Acute oedema in the evaluation of microvascular reperfusion and myocardial salvage in reperfused myocardial infarction with cardiac magnetic resonance imaging

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ABSTRACT

The accurate measurement of myocardial salvage is critical to the ongoing refinement of reperfusion strategies in acute myocardial infarction (AMI). Cardiac magnetic resonance imaging (CMR) can define the area at risk in AMI by the presence of myocardial oedema, identified by high signal intensity on T2-weighted imaging with a short inversion time inversion-recovery (STIR) sequence. In addition, myocardial necrosis can be identified with CMR delayed contrast enhanced imaging. In this prospective study we examined the relationship of acute oedema and necrosis with impaired microvascular reperfusion. We also evaluated acute oedema as a marker of the area at risk in AMI, for the purposes of documenting myocardial salvage. CMR was performed on 15 patients with (AMI), within 24 h of successful percutaneous coronary intervention (PCI). Left ventricular (LV) systolic dysfunction was defined by a systolic thickening <40% (severe <20%). Microvascular reperfusion was evaluated during the acute phase of contrast wash-in. CMR was repeated 3 months post-PCI to evaluate recovery of LV function and final infarct size. Myocardial salvage was defined as the percentage of the area at risk that was not infarcted on follow up CMR. There was a significant correlation between impaired microvascular reperfusion and the extent of segmental oedema (R=0.363, P<0.01), but not myocardial necrosis (R=0.110, P>0.5). The extent of myocardial salvage correlated with recovery of systolic function (R=0.241, P<0.05), which was strongest in LV segments with severely reduced systolic function (R=0.422, P<0.01). Conclusions: In acutely reperfused AMI, oedema can be used to identify the area at risk for the purpose of calculating myocardial salvage. The correlation between myocardial oedema and reperfusion status suggests a pathological role of acute oedema in the impairment of microvascular reperfusion.

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1. Introduction

Myocardial salvage represents the raison d’être of all reperfusion strategies for acute myocardial infarction (AMI) [1,2]. Critical to the ongoing refinement of reperfusion strategies in AMI is the accurate measurement of myocardial salvage [3]. Acutely, reperfusion status, at both a macrovascular and microvascular level, has been shown to correlate with survival [4,5] and/or improvement of cardiac function [6,7]. Whilst acute oedema has been postulated to impair microvascular reperfusion, differentiating the effects of acute oedema from acute necrosis has not been possible.

Recently, cardiac magnetic resonance imaging (CMR) utilising delayed contrast enhancement (DCE) has emerged as an accurate method for documenting the geographic extent of myocardial infarction, in both its acute and chronic phases [8–11].

However, whilst DCE is believed to correspond to areas of necrosis and scar formation in the acute and chronic phases of myocardial infarction respectively, a more definitive CMR method for acutely defining the area at risk in AMI is the presence of myocardial oedema, identified by high signal intensity on T2-weighted imaging. Previously, a strong geographic correlation between myocardial oedema and myocardium at risk has been demonstrated in an animal model using microspheres [12,13]. Using short inversion...
time inversion-recovery (STIR) sequences, T₂-weighted imaging has been shown to reliably identify areas of AMI in human subjects [14–18]. Recently the utility of STIR imaging in the evaluation of AMI has been highlighted [3,16,17], as well as the potential impact of myocardial oedema on microvascular reperfusion [19,20].

In this prospective study we examined the relationship of acute oedema and necrosis with impaired microvascular reperfusion. We also evaluated acute STIR imaging as a marker of the area at risk in AMI, for the purposes of documenting myocardial salvage.

2. Methods

2.1. Patient selection

All subjects were enrolled through the Department of Cardiology, Humboldt-University, Charité; Campus Buch, Franz Volhard Klinik, Berlin Germany. Patients with AMI were considered for enrolment if they had undergone successful emergency percutaneous coronary intervention (PCI) within the preceding 24 h. This study is a subanalysis of a previously published study in which patients were enrolled between January and December 2002 [6]. We have previously reported the impact of microvascular reperfusion status on recovery of left ventricular (LV) systolic function in this group. Patients enrolled in this prior study who also had CMR evaluation of myocardial oedema were included in the present study. The definitions of AMI, as well as the inclusion/exclusion criteria for CMR have been fully described in this prior paper. Informed consent was obtained before CMR, and the study was carried out under the guidelines of the Franz Volhard Klinik Ethics Committee.

