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RESEARCH ARTICLE

Increased ischaemia modified albumin following coronary artery bypass grafting

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Abstract

Background: Any increase of cardiac biomarkers after coronary artery bypass grafting (CABG) indicates myocyte necrosis and is likely to be related to an impaired outcome. We investigated whether ischaemia-modified albumin (IMA), a biomarker of ischaemia, is also raised following CABG. *Methods:* We studied 50 stable consecutive patients undergoing elective isolated CABG on cardiopulmonary bypass, of whom 46 were men and four women, aged 64 ± 9 years. Blood samples were obtained the day before the operation (pre-op) as well as immediately after the operation, 24 h postoperatively (post-op) and the fourth day post-op and assayed for creatine kinase, the MB isoenzyme of creatine kinase, cardiac troponin-I, albumin and IMA. *Results:* The typical rising and falling pattern of myocardial necrosis of all three cardiac enzymes was observed post-op (p <0.0001). IMA increased significantly following CABG at all three time points (113 ± 43, 106.7 ± 22.6 and 110.2 ± 12.5 U ml^{-1}, respectively) compared with pre-op values (91.7 ± 10.5 U ml^{-1}), (p <0.0001); the sample immediately post-op was significantly higher compared with the following samples (immediately post-op vs 24 h, p = 0.008 and immediately post-op vs 4 days, p = 0.03, with no significant difference between the last two). IMA level changes during the study course were independent of the albumin changes. Haemoglobin decreased significantly post-op (p <0.0001 vs baseline) whereas serum creatinine did not differ during the study period. *Conclusions:* IMA increases significantly following CABG but whether or not this carries a prognostic significance remains to be elucidated.

Keywords: *Ischaemia modified albumin; cardiac surgery; ischaemia; biomarkers*

Introduction

Any increase of cardiac biomarkers after coronary artery bypass grafting (CABG) indicates myocyte necrosis and is likely to be related to an impaired outcome. Indeed, studies employing the MB isoenzyme of creatine kinase, demonstrated that 5, 10 and 20 times the upper limit of normal following CABG were associated with worse prognosis (Costa et al. 2001, Klatte et al. 2001, Brener et al. 2002). Likewise, increased troponin levels after CABG predicts a poor outcome, in particular when elevated to the highest quartile or quintile (Januzzi et al. 2002, Groal et al. 2006). Biomarker values more than five times the 99th percentile of the normal reference during the first 72 h following CABG is one of the diagnostic criteria of a CABG-related myocardial infarction (Thygesen et al. 2007). We investigated whether or not ischaemia-modified albumin (IMA), a biomarker of ischaemia, which increases following percutaneous coronary intervention (PCI) (Bar-Or et al. 2001, Sinha et al. 2003, Quiles et al. 2003, Garrido et al. 2004) and in relation to acute coronary syndromes (ACS) (Christenson et al. 2001, Bhagavan et al. 2003, Sinha et al. 2004, Peacock et al. 2006), is also raised following CABG. Regarding IMA, there are limited reports in association to cardioversion (Roy et al. 2004), radiofrequency ablation (Roy et al. 2004, Sbarouni et al. 2007) and pacemaker insertion (Sbarouni et al.); its role in non-invasive evaluation

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of coronary artery disease is under investigation (Van der Zee et al. 2005, Sbarouni et al. 2006, Kurz et al. 2007, Sbarouni et al. 2008). Ischaemia, through hypoxia, acidosis, free radical injury and energy-dependent membrane disruption, may reduce the binding capacity of the amino terminus of albumin to bind metals such as cobalt, copper and nickel; numerous investigations, with a well-validated assay (Morrow et al. 2003, Aslan & Apple 2004, Gidenne et al. 2004, Apple et al. 2005), not only demonstrate a correlation between IMA and myocardial ischaemia but also a link to clinical outcome in both ACS and PCI (Dusek et al. 2006, Consuerga-Sanchez et al. 2008).

Methods

We studied 50 stable consecutive patients undergoing elective isolated CABG on cardiopulmonary bypass (CPB). Patients with ACS were excluded prior to entry into the study. The ethics committee of the hospital approved the present study and written informed consent was obtained from all patients.

