Myocardial viability, coronary flow reserve, and in-hospital predictors of late recovery of contractility following successful primary stenting for acute myocardial infarction

F Beygui, C Le Feuvre, G Helft, C Maunoury, J P Metzger

Objective: To assess the relation between myocardial viability, coronary flow reserve, and recovery of myocardial contractility after stenting for acute myocardial infarction.

Design: Consecutive sample prospective study.

Setting: University hospital.

Patients: 41 patients with single vessel disease and successful primary stenting for a first acute myocardial infarction.

Interventions: 201Tl single photon emission computed tomography, contrast ventriculography, and intracoronary Doppler performed 7 (1) days after primary stenting.

Main outcome measures: Regional contractility recovery assessed by contrast ventriculography at 6 (1) months' follow up.

Results: On univariate analysis, contractility recovery was correlated to prereperfusion anterograde and collateral flow grades \(r = 0.41, p = 0.03\) and \(r = 0.55, p = 0.0004\), viability index \(r = 0.55, p = 0.04\), peak creatine kinase concentrations \(r = -0.55, p = 0.0005\), left ventricular ejection fraction \(r = 0.45, p = 0.005\), end diastolic pressure \(r = -0.62, p < 0.0001\), and systolic volume index \(r = -0.47, p = 0.01\), and the extent of hypokinetic area \(r = -0.48, p = 0.003\), but not the coronary flow reserve. On multivariate analysis, independent predictors of late contractility recovery were prereperfusion anterograde and collateral flow grades and viability index. Relative coronary flow reserve, reflecting the culprit vessel's microvascular function, was correlated only to the extent of the infarct risk area \(r = -0.45, p = 0.003\).

Conclusions: Independent predictors of contractility recovery between the seventh day and the sixth month after successful stenting for acute myocardial infarction are prereperfusion anterograde and collateral flows and myocardial viability. The culprit vessel’s microvascular dysfunction is independent of myocardial viability and contractility and correlated to the extent of “jeopardised microvasculature”.

Percutaneous transluminal coronary angioplasty with systematic stenting is considered to be the ideal primary treatment after acute myocardial infarction (AMI). This confers the advantages of conventional balloon angioplasty, compared with thrombolytic treatment, in terms of coronary flow restoration, major ischaemic events, and death, with lower restenosis rates. However, clinical outcome and recovery of myocardial contractility after successful reperfusion are influenced by the extent of microvascular damage and the persistence of viable myocardium. While the relation between microvascular obstruction following coronary reperfusion (assessed by the incomplete regression of ST segment elevation or myocardial contrast echocardiography), myocardial viability, and contractility is established, the relation between the persistent reduction of coronary artery flow reserve (CFR) and myocardial viability or contractility remains controversial.

The purpose of this study was to analyse the relation between CFR and myocardial viability, assessed 7 (1) days after successful primary stenting for AMI by intracoronary Doppler and 201Tl single photon emission computed tomography (SPECT), and their impact on the late recovery of myocardial contractility.

METHODS
Study population and protocol
The study group consisted of 41 patients successfully treated by primary angioplasty followed by systematic stenting of the proximal portion of a coronary artery for their first anterior or inferior AMI within six hours after onset of the symptom.

The diagnosis of AMI was based on chest pain lasting > 30 minutes and ST segment elevation of > 0.2 mV in at least two contiguous ECG leads. Patients with cardiogenic shock, isolated lateral wall infarction, left main or multivessel disease, unidentified or diffusely diseased infarct related artery, distal coronary occlusion, and complicated in-hospital course were not included. All patients had a 12 lead ECG before the procedure and 30 minutes after restoration of TIMI (thrombolysis in myocardial infarction) grade 3 flow. The ST segment was measured in the lead showing maximal elevation before and after reperfusion. ST segment elevation regression was calculated and expressed as a percentage of the initial elevation.

Predischarge (7 (1) days after reperfusion) 201Tl SPECT followed within 24 hours by coronary and left ventricular angiography was performed in all patients. Both tests were also scheduled for the six month follow up. Intracoronary Doppler assessment of CFR was performed during the predischARGE catheterisation (8 (1) days after reperfusion).

Abbreviations: AMI, acute myocardial infarction; CFR, coronary flow reserve; SPECT, single photon emission computed tomography; TIMI, thrombolysis in myocardial infarction
Angiography and stenting procedure

Before the procedure, all patients received heparin (100 IU/kg) and aspirin (300 mg) intravenously. Coronary angiography was performed according to the Judkins technique after intracoronary injection of 1 mg of lidocaine chloride. Anterograde and collateral coronary flows were graded according to the TIMI and Rentrop classifications. Balloon angioplasty followed by systematic stenting was performed with standard techniques. After the stenting all patients received ticlopidine (500 mg/day) and aspirin (100 mg/day) for 30 days followed by aspirin alone indefinitely. Intravenous heparin infusion was continued ≥72 hours after the procedure (activated partial thromboplastin time 60–80 seconds).

