Early change in invasive measures of microvascular function can predict myocardial recovery following PCI for ST-elevation myocardial infarction

Florim Cuculi†, Erica Dall’Armellina‡, Cedric Manlhiot3, Alberto R. De Caterina1, Sharon Colyer4, Vanessa Ferreira5, Alireza Morovat4, Bernard D. Prendergast1, J. Colin Forfar1, Nicholas J. Alp1, Robin P. Choudhury6, Stefan Neubauer2, Keith M. Channon2, Adrian P. Banning‡, and Rajesh K. Kharbanda1‡*

1Oxford Heart Centre, The John Radcliffe Hospital, University of Oxford, Oxford University Hospitals, OX3 9DU, Oxford, UK; 2Department of Cardiovascular Medicine, University of Oxford, Oxford University Hospitals, Oxford, UK; 3Department of Clinical Biochemistry, University of Oxford, Oxford University Hospitals, Oxford, UK; 4The Hospital for Sick Children, Toronto, Canada; 5Stephenson Cardiovascular MR Centre, Libin Cardiovascular Institute of Alberta, Calgary, Canada; and 6Oxford Acute Vascular Imaging Centre, Radcliffe Department of Medicine, Oxford, UK

Received 18 January 2013; revised 21 August 2013; accepted 26 September 2013; online publish-ahead-of-print 17 October 2013

Aims
Predicting the likely success of primary PCI to salvage potential infarcted myocardium is desirable. We compared early invasive parameters of coronary microcirculation function with the levels of circulating endothelin (ET-1) and 6-month ejection fraction after STEMI.

Methods and results
Forty-four STEMI patients underwent assessment of coronary flow reserve (CFR) and index of myocardial resistance (IMR) on completion of PPCI and one day later. Cardiac magnetic resonance (CMR) at 24 h and 6 months assessed ejection fraction, oedema, late gadolinium enhancement, and salvage. In patients with depressed EF, there was no difference in IMR or CFR measured immediately after PPCI compared with those with preserved EF. However, by Day 1, CFR was significantly lower in those with depressed EF [2.0(1.5–2.3) vs. 2.6(2.1–3.3), \(P = 0.008\)]. In multivariable models, higher CFR post-PPCI [EST: +8.9 (SE 3.7) per 1 CFR unit, \(P = 0.03\)] and greater increase in CFR between post-PPCI and Day 1 [EST: +8.5 (SE 3.4) per 1 CFR unit, \(P = 0.01\)] were associated with higher salvage index. Circulating endothelin levels were significantly elevated in the low EF group at both 6 and 24 h, and 24 h levels correlated with CFR.

Conclusion
Changes of the coronary microcirculation in the first day after PPCI are associated with 6-month ejection fraction and myocardial salvage. Depressed CFR at 24 h is associated with CMR imaging indices of MVO and haemorrhage and elevated endothelin levels.

Keywords
Microcirculation • Myocardial infarction • Magnetic resonance imaging • Angioplasty • Blood flow

Introduction
Primary angioplasty (PPCI) restores TIMI III flow in over 90% of patients and improves clinical outcomes from acute ST-elevation myocardial infarction (STEMI). Microcirculatory no-reflow can be identified in nearly one-third of patients undergoing PPCI and is associated with both the extent of myocardial infarction and left-ventricular (LV) dysfunction. A recent National Heart Lung and Blood Institute Cardioprotection Workshop identified the microcirculation as an important target to further improve the outcomes from reperfusion therapy.

Changes in the coronary microcirculation after STEMI have been described in non-invasive studies using myocardial contrast and Doppler echocardiography, positron-emission tomography, and...
CMR. Early invasive studies investigated coronary flow reserve (CFR) after thrombolysis. Lepper showed CFR > 1.6 at 24 h was associated with contrast echocardiographic measures of reperfusion, and LV function. Feldman extended these observations in 21 patients with anterior STEMI showing that worsening electrocardiographic ST-elevation during PPCI was associated with lower CFR, larger infarct size, and worse LV function, and in a subsequent study that lower procedural post-stent CFR was related to incomplete ST-resolution after PPCI. Recently, the Index of Microcirculatory Resistance (IMR) has been studied at the time of PPCI and in small populations there are correlations with total creatine kinase release, LV function, and myocardial salvage.13,14 There is increasing interest in trying to identify measures of the microcirculation such as CFR and IMR ‘at the time of PPCI’. Not only would this measure reflect the efficacy of reperfusion but it would also allow comparison of different adjunctive strategies designed to improve treatment. However, the impact of changes of microcirculatory function within the early post-reperfusion period on later ejection fraction and salvage and has not been specifically addressed. Furthermore, the mechanisms contributing to impaired microvascular dysfunction after PPCI are unclear.

