Contrast Media–Enhanced Magnetic Resonance Imaging Visualizes Myocardial Changes in the Course of Viral Myocarditis

Matthias G. Friedrich, MD; Oliver Strohm, MD; Jeanette Schulz-Menger, MD; Heinz Marciniak, MD; Friedrich C. Luft, MD; Rainer Dietz, MD

Background—The course of tissue changes in acute myocarditis in humans is not well understood. Diagnostic tools currently available are unsatisfactory. We tested the hypothesis that inflammation is reflected by signal changes in contrast-enhanced magnetic resonance imaging (MRI).

Methods and Results—We assessed 44 consecutive patients with symptoms of acute myocarditis. Nineteen patients met the inclusion criteria revealing ECG changes, reduced myocardial function, elevated creatine kinase, positive troponin T, serological evidence for acute viral infection, exclusion of coronary heart disease, and positive antimyosin scintigraphy. We studied these patients on days 2, 7, 14, 28, and 84 after the onset of symptoms. We obtained ECG-triggered, T1-weighted images before and after application of 0.1 mmol/kg gadolinium. We measured the global relative signal enhancement of the left ventricular myocardium related to skeletal muscle and compared it with measurements in 18 volunteers. The global relative enhancement was higher in patients on days 2 (4.8 ± 0.3 [mean ± SE] versus 2.5 ± 0.2; \( P < .0001 \)), 7 (4.7 ± 0.5, \( P < .0001 \)), 14 (4.6 ± 0.5, \( P < .0002 \)), and 28 (3.9 ± 0.4, \( P = .009 \)) but not on day 84 (3.1 ± 0.3; \( P = \text{NS} \)). On day 2, the enhancement was focal, whereas at later time points, the enhancement was diffuse. In patients with evidence of ongoing disease, the values remained elevated.

Conclusions—Acute myocarditis evolves from a focal to a disseminated process during the first 2 weeks after onset of symptoms. Contrast media–enhanced MRI visualizes the localization, activity, and extent of inflammation and may serve as a powerful noninvasive diagnostic tool in acute myocarditis. (Circulation. 1998;97:1802-1809.)

Key Words: myocarditis ■ magnetic resonance imaging ■ contrast media

Viruses infections of the gastrointestinal or respiratory tract may involve the heart in 5% of patients.\(^1,2\) Frequent causative agents of viral myocarditis are cytomegalovirus in 45% and coxsackievirus B in 30%.\(^3\) Clinical symptoms, such as fatigue, palpitations, and weakness, are often minor and are frequently mistaken as part of the previous infection or delayed convalescence. However, the long-term prognosis of acute myocarditis is not favorable, and the 5-year mortality may be as high as 50%. Causes of fatal outcomes are sudden death and congestive heart failure.\(^4,5\) The diagnosis of acute myocarditis is generally supported by the ECG (ST-segment changes, AV block, arrhythmia), echocardiography (impairment of left ventricular function), and laboratory investigations (creatine kinase, troponin T). Scintigraphic techniques with \(^{67}\)gallium citrate or \(^{111}\)indium-labeled antimyosin antibodies may be also used to visualize leukocytic infiltrates or myocardial necrosis.\(^6,7\) Respectively. However, the usefulness of scintigraphy is limited by low specificity, radiation exposure, and expense. Endomyocardial biopsy evaluated according to the “Dallas criteria”\(^8\) was long considered the gold standard; however, even biopsy reliability has recently been questioned\(^9\) after the results of the Myocarditis Treatment Trial.\(^10-12\) Echocardiographic analysis of the myocardial texture in acute myocarditis\(^13\) is a new but not-yet-established approach. The contrast media gadopentate dimeglumine (Gd-DTPA), which is used for magnetic resonance imaging (MRI), accumulates in inflammatory lesions in tissues other than the myocardium\(^14\); however, its potential role in the assessment of acute myocarditis is unclear. The purpose of our study was to detect the extent and distribution of myocardial tissue changes in the course of acute myocarditis using contrast media–enhanced MRI.