Coronary dimensions were measured on line by the CAAS system (Pie Medical Systems, Maastricht, Netherlands). Left ventricular ejection fraction was quantified off line in the 30° right anterior oblique projection by one observer blinded to all other data. Regional left ventricular systolic shortening was assessed in 20 segments based on the left ventricular systolic shortening when they were <2 SD below the mean of corresponding segments of a reference population (30 patients with chest pain and normal coronary arteries).

Based on the definition of stunned myocardium, a recovery index was defined by the following equation:

\[
\text{n hypokinetic segments at pre-discharge} \times \frac{\text{n hypokinetic segments at follow up}}{\text{n hypokinetic segments at pre-discharge}}
\]

**20TI SPECT**

SPECT was performed using a pharmacological stress–reinjection protocol. A 4.5 MBq × body mass index dose of 20TI was injected 2 minutes after intravenous infusion of dipyridamole and a 1.5 MBq × body mass index dose 4 hours later. Images were acquired 5–10 minutes after 20TI injection by an APEX SPX-4 HR (Elscint, Haifa, Israel) gamma camera. Segments were considered to be hypokinetic when they were <2 SD below the mean of corresponding segments of a reference population (30 patients with chest pain and normal coronary arteries).

Intracoronary flow measurements

Intracoronary flow was measured with a 0.014 inch Doppler tipped flow wire (12 MHz, FloWire, Cardiometrics Inc, Mountain view, California, USA) in the culprit vessel, with the tip at the distal extremity of the stent, and in a normal remote artery. Time averaged peak velocities were measured at baseline and after intracoronary administration of adenosine (12–18 μg). Absolute CFR was calculated as the ratio of baseline to hyperaemic averaged peak velocity. Relative CFR was defined as the ratio of the number of viable segments within the infarct risk area to the size of the risk area.

Statistical analysis

Continuous variables are presented as mean (SD) and analysed by a one way analysis of variance between the patient groups or a simple regression model. A multivariate analysis was performed using a multiple regression model including all univariate parameters with a value of p < 0.05. A χ² test was used to analyse qualitative variables. A p value < 0.05 was considered significant.

RESULTS

Patient population and procedural outcome

Forty one patients fulfilled the inclusion criteria and were included in the study. Clinical follow up was completed in all patients. Follow up SPECT and angiography were performed in 37 (90%) patients 6 (1) months after the myocardial infarction. Four asymptomatic patients refused the follow up tests. At follow up no death, myocardial infarction, or unstable angina had occurred. Exertion angina occurred in seven patients (17.1%), related in all to restenosis, and were treated by balloon angioplasty. Four asymptomatic patients with evidence of ischaemia at the follow up SPECT underwent angioplasty, for restenosis in one and for progression of the lesions in three. Rates of target lesion revascularisation and total revascularisation were 19.5% (8 patients) and 26.8% (11 patients), respectively.

On the basis of the median recovery index (50%) the study population was divided into two groups, with or without contractility recovery. Table 1 reports the baseline characteristics of the two patient groups.

Intracoronary Doppler measurements

Hyeraemic averaged peak velocity and CFR were higher in the remote artery than in the infarct related artery (table 2). There was a strong correlation between the CFR measured in the culprit vessel and CFR in the remote artery (\(r = 0.76\), \(p = 0.001\)).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recovery index ≥50%</th>
<th>Recovery index &lt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 (7)</td>
<td>57 (11)</td>
</tr>
<tr>
<td>Male sex</td>
<td>17 (77%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>10 (45%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>3 (14%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (9%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>14 (64%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Infarct location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>7 (32%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>15 (68%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Symptom to reperfusion time (min)</td>
<td>223 (97)</td>
<td>201 (99)</td>
</tr>
<tr>
<td>ST segment elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mm)</td>
<td>3.2 (1.3)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>After stenting (mm)</td>
<td>0.8 (1)</td>
<td>1.5 (1.6)</td>
</tr>
<tr>
<td>Regression (%)</td>
<td>73 (29)</td>
<td>66 (31)</td>
</tr>
<tr>
<td>Peak creatine kinase (IU/l)</td>
<td>1733 (1631)</td>
<td>3538 (2420)*</td>
</tr>
</tbody>
</table>

