Chapter 3

Quantification of myocardial infarct size and transmurality by delayed contrast-enhanced magnetic resonance imaging in men
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The American Journal of Cardiology 2004;94:284-288

Abstract
Delayed contrast-enhanced magnetic resonance imaging (MRI) allows precise delineation of infarct transmurality. An issue of debate is whether data analysis should be performed visually or quantitatively. Accordingly, a head-to-head comparison was performed between visual and quantitative analyses of infarct transmurality on delayed contrast-enhanced MRI. In addition, infarct transmurality was related to the severity of wall motion abnormalities at rest. In 27 patients with long-term ischemic left ventricular (LV) dysfunction (left ventricular ejection fraction 33 ± 8%) and previous infarction, cine MRI (to assess regional wall motion) and delayed contrast-enhanced MRI were performed. Using a 17-segment model, each segment was assigned a wall motion score (from normokinesia to dyskinesia), and segmental infarct transmurality was visually assessed on a 5-point scale (0: no infarction; 1: transmurality ≤25% of LV wall thickness; 2: transmurality 26% to 50%; 3: transmurality 51% to 75%; and 4: transmurality 76% to 100%). Quantification of transmurality was performed with threshold analysis; myocardium showing signal intensity above the threshold was considered scar tissue, and percent transmurality was calculated automatically. Wall motion was abnormal in 56% of the 459 segments, and 55% of segments showed hyperenhancement (indicating scar tissue). The agreement between visual and quantitative analyses was excellent: 90% of segments (√ 0.86) were categorized similarly by visual and quantitative analyses. Infarct transmurality paralleled the severity of contractile dysfunction; 96% of normal or mildly hypokinetic segments had infarct transmurality ≤25%, whereas 93% of akinetic and dyskinetic segments had
transmurality >50% on visual analysis. In conclusion, visual analysis of delayed contrast-enhanced MRI studies may be sufficient for assessment of transmurality of infarction.

Introduction
Assessment of viability and scar tissue is important to guide treatment of patients with ischemic cardiomyopathy. Recently, delayed contrast-enhanced magnetic resonance imaging (MRI) has emerged as a non-invasive technique that allows imaging of scar tissue with a high spatial resolution. A close correlation has been shown between irreversible myocardial injury and hyperenhancement after administration of a gadolinium-based contrast agent. Furthermore, delayed contrast-enhanced MRI allows precise delineation of the transmurality of infarction. A current issue of debate is whether the analysis of the delayed contrast-enhanced MRI studies should be performed visually or quantitatively. Quantitative analysis may be time consuming, whereas visual assessment of transmurality may be less accurate. Accordingly, the purpose of this study was twofold: (1) to demonstrate the feasibility of quantitative assessment of transmurality and (2) to perform a head-to-head comparison between visual and quantitative analyses. In addition, results of the two techniques were related to the severity of wall motion abnormalities at rest.

Material and methods
Patients and study protocol
The study group consisted of 27 consecutive patients with long-term coronary artery disease and a previous infarction (>1 month before the study). Inclusion criteria were: (1) sinus rhythm, (2) angiographically proven coronary artery disease, and (3) myocardial infarction >1 month before the study.

Exclusion criteria were: (1) recent myocardial infarction (≤1 month) or an episode of unstable angina and/or heart failure that required hospitalization (≤1 month), (2) cardiac pacemakers or intracranial aneurysm clips, and (3) supraventricular arrhythmias.

The study protocol included a cine MRI study at rest to analyze regional and global left ventricular (LV) function, followed by delayed contrast-enhanced MRI.
imaging to measure infarct size. All patients gave written informed consent to the study protocol, which was approved by the local ethics committee.

Data acquisition
Patients were positioned supine in a clinical 1.5-Tesla scanner (Gyroscan NT Intera, Philips Medical Systems, Best, The Netherlands). All images were acquired using 5-element synergy coil during breath-holds and were gated to the electrocardiogram. To determine the final short-axis imaging plane, transverse, oblique sagittal, and double-oblique LV long-axis scout images were obtained as previously described 6. Depending on the size of the heart, the heart was imaged from apex to base with 10 to 12 imaging levels in the short-axis orientation using a sensitivity encoding imaging technique with a balanced fast-field echo sequence. Typical parameters were a 400 × 400 mm field of view, a 256 × 256 matrix size, 10.00 mm slice thickness, 0.00 mm slice gap, 50° flip angle, 1.82 ms echo time, and 3.65 ms repetition time. The number of cardiac phases depended on the heart rate.

