Endothelin (ET-1) is a potent vasoconstrictor. We compared patterns of ET-1 in percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and correlated it with markers of inflammation. Patients with multivessel disease were enrolled in a prospective randomized study of PCI vs. on-pump CABG. Procedural myocardial injury was assessed biochemically (CK-MB) and with new late gadolinium enhancement (LGE) on magnetic resonance imaging (MRI) one week postprocedure. ET-1 was measured at baseline, 1 h, 6 h, 12 h, 24 h and one week postprocedure. Log ET-1 values were compared between PCI and CABG and between patients without significant myocardial injury. Measurement of ET-1 values was performed in 36 PCI and 31 CABG patients. Baseline ET-1 values were similar between PCI and CABG patients (0.91±0.36 vs. 1.0±0.49 pg/ml, P=0.38). Peak values were reached at 1 h in PCI and at 24 h in CABG patients and patients undergoing CABG had significantly higher log ET-1 values at 6 h, 12 h and 24 h. ET-1 did not correlate with biochemical or morphological markers of myocardial injury or change of left ventricular ejection fraction (LV-EF) but good linear correlation between max logET-1 and max logCRP was found (r=0.44, P<0.0002). ET-1 rise is more pronounced in on-pump CABG and ET-1 production could be driven by periprocedural inflammatory reaction.

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1. Introduction

Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor known to play an important role in patients with coronary artery disease (CAD) [1]. ET-1 is associated with the no-reflow phenomenon and increased long-term mortality in the setting of primary percutaneous coronary intervention (PCI) for acute ST elevation myocardial infarction (STEMI) [2] and on-pump coronary artery bypass grafting (CABG) is known to cause increased concentrations of ET-1 leading to worse clinical outcomes and early graft failure [3, 4].

The role of ET-1 in myocardial injury during revascularization procedures and its correlation with systemic inflammation is not known. Using data from myocardial injury following Coronary artery surgery vs. angioplasty (MICASA) study, a prospective, randomized study of on-pump CABG vs. PCI for multivessel coronary artery disease, we aimed to clarify the profile of ET-1 in the periprocedural period of PCI/CABG and enlighten how the inflammatory reaction affects its production.

2. Methods

The (MICASA) trial (prospectively registered: http://www.controlled-trials.com/ISRCTN25699844) was a prospective, single centre, randomized (1:1) trial of myocardial injury following revascularization with PCI or CABG. The primary endpoint was myocardial injury defined by troponin and...
cardiac magnetic resonance imaging (CMR). Details of this study can be found elsewhere [5].

2.1. PCI and CABG details

PCI was performed using drug-eluting stents: Taxus Express (44%) and Promus (19%), Boston Scientific; Xience V (32%), Abbott Vascular; Cypher Select (5%), Cordis. Two patients also received a bare metal stent each.

CABG was performed on-pump with an average of one mammary and two vein grafts.

2.2. Biochemical measurements

Plasma samples were obtained at baseline and at 1 h, 6 h, 12 h, 24 h and one week postprocedure. Samples were stored in an –81°C locked freezer. Cardiac Troponin I and CK-MB were quantified with automated chemiluminescent immunoassay techniques on the Siemens ADVIA Centaur (cTnI ·· Ultra' for the majority) and Siemens IMMULITE, respectively (both Siemens Healthcare Diagnostics, Frimley, UK). ET-1 was measured in serum using an ELISA QuantiGlo Chemiluminescent Immunoassay (R and D Systems, Abingdon, UK). High-sensitivity CRP (hsCRP) was measured using the Luminex xMAP technology (Luminex Corporation, Austin, USA).

2.3. CMR imaging

Patients were studied at 1.5T (Sonata, Siemens Healthcare). Baseline CMR assessment was performed in the fortnight prior to revascularization. Repeat CMR was performed seven days (range 4–10 days) after the revascularization. For analysis of left ventricular function, an experienced observer who was blinded to patient data analyzed the short-axis SSFP images using customized software (Argus; Siemens, Erlangen, Germany). Left ventricular ejection fraction (LV-EF) at baseline was compared with LV-EF at seven days and delta LV-EF was defined as: LV-EF at one week minus LV-EF at baseline.

Late gadolinium enhancement (LGE) imaging was performed as previously described [6, 7]. For analysis of LGE, two experienced observers who were blinded to patient data interpreted the images. In cases of disagreement, a meeting was held with a third observer and a consensus is reached after discussion. Areas of LGE were quantified with automated chemiluminescent immunoassay techniques.

