Early changes in plasma antioxidant and lipid peroxidation levels following coronary artery bypass surgery: a complex response

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Abstract

Objective: Total plasma antioxidant capacity (TPAC) quantitatively defines extracellular fluid antioxidant capacity, the mechanism of which is different from the intracellular mechanism. Patients undergoing surgery for congenital heart defects have suppressed TPAC in the early postoperative periods. Our aim was to study the early changes of TPAC following coronary artery bypass grafting (CABG), in relation to lipid peroxidation, and to identify clinical factors affecting these changes.

Methods: We studied 28 consecutive patients undergoing routine uncomplicated CABG with cardiopulmonary bypass (CPB). Patients taking known antioxidants, such as captopril and allopurinol, and those receiving transfusion of blood or blood products at operation or during the first 72 postoperative hours were excluded. Serial blood samples were obtained for TPAC and lipid hydroperoxide concentration (LPX).

Results: TPAC was suppressed for 72 h after the operation, while LPX exhibited a significant increase only 1 h post-operatively. TPAC time changes resulted from a simultaneous depression (50% of the baseline occurring approximately 6 h after the operation) and production (18% of the baseline occurring approximately 6 h after the operation) of plasma antioxidants. The earlier the peak of plasma antioxidant production the later and the less the plasma antioxidant depression. Plasma antioxidant depression was inversely related to LPX (r = −0.37, P = 0.05 and r = −0.40, P = 0.04 at 1 and 6 h respectively). Ejection fraction and operative myocardial ischaemic times significantly influenced plasma antioxidant depression.

Conclusions: TPAC is suppressed for 72 h following CABG. TPAC depression may be involved in the mechanism of lipid peroxidation and is influenced by clinical factors known to be related to post CABG morbidity and mortality, like low ejection fraction and long ischaemic times.

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1. Introduction

The early postoperative period following coronary artery surgery is associated with high morbidity, which can affect any vital organ. Myocardial dysfunction, dysrhythmia and pulmonary insufficiency are common problems encountered mainly within the first 3 days after surgery. Although the pathogenesis of individual organ dysfunction varies, it has been recognised that whole body inflammatory reaction following cardiopulmonary bypass (CPB) plays a significant role in perioperative complications [1]. It mainly includes a cascade of complement and neutrophil activation and oxygen free radical production. The latter damages cells by breaking DNA and protein strands and by destroying cell membranes by means of lipid peroxidation [2]. The recognition of these pathogenic mechanisms has made the understanding of the natural antioxidant defences, intracellular and extracellular, of clinical importance.

Extracellular fluids, such as blood plasma, possess mechanisms of antioxidant protection different from
intracellular mechanisms and assays that define quantitatively the antioxidant capacity in the aqueous phase of extracellular fluids have been developed \[3,4\]. Human total plasma antioxidant capacity (TPAC) during CPB was firstly reported by Toivonen et al. \[5\] and was found to increase. Pyles et al. \[6\] measured the human TPAC in a group of patients who underwent surgery for congenital heart defects, aged 3 days–16 years and showed that there was a significant TAPC decrease and even complete depletion in the early postoperative period.

The purpose of this study was to describe the early postoperative changes of TPAC in patients undergoing coronary surgery, in relation to lipid peroxidation, and to identify clinical factors that might influence these changes.

2. Patients and methods

We studied 28 patients scheduled for first-time coronary artery surgery. Patients in cardiogenic shock and patients on known antioxidants such as captopril and allopurinol were excluded from the study. Patients who received blood transfusion or blood products during and within 72 h after the operation were also excluded, since the antioxidant properties of such products are not as yet established. The study was approved by the ethics committee of the St. Mary’s hospital, London and informed consent was obtained from all patients. Data was prospectively collected from the hospital charts, surgical and perfusion records.

