MRI of Acute Myocarditis*
A Comprehensive Approach Based on Various Imaging Sequences

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Study objectives: To explore the diagnostic performance of MRI for the diagnosis of acute myocarditis, using a comprehensive imaging approach.

Design and settings: Twenty patients with myocarditis and 7 age-matched and gender-matched control subjects underwent comprehensive MRI. Magnetic resonance (MR) examinations included axial T2-weighted sequences, precontrast and postcontrast ECG-gated T1-weighted sequences in axial and short heart axis, cine-MRI, and serial dynamic turbo fast low-angle shot (turboFLASH) acquisitions in the short axis following Gd injection for a period of 2 min. Precontrast and postcontrast images were postprocessed using subtraction. Two observers read all images qualitatively and quantitatively. Myocardial enhancement was compared between patients and control subjects.

Patients: Myocardial involvement was focal in 6 patients examined within 1 week from clinical onset, and diffuse in the remaining 14 patients examined later.

Results: Qualitatively, contrast-enhanced T1-weighted subtracted images had 100% sensitivity and specificity for myocardial involvement. Postcontrast T1-weighted images were able to discriminate the early phase (nodular enhancement) from the later phase of myocarditis (diffuse enhancement). Quantitatively, myocardial enhancement was 56% ± 3.2% in patients, vs 29% ± 3.1% in control subjects using T1-weighted MRI (p < 0.0001). Serial turboFLASH images displayed greater myocardial enhancement between 25 s and 120 s in patients than in control subjects (p < 0.0001); however, there was marked enhancement of skeletal muscles in both early and late stages of myocarditis compared to control subjects (p < 0.0001).

Conclusion: On the basis of subtracted cardiac-gated T1-weighted images and serial postinjection turboFLASH images, our study shows that myocarditis is largely, at least in the early stages, a focal process in the myocardium. It also provides evidence of transient skeletal muscle involvement, which may actually be useful for diagnosis.

Key words: heart, diseases; heart, magnetic resonance; magnetic resonance, comparative studies; magnetic resonance, pulse sequences; magnetic resonance, rapid imaging; myocarditis

Abbreviations: AMA = antimyosin antibody; MR = magnetic resonance; Te = echo time; TR = repetition time; turboFLASH = turbo fast low-angle shot

Myocarditis is an acute injury of the myocardium caused by a variety of infectious agents, most frequently viruses. Clinical features are often limited to minor signs such as fatigue, palpitations, and weakness in the days following an acute episode of fever and/or angina. However, acute myocarditis can manifest in some cases as an acute cardiac failure.1–3 Because the disease can progress to chronic myocarditis and dilated cardiomyopathy,1,4–6 and because it may masquerade as acute myocardial infarction,7 the availability of accurate diagnostic tools is of paramount importance. The diagnosis of acute myocarditis is often presumptive. Clinical grounds, ECG and laboratory data, echocardiography, and coronary angiography are of limited value except for eliminating acute coronary artery syndromes, and the final diagnosis is generally made after ruling out the most common causes of cardiac disease.

Endomyocardial biopsy has long been considered the “gold standard” in the diagnosis of acute myocarditis, but it may lack sensitivity because the disease may be focal.2,8,9 Sensitivity has been esti-
imated to range from 50 to 63%. Although sensitivity may be increased by using a biventricular approach and an analysis of six or more samples per patient, this remains a highly invasive procedure with potential complications.

67Ga scintigraphy has been shown to be helpful to the diagnosis, demonstrating abnormal Ga accumulation in involved myocardial areas in nonspecific myocarditis and Lyme carditis. Myocardial scintigraphy with 111In monoclonal antimony antibodies (AMAs), which bind specifically to intracellular myosin within damaged cells, has shown a high sensitivity, specificity is limited because the In radiolabel, although tissue-specific, attaches to any myocardial necrosis, whether it is the consequence of a myocardial infarction, cardiotoxicity due to chemotherapeutic agents, and even in dilated cardiomyopathy. A recent study showed a high diagnostic yield of AMA scintigraphy for myocarditis in patients with a clinical presentation of myocardial infarction and normal coronary angiographic findings.

