Cardiovascular Magnetic Resonance Assessment of Human Myocarditis

A Comparison to Histology and Molecular Pathology

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Background—Myocarditis can occasionally lead to sudden death and may progress to dilated cardiomyopathy in up to 10% of patients. Because the initial onset is difficult to recognize clinically and the diagnostic tools available are unsatisfactory, new strategies to diagnose myocarditis are needed.

Methods and Results—Cardiovascular MR imaging (CMR) was performed in 32 patients who were diagnosed with myocarditis by clinical criteria. To determine whether CMR visualizes areas of active myocarditis, endomyocardial biopsy was taken from the region of contrast enhancement and submitted to histopathologic analysis. Follow-up was performed 3 months later. Contrast enhancement was present in 28 patients (88%) and was usually seen with one or several foci in the myocardium. Foci were most frequently located in the lateral free wall. In the 21 patients in whom biopsy was obtained from the region of contrast enhancement, histopathologic analysis revealed active myocarditis in 19 patients (parvovirus B19, n = 12; human herpes virus type 6 [HHV 6], n = 5). Conversely, in the remaining 11 patients, in whom biopsy could not be taken from the region of contrast enhancement, active myocarditis was found in one case only (HHV 6). At follow-up, the area of contrast enhancement decreased from 9 ± 11% to 3 ± 4% of left ventricular mass as the left ventricular ejection fraction improved from 47 ± 19% to 60 ± 10%.

Conclusions—Contrast enhancement is a frequent finding in the clinical setting of suspected myocarditis and is associated with active inflammation defined by histopathology. Myocarditis occurs predominantly in the lateral free wall. Contrast CMR is a valuable tool for the evaluation and monitoring of inflammatory heart disease. (Circulation. 2004;109:1250-1258.)

Key Words: myocarditis ■ biopsy ■ magnetic resonance imaging

Human myocarditis is usually viral in origin, and spontaneous recovery is common. However, active myocarditis can occasionally lead to sudden death, and 5% to 10% of all patients may progress to develop chronic dilated cardiomyopathy. In such patients, viral infection presumably persists or elicits autoimmune responses, causing the inflammation to remain active for an unknown period of time.

The onset of myocarditis is difficult to recognize clinically. Even when the diagnosis is considered, currently used diagnostic procedures suffer from limitations, resulting in many cases being diagnosed only postmortem or after congestive heart failure has occurred. Therefore, new strategies to diagnose and monitor active myocarditis are needed.

Friedrich et al concluded that cardiovascular MR imaging (CMR) may hold promise for diagnosing myocarditis after showing that contrast enhancement evolves from a focal to a disseminated process during the first 2 weeks after the onset of symptoms. However, those findings were not validated against histopathology, and his protocol is not widely used clinically.

New contrast CMR techniques using segmented inversion recovery gradient-echo pulse sequences (IR-GRE) provide an improvement in contrast between diseased and normal myocardium of up to 500% compared with the protocol used by Friedrich et al. This new technique allows visualization of small myocardial injuries that cannot be detected by any other noninvasive technique.
Depiction of such small areas of myocardial damage is of interest in patients with suspected myocarditis, because postmortem studies showed that active myocarditis causes small areas of myocardial necrosis.\textsuperscript{14,15}

The aim of the present study was to determine whether contrast CMR using new IR-GRE techniques visualizes areas of active myocarditis compared with the "gold standard," histopathology. In addition, we intended to evaluate whether CMR could be used to follow the progression of the disease. Our study design consisted of an imaging protocol assessing contrast enhancement in patients with clinically suspected active myocarditis followed by myocardial biopsy in the region affected as indicated by CMR. To allow the evaluation of the disease’s progression, patients were followed up clinically and underwent repeated CMR.

