, often originating from the right ventricular insertion points (Fig. 4), as well as subepicardial LGE, located mainly in the left ventricular lateral wall, in 4 patients (Fig. 4). The remaining patients had focal areas of LGE in various locations of the left ventricular myocardium. Late gadolinium enhancement located in the

### Figure 3  Typical Contrast CMRI of 2 Patients Diagnosed With Cardiac Amyloidosis by EMB

In both patients, LGE was diffusely distributed in large areas of the left ventricle involving the entire subendocardium (TI = 230 ms in both patients). Interestingly, the subepicardial myocardium is affected only in areas of transmural LGE. Note that LGE is also located in the papillary muscles (white arrowheads). Histologic images include Mason’s trichrome with amyloid deposits between myocytes (black arrows, large right panels) and Congo red staining (inset right panels) demonstrating typical green birefringence under cross-polarized light. Abbreviations as in Figures 1 and 2.

### Figure 4  Typical Contrast CMRI of 2 Patients Diagnosed With Other Myocardial Diseases

One patient demonstrated focal intramural LGE at the right ventricular insertion points, which is a typical finding in hypertrophic cardiomyopathy (top row, white arrows, TI = 320 ms). This diagnosis was confirmed by histopathology demonstrating myocyte hypertrophy (red cells) and interstitial fibrosis as shown by Masson’s trichrome staining (blue areas between myocytes, black arrows). Note that LGE is also present in the inferior papillary muscle in this patient (thin white arrow). The second patient was diagnosed with myocarditis exhibiting enhanced numbers of interstitial CD68+ macrophages as well as interstitial edema. Molecular pathology revealed PVB19 in the myocardium. The white arrows in the bottom panel point to typical subepicardial LGE in the left ventricular inferolateral wall (TI = 300 ms). Note that the pattern of LGE found in these patients is completely different from the LGE pattern that is usually present in patients with biopsy proven cardiac amyloidosis (Fig. 3). Abbreviations as in Figures 1 and 2.
papillary muscles could be observed in 13 of 33 patients (Figs. 3 and 4).

Comparing cardiac amyloidosis patients with all other patients. In the group of patients with biopsy-proven cardiac amyloidosis, LGE was typically distributed over the entire subendocardial circumference, extending in various degrees into the neighboring myocardium (Figs. 3 and 5). This pattern (amyloid LGE pattern) (Fig. 5) was found in 12 of the 15 patients diagnosed with cardiac amyloidosis by EMB, compared with only 1 individual in the group of 18 patients diagnosed with other myocardial diseases (Table 2).

In addition to presentation with amyloid LGE pattern, patients with cardiac amyloidosis were much more likely to demonstrate LGE in the papillary muscles than were patients without cardiac amyloidosis (Table 2). All other clinical characteristics, including ejection fraction, left ventricular end-diastolic volume, and myocardial mass, were not significantly different between the cardiac amyloidosis group and all other patients, except the thickness of the interventricular septum (Table 2). Interestingly, all 3 patients initially presenting with atrial fibrillation did not have cardiac amyloidosis by EMB. One was diagnosed with myocarditis, 1 with secondary left ventricular hypertrophy in the setting of hypertension, and 1 with hypertrophic cardiomyopathy.

Using the amyloid LGE pattern as a diagnostic criterion, the sensitivity of CMRI to detect cardiac amyloidosis was 80% compared with the gold-standard EMB, yielding an excellent specificity of 94%. Positive and negative predictive values of typical amyloid LGE pattern are displayed in Table 3.

Discussion

This study is unique in that the diagnostic performance of CMRI for detection of cardiac amyloidosis is evaluated by direct comparison of CMRI results to the gold-standard EMB in clinical routine patients. Our data indicate a distinct LGE distribution pattern in cardiac amyloidosis (Fig. 5) that can be used to noninvasively diagnose or rule out cardiac amyloidosis in a clinical routine setting with good sensitivity (80%) and excellent specificity (94%).