MRI may be a valuable tool to noninvasively identify and assess the extent of myocardial involvement. Previous studies have demonstrated that either T2-weighted or Gd-enhanced T1-weighted magnetic resonance (MR) sequences, are helpful in the diagnosis of myocarditis, mostly by demonstrating an increased cardiac signal relative to the skeletal muscle. Yet, these studies have not studied perfusion using MRI in the context of myocarditis. In addition, there may be skeletal muscle involvement in these viral infectious processes. The aim of the present study was to prospectively compare the value of the various MRI modalities, and specifically perfusion, for the assessment of cardiac and skeletal muscle in patients with acute myocarditis.

Materials and Methods

Patients

Twenty patients (group 1) with a presumptive diagnosis of acute myocarditis and 7 healthy control subjects (group 2) matched for age and gender, and without known cardiac disease, were included. Patients of group 1 included 15 men and 5 women, aged 29 to 76 years (mean ± SD, 43 ± 4 years).

MR examinations were performed after obtaining informed consent, as required by our institutional review board. All the patients of group 1 had previously undergone ECG, transthoracic and transesophageal echocardiography with assessment of left ventricular function, and biochemical dosages including troponin Ic and creatine kinase. All the patients had also undergone myocardial perfusion imaging with 201Th and early (< 48 h after symptom onset) coronary angiography with left ventriculography. Myocardial AMA scintigraphy was not available at the time of the study. Two group 1 patients underwent a left ventricular endomyocardial biopsy, with negative findings in both cases, failing to disclose pathologic signs of myocarditis.

The final diagnosis was made after exclusion of coronary artery disease on the basis of a typical history, transient rise in biochemical markers of myocardial injury, normal 201Th perfusion imaging and coronary angiographic findings, and serologic presumption of recent viral infection. No patient had hypertrophic cardiomyopathy. There were no patients receiving β-blockers.

MRI

MR studies were performed using a superconducting magnet (Magnetom; Siemens; Erlangen, Germany) operating at 1.0 T. MR examinations were performed on average 9.4 ± 1.4 days after the onset of chest pain (all patients; range, 1 to 32 days), and 18.6 ± 4.3 days after an initial infectious episode (12 patients; range, 6 to 60 days); 6 patients underwent MRI within 7 days and 14 patients underwent MRI > 7 days after the onset of chest pain. Three patients underwent follow-up MRI at 2 months.

All the patients were examined with the following sequences (Fig 1): ECG-gated T2-weighted axial MR sequence in which repetition time (TR) equaled two to three R-R intervals according to the heart rate, echo time (TE) was 45 to 90 ms, matrix was 128×256 for a field of view of 270×360 mm, three signals were acquired, and section thickness was 5 mm.

ECC-gated T1-weighted MR sequence in the axial plane and in the short-axis view of the heart, in which TR = R-R interval – 20%, TE was 25 ms with a gradient dephasing in the read-out direction, matrix was 128×256 for a field of view of 270×360 mm, three signals were acquired, and section thickness was 5 mm. These sequences were repeated after IV administration of Gd-tetra-azacyclododecane teta-acetic acid (Guerbet; Aulnay-sous-Bois, France). For precontrast acquisitions, the TR was 875 ± 46 ms (range, 694 to 1,402 ms); for postcontrast acquisitions, the TR remained similar, 575 ± 49 ms (range, 600 to 1,413 ms).

Serial multisection breath-hold T1-weighted turbo fast low-angle shot (turboFLASH) acquisitions were repeated in the short-axis plane of the heart after Gd chelate administration...
injected through a 20-gauge catheter in the right or left antecubital vein, at a dose of 0.1 mmol/kg. For a 75-kg patient, the injected volume of Gd chelate was 15 mL, followed by a 20-mL washout bolus of saline solution. The injection was performed manually at a rate of approximately 2 mL/s. One precontrast and 12 postcontrast measurements were prescribed with a 5-s interval between measurements to allow breathing. For each measurement, three images were acquired in the basal, midpapillary, and apical short-axis planes. The imaging sequence was performed with a TR of 6.5 ms, a T\text{e} of 3 ms, a flip angle of 10°, a 180° inversion pulse with an inversion time of 200 ms, a slice thickness of 15 mm, and a 128 × 256 matrix, as previously described.\textsuperscript{23} The acquisition time was 1 s per section.