The baseline and demographic characteristics of the study group are shown in Table 1. Left ventricular ejection fraction was estimated with the use either of left ventricular angiogram or echocardiography. Twenty-two of our patients had preserved left ventricular function (ejection fraction >50%), 25 moderate (30–50%) and only three poor (<30%). Eleven patients received two grafts, 31 received three and eight received four grafts; all patients received the left internal mammary artery to the left anterior descending. Thirty-day mortality was 2% (one patient died). In terms of morbidity, 12 patients developed atrial fibrillation and three supraventricular tachycardia; all patients were successfully reverted to sinus rhythm with intravenous amiodarone or direct current cardioversion as second line treatment.

Table 1. The baseline and demographic characteristics of the patients.

Age (years)	64 ± 9
Male, *n* (%)	46 (92)
Diabetes, *n* (%)	12 (24)
Hypertension, *n* (%)	21 (42)
Smokers, *n* (%)	30 (60)
Ejection fraction (%)	50.7 ± 8
Number of affected coronary arteries, *n* (%)	
1-vessel	1 (2)
2-vessel	9 (18)
3-vessel	40 (80)
Cardiopulmonary support time (min)	121 ± 35
Cross-clamping time (min)	74 ± 22
Grafts/patient	2.9 ± 0.6
IMA graft use, *n* (%)	50 (100)

Data are expressed as mean ± standard deviation and *n* (%).IMA, internal mammary artery.

Blood samples were obtained the day before the operation (pre-op) for albumin and IMA as well as immediately after the operation at the intensive care unit arrival, 24 h postoperatively (post-op) and the fourth day post-op and assayed for creatine kinase, the MB isoenzyme of creatine kinase, cardiac troponin-I (CPK, CPK-MB, Tn-I), albumin and IMA. Serum IMA was measured with the albumin cobalt binding test on an Integra 800 analyzer (Roche, Rotkreuz, Switzerland), which is an indirect method of IMA measurement. Cobalt not bound to the N-terminus of albumin is detected using dithiothreitol as a colometric indicator. Blood samples were collected in serum separator tubes, centrifuged at 3000 rpm for 10 min and stored at −70°C for 1 month. All samples were tested in one session in triplicates and were thawed only once. The variability in IMA measurements in our lab was calculated in 15 serum samples as follows: three times consecutively for each sample at day 1, once at day 2 and once at day 3. The within-day coefficient of variation was 6.1% while for the between-day variation was 9.22%.

Data are expressed as mean ± standard deviation and median. Data analysis was based on non-parametric statistical methods due to the small sample and the abnormal distribution of the enzymes. Non-parametric repeated measures analysis to evaluate differences of the investigated parameters at all time points was used. Subsequently, Wilcoxon test for pair-wise comparisons for post-hoc analysis was applied. Spearman's correlation coefficient was used to evaluate the correlation between the IMA and all cardiac enzymes. *p*-Values were derived from two-sided hypotheses tests. However, due to the inflation of type I errors because of multiple comparisons, all reported *p*-values were corrected according to the Bonferroni rule. All statistical calculations were performed in SPSS version 14 package (SPSS Inc., Chicago, IL, USA).

Results

The typical rising and falling pattern of myocardial necrosis of all three cardiac enzymes was observed (Table 2). In detail, CPK peaked at 24 h (immediately post-op vs 24 h post-op, $p < 0.0001$) and significantly decreased at 4 days (4 days vs both immediate post-op and 24 h post-op, $p < 0.0001$). CPK-MB peaked immediately post-op and then gradually decreased (immediately post-op vs both 24 h post-op and 4 days post-op, $p < 0.0001$ and 24 h post-op vs 4 days postop, $p < 0.0001$). Tn-I increased immediately and 24 h post-op with no statistical difference between the two and decreased at 4 days (4 days vs both immediately post-op and 24 h post-op, $p < 0.0001$).

