Oxidative stress during extracorporeal circulation

Charles Ian McDonald*, John Francis Fraser, Jeff S. Coombes and Yoke Lin Fung

Critical Care Research Group, The Prince Charles Hospital and The University of Queensland, Brisbane, QLD, Australia

* Corresponding author. Anaesthesia and Perfusion Services, The Prince Charles Hospital, Rode Road, Chermside, Brisbane, QLD 4032, Australia. Tel: +61-7-31394705; fax: +61-7-31394659; e-mail: charles_mcdonald@health.qld.gov.au (C.I. McDonald).

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Summary

There is an increased oxidative stress response in patients having cardiac surgery, haemodialysis or extracorporeal membrane oxygenation that is related to poorer outcomes and increased mortality. Exposure of the patients’ blood to the artificial surfaces of these extracorporeal devices, coupled with inflammatory responses, hyperoxia and the pathophysiological aspects of the underlying illness itself, all contribute to this oxidative stress response. Oxidative stress occurs when there is a disruption of redox signalling and loss of control of redox balance. Ongoing oxidative stress occurring during extracorporeal circulation (ECC) results in damage to lipids, proteins and DNA and contributes to morbidity and mortality. This review discusses reactive species generation and the potential clinical consequences of oxidative stress during ECC as well as provides an overview of some current antioxidant compounds that are available to potentially mitigate the oxidative stress response.

Keywords: Extracorporeal circulation • Cardiopulmonary bypass • ECMO • Dialysis • Oxidative stress • Antioxidants

INTRODUCTION

Oxidative stress has been attributed to increases in morbidity and mortality in cardiac surgical patients, the critically ill and patients requiring haemodialysis (HD) [1–4]. These patients are exposed to various extracorporeal circulatory devices such as cardiopulmonary bypass (CPB), HD and extracorporeal membrane oxygenation (ECMO). Substantive evidence from CPB and HD studies indicates that extracorporeal circulation (ECC) stimulates the inflammatory response generating reactive nitrogen and oxygen species (RNOS) and overwhelming the endogenous antioxidants, resulting in increased oxidative stress [1, 2, 5]. Through an understanding of the multiple factors that occur during ECC responsible for generating RNOS, strategies may be developed which mitigate or reduce their generation and thereby reduce the associated complications. This review examines oxidative stress during CPB, dialysis and ECMO, as well as common antioxidant supplements, which may mitigate this response, leading to improved patient care.

OXIDATIVE STRESS

Definition and basic overview

Oxidative stress can be defined as a ‘disruption of redox signalling and control’ [6]. Under normal physiological conditions RNOS play essential roles in cell signalling (secondary messengers), immunity and cellular defence [1]. Both intra- and extracellular levels of RNOS are controlled by antioxidant moieties to maintain this redox balance [1]. However, during various chronic and acute illnesses an increase in RNOS production and loss of redox control is responsible for tissue and cellular injury. For instance, disturbance of the intracellular redox environment can result in cell apoptosis, senescence and disrupted differentiation [7]. There are three classical mechanisms by which RNOS exert their damaging effects, (i) peroxidation of lipids, (ii) denaturation of proteins or (iii) damage to DNA [1] (Fig. 1).

Lipid peroxidation. Lipid peroxidation is an important component of oxidative stress and is linked to a number of diseases including aging, atherosclerosis, Parkinson’s disease, Alzheimer’s disease, diabetes mellitus, cataracts and rheumatoid arthritis [8, 9]. Lipid peroxidation alters membrane fluidity and permeability, sometimes irreversibly, resulting in physiological changes such as altered ion gradients across the membrane [8]. The lipids in cell membranes, particularly polyunsaturated fatty acids (PUFAs), are susceptible to attack by various RNOS such as hydroxyl radicals and peroxyhydrates [9]. Typically damage in these conditions is a multistep sequence of events beginning with RNOS-mediated extraction of hydrogen from the lipid molecule, creating a fatty acid radical that itself extracts a hydrogen atom from the neighbouring lipid molecule creating another fatty acid radical. This self-propagating phase no longer requires the presence of the initiating RNOS to continue and expand [9]. Stopping the lipid peroxidation sequence requires the intervention of a ‘chain breaking’ antioxidant, such as Vitamin E, or the fatty acid radical to react with another radical, ‘quenching the fire’ [9].

