CHAPTER 2

CARDIOVASCULAR EFFECTS OF HYPOXIA DURING AND AFTER CARDIAC SURGERY
SUMMARY
During and after cardiac surgery with cardiopulmonary bypass, high concentrations of oxygen are routinely administered, with the intention of preventing cellular hypoxia. We systematically reviewed the literature addressing the effects of arterial hyperoxia. Extensive evidence from preclinical experiments and clinical studies in other patient groups suggests predominant harm, caused by oxidative stress, vasoconstriction, perfusion heterogeneity and myocardial injury. Whether these alterations are temporary and benign, or actually affect clinical outcome, remains to be demonstrated. In nine clinical cardiac surgical studies in low-risk patients, higher oxygen targets tended to compromise cardiovascular function, but did not affect clinical outcome. No data about potential beneficial effects of hyperoxia, such as reduction of gas micro-emboli or post-cardiac surgery infections, were reported. Current evidence is insufficient to specify optimal oxygen targets. Nevertheless, the safety of supraphysiological oxygen suppletion is unproven. Randomised studies with a variety of oxygen targets and inclusion of high-risk patients are needed to identify optimal oxygen targets during and after cardiac surgery.
INTRODUCTION

During and after cardiac surgery with cardiopulmonary bypass, high concentrations of oxygen are routinely administered, with the intention of preventing cellular hypoxia\(^1\). Oxygen delivery to the tissues is threatened during bypass due to increased microcirculatory heterogeneity with low- and high-flow capillaries\(^2\). The augmented oxygen diffusion distance may impair oxygen delivery and organ function. Other factors that may reduce oxygen delivery to tissues include: hypothermia; fluid shift; myocardial dysfunction; blood loss; anaemia; and transfusion\(^3\). With this in mind, it may be intuitively correct to maintain a partial arterial oxygen pressure (\(P_aO_2\)) clearly above physiological values (mostly defined as 10–13.3 kPa), to increase the oxygen gradient between capillaries and tissue and reduce the risk of cellular hypoxia. In addition, at key points during general anaesthesia, it is common practice to administer 100% oxygen to prevent hypoxaemia\(^4\).

However, ‘too much’ oxygen is not necessarily the best solution to ‘not enough’ oxygen\(^4\). Dissolved oxygen does not greatly contribute to oxygen transport capacity. Hyperoxia may cause vasoconstriction and increase microcirculatory heterogeneity, thereby compromising perfusion and, hence, actual oxygen delivery\(^5\)–\(^7\). Also, hyperoxia can increase oxidative stress\(^8\) and fuel the systemic inflammatory response syndrome, a major cause of bypass-associated organ injury. In a wide range of conditions, such as ischaemic heart disease, stroke and after cardiac arrest, hyperoxia is associated with increased morbidity and mortality\(^9\).

On the other hand, analysis of a number of published studies and adjustment for confounding factors may abolish the excess mortality and beneficial effects of hyperoxia they originally suggested. The vasoconstrictive stimulus of short-term exposure to hyperoxia before sustained ischaemia may act as a preconditioner, with attenuation of ischaemia-reperfusion injury\(^10,11\). In addition, hyperoxia-induced vasoconstriction may counteract systemic inflammation-induced vasoplegia, and reduce vasopressor requirements. Furthermore, hyperoxia may lower damage by gas microemboli by denitrogenation\(^12\), and reduce postoperative infections\(^13\). Interestingly, in a recent study of patients after cardiac arrest, severe hyperoxia (\(P_aO_2>40\) kPa) was associated with decreased survival, but moderate hyperoxia (\(P_aO_2 13.3–40\) kPa) with improved Sequential Organ Failure Assessment score after 24h\(^14\). Current
guidelines do not specify oxygen targets during and after bypass. Over the years, several clinical studies have addressed the effects of hyperoxia in patients undergoing bypass, although the number of both studies and included patients are small. In this review, we summarise the current knowledge about hyperoxia during bypass-assisted cardiac surgery, emphasising cardiovascular performance. We elaborate on the molecular and pathophysiological mechanisms and summarise the results of all the clinical studies investigating hyperoxia in cardiac surgical patients. Hyperoxia may also induce lung injury, especially in combination with bypass, but this is beyond the scope of this review.