Data are mean (SD). *p=0.01.
In-hospital factors correlated to the CFR of the culprit vessel were age \((r = -0.4, p = 0.01)\), residual ST segment elevation and its decrease after stenting \((r = -0.53, p = 0.0004\) and \(r = 0.51, p = 0.0008)\), heart rate \((r = -0.39, p = 0.01)\), left ventricular end diastolic pressure \((r = -0.39, p = 0.02)\) and volume index \((r = -0.32, p = 0.04)\), number of hypokinesic segments \((r = -0.51, p = 0.0006)\), viability index \((r = 0.49, p = 0.001)\), and infarct risk area \((r = -0.58, p = 0.0001)\). On multivariate analysis only left ventricular end diastolic volume index \((p = 0.008)\) and infarct risk area \((p = 0.02)\) were correlated to the CFR in the culprit vessel.

Relative CFR was correlated to the extent of infarct risk area \((r = -0.45, p = 0.003)\).

**Recovery index**

Recovery index was 95 (12)% in patients with and without cardiogenic shock and 96 (12)% in patients with and without cardiogenic shock, respectively). Relative CFR is correlated to the extent of the infarct risk area but neither to myocardial viability nor to contractility recovery. Absolute CFR are correlated to the myocardial viability but not to the late recovery of contractility. Relative CFR is correlated to the extent of the infarct risk area but neither to myocardial viability nor to contractility recovery.

DISCUSSION

The present study shows that the improvement of myocardial contractility between the seventh day and the sixth month after primary stenting for AMI is independently correlated to the quality of the residual anterograde and collateral blood flow before reperfusion and to myocardial viability. Postreperfusion regression of ST segment elevation and predischarge absolute CFR are correlated to the myocardial viability but not to the late recovery of contractility. Relative CFR is correlated to the extent of the infarct risk area but neither to myocardial viability nor to contractility recovery.

To our knowledge, this is the first study of the relation between acute phase and predischarge predictors of myocardial viability and contractility, CFR, and the late improvement of myocardial contractility.

By design, this study included patients at low risk compared with previous studies,1,4 The rates of angiographic restenosis and target lesion revascularisation were nevertheless comparable with those previously reported.
Myocardial viability, infarct size, and contractility recovery

The relation between $^{20}$ $^{21}$ Tl SPECT assessed myocardial viability and the recovery of late contractility supported in our study has been widely established, as well as the benefit of primary angioplasty in terms of infarct size reduction and contractility improvement $^{20}$ $^{21}$.

The distinction between myocardial viability and infarct size is artificial, as they represent two views—half empty or half full glass—of the same concept. Nevertheless, the infarct size is indirectly correlated to the recovery of contractility through its complementarity with myocardial viability. Moreover, there is a complex relation between viability and contractility with a spectrum of contractile dysfunction related not only to the balance between necrosis and viability but also to the extent of metabolic damage in viable myocytes. This explains the recovery of contractility in some but not all of the regions with preserved metabolic viability. $^{21}$ Consequently, on multivariate analysis, the recovery index is independently correlated to the myocardial viability but not to the infarct size.

In the present study, among multiple factors reflecting the extent of the infarction, in-hospital left ventricular end diastolic pressure was most strongly correlated to the recovery index on univariate analysis. Left ventricular end diastolic pressure may be the expression of the balance between viability and necrosis, reflecting not only the systolic function but also the diastolic function. Hence, low left ventricular end diastolic pressure may be used as a predictor of reversible contractile dysfunction.

Prestenting collateral and anterograde flow and late contractility

Sabia and colleagues $^{22}$ reported an association between collateral blood flow detected by myocardial contrast echocardiography, but not angiography, and contractility recovery after angioplasty of totally occluded vessels for recent (48 hours to 5 weeks) myocardial infarction. The authors blame the inability to visualise vessels smaller than 100 µm on the low resolution of angiography. In our study collateral blood flow was assessed after systematic intracoronary injection of vasodilators, which may have improved visibility. Furthermore, collateral blood flow functional during the first six hours after a myocardial infarction may disappear during the following days as the microvascular obstruction extends. $^{23}$ $^{24}$ Other studies underline the importance of preangioplasty residual anterograde or collateral flow as predictors of in-hospital infarct size after myocardial infarction. $^{25}$ $^{26}$ Our study shows a direct and independent correlation between prereperfusion collateral and anterograde blood flows and late contractility recovery. These findings indirectly support the potential benefit of primary stenting facilitated by previous antithrombotic treatment, reported to improve the prereperfusion TIMI grade. $^{27}$

Microvascular dysfunction and recovery of contractility

CFR after coronary occlusion has been studied in animal models and a few human studies. Apparently controversial results concerning the relation between CFR and contractility have been reported.