All patients were on standard anti-anginal treatment and they all stopped taking aspirin 7 days before the operation. The premedication consisted of scopolamine (4 µg/kg) and morphine (130 µg/kg) intramuscularly 1 h before arrival to the operation area. They all received standard anaesthesia, which included induction with Fentanyl 5–10 µg/kg and Pancuronium 0.1 mg/kg intravenously, and maintenance with Isoflurane 0.5–15 as required. After a median sternotomy and harvesting of the internal mammary artery, 300 IU/kg of body weight of heparin sulphate were intravenously administered. When the activated clotting time was 480 s or more, CPB was established between a two-stage venous cannula in the right atrium and arterial clamp was released and the proximal anastomoses were performed with the heart beating. Systemic rewarming was initiated shortly before the completion of the last distal anastomosis. After CPB, the remaining heparin was reversed with protamine sulphate given at a dose of 1.5 mg/100 IU of heparin.

All patients were on nitroglycerine infusion for the first 12 postoperative hours. The central venous pressure was monitored and maintained between 8 and 12 mmHg with infusion of Haemacel. All patients received Aspirin 150 mg once daily.

2.1. Measurement of TPAC and lipid hydroperoxide concentration

Peripheral blood samples for TPAC and plasma lipid hydroperoxide concentration (LPX) were obtained before the operation, and 1, 6, 24 and 72 h after cessation of CPB. The venous samples were drawn into vacuum tubes containing dry Lithium-heparin. The tubes were placed immediately on ice, and the plasma was separated on a centrifuge (4 °C, 3000 rpm for 10 min) within 30 min. The separated plasma was then immediately frozen to −75 °C until assayed.

TPAC was measured by using an assay based on the inhibition by antioxidants of the absorbance of the free radical cation 2,2′ azinobis (ABTS⁺; 3-ethylbenothiazoline 6-sulphonate) which has a characteristic long wavelength absorption spectrum showing maxima at 660 and 734 nm (Randox Ltd., Ardonmore, Crumlin, Co Antrim, UK). The ABTS⁺ radical cation is formed by the interaction of ABTS (610 µmol/l) and H₂O₂ (250 µmol/l) carried out in a phosphate buffered saline at pH 7.4. Antioxidant compounds suppress the absorbance of ABTS⁺ radical cation to an extent and on a time scale dependent on the antioxidant capacity of the plasma \[4\].

LPX concentrations were measured by using the Peroxoquant kit (Lipid compatible formulation, Pierce and Warner, Chester, UK). The lipid hydroperoxides in the plasma convert ferrous iron to ferric iron at an acidic pH. The ferric iron then complexes with xylenol orange dye in the Peroxoquant reagent to give a purple/blue colour \[7\]. For each sample to be tested a ‘blank’ and ‘test’ samples were prepared. In the blank, the plasma was pre-treated with Tris (2 carboxyethyl) phosphine hydrochloride to reduce all the hydroperoxides in the sample. All samples were centrifuged at 12 000 g for 10 min. The absorbency of the supernatant was measured at 595 nm on a laboratory mark 2 plus ELISA plate reader (Life Science International Ltd, Basingstoke, Hampshire, UK). The absorbency difference between the blank and test plasma was read from a standard curve generated with 0–15 µmol H₂O₂ (Sigma Chemical Company, Poole, Dorset, UK).

2.2. Statistical analysis

Data were analysed with STATGRAPHICS statistical program (STATGRAPHICS, version 6.0, Manugistics, Inc.). The Komogorov–Smirnov test was used to compare the distribution of each variable with the normal distribution.
Variables not following the normal distribution underwent a logarithmic transformation. Non-linear regression analysis was used to calculate the best-fit line for time-changes. Summary statistics for serial measurements included: (1) first maximum change (peak or troph) from baseline; (2) time to achieve first maximum deviation from baseline; and (3) areas under the curves (AUC) at 1, 6, 24 and 72 h. The AUC were calculated as deviations from the baseline (preoperative value) (Fig. 1). Univariate and multivariate analyses were used for identifying relations between variables. Time changes were analysed with multi-factor analysis of variance for time changes. Mann–Whitney U-test was used to compare differences between groups. Results were expressed as mean ± standard deviation or median and lower/upper quartiles. Differences were considered significant at a probability level of \( P < 0.05 \).