METHODS
We conducted a systematic search of both pre-clinical and clinical studies published between 1960 and March 2015 in Medline and Embase to identify all articles addressing the effect of hyperoxia before, during and/or after all bypass-assisted cardiac surgical procedures, such as coronary artery bypass graft surgery, cardiac valve replacement or repair, and combined surgery.

Search terms were used in every possible spelling, as synonyms, acronyms, key or text words, and these groups were combined with an ‘AND’ operator. Two investigators (A.M.E.S. de Man and B.S.) independently performed the data extraction. The references in the reviewed articles were manually scanned for other published articles.

RESULTS
Molecular mechanisms
Inflammation and oxidative stress play a pivotal role in the effects of hyperoxia, but are also independently induced by bypass. The two are interrelated: oxidative stress is part of the inflammatory response; and there is reciprocal amplification (Figure 1). Cardiopulmonary bypass induces biomaterial-dependent and -independent systemic inflammation. Biomaterial dependent inflammation is caused by the exposure of blood to artificial surfaces, and changes such as conversion into a continuous flow pattern during bypass. Biomaterial-independent inflammation is caused by: anaesthesia; surgical trauma; cardioplegia; ischaemia-reperfusion; release of endotoxin; transfusion; and changes in body temperature (Figure 1). These factors initiate a
Cardiopulmonary bypass surgery

Material-dependent activation
- Non-physiologic surfactant
- Shear stress

Material-independent activation
- SIRS
- Organ injury and dysfunction

Note: CPB, cardiopulmonary bypass; SIRS, systemic inflammatory response syndrome; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; eNOS, endothelial nitric oxide synthase; SIRS, systemic inflammatory response syndrome; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase.

Figure 1 - The interaction between cardiopulmonary bypass and hyperoxia with oxidative stress and inflammation. Abbreviations: CPB, cardiopulmonary bypass; SIRS, systemic inflammatory response syndrome; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; eNOS, endothelial nitric oxide synthase.
complex cascade of humoral and cell-mediated inflammatory responses, including activation of the complement system and production of cytokines, adhesion molecules, arachidonic acid metabolites, endothelins and platelet activating factors\textsuperscript{19,20}. The total white blood cell count and number of circulating neutrophils increase.

Activated neutrophils are the main source of reactive oxygen species production during and after cardiac surgery with bypass\textsuperscript{21–23}. They generate superoxide by the nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) pathway. Stimulated endothelial cells, vascular smooth muscle cells and cardiomyocytes contribute to reactive oxygen species production and also utilise the NADPH oxidase pathway to form intracellular superoxide, which subsequently dismutates to hydrogen peroxide\textsuperscript{19,24–26}. Hydrogen peroxide in turn triggers the release of reactive oxygen species by other enzymes. NADPH oxidase can be activated by both inflammatory and ischaemic/reperfusion stimuli. Together with the burst of reactive oxygen species, a large amount of nitric oxide is produced during reperfusion due to upregulation of inducible nitric oxide synthase. Nitric oxide reacts with superoxide to form the highly reactive peroxynitrite. Peroxynitrite is the most damaging reactive oxygen species, with an oxidative capacity of up to 1000-fold greater than that of hydrogen peroxide. The large amount of reactive oxygen species oxidises tetrahydrobiopterin, the essential cofactor for all three nitric oxide synthase isoforms. Nitric oxide synthase becomes uncoupled, leading to depletion of nitric oxide and producing superoxide, which further contributes to reactive oxygen species production\textsuperscript{27}.

Another important enzyme during reperfusion is xanthine oxidase. In ischaemia, hypoxanthine is formed as a breakdown product of adenosine triphosphate metabolism. Reoxygenation after declamping of the aorta provides the substrate for activity of xanthine oxidase in ischaemic endothelium, which catalyses the oxidation of hypoxanthine with abundant production of superoxide and hydrogen peroxide\textsuperscript{19}. Superoxide and hydrogen peroxide are also generated by the mitochondria due to uncoupling of oxidative phosphorylation (electrons are lost during the transfer between electron transport chain complexes).