Before the acquisition of the delayed contrast-enhanced images, optimization of inversion time was performed for each patient starting 15 minutes after a bolus injection of gadolinium DTPA (0.15 mmol/kg, Magnevist; Schering/Berlex, Berlin, Germany). To achieve maximum contrast between viable and nonviable myocardial tissues, a series of real-time plan-scan images with decreasing inversion time, starting at approximately 300 ms, were obtained. Real-time plan scanning allows immediate adjustment of inversion time by instant acquisition of short-axis test slices, without the need for breath holding. In 50 to 70 seconds, a series of images with different inversion times in steps of 5 ms can be acquired to obtain the optimum inversion time with nulled (black) myocardium and high signal intensity of infarcted tissue. The following parameters were applied: 400 × 400 mm field of view, 256 × 256 matrix size, 6.00 mm slice thickness, 15° flip angle, 1.44 ms echo time, and 4.3 ms repetition time.

Delayed contrast-enhanced images were acquired 17 to 19 minutes after contrast administration, with an inversion-recovery gradient echo sequence, in the same views as those used for cine MRI imaging. Depending on the patient's heart rate and heart size, 20 to 24 slices were obtained in two breath-hold acquisitions of approximately 15 seconds. Typical parameters were a 400 × 400 mm field of view, 256 × 256 matrix size, 5.00 mm slice thickness, 15° flip angle, 1.36 ms echo time, and 4.53 ms repetition time.
Data analysis

Regional and global function.
For assessment of regional wall motion, cine magnetic resonance images were visually interpreted by two experienced observers (blinded to other magnetic resonance and clinical data) according to a previously described 17-segment model \(^7\). Each segment was assigned a wall motion score using a 5-point scale (0: normokinesia; 1: mild hypokinesia; 2: severe hypokinesia; 3: akinesia; 4: dyskinesia).

To determine global function, endocardial borders were outlined manually on the short-axis cine images by using previously validated software (MR Analytical Software System 5.0 Medis, Leiden, The Netherlands). Papillary muscles were regarded as part of the ventricular cavity. LV end-systolic and LV end-diastolic volumes were calculated. Subsequently, the related left ventricular ejection fraction (LVEF) was derived by subtracting the end-systolic volume from the volume at end-diastole and dividing the result by the end-diastolic volume.

Visual analysis of scar tissue.
Delayed contrast-enhancement images were scored visually by two experienced observers (blinded to other magnetic resonance and clinical data) according to the same 17-segment model used for function analysis. Each segment was graded on a 5-point scale (0: no hyperenhancement; 1: hyperenhancement 1% to 25% of LV wall thickness; 2: hyperenhancement extending from 26% to 50% of LV wall thickness; 3: hyperenhancement extending from 51% to 75%; 4: hyperenhancement extending from 76% to 100% of LV wall thickness) \(^8\). To assess intra- and interobserver agreements, ten patients were reanalyzed. The resulting intra- and interobserver agreements were 97% and 94%, respectively.

Quantitative analysis of scar tissue.
The transmural extent of infarction was also determined with threshold analysis (Figure 1). In one representative slice of each delayed contrast-enhancement set, two regions of interest were manually drawn, with one in a region showing the highest signal intensity (center of infarction) and another region of interest of the same size in normal myocardium (with normal wall motion). A threshold value was calculated by dividing the sum of the signal intensities in the two regions of interest by 2. Myocardial tissue showing a signal intensity of at least the threshold value was considered scar tissue.
The extent of transmurality was subsequently determined using the modified centerline method. Using ten points along each centerline chord, percent LV wall thickness with increased signal intensity was determined and expressed as an average per segment to allow comparison with the visual analysis. Signal intensity of the ten equidistant points was determined by bipolar interpolation. No zoom was used. To assess inter- and intraobserver variabilities of quantitative analysis (to assess extent of infarcted tissue), ten patients were reanalyzed. The inter- and intraobserver variabilities were 4.2 ± 6.6% and 3.0 ± 5.1%, respectively.