In vitro studies first showed evidence of microvascular dysfunction following prolonged or short ischaemia. $^{27}$ $^{28}$ Bolli and colleagues $^{29}$ reported a prolonged impairment of CFR after a 15 minute coronary occlusion in dogs, introducing the concept of microvascular stunning. In their study, the microvascular dysfunction appeared to be independent of wall thickening. A persistent limitation of CFR has also been reported after coronary revascularisation in the absence of infarction. $^{30}$ $^{31}$ Persistence of impaired CFR of the infarct related artery after primary angioplasty, compared with a non-infarct population, has been reported to last as long as six months after the myocardial infarction, with no evidence of a correlation between CFR and wall motion in 14 patients. $^{2}$ On the contrary, another study using angiographic measurements of CFR immediately after intracoronary thrombolysis followed by balloon angioplasty reported a significant correlation between postangioplasty and predischarge CFR and in-hospital wall motion improvement in 22 patients. $^{32}$ Improved CFR 24 hours after primary angioplasty for AMI has also been reported to be correlated to myocardial contrast echocardiography score 24 hours, and echocardiographic wall motion index four weeks, after an AMI in 25 patients. $^{33}$

Being based on parameters measured during the first 24 hours after myocardial infarction, the previous studies assessed the combined effect of the microvascular obstruction and the vasodilator reserve limitation. During these first 24 hours, microvascular obstruction, reflected by the incomplete regression of ST segment elevation or myocardial contrast echocardiography, leads to necrosis, absence of contractility recovery, and poor clinical outcome. $^{3}$ $^{4}$ The higher vascular resistance and the modifications of baseline flow velocity patterns reported immediately after reperfusion reflect also the microvascular obstruction. $^{35}$ $^{36}$

To assess microvascular dysfunction without the effects of microvascular obstruction, which has been reported to increase in the first 48 hours after reperfusion, $^{26}$ we measured CFR 7 (1) days after reperfusion in patients with angiographically normalised coronary arteries and treated for > 72 hours by intravenous heparin. In such patients, without coronary stenosis, the CFR reflects the microvascular function.

Several factors such as age, heart rate, and haemodynamic factors $^{36}$ $^{37}$ modify both infarct related and remote artery vasodilator reserves in a common direction. Moreover, a reduction of both infarct related artery and normal remote arteries has been reported one week after AMI as a response to systemic and local neurohormonal constrictor stimuli. $^{38}$ Postreperfusion microvascular dysfunction in the culprit vessel is more specifically assessed by the relative CFR, excluding the effects of parameters that globally modify CFR in all coronary arteries, than by the absolute CFR. In our study relative CFR was correlated only to the extent of the infarct risk area. This finding supports the concept of a microvascular dysfunction correlated to the extent of “jeopardised microvascular” but independent of infarct size or myocardial viability. The more important amount of resistance vessels in arteries with extended vascular territories may explain the more severe limitation of the vasodilator reserve in response to the neurohormonal constrictor stimuli in such arteries than in territories with less extended territories. $^{39}$ This results in higher hyperaemic resistance and consequently lower relative CFR in arteries with extended territories than in those with small territories.

The comparable baseline averaged peak velocities in the infarct related and the remote arteries are suggestive of a sufficient baseline flow in the culprit vessel, allowing for recovery of rest contractility despite a decreased vasodilator reserve. Nevertheless, a limitation of inotropic contractile reserve, not assessed by our study, could not be excluded.

Limitations of the study

Although our study was larger than previous studies, it is still limited by the number of patients included and the selective inclusion criteria. Our results cannot be extended to all cases of reperfused myocardial infarction.

To assess late recovery of contractility we used an index that reflects the amount of stunned myocardium regardless of the extent of the infarction. Although the clinical relevance of such an index in a given patient should be viewed with caution, it is an independent and quantitative tool for the assessment of stunned myocardium. The strong correlation between the recovery index and the follow-up left ventricular ejection fraction underlines its reliability.
Conclusions
Our results show that microvascular dysfunction persists in the infarct related artery seven days after successful stenting for AMI. This microvascular dysfunction is independent of myocardial viability or rest contractility but correlated to the extent of the infarct risk area. Independent predictors of improvement in contractility between the seventh day and the sixth month after primary stenting for AMI are persistence of viable myocardium on predischarge SPECT and preserved prereperfusion anterograde and collateral blood flows, supporting the benefit of primary stenting facilitated by preprocedure antithrombotic treatment.

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REFERENCES
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