Clinical research
Imaging

Influence of time-to-treatment, TIMI-flow grades, and ST-segment resolution on infarct size and infarct transmurality as assessed by delayed enhancement magnetic resonance imaging

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Aims The time-to-treatment, ST-segment resolution (STR), and TIMI-flow might be associated with infarct size (IS) and infarct transmurality in humans. Delayed enhancement magnetic resonance imaging (DE-MRI) has excellent spatial resolution to uncover these relations.

Methods and results This study analysed 135 ST-elevation myocardial infarction (STEMI) patients randomized to prehospital fibrinolysis or prehospital initiated facilitated percutaneous coronary intervention (PCI). Reperfusion-times, 90 min STR, and TIMI-flow grades were assessed. IS at 6-month follow-up was determined as percentage of left ventricular mass (% LV). Transmurality was defined if segments exceeded >50% DE. The median time-to-treatment was 93 min [interquartile range (IQR) 66.5; 158.8] for prehospital fibrinolysis and 85 min (IQR 60.0; 143.5) for facilitated PCI patients (P = 0.35).

In facilitated PCI, the pre-interventional TIMI-flow correlated with IS [TIMI 0–1 10.8% LV (IQR 7.6; 17.3) vs. TIMI 2–3 3.9% LV (IQR 0.9; 9.6); P = 0.002] and segments with transmurality 1.5 (IQR 0.0; 3.0) vs. 0 (IQR 0.0; 1.5; P = 0.02). In a multivariable model, incomplete STR, 70% was the strongest predictor of high IS [odds ratio (OR) 6.96, P < 0.001] and transmurality (OR 5.71, P < 0.001) followed by time-to-treatment delay (OR/30 min, 1.24; P = 0.01 for high IS and 1.23, P = 0.01 for transmurality).

Conclusion Time-to-treatment, STR, and TIMI-flow correlate with IS and transmurality underlining the assumed pathophysiological link between early flow restoration and perfusion in the infarct-related artery.

KEYWORDS
Infarct size;
Infarct transmurality;
Magnetic resonance imaging;
Myocardial infarction;
Reperfusion time;
ST-segment resolution

Introduction

Myocardial salvage and limitation of infarct size (IS) expansion are the principal mechanisms by which patients with ST-elevation myocardial infarction (STEMI) benefit from reperfusion.1 The time-to-treatment mainly determines the outcome of patients treated by fibrinolysis or primary percutaneous coronary intervention (PCI) with respect to the above-mentioned parameters.2,3 A simple method to assess reperfusion is measurement of early ST-segment resolution (STR).4 This method allows prediction of myocardial salvage and final IS measured by single photon computed tomography (SPECT), and subsequently of left ventricular (LV) function and clinical outcome after both fibrinolysis and PCI.5–7

Delayed enhancement (DE) magnetic resonance imaging (MRI) is a relatively new imaging method for IS assessment with high spatial resolution, which in contrast to SPECT allows to discriminate transmural and subendocardial infarcts.8 As a consequence, the association between ischaemia duration and extent of reperfusion with IS and more importantly with transmurality might be characterized. This so-called ‘wavefront phenomenon’ is well characterized in animal studies,9,10 but has not been assessed in humans. The objective of this study was therefore to evaluate the association between time-to-treatment, extent of early STR, and TIMI-flow on final IS and transmurality assessed by DE-MRI at 6-month follow-up in patients with STEMI, reperfused either by prehospital combination-fibrinolysis or prehospital initiated facilitated PCI.

Methods

Study patients

Between December 2000 and March 2004, 164 patients with STEMI were randomly assigned to prehospital combination-fibrinolysis with standard care (n = 82) or prehospital initiated facilitated PCI...
were as follows: death (last non-normalized measurement. Reasons for not pursuing MRI normalized values or if there was an increase of kinase (CK) and MB level above a reference limit in patients with symptoms, new ST-segment changes, and increase in the creatine cardiac event. The diagnosis of re-infarction was based on clinical MRI at 6 months follow-up without any recurrent ischaemic local Institutional Ethics Committee approved the study.

Study patients used for this analysis, were those 135 undergoing MRI at 6 months follow-up without any recurrent ischaemic cardiac event. The diagnosis of re-infarction was based on clinical symptoms, new ST-segment changes, and increase in the creatine kinase (CK) and MB level above a reference limit in patients with normalized values or if there was an increase of >50% from the last non-normalized measurement. Reasons for not pursuing MRI were as follows: death (n = 11), neurological deficit (n = 2), re-infarction in the same territory (n = 7), claustrophobia (n = 2), lost-to-follow-up (n = 1), pacemaker (n = 1), refusal (n = 1). For the purpose of examining the time-dependency of IS and infarct transmurality, the time-to-treatment was calculated from symptom-onset to first fibrinolytic bolus initiation.

