Persistence of systolic coronary flow reversal predicts irreversible dysfunction after reperfused anterior myocardial infarction

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Objective: To investigate serial assessments of systolic coronary flow reversal in the infarct related artery for predicting poor left ventricular functional recovery after reperfused acute myocardial infarction.

Setting: Regional hospital.

Patients and methods: 49 patients with anterior acute myocardial infarction had transthoracic Doppler echocardiography to record coronary flow velocity in the left anterior descending coronary artery immediately after successful primary coronary angioplasty (day 0), and at 48 hours, one week, and three weeks.

Main outcome measures: Coronary flow velocity at each time point; regional wall motion score index (RWMSI) at day 0 and at three weeks. Irreversible dysfunction was defined as a decrease in RWMSI to < 0.22.

Results: Measurements of coronary flow velocity could be made in 45 patients. Patients were divided into three groups: no systolic flow reversal (group 1, n = 27), systolic flow reversal observed only on day 0 (group 2, n = 8), and systolic flow reversal persisting until 48 hours (group 3, n = 10). Although baseline RWMSI was similar among the three groups, the value at three weeks was significantly higher in group 3 than in the other two groups. In predicting irreversible dysfunction, the persistence of systolic flow reversal up to 48 hours had a higher positive predictive value (100%) than the presence of systolic flow reversal on day 0 (67%, p < 0.04). The negative predictive value of systolic flow reversal at 48 hours (83%) was comparable in accuracy to the presence of systolic flow reversal on day 0 (85%, NS).

Conclusions: In reperfused anterior acute myocardial infarction, serial assessment of coronary flow velocity in the left anterior descending coronary artery is feasible using transthoracic Doppler echocardiography, and the persistence of systolic flow reversal at 48 hours is a more specific marker of irreversible dysfunction than peak creatine kinase or diastolic deceleration time.

Primary coronary angioplasty is an effective method for improving prognosis in patients with acute myocardial infarction. However, successful angioplasty does not always guarantee adequate tissue perfusion of the myocardium distal to the previously occluded vessel. Some patients develop the no reflow phenomenon, which is associated with sustained left ventricular dysfunction, left ventricular remodelling, and subsequent poor outcome. The characteristic coronary flow velocity profile of systolic flow reversal is observed immediately after reperfusion has been achieved in patients with the no reflow phenomenon and is associated with poor functional recovery. Although early prediction of the recovery of left ventricular dysfunction is important for identifying high risk patients and selecting the appropriate therapeutic strategy, many confounding factors—including coronary hyperaemia, reperfusion injury, and microvascular stunning—affect coronary flow to the previously ischaemic myocardium over time.

Transthoracic Doppler echocardiography may be suitable for the serial assessment of coronary flow velocity in the left anterior descending coronary artery, and previous studies have shown it to be accurate in comparison with Doppler guide wire studies. We undertook this investigation to test the following hypotheses: first, that serial assessment of coronary flow velocity in the distal left anterior descending coronary artery is feasible after reperfused anterior acute myocardial infarction; and second, that the serial changes in coronary flow velocity profile, especially the presence of systolic flow reversal, are correlated with recovery of left ventricular function.

METHODS

Study group

The study population consisted of 49 consecutive patients with their first anterior acute myocardial infarct. They underwent primary coronary angioplasty or stenting for a totally or subtotally occluded left anterior descending coronary artery within 12 hours of symptom onset. The diagnosis of myocardial infarction was based on prolonged chest pain for more than 20 minutes, ST segment elevation in more than two contiguous precordial ECG leads, and a more than threefold increase in serum creatine kinase. Exclusion criteria were as follows:

- more than 25% diameter stenosis in the left main coronary artery or more than 75% stenosis in the right or left
circumflex coronary artery, which provide collateral vessels to the left anterior descending artery.

- unstable clinical condition or a cardiac event during follow-up
- significant residual stenosis in the left anterior descending coronary artery on predischarge coronary angiography.

The local ethics committee approved the study protocol and all patients gave their written informed consent at the start of the study.

**Coronary angiography and angioplasty**

Emergency coronary angiography was done by the standard femoral approach. All patients were given chewable aspirin (≥162 mg) and an intravenous injection of 10 000 U of heparin followed by a continuous heparin infusion for 48 hours. Coronary angioplasty was undertaken using standard techniques, and if the patient showed a suboptimal result, coronary stenting was employed. Per cent diameter stenosis and minimum lumen diameter of the culprit lesion before and after the intervention were analysed quantitatively, using the Philips QCA DCI-ACA system.10 The guiding catheter was employed as a scaling reference. The angiographic TIMI flow grade11 of the left anterior descending coronary artery was also assessed before and after the intervention. Angiographic collateral flow grade was determined by the method of Rentrop and colleagues.12 Success was defined as less than 30% residual stenosis with TIMI 2 or 3 flow grade.