The burst of reactive oxygen species engulfs the capacity of the endogenous antioxidants, such as superoxide dismutase, glutathione peroxidase,
and vitamins C and E. Reactive oxygen species that are unopposed by endogenous antioxidants lead to oxidative stress and can cause damage to biological molecules such as DNA, lipids and proteins, with dysfunction and loss of structural integrity.

The enhanced reactive oxygen species production following bypass triggers common signal transduction pathways, amplifying inflammation and the systemic inflammatory response syndrome through activation of mitogen-activated protein kinases and nuclear factor kappa B. This promotes gene expression of the pro-inflammatory cytokines tumour necrosis factor-a, interleukin-1b and interleukin-6. Inflammation thus induces oxidative stress and vice versa, generating a vicious circle (Figure 1)24.

Due to the volatile nature of reactive oxygen species, direct measurement of the effect of hyperoxia on reactive oxygen species production in clinical situations is very difficult. Thus, most of the available evidence about the association of hyperoxia with reactive oxygen species production is derived from preclinical studies. In vitro studies show a linear correlation between increasing oxygen levels up to 60% (60 kPa) and reactive oxygen species production, and an exponential rise at higher levels. These experiments were performed in porcine lung mitochondria28, capillary endothelial cells from rat lungs29 and in a reperfusion/reoxygenation model of cultured hepatocytes30. Reactive oxygen species were generated by the mitochondrial electronic transport chain29–31, activated NADPH oxidase29,32 and non-enzymatic reactions30. Investigation of the contribution of xanthine oxidase to hyperoxia-induced reactive oxygen species yielded contradictory results33,34 (Figure 1). Extrapolation of these in vitro experiments to in vivo situations and clinical conditions is difficult. Even room air saturated cell medium is hyperoxic compared with cells’ physiological environment. Furthermore, most studies were performed in the lungs, whereas underlying mechanisms may vary between different organs and cell types.

During in vivo experiments of healthy mice, 100% oxygen induced cellular infiltration of the lungs with release of the pro-inflammatory cytokines tumour necrosis factor-a and interleukin-6. Simultaneously, oxidative stress increased as demonstrated by reduced antioxidative activity35. Induction of hyperoxia in different septic models (lipopolysaccharide-induced lung inflammation or a caecal ligation and puncture sepsis model) increased the
inflammatory and oxidative stress response\textsuperscript{36}, organ inflammation and mortality\textsuperscript{37}. However, some studies show conflicting results, with attenuation of inflammation markers\textsuperscript{38,39}.

**Pathophysiology of cardiovascular effects**

Increased oxidative stress and inflammation can substantially affect cardiovascular performance. Preclinical experiments (Table 1) and studies in healthy volunteers and cardiovascular compromised patients (Table 2) suggest several pathophysiological mechanisms for harm. Figure 2 illustrates the potential underlying mechanisms.

Hyperoxia-induced vasoconstriction has been demonstrated in the brain\textsuperscript{61}, heart\textsuperscript{56,57}, retina\textsuperscript{62} and skeletal muscle\textsuperscript{63}. A hyperoxia-induced decline in vessel diameter reduced lower limb blood flow by up to 30\% in healthy volunteers\textsuperscript{47}. Hyperoxia disturbed microvascular flow with loss of functional capillary density and increased regional perfusion heterogeneity in animal studies\textsuperscript{40–43}. Most likely, hyperoxia exerts a direct effect on blood vessels. Increased reactive oxygen species may directly affect vascular smooth muscle cells by closure of adenosine triphosphate-dependent potassium channels\textsuperscript{64}, or agonistic action on L-type calcium channels\textsuperscript{65}. Alternatively, reactive oxygen species may affect vascular tone via the endothelium, due to increased endothelin-1, reduced availability of prostacyclin or decreased nitric oxide\textsuperscript{7,66}.