The aims of our study were to identify how measures of microcirculatory function at PPCI and Day 1 after STEMI relate to the extent of injury measured by troponin release, levels of endothelin-1, and ejection fraction and myocardial salvage measured by MRI.

**Methods**

**Study patients**

The study population consisted of 45 prospectively enrolled STEMI patients who underwent PPCI at the John Radcliffe Hospital, Oxford (Oxford Studies In Acute Myocardial Infarction (Ox-AM) Cohort). STEMI was defined as chest pain continuing for > 30 min and ST elevation > 2 mm in > 2 contiguous leads. Exclusion criteria were symptom duration > 12 h, the presence of severe haemodynamic instability, and contraindication to the use of adenosine. The study was conducted in accordance with the Declaration of Helsinki. The local Ethics Committee approved the protocol and all participants gave written informed consent (REC number 10/H0408/24).

**Coronary intervention**

PPCI was performed in a standard fashion in line with international guidelines. Patients received oral aspirin (300 mg) and thienopyridines (600 mg clopidogrel or 60 mg prasugrel) pre-procedure. Thrombus aspiration and use of abciximab (ReoPro®, Eli Lilly, USA) and bivalirudin (Angiox, The Medicines Company, USA) before pre-dilatation and stent deployment were recommended but were at the discretion of the primary operator.

**Evaluation of coronary microcirculation**

The pressure wire (Certus, St Jude Medical, St Paul, MN, USA) was placed in the distal third of the infarct-artery (IRA) to perform invasive assessment of the coronary microcirculation immediately after stent implantation ± post-dilatation. Care was taken that the wire remained stable and its position was documented for repeat study. Side branches were used as anatomical landmarks. CFR, IMR, and fractional flow reserve (FFR) were measured using previously described methods. Briefly, the shaft and the sensor near the tip of the pressure wire act as thermostors, and by detecting changes in temperature after the injection of room-temperature saline transit times can be measured. The transit time (Tmn) was calculated as a mean from three injections of 5 mL room-temperature saline through the guiding catheter. Tmn was recorded at baseline and after induction of hyperaemia with intravenous adenosine infusion (140 μg kg⁻¹ min⁻¹ for 120 s) into the right femoral vein. Simultaneous measurement of mean aortic pressure (Pa, by guiding catheter) and mean distal coronary pressure (Pd, by pressure wire) was made in the resting and maximal hyperaemic states. CFR was calculated as the ratio of the transit times at baseline and hyperaemia. IMR was calculated as the distal coronary pressure at maximal hyperaemia multiplied by the hyperaemic Tmn (in seconds). FFR was calculated by the ratio of Pd/Pa at maximal hyperaemia.

**Follow-up coronary angiography and evaluation coronary microcirculation**

Repeat informed consent was obtained from eligible patients and repeat angiography and pressure wire assessment of the infarct-related artery microcirculatory function was performed the next day following PPCI. Care was taken to use the same type of guiding catheter and wire positioning as at index PPCI.

**Angiographic analysis**

Coronary flow was graded using the standard Thrombolysis In Myocardial Infarction (TIMI) criteria 16, while corrected TIMI frame count (CTFC) was measured according to Gibson. Myocardial blush grade (MBG) at the end of the procedure was evaluated according to van’t Hof.20 Angiographic no-reflow was defined as TIMI flow less than grade 3 and/or TIMI 3 flow with MBG less than 2 at completion of the procedure. Angiographic analysis was performed by two interventional cardiologists and disagreement resolved by consensus.