**Echocardiography**

We carried out the following serial studies, beginning on the day of infarction (day 0, immediately after primary percutaneous transluminal coronary angioplasty (PTCA)), and then at 48 hours, one week, and three weeks: parasternal long and short axis views; apical four and two chamber views with second harmonic imaging; and coronary flow velocity in the left anterior descending coronary artery by transthoracic Doppler echocardiography. We used a commercially available ultrasound machine (Sonos 5500, Philips Medical Systems, Andover, Massachusetts, USA). For transthoracic Doppler echocardiography we used a broadband high frequency transducer.
In B mode colour Doppler flow mapping, the velocity was set in the range of ±7 to ±24 cm/s, colour gain was adjusted to 70–90%, and the sample volume was adjusted to around 2.5–3.1 mm width.

Colour Doppler detection of flow in the left anterior descending coronary artery was achieved using a modified apical approach. With a sample volume positioned on the colour Doppler signal in the artery, pulsed Doppler signal tracings of flow velocity were recorded. Pulse Doppler gain was 50–70%. Much attention was paid to ensuring that the sample volume was not placed in the great cardiac vein or the septal arteries by adjusting the transducer position and its angulation (great cardiac vein flow shows almost pansystolic reverse flow toward the base, and no diastolic flow).

The wall motion filter was set between 200–300 Hz to reduce wall motion artefacts. The image was also carefully adjusted to minimise the angle between the Doppler beam and the left anterior descending coronary artery flow. If this angle could not be reduced to less than 30°, angle correction was undertaken. After obtaining the best quality coronary flow velocity envelope, the transducer position was marked on the chest wall by felt pen and this position was used for the serial studies.

All images were stored on magneto-optical disk, and also recorded on S-VHS videotape for later analysis.

**Echocardiographic measurements**

**Wall motion analysis**

After obtaining four standard cross sectional echocardiographic views, the left ventricle was divided into 16 segments according to the recommendation of the American Society of Echocardiography. Wall motion in each segment was assessed using a four point scoring system: 1, normal; 2, hypokinesis; 3, akinesis; 4, dyskinesis. For the evaluation of regional wall motion, nine segments (basal anteroseptal, basal anterior, mid-interventricular septum, mid-anteroseptal, mid-anterior, and four apical segments) were assigned to the left anterior descending coronary artery territory. These nine segmental scores were summed and divided by 9 to yield a regional wall motion score index (RWMSI) on day 0 and at three weeks after the infarct. Reversible dysfunction was defined as improvement of wall motion in more than two contiguous segments in the left anterior descending coronary artery territory during follow up. This implies a decrease in RWMSI by ≥0.22 between day 0 and three weeks (that is, RWMSI at day 0 minus RWMSI at three weeks: \( \Delta \text{RWMSI} \)). A \( \Delta \text{RWMSI} \) value < 0.22 was defined as irreversible dysfunction.

**Coronary flow velocity analysis**

The envelopes of coronary flow velocity were traced manually. Time averaged peak systolic velocity, time averaged peak diastolic velocity, and diastolic deceleration time were calculated using the built in system. Measurements were averaged over three cardiac cycles. Systolic flow reversal was defined as a coronary flow reversal showing a peak velocity of ≤−10 cm/s and a duration of ≥60 ms during systole. Its presence was recorded at each examination. According to the presence or persistence of systolic flow reversal, patients were divided into the following three groups:

- group 1: no systolic flow reversal during the examination period
- group 2: systolic flow reversal only observed immediately after coronary reflow (day 0)
- group 3: systolic flow reversal persistently observed for at least 48 hours.

**Statistical analysis**

Continuous data are expressed as mean (SD). We used \( \chi^2 \) analysis to compare categorical variables, and Student’s t test to compare continuous variables between two groups. Differences in parametric data among the three groups were tested.
for using analysis of variance (ANOVA), and then, for multiple comparisons, Fisher’s protected least significant difference test. We examined the positive and negative predictive value of the presence of systolic flow reversal for predicting irreversible dysfunction in the left anterior descending coronary artery territory. A probability value of $p < 0.05$ was considered significant.