Methods

Patient Population

Fifty-eight consecutive patients presenting with symptoms of chest discomfort, dyspnea, altered ECG, and signs of inflammation were initially identified. Patients were excluded if they had concomitant coronary artery disease, had coronary spasm defined by catheterization (n=18), or had refused to undergo CMR followed by myocardial biopsy (n=3). Thirty-two of the remaining 37 patients fulfilled the following criteria: (1) history of flu-like symptoms within 8 weeks before admission; (2) one of the following symptoms: fatigue/malaise, chest pain, dyspnea, or tachycardia; (3) and one of the following ECG signs: AV block, ST-segment depression, or fatigue/malaise, chest pain, dyspnea, or tachycardia. The other samples were analyzed histopathologically to assess myocardial inflammation.

CMR Protocol

ECG-gated CMR imaging was performed in breath-hold using a 1.5-T Magnetom Sonata (Siemens Medical Systems). Both cine and contrast-enhanced short-axis CMR images were prescribed every 10 mm (slice thickness, 6 mm) from base to apex. In-plane resolution was typically 1.2×1.8 mm. Cine CMR was performed using a steady-state free-precession sequence (SSFP). Contrast CMR images were acquired on average 5 to 10 minutes after contrast (power injector) using a segmented IR-GRE technique\textsuperscript{11} constantly adjusting inversion time to null normal myocardium.\textsuperscript{16} For each slice, a breath-hold of \textasciitilde15 seconds (depending on RR interval) was necessary. Therefore, total acquisition time was between 20 and 30 minutes for all cine and contrast images. All patients were able to tolerate lying flat in the magnet until the examination was completed. The contrast dose (Magnevist [gadoteridol], Schering AG) was 0.1 mmol/kg. If contrast enhancement was located in the epicardial quartile of the ventricular wall, fat-saturated and T2-weighted half Fourier acquisition single-shot turbo spin-echo (HASTE) images were obtained to allow differentiation between contrast enhancement, epicardial fat, and pericardial effusion.

CMR Analysis

Cine and contrast images were evaluated separately by 2 blinded observers. Endocardial and epicardial borders were outlined on the short-axis cine images. Volumes and ejection fraction (EF) were derived by summation of disks. The extent of contrast enhancement was planimetered on the short-axis contrast images (Figure 1) using an image intensity level \textasciitilde2 SD above the mean of remote myocardium to define contrast enhancement.\textsuperscript{17}

Regional parameters were assessed using a model dividing each short axis into 12 circumferential segments (Figure 1). For each segment, the extent of contrast enhancement was measured using the NIH Image analysis software package (National Institutes of Health), and the results were expressed as a percentage of the total segment area as well as a percentage of the area of the outer, outer-middle, inner-middle, and inner quartiles of each segment.

Myocardial Biopsy Protocol

Endomyocardial biopsies (EMBs) were taken from the region showing contrast enhancement. At least 5 biopsies were obtained transarterially from the left ventricle (LV) using a Cordis or Meyer bioptome (Meyer Medical Systems). To place the bioptome in the region of contrast enhancement indicated by CMR, the guiding sheath was chosen according to the localization of the main focus of contrast enhancement. In case of midventricular or more basal contrast enhancement, a long sheet with angulated tip was used to place the biopsy catheter under fluoroscopic guidance, whereas in cases of more apical contrast enhancement, a long sheath with straight tip was used. The midventricular lateral free wall was the most frequent location for biopsies to be taken. If the region of contrast enhancement was located anterobasally and thus could not be reached, biopsies were taken from the right ventricular (RV) side of the septum (IVS). This was also done in patients with contrast enhancement of the IVS and in patients in whom no contrast enhancement was present. All samples were fixed in 4% phosphate-buffered formalin or stored in liquid nitrogen to preserve nucleic acids. Two biopsies were submitted to molecular biological evaluation. The other samples were analyzed histopathologically to assess myocardial inflammation.

