SCIENTIFIC LETTER

Effects of balloon occlusion during percutaneous coronary intervention on circulating Ischemia Modified Albumin and transmyocardial lactate extraction

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Studies have shown that human albumin undergoes a considerable reduction in its capacity to bind exogenous cobalt (Ischemia Modified Albumin (IMA); Ischemia Technologies, Denver, Colorado, USA), as measured by the albumin cobalt binding test, when exposed to an ischaemic insult. We have recently observed that plasma IMA levels increase soon after transient balloon inflation during percutaneous coronary intervention (PCI), even in the absence of considerable elevations of cardiac troponin.[1] Higher IMA levels have also been reported in patients with acute coronary syndrome attending the emergency department with recent-onset chest pain.[2] At present however, no data exist regarding the relationship between IMA and an accepted gold standard for myocardial ischaemia—that is, myocardial lactate extraction.[3] We therefore sought to assess whether increased IMA plasma levels documented in patients after PCI correlate with an increased production of lactate by the myocardium.

METHODS

We simultaneously measured coronary sinus and arterial lactate concentrations and plasma IMA levels before and after balloon inflation in 10 patients with chronic stable angina undergoing PCI to the proximal left anterior descending coronary artery. The study protocol was approved by the local ethics committee, and informed written consent was obtained from all patients before study entry. Patients with signs or symptoms of acute or chronic ischaemic conditions, including stroke, transient ischaemic attack, leg claudication or shock, were not included. Blood was drawn for detecting IMA and lactate: (1) immediately before PCI, using arterial and venous sheaths; (2) 1 min after the last balloon inflation (arterial and coronary sinus measurements); (3) 5 min after PCI (arterial and coronary sinus measurements); (4) 1 h after PCI (peripheral vein) for IMA; and (5) 6 h after PCI (peripheral vein) for IMA. For coronary sinus lactate sampling, a multi-purpose catheter was inserted via right femoral vein puncture and positioned in the coronary sinus just proximal to the great cardiac vein. The position was checked repeatedly by injections of small amounts of contrast medium. IMA was measured using the albumin cobalt binding test on the Roche Cobas MIRA PLUS instrument (Rotkreuz, Switzerland).[1 2] In our laboratory, the albumin cobalt binding test within-run duplicate percentage of coefficient of variation (CV%) of patient samples ranged from 0% to 6.5%, with an average of 1.9%. Lactate concentration was measured by an enzymatic kit (Boehringer Mannheim, Mannheim, Germany) with intra-assay and interassay CVs of 3.7% and 4.8%, respectively. The analytical range for the study was 0.3–11.1 mmol/l. Net lactate extraction was calculated using the formula: (arterial lactate−sinus lactate)/arterial lactate ×100%, with the normal range being 10–60% and ischaemia developing with lactate extraction of $\leqslant 10\%$.[4]

Non-parametric descriptive and comparative statistics for continuous variables were determined using Analyse-it v.1.62 (Analyse-it Software, Leeds, UK). The Wilcoxon's signed ranks test was used to test for statistical difference between medians of two related samples. The exact binomial method was used for calculation of the closest computable confidence interval (CI) to 95%. Pearson's correlation coefficient was used to compare IMA levels with the lactate gradient. Differences were considered significant at $p<0.05$.

RESULTS

PCI was successful in all patients and there were no complications related to the research procedure. The arterial and sinus samples used for comparison were the baseline, 1-min and 5-min samples, when the arterial sheath was in place. The 1-h and 6-h comparisons were between the initial baseline IMA and 1-h and 6-h peripheral venous sample. Baseline IMA venous and arterial IMA levels were similar ($p = 0.3$). Compared with baseline (101 U/ml, 95% CI 83 to 128), median IMA arterial levels were higher after PCI balloon inflation: immediately after PCI, 114 U/ml (95% CI 101 to 139), $p = 0.04$, and 5 min after PCI, 120 U/ml (95% CI 97 to 129), $p = 0.01$. Peripheral venous IMA levels at 1 h after PCI were similar to baseline arterial IMA concentration ($p = 0.5$). There was a consistent rise in IMA following balloon inflation in our patients.