Oxidative protein damage. Similar to lipids, proteins are also a major component of cell membranes, as well as being part of various essential enzymes throughout the body. Proteins are susceptible to both direct and indirect damage from RNOS. The hydroxyl and nitrogen-based radicals can damage various amino acids, additionally proteins that contain sulphur in their structure (such as cysteine and methionine) are also susceptible to oxidative...
damage [1]. Several RNOS can also interact directly with proteins, disrupting membrane ion transport mechanisms or causing the inactivation of enzymes and amino acids [1].

Oxidative DNA damage. DNA is normally a stable molecule; however, in the presence of high concentrations of the radical hydroxyl, oxidative damage occurs [10]. Oxidative DNA damage is associated with carcinogenesis, neurodegenerative diseases, cardiovascular disease and aging [8, 10]. Uncontrolled increases in RNOS result in modification of DNA bases, single and double DNA breaks, loss of purines, damage to the deoxyribose sugar, DNA–protein cross-linkage and damage to the DNA repair system [10]. Some oxidative DNA damage can either be prevented by antioxidants or repaired by various endogenous DNA repair enzymes; conversely, reduced antioxidant or trace element levels can undermine repair mechanisms, leading to permanent damage [10, 12].

ANTIOXIDANT DEFENCE AGAINST OXIDATIVE STRESS

The endogenous antioxidant response is a coordinated effort between enzymes, proteins and vitamins to remove, alter or inactivate excessive build-up of RNOS. This is a multilayered defence system and the exact nature of the antioxidant response is influenced by (i) the solubility of the antioxidant (lipid or water solubility), (ii) whether it is an enzyme/non-enzyme and (iii) the relative concentration of specific antioxidants in cytosol, plasma or tissue [1].

From a redox point of view, enzymatic antioxidants represent the first line of defence in cells and plasma [1]. These primary antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase [1]. SOD enzymes are present in most extracellular fluids as well as aerobic cells within the mitochondria and cytosol. The function of all forms of SOD is the dismutation of the superoxide radical ($O_2^-\rightarrow 2H^+\rightarrow [SOD] \rightarrow O_2 + H_2O_2$).

Figure 1: Simplified mechanism of oxidative stress, cellular RNOS generation and antioxidant action of SOD and GPx. $O_2^-$: superoxide radical; $H_2O_2$: hydrogen peroxide; $ONOO^-$: peroxo radical; $OH^{-}$: hydroxyl radical; $NO^-$: nitric radical; SOD: superoxide dismutase; GPx: glutathione peroxidase; GSH: glutathione; GSSH: oxidised glutathione; GSSG-R: glutathione reductase.

Equation 1: $2O_2^→ 2 H^+ → [SOD] → O_2 + H_2O_2$
Equation 2: $2GSH (\text{reduced}) + H_2O_2 → [GPx] → GSH (\text{oxidized}) + 2H_2O$
Equation 3: $GSH (\text{reduced}) + NADPH + H^+ → 2 GSH + NADP^+$
Equation 4: $2H_2O_2 → Catalase → 2H_2O + O_2$

Figure 2: Mechanism of action of SOD, GPx and catalase.

These antioxidant enzymes react directly with RNOS before they can react with lipids or proteins, thus preventing or delaying the generation of secondary and tertiary radicals. Trace metals are required for their normal functioning, i.e. selenium for GPx, copper/zinc or manganese for SOD and iron for catalase [13]. The non-enzymatic antioxidants include β-carotene, Vitamin E, Vitamin C, GSH and coenzyme Q, which act primarily as scavenger and chain-breaking antioxidants [8, 13]. The potential benefits of various antioxidant supplements are discussed below.

