Impact of microvascular integrity and local viability on left ventricular remodelling after reperfused acute myocardial infarction

P Garot, O Pascal, M Simon, J L Monin, E Teiger, J Garot, P Guéret, J L Dubois-Randé

Objective: To assess left ventricular remodelling in patients with reperfused acute myocardial infarction and to study its relation to microvascular damage.

Patients: 25 patients successfully treated by primary percutaneous coronary angioplasty for acute myocardial infarction.

Setting: University hospital

Methods: Indexed end diastolic (EDVi) and end systolic (ESVi) volumes were assessed on admission and repeated at days 1 and 8. Coronary flow reserve (CFR) was assessed in the infarct related artery on day 1. Myocardial blood volume was assessed on admission and at day 8 by myocardial contrast echocardiography. In patients who manifested persistent myocardial dysfunction at hospital discharge (n = 21), local inotropic reserve was assessed by dobutamine echocardiography at day 8.

Results: On admission, patients with and without local viability had similar EDVi and ESVi (EDVi 67 (9) and 73 (14) ml/m², respectively; ESVi 34 (8) and 40 (11) ml/m², respectively; NS). EDVi increased to 97 (22) ml/m² in patients without local viability (p < 0.01 vs admission) but remained unchanged at 70 (11) ml/m² in patients with viable myocardium (NS vs admission). For pooled patient data, the percentage change in EDVi correlated with CFR (r = 0.76, p < 0.0001) and myocardial blood volume in the infarct territory (r = 0.80, p < 0.0001).

Conclusion: Left ventricular dilatation may preferably occur in patients without local viability and is correlated with early CFR and extent of myocardial blood volume in the infarct territory.

Infarct size, location, and transmurality, as well as the patency of the infarct related artery and the presence of collateral flow, are involved in the process of left ventricular remodelling after acute myocardial infarction. Coronary reflow has beneficial effects in preventing left ventricular dysfunction and dilatation, thus improving the outcome in large populations of patients who have had an infarct. However, a substantial population of patients with reperfused acute myocardial infarction still manifests persistent left ventricular dysfunction along with significant dilatation, which worsens morbidity and mortality. Recently the concept has emerged that the ischaemia-reperfusion induced injury of the microvasculature may have an important role in left ventricular remodelling. As a consequence of reperfusion injury, the no reflow phenomenon may involve a combination of capillary obstruction and microvascular dysfunction responsible for prolonged ischaemia and myocardial cell death.

METHODS

Screened population

The screened population comprised 30 consecutive patients successfully treated (residual stenosis < 30%, TIMI (thrombolysis in myocardial infarction) grade 3 flow) by direct angioplasty < 8 hours after the onset of acute myocardial infarction. To be included, patients had to have a coronary occlusion deemed suitable for balloon angioplasty and stent placement, single vessel disease, and a large myocardial infarction on left ventricular cineangiograms assessed before angioplasty (that is, involving > 25% of myocardial segments). Patients with cardiogenic shock, prior myocardial infarction, and a history of diabetes mellitus or severe left ventricular hypertrophy were excluded. Informed consent was obtained for all patients.

Study protocol

Primary angioplasty was performed using standard techniques. The collateral flow to the infarct related artery was graded before angioplasty according to the usual angiographic classification. Stenting was systematically performed to optimise coronary blood flow. Left ventricular angiogram was systematically performed. After the angioplasty was completed, myocardial contrast echocardiography was performed in the catheterisation laboratory. Repeat left ventricular and coronary angiograms were performed in all patients on day 1 and a mean (SD) of 8 (2) days after the onset of symptoms.

Abbreviations: CFR, coronary flow reserve; CFRIRA, coronary flow reserve in the infarct related artery; EDVi, indexed end diastolic volume; ESVi, indexed end systolic volume; TIMI, thrombolysis in myocardial infarction.
In all patients, CFR and myocardial contrast echocardiography measurements were scheduled on day 1 and on day 8, respectively. Dobutamine echocardiography was performed 7 (1) days after myocardial infarction onset in patients in whom there was evidence of persistent myocardial wall dysfunction (n = 21). Assessment of left ventricular ejection fraction and volumes was available in 60% of the patients at a mean range of 4 (1.5) months after inclusion (5 of the 7 patients without local viability and 10 of the 15 patients with local viability).

