Perioperative metabolic therapy improves redox status and outcomes in cardiac surgery patients: A randomised trial

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goal. Perioperative therapy with antioxidants and metabolic substrates has the potential to reduce oxidative stress and improve recovery from cardiac surgery, particularly in elderly and high risk cases. The aim of this study was to assess the effect of perioperative metabolic therapy at a biochemical, clinical and economic level in cardiac surgical patients.

Methods: Patients (n = 117, mean age 65 ± 1.0 years, 74% male) undergoing elective coronary artery bypass graft (CABG) and/or valve surgery in 2004–2006 were randomised to receive in double blinded fashion, while on the waiting list for surgery (approximately two months) and one month after surgery, either metabolic therapy (coenzyme Q10, magnesium orotate, lipoic acid, omega-3 fatty acids and selenium) or placebo. Biochemical and clinical outcomes were assessed.

Results: Cardiac surgery increased oxidative stress and decreased plasma levels of key antioxidants. Metabolic therapy for a mean of 76 ± 7.5 days increased antioxidant levels preoperatively so that the adverse effect of surgery on redox status was attenuated. Metabolic therapy reduced plasma troponin I, 24 hours postoperatively from 1.5 (1.2–1.8) (geometric mean 95% CI) to 2.1 (1.8–2.6) (P = 0.003) and shortened the mean length of postoperative hospital stay by 1.2 days from 8.1 (7.5–8.7) to 6.9 (6.4–7.4) days (P = 0.004) and reduced hospital costs. Metabolic therapy was inexpensive and had no clinically significant side effects.

Conclusions: Perioperative metabolic therapy for cardiac surgery is safe and inexpensive and is associated with improved redox status, reduced myocardial damage, and shortened length of postoperative hospital stay.

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Introduction

A n increasing proportion of patients presenting for cardiac surgery in the present era are elderly, with a high incidence of co-morbidities such as diabetes, heart failure, previous myocardial infarction and renal impairment. Advanced age and significant co-morbidities are associated at a biochemical level with an enhanced degree of oxidative stress [1] and clinically with higher rates of postoperative complications and an increased length of hospital stay [2]. We postulated that by the perioperative use of metabolic agents we could favourably influence myocardial metabolism and improve clinical outcomes.

The term "metabolic agent" is used to describe a naturally occurring substance that when administered to the body can produce a beneficial effect on metabolism [3]. The following metabolic agents have been clearly demonstrated to have beneficial effects on the heart and were therefore included in our regimen of cardiac metabolic therapy: coenzyme Q10 (CoQ10) [4–6], lipoic acid [7], selenium [8,9], orotic acid [10,11], and omega-3 polyunsaturated fatty acids [12–15]. Following a promising pilot study [3] we evaluated the efficacy of this regimen in the current prospective randomised clinical trial in patients having elective cardiac surgery.

The aims of the study were to determine in patients undergoing elective cardiac surgery, the effect of perioperative metabolic therapy on oxidative stress, antioxidant
supplemented with 15 mM aspartate. St. Thomas' potassium, magnesium, lignocaine solution

<table>
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<tr>
<th>Table 1. Components of Metabolic Therapy.</th>
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<td>Carnitine CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
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<td>Lipolic acid</td>
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levels, incidence of postoperative complications, hospital length of stay and costs.

Methods

Patients

The study included patients undergoing elective coronary artery bypass graft (CABG) and/or valve surgery at the Alfred Hospital, Melbourne between November 2004 and June 2006. Patients were excluded if they had urgent or emergency surgery, were in NYHA class IV heart failure, or had taken antioxidant supplements in the previous month. Patients were randomised in blocks of eight to receive either oral metabolic therapy (Table 1) or placebo in capsule form before surgery (for a minimum of two weeks), while in hospital and for four weeks after surgery. All investigators and patients were blinded to treatment allocation; all medication preparation was done by the hospital pharmacy. The trial was conducted according to the principles contained in the CONSORT statement 2001 and registered at www.clinicaltrials.gov, registration number NCT00906646.