Table 1
Clinical and operative data \((N = 28)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.2 ± 1.9</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>75%</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>1.88 ± 0.03</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>64%</td>
</tr>
<tr>
<td>35–50%</td>
<td>32%</td>
</tr>
<tr>
<td>&lt; 35%</td>
<td>4%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>21%</td>
</tr>
<tr>
<td>Left main stem disease</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57%</td>
</tr>
<tr>
<td>Smoking</td>
<td>11%</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>42.4 ± 3.4</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>84.2 ± 8.0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>75%</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>71%</td>
</tr>
<tr>
<td>Beta adrenergic receptor antagonists</td>
<td>32%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>36%</td>
</tr>
</tbody>
</table>

3. Results

No patient received inotropic support during or after the operation and none developed any significant complication over the 72 h of observation, i.e. stroke, arrhythmia, pulmonary insufficiency, renal failure, excessive bleeding or infection. They were all discharged within 6–8 days following the operation. Patients’ data are summarised in Table 1.

TPAC and LPX changes after the operation are presented in Fig. 2a,b. TPAC was suppressed for 72 h after the operation, while LPX presented a significant increase only 1 h after the operation. TPAC presented a sharp initial fall followed by a tendency for partial recovery after approximately 6 h, not reaching preoperative levels. A second fall between 6 and 24 h was followed by slow progressive recovery, which also did not reach the preoperative levels within the 72 h of observation (Fig. 2a). This pattern was...
assumed to result from the combination of two simultaneous time curves, one with negative deviation from the baseline representing depression of plasma antioxidants and one with positive deviation representing production (or release) of antioxidants into the plasma. Curve analysis and definition of curve characteristics were performed for both depression and production of antioxidants in each individual. There were three distinct patterns presented in Fig. 3a–c. Overall maximum plasma antioxidant depression was 50% [46%–70%] of the baseline and occurred approximately 6 h after the operation [range 1–24 h]. Overall maximum plasma antioxidant production was 18% [8%–31%] of the baseline and also occurred approximately 6 h after the operation [range 1–24 h].

TPAC cumulative changes, expressed as AUC, were rationally divided into early (1–6 h) and late (24–72 h) phases. In the early phase there was no direct relationship between the magnitudes of plasma antioxidant depression and production, as expressed by the areas under the curves (Table 2). However, the time when plasma antioxidant production reached a peak presented a linear relationship with the cumulative plasma antioxidant depression at 1 and 6 h \( r = 0.66, P = 0.0001 \) and \( r = 0.50, P = 0.007 \) respectively, Appendix A.3.1. It also presented an inverse linear relationship with the time the plasma antioxidant depression reached its trough \( r = -0.45, P = 0.01 \), Appendix A.3.2. Thus, the earlier the peak of plasma antioxidant production the later and the less the plasma antioxidant depression. This was particularly obvious in the five patients whose plasma antioxidant changes followed the ‘pattern 3’ (Fig. 3c). These patients exhibited an early antioxidant production (1 [1/1] h) that was followed by a late antioxidant depression (12 [12/14] h). The corresponding values for production and depression in ‘pattern 1’ were 6 [6/24] and 4 [3/6] h and in ‘pattern 2’ 6 [6/6] and 6 [6/6] h, respectively. Unlike the early phase, in the late phase there was a quantitative positive correlation between plasma antioxidant production and consumption (Table 2). Thus, the more the plasma antioxidant depression the more the plasma antioxidant production.