Methods

Study Population
We evaluated 44 consecutive patients who presented with symptoms of acute myocarditis and a history of a flulike illness with diarrhea and/or respiratory symptoms within the preceding 4 weeks in the urban emergency department of our institution. All patients were carefully interviewed and assessed by experienced physicians. The following diagnostic tests were performed: ECG, Holter ECG,
TABLE 1. Inclusion Criteria for the Study

| History of a febrile disease with diarrhea or flulike symptoms within the preceding 4 weeks |
| At least one of the following symptoms: Fatigue, Malaise, Dyspnea, Precordial discomfort |
| At least one of the following clinical signs: Tachycardia, Fever |
| At least one of the following ECG changes: ST-segment depression and/or elevation in more than three leads |
| Recurrent supraventricular and/or ventricular arrhythmia |
| At least mild regional or global impairment of left ventricular function as assessed by left ventricular angiography (on day 2 in 16 patients; on day 3 in 3 patients) and echocardiography |
| Angiographic exclusion of coronary artery disease |
| Serological evidence of recent viral infection (positive IgM titers for coxsackie virus B in 11 patients, cytomegalovirus in 4 patients, Epstein-Barr virus in 3 patients, and influenza A in 1 patient) |

Echocardiography, laboratory testing—including troponin T, creatine kinase, and serological tests (IgM antibodies against coxsackievirus B, cytomegaly, influenza, or Epstein Barr virus, respectively)—chest x-ray, left ventricular angiography (including coronary angiography), and an antimitosin antibody scan. Patients were included only if other possible causes of symptoms could be excluded and all results were positive for acute viral myocarditis. Nineteen patients (age, 26±10 years) met these criteria (see Table 1). All patients had at least one of the following symptoms on review of systems: fatigue, malaise, dyspnea, and precardial discomfort. All patients had resting tachycardia, fever, or both. One or more of the following ECG changes were present: AV block, ST-segment depression and/or elevation in more than three leads, or supraventricular tachycardia. Angiographically and echocardiographically determined left ventricular function was at least locally reduced in all patients. The mean global ejection fraction was 56±6% as assessed by left ventricular angiography. All patients had normal coronary arteries at angiography. Furthermore, all patients had an antimitosin antibody scan (11°indium) that was positive as defined by a heart-to-lung uptake ratio of ≥1.7. Finally, 7 of 19 patients underwent myocardial biopsy.

MR Tomography

The MRI studies were performed on a conventional MR tomograph (Siemens Impact Expert, 1.0 T) by use of a body coil. The functional and morphological data were evaluated by the standard software as provided by the manufacturer. Regions of interest were drawn manually. For analysis of the data for functional analysis and calculation of global signal intensity, the myocardial borders to the ventricular cavity and to the epicardial layers were followed. Only for evaluation of focal enhancement were regions of interest of these particular areas drawn. These data, although mentioned in the text, were not included in the analysis of the global relative enhancement. Regions of interest in the skeletal muscle were drawn into muscle dividing the enhancement of the myocardium by the enhancement of skeletal muscle.

Clinical Characteristics and Biopsy

Eighteen healthy volunteers (age, 33±7 years [mean±SD]) with no evidence of heart disease or recent infection served as control subjects. In all studies, image quality was sufficient for the evaluation of muscular and myocardial signal intensity. We excluded the right ventricle from evaluation because the right ventricular image quality did not allow a reliable and reproducible measurement. However, inclusion of the right ventricle in the calculations, which was reliable in 9 patients, did not change the results in any case.