CLINICAL SIGNIFICANCE OF OXIDATIVE STRESS DURING EXTRACORPOREAL CIRCULATION

Cardiopulmonary bypass

Patients with underlying atherosclerosis, diabetes or chronic kidney disease (with or without dialysis) have increased levels of...
Cardiac surgical operations are often managed with hyperoxic (PO₂ > 200 mmHg) anaesthesia and CPB. Hyperoxia has been shown to stimulate neutrophils and mitochondria to increase production of RNOs, especially in the lungs [26]. While there are no controlled studies of hyperoxia vs normoxia and oxidative stress, it is plausible that hyperoxia, especially during reperfusion of the ischaemic lung postaortic clamping, may contribute to the overall oxidative stress profile. Further studies are needed to determine if oxidative stress profiles and clinical outcomes are improved when using a normoxic CPB strategy.

Cardiac surgical patients are frequently transfused with blood products. Packed red blood cell (PRBC) transfusions have been associated with increases in lipid peroxidation and oxidative stress in a small number of studies, presumably the consequence of a combination of the storage lesion, increased iron load, and decreased antioxidant profile of the stored red cells [27, 28]. Some patients, especially those with more complex procedures such as reoperations or aortic arch repairs, may require massive transfusions. Thus, the high number of PRBC transfusions may contribute to increased oxidative stress and compromise patient outcome. Platelet transfusions are not uncommon during cardiac surgery and mostly occur at the end of CPB, when the inflammatory response is already activated. Platelets are an important source of RNOs, primarily generating superoxide [29], and studies indicate that stored platelets, similar to stored red cells, will undergo a time dependent storage lesion [30]. Whether the transfusion of these platelets into a patient will affect the oxidative response has not been investigated.

Dialysis

Haemodialysis is the most prevalent form of renal therapy for AKI in the critically ill/post-surgical setting or more commonly for chronic end-stage renal failure [31]. HD may be applied as conventional HD in the chronic setting or in a variety of modes for the acute setting (i.e. slow low efficient dialysis, slow continuous ultrafiltration, continuous veno-venous haemofiltration). All forms of HD utilize artificial circuits to remove uremic waste and restore fluid and electrolyte balance. These circuits can have surface areas approaching mini-CPB circuits and thus are also associated with the activation of the coagulation and inflammation systems like CPB [32].

Evidence that patients with renal failure have increased oxidative stress and decreased antioxidant responses both pre- and post-HD has been reviewed previously [33]. Increases in oxidative stress after HD are associated with increased morbidity (specifically cardiovascular disease) and mortality. The mechanisms of increased oxidative stress in these patients is multifactorial and includes the renal disease itself, reduced antioxidant intake associated with malnutrition, loss of antioxidants during HD and the interaction between blood and the HD membrane [34]. Additionally, the overall ureaemic state of the patient and haemo-incompatibility of circuits (polysulfone vs cuprophane) are recognized as the major factors associated with both inflammation and oxidative stress [35].

Attempts to reduce the oxidative stress response due to blood contact with the dialysis circuit have been investigated using dialyser membranes that are more biocompatible. A 2006 meta-analysis of 14 studies using Vitamin E coated cellulose filters demonstrated an overall reduction in lipid peroxidation levels as measured by malondialdehyde, thiorbarbituric acid reactive substances and low-density lipoproteins [36]. More recently, companies have coated polysulfone dialysers with Vitamin E and early findings have demonstrated better reductions in oxidative stress.
markers as well as reduced markers of inflammation [37]. Further studies are needed to determine if reductions in oxidative stress levels during HD equates to better clinical outcomes.

**Extracorporeal membrane oxygenation**

ECMO is a rescue therapy for critically ill patients with potentially reversible cardiac and/or respiratory failure refractory to maximal conventional medicine [38]. In spite of the potential benefits of ECMO in these patients, the prolonged exposure of the blood to these artificial circuits is associated with a variety of deleterious pathophysiological changes and complications [38].