LPX values 1 h after the operation showed an inverse linear relationship with the cumulative plasma antioxidant depression at 1 and 6 h \( r = -0.37, P = 0.05 \) and

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Table 2

Relationship between total plasma antioxidant depression and production after coronary artery bypass surgery

<table>
<thead>
<tr>
<th>ln PAD-AUC [h mmol/l]</th>
<th>0–1 h</th>
<th>0–6 h</th>
<th>0–24 h</th>
<th>0–72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln PAP-AUC [h mmol/l]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–72 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data were analysed with linear regression analysis. PAP, plasma antioxidant production; PAD, plasma antioxidant depression; AUC, area under curve; ln, natural logarithm; r, correlation coefficient; P, probability value; h, hour.
the intermediate radicals during the propagation of lipid peroxidation. There were no such relationships in the late phase. Also, there was no direct relationship between LPX and plasma antioxidant production.

Relationships between plasma antioxidant depression and clinical and operative variables, as evident by stepwise multiple regression analysis, are presented in Table 3. In the early phase, left ventricular ejection fraction (LVEF) and cross-clamp time (operative myocardial ischaemic time) showed an inverse relationship with plasma antioxidant depression. Thus, the lower the preoperative LVEF the more the depression of plasma antioxidants, while the longer the ischaemic time the less the depression of plasma antioxidants. Aortic cross-clamp time presented also a linear relationship with LPX 1 h after the operation \( (r = 0.41, P = 0.03, \text{Appendix A.3.4}) \). There was no relationship between LVEF and preoperative TPAC or postoperative LPX values.

### 4. Discussion

Extracellular fluids of the human body, such as blood plasma, possess mechanisms of antioxidant protection different from intracellular fluids. In blood plasma there is a very little concentration of the major intracellular antioxidant enzymes catalase, glutathione peroxidase and superoxide dismutase. Its antioxidant defence system comprises transferrin, caeruloplasmin, lactoferrin, albumin, haptoglobins, haemopexin, bilirubin, carotene, vitamin C, vitamin E, uric acid and acute phase proteins (C3, antiproteases, CRP and serum amyloid A). Transferrin and caeruloplasmin prevent the initiation of lipid peroxidation mainly by binding metal ions, like iron and copper. These plasma antioxidants are called preventive antioxidants, since they are not damaged by these metal ions and therefore they are not consumed during the course of reactions. Unlike them, other antioxidants are damaged and consumed during the course of reactions and they are called sacrificial antioxidants (chain-breaking antioxidants). They are acting by either metal ion binding or by combining with the intermediate radicals during the propagation of lipid peroxidation. Albumin is a typical example of a sacrificial antioxidant. If the plasma preventive antioxidant, first line, defence is overwhelmed, a second line of scavenging, chain-breaking, consumable antioxidant defence exists. TPAC assay is largely determined by the second line defence antioxidants, especially albumin, vitamin C, vitamin E and uric acid [8–10]. Previous studies have shown that there is a significant fall of human albumin during CPB, which continues after its termination with a slow recovery within 6 to 24 h [11–13]. The response of plasma ascorbic acid to coronary surgery is controversial. Tangney et al. [14] and Cavarocchi et al. [15] have shown elevation of ascorbic acid during CPB persisting for the following 24 h, while Ballmer et al. [16] have shown a significant depletion, which persisted for at least 24 h. Uric acid has been reported of being elevated immediately and for 24 h after CABG with CPB [14,17]. Therefore, most of the compounds that determine TPAC are affected in the post-coronary surgery period moving towards different directions.

In the present study, TPAC changes appeared to result from a combination of simultaneous depression and production (or release) of plasma antioxidants, which may explain the conflicting results between Toivonen et al. [5] and Pyles [6] reports. It is worth noting that, Toivonen et al. [5] used the assay developed by Wayner et al. [3] which has a high degree of inherent imprecision caused by the instability of the oxygen electrode used [18]. Our study suggests that there is a simultaneous production (or release) and depression of antioxidants in the first few postoperative days. The overall TPAC may be due to a more pronounced depression than production. Notably, there was a significant variability in the form of these changes especially within the first few hours after surgery.