Surgery

Coronary artery bypass graft and/or valve surgery was performed using standard surgical techniques on cardiopulmonary bypass. Myocardial protection comprised antegrade and intermittent retrograde tepid blood cardioplegia (myocardial temperature 20–25 °C) using modified St. Thomas’ potassium, magnesium, lignocaine solution supplemented with 15 mM aspartate.

Haemodynamics

Heart rate and mean arterial blood pressure were recorded and together with measures of pulmonary capillary wedge pressure and cardiac output from a pulmonary artery catheter (Edwards Life Sciences®) were used to calculate left ventricular stroke work index. In the intensive care ward, four hours after the completion of surgery, haemodynamic measures were taken during head down tilt to increase cardiac filling. Inotropic therapy was instituted when indicated according to a standard protocol. Cardiac rhythm was monitored continuously by ECG for the first 72 hours. Atrial fibrillation was recorded as present when it was sustained for at least 10 minutes.

Biochemical Measurements

Blood and urine samples were taken for biochemical assay before therapy (pre-admission clinic baseline), after therapy (immediately before surgery), and six hours post-operatively. Samples were analysed for oxidative stress (plasma protein carbonyls and urinary isoprostanes) and antioxidant status (plasma CoQ<sub>10</sub>, plasma glutathione peroxidase activity, plasma selenium). A blood sample was obtained 24 hours postoperatively for measurement of plasma troponin I level.

Total plasma CoQ<sub>10</sub> was measured by means of high performance liquid chromatography and UV spectrophotometric analysis after solvent extraction of serum (with a mixture of hexanes and ethanol) [4]. Plasma selenium was analysed by inductively coupled plasma mass spectrometry. Glutathione peroxidase (GSH-Px) activity was measured using a continuous spectrophotometric rate determination technique modified to work in a 96-well microplate. The degree of plasma protein oxidation was measured using the ELISA which quantifies protein carbonyls in biological samples after reaction with 2,4-dinitrophenyl hydrazine (DNPH). All six hour postoperative plasma levels were corrected for haemodilution based on the ratio of preoperative to postoperative plasma urea. Urinary isoprostane assays were performed with a commercial kit (Neogen Corporation, USA) which uses an ELISA technique to quantify 15-isoprostane F<sub>2α</sub> (also known as 8-epi-PGF<sub>2α</sub> or 8-iso-PGF<sub>2α</sub>). Urinary isoprostane levels were then normalised against urinary creatinine levels. Plasma troponin I assays were performed using an automated chemiluminescent microparticle immunoassay (Abbott ARCHITECT ci8200 Integrated System, Abbott, USA).

Length of Stay

Length of ICU and total hospital stay data were obtained from hospital records. The criteria for hospital discharge used by the clinical team were in general the absence of postoperative complications and the ability of the patient to be managed at home. Members of the clinical team were unaware of presence or absence of metabolic therapy.

Cost Analysis

An analysis of average costs to the hospital per CABG patient (to avoid the influence of prosthesis costs) was carried out by the hospital Clinical Performance Unit according to best practice of the Clinical Costing Standards Association of Australia. Costs allocated included operating room, ward, nursing, drugs, imaging and overheads.

Statistical Analysis

The primary outcomes were 24 hour troponin level and hospital length of stay. Variables were initially assessed for normality, with 24-hour troponin levels and hospital length of stay both found to be well approximated by log-normal distributions. Comparisons between groups were made using the chi-square test for proportions (or Fisher exact test where numbers were small), student t-test for continuous parametric data, and the Wilcoxon rank sum tests otherwise. In accordance with log-transformed data, metabolic and placebo groups are reported as geometric means (95% CI). Following log-transformation, multivariate linear regression models for 24 hour troponin and hospital length of stay were constructed using both step-
wise selection and backwards elimination procedures. All variables were considered for inclusion into models with the final model undergoing an assessment for clinical and biological plausibility. To further ensure that observed differences between groups were not due to a baseline imbalance in procedure type, the variable procedure type was forced into the final model. With the exception of procedure type, which was not a significant predictor of either troponin or length of stay, all remaining variables in the multivariate model were statistically significant (P < 0.05).