**Left ventricular angiography**

Global and regional left ventricular wall motion were analysed off line by two independent operators blinded to patients’ data (CAAS II, Pie Medical, Maastricht, Netherlands). The average measurements were used for analysis. Indexed end diastolic (EDVi) and end systolic (ESVi) volumes and left ventricular ejection fraction were calculated according to the area–length method. To assess the impact of microvascular integrity on left ventricular remodelling, we defined a 25% variation of EDVi at discharge relative to the baseline value as a cut off value for presence or absence of left ventricular remodelling. Segmental wall motion was calculated by a modification of the centreline method. The regional wall motion score was calculated as the average wall motion score in SD/chord from normal values in a control population in the same segment. One hundred equidistant chords were drawn perpendicular to the centreline, and the left ventricular contour was divided in 20 segments whose motion was calculated by averaging the motion of consecutive sets of five chords. We defined a 20% variation of regional wall motion score at discharge relative to baseline value as a cut off for the presence or absence of segmental contractile recovery. The mean interobserver variability of measurements of ejection fraction, ventricular volumes, and regional wall motion score was < 5%.

**Myocardial viability**

In the absence of subsequent segmental myocardial contraction, dobutamine echocardiography was used to assess local viability in the infarct territory. The presence of inotropic reserve was defined as an improvement of myocardial thickening in ≥ 2 adjacent segments located in the infarct area and a > 20% decrease in wall motion score index during dobutamine infusion. Dobutamine echocardiography was performed on a Sequoia (Acuson, Mountain View, California, USA) equipped with harmonic technology (2–3.5 MHz) using a standardised, previously described technique.

**Coronary flow reserve**

CFR was measured (in duplicate with < 15% variations) using a 0.014 inch Doppler guidewire (FloWire, Jomed, Helsingborg, Sweden), and coronary hyperaemia was induced with the intracoronary injection of adenosine. The CFR was first measured in the reference vessel followed by the CFRISA after the tip of the guide wire was placed at least 2 cm distal to the site of the occlusion. Relative CFR was computed as the ratio of CFRISA to the CFR of the reference vessel.

**Myocardial contrast echocardiography**

Myocardial contrast echocardiography was performed by repeating an intracoronary bolus of 3 ml sonicated ioxaglate (Hexabrix-360, Guerbet, Villepinte, France) on the Sequoia. Gain settings were kept constant throughout the procedure. Two apical echocardiographic views were stored on optical disks for subsequent analysis. Echocardiographic images with the best delineation between contrast enhanced and non-enhanced myocardium were selected to determine the risk area, defined as the area showing no contrast enhancement before coronary reopening. The extent of the no reflow area (percentage of left ventricular surface area) was defined as the ratio of the area with residual contrast defect after coronary opening to the total area of the left ventricular myocardium. Quantitative videodensitometric analysis (NIH Image, National Institutes of Health, Bethesda, Maryland, USA) was performed for the assessment of contrast intensity in the entire risk area. The peak intensity ratio was determined as the ratio of contrast peak intensity in the risk area to the baseline contrast intensity in the remote wall. In accordance with previous reports, the interobserver variability for the magnitude of echocardiographic measurements was 7.2% for the peak intensity ratio and 6.4% for areas of residual contrast defect.

**Statistical analysis**

Data are presented as mean (SD). Two way analysis of variance with repeated measures were used to assess differences in continuous variables between patients with and those without local viability, as well as between patients with and those without left ventricular remodelling. Paired and unpaired Student’s t tests were used when appropriate. Logarithmic regression analysis was used to analyse the relation between left ventricular remodelling at follow up and both CFR and myocardial blood volume.

**RESULTS**

**Study population**

Of the 30 initial subjects, 25 patients satisfied the study criteria. All patients were successfully treated (residual stenosis < 30%, TIMI 3 flow) by primary angioplasty < 8 hours after the onset of symptoms. All of them received angiotensin converting enzyme inhibitors early. Five patients could not be included because myocardial dysfunction involved < 25/100 chords (n = 2) and because of prior myocardial infarction (n = 1), diabetes mellitus (n = 1), and cardiogenic shock (n = 1).