All post-op albumin levels were significantly lower vs baseline (p <0.0001) but the 24 h post-op and the 4 days values were significantly higher compared with the immediately post-op levels (p <0.0001) (Table 2). IMA increased significantly following CABG at all three time points compared with pre-op values (p <0.0001) but the immediately post-op sample was significantly higher compared with the following samples (immediately post-op vs 24 h, p = 0.008 and immediately post-op vs 4 days p = 0.03, with no significant difference between the last two), (Table 2, Figure 1). IMA level changes during the study course were independent of the albumin changes. We further tested the covariance between cardiac enzymes and IMA and we found no significant relationship between CPK and IMA (p = 0.48), CPK-MB and IMA (p = 0.167) and Tn-I and IMA (p = 0.1), at all time points. As expected, haemoglobin fell significantly at all post-op time points (p <0.0001) compared with baseline (13.75 ± 1.57 g dl^{-1}), the immediately post-op value (10.34 ± 1.26 g dl^{-1}) being significantly lower compared with the 24 h post-op sample (10.91 ± 1.101, p = 0.041) and with no significant difference between the 24 h and the 4th day values (10.96 ± 1.27, p = 0.073). Serum creatinine levels did not differ significantly during the study course (1.11 ± 0.21 mg dl^{-1} pre-op vs 1.01 ± 0.17, 1.07 ± 0.11, 1.14 ± 0.15 post-op, p = NS). In addition, the IMA changes we observed during the study were independent of the changes in haemoglobin.

Discussion

We found that IMA significantly increases following isolated elective CABG; it peaks immediately

Table 2. Cardiac enzymes, ischaemia-modified albumin (IMA) and albumin changes following coronary artery bypass grafting.

	Baseline	Immediately post-operation	24 h post-operation	4 days post-operation	p-Value for trend
CPK (mIU ml^{-1})	62 ± 31	507 ± 300	717 ± 460	239 ± 562	0.006
CPK-MB (ng ml^{-1})	0.96 ± 0.6	41 ± 31	28 ± 31	1 ± 1	<0.001
Tn-I (ng ml^{-1})	0.05 ± 0.05	8.3 ± 8.1	9.2 ± 7.7	1.1 ± 2.3	<0.001
IMA (U ml^{-1})	91.7 ± 10.5	113 ± 43	106.7 ± 22.6	110.2 ± 12.5	<0.001
Albumin (g dl^{-1})	4.2 ± 0.3	2.8 ± 0.4	3.3 ± 0.4	3.3 ± 0.3	<0.001

Data are expressed as mean ± standard deviation.CPK, creatine kinase; CPK-MB, MB isoenzyme of creatine kinase; Tn-I, cardiac troponin-I.