To classify the clinical status of the patients, we calculated a symptom score by adding the NYHA class to the following symptom score points: (1) precardial discomfort (none=0, occasionally=1, frequently=2), (2) fatigue (none=0, on daily workload=1, at rest=2), and (3) malaise (none=0, occasionally=1, frequently=2). Morphological and functional analyses of the left ventricle were performed using gradient echo sequences in the long-axis planes (four-chamber view and cross-sectional two-chamber view). End-diastolic and end-systolic volumes, left ventricular mass, and ejection fraction were measured by biplanar evaluation. End-systolic wall stress was calculated with the formula reported as the most reliable and reproducible by Pattynama et al.6 Systolic blood pressure was averaged from the values measured during data acquisition by a sphygmomanometer (Nippon Co).

All MRI studies were performed by observers who were not aware of the clinical course and any results of other studies in the patients after inclusion.

Statistical Analysis

Statistical evaluation was performed by use of unpaired t tests and ANOVA factorial analyses. A value of P<.05 was accepted as significant. Data are shown as mean±SE.

Results

Clinical Characteristics and Biopsy

All 19 of our patients had myocarditis on clinical grounds and on the basis of scintigraphic imaging as part of the entry criteria (see Table 1). Seven biopsies were obtained; four showed florid myocarditis, and three were interpreted as negative.
Left Ventricular Functional Parameters
All patients underwent catheterization of the left side of the heart on day 2. All patients had findings demonstrating locally or globally decreased left ventricular function. The mean value of left ventricular end-diastolic pressure in the patients was 20±7 mm Hg. Table 2 shows the left ventricular functional parameters as calculated from MR images. The systolic left ventricular function in the patients was significantly impaired compared with control subjects for at least 4 weeks, and the ejection fraction reached the level of control values after 3 months or more. The end-systolic volume index was increased for the first 4 weeks of the disease and tended to remain high. On day 2 after the onset of symptoms, there was an inverse relationship between the global relative myocardial enhancement and left ventricular ejection fraction (\( R^2 = 0.31; P < 0.05 \)).

Five of our patients did not recover normal left ventricular function after myocarditis as defined by a ejection fraction of <55% on day 84. Initial signal enhancement of these patients compared with those with normalization of left ventricular function showed slightly elevated values, but this did not reach statistical significance (4.9±0.6 [mean±SE] versus 4.4±0.3, \( P = \text{NS} \)).

MRI of the Inflammation
T2-Weighted Images
Image quality of conventional T2-weighted images was limited but adequate for evaluation in all subjects. There was no significant difference in T2-weighted signal intensity at any stage of myocarditis, compared to controls. The signal ratio of the myocardium to skeletal muscle was 1.3±0.2 (SE) for control subjects, 1.6±0.3 for day 2, 1.7±0.2 for day 7, 1.6±0.2 for day 14, 1.6±0.1 for day 28, and 1.8±0.2 for day 84 after onset of symptoms. None of these differences reached statistical significance.

Contrast Media–Enhanced T1-Weighted Images
The relative enhancement in volunteers was homogeneous in all cases and ranged from 1.3 to 3.7; the mean value was 2.5±0.2. The signal-to-noise ratio of the skeletal muscle was 5.9 before and 5.8 after administration of Gd-DTPA. For the left ventricle, it was 4.9 before and 4.9 after Gd-DTPA. In patients, the corresponding signal-to-noise ratios before and after Gd-DTPA were 6.3 and 5.4 for the skeletal muscle and 5.4 and 5.3, respectively, for the myocardium. Fig 1 shows an image set of a normal volunteer before and after the admin-

![Figure 1. T1-weighted cross-sectional views at the midventricular level of a normal volunteer. Left, View obtained before gadopentate dimeglumine (Gd-DTPA); right, same view after the administration of 0.1 mmol/kg Gd-DTPA. The images appear very similar with respect to signal intensity. There is no localized accumulation of Gd-DTPA. The global relative enhancement was 2.5. The diagonally placed black areas are saturation slices that reduce artifacts of blood on the signal intensity of the myocardium.](http://circ.ahajournals.org/)

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<th>TABLE 2. Magnetic Resonance Functional Measurements in Control Subjects and Myocarditis Patients</th>
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<td>Control Day 2 Day 7 Day 14 Day 28 Day 84</td>
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LV indicates left ventricular. Values are expressed as mean±SE. *Statistical difference to control values (\( P < 0.05 \)).
administration of 0.1 mmol/kg Gd-DTPA. The images appear almost identical. In contrast, in Figs 2 and 3, we show the corresponding image sets of two representative patients on days 2, 14, and 84 after the onset of symptoms.