2.2. Coronary angiography and angioplasty procedure

All patients underwent coronary angiography on a Siemens angiography suite (Hicor, Siemens, Germany). All patients received standard post-infarct PCI care, which included combined oral antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day following an oral bolus of 300 mg) for a minimum of 1 month after PCI. The administration of intravenous antiplatelet agents, such as abciximab or tirofiban was at the proceduralist’s discretion. Heparin was administered as an intravenous bolus during PCI to attain an activated clotting time >300 s. Procedural success in AMI patients was defined by an open coronary artery with less than 50% residual stenosis.

2.3. Cardiac MRI protocol

We performed CMR in 15 AMI subjects within 24 h of successful emergency PCI, and then 3 months following AMI, on a clinical 1.5 T CMR scanner (General Electric CV/i, Milwaukee, USA). All CMR sequences were performed in three standard short axis slices (apical, mid and basal), kept identical for each sequence throughout the study. From a four-chamber long axis view, five equally spaced slices were planned, so that the two outer slices lined up exactly with the tip of the apex or the mitral annulus. The two outer slices were then deleted, leaving three slices corresponding to typical basal, mid and apical short axis views. The slice thickness and separation were individually determined to null the myocardial signal, range 180–250 ms, slice thickness 15 mm, matrix 256 × 192, number of acquisitions = 2). Cine imaging of the LV was obtained with a steady state free precession pulse sequence (TR 3.8 ms, TE 1.6 ms, 30 phases, slice thickness 15 mm) on both acute and 3-month follow-up CMR scanning. Systolic function was assessed on a segmental basis and percent myocardial thickening was calculated, defined as ratio of the systolic thickness minus the diastolic thickness divided by the diastolic thickness. This ratio was then converted to a percentage by multiplying by a factor of 100. Systolic dysfunction was deemed to be present if systolic thickening was less than 40%, and severe if systolic thickening was less than 20%. Recovery of systolic dysfunction was defined as the difference in systolic thickening between acute and 3-month CMR scans.

2.3.1. Analysis of wall motion

Cine imaging of the LV was obtained with a steady state free precession pulse sequence (TR 3.8 ms, TE 1.6 ms, 30 phases, slice thickness 15 mm) on both acute and 3-month follow-up CMR scanning. Systolic function was assessed on a segmental basis and percent myocardial thickening was calculated, defined as ratio of the systolic thickness minus the diastolic thickness divided by the diastolic thickness. This ratio was then converted to a percentage by multiplying by a factor of 100. Systolic dysfunction was deemed to be present if systolic thickening was less than 40%, and severe if systolic thickening was less than 20%. Recovery of systolic dysfunction was defined as the difference in systolic thickening between acute and 3-month CMR scans.

2.3.2. Analysis of acute oedema

Acute myocardial oedema was identified by bright signal intensity on a short inversion time inversion-recovery sequence.

Table 1

<table>
<thead>
<tr>
<th>Cardiac MRI protocol.</th>
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<td>1. Analysis of wall motion: Short axis imaging</td>
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<tr>
<td>- Steady state free precession pulse sequence (TR 3.8 ms, TE 1.6 ms, 30 phases), slice thickness 15 mm.</td>
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<tr>
<td>2. Analysis of acute oedema: Short inversion time inversion-recovery (STIR) sequence. T₂-weighted triple inversion-recovery sequence (repetition time 2 × R-to-R interval; echo time 65 ms; inversion time 140 ms), slice thickness of 15 mm.</td>
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<tr>
<td>3. Evaluation of microvascular: Perfusion: Short axis image</td>
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<td>- First-pass perfusion CMR (saturation recovery, gradient echo/echo planar-readout sequence, TR/TE 113–134 ms/1.3–1.7 ms, flip angle 25°, slice thickness 15 mm) following a bolus of Gadolinium-DTPA (0.1 mmol/kg body weight).</td>
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<td>4. Delayed contrast enhancement: Short axis imaging</td>
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<td>- Inversion-recovery gradient echo technique (TR 7.1 ms; TE 3.1 ms; TI individually determined to null the myocardial signal, range 180–250 ms, slice thickness 15 mm, matrix 256 × 192, number of acquisitions = 2). Evaluate 10 min following Gadolinium-DTPA administration.</td>
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Table 2