2.4. Definition of periprocedural myocardial infarction

In the PCI group periprocedural myocardial infarction was defined as CK-MB >3×99th percentile upper reference level (URL) or appearance of new LGE on CMR. In the CABG population, periprocedural myocardial position was defined as new appearance of LGE on CMR.

2.5. Statistical analysis

Continuous variables were tested for normal distribution by using Kolmogorov-Smirnov test. Normally distributed variables are presented as means±standard deviation, while non-normally distributed variables were log-transformed for analysis and are presented as log-transformed values. Continuous variables were compared between groups by using unpaired t-test, while comparisons of the changes of variables within and between the two groups were performed by using two-way ANOVA for repeated measures with time×group interaction. When multiple comparisons were performed, the P-values were corrected by using Bonferroni post-hoc correction. For categorical outcomes, χ² or Fisher’s exact test was performed where appropriate. Correlations between variables were examined by using bivariate analysis, and the Pearson’s r coefficient was calculated. A probability of P<0.05 was considered statistically significant. SPSS v18.0 was used for statistical analyses.

2.6. Ethics

The local Ethics Committee approved the study and informed written consent was obtained from each patient.

3. Results

A total of 80 patients were included in the MICASA study. Forty patients were randomized to PCI and 40 patients to CABG. Blood sampling was incomplete in four patients from the PCI group and in nine patients from the CABG group. Thirty-six patients from the PCI group and 31 patients from the CABG group were included in the final analysis (Fig. 1). There were no significant differences in baseline characteristics between PCI and CABG groups (Table 1).

3.1. Periprocedural myocardial injury

The results for baseline and peak Troponin I/CK-MB values are summarized in Table 2. Baseline Troponin I and CK-MB values were similar between PCI and CABG patients. Peak Troponin I was 2.72±5.87 in the PCI and 10.43±8.74 in the CABG group (P=0.0003). Peak CK-MB values were also higher in CABG patients (7.98±10.8 vs. 33.6±22.8, P<0.0001).

New LGE on CMR was present in 15 of 67 patients (22.4%). Appearance of new LGE was 29% in CABG patients (9/31) and 17% in PCI patients (6/36).

[Fig. 1. Consort diagram.]

80 patients included in the study

40 patients randomized to PCI

36 patients included in final analysis

4 excluded due to incomplete blood sampling

31 patients included in final analysis

9 excluded due to incomplete blood sampling
3.2. Endothelin-1 in PCI and CABG patients

Baseline ET-1 values were similar between PCI and CABG patients (0.91±0.36 vs. 1.0±0.49 pg/ml, P=0.38). Peak ET-1 was significantly higher in CABG patients compared to PCI (2.44±0.64 vs. 1.35±0.64, P<0.0001).

Mean log ET-1 values for the different time points are summarized in Fig. 2a. No significant differences were found at baseline (P=0.49) and at 1 h (P=0.9) between PCI and CABG patients. Overall there was a significantly greater elevation of ET-1 in the CABG compared to the PCI group over the study period (P=0.006). CABG patients had significantly higher log ET-1 values at 6 h (P=0.0002), 12 h (P<0.0001) and 24 h (P<0.0001) compared to PCI. ET-1 continues to be higher in CABG patients at one week but this did not reach statistical significance (P=0.07).

Table 2. Mean baseline/peak troponin I and CK-MB values in PCI and CABG

<table>
<thead>
<tr>
<th>Troponin I (µg/l)</th>
<th>PCI (n=36)</th>
<th>CABG (n=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.06 (±0.26)</td>
<td>0.06 (±0.06)</td>
<td>0.24</td>
</tr>
<tr>
<td>Peak</td>
<td>2.72 (±5.87)</td>
<td>10.43 (±8.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB (U/l)</td>
<td>1.64 (±1.31)</td>
<td>1.49 (±0.91)</td>
<td>0.60</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.96 (±10.8)</td>
<td>33.6 (±22.84)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

There were no significant changes in baseline troponin I or CK-MB levels between the two groups. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. Values expressed as means±standard deviation.

3.3. Relationship of endothelin-1 to periprocedural injury

Fig. 2b demonstrates log ET-1 values at different time points for patients with periprocedural myocardial infarction or those without. No significant differences were found between the two groups at any of the time points.