Fig 4 shows the values of the relative myocardial signal enhancement for the patients and control subjects. A significant difference was observed on days 2, 7, 14, and 28. Thereafter, no significant difference was discernable. The mean values were 4.7±0.3 (mean±SE, P<.0001) on day 2, 4.7±0.5 (P<.0001) on day 7, 4.6±0.5 (P=.0002) on day 14, 3.9±0.4 (P=.013) on day 28, and 3.1±0.3 (P=.34) on day 84 after the onset of symptoms. The enhancement on days 2, 7, and 14 were also significantly increased compared with the values obtained on day 84. The mean results of days 2, 7, and 14 were not statistically different from each other.

In 16 of 19 patients, signal enhancement on days 2 and 7 led to a localized appearance with areas of very strong signal increases after Gd-DTPA. The local relative enhancement in these areas on day 2 ranged from 3.7 to 25.4. In 5 patients, the signal enhancement was heavily pronounced in the interventricular septum. The focus was localized in the septal and lateral walls in 2 patients, in the septal and inferior walls in 2 patients, in the inferior wall in 2 patients, in the posterior lateral wall in 2 patients, in the inferior and lateral walls in 1 patient, in the lateral wall in 1 patient, and in the anterior wall in 1 patient. In 1 patient, there was a global subendocardial enhancement of the myocardium. The focal signal enhancement in the other patients was detected in the subendocardial layers of the myocardium in 8 patients, in the subepicardial layers in 4 patients, and within the midportions of the myocardial wall in another 4 patients.

On days 7 (partly), 14, and 28, there was a more diffuse localization of signal increases with only modest additional enhancement of the primarily affected tissue. In these stages
of the disease, the former area of high signal enhancement appeared with an increased intensity before application of contrast media. Thus, the relative local signal increase after Gd-DTPA was reduced compared with the observation on day 2, although the absolute signal intensity remained elevated. Global relative enhancement, however, was clearly elevated because of a diffuse increase in the relative enhancement of the other parts of the myocardium.

Measurements in symptomatic patients (symptom score $\geq 1$) revealed significant higher values than those in patients without symptoms ($4.5 \pm 0.2$ versus $3.1 \pm 0.3$, $P<.001$). The correlation of global relative enhancement and symptom score was statistically significant ($0.35$; relative enhancement $= 3.50 + 0.26 \times$ symptom score; $P<.001$; $R^2 = .12$). Ten patients with clinically ongoing disease on day 84 as defined by a symptom score of $\geq 1$ had a continued significant increase in global relative enhancement ($3.6 \pm 0.3$ versus $2.4 \pm 0.2$, $P<.005$).

Discussion

This is the first comprehensive study of acute myocarditis patients with contrast-enhanced MRI techniques. Our study is unique in that all patients underwent cardiac catheterization and that functional and clinical parameters were followed longitudinally. We were able to show that early in the course of the disease, the extent and localization of inflammation within the myocardium can be visualized by contrast-enhanced MRI. The inflammatory process seems to spread from a focal to a disseminated involvement of the myocardium within the first 2 weeks after the onset of the disease. The extent of the relative myocardial enhancement reveals a correlation to the clinical status and, in the very early stage of the disease, to left ventricular function. Furthermore, the presence of symptoms after 3 months seems to be accompanied by a sustained elevation of global relative myocardial enhancement after Gd-DTPA in these patients.
studies are needed to clarify the role of these techniques in cases is too small to draw any conclusion so far. Further trend toward higher values on day 14, but the number of three patients with negative biopsy findings did not change.