<table>
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<tr>
<th>Parameter</th>
<th>Findings pre PCI</th>
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<tr>
<td>Infarct related artery</td>
<td>Left anterior descending 8 (53.3) Left circumflex 5 (33.3) Right coronary 2 (13.3)</td>
</tr>
<tr>
<td>Lesion grade</td>
<td>A or B1 2 (13) B2 or C 10 (67)</td>
</tr>
<tr>
<td>TIMI flow</td>
<td>0 9 (60) I 5 (33) II 1 (7) III 0</td>
</tr>
<tr>
<td>Time to reperfusion (h)</td>
<td>8.3 ± 1.1</td>
</tr>
<tr>
<td>Peak creatine kinase level (IU)</td>
<td>1903 ± 303</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>3 (20)</td>
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</table>

Values are n (%) or mean ± SEM. CAD – coronary artery disease.
This sequence consisted of a black-blood, T2-weighted triple inversion-recovery sequence (repetition time \(2 \times R\)-to-\(R\) interval; echo time 65 ms; inversion time 140 ms). Three standard short axis slices (basal, mid-ventricular, and apical) were obtained at a slice thickness of 15 mm according to the landmarks described above. The area a risk was defined in each segment with acutely impaired systolic thickening as the percentage of the segment with signal intensity greater than two standard deviations above a normal remote region in the same slice.

2.3.3. Delayed contrast enhancement

We performed DCE at the time of acute scanning, as well as 3 months post AMI. In both cases this was evaluated 10 min following Gadolinium-DTPA administration to identify the infarct region using an inversion-recovery gradient echo technique (TR 7.1 ms; TE 3.1 ms; TI individually determined to null the myocardial signal, range 180–250 ms, slice thickness 15 mm, matrix 256 × 192, number of acquisitions = 2). The cut-off for the presence of DCE was signal intensity greater than two standard deviations above that of a non-infarcted remote segment in the same slice [6,8]. Final infarct size in each segment was defined as the percentage area of the segment with signal intensity above our defined cut-off on 3-month CMR scanning.

2.3.4. Evaluation of microvascular perfusion

Microvascular perfusion was assessed on a segmental basis at rest by first-pass perfusion CMR (saturation recovery, gradient echo/echo planar-readout sequence, TR/TE 113–134 ms/1.3–1.7 ms, flip angle 25°, slice thickness 15 mm) following a bolus of Gadolinium-DTPA (0.1 mmol/kg body weight; Magnevist®, Schering, Germany). Semi-quantitative perfusion analysis was performed by calculating the time to 50% maximum myocardial enhancement \(T_{\text{50\% max}}\) during the first pass of contrast in each myocardial segment, utilising a specialized software package (MASS 6.0®, Medis, Leiden, The Netherlands). The contrast delay in AMI segments was then calculated by subtracting the \(T_{\text{50\% max}}\) of these segments from that of a remote myocardial segment. Impairment of microvascular reperfusion was defined by the presence of contrast delay in the AMI segment relative to the remote segment. The criteria for the selection of the remote segment were the complete absence of infarction (as assessed by delayed hyper-enhancement) as well as uniform wash-in over all three slices in that myocardial segment.

2.3.5. Calculation of myocardial salvage

Myocardial salvage was calculated using the area at risk according to acute STIR in each segment with acutely impaired systolic dysfunction, defined as the percentage of the area at risk that was not infarcted on follow up CMR. In some instances, the final area of infarction was actually greater than the initial “at-risk” area, yielding a negative value for myocardial salvage. The correlation between myocardial salvage and recovery of LV systolic function was then evaluated.