Post hoc subgroup analyses for CABG and valve patients were performed for major clinical endpoints. All analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and a two-sided P-value of 0.05 was considered to be statistically significant.

**Sample size.** With a minimum of 50 subjects per group this study had an 80% power to detect a difference of about 13%, which was judged to be of clinical importance for both troponin and length of stay. Given that one standard deviation is approximately equivalent to 56% of the range of the data, this difference equates to a difference of about 13%, which was judged to be of clinical importance for both troponin and length of stay.

**Results**

A total of 137 patients were assessed for possible enrolment. Of these a total of 20 were excluded, including 14 who failed to meet all inclusion criteria, four who refused for a variety of reasons and two patients (one in each group) who received the supplements for less than two weeks before surgery. Of the 117 patients completing the study, 60 (51%) were in the metabolic group and 57 (49%) were in the placebo group. There were no significant differences in demographics between the two treatment groups (Table 2). Also there were no differences in preoperative therapy with ACE inhibitors, statins or beta-blockers between the two groups. The mean duration of treatment was similar in the two groups: 76 ± 7.5 days in the metabolic group and 64 ± 5.7 in the placebo group (P = 0.19). There were no side effects requiring the discontinuation of metabolic therapy. The operative variables were similar in the two groups except that due to chance, in the metabolic group compared to the placebo group, there was a higher proportion of patients having CABG surgery and correspondingly a lower proportion of patients having valve surgery (Table 3).

**Oxidative Stress**

**Protein carbonyls.** Protein carbonyl levels did not change in the treatment phase before surgery in either group, but surgery produced increases in protein carbonyls (increased protein oxidation) in the placebo and the metabolic group (P < 0.0001 in both (Fig. 1)). The metabolic group had a significantly lower postoperative protein carbonyl level than the placebo group (P = 0.007).

**Urinary isoprostanes.** Urinary isoprostane levels in both metabolic and placebo groups increased significantly with surgery (P < 0.001 in both groups) (Fig. 2). Overall, there was no significant difference between the two groups (P = 0.25).

**Antioxidants**

**Plasma Coenzyme Q10.** There were no between-group differences in baseline CoQ10 levels (metabolic, 882 (749-1039), placebo 840 (712-991) nmol/L (P = 0.86) but both were near the lower limit of normal (normal range, 709-1392 nmol/L).

![Figure 1. Protein carbonyls measured at pre-admission clinic (Baseline), immediately before surgery (Pre-Op), and 6 h postoperatively (Post-Op), *metabolic vs placebo at same time point.](image-url)
Perioperative metabolic therapy

Figure 2. Urinary isoprostane levels measured at pre-admission clinic (Baseline), immediately before surgery (Pre-Op), and 6 h postoperatively (Post-Op). *overall group effect.

(Fig. 3). Metabolic therapy produced a highly significant increase in CoQ10 over the pre-admission levels ($P<0.0001$). Surgery produced a decrease in CoQ10 in both groups and that in the placebo group (median 628, IQR 467–830) fell below normal levels. After supplementation levels were higher in the metabolic group than in the placebo group ($P<0.0001$).

PLASMA SELENIUM. There were no differences in the baseline plasma selenium levels, both groups being at the lower limit of normal 100–262 mg/L (Fig. 4) [8]. Metabolic therapy produced a marked increase in selenium levels over baseline ($P<0.001$). Surgery produced a decrease in selenium levels ($P<0.001$) which remained in the normal range in the metabolic group but not in the placebo group. Overall, selenium levels were significantly higher in the metabolic group than in the placebo group ($P<0.0001$).

Clinical Outcomes

INTENSIVE CARE UNIT PARAMETERS. There were no significant between-group differences in intensive care unit parameters (Table 4).
The aim of this study was to assess the efficacy and safety of perioperative therapy with a combination of metabolic supplements and antioxidants in reducing oxidative stress and improving clinical recovery after elective coronary bypass and/or valve surgery. We found that surgery decreased serum levels of selenium, and the antioxidants, CoQ10 and glutathione peroxidase and increased protein oxidation whereas metabolic therapy counteracted these effects. Clinically metabolic therapy reduced myocardial troponin I release and shortened postoperative hospital stay. Impor-
tantly, the cost of the metabolic supplements was small, $118 for six weeks and $292 for 15 weeks of therapy, making this therapy highly cost-effective.