Coronary sinus IMA levels, however, did not show a significant rise from baseline (110 U/ml, 95% CI 98 to 132, to 111 U/ml, 95% CI 98 to 124; $p = 0.94$) despite balloon inflation. Baseline median arterial lactate concentration was 0.85 mmol/l (95% CI 0.5 to 1.1), which was statistically different from the median baseline sinus lactate concentration (0.60 mmol/l (95% CI 0.4 to 0.8); $p = 0.002$). Median arterial lactate concentration was 0.75 mmol/l (95% CI 0.5 to 1) 1 min after balloon inflation and 0.60 mmol/l (95% CI 0.5 to 0.9) 5 min after balloon inflation ($p = 0.01$). Median coronary sinus lactate concentration 1 min after balloon inflation was 0.8 mmol/l (95% CI 0.5 to 2.1), which rose from a baseline of 0.6 mmol/l ($p = 0.01$) At 5 min after balloon inflation, median coronary sinus lactate concentration fell to baseline level: 0.5 mmol/l (95% CI 0.3 to 0.7). Median net lactate extraction changed from 29.4% (95% CI 9.1 to 40) at baseline to −6.7% (95% CI −162.5 to −30) immediately after PCI ($p = 0.006$). Median myocardial lactate extraction after PCI was still significantly different, 16.6% (95% CI 0 to 28.6) at 5 min after PCI compared with that of baseline ($p = 0.01$) (table 1). There was, however, no significant correlation between changes in IMA and lactate gradient, $r = -0.3$.

Abbreviations: IMA, Ischemia Modified Albumin; PCI, percutaneous coronary intervention

Table 1 Ischemia-Modified Albumin (IMA) and lactate levels during percutaneous coronary intervention

Time point	n	Arterial IMA median (95% CI)	p	n	Sinus IMA median (95% CI)	p	n	Lactate extraction % median (95% CI)	p
Baseline	10	101 (83 to 128)	NA	10	110 (98 to 132)	NA	10	29.4 (−40 to −10)	NA
1 min after	10	114 (101 to 139)	0.04	10	111 (94 to 142)	0.92	10	−6.7 (−162.5 to −30.0)	0.006
5 min after	10	120 (97 to 129)	0.01	10	111 (98 to 124)	0.94	10	16.6 (0.0 to 28.6)	0.01

NA, not applicable; p = Wilcoxon's W statistic, two-tailed p for difference from baseline.

DISCUSSION

Transient coronary artery occlusion during PCI can be considered to represent a model of ischaemia reperfusion. A marked, albeit transient, increase in cardiac oxidative stress has consistently been shown to occur after ischaemia–reperfusion injury.[4] Under ischaemic conditions, there is depletion of endogenous antioxidants. With re-oxygenation of ischaemic tissue there is a rapid release of reactive oxygen species, followed by the release of lipids, protein peroxidation products and lactate into the circulation that peaks in the first 1–5 min of reperfusion, and declines after 2–5 min.[5] This is the first study to compare transmyocardial lactate production and plasma IMA changes in the context of cardiac ischaemia induced by balloon inflation. Baseline IMA levels in our patients (101 U/ml) were higher than those reported by the manufacturers (ie, 85 U/ml). The reasons for this are speculative, but recurring silent ischaemia in these patients with significant coronary stenoses is a possible explanation. It is not clear why arterial lactate continues to fall despite a rise in coronary sinus lactate level, but the difference could be explained by a dilution effect in the arterial blood and possibly also by the rapid elimination/uptake of lactate from the peripheral circulation. Coronary sinus IMA levels did not change considerably, and this may be explained by the more gradual accumulation of IMA in arterial blood versus little change in coronary sinus blood. This may represent rapid wash-out of IMA from the heart and its gradual accumulation in arterial blood, as unlike lactate, it is not likely to be rapidly removed or the N-terminus converted back to the native state. Also, technical difficulties related to coronary sinus sampling may explain this discrepancy at least partly. The continued elevation in coronary sinus lactate levels most likely results from metabolic wash-out after reperfusion injury.

We conclude that the rise in IMA level observed in the study after PCI paralleled that of transmyocardial lactate, an accepted gold standard for ischaemia. There was a consistent pattern of myocardial lactate extraction and IMA release after obstructive PCI balloon inflation, which suggests both that balloon inflation during PCI induces ischaemia and that IMA is a reliable marker of ischaemia–reperfusion injury. Although IMA measurements may not have a role during PCI, our findings are of clinical importance, as elevations in this marker correlate with metabolic signs of myocardial ischaemia, thus endorsing our previous findings and conclusions in patients attending the emergency department with severe chest pains suggestive of acute coronary syndrome.[2]

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