Figure 1. Subsequent steps of quantitative analysis of transmurality of infarction. (A1) Representative delayed contrast-enhanced, short-axis slice. (A2) Two manually drawn regions of interest; one in the center of infarction (black arrow) and another in normal myocardium (white arrow). (A3) Delayed contrast-enhanced slice after application of the threshold value. (B1) Application of the modified centerline method, resulting in 100 equidistant chords along the left ventricular wall. (B2) Enlargement of the dashed box in B1. (B3) A signal-intensity curve of one of these centerline chords, showing the signal intensity in ten points along this particular centerline chord, revealing an infarction of 50% of left ventricular wall thickness.
**Statistical analysis**

Continuous data were expressed as mean ± standard deviation and compared with the two-tailed Student's *t* test for paired and unpaired data when appropriate. Simultaneous comparison of >2 mean values was performed with one-way analysis of variance. Relations were determined by linear regression analysis. Agreements for segmental wall motion and scar score and for visual and quantitative analyses of scar tissue were assessed from 5 × 5 tables using weighted kappa statistics. Kappa values <0.4, 0.4 to 0.75, and >0.75 were considered to represent poor, fair to good, and excellent agreement, respectively, based on Fleiss's classification. The kappa values are reported with their standard error values. A p-value <0.05 was considered statistically significant.

**Results**

**Patients**

Patient characteristics are listed in Table 1. The study group consisted of 27 men, with a mean age of 65 ± 7 years. All patients had a history of myocardial infarction (>3 months before the study) and showed Q waves on the electrocardiogram (11 inferior and 16 anterior). Patients had on average 2.7 ± 0.6 stenosed coronary arteries. Cardiac medication was continued during the study period and consisted of β-blockers (n=12), angiotensin converting enzyme inhibitors (n=16), diuretics (n=16), statins (n=15), calcium antagonists (n=10), nitrates (n=9), and oral anticoagulation or aspirin (n=27).

| Table 1. Clinical characteristics of the study population (n=27). |
|------------------|--------------------|
| **Age (years)**  | 65 ± 7             |
| **Previous infarction** | 27 (100%)         |
| **Q wave on electrocardiogram** | 27 (100%) |
| **Multivessel disease** | 24 (89%)          |
| **Angina Pectoris** |            |
| CCS class I/II   | 23 (85%)           |
| CCS class III/IV | 4 (15%)            |
| **Heart Failure** |            |
| NYHA class I/II  | 15 (56%)           |
| NYHA class III/IV| 12 (44%)           |

CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association.
Regional function, global function

Systolic wall thickening was normal in 200 of 459 segments (44%). End-diastolic volumes measured from the short-axis cine images were 187 to 407 ml (mean 269 ± 70 ml). End-systolic volumes were 99 to 313 ml (mean 184 ± 68 ml). Accordingly, LV ejection fraction was 21% to 52% (mean 33 ± 8%). Because assessment of viability is most important in patients with severely depressed LVEF, a separate analysis was performed in 15 patients with LVEF ≤35%. In these patients, end-diastolic and end-systolic volumes were 218 to 407 ml (mean 311 ± 66 ml) and 155 to 313 ml (mean 229 ± 58 ml), respectively. Mean LVEF was 27 ± 4% (range 21 to 35). Linear regression shows good correlations \( y = -0.37x + 22.0, \) \( r = 0.79, \) \( p < 0.01 \) and \( y = -0.37x + 17.8, \) \( r = 0.79, \) \( p < 0.01 \) between LVEF and the number of dysfunctional segments and between LVEF and the number of severe dysfunctional segments, respectively.

Visual analysis of scar tissue

Of the 459 segments evaluated, 253 (55%) showed hyperenhancement. The extent of hyperenhancement paralleled the severity of contractile dysfunction (Figure 2), and
the likelihood of hyperenhancement of >50% of LV wall thickness was significantly higher in akinetic or dyskinetic segments than in mildly hypokinetic or normal segments (93% versus 2% versus 0%, p <0.05). Precise data are presented in Table 2. Percent visual scar scores in relation to segmental wall motion score are shown in Figure 2.

Table 2. Relation between visual hyperenhancement score and severity of contractile dysfunction.

<table>
<thead>
<tr>
<th>Wall motion score</th>
<th>Hyperenhancement score (visual analysis)</th>
<th>Total</th>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
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<td>128</td>
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</table>

*Expressed as wall motion score (65%, kappa 0.51).

Quantitative analysis of scar tissue

Quantitative percent transmurality on delayed contrast-enhancement images also paralleled the severity of wall motion abnormalities at rest and increased from an average of 14% in mild hypokinetic segments to an average of 85% in dyskinetic segments (p <0.05). Average percent transmurality for each wall motion score are shown in Figure 3. An excellent agreement was found between the visual and quantitative analyses: 90% of 459 segments were scored identically (kappa 0.86, SE 0.02). Quantitative assessment of scar tissue yielded a different result in 45 segments (10%) and shifted 13 (29%) of these discrepant segments to a lower transmurality score and 32 (71%) to a higher transmurality score (Table 3). Average quantitative scores for the different visual scores are shown in Figure 4.
Table 3. Agreement between quantitative and visual scoring of scar tissue (90%, kappa 0.86).