Endomyocardial Biopsy

Evaluation of endomyocardial biopsy specimens by use of the Dallas criteria may give negative results despite clear clinical evidence for acute myocarditis. Accordingly, three of our patients had biopsies reported as “negative” by the pathologist even though the clinical picture and the MRI and catheterization data suggested myocarditis. The lack of sensitivity can be explained in part by the focal nature of the inflammatory disease in its early phase. Contrast-enhanced MRI indicated focal accumulation of Gd-DTPA on day 2 and partly on day 7 but a more disseminated myocardial involvement on days 14 and 28. These findings correspond in part to changes observed in the ECG, which early in the disease also reflects a more focal involvement of the myocardium and even mimics acute myocardial infarction. Analysis of the data with exclusion of the three patients with negative biopsy findings did not change the result.

Reports on MRI in Myocarditis

There are several case reports on patients with acute myocarditis using T2-weighted images to visualize tissue edema. However, T2-weighted images are susceptible to motion, and the image quality of the myocardium is poor. In our study, there was no significant myocardial signal increase in T2-weighted images. New developments (breath-hold sequences with short acquisition times) have led to a much better image quality. In a small subgroup of six patients, we were able to apply such a fast breath-hold sequence with a strong T2 weighting. There was a significant higher signal ratio of the myocardium to skeletal muscle on day 7 (1.8 ± 0.2 versus 1.1 ± 0.1, \(P < .05\)) and a trend toward higher values on day 14, but the number of cases is too small to draw any conclusion so far. Further studies are needed to clarify the role of these techniques in acute myocarditis. Contrast-enhanced MRI was reported in two patients with myocarditis and in two patients with amyloidosis. Both exhibited marked signal enhancement after application of Gd-DTPA; however, the report on these patients lacks control data and quantification of changes and intraindividual standard measurements.

Mechanism of Signal Enhancement and Contrast Media Accumulation

Gadolinium profoundly enhances relaxivity of the excited protons, thereby increasing the signal of T1-weighted images, although susceptibility effects may also be of value. Gadolinium is a hydrophilic contrast medium with low molecular weight (<1000 D), which easily penetrates into the extracellular fluid space but not into living cells. Thus, Gd-DTPA accumulation is markedly increased in water-containing tissues and correlates with extracellular volumes 5 to 10 minutes after Gd-DTPA application. However, in acute cell damage, the loss of membrane integrity leads to diffusion into the intracellular space. The strong postcontrast signal enhancement of infarcted myocardium (not that of the surrounding edema) seems to be caused by this mechanism. The signal enhancement of myocardial tissue is stronger than that of skeletal muscle and seems to correlate with myocardial blood flow during the first 5 minutes after application.

During the early phase of myocarditis, the histological pattern is characterized by interstitial lymphocytic infiltration, cell damage, and interstitial edema. Furthermore, hyperemia is one of the main features of acute inflammation. Thus, accumulation of Gd-DTPA in our patients with acute myocarditis provides an estimate of the sum of increased blood flow, acute cell damage, and extravasation of fluid in areas of inflammation.

Influence of Heart Rate on Signal Intensity of Myocardium and Skeletal Muscle

Signal intensity in T1-weighted images is related to the time of repetition of the spin echo sequence. With ECG-triggered MRI, the repetition time is determined by heart rate, so heart rate has an influence on signal intensity of the myocardium. Because of early therapy with \(\beta\)-blockers, there was no significant difference in the heart rate of patients on days 2 (78 ± 4 bpm), 7 (74 ± 3 bpm), 14 (75 ± 2 bpm), 28 (73 ± 3 bpm), and 84 (68 ± 3 bpm) compared with control subjects (73 ± 2, \(P = \text{NS}\)). Furthermore, because we used the skeletal muscle (erector spinae muscle) as an internal reference in the same set of signal acquisition, we presumably could exclude the influence of the heart rate. In our data set, the signal intensity of myocardium and skeletal muscle was significantly lower with increased heart rate (\(P < .0001\) for both). In contrast, relative myocardial enhancement was positively correlated with a higher pulse rate in early stages of myocarditis (\(P < .05\)). Thus, a systematic influence of the heart rate on signal intensity is unlikely.