TPAC changes seemed to have two distinct pathophysiological phases, an early around 1–6 h and a late around 24–72 h. Lipid peroxidation occurred only in the early phase. In this early phase, plasma antioxidant depression was inversely related to lipid peroxidation. As we have postulated in a previous report, this depression is likely to represent consumption of antioxidants. However, the fact that 18% of the patients had TPAC values higher than baseline in the 1st h after CPB makes obvious that the model is more complicated than originally assumed. This
aberration seems to result from a simultaneous production (or release) of antioxidants into the plasma, which is not directly correlated to the magnitude of lipid peroxidation. This production of antioxidants delays and minimises the antioxidant depression. Although, the mechanism of this interaction is unclear, the fact that some antioxidants in the plasma prevent the consumption of other antioxidants may be of clinical relevance. It implies that the presence of a particular brand of antioxidants may antagonise the consumption of other antioxidants, which may be important for the prevention of lipid peroxidation, as implied by the inverse relationship between plasma antioxidant depression and lipid peroxidation. Antioxidant production may be related to the release of acute phase proteins [8] or liberation of intracellular antioxidant compounds through cellular breakdown [5].

Patients with low LVEF did not have lower preoperative TPAC values or higher lipid peroxidation following CABG. However, they exhibited a more prominent plasma antioxidant depression immediately after their operation. This might be due to exacerbation of albumin loss into the extracellular space and through the kidneys as well as decreased levels of vitamin C, observed in chronic heart failure.

CABG results in lipid peroxidation through various mechanisms [2]. Cohen et al. [19], using the same assays, showed found no difference in TPAC and LPX levels following CABG using intermittent cross-clamp fibrillation vs. crystalloid cardioplegia for myocardial protection.

In this study longer operative myocardial ischaemic times, and consequently longer CPB times, resulted in higher lipid peroxidation and less plasma antioxidant consumption. These findings are not in line with those of Pyles et al. [6], who showed that longer CPB times result in more TPAC depression. In our study, although there was a statistically strong correlation between cross-clamp time and CPB time, the former was a much stronger predictor of both lipid peroxidation and plasma antioxidant depression than the later. This suggests that impaired plasma antioxidant consumption may not be secondary to the damaging effects of CPB alone, but, also, due to the stress imposed by surgical trauma and myocardial ischaemia.

LPX was inversely related to plasma antioxidant depression and cross-clamp times were associated with less depression of plasma antioxidants. Considering these findings together, we hypothesise that long CXT may result in acute phase proteins release, which posses some antioxidant effect, but not strong enough to prevent LPX. These acute phase proteins, though, may delay and suppress the consumption of other plasma antioxidants, which are far more important for LPX prevention.

In the late phase antioxidant production into the plasma seemed to match the antioxidant depression. Decreased stress related catabolism and oral intake of amino-acids, vitamin C and E may contribute to the rebuilding the plasma antioxidant defence system. Release of intracellular antioxidants into the plasma may also play a part in this interaction. The exact mechanism of TPAC rebuilt, however, remains to be elucidated. Interestingly, late plasma TPAC suppression is not associated with prolonged LPX. Decreased oxygen free radical activity in the late phase and the contribution of other antioxidant mechanisms, i.e. intracellular antioxidants, may explain this finding.

The methodology used to determine TPAC and the absence of correction of reported values for haemodilution merit further discussion.

There is no single ideal way to assess TPAC. We have used the method described in the Section 2 of this paper because our objective was to describe the early post-CABG changes of TAPC in relation to LPX, and to identify clinical factors that might affect these changes. Additional laboratory techniques, in order to capture all possible TACP events, could have been used but this would have made the statistical analysis, interpretation and presentation of the data cumbersome and complex.