Histopathological results. Using EMB as a gold standard, we could identify 15 individuals with cardiac amyloidosis among our group of patients presenting for workup of diastolic heart failure and/or myocardial hypertrophy. This high prevalence of 45% is most likely explained by our inclusion criteria, because in addition to signs of heart failure with restrictive filling pattern, most patients had myocardial hypertrophy (n = 24) and/or had conditions

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Amyloidosis (n = 15)</th>
<th>Others (n = 18)</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI (OR ≠ 1)</th>
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<tr>
<td>Age (yrs)</td>
<td>66 ± 13</td>
<td>62 ± 14</td>
<td>0.26</td>
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<tr>
<td>EF (%)</td>
<td>56 ± 16</td>
<td>58 ± 15</td>
<td>0.96</td>
<td>—</td>
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<td>EDV (ml)</td>
<td>128 ± 43</td>
<td>130 ± 42</td>
<td>0.93</td>
<td>—</td>
<td>—</td>
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<tr>
<td>IVS max (mm)</td>
<td>17 ± 4</td>
<td>13 ± 3</td>
<td>0.011</td>
<td>—</td>
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<tr>
<td>LV mass (g)</td>
<td>188 ± 59</td>
<td>166 ± 66</td>
<td>0.31</td>
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<td>LGE (n)</td>
<td>14 (93%)</td>
<td>11 (61%)</td>
<td>0.05</td>
<td>8.38</td>
<td>0.9–428.5</td>
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<td>PAP LGE (n)</td>
<td>11 (80%)</td>
<td>2 (11%)</td>
<td>0.0004</td>
<td>19.29</td>
<td>2.7–248.2</td>
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<tr>
<td>Amyloid LGE pattern (n)</td>
<td>12 (80%)</td>
<td>1 (5%)</td>
<td>0.00014</td>
<td>54.73</td>
<td>5.3–2,993.9</td>
</tr>
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**Bold** indicates statistical significance; 2-tailed p value < 0.05.

Amyloid LGE pattern = diffuse subendocardial LGE distribution, as displayed in Figure 5; CI = confidence interval; OR = odds ratio (Fisher exact test); other abbreviations as in Table 1.
Necropsy from Becker AE and Anderson HR

dritis is often difficult to achieve (21,22). be underestimated because the clinical diagnosis of myocarditis might contradict the conclusions of Perugini et al. (11) that the prevalence of myocarditis in our patient population is some-
tive hypertrophy and hypertrophic cardiomyopathy (Table 1). One would expect a relatively high prevalence of secondary hypertrophy and hypertrophic cardiomyopathy in elderly pa-
tients presenting with diastolic heart failure (19), but the high prevalence of myocarditis in our patient population is somewhat surprising. However, this finding may be explained by 2 facts: first, myocarditis is also known to cause diastolic heart failure (20), which was an inclusion criteria for this study; second, the general prevalence of myocarditis might be underestimated because the clinical diagnosis of myocarditis is often difficult to achieve (21,22).

**CMRI results.** Late gadolinium enhancement was present in 79% of patients, indicating that LGE is a frequent finding in clinical routine patients presenting for workup of heart failure with restrictive filling pattern in combination with myocardial hypertrophy and/or conditions often associated with cardiac amyloidosis.

In the group with biopsy-proven cardiac amyloidosis, we found a distinct pattern of myocardial LGE. Twelve of the 15 patients had LGE distributed over the entire subendo-
cardial circumference, extending in various degrees into the neighboring myocardium (Figs. 3 and 5). This finding is in line with the report of Maceira et al. (10) describing a substantially lower T1 relaxation time in the subendocardium of patients with cardiac amyloidosis after administra-
tion of gadolinium using a T1 mapping CMRI technique. However, our finding of a distinct “amyloid LGE pattern” contradicts the conclusions of Perugini et al. (11) that the distribution of LGE in cardiac amyloidosis is highly variable. This discrepancy may be explained by the fact that Perugini et al. (11) started the acquisition of contrast images 10 to 15 min after gadolinium injection. Because LGE in cardiac amyloidosis fades with equalization of T1 between the subendocardium and subepicardium approximately 8 min after gadolinium injection owing to altered contrast agent kinetics (10), the late start of image acquisition at 15 min after gadolinium administration might have signifi-
cantly affected imaging results in the study of Perugini et al. (11).