**Biochemical assessments**

Plasma samples obtained at arrival, immediately post-PPCI and at 6, 24, and 48 h post-PPCI were stored at −81°C. Cardiac Troponin I (cTnI) and quantified with automated chemiluminescent immunoassay techniques on the Siemens ADVIA Centaur (Siemens Healthcare Diagnostics, Frimley, UK). Area under the curve was calculated using the trapezoidal rule to express this as summary measure of infarct size.21,22 Endothelin levels were measured using an ELISA QuantiiGlo Chemiluminescent Immunoassay (R and D systems, Abingdon, UK).

**Magnetic resonance imaging of myocardial injury and salvage**

Patients underwent CMR at Day 1 and 6 months. CMR examinations were performed on a 3 Tesla MR scanner (either MAGNETOM TIM-Trio or MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) using a spine coil and a phased array 6-channel flexible surface coil. Left ventricular function and myocardial injury were assessed using Steady State Free Precession (SSFP), T2-weighted and late gadolinium enhancement (LGE) imaging. The images were acquired with each technique on matching short-axis slices. SSFP cine images were acquired using retrospective gating. Oedema imaging (T2W) was performed using a T2-prep-SSFP single shot sequence with surface coil correction. LGE-CMR was performed with a T1-weighted segmented inversion-recovery gradient echo-phase sensitive-inversion recovery sequence. Images were collected 10–15 min after the administration of 0.1 mmol/kg contrast agent (Gadodiamide, Omniscan™, GE Healthcare, Amersham, UK). The inversion time was adjusted for optimal nulling of remote normal myocardium. Quantification of LV volumes and ejection fraction (EF) was performed as previously described using Argus.
software (Version 2002B, Siemens Medical Solutions). For objective quantification of oedema or LGE, a reference region of interest (ROI) was placed in remote myocardium. The signal intensity threshold indicating oedema/LGE was imposed 2 standard deviations above the mean intensity of the reference ROI, as previously described. In the presence of microvascular obstruction (MO) or haemorrhage, both were included in the measurements of LV myocardial damaged volume by LGE and T2W. Furthermore, the amount of haemorrhage and MVO was assessed by manual delineation of the hypointense areas and calculated as percentage fraction of the LV, as previously described (illustrated in Figure 1).

In patients with first myocardial infarction and no previous events, salvaged myocardial index was derived from the difference in area between acute oedema and the area of scar by LGE assessed at 6 months.

Statistical analysis

Sample size estimates were based on prior studies showing that a CFR difference of 1.0 between groups was associated with significant differences in infarct size and ejection fraction. Estimated CFR and standard deviation was based on published studies. For 80% power, alpha 0.05, a sample size of 14 was calculated for each group. Recruitment was continued to compensate for potential dropouts and total sample size was set at 45 patients.

Normally distributed parameters are reported as mean ± standard deviation (SD) while those with a skewed distribution are reported as median (IQR). For the non-normally distributed variables we used the Mann–Whitney test for unpaired comparisons and the Wilcoxon signed rank test for paired comparisons. For normally distributed variables, we used Student’s t-test and Fisher’s exact χ² was used for binary variables. Correlation was assessed using Pearson’s correlation.

For salvage, effect of post-PPCI CFR and change in CFR between post-PPCI and Day 1 CFR were initially evaluated together in a linear regression model, and clinical factors associated with salvage were sought from standard clinical variables for this patient population. Clinical variables in addition to CFR and IMR were included in a bootstrap resampling procedure (250 re-samples), factors selected in more than 45% of the sample were then included in a multivariable model with backward selection of variables to obtain a final multivariable regression model. Factors included were age, gender, smoking, hypercholesterolaemia, hypertension, diabetes, glycoprotein IIb/IIIa inhibitor, thrombectomy, symptom to reperfusion time, door-to-balloon time, culprit artery, stent size and volume, pre-dilatation, TIMI flow, and ST-segment resolution. All statistical analyses, except ANOVA, were performed using SAS v9.3 (The SAS Institute, Cary, NC, USA). ANOVA was performed using Graphpad Prism. Low EF and high EF group comparisons were made by repeated measures 2-way ANOVA. Time differences within group were analysed by 1-way ANOVA with post hoc Dunn’s multiple comparison. A P-value of <0.05 was considered statistically significant and the tests were two-sided.

