Ischemia Modified Albumin Is a Sensitive Marker of Myocardial Ischemia After Percutaneous Coronary Intervention

Manas K. Sinha, MRCP; David C. Gaze, BSc; John R. Tippins, PhD; Paul O. Collinson, FRCP; Juan Carlos Kaski, MD, DSc, FRCP, FESC

Background—Ischemia modified albumin (IMA; Ischemia Technologies, Inc) blood levels rise in patients who develop ischemia during percutaneous coronary intervention (PCI). It is not known whether IMA elevations correlate with increases in other markers of oxidative stress, ie, 8-iso prostaglandin F2-A (iP).

Methods and Results—We compared IMA versus iP plasma levels in 19 patients (mean age 62.8 ± 11.9 years) undergoing PCI and 11 patients (mean age 64 ± 13.6 years) undergoing diagnostic angiography (controls). In the PCI patients, blood samples for IMA and iP were taken from the guide catheter before PCI and after balloon inflations, and from the femoral sheath 30 minutes after PCI. IMA was measured by the albumin cobalt binding (ACB) test and plasma iP by enzyme immunoassay. During PCI, all 19 patients had chest pain and 18 had transient ischemic ST segment changes. IMA was elevated from baseline in 18 of the 19 patients after PCI. Median IMA levels were higher after PCI (101.4 U/mL, 95%CI 82 to 116) compared with baseline (72.8 U/mL, CI 55 to 93; \( P<0.0001 \)). Levels remained elevated at 30 minutes (87.9 U/mL, CI 78 to 99; \( P<0.0001 \)) and returned to baseline at 12 hours (70.3 U/mL, CI 65 to 87; \( P=0.65 \)). iP levels were raised after PCI in 9 of the 19 patients. However, median iP levels were not significantly different immediately (\( P=0.6 \)) or 30 minutes after PCI (\( P=0.1 \)). In the control group, IMA and iP levels remained unchanged before and after angiography (\( P=0.2 \) and 0.16, respectively).

Conclusions—IMA is a more consistent marker of ischemia than iP in patients who develop chest pain and ST segment changes during PCI. (Circulation. 2003;107:2403-2405.)

Key Words: ischemia • proteins • angioplasty

Ischemia modified albumin (IMA; Ischemia Technologies, Inc), measured by the albumin cobalt binding test (ACB; Ischemia Technologies), has been shown to be a marker of myocardial ischemia.\(^1\) ACB measures the ability of the amino terminus (N-terminus) of human albumin to bind exogenous cobalt. Under physiological conditions, transition metals can bind tightly to the exposed N-terminus of albumin.\(^2\) In the presence of myocardial ischemia, structural changes take place in the N-terminus of the protein,\(^3,4\) which reduce its binding capacity, possibly, in part, as a result of exposure to reactive oxygen species (ROS). IMA rises in patients who develop myocardial ischemia during percutaneous coronary intervention (PCI).\(^5\) PCI offers a clinical model of myocardial ischemia-reperfusion characterized by an increase in oxidative stress.\(^6-8\)

ROS are produced after myocardial ischemia-reperfusion and result in the production of lipid and protein peroxidation products in the local myocardial environment. This occurs irrespective of the mechanism responsible for ischemia, ie, increased oxygen demand or a primary reduction of coronary blood flow.\(^9\) 8-epi prostaglandin F\(_\text{2a}\) (iP), a prostaglandin isomer, is formed by free-radical catalyzed oxidation of arachidonic acid esterified in membrane phospholipids.\(^10\) It represents a chemically stable end-product of lipid peroxidation that circulates in plasma and is excreted in the urine.\(^11\)

In the present study, we sought to compare blood levels of IMA and iP in angina patients before and after elective PCI and evaluate the correlation of these biomarkers to evidence of transient ischemia induced by PCI balloon inflation.