Importantly, the distinct pattern of LGE in cardiac amyloidosis, as described in the current study, may be explained by the uneven transmural distribution of amyloid seen in necropsy. Becker et al. (23) reported that cardiac amyloid deposits are predominantly located diffusely in the subendocardial region and that they may even produce a “sandy sensation” when the formalin-fixed subendocardial area is palpated during post-mortem examination (23). Maceira et al. (10) also found a subendocardially pro-
nounced distribution of amyloid protein in their study (subendocardium 42.4%, subepicardium 17.6%). Because amyloidosis causes accumulation of abnormal interstitial protein, resulting in an enlargement of the extracellular space, it is highly likely that on the basis of the general mechanism of LGE (12), amyloid deposits alone will result in LGE in the absence of significant myocardial fibrosis or necrosis. However, if amyloid deposits result in LGE, it conceptually follows that the pattern of LGE in patients with cardiac amyloidosis is supposed to match the distribution of cardiac amyloid protein demonstrated post-mortem. Figure 6 compares a long-axis contrast CMRI from a patient included in this study to a necropsy image from a different cardiac amyloidosis patient published by Becker et al. (23). The typical diffuse LGE affecting the subendocar-

![Contrast CMR in patient 2](image1.png)

![Necropsy from Becker AE and Anderson HR](image2.png)

**Figure 6** Contrast Long-Axis CMR Compared to Necroscopy

Long-axis contrast CMRI (Left) patient #2 (TI = 230 ms). (Right) necropsy sample of a different patient diagnosed with cardiac amyloidosis. Interestingly, the pattern of diffuse LGE originating from the subendocardium nicely matches the pattern of pale subendocardial amyloid deposits indicated by white arrow-
heads in the necropsy sample. Right panel adapted with permission from (23).

Abbreviations as in Figures 1 and 2.
dial areas nicely matches the pale subendocardial regions of amyloid deposits in the necropsy case.

However, despite this match between LGE and the distribution of amyloid seen in necropsy, it needs to be kept in mind that in the present study 3 patients with biopsy-proven cardiac amyloidosis did not demonstrate this typical “amyloid LGE pattern” (Patients #16, #31, and #33). Patient #31 had significant left anterior descending artery stenosis, and CMRI showed typical subendocardial LGE in the left anterior descending artery territory indicative of nontransmural myocardial infarction. In this patient, EMB revealed only very small amounts of cardiac amyloid due to multiple myeloma. Thus, this very small amount of cardiac amyloid was most probably beyond the spatial resolution of CMRI (12), which typically was about 1.2 × 1.8 mm in plane. This mechanism may also explain the absence of any LGE in Patient #33. Patient #16 had patchy subendocardial, as well as diffuse intramural posterolateral LGE, maybe reflecting heterogeneous cardiac amyloid deposition, as reported to occur in some patients by post-mortem exam (24).

Interestingly, in 1 other patient (Patient #22) in whom the typical LGE pattern of cardiac amyloidosis was present, no evidence of cardiac or systemic amyloidosis could be found by histopathology. One possible explanation for this finding might be that the “amyloid LGE pattern” may also occur in other myocardial diseases. However, it is also possible that Patient #22 was erroneously assigned to the “no amyloidosis” group because of a sampling error in endomyocardial biopsies. In fact, the clinical history of this patient with a systemic disease, hepatomegaly, as well as echocardiographic and CMRI findings would be much more indicative of cardiac amyloidosis than of hypertrophic cardiomyopathy, as suggested by EMB.