### Table 1 - Preclinical studies on the cardiovascular effects of hyperoxia

<table>
<thead>
<tr>
<th>First Author</th>
<th>Animals</th>
<th>Intervention</th>
<th>n</th>
<th>Effect of hyperoxia</th>
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</thead>
<tbody>
<tr>
<td><strong>Microcirculation</strong></td>
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<tr>
<td>Tsai\textsuperscript{40}</td>
<td>Hamsters</td>
<td>30 min F\textsubscript{O\textsubscript{2}} 1.0</td>
<td>6</td>
<td>FCD ↓ by 26% (16, P&lt;0.05)</td>
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<tr>
<td>Kamler\textsuperscript{41}</td>
<td>Hamsters</td>
<td>30 min F\textsubscript{O\textsubscript{2}} 1.0</td>
<td>14</td>
<td>FCD ↓ by 30% (P&lt;0.05)</td>
</tr>
<tr>
<td>Cabrales\textsuperscript{42}</td>
<td>Hamsters</td>
<td>10 min F\textsubscript{O\textsubscript{2}} 0.1/1.0</td>
<td>12</td>
<td>FCD ↓ by 21% (8, P&lt;0.05)</td>
</tr>
<tr>
<td>Riemann\textsuperscript{43}</td>
<td>Mice</td>
<td>F\textsubscript{O\textsubscript{2}} 0.95</td>
<td>36</td>
<td>AD ↓ by 12.3% (2.7, P&lt;0.01)</td>
</tr>
<tr>
<td><strong>Myocardial function</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Ishikawa\textsuperscript{44}</td>
<td>Dogs</td>
<td>7–10 min F\textsubscript{O\textsubscript{2}} 1.0</td>
<td>10</td>
<td>CBF ↓ by 19.5% (2.2)*</td>
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</table>

Values are presented as mean (standard deviation). Abbreviations: FCD, functional capillary density; MF, microvascular flow; AD, arteriolar diameter; CBF, coronary blood flow. * no P-values available.
Due to vasoconstriction, blood pressure increases, inducing cardiac parasympathetic activation and arterial-cardiac baroreflex function. This leads to a decrease in heart rate and stroke volume, thereby reducing cardiac output. 

Vasoconstriction of coronary vessels can decrease myocardial oxygen delivery and contribute to increased susceptibility to ischaemia, as well as reduced myocardial contractility. A systematic review of patients with cardiac disease showed that hyperoxia reduced coronary blood flow by 8–29% (six studies), and myocardial oxygen consumption by 15–27% (three studies). The diameter of the large conduit arteries remained equal, suggesting that vasoconstriction mainly occurred at a microvascular level. Myocardial function also responds to changes in coronary flow. In dogs with cardiac ischaemia, 100% oxygen reduced coronary blood flow by constriction with reduced oxygen delivery, oxygen consumption and contractility of the ischaemic area.
Table 2 - Clinical studies on the cardiovascular effects of hyperoxia