![Table 1](image)
Among the 25 patients enrolled in the study, 18 had local viability. Segmental left ventricular function recovered almost fully in four of them. Fourteen had significant inotropic reserve. When the study population was broken down according to presence (n = 18) or absence (n = 7) of local viability, there were no differences between the two groups with regard to infarct territory, peak creatine kinase concentration, and troponin I concentration, nor in mean time elapsed from pain onset to achievement of TIMI 3 (table 1). On dobutamine echocardiography, the wall motion score was improved during dobutamine infusion in 4.2 (2.8) segments in patients with inotropic reserve and in 1.2 (1.8) segments in those without inotropic reserve (p = 0.02).

**Figure 1** Serial changes in indexed end diastolic (EDVi) and end systolic (ESVi) volumes are depicted for patients with [open bars] and without [solid bars] local viability. EDVi and ESVi increased relative to baseline at day 8 and at four months' follow up among patients without local viability. Both remained unchanged among patients with viable myocardium.

**Figure 2** Relation between changes in EDVi assessed at day 8 and (1) coronary flow reserve in the infarct related artery (CFR IRA) assessed at day 1 (top) and (2) myocardial blood volume assessed by myocardial contrast echocardiography at day 8 (bottom). The early determination of CFR IRA was highly correlated with the degree of left ventricular dilatation at the day 8 follow up, as was myocardial blood volume assessed in the infarct territory.

**Myocardial viability**

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**Relation between left ventricular remodelling, myocardial blood volume, and microvascular function**

Although EDVi and ESVi were similar between patients with and those without local viability on admission (fig 1), substantial myocardial dilatation was observed at day 8 among patients without local viability (p < 0.01 v patients with local viability for both EDVi and ESVi). At four months' follow up, EDVi was still higher among patients without local viability (p < 0.01 v patients with local viability).

Left ventricular remodelling was observed at day 8 in all patients without inotropic reserve and in one patient with viable myocardial wall dysfunction. The region at risk was similar in patients with and those without left ventricular remodelling, as were the mean time elapsed from pain onset to achievement of TIMI 3 in the infarct related artery and the mean ejection fraction on admission (table 2). In contrast, CFR at day 1 and peak intensity ratio at day 8 were severely depressed in patients with left ventricular remodelling relative to those with no change in EDVi at the day 8 follow up.

**Table 2** Characteristics of patients with and without early left ventricular remodelling

<table>
<thead>
<tr>
<th></th>
<th>Remodelling absent (n=17)</th>
<th>Remodelling present (n=8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 (12)</td>
<td>61 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Men</td>
<td>16</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior AMI</td>
<td>8</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Time to TIMI 3 (minutes)</td>
<td>256 (109)</td>
<td>267 (104)</td>
<td>NS</td>
</tr>
<tr>
<td>Region at risk</td>
<td>34.5 (10.6)</td>
<td>35.9 (10.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 1 CFR</td>
<td>2.4 (0.6)</td>
<td>1.4 (0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 1 relative CFR</td>
<td>0.9 (0.2)</td>
<td>0.7 (0.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 8 peak intensity ratio</td>
<td>3.0 (0.9)</td>
<td>1.3 (0.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 8 residual contrast defect ratio</td>
<td>5.4 (2.2)</td>
<td>20.2 (7.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Day 8 EF (%)</td>
<td>49 (8)</td>
<td>46 (8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are numbers or mean (SD). Region at risk and residual contrast defect ratio are expressed as percentages of left ventricular area. CFR, coronary flow reserve.
patients with local viability at hospital discharge (51 (9)
the left ventricular ejection fraction was statistically higher in
sacrificed among patients without local viability than
graphy (intensity ratio as assessed by myocardial contrast echocardi-
Interestingly, the change in EDVi at four months and both
ESVi at four months among patients with local viability was
relative to day 8 in both groups, suggesting that a decrease in
mean EDVi remained unchanged at four months' follow up
(5)% in patients without local viability). Our data show that

colleagues
myocardial infarction onset. More recently, Gerber and
frequent left ventricular dilatation at a mean of 25 days after
microvascular damage, independently of infarct size and left
ventricular ejection fraction. Additionally, our results indicate
that the extent of ischaemia-reperfusion induced microvascu-
lar damage assessed within the first days after reperfused
acute myocardial infarction may be able to predict left
ventricular remodelling at later follow up (four months).