Cine-MRI was performed in 13 patients, in the long-axis, short-axis, and four-chamber planes of the heart. It consisted of two-dimensional ECG-gated segmented k-space free breathing acquisitions. Typical imaging parameters were a TR of 25 ms per section, a T\text{e} of 12 ms, delay between each set of phase encoding

Figure 2. T1-weighted MRI of a focal form of acute myocarditis. Precontrast axial (top left, A) and short-axis (middle left, B, and bottom left, C) views display an homogeneous low signal of the left ventricular myocardium. Postcontrast axial (top right, D) and short-axis (middle right, E, and bottom right, F) views at the same level show subepicardial focal enhancement of lateral (arrows) and inferior walls of left ventricle, as well as homogeneous subendocardial enhancement (bottom right, F).
steps (R-R interval), flip angle of 30°, a 144 × 256 matrix, three signals acquired, field of view of 350 × 350 mm, and section thickness of 7 mm.

Postprocessing

The precontrast and postcontrast T1-weighted data sets from axial and short-axis acquisitions were respectively subtracted from each other to generate images in which abnormal areas of enhancement were emphasized.

Reading Criteria

Readers underwent training prior to this study, using normal MRI findings from control subjects to ensure the use of consistent criteria for image interpretation. In a second step, data from each study were collected prospectively and analyzed in a blinded manner.

A consensus interpretation was made by two readers who assessed qualitatively the presence and distribution of myocardial abnormalities, and left ventricular wall motion abnormalities on cine-MRI reviewed on a cine loop. Cine-MRI findings were evaluated by operators blinded to the echocardiography data. Myocardial abnormalities included areas of high signal on T2-weighted images and on Gd-enhanced spin-echo–weighted images, judged as focal or diffuse in distribution. Focal disease was defined as single or few patchy, round or nodular-shaped areas of increased enhancement < 2 cm in diameter; diffuse disease corresponded to more extensive confluent or transmural hyperenhancing areas with smooth margins toward normal myocardium. Additional findings such as pericardial effusion were recorded, when present. Nonsubtracted and subtracted contrast-enhanced T1 images were compared.

Quantitative measurements were performed on precontrast and postcontrast spin-echo T1-weighted images, as well as on serial turboFLASH images. They were performed twice, and the results were averaged. Measurements were made with regions of interest encompassing at least 20 pixels at different locations of the apex, the interventricular septum, and the lateral wall on axial and short-axis views, as well as the anterior and inferior walls on short-axis views. Nodular enhancement was measured separately, when present. Myocardial enhancement values on serial turboFLASH and T1-weighted images were measured as follows: percentage of myocardial enhancement = postcontrast signal − precontrast signal/precontrast signal. Enhancement values of paraspinal muscles were calculated using the same formula. Signal intensity–time curves were generated from serial turboFLASH images.

Statistical Analysis

The different sequences, including presubtraction and subtraction T1 images, were compared qualitatively in terms of sensitivity and specificity, given that each abnormality observed on one sequence is considered as a positive finding. A nonparametric test (Mann-Whitney) was used to compare myocardial enhancement between patients of group 1 and patients of group 2.

Figure 3. Focal myocarditis involving the apex. Top, A: nodular subepicardial hypersignal (arrow) of the lateral wall of the left ventricle close to the apex is present on axial T2-weighted image. Postcontrast axial (middle, B) and short-axis (bottom, C) images show abnormal enhancement in this area (arrows), as compared with the normal myocardium.
The enhancement profiles of myocardium and paraspinal muscles on serial turboFLASH images were compared two-by-two between patients of both groups, using analysis of variance with repeated measures and calculating the time × product interaction. Regression analysis was used to study the relation between troponin levels and clinical symptoms, or myocardial enhancement.