Histopathologic Analysis

EMBs were stained with Masson’s trichrome as well as Giemsa stain and examined by light microscopy.\textsuperscript{19} For immunohistological identification of cardiac immune cells, tissue sections were treated with an avidin-biotin-immunoperoxidase method according to the manufacturer’s protocol ( Vectastain Elite ABC Kit, Vector), applying the following monoclonal antibodies: CD3 (T cells, Novocastra Laboratories) and PGM1 (macrophages, Dako).
Detection of Viral Genomes
DNA and RNA were extracted simultaneously using protein K digestion followed by extraction with phenol/chloroform. Nested PCR/RT-PCR was performed for the detection of enteroviruses (including coxsackieviruses and echoviruses), parvovirus B19, adenoviruses, human cytomegalovirus, Epstein-Barr virus, and human herpes virus type 6 (HHV 6). As a control for successful extraction of DNA and RNA, oligonucleotide sequences were chosen from the GAPDH gene. The specificity of all amplification products was confirmed by automatic DNA sequencing.

Statistical Analysis
Continuous data are expressed as mean±SD except where specified. The relationships between continuous variables were examined by least-squares linear regression analysis. All statistical tests were tailed; a value of P<0.05 was regarded as statistically significant. To account for the nonindependence of the segmental data, a repeated-measures variable for the patient was added to the linear regression analysis by use of a mixed-effects model (S-PLUS 2000 software).

Results
Patient Characteristics
The patients’ clinical features are summarized in Table 1. There were 26 men and 6 women. The primary reason to seek medical attention was chest pain or dyspnea (n=27). Of the remaining patients (n=5), 3 underwent workup for resting tachycardia and 2 for syncope. ST-segment depression was found in 25 patients and sustained or nonsustained VT in 5 patients. The remaining 2
patients had external defibrillation for sustained VT. Troponin I was elevated in 14 patients (Table 1). Pericardial effusion was present in 5 patients. Coronary artery disease was ruled out in all patients by cardiac catheterization.

CMR in the Acute Setting
Figures 2 and 3 show typical examples of CMR images. The full-motion cines corresponding to Figure 2 may be viewed in the online-only Data Supplement. Ejection fraction (EF) in the acute setting, maximal end-diastolic volumes (EDVs), and maximal end-systolic volumes (ESVs) are shown in Table 2. Contrast enhancement was present in 28 of 32 patients (88%). Regions of contrast enhancement were usually seen in a patchy distribution originating primarily from the epicardial quartile of the wall with one or several foci within the myocardium and were most frequently located in the lateral free wall (Figures 2 and 3). Contrast enhancement was also occasionally present in the septum but was never found originating from the subendocardial portion of the wall, as would be typical for myocardial infarction (Figure 2). Results of segmental analysis with regard to distribution of contrast enhancement are displayed in Figure 4.

Histopathologic Results
EMB was performed in all 32 patients (Table 1). In 21 of the 28 patients in whom contrast enhancement was present, biopsies could be obtained from the region of contrast enhancement (17 lateral free wall via LV, 2 apex via LV, 2 IVS via RV). In the remaining 7 patients, in whom the region of enhancement could not be reached with the bioptome, as well as in the 4 patients without contrast enhancement, biopsy was taken from the RV portion of the IVS.

In 19 of the 21 patients in whom biopsies were taken from the region of contrast enhancement, histopathologic analysis revealed active acute or chronic myocarditis. CMR findings correlated well with a predominantly macrophage-rich inflammation associated with myocyte damage, as demonstrated in Figure 4. Parvovirus B19 was found in 13 and
HHV6 in 6 cases (n=19). The remaining 2 patients had histological evidence of hypertrophic cardiomyopathy (HCM) but no signs of myocarditis (Tables 1 and 2).

In the 7 patients in whom biopsy could not be taken from the region of contrast enhancement, histopathology revealed active myocarditis in one case only (HHV6, patient 27). In 4 of the remaining 6 patients, histopathologic evidence for healed myocarditis and in the other 2 patients evidence for dilated cardiomyopathy was found. No infectious agent could be detected.

In the 4 patients without contrast enhancement, histopathology revealed healed myocarditis without evidence for virus infection (Tables 1 and 2).

CMR at Follow-Up

Three months after initial CMR, 20 patients who all had shown contrast enhancement in the acute setting were available for follow-up. Figure 5 compares typical follow-up images with acute images. At follow-up, the mean EF improved and the mean maximal EDV and the mean ESV decreased, as well as the average area of enhanced tissue (Table 2). In 3 patients, the enhancement disappeared completely (patients 2, 22, and 24). Results of the segmental analysis comparing the distribution of contrast enhancement at follow-up with acute images are displayed in Figure 4.