There are currently very limited data on oxidative stress or antioxidant changes during ECMO, either clinically or experimentally. Increased lipid peroxidation has been measured at the initiation of ECMO in plasma and lung tissue of rabbits [39]. However, in a lamb model of ECMO no increases in lipid peroxides were detected; instead there were decreases in the antioxidant enzymes SOD and GPx [40]. In the only clinical study investigating oxidative changes during ECMO, Hirthler et al. [41] showed increases in lipid peroxides for up to 96 h after initiation of ECMO in a paediatric population. In this study, non-survivors had increasing lipid peroxidation levels, while the levels plateaued after 24 h in the survivor group. There are significant differences between paediatric and adult ECMO such as the ratio of ECMO surface area to body size; this aspect limits the ability to translate paediatric or small animal ECMO studies to the adult. To date, there are no studies investigating oxidative stress in adult ECMO.

Despite a lack of current data on the oxidative stress response in the adult ECMO population, there is considerable evidence from the critically ill population to indicate that oxidative stress is a major contributor to morbidity and mortality. Specific RNOS triggering events in the critically ill that are especially relevant to the ECMO patient are listed in Table 1.

Two of these triggers are specifically relevant in the ECMO patient. The first major trigger, unique to patients on ECMO, is the initial and continued contact of whole blood with the ECMO circuit for days and weeks. Initial contact of blood with the ECMO circuit elicits a SIRS as measured by increased production of cytokines such as IL-6 [47]. Studies in CPB show that patients with SIRS also have a disturbed redox equilibrium [48], which is a result of both increased RNOS production and decreased antioxidant levels. Hence, it is reasonable to also expect oxidative injury via this mechanism during ECMO. However, whether prolonged exposure to the ECMO circuit continues to increase oxidative injury is unknown.

The second important trigger during ECMO is hyperoxia [49], which may be particularly relevant in the venovenous-ECMO (VV-ECMO) patient. During VV-ECMO, hyperoxic blood is returned directly to the venous system, where it flows directly to the damaged pulmonary vasculature. Worsening lung function as determined by radiographic evidence of consolidation is evident within the first 24–48 h of ECMO initiation (Fig. 4). Limited experimental data suggest that hyperoxia in this setting may facilitate neutrophil sequestration to the lungs, leading to increased pulmonary endothelial RNOS production and lipid peroxidation [26, 39]. Given that all of these oxidative stress triggers may increase ECMO morbidity and mortality, it highlights the need for detailed oxidative stress studies in this cohort.

**ANTIOXIDANT SUPPLEMENTS TO REDUCE OXIDATIVE STRESS**

The endogenous antioxidant defence system consists of both intra- and extracellular antioxidants that regulate the quantity of RNOS. There are considerable disturbances to this antioxidant system during critical illness as well as during cardiac surgery and HD. Specifically, there are reductions in antioxidant micronutrient levels such as selenium, zinc and Vitamin C [50]. Some of these reductions during ECC are a result of (i) an acute-phase redistribution as a result of the increased inflammatory response, (ii) absorption to the ECC circuit and (iii) excretion in bodily fluids/dialysate [19, 50, 51]. In addition to providing appropriate nutritional support in patients exposed to ECC, replacement of these antioxidant micronutrients may be a relatively low cost and safe intervention to mitigate the effects of oxidative stress [50, 52]. Various compounds with antioxidant properties that have been investigated, either as individual supplements or in combination therapy are discussed in brief below.