Angiographic analysis

Angiographic analysis included initial and final TIMI-flow grade of the culprit vessel, assessed offline in the angiographic core laboratory by two blinded observers with averaging of the TIMI-flow, if not in agreement. In patients assigned to prehospital combination-fibrinolysis with standard care angiograms were performed elec-

Electrocardiographic analysis

A 12-lead ECG was recorded in the prehospital setting and approximately 90 min after reperfusion (first lytic bolus application) in all patients. In facilitated PCI patients ECG II was recorded immedi-

Enzymatic infarct size

According to protocol, the IS was additionally assessed indirectly by the QRS complex in ECG I and II. STR was calculated as the sum of ST-segment elevation ECG I minus the sum of ST-segment elevation ECG II divided by the sum of ST-segment elevation ECG I. STR was expressed as percentage. For the purpose of examining STR dependency of IS and transmurality, patients were also categorized into three groups as complete (>70%), intermediate (70-30%), or no STR (<30%).

Magnetic resonance imaging

IS was determined at 6-month follow-up by MRI. Imaging was performed on a 1.5 T scanner (Philips Intera CV, Best, The Netherlands). All images were acquired with breath-holding and were gated by a vector cardiacogenic method. LV function was assessed by a standard steady-state free precession technique (20–25 phases per cardiac cycle; repetition time 3.2 ms, echo time 1.2 ms, flip angle 60°, typical voxel size 1.8 × 1.8 × 8.0 mm). DE images covering the whole ventricle were acquired 15–20 min after administering Gadobutrol intravenously (Gadovist, Schering, Germany) at a dose of 0.2 mmol/kg body weight. An inversion-recovery gradient echo sequence (repetition time 2.8 ms, echo time 1.1 ms, flip angle 15°, voxel size 2.0 × 2.0 × 5.0 mm) was used and the inversion time adapted individually to null normal myocardium. All measures-

Figure 1A

Struc
tural analysis

The data are presented as median with interquartile range (IQR) or frequencies and percentages. Differences between means of continuous variables were tested by the Kruskal–Wallis test. Frequencies were compared using the exact χ² test. Differences were considered significant at a two-sided P-value < 0.05.

Logistic regression analysis with step-wise backward exclusion procedure was carried out to identify independent predictors for IS >10% and transmurality >50% in at least one segment. For each of both outcomes three models were computed. The first model included only clinical variables known prior to fibrinolysis. In the second model, TIMI-flow pre-PCI was added as a potential predictor, and in the third model TIMI-flow and STR were added.

For graphical presentation of the influence of time-to-treatment and reperfusion strategy on IS and transmurality, a logistic regres-

Results

Time-to-treatment—infarct size and transmurality

The median time-to-treatment was 93 min (IQR 66.5; 158.8) for prehospital combination-fibrinolysis and 85 min (IQR 60.0; 143.5) for facilitated PCI patients (P = 0.35). Prehospital initiated facilitated PCI resulted in lower IS (5.2% LV; IQR 1.3; 11.2) and lower number of segments with transmurality (0.0; IQR 0.0; 2.0) when compared with prehospital combination-fibrinolysis (10.4% LV; IQR 3.4; 16.3; P = 0.001; 1.0; IQR 0.0; 3.0; P = 0.005).

Logistic regression analysis showed for each 30 min increase in time-to-treatment, a risk increase to have an IS >10% or transmural infarction >50% in ≥ one segment for both reperfusion strategies. Figure 1A and B illustrate this relation. There was no significant interaction between
anterior and inferior infarctions. The final IS closely correlated with the number of transmural segments \(r = 0.91; P < 0.001\).

**TIMI-flow—infarct size and transmurality**

In those patients undergoing facilitated PCI, the pre-interventional TIMI-flow showed a significant association with final IS. Patients with TIMI-flow 0–1 pre-PCI \(n = 8\) TIMI 0; \(n = 4\) TIMI 1 had a median IS of 10.8% LV (IQR 7.6; 17.3), whereas in patients with re-opened infarct-related artery \(n = 8\) TIMI 2; \(n = 48\) TIMI 3 median IS was 3.9% LV (IQR 0.9; 9.6; \(P = 0.002\)). Similar results were observed for transmurality. In pre-interventional TIMI-flow 2–3, the number of segments with high transmurality was significantly lower \(0.0; IQR 0.0; 1.5\) in comparison with TIMI-flow 0–1 \(1.5; IQR 0.0; 3.0; P = 0.02\). There was no significant interaction of the post-interventional TIMI-flow on IS or transmurality.