Methods

Patients

We assessed 19 consecutive chronic stable angina patients undergoing PCI for management of single-vessel coronary artery disease (>70% stenosis in a major coronary artery with no evidence of significant collateral coronary circulation around the single stenotic vessel) and 11 controls (patients undergoing diagnostic angiography,
with coronary artery disease). None of the patients had other acute or chronic ischemic conditions including stroke, transient ischemic attack, claudication, peripheral vascular disease, kidney failure, shock, or objective evidence of acute myocardial infarction <72 hours before angiography (unequivocal ECG abnormalities, serial cardiac troponin elevations, or angiographic evidence). PCI patients received ticlopidine 24 hours before the procedure. The study was approved by the local research ethics committee, and all patients signed written informed consent.

**PCI and Sample Acquisition**

PCI was performed via the femoral approach using a standardized procedure. Basal, pre-PCI samples were obtained from the guide catheter for measurements of IMA and iP. PCI was then performed with stent deployment as required. Blood samples were obtained from the guide catheter immediately after balloon deflation, from the femoral sheath 30 minutes after, and from peripheral blood 12 hours after PCI for measurement of both IMA and iP. ECGs were recorded at baseline and after balloon inflations to assess ST segment shifts. Cardiac troponin (cTnT) was measured at approximately 12 hours after PCI. In the 11 control patients who underwent uncomplicated diagnostic angiography, blood samples for IMA and iP were taken from the guide catheter before and after coronary angiography.

**Biochemical Assessment**

Serum IMA was measured by the albumin cobalt binding (ACB) test on a Roche Cobas MIRA PLUS instrument (ABX Diagnostics). The first generation ACB test method has been validated and described in previous publications.12,13 We used a newer generation ACB test and in our laboratory, and assay CV was 5.09% in the range of 56.67 to 66.57 U/mL and 3.05% in the range 147.17 to 158.03 U/mL. The IMA upper limit of normal, 85 U/mL (95th percentile of a population of 283 apparently healthy individuals), was used as a cutoff point for cardiac ischemia in the study, according to the manufacturer’s data.

Plasma samples for iP analysis were immediately frozen in liquid nitrogen and stored at −70°C until assessment. To estimate total iP, an internal standard of [3H]PGF2α, was added to the thawed sample, and protein was precipitated with ethanol. After centrifugation, isoprostanes in the supernatant were hydrolyzed from lipids by incubation with potassium hydroxide at 40°C for 1 hour. The samples were brought to pH 3 with hydrochloric acid and purified by solid phase extraction. Samples were then eluted with ethyl acetate, evaporated to dryness under a stream of nitrogen, and re-dissolved in assay buffer. Half the sample was used to determine recovery by scintillation counting of the [3H] PGF2α, for an enzyme immunoassay, and iP was then quantified using a competition enzyme immunoassay, which has been previously validated by gas chromatography-mass spectrometry (Cayman Chemicals).14–16

cTnT was measured by electrochemiluminescence with an Elecsys 1010 analyser (Roche Diagnostics). cTnT concentrations >0.1 ng/mL were considered positive.

**Statistical Analysis**

Nonparametric, descriptive, and comparative statistics for continuous variables were performed using Analyze-it v1.62, software. The exact binomial method was used for calculation of the lowest computable confidence interval to 95%. The Wilcoxon signed ranks test was used to test for statistical difference between medians of two related samples. Differences were considered significant at a value of P > 0.05.

**Results**

The clinical and procedural characteristics of all patients included in the study are described in the Table. There were no acute vessel closures or dissections and no patients suffered a myocardial infarction during PCI or angiography. None of the patients had cTnT levels >0.1 ng/mL 12 hours after procedure. However, 4 patients had cTnT levels >0.05 ng/mL but <0.1 ng/mL. Control patients had no chest pain or ECG changes during angiography. During PCI, all patients experienced chest pain, and 18 had transient ischemic ST segment changes. Median IMA levels were higher immediately after PCI (101.4 U/mL, 95% confidence interval (CI) 82 to 116) compared with baseline (72.8 U/mL, CI 55 to 93; P < 0.0001) and remained elevated for at least 30 minutes (87.9 U/mL, CI 78 to 99; P < 0.0001). IMA levels returned to baseline at 12 hours (70.3 U/mL, CI 65 to 87; P = 0.65). Median iP levels increased from 62.6 pg/mL (95% CI 45 to 83) at baseline to 63.6 pg/mL (CI 45 to 104) and 69.3 pg/mL (CI 50 to 165) immediately and 30 minutes after PCI; P = 0.6 and 0.1, respectively. The Figure shows the percentage change in IMA and iP from baseline to after PCI levels in every study patient. Eighteen of the 19 patients PCI patients had elevated levels of IMA after PCI compared with baseline, whereas 9 patients had increased iP levels after PCI. In the control group, median IMA was 86.2 U/mL preangiography compared with 86.7 U/mL after angiography (P = 0.2), and median iP levels were 47 pg/mL preangiography and 75 pg/mL after angiography (P = 0.16). There was no correlation between the highest postprocedural IMA value and number of inflations, duration of inflation, or balloon pressures.