<table>
<thead>
<tr>
<th>First Author</th>
<th>Design</th>
<th>Intervention</th>
<th>n</th>
<th>Effect of hyperoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td></td>
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<td></td>
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<tr>
<td>Harten(^45)</td>
<td>Single arm, intervention</td>
<td>Increasing F\text{O}_2 up to 1.0</td>
<td>15</td>
<td>CI ↓ by 11% (range 0 to 19, P&lt;0.001) HR ↓ by 11% (range -2 to 22, P&lt;0.001)</td>
</tr>
<tr>
<td>Waring(^46)</td>
<td>Randomised, cross-over</td>
<td>1 h 15 l O\text{2}/min</td>
<td>8</td>
<td>CI ↓ by 17% (P&lt;0.05) HR ↓ by 11% (P&lt;0.05)</td>
</tr>
<tr>
<td>Rousseau(^47)</td>
<td>Single arm, intervention</td>
<td>30 min F\text{O}_2 1.0</td>
<td>12</td>
<td>Calf blood flow ↓ by 27% 2.2 ml/min (1.1) vs 1.6 (0.9, P&lt;0.001)</td>
</tr>
<tr>
<td>Shibata(^48)</td>
<td>Single arm, intervention</td>
<td>Increasing F\text{O}_2 up to 1.0</td>
<td>10</td>
<td>HR ↓ by 8% 65 bpm (9) vs 60 (8, P&lt;0.05)</td>
</tr>
<tr>
<td>Bak(^49)</td>
<td>Single arm, intervention</td>
<td>Increasing tcPO\text{2} till 60 kPa</td>
<td>9</td>
<td>CO ↓ by max 20% 5.5 l/min (0.9) vs 4.4 (0.6, P&lt;0.05)</td>
</tr>
<tr>
<td>Bourassa(^53)</td>
<td>Single arm, intervention</td>
<td>6 min F\text{O}_2 1.0</td>
<td>13</td>
<td>CI ↓ by 13% 3.8 l/min/m² (1.3) vs 3.3 (1.0)*</td>
</tr>
<tr>
<td>Ganz(^54)</td>
<td>Single arm, intervention</td>
<td>7 min 10-15 l O\text{2}/min</td>
<td>6</td>
<td>CI ↓ by 11% 3.6 l/min/m² (0.3) vs 3.2 (0.4, P=0.01)</td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation). Abbreviations: FCD, functional capillary density; MF, microvascular flow; AD, arteriolar diameter; CBF, coronary blood flow. * no P-values available.

Hyperoxia may also exert a direct negative inotropic effect. Reactive oxygen species can induce intracellular calcium overload due to modification of the sarcolemmaal and sarcoplasmic reticular calcium handling mechanisms. Intracellular calcium overload can contribute to cardiac contractile failure and cell death\(^67\). In rats, increased concentrations of reactive oxygen species reduced active tension of isolated papillary muscles up to 38%\(^68\), and in rabbits up to 31% of baseline values\(^69\). In addition, disturbed cardiomyocyte calcium homeostasis can impair diastolic function\(^51\). Studies in patients with and without congestive heart failure demonstrate prolongation of the relaxation time constant and increased left ventricular filling pressures, which supports this hypothesis\(^50\),\(^51\). As can be expected, patients with congestive heart failure are especially vulnerable to hyperoxia\(^50\),\(^51\),\(^53\),\(^70-72\).

Hyperoxia can also aggravate ischaemia/reperfusion injury of the myocardium and augment myocardial stunning\(^8\),\(^73-76\). Major harm occurs after ischaemia during reperfusion, with a crucial role for oxidative stress. Reperfusion of ischaemic tissues causes microvascular injury with endothelial production of reactive oxygen species, reduced nitric oxide production and increased
release of cytokines and reactive oxygen species by leucocytes in the returning blood. These inflammatory mediators induce further tissue damage and functional impairment.\(^7\)

Re-oxygenation with lower oxygen targets may limit reperfusion injury, as has been demonstrated in animal models of cardiopulmonary bypass and in several animal models of regional ischaemia. These experimental data are supported by a recent Cochrane analysis of four studies of patients with acute myocardial infarction. This meta-analysis showed a
trend for higher mortality (Table 2) in patients breathing oxygen compared with air\textsuperscript{59}. However, the available evidence lacks power, so this could be due to chance. Further support for reduction of reperfusion injury with lower oxygen targets comes from the recently performed Air Versus Oxygen in ST-elevation Myocardial Infarction (AVOID) trial. In patients with ST-segment elevation myocardial infarction, but without hypoxia, supplemental oxygen therapy increased myocardial injury (creatine kinase 20\% higher), and was associated with 55\% (\(P=0.04\)) larger myocardial infarct size assessed using cardiac magnetic resonance imaging at six months\textsuperscript{60}.

**Clinical trials in cardiac surgery**

To what extent these potential adverse effects of hyperoxia translate into clinical effects during and after cardiac surgery have been investigated in nine clinical studies (Table 3): five randomised controlled trials; two uncontrolled interventions; and two retrospective studies. In these studies, patients with poor left ventricular function and valvular or combined surgery were frequently excluded. Patients were exposed to different oxygen regimens.