We assessed the interobserver and intraobserver variabilities for coronary flow velocity measurement and wall motion analysis in 45 recordings from 15 randomly selected patients. Interobserver variability was calculated as the standard deviation of the differences between the measurements of two independent observers who were blinded to the patient’s data. Intraobserver variability was calculated as the standard deviation of the differences between the first and second analysis (six weeks interval) for a single observer. These data were expressed as a percentage of the averaged value.

**RESULTS**

Clinical characteristics in the study patients are shown in table 1. We were unable to obtain coronary flow velocity measurements on day 0 or at later stages of follow up in four of the 49 patients, including two with obstructive lung disease. Thus the final group consisted of 45 patients. The time required for coronary flow velocity measurements was less than 10 minutes. The mean time intervals between coronary reflow and the examinations on day 0 and 48 hours were 6.0 (2.7) hours (range 4–9) and 48.7 (5.7) hours (range 34–57), respectively. All patients had exact timings of the measurements taken one week and three weeks after their infarction.

Clinical and coronary flow velocity data in patients with reversible and irreversible dysfunction

According to the definition, 29 patients had reversible dysfunction and the remaining 16 had irreversible dysfunction. Table 2 shows the clinical, echocardiographic, and angiographic data in patients with reversible and irreversible dysfunction. The peak creatine kinase concentration was significantly higher in patients with irreversible dysfunction. Percent diameter stenosis and minimum lumen diameter in the culprit lesion at emergency angiography and at predischARGE angiography did not differ between the two groups.

Serial changes in time averaged peak systolic and peak diastolic velocity between the reversible and irreversible dysfunction groups are shown in fig 1. There were no significant differences in time averaged peak diastolic velocity at the various examinations. Although time averaged peak systolic velocity at 48 hours was significantly lower in patients with irreversible dysfunction than in those with reversible dysfunction (8.2 (4.3) vs 1.3 (7.6) cm/s, $p < 0.005$), individual values showed a great deal of overlap.

**Systolic flow reversal and wall motion recovery**

Systolic flow reversal was observed in 18 patients on day 0. Ten patients showed systolic flow reversal at 48 hours, four at one week, and none at three weeks. Twenty seven patients did not show systolic flow reversal on day 0, and none of these developed it during the later stages of follow up.

Figure 2 shows representative cases of serial assessment of coronary flow velocity after coronary reflow. According to the subgroup definition given above relating to the presence/persistence of systolic flow reversal, the number of patients in group 1 was 27, in group 2, eight, and in group 3, 10.

The RWMSI values on day 0 and at three weeks along with the ARWMSI values among the three groups are shown in fig 3. Although mean (SD) RWMSI on day 0 did not differ among the three groups (group 1, 2.30 (0.45); group 2, 2.85 (0.37); group 3, 2.76 (0.19)), RWMSI at three weeks was significantly higher in group 3 (2.81 (0.28)) than in group 2 (2.27 (0.46), $p < 0.05$) or group 1 (1.88 (0.60), $p < 0.0001$). There was no significant difference in RWMSI at three weeks between groups 1 and 2. Thus ARWMSI—that is, the degree of recovery of wall motion abnormality in the left anterior descending coronary artery territory—was significantly lower only in
group 3 (0.01 (0.26)) compared with group 1 (0.61 (0.44), p < 0.001) or group 2 (0.52 (0.49), p < 0.01).

Figure 4 shows serial change of RWMSI in patients with or without systolic flow reversal at 48 hours. There was a significant difference of RWMSI between the two groups.

**Diastolic deceleration time and wall motion recovery**

Table 3 shows the diastolic deceleration time between patients with reversible dysfunction and those with irreversible dysfunction. Although diastolic deceleration time on day 0 and at 48 hours tended to be shorter in patients with irreversible dysfunction, there was no significant difference owing to the large standard deviation. Diastolic deceleration times at one week and three weeks were significantly shorter in patients with irreversible dysfunction than in those with reversible dysfunction.

**Coronary flow velocity and creatine kinase for predicting irreversible dysfunction**

Table 4 shows the diagnostic accuracy of creatine kinase concentration, systolic flow reversal, and diastolic deceleration time for predicting irreversible dysfunction. Although the negative predictive value did not differ significantly, the persistence of systolic flow reversal up to 48 hours had a greater positive predictive value for irreversible dysfunction.

**Observer variability**

Interobserver and intraobserver variabilities for the measurement of coronary flow velocity recordings and wall motion analysis were 5.4% and 6.2%, and 3.8% and 4.0%, respectively.