Figure 1  Acute MRI findings in patients with STEMI. Top row: Matching short axis images in a patient with acute anterior STEMI. On T2W images (left panel), there is transmural septal oedema with a large hypointense core in keeping with presence of haemorrhage. On LGE images (right panel), there is a corresponding area of transmural enhancement with a dark core due to microvascular obstruction. Bottom row: a different patient with anterior STEMI. Transmural septal myocardial oedema (left panel) is seen in an area corresponding to transmural septal enhancement on LGE (right panel). LGE, late gadolinium enhancement.
Results

A total of 101 patients with acute STEMI (presenting throughout the 24 h cycle of clinical activity) were screened for inclusion. Eighty-two (81%) patients were recruited and underwent invasive assessment of the coronary microcirculation at PPCI, 61 underwent repeat coronary angiography and coronary microcirculation assessment at Day 1. All patients tolerated adenosine infusion. No significant bradycardia or AV block was observed, and no patient required temporary pacing. Forty-five consented for CMR. Three patients had prior myocardial infarction and were excluded for calculation of salvage index. Clinical characteristics of the 45 patients and angiographic measures of flow are shown in Table 1.

We stratified the cohort (n = 45) by tertiles of ejection fraction and compared Group 1—those with EF in the lower third (n = 15)—with those patients with preserved ejection fraction in the upper two-thirds Group 2 (n = 30). Clinical characteristics are

Table 1  Baseline characteristics (at PPCI) of the study population (n = 45)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low EF (n = 15)</th>
<th>High EF (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.1 ± 9.7</td>
<td>60.3 ± 10.3</td>
<td>0.95</td>
</tr>
<tr>
<td>Male : Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous medical therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>6/15 (40)</td>
<td>5/30 (17)</td>
<td>0.09</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>5/15 (33)</td>
<td>6/30 (20)</td>
<td>0.33</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0/15 (0)</td>
<td>2/30 (7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>0/15 (0)</td>
<td>3/30 (10)</td>
<td>0.20</td>
</tr>
<tr>
<td>Pain-to-balloon time (min)</td>
<td>159 ± 67</td>
<td>229 ± 170</td>
<td>0.13</td>
</tr>
<tr>
<td>Door-to-balloon time (min)</td>
<td>19 ± 13</td>
<td>20 ± 15</td>
<td>0.87</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124 ± 21</td>
<td>137 ± 25</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75 ± 10</td>
<td>86 ± 18</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>76 ± 20</td>
<td>74 ± 19</td>
<td>0.68</td>
</tr>
<tr>
<td>Coronary risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary flow at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 0</td>
<td>31/45 (69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI I</td>
<td>4/45 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI II</td>
<td>5/45 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI III</td>
<td>5/45 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary flow at procedure end</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI III, n (%)</td>
<td>40/45 (89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected TIMI frame count</td>
<td>16.7 ± 6.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBG 0 or MBG I, n (%)</td>
<td>8/45 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBG II or MBG III, n (%)</td>
<td>37/45 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic reflow (TIMI 3 and MBG &gt;2), n (%)</td>
<td>36/45 (80)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; MBG, myocardial blush grade.
described in Table 2. Median (IQR) EF was 43.0(35–47) in Group 1 compared with 60.5(56.8–64.2) in Group 2 (P = 0.001).

**Relationship between cardiac magnetic resonance measures of infarct size, MVO, and haemorrhage stratified by ejection fraction**

Median (IQR) LGE at 6 months was 34.5% of LV (29.5–41.5) in Group 1 and 19.0% of LV (7.0–24.0) in Group 2 (P = 0.001). MVO was 6.0% of LV (0–10) vs. 0% (0–1) and haemorrhage was 11.0% of LV (0.0–15.0) vs. 0% of LV, respectively, in these groups (Group 1 vs. Group 2, P = 0.007 and 0.008).