<table>
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<tr>
<th>Visual analysis</th>
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<th>1-25%</th>
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<tr>
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<td>138</td>
<td>37</td>
<td>50</td>
<td>41</td>
<td>459</td>
</tr>
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</table>

Figure 3. Relation between the severity of contractile dysfunction (expressed as wall motion score) and the average quantitative percent of hyperenhancement through the left ventricular wall. Average quantitative percentage of hyperenhancement increased from 14% in mild hypokinetic segments to an average of 85% in dyskinetic segments (p<0.05). AK: akinesia; DYSK: dyskinesia; MHK: mild hypokinesia; NORM: normokinesia; SHK: severe hypokinesia.
Discussion

Recently, gadolinium-based contrast agents have been used extensively in combination with MRI imaging to identify infarcted myocardium \(^8,11\). The accuracy of delayed contrast-enhanced MRI in the assessment of infarcted myocardium has been evaluated by Kim et al. In an animal model of occlusion and reperfusion, these investigators demonstrated excellent agreement between the transmural and circumferential extents of infarction assessed by delayed contrast-enhanced MRI compared with histology. In addition, in patients after acute myocardial infarction, the extent of scar tissue on delayed contrast-enhanced MRI correlated well with enzymatically assessed damage \(^8\).

In patients with chronic ischemic cardiomyopathy, direct comparisons with positron emission tomography and fluorine-18 fluorodeoxyglucose have demonstrated good agreement between the two techniques for assessing viability \(^12\). Moreover, Kim et al demonstrated that the extent of scar tissue on delayed contrast-enhanced MRI is predictive of improvement of function after revascularization \(^13\). Patients with small subendocardial necrosis had a high likelihood of functional recovery after revascularization compared with a low likelihood of recovery in patients with transmural infarction.
The major advantage of MRI over other imaging techniques is the extremely high resolution, which allows assessment of minimal infarction. Wagner et al \(^{14}\) performed a head-to-head comparison between delayed contrast-enhanced MRI and single-photon emission computed tomography and found that 47\% of segments with small subendocardial infarctions on delayed contrast-enhanced MRI were not detected by single-photon emission computed tomography.

Currently, delayed contrast-enhanced MRI studies are analyzed visually, and the transmurality of infarction is divided into quintiles based on visual inspection \(^8\,^{13}\). However, the high resolution of MRI makes the technique extremely well suited for quantitative analysis. Various MRI derived parameters have been evaluated quantitatively, including LV volumes, LVEF, segmental systolic wall thickening, and end-diastolic wall thickness, \(^{15-17}\) thereby providing extreme precision to assess these parameters. Similarly, quantitative evaluation of transmurality of infarcted tissue on delayed contrast-enhanced MRI would allow higher precision to define the exact percent of infarcted tissue of the LV wall. However, all previous studies have relied on visual analysis; in the present study, the feasibility of a more objective, quantitative approach was demonstrated. By using threshold analysis for signal intensity, a precise delineation of the transmural extent of infarcted tissue was possible (although animal experiments are needed to validate the technique). However, when the quantitative approach was compared directly with visual analysis, there was excellent agreement, with 90\% of segments classified in the same quintiles of transmurality (Table 3) and only 10\% of segments shifted to a lower or higher quintile when quantitative analysis was compared with visual analysis. Based on these findings, one can conclude that visual analysis may be sufficient for clinical assessment of the extent and transmurality on delayed contrast-enhanced MRI. Eventually, a head-to-head comparison between visual and quantitative analyses is needed in patients undergoing revascularization to determine whether precise quantification results in superior prediction of improvement of function after revascularization.

Aside from the comparison between visual and quantitative analyses, transmurality on delayed contrast-enhanced magnetic resonance imaging was compared with the severity of contractile dysfunction. Comparable to the findings by Mahrholdt et al \(^{18}\), the extent of transmurality paralleled the severity of wall motion abnormalities. Segments with normal function had no or minimal infarction, whereas segments with akinesia or dyskinesia had extensive scar tissue.
References


Quantification of myocardial infarct size and transmurality by delayed CE-MRI in men