Discussion
The calculated average total hospital costs per CABG-alone patient (US dollar equivalent) in the metabolic group was $34,978 compared to $39,421 in the placebo group, a saving of $4,443 (11%) which is consistent with the 1.9 day shorter length of hospital stay in this subgroup. Impor-
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Troponin I
At a univariate level in the metabolic group 24-hour tro-
ponin levels were significantly lower than in the placebo group (1.3 (1.0–1.7) vs 2.3 (1.8–3.0) µg/L, p = 0.002) (Table 5). After adjustment for significant covariates (bypass time, Euroscore, statin use and use of transfusions) and procedure type the difference remained highly significant (1.2 (1.2–1.8) vs 2.3 (1.8–2.6) µg/L, p = 0.003).

Length of Hospital Stay
At a univariate level, length of stay was found to be sig-
nificantly shorter in the metabolic group compared to the placebo group (6.6 (5.7–7.7) vs 8.3 (7.1–9.7) days, p = 0.006) (Table 5). After adjustment for significant covariates (re-
operation for bleeding, ASA severity score, haemodialysis, procedure duration, Euroscore, insulin dependent dia-
betes and leg wound infection) and procedure type, patients in the metabolic group were found to stay 1.2 days shorter than those in the placebo group: [6.9 (6.4–7.4) vs 8.1 (7.5–8.7) days, p = 0.004].

Postoperative Complications
Four patients in the metabolic group and six in the placebo group were in atrial fibrillation prior to surgery. There was no significant difference overall in the rate of develop-
ment of new atrial fibrillation, in the metabolic group vs the placebo group (25% vs 33%, p = 0.32) (Table 5). There were no between-group differences in blood transfusion requirements or in any postoperative complications.

Subgroup Analysis
For CABG-alone patients (n = 71) in the metabolic group univariate analysis revealed significant reductions in 24 hour troponin I, length of hospital stay and postoperative atrial fibrillation. After adjusting for statistically signif-
ificant covariates, the reduction in troponin I and length of hospital stay remained significant. However there were insufficient events to facilitate covariate analysis for postoperative atrial fibrillation. In valve replacement patients (n = 46) including valve plus CABG (n = 20) tro-
ponin release and length of stay showed similar patterns to
CABG-alone patients but differences were not significant in these small numbers (Table 5).

Hospital Costs
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Oxidative Stress in Cardiac Surgery
Oxidative stress accompanies major surgery, especially cardiac surgery with cardiopulmonary bypass [16,17].
Oxidative stress occurs as a result of augmented production of reactive oxygen species (ROS) such as superoxide (O$_2^-$), the hydroxyl radical (OH$^-$) and hydrogen peroxide (H$_2$O$_2$) that exceeds their normal rate of metabolism by antioxidants to more inert metabolite products. Release of ROS during cardiac surgery is triggered by cardiopulmonary bypass and by ischaemia/reperfusion injury in the heart and lungs [16]. Excess ROS reacts with cellular components including proteins, fats and carbohydrates, which leads to post-oxidative molecular modification and triggers inflammatory processes, ultimately impairing efficient energy production and homeostatic cellular maintenance [14]. In the present study we found that cardiac surgery increased levels of protein carbonyls indicating oxidative damage to proteins and increased levels of urinary isoprostanes indicating damage to lipids. Surgery also reduced serum levels of the antioxidants, CoQ$_{10}$, glutathione peroxidase and selenium, the antioxidant co-factor. Whereas metabolic supplementation, compared to placebo, reduced the impact of surgery on protein carbonyls but not isoprostanes. Perioperative supplementation was able to ameliorate reductions in antioxidant levels and maintain postoperative antioxidant levels within the normal range. Reducing oxidative stress by antioxidant therapy has been shown to be beneficial in cardiac [18] and other forms of major surgery [19]. We could therefore attribute at least some of the clinical benefits we observed in the present study to the antioxidant action of the supplements given.