### Extent of Myocarditis Related to Global Parameters

The upper and middle panels of Figure 6 demonstrate that the extent of contrast enhancement as a percentage of the LV correlated poorly with the EF or the improvement in EF. There was no correlation of the extent of enhancement to the

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**TABLE 2. Follow-Up**

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All indicates mean; CE, contrast enhancement; %LV, percent of left ventricular mass; EF%, ejection fraction in %; N/A, not applicable; and FU, follow-up.
EDV \( (r=0.04, P=0.78, \text{no graph}) \) or ESV \( (r=0.003, P=0.98, \text{no graph}) \) and only a poor correlation to the decrease in EDV \( (r=0.18, P=0.41, \text{no graph}) \) and ESV \( (r=0.06, P=0.84, \text{no graph}) \). However, as displayed in the bottom panel of Figure 6, there was a moderate positive correlation between the decrease of enhancement and the improvement in EF that almost achieved statistical significance.

**Discussion**

This study is unique in that patients not only underwent new IR-GRE contrast CMR but also “CMR-guided” biopsies in the area of contrast enhancement. We found that contrast enhancement occurs frequently in the setting of suspected myocarditis and that contrast enhancement is associated with active myocarditis as defined by histopathology. Our data indicate that myocarditic infiltration is most frequently located in the lateral free wall (Figure 4) and that areas of contrast enhancement decreased over time as EF and EDV returned toward normal (Table 2).

**Endomyocardial Biopsy**

Histopathology has been used as the gold standard. However, reliance on the Dallas criteria alone has been shown to give false-negative results.\(^{10,22}\) Sensitivity can be enhanced by the
small and are normally taken from the RV portion of the IVS without information about the localization of inflammatory lesions: they occurred predominantly in the lateral free wall and originated from the epicardial quarter of the ventricular wall (Figure 4). Contrast enhancement was never seen to originate from the subendocardium, which is typical for myocardial infarction. The finding of the lateral wall as the preferred location of inflammatory lesions has been shown previously in postmortem evaluations. Shirani et al demonstrated in a necropsy study of myocarditis patients who died suddenly that the predominant location of myocardial lesions was the subepicardial region of the lateral free wall. In contrast, a relatively low density of inflammatory cells was found in the RV half of the septum, which is the usual location of EMB. The present study demonstrates the same pattern of myocardial lesions in vivo.

Interestingly, contrast enhancement was present in 28 patients, but troponin was elevated in only 14. This finding, however, does not necessarily mean that contrast enhancement may occur without enzyme evidence of myocardial necrosis. The likely reason for a CMR demonstration of myocardial damage in the absence of elevated troponin is that patients were included in whom the acute viral illness had occurred up to 8 weeks earlier. Therefore, CMR most likely showed chronic damage in those patients who had no troponin elevation at the time of the scan.

**Possible Mechanism for Contrast Enhancement**

The cellular-level mechanism responsible for contrast enhancement has not been fully elucidated, and most reports discuss mechanisms in the setting of myocardial infarction. The hypothesis is that in acutely infarcted regions, myocyte membranes rupture, allowing the contrast agent to diffuse into the cells and resulting in an increased tissue-level concentration and therefore contrast enhancement. Chronic infarcts have a significantly larger extracellular space than normal myocardium, mostly because of larger intercellular gaps in fibrous replacement tissue. This increased distribution space for the contrast agent causes higher concentrations per voxel, also resulting in contrast enhancement. During postinfarction remodeling, the areas of contrast enhancement shrink as infarcts shrink. Normal myocardium does not enhance because extracellular CMR contrast agents, such as Gd-DTPA, are excluded from the myocyte intracellular space by intact sarcolemmal membranes and also, little interstitial space is available between densely packed myocytes.