**Relationship between coronary flow reserve and index of myocardial resistance at PPCI and Day 1 after STEMI stratified by ejection fraction groups**

CFR and IMR data were available for 44 patients at both timepoints. One patient did not have CFR and IMR measurement at PPCI (due to technical difficulties) and one patient did not undergo repeat cardiac catheterization at Day 1 (withdrew consent).

The haemodynamic measures and transit times are summarized in Tables 3 and 4. Importantly, baseline transit times did not differ at these timepoints but hyperaemic transit times shortened significantly at Day 1.

After PPCI, median (IQR) CFR was 1.4 (1.1–2.0) in Group 1 and 1.8 (1.1–2.4) in Group 2 (P = 0.39). At Day 1 after PPCI, median (IQR) CFR was 1.9 (1.5–2.2) in Group 1 vs. 2.6 (2.1–3.2) in Group 2 (P = 0.005) (Figure 2, Table 4). After PPCI, median (IQR) IMR was 30 (18–65) in Group 1 and 37 (19–50) in Group 2 (P = 0.67).

### Table 3 Coronary physiology parameters at PPCI according to low- and upper tertiles ejection fraction 1 (n = 44*)

<table>
<thead>
<tr>
<th></th>
<th>Group 1, Low EF (n = 15)</th>
<th>Group 2, High EF (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting gradient</td>
<td>0.94 ± 0.05</td>
<td>0.97 ± 0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>0.92 ± 0.06</td>
<td>0.94 ± 0.06</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline transit time (s)</td>
<td>0.76 ± 0.43</td>
<td>0.93 ± 0.60</td>
<td>0.34</td>
</tr>
<tr>
<td>Hyperaemic transit time (s)</td>
<td>0.53 ± 0.41</td>
<td>0.62 ± 0.56</td>
<td>0.61</td>
</tr>
<tr>
<td>Baseline distal pressure (mmHg)</td>
<td>85 ± 14</td>
<td>91 ± 17</td>
<td>0.21</td>
</tr>
<tr>
<td>Hyperaemic distal pressure (mmHg)</td>
<td>73 ± 10</td>
<td>81 ± 18</td>
<td>0.15</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>1.4 (1.1–2.0)</td>
<td>1.8 (1.1–2.3)</td>
<td>0.52</td>
</tr>
<tr>
<td>Index of microcirculatory resistance</td>
<td>30 (18–58)</td>
<td>37 (19–50)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Complete coronary physiology data at PPCI were available for 44 patients (15 in the low EF group and 29 in the high EF group).

### Table 4 Coronary physiology parameters at Day 1 according to low- and upper tertiles ejection fraction 1 (n = 44*)

<table>
<thead>
<tr>
<th></th>
<th>Group 1, Low EF (n = 15)</th>
<th>Group 2, High EF (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting gradient</td>
<td>0.93 ± 0.05</td>
<td>0.96 ± 0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>0.90 ± 0.06</td>
<td>0.92 ± 0.06</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline transit time (s)</td>
<td>0.81 ± 0.39</td>
<td>0.99 ± 0.50</td>
<td>0.24</td>
</tr>
<tr>
<td>Hyperaemic transit time (s)</td>
<td>0.50 ± 0.38</td>
<td>0.40 ± 0.20</td>
<td>0.23</td>
</tr>
<tr>
<td>Baseline distal pressure (mmHg)</td>
<td>78 ± 12</td>
<td>84 ± 16</td>
<td>0.16</td>
</tr>
<tr>
<td>Hyperaemic distal pressure (mmHg)</td>
<td>65 ± 10</td>
<td>73 ± 16</td>
<td>0.09</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>1.9 (1.5–2.2)</td>
<td>2.6 (2.1–3.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Index of microcirculatory resistance</td>
<td>23 (15–40)</td>
<td>23 (18–34)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*Complete coronary physiology data at Day 1 were available for 44 patients (15 in the low EF group and 29 in the high EF group).
At Day 1, median (IQR) IMR was 23(15–40) in Group 1 and 23(18–34) Group 2 ($P = 0.85$) (Figure 3).