Metabolic Regimen

These metabolic agents occur naturally in the diet and are virtually devoid of side effects. We hypothesised that when used in combination they would produce a combined benefit greater than any of their activities when given alone. These agents were given for as long as the patient remained on the preoperative waiting list (approximately two months) which would have allowed maximum therapeutic benefit. Also the agents were given for one month after surgery to improve energy production in the early post-discharge period.

Coenzyme Q$_{10}$ is an essential component of all cells of the body. It is found in high concentrations in organs with high rates of oxygen consumption such as the heart and the brain [6]. In the cell, coenzyme Q$_{10}$ is found in highest concentrations in mitochondria as it is an integral component of the mitochondrial respiratory chain for energy production and is also a fat soluble antioxidant. CoQ$_{10}$ has recently been shown to have gene regulatory functions involving energy production in the cell [20]. There have altogether been 12 trials of CoQ$_{10}$ in cardiac surgery; all but one has shown a positive result [6]. CoQ$_{10}$ levels are lowered by age and cardiac disease [1]. In our previous study, CoQ$_{10}$ levels were below the normal range even at baseline [4]. In the present study before therapy, plasma CoQ$_{10}$ levels in both groups were at the low end of the normal range. Therapy with CoQ$_{10}$ increased levels fourfold so that levels remained high in the metabolic group whereas in the placebo group after surgery levels became abnormally low (Fig. 3). In our previous study using the same dosage, enhanced plasma levels of CoQ$_{10}$ were indicative of raised levels in cardiac mitochondria and were accompanied by enhanced mitochondrial energy production [4]. Thus in the current study, preservation of normal serum CoQ$_{10}$ levels may have contributed to improved myocardial recovery after surgery.

Lipoic acid is both a water and a fat soluble antioxidant and functions as a co-factor in the Krebs cycle. Because of its ease of penetration of the mitochondrial membrane, it is effective in neutralising free radicals at their site of origin in the mitochondria [7]. Lipoic acid has the ability to regenerate other antioxidants such as CoQ$_{10}$, vitamin C and vitamin E [7]. Lipoic acid could thus contribute to the reduction in oxidative stress and preservation of antioxidant capacity that we observed in the treated group.

Selenium is an important co-factor for the antioxidant enzymes glutathione peroxidase (GSH-Px) and thioredoxin reductase that are important in controlling intracellular oxidative stress. We have recently reported that elderly patients presenting with cardiovascular disease have lower plasma levels of selenium and GSH-Px activity than age-matched healthy volunteers [9]. In the present study surgery markedly lowered the plasma levels of both selenium and GSH-Px activity compared to placebo, reduced the impact of surgery on protein carbonyls but not isoprostanes. Supplementation with our antioxidant regimen was able to prevent this surgically induced decrease in selenium and associated GSH-Px activity.

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are important components of cell membranes including intracellular membranes. Advanced age and a diet rich in n-6 PUFAs derived from animal tissue (such as arachidonic acid) adversely impacts mitochondrial metabolic efficiency and vulnerability to ischemia-reperfusion injury [14]. The cardioprotective effects of n-3 PUFAs have been established in multiple animal and experimental studies, epidemiological observations and randomised clinical trials [15,21]. In an open-label randomised trial Calò et al reported that 2 grams per day of n-3 PUFA supplementation given for five or more days before elective coronary artery bypass surgery and during the in-hospital stay reduced the incidence of postoperative atrial fibrillation by 54% and reduced hospital stay by one day [13]. Thus the reduction in atrial fibrillation and length of stay in CABG patients achieved in the present trial may have been, at least in part, a consequence of the fish oil component of the metabolic therapy.