**DISCUSSION**

In this study we show that the serial assessment of coronary flow velocity in the distal part of the left anterior descending coronary artery by transthoracic Doppler echocardiography is feasible in the majority of cases with reperfused anterior acute myocardial infarction. Because the sampling point for coronary flow velocity measurement often showed wall motion abnormality and thus no vigorous movement during systole, it was relatively easy to record systolic and diastolic velocities. As transthoracic Doppler echocardiography allows noninvasive measurements of coronary flow velocity, this is a promising method for serial evaluation of the coronary circulation after reperfusion. Continuous flow velocity recording using a Doppler guide wire is reported to be safe and useful, but it is somewhat impractical in the daily clinical situation.

**Accuracy of systolic flow reversal as a predictor of irreversible dysfunction**

Although the presence of systolic flow reversal immediately after reperfusion generally reflects poor functional recovery,6 to the best of our knowledge there are no published studies on the effect of serial changes in systolic flow reversal of the infarct related artery on functional outcome. We conclude that the persistence of systolic flow reversal at 48 hours is a more specific marker for predicting subsequent irreversible dysfunction than the presence of systolic flow reversal immediately after coronary reperfusion. These results suggest that the condition of the microcirculation in a reperfused but previously occluded coronary bed may be changing dynamically, at least within the first couple of days. Thus the assessment of microvascular status immediately after coronary reflow may not be an accurate predictor of subsequent poor functional outcome in some patients.

Several recent studies have shown the value of measuring coronary flow velocity in the infarct related artery immediately after coronary reflow by Doppler guide wire.7,14 Characteristic coronary flow patterns such as the appearance of systolic flow reversal or rapid deceleration of diastolic coronary flow are associated with the no reflow phenomenon,13 and are also markers predicting poor recovery of left ventricular function.7 In those studies, however, the predictive accuracy of the findings was not discussed. Recently, Kawamoto and colleagues measured coronary flow velocity using a Doppler guide wire immediately after primary PTCA in patients with anterior acute myocardial infarction.7 Although they found that a relatively preserved time averaged peak systolic velocity and a prolonged diastolic deceleration time obtained 10 minutes after the last balloon inflation had good sensitivity and specificity for predicting myocardial viability, there was only a weak correlation between these variables and the magnitude of wall motion recovery (r = 0.46 to 0.49). These findings stress that dynamic coronary flow change after reperfusion of acute infaracts affects the coronary flow velocity profile, and that continuous observations by transthoracic Doppler echocardiography of alterations in coronary flow velocity for several days after reperfusion can resolve these issues.

**Alteration of coronary flow velocity in the infarct related artery after reperfusion**

Microvascular function and coronary flow in the infarct zone may alter with time, particularly early after coronary reperfusion. Experimental studies have shown that microvascular occlusion can develop in the area at risk after

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Diastolic deceleration time data (ms) comparing reversible dysfunction and irreversible dysfunction groups</th>
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</thead>
<tbody>
<tr>
<td>Time after infarction</td>
<td>Reversible dysfunction (n=29)</td>
</tr>
<tr>
<td>Day 0</td>
<td>550 (458)</td>
</tr>
<tr>
<td>48 Hours</td>
<td>565 (310)</td>
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<tr>
<td>1 Week</td>
<td>789 (487)</td>
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<tr>
<td>3 Weeks</td>
<td>922 (419)</td>
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</table>

Data are mean (SD).

<table>
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<tr>
<th>Table 4</th>
<th>Diagnostic accuracy of peak creatinine kinase, systolic flow reversal, and diastolic deceleration time for predicting irreversible dysfunction</th>
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<tr>
<td>Variable</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>Peak CK &gt;3500 U/l</td>
<td>88</td>
</tr>
<tr>
<td>Peak CK &gt;4000 U/l</td>
<td>81</td>
</tr>
<tr>
<td>Peak CK &gt;4500 U/l</td>
<td>44</td>
</tr>
<tr>
<td>Presence of SFR at day 0</td>
<td>75</td>
</tr>
<tr>
<td>Presence of SFR at 48 hours</td>
<td>76</td>
</tr>
<tr>
<td>DDT &lt;600 ms at day 0</td>
<td>81</td>
</tr>
<tr>
<td>DDT &lt;600 ms at 48 hours</td>
<td>69</td>
</tr>
</tbody>
</table>

*p < 0.01 v presence of systolic flow reversal at 48 hours.