**Results**

**Clinical Description and Outcome**

A clinically obvious infectious episode involving the upper respiratory tract had occurred 20 ± 3 days prior to MR examination in 16 of 20 patients (80%).

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**Figure 4.** Diffuse form of acute myocarditis. Axial T2-weighted image shows a diffuse micronodular hypersignal of the myocardium (top left, A). Precontrast (top right, B) and postcontrast axial T1-weighted (middle left, C) and subtracted images (middle right, D) at the same level show diffuse micronodular enhancement of the myocardium, as well as postcontrast short-axis view (bottom, E).
MR examination was performed 9 ± 1 days following the first episode of chest pain, present in all patients; six patients underwent MRI within 6 days from the onset of thoracic pain. Clinically, all patients of group 1 had a favorable outcome within weeks. No alternate diagnosis was made at hospital discharge.

T1- and T2-Weighted MRI

All the patients displayed myocardial abnormalities on subtracted T1-weighted MRI. Ten patients of this group (50%) displayed a small pericardial effusion < 1 cm thick. Control subjects of group 2 had no abnormalities of either myocardial signal or cardiac wall motion. There was no false-positive study regardless of the sequence used, resulting in a specificity of 100%.

Patients of group 1 displayed myocardial abnormalities (Figs 2–4), which were either focal (all the patients examined within 7 days from the onset) or diffuse (all the patients examined after 7 days). In patients with focal involvement, abnormal areas consisted of nodular foci arising from the apex to either the interventricular, lateral, inferior, or anterior walls. These foci were either subepicardial or transmural, never only subendocardial. The sensitivity of precontrast and postcontrast T1 images for the diagnosis of myocardial involvement was 0% and 90%, respectively, for a sensitivity of subtracted images of 100% (Table 1). T2-weighted images showed eight cases of diffuse hypersignal and one nodular form. In other patients, there were too many artifacts to accurately assess myocardial involvement, resulting in an overall sensitivity of 45% (Table 1).

Table 1—Qualitative Assessment of Myocarditis According to the MR Sequences*

<table>
<thead>
<tr>
<th>Myocardial Involvement</th>
<th>Sensitivity</th>
<th>Nodular (n = 6)</th>
<th>Diffuse (n = 14)</th>
<th>Total (n = 20)</th>
</tr>
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<tbody>
<tr>
<td>T2-weighted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T1-weighted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcontrast</td>
<td></td>
<td>6 (100)</td>
<td>12 (86)</td>
<td>18 (85)</td>
</tr>
<tr>
<td>T1-weighted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtracted</td>
<td></td>
<td>6 (100)</td>
<td>14 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>T1-weighted</td>
<td></td>
<td>2 (50)</td>
<td>6 (67)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Cine-MRI</td>
<td></td>
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</tbody>
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*Data are presented as No. of patients (sensitivity).
†Only 13 patients (4 patients seen < 7 d and 9 patients seen > 7 d).

On serial dynamic turboFLASH images (Fig 6), the time to the peak of myocardial enhancement was obtained with a similar delay (ie, 25 s) in patients of both groups, but it reached significantly higher values in patients of group 1 with a myocarditis evolving for > 7 days (192% ± 21%) vs patients of group 2 (107% ± 14%; p < 0.0001) [Fig 7, top]. In contrast to the overlap seen between early stages of myocarditis and normal myocardium with respect to myocardial enhancement, the examination of paraspinal muscle enhancement allowed discrimination of myocarditis patients from normal control subjects (Fig 7, middle); abnormal paraspinal muscle enhancement was observed in 19 of 20 patients (95%) both in early and late stages of myocarditis (average muscle enhancement, 50% ± 5% in patients of group 1 vs 9% ± 2% in patients of group 2, p < 0.001) [Fig 7, bottom].

Assessment of Troponin Ic According to the Delay of Symptoms and MR Patterns

The increase in troponin Ic levels was closely correlated with an increased delay of infection (r > 0.7, p = 0.05), as well as with an increased delay of chest pain (r = 0.72, p = 0.006). There was a nonsignificant trend toward higher levels of troponin Ic in the serum of patients exhibiting a diffuse form of myocarditis (20.73 ± 5.7 µg/mL) than in patients with a focal form (8 ± 3.9 µg/mL, p = 0.06). However, the degree of serial enhancement on turboFLASH images did not correlate to troponin Ic (p = 0.67).