**Selenium**

Selenium is an essential trace element that is incorporated into selenoproteins, some of which have antioxidant properties (i.e. GPx, Selenoprotein P and thioredoxin) [53]. There are many potential benefits to selenium supplementation but most are centred around its link with increasing the activity of the antioxidant GPx [54]. The relationship between GPx and selenium is such that when selenium levels fall below plasma levels of 90–100 µg/l,
there is a direct reduction in GPx activity [54]. Significant reductions in selenium occur after cardiac surgery and dialysis [51, 55]. In both these patient groups, the reductions are inversely associated with increased complications and morbidity [55, 56]. Similarly in critical illness (without ECMO), selenium reductions occur, especially during sepsis and are associated with adverse outcomes [57]. Selenium supplementation has been investigated in cardiac surgical patients undergoing CPB [58] and in the critically ill [59]. A recent meta-analysis of micronutrient use in the critically ill population (not on ECMO) concluded that the treatment effect of selenium supplementation was greatest in patients with the more severe illness [52]. It is worth noting that those benefits were only seen when doses were greater than 500 µg/day, a dose far in excess of the 50–70 µg/day recommended dose. Despite the inconsistent beneficial findings, Visser et al. [50] have recommended that micronutrients, including selenium, should at least be given at the current recommended daily dosages in the critically ill as a safe and effective way to prevent clinical deficiencies. Additionally, the 2013 Canadian Clinical Practise Guidelines recommend the use of parenteral selenium in the critically ill [60].

**Vitamin C**

Vitamin C (L-ascorbic acid) is an essential nutrient with potent hydrophilic antioxidant properties. It acts as an aqueous phase antioxidant that has the ability to stop the propagation of free radicals that cause lipid peroxidation, termed ‘chain breaking antioxidant’, and is also required for the regeneration of the oxidized form of α-Tocopherol [61]. Studies in surgical and critically ill patients indicate an acute reduction in plasma Vitamin C levels that is explained only partly by increased antioxidant demand in the tissues [61]. Levels are further decreased in patients who develop postoperative complications. The well-established link between oxidative stress and atrial fibrillation studies has led investigators to assess the preventative effect of Vitamin C supplementation (isolated or combination therapy) on the development of POAF [61, 62]. Experimental and clinical evidence demonstrates a reduction POAF following ascorbate supplementation [63]. A recent study demonstrated that the preventative effect of Vitamin C supplementation on POAF was greater when given in association with β-blockers compared with β-blockers alone [64]. However, more studies are required to confirm these results.

In dialysis patients Vitamin C deficiency has been reported after extended hours of HD. Vitamin C supplementation in these patients has been shown to restore plasma levels and reduce levels of oxidative stress, as evidenced by markers of lipid peroxidation [65]. However, caution must be used when considering Vitamin C supplementation in patients with renal disease as Vitamin C is metabolized to oxalate. Oxalate causes the build-up of calcium oxalate in tissues, which can have cardiovascular consequences [66]. While there are no studies investigating the clinical outcome benefits of Vitamin C supplementation during ECMO, it has been shown that supranormal doses of intravenous Vitamin C in the critically ill can restore endothelial function and thereby modulate redox signalling [67].

**Vitamin E**

Vitamin E (α-Tocopherol) is a fat soluble antioxidant that reacts with lipid peroxides to prevent lipid peroxidation. It acts synergistically with Vitamin C at the lipid-water interface of cell membranes where Vitamin C can act as an electron donor to regenerate Vitamin E [62]. Based on its known antioxidant properties, the ability of Vitamin E to prevent cardiovascular disease has been investigated in a study of 9551 patients [68] but found no positive effect in this regard. Although Vitamin E levels are reduced during cardiac surgery and can be normalized with supplementation, another study showed that there was no reduction in lipid peroxidation after supplementation [69]. Studies that have investigated the ability of prophylactic Vitamin E to reduce POAF have also produced conflicting results. When used in isolation, the results indicate that Vitamin E has no protective effect [69], while studies using combination antioxidant therapy have shown reductions in POAF in the treatment groups [70, 71]. Such studies suggest a synergistic effect which needs to be confirmed by more rigorous studies.