Ischaemia-reperfusion induced microvascular damage
and left ventricular remodelling
Since a combination of microvascular obstruction (down-
stream microemobolism of platelets, de novo thrombosis, and
neutrophil capillary plugging) and stunning (endothelial dys-
function) is involved in the no reflow phenomenon,11111 we
sought to study the integrity of the microvasculature charac-
terised by both the extent of microvascular obstruction on
myocardial contrast echocardiography (capillary blood vol-
ume) and its functional response to hyperaemia (capillary
vasodilatation and recruitment). Recent studies have reported
that microvascular obstruction is a dynamic process that
gradually increases over the first days after coronary reflow.
However, microvascular damage may also regress within the
first days after acute myocardial infarction with subsequent
recovery of myocardial function. Additionally, our results indicate
that microvascular obstruction is a dynamic process that
gradually increases over the first days after coronary reflow.

The present study supports and extends the conclusions of
previous reports concerning the relation that exists between
cardiac infarction and microvascular damage induced by
ischaemia-reperfusion injury.1722 Ito and colleagues’ showed
that the presence of no-reflow was associated with more
frequent left ventricular dilatation at a mean of 25 days after
myocardial infarction onset. More recently, Gerber and
colleagues’ emphasised the role of microvascular obstruction
in increased postinfarct left ventricular remodelling through
decreased systolic myocardial deformation in regions of
microvessel damage. As opposed to thrombolysis, which was
shown to attenuate left ventricular remodelling, the direct
effects of primary angioplasty of an acutely occluded infarct
related artery on left ventricular dilatation remain uncertain
in humans.23 Our data clearly indicate that early left ventricu-
lar remodelling may preferably occur in patients with major
microvascular damage, independently of infarct size and left
ventricular ejection fraction. Additionally, our results indicate
that the extent of ischaemia-reperfusion induced microvascu-
lar damage assessed within the first days after reperfused
acute myocardial infarction may be able to predict left
ventricular remodelling at later follow up (four months).

DISCUSSION
The present study supports and extends the conclusions of
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myocardial infarction and microvascular damage induced by
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frequent left ventricular dilatation at a mean of 25 days after
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associated with subsequent left ventricular dilatation. Indeed, the presence of tissue viability in the infarct area may have beneficial effects in preventing left ventricular dilatation independently on infarct size and myocardial function. This may be related to preserved mechanical properties in viable and dysfunctional tissue as opposed to scar myocardium, as recently mentioned. The present data suggest that the preservation of microvascular function early after reperfused acute myocardial infarction is associated with the complete benefit of myocardial reperfusion at the muscle level (that is, myocardial blood volume, myocardial salvage, and limitation of remodelling) and finally with the presence of viable myocardium despite wall dysfunction at rest (myocardial stunning).

Study limitations
CFR was determined through the use of an intracoronary Doppler guidewire and therefore cannot be used routinely. Other promising approaches such as magnetic resonance imaging, positron emission tomography, and transethoracic Doppler echocardiography have the potential for the non-invasive assessment of CFR. CFR depends on factors other than microvasculature integrity, such as haemodynamics and residual stenosis. There was no difference in residual stenosis, heart rate, and systolic blood pressure between the groups at initial angiography and during follow up, and the use of relative CFR helped to control for individual variations in haemodynamics. Because of the relatively small population of patients included in the present study, the territory of myocardial infarction, one of the main factors involved in the phenomenon of left ventricular remodelling, could not be characterised as an independent predictor of ventricular remodelling.

Conclusion
Subsequent left ventricular dilatation is associated with impaired microvasculature during the early convalescent period after reperfused acute myocardial infarction. The presence of altered microvascular function is therefore associated with altered perfusion at the tissue level at follow up and with non-viable myocardium. The present study helps clarify the relation between microvascular integrity and left ventricular remodelling after reperfused acute myocardial infarction and may therefore have important clinical implications.

References
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