2.4. Statistics

All data are expressed as mean ± SE except where otherwise stated. Comparisons between groups were made using paired or unpaired Student’s \(t\)-tests. The Pearson Product Moment was calculated to assess correlation. Statistical power of the correlation between myocardial salvage and recovery of LV function was >0.8, given an alpha value of 0.05 and an estimated correlation coefficient of 0.3 and a sample size of 90 AMI segments. A computerised statistical program (SPSS for Windows©, Release 14.0 SPSS Inc) was used for all analyses.

3. Results

Fifteen subjects with AMI (14 males) were enrolled in our study. The mean age was 54 ± 2 years. The infarct locations were anterior (8), anterolateral (1), lateral (3), inferior (2) and inferolateral (1). Infarct PCI was performed in all cases, with procedural success being achieved in all. The TIMI 3 and 2 flows were achieved in 14 and 1 patients, respectively (Table 2). A total of 89 segments within the corresponding AMI location with impaired systolic function were identified. Of these, 41 had severe impairment of systolic function. Acute CMR scanning was carried out in all patients without complication. After 3 months post AMI all patients returned for repeat CMR scanning.

3.1. Acute CMR scanning for oedema and necrosis

Of 89 segments, 84 segments were evaluable by STIR and 87 segments were evaluable by DCE. The mean extent of myocardial oedema was 12.55 ± 0.85% of the left ventricular short axis slice. The mean extent of myocardial oedema in AMI segments was 59.4 ± 3.4% of the segment area. The mean extent of acute DCE was 11.27 ± 1.00% of the left ventricular short axis slice and 56.9 ± 4.3% of...
the segmental area for each AMI segment. There were 10 segments with an area at risk defined by STIR without evidence of necrosis defined by DCE (Fig. 1).

3.2. Relationship of acute oedema to microvascular reperfusion

Of a total of 89 AMI segments with acute systolic dysfunction, 55 (62%) had impaired microvascular reperfusion. The extent of myocardial oedema documented by acute STIR correlated with the degree of impairment of microvascular reperfusion ($R = 0.363$, $P < 0.01$, Fig. 2). Considering the degree of impaired myocardial reperfusion in quartiles, there was a significant difference in the extent of myocardial oedema amongst groups ($P < 0.001$). There was no correlation between the extent of acute DCE and the degree of impairment of microvascular reperfusion ($R = 0.135$, $P = NS$).

3.3. Follow up CMR scanning

Three months post AMI, acute changes seen on STIR imaging had resolved in all cases. There was a significant reduction in the mean segmental extent of DCE on follow up CMR scanning compared with acute scanning ($40.5 \pm 4.1\%$ on chronic scanning vs. $56.9 \pm 4.3\%$ on acute scanning, $P < 0.001$). Of 89 infarct segments with acutely impaired systolic function, 76 (85%) demonstrated improved function, with 57 (64%) returning to normal. The mean improvement in LV systolic function at a segmental level was $30.7 \pm 3.8\%$. There was a significant negative correlation on 3-month scanning between the final infarct size by DCE and systolic contraction ($R = -0.39$, $P < 0.001$).

3.4. Myocardial salvage and its relationship to recovery of LV function

There was a significant correlation between the extent of myocardial salvage and recovery of systolic function when acute oedema was used to define the area at risk ($R = 0.241$, $P < 0.05$, Fig. 3A). This correlation was strongest in LV segments with severely reduced systolic function ($R = 0.422$, $P < 0.01$, Fig. 3B).

4. Discussion

Our data provide further evidence for the utility of acute myocardial oedema, defined by high signal intensity on T2-weighted imaging, in identifying the area of myocardium at risk in acutely reperfused myocardial infarction. Furthermore, the extent of myocardial oedema correlated with impairment of microvascular reperfusion, suggesting a pathological role of myocardial oedema in the impairment of reperfusion.

Interestingly, there was no such correlation between the extent of acute necrosis and impairment of microvascular reperfusion, implying that impaired microvascular reperfusion is at least in part a dynamic process not simply related to necrosis, which may therefore be reversible. When acute oedema was utilised to delineate the area at risk for the calculation of myocardial salvage, a significant correlation between myocardial salvage and recovery of systolic function was obtained, that was more pronounced when the analysis was limited to myocardial segments with initially severely reduced systolic function.