Relationship between coronary flow reserve and myocardial salvage and biochemical infarct size

Average salvage index at 6 months was 44.4 ± 32.5 ($n = 42$). Higher CFR post-PPCI [EST: +8.9 (3.7) per 1 CFR unit, $P = 0.03$] and greater increase in CFR between post-PPCI and Day 1 [EST: +8.5 (3.4) per 1 CFR unit, $P = 0.01$] were associated with higher salvage index at 6 months (Figure 3). In multivariable regression models including clinical variables selected by the bootstrap bagging procedure, (i) CFR post-PPCI and (ii) CFR change between post-PPCI and Day 1, were selected as being associated with higher salvage index at 6 months. The IMR was not predictive of myocardial salvage (Figure 4A).

At 6 months follow-up, mean LGE was 24 ± 13% ($n = 41$). There was a significant correlation of LGF at 6 months with log AUC Troponin ($r = 0.68, P < 0.001$) and log AUC CK-MB ($r = 0.65, P < 0.001$). There was a significant correlation between log AUC Troponin and CFR post-PPCI ($r = -0.44, P < 0.001$) and CFR at Day 1 ($r = -0.47, P < 0.001$). Higher CFR post-PPCI [EST: −0.673 (0.129) log ng/L per 1 CFR unit, $P < 0.001$] and greater increase in CFR between post-PPCI and Day 1 [EST: −0.432 (0.109) log ng/L per 1 CFR unit, $P < 0.001$] were associated with lower log AUC Troponin (Figure 4B).

In multivariable regression models including clinical variables selected by the bootstrap bagging procedure, variables selected as independently associated with higher log AUC Troponin were (i) lower TIMI flow, (ii) non-RCA culprit vessel, (iii) female gender, (iv) aspiration, (v) CFR post-PPCI, and (vi) CFR at Day 1, confirming that CFR post-PPCI and change in CFR between post-PPCI and Day 1 were independent predictors of log AUC Troponin. The IMR was not independently associated with log AUC Troponin (Table 5).

Relationship between endothelin, coronary flow reserve, and invasive measures stratified by ejection fraction

The time course for endothelin release is shown in Figure 5.

In Group 1, endothelin levels remain elevated at 6 and 24 h compared with admission levels [2.28 (1.1–3.6) pg/mL and 0.73 (0.3–1.0) pg/mL, 1-way ANOVA $P = 0.001, P = 0.001, P = 0.02$ compared with baseline]. In Group 2, endothelin is only elevated above baseline values at 6 h after PPCI [0.59 (0.32–1.02) and 1.23 (0.91–1.56) pg/mL, 1-way ANOVA $P = 0.02, P = 0.04$]. Furthermore, the endothelin level at 6 and 24 h are significantly lower in Group 2 compared with Group 1 [2.28 (1.1–3.6) vs.
Peak endothelin levels showed a significant relationship to 6-month EF and LGE \((r = -0.35, P = 0.03\) and \(r = 0.43, P = 0.01\), respectively). Endothelin levels post-PPCI, at the time of measurement of PPCI CFR, show no significant relationships \((r = -0.2, P = 0.23)\), but levels at 24 h are significantly correlated with CFR at Day 1 \((r = -0.4, P = 0.005)\), and also relate to 6-month EF and LGE \((r = -0.41, P = 0.01\) and \(r = 0.4, P = 0.02)\).
Discussion

The key findings from our study are that invasive measures of microcirculatory function in patients immediately following PCI for acute MI are a poor reflection of likely myocardial salvage. However, CFR measured the day following PPCI is significantly lower in patients with reduced EF compared with those patients with preserved EF. These differences in CFR also reflect significant observed differences in both MVO and haemorrhage imaged by MRI.

In a multivariate analysis, ‘both’ the CFR at PPCI and the change in CFR over the first day related to myocardial salvage index. Systemic endothelin levels were significantly different between groups with low and high EF, with a different time course and more significant elevation for a longer duration in the group with lower EF. Furthermore, endothelin correlated with CFR at 24 h but not immediately after PPCI. These findings imply that measurement of microvascular function may change within individuals after infarction and that recovery of CFR over the first 24 h after PPCI is associated with better myocardial outcomes.