**ST-segment resolution—infarct size and transmurality**

STR was significantly better in facilitated PCI patients \(92.0\%\); IQR 78.2; 100.0 vs. 77.3%; IQR 30.8; 99.3; \(P < 0.001\). Dividing patients into three groups according to the extent of STR, there were few differences in the baseline characteristics (Table 1). The percentage of patients with anterior infarction was significantly higher in the intermediate and no STR group when compared with the complete STR group. In addition, there were more patients with facilitated PCI in the group with complete STR. As a continuous variable, STR correlated inversely with final IS \(r = −0.53; P < 0.001\). As shown in Figure 2A, IS was smaller in complete STR group in comparison with intermediate, and no STR \(P < 0.001\) for either prehospital combination-fibrinolysis or facilitated PCI. There was also a significant association between STR and transmurality \(P < 0.001, Figure 2B\).

The relation between clinical parameters, pre-interventional TIMI-flow, and STR with IS as with...
transmurality was also assessed in three separate multivariable models (Tables 2 and 3). After adjustment for multiple variables, each 30 min delay in time-to-treatment resulted in 23, 18, or 24% (P < 0.05) higher risk of having IS >10% based on the model used. Similarly, each 30 min increase in time-to-treatment resulted in a 21–24% (P < 0.04) risk increase in transmurality. When adding STR to the model, incomplete STR (<70%) was the strongest predictor of IS >10% (OR 6.96; 95% CI 2.93–16.56; P < 0.001) or transmurality (OR 5.71; 95% CI 2.36–13.81).

**Enzymatic infarct size, left ventricular ejection fraction—infarct size and transmurality**

IS determined by MRI showed excellent correlation with enzymatic IS for the entire patient population, which was slightly better for the area under the curve in comparison with the CK max (Figure 3A and B). The type of reperfusion did not affect the correlation in enzymatic and MR IS. Slightly worse correlation could be found for transmurality and the CK area under the curve (r = 0.72, P < 0.001) and the CK max (r = 0.70, P < 0.001).

IS was also inversely correlated with the LVEF (r = −0.67, P < 0.001). A larger IS was associated with higher LV end-systolic (r = 0.59, P < 0.001) and end-diastolic volumes (r = 0.43, P < 0.001).

**Discussion**

In animal models, the association between ischaemia duration and extent of reperfusion with IS, transmurality, and no-reflow extent has been well characterized.9,10 To our best knowledge, this is the first prospective investigation of the correlation between time-to-treatment, pre-PCI TIMI-flow, and indirect markers of reperfusion such as STR with final IS and transmurality assessed by DE-MRI in humans, giving information on the pathology of infarct evolution over time and confirming the so-called ‘wavefront phenomenon’.

**Time-to-treatment—infarct size and transmurality**

Currently, data on IS and ischaemia duration in humans are restricted mainly to fibrinolytic trials and SPECT imaging without assessment of infarct transmurality.15–17 Interestingly, one study showed a time-dependent increase in IS for patients undergoing fibrinolysis, whereas in PCI patients there was no time-dependency.18 This result might be