The randomised controlled trials investigated the following phases:

- before cardioplegia, F\(_{\text{IO}_2}\) >0.96 vs 0.4 for 120 and 60 min, respectively\textsuperscript{81,82}
- during the entire bypass period, F\(_{\text{IO}_2}\) 0.4–0.6 during rewarming vs. 0.4–0.5, or 0.35–0.45\textsuperscript{80} and P\(_{\text{O}_2}\) 53 vs. 19 kPa\textsuperscript{18}
- during reperfusion after aortic unclamping, P\(_{\text{O}_2}\) 60–73 vs 27–33 kPa\textsuperscript{8}

The two uncontrolled intervention studies applied 100\% oxygen during single\textsuperscript{1} and multiple\textsuperscript{83} short periods of time (about 10 min) throughout surgery. Hyperoxia was defined as P\(_{\text{O}_2}\) of 40–47 kPa\textsuperscript{84} and \(\geq 40\) kPa, respectively (physiological P\(_{\text{O}_2}\) levels: 10–13.3 kPa)\textsuperscript{85}.

Two randomised controlled trials\textsuperscript{18,80} and two retrospective investigations\textsuperscript{84,85} evaluated clinical endpoints, mainly length of stay and mortality. Because of the paucity of clinical data, we included both retrospective studies in Table 3, but the outcome measures in these studies may be substantially affected by confounding by indication. In the large retrospective study, there was no association between hyperoxia and hospital mortality compared with normoxia. There was a small but statistically significant increase
in ICU and hospital length of stay for the hyperoxic patients (1.9 vs 1.8 and 10.0 vs 9.9 days, respectively, both \( P<0.05 \))\(^{85} \). In the small retrospective study, ICU stay and mechanical ventilation time\(^{84} \) tended to be slightly (10 and 2 h, respectively), but non-significantly longer in the hyperoxic groups. One study specifically addressed the risk of hypoxia\(^{80} \). Reduction of oxygen administration during cardiac surgery down to an \( FIO_2 \) of 0.35 did not cause hypoxic episodes. Even in the lower oxygen groups, patients were frequently hyperoxic (30% patients had \( P_aO_2 >24 \) kPa).

**Cardiovascular function**

Of six studies, four suggested impaired cardiovascular function with higher oxygen targets, while two studies showed no difference (Table 3). Hemodynamic variables were measured by thermodilution\(^{8,18,81–83} \), or lithium dilution technique\(^1 \). Patients with higher oxygen targets during bypass showed increased systemic vascular resistance (by up to 24%) compared with patients with lower targets\(^1,8 \). In two studies, higher \( P_aO_2 \) targets significantly reduced cardiac index during and/or after cardiac surgery, by more than 10% compared with lower targets\(^1,8 \). A trend for a lower cardiac index remained detectable 45 hours after bypass\(^8 \). Two other studies showed a non-significantly lower\(^18 \) or similar cardiac index\(^83 \). Pretreatment by 60 or 120 minutes of hyperoxia did not affect cardiac index\(^81,82 \).

In one study, hyperoxia aggravated microcirculatory perfusion heterogeneity\(^83 \). Assessment of tissue oxygenation by an oxygen microelectrode in the anterior tibial muscle of patients alternately exposed to normoxaemia and hyperoxaemia during surgery showed increased heterogeneity of distribution of tissue oxygen during hyperoxaemia. This occurred especially after bypass, resulting in even lower surface oxygen tensions in the hyperoxic vs. normoxic group: 0.8 vs 1.7 kPa (Table 3)\(^83 \).