CK, creatine kinase; DDT, diastolic deceleration time; NPV, negative predictive value; PPV, positive predictive value; SFR, systolic flow reversal.
Systolic flow reversal after myocardial infarction

reperfusion, resulting in a progressive increase in the no/low reflow area. Other animal studies have shown recovery of microvascular damage after coronary reflow; thus many confounding factors can favourably or adversely affect coronary flow in the infarct zone immediately after coronary reflow, and the assessment of coronary flow velocity early after coronary reflow could underestimate or overestimate the prediction of ultimate recovery of left ventricular function. Because temporal changes in microvascular function may vary among patients, we were unable to determine whether the assessment of coronary flow velocity at 48 hours was the best point for predicting functional recovery. However, it has been reported in several studies that the assessment of microvascular function at 24–48 hours by myocardial contrast echocardiography; magnetic resonance imaging; or transcorporal Doppler echocardiography is a reliable way of predicting functional recovery in patients with reperfused acute myocardial infarcts. These results suggest that microvascular function has settled down by 48 hours postinfarction in many patients, and assessment of microvascular status at this point would provide a more precise estimate of the subsequent clinical outcome. Our study also showed that the prevalence of systolic flow reversal decreased over the time and no patients showed systolic flow reversal by three weeks after the infarct. This may reflect the healing process of the microcirculation in the infarct zone.

Study limitations
Some potential methodological limitations need to be addressed in this study.

First, we tried to record coronary flow velocity at the same point on the chest wall during serial studies. The sample point in the left anterior descending coronary artery and angle of incidence between flow and Doppler beam could change during the study period because of alterations in left ventricular volume and shape. Although we were very careful not to record anterior interventricular vein flow or septal branch flow in the myocardium, some contamination of these flow velocities might erroneously define the patient as having systolic flow reversal.

Second, diastolic deceleration time immediately after coronary reflow is reported to be another useful index for predicting left ventricular functional recovery, but we could not find any difference in diastolic deceleration time between the reversible and irreversible dysfunction groups on day 0 or at 48 hours. A substantial angle of incidence between the transducer beam and the flow direction, and incomplete delineation of the outer edge of coronary flow velocity, would affect the calculation of diastolic deceleration time. Whether the simultaneous use of an intravenous contrast agent could improve the whole coronary flow velocity envelope remains to be determined.

Third, the measurement of coronary flow velocity by transthoracic Doppler echocardiography is only applicable in the distal part of the left anterior descending coronary artery. Our study population was thus limited to patients with anterior acute myocardial infarction. However, a recent study reported the feasibility of measuring coronary flow velocity and flow reversal in the posterior descending coronary artery. With further advances in ultrasound technology, measurements of coronary flow velocity in other coronary arteries may become possible, increasing the clinical relevance of this method in patients with acute myocardial infarction.

Clinical implications and conclusions
Transcorporal Doppler echocardiography is an inexpensive, versatile, and non-invasive method for measuring coronary flow velocity in the left anterior descending coronary artery. This permits serial assessment of coronary flow velocity at the bedside after primary coronary angioplasty in patients with anterior infarcts. The persistence of systolic flow reversal after 48 hours is a more specific marker of irreversible postischemic dysfunction than its presence immediately after reflow. This method is useful for stratifying high risk patients and selecting appropriate therapeutic strategies relatively early after acute myocardial infarction.

References

IMAGES IN CARDIOLOGY

Patency of coronary artery lumen surrounded by metallic stent evaluated by three dimensional volume rendering images using ECG gated multislice computed tomography

A 78 year old man came to our hospital because of chest pain on effort. Conventional coronary angiography revealed high grade stenosis at the proximal portion of the left anterior descending branch (LAD). Therefore, percutaneous transluminal coronary angioplasty with metallic stent implantation was performed. Four months after the stent placement, enhanced multislice computed tomography (CT) (Aquilion, Toshiba, Tokyo) was performed with a 1 mm slice thickness, helical pitch 0.8. Following intravenous injection of 100 ml of iodinated contrast material (300 mg/ml), CT scanning was performed with retrospective ECG gated reconstruction. In the maximum intensity projection image, the metallic stent and calcifications were observed in addition to the vessel lumen filled with contrast material. However, it was difficult to evaluate the patency of the proximal portion of the LAD surrounded by the metallic stent, even though the peripheral portion from the implantation site was enhanced. In the volume rendering image in which the vessel lumen filled with contrast material, metallic stent and calcification were observed with the high grade opaque levels, but the patency of the coronary arterial lumen surrounded by the metallic stent could not be evaluated. In another volume rendering image in which metallic stent and calcification were recognised as half transparency and the vessel lumen filled with contrast material was recognised as high grade opaque, the coronary arterial lumen surrounded by the metallic stent could be observed through the half transparent metallic stent.

Conventional coronary angiography was performed and mild diffuse stenosis of the proximal portion of the LAD, at which the metallic stent was located, was observed.

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