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**Table 2** Multivariable predictors of infarct size >10% LV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.17 (0.79–1.75)</td>
<td>0.44</td>
<td>1.18 (0.78–1.77)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.54 (0.59–4.00)</td>
<td>0.38</td>
<td>1.56 (0.58–4.12)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.36 (0.60–3.09)</td>
<td>0.47</td>
<td>1.47 (0.63–4.33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.66 (0.30–1.47)</td>
<td>0.31</td>
<td>0.60 (0.26–1.35)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1.77 (0.72–4.22)</td>
<td>0.32</td>
<td>1.79 (0.71–4.24)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.52 (0.60–3.83)</td>
<td>0.38</td>
<td>1.54 (0.60–3.93)</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>2.25 (1.06–4.77)</td>
<td>0.03</td>
<td>2.25 (1.05–4.85)</td>
</tr>
<tr>
<td>Time-to-treatment (per 30 min)</td>
<td>1.23 (1.05–1.43)</td>
<td>0.01</td>
<td>1.18 (1.01–1.39)</td>
</tr>
<tr>
<td>Reperfusion strategy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilitated PCI</td>
<td>0.37 (0.18–0.80)</td>
<td>0.01</td>
<td>0.36 (0.16–0.77)</td>
</tr>
<tr>
<td>TIMI-flow pre-PCI &lt;2</td>
<td>–</td>
<td>–</td>
<td>2.84 (1.01–8.02)</td>
</tr>
<tr>
<td>ST-segment resolution (&lt;70%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention; OR, odds ratio; CI, confidence interval.
explained by the much longer time-to-treatment interval in comparison with the current trial. In addition, due to the low spatial resolution in SPECT, infarct transmurality was not assessed. In contrast, a recent MRI study has shown that ischaemia duration is a major determinant of transmurality and microvascular obstruction after PCI.19 However, IS was not assessed.19 Thus, the current trial combined the association between IS and transmurality with time-to-treatment using very early reperfusion strategies and an imaging method, which allows discrimination of transmural from subendocardial infarcts.20,21 In addition, this imaging method has excellent image quality with favourable reproducibility and intra- and interobserver variability.13 For each 30 min delay in time-to-treatment, the risk of developing IS is greater than 10% or high transmurality increased by 18–24% and 21–23%, respectively. Tarantini et al.19 observed a risk increase in transmurality by 37% using a different less-sensitive definition of transmurality (>75% in greater than or equal to two contiguous segments). Applying this definition to our patient cohort, 15% would have had transmural infarctions, which might be related to the much shorter time-to-treatment interval in our trial (116 vs. 190 min). In other words, the earlier the treatment, the smaller the IS and transmurality. Very early treatment leads to a higher rate of aborted myocardial infarctions, as previously shown.22 In the current trial, 10% of patients in the facilitated PCI and 4% of patients in the prehospital combination-fibrinolysis group had no scar in DE-MRI underlining this concept of aborted myocardial infarction. These mechanistic data on IS and transmurality are confirmed by clinical trials, since early treatment results in improved survival for patients undergoing fibrinolysis or PCI.2,3

TIMI-flow—infarct size and transmurality

Another key fact underlining the importance of early reperfusion is that the presence of blood flow in the infarct-related artery before PCI is associated with better outcome for patients undergoing primary PCI.23 In line with these clinical results, in the current analysis, IS and transmurality were significantly smaller in facilitated PCI patients with antegrade flow before PCI. Similar results, were recently found in a trial of primary PCI with abciximab were the median final IS measured by SPECT was 11% for patients with pre-PCI TIMI-flow >2 and 6% in TIMI-flow >1.24 However, infarct transmurality was not assessable. Therefore, from a pathophysiological point of view, our data further support the prognostic role of early reperfusion as a predictor of outcome.

ST-segment resolution—infarct size and transmurality

Irrespective of TIMI-flow in the epicardial infarct-related artery, STR has the advantage of measuring successful
reperfusion at the myocardial tissue level. In the current trial, the extent of STR correlated with final IS, as shown previously by SPECT imaging, but we also found a significant correlation with the extent of transmurality. Incomplete STR was the strongest predictor of IS and transmurality after adjustment for clinical variables in a multivariable model. Therefore, STR may serve as a simple marker of the extent of final IS achieved by reperfusion.

Enzymatic infarct size, left ventricular ejection fraction, volumes—inferior size and transmurality

The correlation of peak CK was similar to the relationship in previous acute and chronic infarction trials, and was better than that reported for SPECT. However, previous MR trials were limited by small sample size. Thus, the current study confirmed this relationship in a large patient population with early reperfusion. Another important aspect is that correlation between enzymatic and MR IS was even stronger for the area under the curve of CK-release. This underlines histologically confirmed results, which have shown that single peak CK or CK-MB measurements are not ideal for IS estimation. This is true for patients with or without reperfusion. As all patients underwent reperfusion at an early stage after the onset of symptoms, the time-course of CK-release might have been quite uniform, resulting in excellent relationship to peak CK and better still to the area under the curve. The relation of IS to LVEF and volumes were in line with previously published trials, but similarly with enzymatic IS results, these trials were limited by relatively small patient numbers.

Limitations

A limitation is that imaging was performed at 6 months that precludes assessment of microvascular obstruction, which has prognostic impact. In addition, microvascular obstruction might influence infarct shrinkage behaviour in a nonlinear fashion. However, infarct shrinkage over time decreases relatively to the same extent in small and large infarctions and due to the consistency of our transmurality decreases relatively to the same extent in small and large patients. This may explain why these clinical, angiographic, and electrocardiographic measures are associated with long-term survival.

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Conflict of interest: none declared.

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