In the present study values were not corrected for hemodilution for three reasons. First, oxygen free radicals (OFR) are very short lived and they act in the vicinity of a fraction of a millimetre. Correction for hemodilution may represent the total amount of antioxidants in the extracellular space, which, however, may not be available in the vicinity of localised OFR production. Second, correction for hemodilution over a prolonged period of time may be misleading since: (a) hematocrit is not reduced only because of dilution but also due to variable erythropoietin production [20] and bone marrow response [21]; (b) plasma albumin may be denatured; and (c) in the early postoperative period there are variable fluid movements between compartments (pleural and pericardial effusions, tissue oedema, etc). Third, there is accumulating evidence in the literature suggesting that hemodilution itself is a pathological condition, which significantly affects the heart and renal functions, the blood pressure [22–24] and the overall outcome of surgery [25]. Whether haemodilution affects the TPAC is unclear, but this possibility cannot be excluded.

5. Conclusions

TPAC changes in the early postoperative period after CABG seem to result from a combination of simultaneous depression and production (or release) of plasma antioxidants, which would explain the conflicting results of previous reports. Depression was more pronounced than production and therefore the overall TPAC was suppressed. TPAC depression may contribute to lipid peroxidation seen after CABG and is influenced by clinical factors known to be related to morbidity and mortality, such as low ejection fraction and long surgical ischaemic times. Further research is necessary to define whether manipulation of TPAC in the early postoperative period influences the morbidity pertaining to CABG.
References


Appendix A

A.1. TPAC best-fit line formula

\[
TPAC_{[\text{mmol/l}]} = 1.67 - ((0.356^{-1} + 0.069 \times (ln \text{time} [h] - ln 4.93 [h])^2)^{-1} + (0.068^{-1} + 200 \times (ln \text{time} [h] - ln 6 [h])^2)^{-1}, r = 0.49
\]

A.2. LPX best-fit line formula

\[
LPX_{[\text{mmol/l}]} = 4.72 + ((1.138^{-1} + 0.5 \times (ln \text{time} [h] - ln 1 [h])^2)^{-1} - (0.448^{-1} + 2.847 \times (ln \text{time} [h] - ln 6 [h])^2)^{-1}, r = 0.13
\]

A.3. Linear regression formulas (LRF)

\[
\begin{align*}
1. & \quad \ln PAP_{\text{peak-time}} [h \times \text{mmol/l}] = 1.9 \pm 0.4 \times \ln PAP \text{ peak-time} [h] \pm 0.8, r = 0.66, P = 0.0013 \text{ and } \ln PAP_{\text{peak-time}} [h \times \text{mmol/l}] = 0.8 \pm 0.3 \times \ln PAP \text{ peak-time} [h] \pm 0.8, P = 0.00686 \text{ at } 3 \text{ and } 6 \text{ h respectively} \\
2. & \quad \ln PAP_{\text{peak-time}} [h] = 2.4 \pm 0.4 \pm 0.4 \pm 0.4 \times \ln PAP \text{ peak-time} [h], r = -0.45, P = 0.01
\end{align*}
\]

3. \[LPX_{[\text{mmol/l}]} = 4.2 \pm 1.0 \pm 0.5 \pm 0.2 \pm \ln PAP - \ln PAP_{\text{peak-time}} [h \times \text{mmol/l}], r = -0.37, P = 0.05 \text{ and } LPX_{[\text{mmol/l}]} = 6.3 \pm 0.7 \pm 1.0 \pm 0.4 \pm \ln PAP - \ln PAP_{\text{peak-time}} [h \times \text{mmol/l}], r = -0.40, P = 0.04 \text{ at } 1 \text{ and } 6 \text{ h respectively}
\]

4. \[LPX_{[\text{mmol/l}]} = 2.3 \pm 1.6 \pm 0.1 \pm 0.03 \times \text{CXT} \text{ [min], r = 0.41, P = 0.03}
\]

1. PAD, plasma antioxidant depression; PAP, plasma antioxidant production; AUC, area under curve; LPX1, lipid hydroperoxide concentration 1 hour after cardiopulmonary bypass; CXT, cross clamp time.