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 5–7.

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 v admission) but remained unchanged at 70 (11) ml/m² in patients with viable myocardium (NS v 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.

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 angiograms were performed in all patients on day 1 and a mean (SD) of 8 (2) days after the onset of symptoms.
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 offline by two independent observers 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 20% variation of EDVI at discharge relative to the baseline value as a cut off value for presence or absence of left ventricular remodelling.14 Segmental wall motion was calculated by a modification of the centreline method.14 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.15 One hundred equidistant chords were drawn perpendicular to the centreline, and the left ventricular contour was divided in to 20 segments whose motion was calculated by averaging the motion of consecutive sets of five chords.16 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.17 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 ischemic 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.18 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.19

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 CFRnasa after the tip of the guide wire was placed at least 2 cm distal to the site of the occlusion.20 Relative CFR was computed as the ratio of CFRnasa 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,20 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 Clinical and angiographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Viability present (n=18)</th>
<th>Viability absent (n=7)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Anterior AMI</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Admission SBP (mm Hg)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Admission HR (beats/min)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Collateral (Rentrop 2 and 3)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Time to TIMI 3 (minutes)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Residual stenosis (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Admission EF (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are numbers or mean (SD). AMI, acute myocardial infarction; EF, ejection fraction; HR, heart rate; LDL, low density lipoprotein; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.
Myocardial viability

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).

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

<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 (10.0)</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.
The left ventricular ejection fraction was statistically higher in those with local viability (p < 0.001 for both, fig 1). Significantly higher among patients without local viability than...graphy (CFRIRA and peak intensity ratio remained highly correlated relative to day 8 in both groups, suggesting that a decrease in...ischaemia-reperfusion injury. 

DISCUSSION

For pooled patient data, the change in EDVi at day 8 was correlated with CFR<sub>max</sub> (r = 0.76, p < 0.0001) (fig 2) and peak intensity ratio as assessed by myocardial contrast echocardiography (r = 0.80, p < 0.0001) (fig 3).

At four months’ follow up, EDVi and ESVi remained significantly higher among patients without local viability than among those with local viability (p < 0.001 for both, fig 1). The left ventricular ejection fraction was statistically higher in patients with local viability at hospital discharge (51 (9) vs 42 (5)% in patients without local viability). Our data show that mean EDVi remained unchanged at four months’ follow up relative to day 8 in both groups, suggesting that a decrease in ESVi at four months among patients with local viability was primarily responsible for the differences in ejection fraction. Interestingly, the change in EDVi at four months and both CFR<sub>max</sub> and peak intensity ratio remained highly correlated indicating that the extent of microvascular damage measured during the early convalescent period after reperfused acute myocardial infarction may be able to predict left ventricular remodelling at later follow up.

Ischaemia-reperfusion induced microvascular damage and left ventricular remodelling

Since a combination of microvascular obstruction (downstream microembolism of platelets, de novo thrombosis, and neutrophil capillary plugging) and stunning (endothelial dysfunction) is involved in the no reflow phenomenon, we sought to study the integrity of the microvasculature characterised by both the extent of microvascular obstruction on myocardial contrast echocardiography (capillary blood volume) 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. Since microvascular obstruction is thought to vary during the first days after coronary reflow, the accuracy of the exclusive analysis of myocardial blood volume early after reperfused acute myocardial infarction for differentiation between patients with and those without microvascular damage at follow up remains questionable on an individual basis.

Recently, our group reported that subsequent improvement of myocardial perfusion was preceded by the recovery of recruitable microvascular function in the infarct related artery and was associated with local tissue viability after reperfused acute myocardial infarction. Our data indicate that a clear relation exists between the extent of early and late left ventricular dilatation and both microvascular function assessed on day 1 and myocardial blood volume as measured on day 8. Accordingly, the relation between myocardial perfusion at the tissue level and left ventricular remodelling provides mechanistic insights relevant to cardiac remodelling following direct angioplasty. The relation between ventricular remodelling and coronary reperfusion has so far been reported especially after thrombolysis. The present data may therefore have important clinical implications, since they suggest that the early determination (from day 1) of the CFR in the infarct related artery may therefore be useful to predict individually early and left ventricular dilatation after reperfused acute myocardial infarction.

The beneficial effects of myocardial reperfusion on left ventricular remodelling may be partly independent of its direct effect on infarct size reduction. This concept is known as the “open artery hypothesis”. Although the restoration of adequate reflow in the epicardial coronary artery is not constantly associated with prompt reperfusion at the tissue level, it is unknown whether the benefits of reperfusion on left ventricular remodelling result from reduced injury to the microvasculature. However, preliminary clinical observations suggest that patients in whom reperfusion failed or was not attempted have more severe microvascular injury and worse left ventricular remodelling. Our data show that the persistence of myocardial wall dysfunction in the first days after reperfused acute myocardial infarction may be variably...
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 transthoracic 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.

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