Published studies show that IMR measured at PPCI is associated with biochemical measures of infarct size, salvage, and relates to 3-month EF. Our data confirm that using univariate analysis there is a relationship between IMR and infarct size. In this study, we wished to identify the optimal measures of microvascular function and so we stratified by tertiles and compared the lower tertile of EF patients with the upper two tertiles so that we could compare groups with clinically meaningful differences in EF.

Although relatively easy to perform, angiographic reflow was not different between patients with low and high EF. Using this approach, IMR measured at PPCI did not differentiate between the groups, but a preserved CFR at 24 h was significantly higher in the group with higher EF. To our knowledge, CFR has not been included in recent studies reporting PPCI IMR, and in the original study reporting the predictive value of IMR the authors recognized that small sample size may explain why other measures of microcirculatory function did not correlate with infarct size. Thus it appears that IMR measured at PPCI can differentiate large infarcts from small infarcts within a studied population, but the efficacy of reperfusion and the final outcome of individual patients are more complex than may have originally been considered. Our data highlight the importance of taking into account the changes of the microcirculation over the first 24 h in predictive models as we find associations between CFR at PPCI and that the change over 24 h relates to the prognostically important CMR salvage index measured at 6 months with a 1-unit difference in CFR associated with ~8% change in myocardial salvage relating to both PCI and 24 h measures.

A number of studies have investigated the concept that microvascular dysfunction after acute myocardial infarction is not fixed, and that the recovery of microvascular function is associated with reduced myocardial injury and improved functional outcome. Two studies have reported sequential invasive assessment of CFR in this context: Neumann described 19 patients in whom CFR of the infarct-related artery increased from 1.6 (post-stent) to 2.0 (after 1 h) and to 2.6 (after 14 days) after PCI. The very early change in CFR within the first hour correlated with biochemical measures of infarct size (peak CK), but not recovery of contractility. The majority of the change in CFR occurred within the first 2 days, assessed using PET, but the clinical impact of this change was not studied. Lepper studied 25 patients and demonstrated a correlation between CFR and perfusion defects on MCE. In that study, patients with persistently abnormal CFR (<1.6 at PPCI and 24 h) had reduced wall motion score index compared with those that improved, but the relationship between changes in CFR and infarct size were not reported. These studies differ from our larger study, in the context of contemporary PPCI practice, with associated short symptom-to-reperfusion times in a number of ways: (i) we have not used a specific cut-off value to define microcirculatory dysfunction and (ii) we have analysed outcomes using CMR salvage to take into account the influence of area-at-risk.

The underlying mechanisms for the improvement or deterioration of CFR after successful PPCI are unknown. At a conceptual level, these can be considered as mechanical (perivascular oedema, haemorrhage, distal embolization of microthrombi) or vasoactive (abnormal vascular function, imbalance between dilatation and constriction). Animal studies have shown that the area of microvascular dysfunction increases after reperfusion and can remain disturbed for some time after ischaemia—reperfusion injury. In our study, patients with low EF had more extensive imaging markers of mechanical disruption such as MVO and haemorrhage but in addition we also identified that there were important differences in circulating endothelin between these groups.

Endothelin (ET-1) is a potent vasoconstrictor with effects mainly at the small resistance vessels. Endothelin levels increase 3–4 h after STEMI. High endothelin levels after PPCI are associated with CMR measures of MVO, lower salvage, and angiographic no-reflow. In animal models modulating endothelin can limit reperfusion injury. A recent pilot clinical study demonstrated improved first-pass perfusion assessed by CMR in STEMI patients treated with short-term endothelin type A receptor antagonist BQ123. Our study investigated the time course release of endothelin and correlates these with invasive measures. The observation that more prolonged endothelin release maybe associated with adverse outcomes after STEMI and maybe a marker of microvascular dysfunction has been suggested previously. Our study has found interesting correlations with CFR at 24 h. We cannot extrapolate any causal link, but endothelin blockade increases coronary blood flow in humans, suggesting that increased endothelin levels maybe contributing to the impairment of CFR in the group with low EF.