Follow-up

All the patients recovered within 2 months, with normal clinical, laboratory, and ECG findings. In the three patients who underwent a follow-up MR examination, no residual abnormalities were present qualitatively on contrast-enhanced spin-echo T1-weighted images, and there was a normalization of enhancement values. However, on serial turbo-
FLASH imaging, there was normalization of skeletal muscle but not of myocardial enhancement values (Fig 8). None of them were evolving to a dilated cardiomyopathy, as demonstrated on T1-weighted and cine-MRI.

**Discussion**

Our results confirm that MRI is able to diagnose myocardial involvement and to assess the extent of abnormalities in acute myocarditis. Qualitatively, the most useful sequences were those using IV contrast administration. In two patients with a diffuse form, the subtraction helped identify abnormalities that were missed when only nonsubtracted spin-echo T1-weighted contrast-enhanced images were studied.

Quantitatively, significant differences in myocardial enhancement were observed between the two groups. This is consistent with the results of Friedrich et al.5 who found similar enhancement values on T1-weighted enhanced images were studied.

Dynamic studies using serial postcontrast turboFLASH imaging provided new avenues in the comprehension of myocarditis, by showing different enhancement patterns in the early and late stages of myocarditis. Increased myocardial enhancement in patients seen at the "late" stage (≥ 7 days) of acute myocarditis is likely related to the fact that interstitial diffusion of the contrast medium is increased by inflammation, because of increased capillary permeability and blood flow; Gd accumulation is also increased in tissues with expanded water compartments.24-26 Moreover, the membrane destruction in acute cell damage induces intracellular diffusion of Gd.25-27 This is in keeping with histologic findings in acute myocarditis. The disease begins by interstitial edema and infiltration by lymphocytes with myocyte necrosis5; subsequently, cell damage occurs in the hours or days following the initial infection.

Our results showed a nodular form in all patients examined within 7 days, and a diffuse form later on, consistent with the hypothesis that acute myocarditis may progress from a primarily focal to a diffuse process within approximately 1 week. These results, reported on previous serial follow-up MR examinations,5 are in agreement with the evolution of ECG and scintigraphic abnormalities.15 The nodular subepicardial form has also been described in patients with Lyme carditis, although the delay between the onset of symptoms and MR examination was not mentioned.19 One patient of our series, with Lyme borreliosis, corresponded to this pattern, but it is unclear whether it is specific of this disease.

Theoretically, T2-weighted images would be thought to provide exquisite demonstration of edematous myocardial involvement. Even if edema is not specific of acute myocarditis and is delayed after the onset of clinical symptoms (2 to 4 days), it is a substantial clue for the diagnosis. Yet, the actual performance has been variable4-5,21 and was poor in our experience. It is likely that the discrepancies with respect to the performance of T2-weighted imaging of myocarditis are largely related to differences in

**Figure 5.** Percentages of myocardial enhancement on T1-weighted images in patients (group 1) and control subjects (group 2).
the performance of the various MRI devices, such as magnetic field intensity. Cine-MRI displayed regional wall motion abnormalities in 62% of cases, as did echocardiography. These abnormalities, although nonspecific, were located in those diseased areas seen on contrast-enhanced MRI. Cine-MRI helped to assess the severity of the disease, but in no case to diagnose myocarditis.