Log ET-1 values were not significantly different for patients with new appearance of LGE and those without at any of the time points. No correlation was found between peak log ET-1 and peak troponin I (r=0.169, P=0.17).

3.4. Association of ET-1 with periprocedural inflammatory reaction

Log peak-ET-1 correlated with log peak-CRP values (r=0.44, P=0.0002). In CABG patients no correlation was...
found between ET-1 values and bypass time or cross-clamp time but a significant correlation was demonstrated between lowest core temperature and log ET-1 values at 6 h (r=0.426, P=0.026).

3.5. Periprocedural change of left ventricular ejection fraction

Mean LV-EF did not change significantly during PCI and CABG (LV-EF baseline: 69±8.5 vs. LV-EF at one week: 68.1±11.5%, P=0.47). Fig. 3 demonstrates the lack of significant correlation between delta LV-EF and log max ET-1 values measured during the one-week period (r=0.23, P=0.09).

4. Discussion

This is the first study to compare ET-1 release patterns after PCI and on-pump CABG in patients with multivessel CAD and we demonstrate that patients who are randomized to on-pump CABG show major differences in ET-1 profiles after the procedure compared to subjects with similar characteristics randomized to PCI (Fig. 2a). Peak ET-1 values are reached 1 h after the procedure in the PCI group but in patients undergoing CABG, ET-1 levels peak at 24 h and continue to be elevated well beyond 24 h.

A range of different studies have described elevated ET-1 after on-pump CABG and some investigators have linked endothelin to negative clinical outcomes in the perioperative period [3, 8, 9]. Interestingly clinical and angiographic outcomes have been compared to ET-1 values before [9] and early (1 h) [3] after CABG, and our study suggests that future studies might consider comparing the 24-h ET-1 values as it is well known that complications [e.g. myocardial stunning, onset of atrial fibrillation (AF) etc.] often arise >24 h after the operation.

We used a combined biochemical (CK-MB) and morphological (LGE on CMR) definition to describe periprocedural myocardial infarction. In the PCI group we used the current universal definition [10] (CK-MB >3×URL) and in the CABG population the presence of new LGE was used to diagnose periprocedural infarction. No significant difference in ET-1 values was found at any of the time points between patients with periprocedural myocardial infarction and those without (Fig. 2b).

While it is well-known that myocardial injury is primarily driven by distal embolization, side-branch occlusion and disruption of collateral flow in PCI [11, 12], the mechanisms of PMI in CABG are not entirely understood. The results of our study suggest that ET-1 does not seem to play a major role in this setting.

It has not been definitely established which organs are responsible for the elevated ET-1 during CABG and PCI. In CABG patients simultaneous measurements of ET-1 concentrations in the ascending aorta and coronary sinus indicated a production outside the coronary circulation [3, 13]. It needs to be highlighted that in our CABG population all patients underwent on-pump surgery and it is possible that off-pump CABG (avoiding manipulation of endothelium in the aorta) could have revealed entirely different results.

As demonstrated in Fig. 4 a significant correlation was demonstrated between Log max CRP and max Log ET-1. This suggest ET-1 might be produced a response to inflammatory stress [14]. Within this study patients underwent on-pump surgery and statin therapy was prescribed less often in CABG patients – both factors may be relevant in aggravating the inflammatory response. ET-1 could have a role in the initiation of atrial fibrillation (AF) after CABG and this may be influenced by steroid therapy 15.

Future efforts to identify potential drugs and interventions, which reduce the production of inflammatory agents and ET-1 are likely to be beneficial.

ET-1 is not only a powerful vasoconstrictor (it can act as a vasodilator depending on the target receptors) and is
also known to have inotropic effects on the myocardium. Fig. 3 demonstrates the comparison of log max ET-1 values and delta LV-EF (between baseline and one week postprocedure) but no significant correlation was found. However, mean LV-EF did not change significantly in our study patients and it is possible that an inotropic effect of ET-1 could be demonstrated in a population with more profound changes of systolic function.  

5. Conclusions  
This study demonstrates marked differences in ET-1 concentrations between similar populations of patients with multi-vessel CAD randomized to PCI or on-pump CABG. Peak ET-1 values are reached after 24 h in CABG and remain elevated up to one week after the procedure and ET-1 does not seem to play a role in periprocedural myocardial injury. The strong correlation of ET-1 and CRP values indicates that the inflammatory stimulus during CABG and PCI might warrant further attention and presents a potential therapeutic target.  

References  