Comparing cardiac amyloidosis patients with all other patients. Comparing patients with biopsy-proven cardiac amyloidosis with patients without amyloidosis, we did not find a significant difference in left ventricular ejection fraction, end-diastolic volume, or myocardial mass (Table 2). These data, furthermore, underscore the difficulties of diagnosing cardiac amyloidosis based on morphological or functional features. Interestingly, the average thickness of the interventricular septum was significantly different between the groups. Patients with cardiac amyloidosis had an average septal thickness of 17 ± 4 mm compared with 13 ± 3 mm in nonamyloid patients, which is consistent with echocardiographic data (25). In the clinical routine, however, this sign is not helpful in making the diagnosis of cardiac amyloidosis, because advanced patient age (64 ± 13 years in the present study) and common comorbidities such as hypertension render septal ventricular hypertrophy nonspecific to the underlying disease process (5,13,19). Moreover, cardiac amyloidosis can be present in patients without any septal hypertrophy (e.g., Patients #31 and #33 in Table 1).

In the present study, the incidence of LGE located within the papillary muscles was significantly higher in patients with cardiac amyloidosis than in all other patients (Table 2). This finding is consistent with post-mortem data (23) reporting amyloid deposits in the entire subendocardial region, including the papillary muscles. Some authors (26) have also described the papillary muscles to be “more dense than normal” on echocardiographic images as an additional feature of myocardial “sparkling” observed by echocardiography in cardiac amyloidosis patients. However, changes in echocardiographic technology have rendered this finding less noticeable in the current clinical routine (25). In the present study, papillary LGE was almost always seen in combination with “amyloid LGE pattern” except for 2 cases of hypertrophic cardiomyopathy (Patients #15 and #22) (Fig. 4). Thus, the role of papillary LGE for the diagnosis of cardiac amyloidosis needs to be further investigated.

Clinical implications. On the basis of our findings, non-invasive CMRI can be used to identify patients with cardiac amyloidosis with good sensitivity and excellent specificity compared with the gold-standard EMB. Importantly, this was shown in a clinical routine setting, because patients with dyspnea at rest, atrial fibrillation, and other frequent cardiac disorders such as coronary artery disease were not excluded. Thus, in the future it may be possible to establish the diagnosis of cardiac amyloidosis on the basis of clinical criteria in combination with the presence of the “amyloid LGE pattern.” In those patients, treatment may be initiated without the need for EMB, except if the exact type of amyloid is needed for therapy planning. However, if no “amyloid LGE pattern” is present, EMB will probably remain necessary to detect “CMRI-negative” amyloidosis or other myocardial pathology.

Although still a small sample, the data of the present study point to a lower index of suspicion required to begin the search for amyloid with this new technique. This is also underscored by the fact that our data suggest that cardiac amyloidosis might occur more frequently without any evidence of systemic amyloidosis than currently suspected.

Nevertheless, before any evidence-based clinical recommendations can be made, all these findings need to be further investigated in a larger patient population and a multicenter setting.

In addition to the diagnosis of cardiac amyloidosis itself, contrast CMRI provides direct information on the spatial distribution of cardiac amyloid protein in the myocardium and thus might be proven useful by further investigations to monitor progression or regression of cardiac amyloid deposits, with or without therapy. However, because of recent reports of nephrogenic systemic fibrosis (27), the use of gadolinium-based contrast agents may be limited in patients with severe renal problems. This also needs further investigation, as well as the question whether CMRI techniques without gadolinium-based contrast agents may be helpful in identifying cardiac amyloidosis in the subgroup of renal patients.
Conclusions

On the basis of the gold-standard EMB, noninvasive CMRI can be used to diagnose or rule out cardiac amyloidosis with good sensitivity and excellent specificity in a clinical routine setting. In patients with biopsy-proven cardiac amyloidosis, LGE frequently occurs in a peculiar pattern, diffusely distributed over the entire subendocardial circumference and extending in various degrees into the neighboring myocardium. This pattern may directly reflect the spatial distribution of amyloid protein in the myocardium.

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REFERENCES