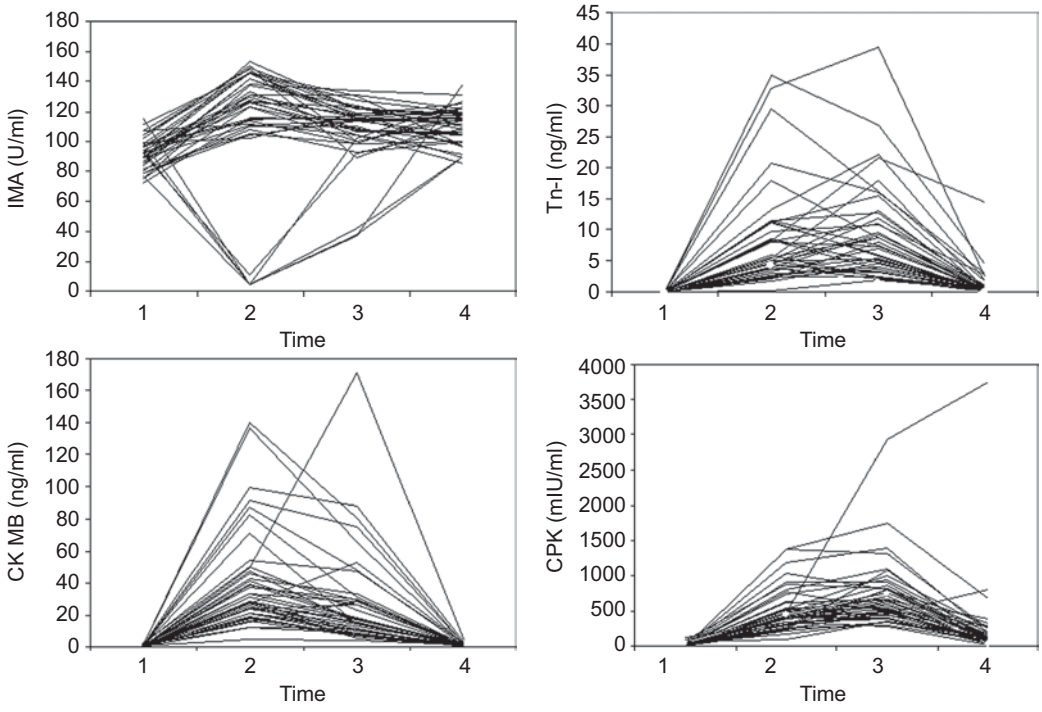

Figure 1. Dot-plots of all participants for ischaemia-modified albumin (IMA), creatine kinase (CPK), MB isoenzyme of creatine kinase (CPK-MB) and cardiac troponin-I (Tn-I) (line connecting individual values) for all time points (1: the day before the operation, 2: immediately postoperatively, 3: 24 h postoperatively and 4: the fourth day post-operatively).

postoperatively and gradually falls over the next 4 days, although it remains significantly higher, when compared with the baseline values, until the fourth day.

The N-terminus of albumin is a strong binding site for transition metals such as copper, cobalt and nickel and damage to this site by oxygen free radicals or the occupation of this binding site by copper released from carrier proteins contributes to the increased unbound cobalt during ischaemia. Recent evidence, however, demonstrated that the determinants of the performance of the albumin-cobalt binding assay are not only albumin levels and the proportion of intact N-terminus of albumin but also plasma pH, plasma cysteine/cystine ratio and the state of oxidation of cys34 of albumin (Bar-Or et al. 2008).

Perioperative and postoperative myocardial ischaemia, due to manipulation of the heart, inadequate myocardial protection, reperfusion injury and incomplete revascularization, leading to myocardial necrosis, can occur to varying degrees, after cardiac surgery. Numerous studies have evaluated the impact of peri-CABG enzyme elevation on medium term survival (Costa et al. 2001, Klatte et al. 2001, Brener et al. 2002, Januzzi et al. 2002, Groal et al. 2006). Likewise, enzyme rise following PCI carries prognostic significance in terms of adverse outcomes including mortality (Bhatt & Topol 2005). In addition, IMA elevation in stable patients undergoing elective single vessel PCI, is associated with higher frequency of target lesion revascularization at a follow-up of 4 years (Dusek et al. 2006). It is known from PCI studies that IMA increases immediately after the ischaemic insult, and returns to baseline values in 6–12 h (Bar-Or et al. 2001, Sinha et al. 2003, Quiles et al. 2003, Garrido et al. 2004). In the CABG setting, IMA similarly increased immediately following the operation and although significantly decreased thereafter, it remained considerably higher compared with the baseline values until the fourth day, implying different kinetics in cases of PCI or CABG. IMA elevation is related to reactive oxygen species production during ischaemia (Roy et al. 2006) and cardiac surgery is associated with severe oxidative stress (Luyten et al. 2005). However, IMA seems to be sensitive but not specific as is not only related to cardiac ischaemia, but to muscle (Falkensammer et al. 2007), gastrointestinal (Apple et al. 2002), brain (Abboud et al. 2007) and pulmonary ischaemia (Turedi et al. 2007). CPB induces a systemic inflammatory response syndrome (SIRS) due to the release of inflammatory mediators and the activation of the complement system, possibly causing an increase in microvascular permeability to plasma proteins (Tassani et al. 2002); this may be the mechanism underlying the significant albumin decrease we observed following CPB. We assessed plasma albumin levels as IMA measurements may be affected by either extremely low or extremely high serum albumin but the IMA changes in our study were independent of albumin variations.

In conclusion, IMA increases following CABG but whether or not this carries a prognostic significance remains to be elucidated. Routine measurement for further delineation of the long-term risk cannot be currently recommended.

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