Orotate is a precursor of pyrimidines (such as uridine) that are important precursors of RNA and glycogen. Orotate supplementation in animal models of recent myocardial infarction enhances pyrimidine metabolism and improves tolerance to cardioplegic arrest following recent myocardial infarction [10]. CoQ$_{10}$ in mitochondria is an essential co-factor in the synthesis of orotate so that these two supplements may have a synergistic effect. A recent trial has shown the benefit of magnesium orotate in cardiac failure [11]. Magnesium has been clearly shown to reduce arrhythmias after coronary bypass surgery [22].
In our previous study we showed that CoQ10 improved the efficiency of energy production in terms of ATP generation in the myocardium. This translated into improved recovery of contractile function in excised atrial trabeculae following an in vitro hypoxia/reoxygenation stress [4]. We have recently, in a study in rats, shown that CoQ10 therapy can improve the tolerance of the lung to stress produced by mechanical ventilation [21]. We therefore postulate that metabolic therapy with CoQ10 and other antioxidant supplements in the present study may have produced an improvement in cellular function in multiple organs so as to accelerate overall recovery of the patient.

Limitations
A limitation of the study is that with multiple ingredients in a therapy, it is unclear what is the efficacy of each component, and whether all components actually contribute to the benefits observed. Each of the components utilised have previously been shown to be individually beneficial in cardiac surgery or cardiovascular disease. Antioxidants are known to be more effective when working as a network, where they can regenerate each other, rather than as single agents. The present trial has shown a more powerful effect of the combination therapy than any of the individual components in our own studies [4,10] and those published elsewhere [13]. We therefore believe that enhancement of antioxidant reserves, the reduction in oxidative stress and the improved clinical outcomes more than justify the multiple component therapy we used even if it is difficult to directly demonstrate the specific benefit exerted by each agent. In any case for low cost therapies with negligible side effects, the downside to including a non-essential ingredient in a cocktail is small. Since completing the study we have access to a formulation that reduces the number of capsules to be ingested daily from 13 to seven. We now administer this formulation in the perioperative period to all cardiac surgery patients in our unit.

Another limitation is the chance occurrence of a base-line imbalance in procedure type between the treatment groups with more valve patients in the placebo group. To address this we performed an additional sensitivity analysis by including procedure type into the multivariate models to ensure that observed results were not due to this imbalance. Subgroup analysis showed metabolic therapy was effective in improving clinical outcomes (Troponin I release, atrial fibrillation and length of stay) in CABG – alone but not in valve patients (Table 5). There was no effect of procedure type on oxidative stress or antioxidant capacity. The reduction in atrial fibrillation in CABG-alone patients accords with published studies [13] but requires confirmation in larger trials.

We used troponin I measured 24 hours postoperatively as an index of myocardial damage because this single measure has been shown to be a significant predictor of postoperative ICU and total hospital stay in a study of 300 CABG patients in our unit [24]. We elected to include both valve replacement and CABG patients because we were looking for a therapy that would benefit patients undergoing all forms of cardiac surgery and possibly other forms of surgery as well. Furthermore we had already demonstrated a benefit of CoQ10 therapy at a myocardial level in a valve replacement and CABG cohort [4].

As a consequence of prolonged waiting list time for elective surgery in a public hospital the duration of therapy was nearer to two months than the planned six weeks: two preoperatively and four postoperatively. Whether the beneficial effect we observed could have been achieved by a shorter duration of therapy is unknown but we believe it could have been, because in our previous similar study of CoQ10 alone [4], we observed beneficial effects, at least at a cellular level, after only two weeks of therapy. Similarly an open-label randomised trial before elective coronary artery bypass surgery, in which patients were treated pre-operatively with n3-PUFAs, some for as little as five days, and while in hospital, showed a reduction in the rate of postoperative atrial fibrillation and hospital length of stay [13].

Conclusions
In this study multiple markers of redox status indicated that cardiac surgery is associated with increased oxidative stress and a reduction in antioxidant reserves and that perioperative metabolic therapy can reduce oxidative stress and improve antioxidant defences. Such benefits at a biochemical level may be associated with reduced myocardial damage, a reduced incidence of atrial fibrillation (in CABG patients) and shortening of hospital length of stay. Thus metabolic therapy is safe, inexpensive, has negligible side effects and can confer clinical and economic benefits.

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References
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