**Discussion**

This study showed that IMA is an early marker of myocardial ischemia in the PCI setting. Our finding of raised IMA levels in patients who developed chest pain and ischemic ECG changes after PCI is comparable to previous results by other authors.5 Increased IMA levels indicate a reduced metal binding capacity of albumin associated with cardiac ischemia and the production of oxygen free radical species.17 It is possible that albumin acts as a “sacrificial” antioxidant to reduce injury during reperfusion.18

Isoprostanes represent products of lipid peroxidation and are indicative of superoxide production.19 In our study, iP increased in response to coronary artery occlusion during PCI in 9 of 19 patients similar to data from previous studies.14–16 but was not a reliable marker of ischemia. IMA, however, was a more consistent marker of ischemia, with 18 of the 19

---

**Clinical and Procedural Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population, n</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>62.8±11.9</td>
<td>64±13.6</td>
</tr>
<tr>
<td>Men, n</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Cigarette smoking, n</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hypercholesterolemia &gt;5 mmol/L, n</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Previous MI, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Family history of CAD, n</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Stent insertion, n</td>
<td>19</td>
<td>...</td>
</tr>
<tr>
<td>Mean No. of balloon inflations, n (±SD)</td>
<td>4.5 (2.3)</td>
<td>...</td>
</tr>
<tr>
<td>Mean total balloon inflation time, s (±SD)</td>
<td>157 (67)</td>
<td>...</td>
</tr>
<tr>
<td>Mean inflation pressure, Atm (±SD)</td>
<td>11.1 (1.9)</td>
<td>...</td>
</tr>
</tbody>
</table>
patients who had angina and ischemic ECG shifts during PCI showing a statistically significant rise in IMA concentration.

The reason for the lack of elevated iP levels in approximately 50% of patients is not clear. However, isoprostanes are thought to be a very early marker of lipid peroxidation and our sampling method may not have been quick enough to detect its rise in blood after PCI. The possibility of a dilution effect when measurements are performed in peripheral blood has to be considered, and it is also possible that in some patients the magnitude of myocardial ischemia was mild and could have escaped detection by iP measurement, unlike IMA, which appears to be sensitive to transient ischemia.

The present study confirms and expands previous suggestions that IMA is a useful marker of ischemia in the PCI setting. Further studies however are required to investigate the role of IMA in the broader clinical setting of patients with acute chest pain. In conclusion, our findings indicate that the role of IMA in the broader clinical setting of patients with acute chest pain. Further studies however are required to investigate the possibility of dilution effect when measurements are performed in peripheral blood has to be considered, and it is also possible that in some patients the magnitude of myocardial ischemia was mild and could have escaped detection by iP measurement, unlike IMA, which appears to be sensitive to transient ischemia.

Acknowledgments

M. Sinha is the recipient of an unrestricted educational grant from Ischemia Technologies. We thank Deborah Morris for invaluable statistical analysis and critical comments.

References

Ischemia Modified Albumin Is a Sensitive Marker of Myocardial Ischemia After Percutaneous Coronary Intervention
Manas K. Sinha, David C. Gaze, John R. Tippins, Paul O. Collinson and Juan Carlos Kaski

Circulation. 2003;107:2403-2405; originally published online May 12, 2003; doi: 10.1161/01.CIR.0000072764.18315.6B
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/19/2403

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/