The same mechanism may explain contrast enhancement in the setting of inflammatory heart disease. The major difference is that areas of tissue damage within a myocarditic focus are usually smaller than in infarcts. Islands of necrotic cells are dispersed in a “cougar-like pattern” throughout the focus, characterized by ruptured membranes that also allow the contrast to diffuse into the cells. This results in contrast enhancement in the setting of myocarditis. However, contrast enhancement associated with myocarditis may not be as bright as infarct enhancement, because compared with infarcts, the inflammatory area will usually contain more living myocytes between the islands of necrosis. During healing, necrotic myocytes are replaced by fibrous tissue,
comparable to small chronic infarcts. Therefore, the contrast enhancement may remain present in the chronic phase. When the inflammation is finally healed, those scars shrink and remodel, as chronic infarcts are known to do, explaining why myocarditis contrast enhancement decreases significantly after healing. In some cases, depending on size and distribution, remaining “microscars” might shrink smaller than CMR voxels, causing all visible contrast enhancement to disappear, leaving only minimal diffuse signal enhancement, as reported by Friedrich et al.\textsuperscript{10} and Wagner et al.\textsuperscript{32} (patients 2, 22, and 24).

Contrast Enhancement and Myocardial Function
There was no close correlation between the initial extent of contrast enhancement and the initial EF, EDV, ESV, or the improvement of EF during follow-up (Figure 6). Although it is possible that this relation could have reached statistical significance with a larger population, it is clear from the present data that there is not a 1-to-1 relationship. Nevertheless, at follow-up, average areas of enhancement were found to have decreased as average EF and EDV returned toward normal. This is in good agreement with the fact that viral invaders are generally eliminated within a few weeks, followed by a healing process in most cases.\textsuperscript{33}

There were 2 patients with normal EF who had relatively large areas of contrast enhancement (patients 1 and 6). One possible explanation for this phenomenon might be that the enhancement was located subepicardially, indicating that this area of the wall was most strongly affected. Because some investigators postulated “a disproportionate role of the subendocardial layer of myocardium in overall wall-thickening,”\textsuperscript{34} one could speculate that the subepicardial damage found in our patients might not impair wall motion as much as the same amount of subendocardial damage would do. A different, or an additional, explanation for the finding of normal EF might be that the amount of damage is overestimated by contrast enhancement in the acute setting, because not all the cells in the enhanced areas have died, as they would have in the setting of infarction. It is possible, however, that the size of “irreversible damage,” as determined by follow-up CMR, might be predictive of long-term outcome. This is suggested by the findings of Wagner et al.\textsuperscript{32} who found that contrast enhancement 4 weeks after onset of symptoms was predictive of functional and clinical outcome.

Conversely, there were also patients who had little contrast enhancement even though their EF was severely impaired. Interestingly, all of these patients showed a remarkable recovery of EF at follow-up (eg, patient 21). The initial impairment of EF was obviously not related to large areas of necrosis induced by infection. However, Bültmann et al.\textsuperscript{19} recently reported that parvovirus B19 infection of endothelial cells seriously impairs coronary microcirculation. Consequently, the transient EF impairment in those cases could be related to “microvascular myocardial stunning” caused by endothelial dysfunction as a result of virus infection. Another possible explanation for the transient LV dysfunction could be that inflammatory products lead to reduction of contractile function without necrosis. With recovery and disappearance of inflammatory products, contractile function returns to normal.

Clinical Implications
On the basis of our findings, contrast CMR can be used to identify patients with active myocarditis in the setting of suspected myocardial infection or new onset of heart failure. Furthermore, contrast CMR provides information on the exact localization of myocardial damage caused by myocarditis that can be used to guide biopsy, enhancing sensitivity and specificity. The role of myocardial damage as measured by contrast CMR as a predictor for long-term outcome warrants further investigation.

Conclusions
Contrast enhancement assessed by segmented IR-GRE CMR is a frequent finding in the setting of suspected myocarditis and is associated with active myocarditis defined by histopathology. Myocarditic infiltrations occur in a peculiar pattern, predominantly in the lateral free wall, originating from the epicardial quartile of the ventricular wall. Contrast CMR is a valuable tool for the evaluation and monitoring of progression or regression of inflammatory heart disease.

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References


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