Previously, both STIR and DCE imaging have been utilised as part of CMR scanning at the time of acute infarction [17,21,22]. Temporal changes in DCE have been demonstrated post-infarction, with the area of DCE being largest early in the course of myocardial infarction, with subsequent reduction in size over ensuing months [21,22]. However whilst DCE in the chronic phase of infarction closely approximates myocardial scar [8], DCE in the acute phase of infarction is thought to identify areas of myocardial necrosis and not the area at risk [8,10]. In contrast, a number of studies have confirmed the reliability of STIR imaging to identify AMI in the acute setting [14–17], with an animal model of infarction documenting a close correlation between the area of acute oedema and the area at risk defined by microspheres [12].

The evaluation of myocardial salvage post AMI is a powerful tool for assessing reperfusion strategies. As it is defined as the proportion of the initial area at risk that is salvaged, it represents a method of standardising groups that may not be equal in infarct size on presentation. To date, the most utilised method for the calculation of myocardial salvage post AMI has been single photon emission computed tomography (SPECT) [3]. Whilst of proven utility in a number of larger trials, SPECT imaging requires multiple injections.
Fig. 3. There was a significant correlation between myocardial salvage using acute STIR to define myocardium at risk and recovery of myocardial systolic function (A), which was strongest in segments with acutely severe systolic dysfunction (B).

of radioactive contrast, and provides little extra data apart from that of viability. The application of CMR imaging in the assessment of myocardial salvage is attractive, as besides accurately identifying the area at risk with STIR imaging, functional imaging as well as final infarct size can be determined with a high degree of spatial accuracy. Recently Friedrich et al. have demonstrated the utility of STIR imaging in quantifying the extent of both reversible and irreversible myocardial injury. The extent of myocardial injury defined by STIR imaging was greater than that of irreversible myocardial injury defined by DCE [23]. In addition, more specialised sequences such as first-pass perfusion imaging can be easily performed to investigate the interplay between factors such as acute oedema and microvascular reperfusion. In our study, we identified a significant correlation between the extent of myocardial oedema and impairment of microvascular reperfusion. Previously, myocardial oedema has been muted as a potential factor inhibiting microvascular reperfusion [19,20], setting up a “vicious cycle” wherein acute infarction precipitates oedema, which may then further exacerbate ischaemia.

The small number of patients enrolled in this study did not provide sufficient numbers to evaluate the relationship of myocardial salvage to clinical endpoints. Prior studies utilising SPECT imaging have related final infarct size to improved survival [24]. Similarly, the peri-infarct zone identified with CMR has recently been shown to be a powerful predictor of post-MI mortality [25]. However to date the effect of myocardial salvage assessed by either imaging modality on mortality has not been documented. Another
limitation of our data is that repeat coronary angiography was not performed at the time of follow-up CMR scanning; therefore we are unable to confirm the presence of a persisting open artery. In a number of cases, the final infarct size actually extended beyond the initial at-risk area, possibly due to subsequent closure of the IRA, which may have limited the strength of correlation between myocardial salvage and recovery of LV function. Whilst the final infarct size in our study strongly related to recovery of LV systolic function, the identification of the area at risk also has important potential applications. At a clinical level the area of myocardium at risk may be important when considering therapeutic strategies on an individual risk/benefit level, whilst at a research level the interplay between the area at risk, factors such as reperfusion status and clinical outcome can be examined.

The accurate identification of the area at risk in AMI is crucial to the evaluation of future reperfusion therapies and their impact on myocardial salvage. Our data provide further support for the use of acute oedema, defined by high signal intensity on T2-weighted CMR imaging, in the identification of the at-risk area in AMI as well as a potential role for acute oedema in the impairment of microvascular reperfusion.

5. Conclusions

In acutely reperfused AMI, oedema may be used to identify the area at risk for the purpose of calculating myocardial salvage. The correlation between myocardial oedema and reperfusion status suggests a pathological role of acute oedema in the impairment of microvascular reperfusion.

Conflict of interest

There is no conflict of interest.

References