The findings of this study have implications for improving the treatment of patients with acute STEMI. Our data highlight that a single measure of microvascular function performed after PPCI may not provide sufficient information to predict final outcomes. Importantly, we are not suggesting that repeat invasive assessment is indicated, but rather that these insights from clinical pathophysiology could support therapeutic approaches beyond the PPCI procedure itself. Thus, efforts to improve and/or prevent worsening of the coronary microcirculation in the first day after PPCI might reduce infarct size and optimize final outcome.

Limitations

There are a number of important limitations to our study. As with most invasive studies, small numbers limit our study and therefore these results should be considered hypothesis generating. However, the sequential approach allows patients to act as their
own controls and the magnitude of physiological changes we describe are clinically meaningful. It has been suggested that the infarct-related microcirculation may have attenuated response to adenosine. CFR may be influenced by epicardial stenosis and baseline haemodynamics. However, we measured FFR and demonstrated no residual flow limiting lesions, nor found significant differences between baseline transit times suggesting no measurable difference in basal flow. However, CFR does not result from a simple comparison of two flow values as the ratio indicates, but rather from the area limited by the pressure–flow relations obtained in the presence and in the absence of arteriolar tone. Two flow measurements may lead to different values of CFR depending on the corresponding coronary pressure. To reflect microvascular abnormalities and changes, comparison at baseline and after 24 h must be made with identical coronary pressures and this maybe an important confounder in our analysis. Furthermore, we cannot account for confounding the influence of active cardiovascular medication taken prior to admission, although patients received standard therapy after PPCI.

Acknowledgements

This study would not have been possible without the tireless support of the coronary care unit and catheter laboratory staff at the John Radcliffe Hospital.

Funding

F.C. was supported by fellowship grants from the Swiss National Foundation and the European Association for Percutaneous Coronary Intervention (EAPCI).

The Oxford National Institute for Health Research (NIHR) Biomedical Research Centre funded this study. K.C., R.C., and S.N. acknowledge support from the BHF Centre of Research Excellence, The Alberta Innovates Health Solutions (AIHS) Clinical Fellowship, and the University of Oxford Clarendon Scholarship fund (N. VMF).

Conflict of interest

none declared.

References

Neoatherosclerosis as reason for stent failures beyond 5 years after drug-eluting stent implantation

Masanori Taniwaki, Stephan Windecker, and Lorenz Räber*

Department of Cardiology, Swiss Cardiovascular Center, Bern University Hospital, Bern 3010, Switzerland
*Corresponding author. Tel: +41 316320929; Fax: +41 316324770; Email: lorenz.raeber@insel.ch

A 69-year-old male (case 1) was admitted due to acute non-ST-segment elevation myocardial infarction (NSTEMI). Eight years earlier, he had previously undergone treatment with a sirolimus-eluting stent (SES). Four years after stent implantation, a follow-up angiography was obtained showing a patent stent without obstructive in-stent restenosis (Panel A). Angiograms obtained at the time of NSTEMI (Panel B) disclosed subtotal occlusion in the middle of the SES (arrowheads). Optical coherence tomography revealed a signal intense luminal layer with an underlying, highly attenuating, diffusely demarcated area, suggestive for an intact fibroatheroma (Panel D) with a minimal cap thickness of 80 μm. Accordingly, ischaemia was caused by the high degree of stenosis (Panel E). Similarly, a 59-year-old male (case 2) was admitted due to STEMI. Nine years before, he had received a paclitaxel-eluting stent (PES). Five years after stent implantation, a follow-up angiography revealed a patent stent (Panel F). Angiograms obtained at the time of STEMI (Panel G) disclosed total occlusion in the proximal of PES (arrowheads). Optical coherence tomography showed a rupture of thin cap fibroatheroma within the stented segment (Panel I). The thin cap fibroatheroma caused a severe stenosis with superimposed thrombus (Panel J).

Neoatherosclerosis has been recently described as particular disease entity being responsible for very late stent failures. These two cases illustrate that the presence of a favourable long-term angiographic result years after DES implantation does not exclude a future neoatherosclerosis-related event (restenosis or stent thrombosis). Large observational and long-term intracoronary imaging studies are required to fully elucidate the dynamics and clinical relevance of neoatherosclerosis.

This paper was guest edited by Brahmajee Nallamothu (bnallamo@umich.edu, University of Michigan).

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: journals.permissions@oup.com