Vitamin E supplementation has also been investigated during HD as a way of reducing the adverse effects associated with oxidative stress. One of the larger of such studies, the SPACE study [72], concluded that Vitamin E supplementation in HD patients with cardiovascular disease reduced the incidence of myocardial infarction and other composite end points, but they did not measure markers of oxidative stress. A review of 25 studies where Vitamin E supplementation was used and oxidative stress markers were measured found that in 20 studies there was a reduction in a variety of oxidative stress markers [34].

**Zinc**

Zinc is a trace element important to human health, including an essential role supporting SOD activity. Supplementation with zinc has been shown to improve plasma zinc levels but it is unclear if it improves SOD activity. Transient zinc deficiencies occur after cardiac surgery, HD and during critical illness [73]. Zinc levels have been shown to be inversely proportional to SOFA scores and organ failure in critical illness [74]. However, we could find no studies demonstrating a mortality benefit when zinc supplementation was used alone. Nevertheless, reports of toxic side effects are rare and, given the purported benefits of zinc supplementation in the mentioned patient populations, it is often added to the standard nutritional profile for many critically ill patients.

**N-acetylcysteine**

N-acetylcysteine (NAC) is a free radical scavenger antioxidant useful in chronic lung disease and has been shown to reduce RNOS and proinflammatory cytokine production [75, 76]. These properties have led to investigating the benefits of prophylactic NAC supplementation in cardiac surgical patients with the specific aim to reduce the incidence of POAF [76]. While selected studies such as this have shown improved outcomes in patients supplemented with NAC, a recent meta-analysis involving 1163 cardiac surgical patients concluded that the evidence did not support the use of NAC for the prevention of AKI [75].

**Glutamine**

Glutamine is a non-essential amino acid that is metabolized to glutamate, a precursor to GSH synthesis. GSH is the major endogenous antioxidant produced by cells and it exists mostly in the reduced form (GSH). The body has the capacity to synthesize...
sufficient glutamine under normal physiological conditions; however, significant reductions in glutamine occur during critical illness, after cardiac surgery and after prolonged dialysis [77]. Despite these reductions there is a sparse amount of data on the beneficial effects of glutamine supplementation during cardiac surgery. In the cardiac surgical population, studies have demonstrated that glutamine supplementation maintains GSH activity and increased glutamine levels, but had no effect on organ dysfunction or length of stay in the intensive care unit [78]. Although high quality evidence supporting parenteral glutamine supplementation in the critically ill has recently emerged [79], we could find no study solely investigating the effects of glutamine in ECMO patients. The recommendations from the Canadian Clinical Practise Guidelines for the critically ill have since updated their support for the ‘use of parenteral glutamine in the critically ill except in those with multiorgan failure’ [80].

CONCLUSION

Oxidative stress has been shown to be clinically relevant to patient outcomes and this review has highlighted the mechanisms leading to increased oxidative stress in patients exposed to ECC, and discussed some antioxidant supplements commonly used to modulate this response. Other avenues for possibly controlling ECC-induced oxidative stress include reducing ECC surface areas, designing circuits with better biocompatibilities, implementing normoxia and investigating the effects of pulsatile flow (during CPB) on endothelial NOS2 production. In addition, there are a range of pharmaceutical compounds beyond the scope of this review, such as statins and antithrombinolytics, that also exhibit antioxidant properties. However, many of these interventions require further confirmation of efficacy.

Redox control via antioxidant supplementation presents an attractive low-risk and low-cost avenue in this pursuit. Already the benefits of antioxidant supplementation have been reported in critically ill patients and has led to recent recommendations for the use of antioxidant supplements, specifically glutamine (and possibly selenium). Despite the theoretical benefits of antioxidant therapy, the practicality of implementing widespread antioxidant supplementation in patients exposed to ECC has been challenged by the available evidence. This evidence has suffered from poor study design, low sample numbers, heterozygous patient groups and a lack of consensus as to the best biomarker for oxidative stress. Thus, improved prospective randomized controlled trials of antioxidant supplementation are needed to define not only the most appropriate patient groups but also antioxidant dosing and timing.

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