Possible Role of Contrast Media–Enhanced MRI

What is needed for detection and monitoring of acute myocarditis is a noninvasive method that can detect changes after
the onset of symptoms and can be repeated several times without application of radiation or radioactive material and invasive procedures. We included serial measurements in our study and were able to show the development of the myocardial inflammation in its course. The results obtained correlate partly with observations from serial biopsies as shown by Keogh et al., in which myocardial cell damage was detectable only within the first 2 weeks. Because of poor sensitivity and specificity, endomyocardial biopsy is not an adequate tool for monitoring the activity of the disease. We suggest that MRI with gadolinium-induced signal enhancement as a marker of inflammation is an excellent candidate. The option of longitudinal follow-up of the same patient with a changing clinical picture and suspicion of recurrence or persistence of disease makes MRI an attractive new diagnostic tool.

**Study Limitations**

This study has several limitations. In the literature, the specificity of contrast enhancement in MRI of the myocardium has been low. Significant signal enhancement in averaged T1-weighted images of the myocardium after application of Gd-DTPA has been observed in hypertrophic cardiomyopathy, dilated cardiomyopathy, amyloidosis, and ischemic heart disease. In the latter, Gd-DTPA–enhanced imaging was useful for selective visualization of regions with prolonged relaxivity times, such as in acute ischemia and acute myocardial infarction. In particular, for myocardial damage caused by acute reperfused infarction, a comparable pattern of regional signal enhancement of the jeopardized myocardium was reported.

We cannot exclude other noninflammatory mechanisms contributing to the observed changes in signal enhancement. However, the acuteness of the clinical picture and its subsequent development was not suggestive of a chronic cardiac disease. Second, the observed signal regression over time would not have occurred in a chronic disease; rather, signal intensity would have remained constant. Third, in our patients, there was no angiographic evidence for ischemic heart disease, which could have led to acute transient myocardial injury and similar findings in contrast enhancement. Nevertheless, the problem of impaired specificity (inflammatory versus ischemic or toxic injury) remains to be addressed in future studies.

The images in our study were averaged over a period of 6 to 12 minutes. Therefore, specific changes in signal intensity during a short time interval within this period could be missed. A recent study by Kim et al. suggests that regional differences of the wash-in and washout kinetics may play a key role in the timing and extent of signal enhancement of acutely injured myocardium after reperfusion. Because the exchange of Gd-DTPA between different compartments would happen with certain velocities and at certain time windows, an increased temporal resolution would probably offer more specific information.

An increase in signal caused by the impact of Gd-DTPA on relaxivity is observable only in T1-weighted images. T1 weighting depends on short repetition times (≤800 ms). In ECG-triggered studies, the time of repetition is determined by heart rate. We could exclude a systematic error by using the skeletal muscle as an internal standard. However, the sensitivity could possibly be enhanced by using sequences with a stronger T1 weighting (eg, saturation recovery techniques), especially in patients with a slow heart rate. Some of these sequences would also allow data acquisition within one breath-hold.

Finally, we studied the heart in two planes only, the longitudinal axis and the cross section. We possibly missed areas of inflammation, which seems to occur in a patchy fashion. In a pilot study, we compared the information obtained by our approach with an entire examination of myocardial signal enhancement using a multislice short-axis technique in 10 patients. We found no detectable difference in the sensitivity of the methods.

**Conclusions**

We conclude that acute viral myocarditis evolves from a focal to a disseminated involvement of the myocardium during the first 2 weeks after the onset of symptoms. Contrast media–enhanced MRI visualizes the localization, activity, and extent of inflammation and may serve as a powerful noninvasive diagnostic tool in acute myocarditis. This may be important not only for the management of this disease but also for the understanding of its different courses and the transition to the clinical picture of dilated cardiomyopathy.

**References**


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