Original findings were obtained using serial post-contrast turboFLASH acquisitions; quantitative data showed abnormal myocardial enhancement occurring beyond 1 week of chest pain onset, and abnormal peripheral skeletal enhancement; this finding may be related to associated “myositis” present since the early stage (ie, < 7 days) of myocarditis. Such skeletal muscle involvement is important for three reasons: (1) The disease may be a more generalized process than previously thought, as it may extend to skeletal muscles. (2) If this is confirmed, it may be possible to diagnose the disease on peripheral muscle rather than on endomyocardial biopsy. The hypothesis that myocarditis belongs to a more general infectious state affecting skeletal muscles is supported by the fact that, in the three patients in whom MR

Figure 6. Serial short-axis turboFLASH images obtained at 9 s (top left, A), 18 s (top right, B), 27 s (bottom left, C), and 54 s (bottom right, D) after Gd injection show abnormal myocardial enhancement of the inferior and lateral walls of the left ventricle, with respect to the interventricular septum.
Figure 7. Enhancement curves over time of myocardium (top) and muscle (middle) on serial turboFLASH images, in the early and late stages of acute myocarditis and in control subjects. Each data point represents the peak signal enhancement averaged for each group at a given acquisition time. Bottom: maximum percentage of paraspinal muscle enhancement during serial postcontrast turboFLASH acquisitions. %age = percentage.
follow-up was available, all had recovered muscular enhancement values similar to those of control subjects. (3) This implies that normalizing myocardial to muscular enhancement values as an internal reference on contrast-enhanced T1-weighted images, as previously done,⁵ may be invalid.

In our series, the follow-up MR study showed that after clinical recovery, MR findings improved in three patients, despite abnormal serial postcontrast turboFLASH enhancement values. However, the outcome is not always favorable, and worsening of the cardiac function leading to dilated cardiomyopathies and sudden death has been reported as a consequence of previously unknown myocarditis. In a serial follow-up study of 19 patients until day 84, 5 patients (26%) had not recovered a normal heart function.⁵ Another study¹⁰ has reported that up to 16% of patients will evolve to dilated cardiomyopathy.

Our study has some limitations. While it is not a true prospective study, all the patients were prescribed an identical acquisition scheme, except for cine-MRI. Endomyocardial biopsy is an important reference technique for the diagnosis of myocarditis, the assessment of myocardial activity, and in some instances the identification of causal microorganisms. These cannot be assessed by imaging techniques. Yet, endomyocardial biopsy is not routinely performed in many patients with suspected myocarditis, because of its invasive nature (especially considering that multiple sampling from biventricular biopsy is required to avoid lack of sensitivity), and it does not reach perfect sensitivity. Considering the clinical presentation of our patients, we chose not to perform such an invasive procedure on a routine basis; in fact, all patients underwent complete clinical healing within 2 months of presentation. Yet, there is no alternate diagnosis in these patients with specific biochemical evidence of myocardial necrosis and an extensive and negative coronary workup, including a negative early coronary angiographic findings.

We did not use fast breath-holding T2-weighted techniques that, from a preliminary report,⁵ may limit motion artifacts and consequently provide images more adequate for interpretation. The Gd chelates are not tissue specific. Focal contrast enhancement can be observed as well in ischemic heart disease as in inflammatory conditions, amyloidosis, and thyrotoxicosis.¹¹,¹⁷,²³

The influence of heart rate on myocardial signal intensity may have varied the T1-related contrast between individuals; however, there was no significant R-R interval variation (only 0.34%) during time between precontrast and postcontrast images within the same patient. No patients were receiving β-blockers, which are known to decrease the heart rate and, consequently, increase the TR; this effect leads to less T1 weighting and more proton density weighting.

In conclusion, subtraction Gd-enhanced T1-weighted MRI helps noninvasive diagnosis and recognition of areas of involvement in acute myocarditis. The diagnosis of early stages can be

![Figure 8. Follow-up serial turboFLASH images in three patients at 2 months (group 1) vs control subjects (group 2). A significant difference in myocardial enhancement remains between patients with previous acute myocarditis (myocardium follow-up) and control subjects (myocardium controls), whereas muscular enhancement has returned to normal values. See Figure 7 for expansion of abbreviation.](http://www.chestjournal.org/pdfaccess.ashx?url=/data/journals/chest/21984/)
differentiated from that of later stages qualitatively as well as quantitatively. Measurements of postcontrast enhancement may confirm this diagnosis when this enhancement is >45%. Serial turboFLASH acquisitions help confirm myocardial involvement, and also provide evidence of transient skeletal muscle involvement, which may actually be useful for diagnosis.

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