Animal studies suggest that hyperoxia has favourable effects on myocardial ischaemic injury through a preconditioning effect on cardiac muscle\(^86,87 \). A similar study in humans, exposing patients to hyperoxia (\( FIO_2 >0.96 \)) for 130 and 60 min before coronary artery bypass grafting, had no effect on the cardiac enzymes creatine kinase MB (CK-MB) and troponin\(^{81,82} \). However, hyperoxia applied during cardiac surgery, during reperfusion\(^8 \) or the entire bypass period\(^18 \) increased ischaemia-reperfusion injury as estimated by troponin-T\(^8 \).
### Table 3 - Clinical studies on hyperoxia during/after cardiac surgery

<table>
<thead>
<tr>
<th>First Author</th>
<th>Design, intervention period and type of cardiac surgery</th>
<th>Oxygen groups</th>
<th>n</th>
<th>Effect on clinical outcome and hemodynamic variables</th>
<th>Effects on biochemical variables</th>
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<tbody>
<tr>
<td><strong>Controlled studies</strong></td>
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</tbody>
</table>
| Ihnken\(^8\) | RCT, during bypass, CABG | I \(P_o_2\) 53 kPa  
II \(P_o_2\) 19 kPa | 20 | Decreased cardiac index: 3.1 l/min/m\(^2\) (0.2) vs 3.3 (0.3, \(P=0.6\)) | Increased CK, end-CPB: 672 U/l (130) vs 293 (21, \(P=0.002\)) |
| Inoue\(^8\) | RCT, during reperfusion, CABG | I \(P_o_2\) 60-73 kPa  
II \(P_o_2\) 60-73 kPa + diltiazem  
III \(P_o_2\) 27-33 kPa | 10 | Decreased cardiac index: group I vs III, 3h after CPB: 4.1 l/min/m\(^2\) vs 2.9 (\(P<0.05\)) | Increased troponin T, group I vs III, 3h after CPB: 2.1 ng/ml vs 0.8 (\(P<0.05\)) |
| Toraman\(^8\) | RCT, during bypass (rewarming), CABG | I CPB F\(_O_2\) 0.4-0.6  
II CPB F\(_O_2\) 0.4-0.5  
III CPB F\(_O_2\) 0.35-0.45 | 30 | Hospital length of stay, 5.3 days (2.7) vs 5.5 (2.9) vs 5.2 (2.2, \(P=ND\)) | Lactate, end of rewarming: 1.9 mmol/l (0.4) vs 1.6 (0.4) vs 1.9 (0.6, \(P=NS\)) |
| Karu\(^6\) | RCT, during bypass (120 min before cardioplegia), CABG | I \(F_o_2\) >0.96  
II \(F_o_2\) 0.4 | 20 | Cardiac index: ND | Troponin T, 60 min after bypass: 8.24 ng/ml (IQR 3.53-18.0) vs 7.00 (4.10-14.1, \(P=NS\)) |
| Karu\(^6\) | RCT, during bypass (60 min before cardioplegia), CABG | I \(F_o_2\) >0.96  
II \(F_o_2\) 0.4 | 20 | Cardiac index: ND | Troponin T, first postoperative morning: 0.45 ng/ml (IQR 0.37-0.71) vs 0.44 (0.26-0.55, \(P=?\)) |

Values are presented as mean (standard deviation) or median (interquartile range). Abbreviations: RCT, randomized controlled trial; CABG, coronary artery bypass graft; CI, cardiac index; CPB, cardiopulmonary bypass; CK, creatine kinase; NS, not significant and exact \(P\)-value not reported; ND, no difference; AVR, aortic valve replacement; ASD, atrial septal defect. Symbols: *, no further specification of type of cardiac surgery.
### Table 3 (continued) - Clinical studies on hyperoxia during/after cardiac surgery

<table>
<thead>
<tr>
<th>First Author</th>
<th>Design, intervention period and type of cardiac surgery</th>
<th>Oxygen groups</th>
<th>n</th>
<th>Effect on clinical outcome and hemodynamic variables</th>
<th>Effects on biochemical variables</th>
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<tbody>
<tr>
<td><strong>Uncontrolled intervention studies</strong></td>
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<tr>
<td>Joachimsson⁶³</td>
<td>Single arm intervention, during and after bypass, AVR, ASD closure and CABG</td>
<td>Alternating $P_aO_2$ between 10–15 kPa and &gt;25 kPa</td>
<td>10</td>
<td>Decreased tibialis anterior PO$_2$: 54% ($P&lt;0.001$)</td>
<td></td>
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<tr>
<td>Harten¹</td>
<td>Observational, after CPB, CABG</td>
<td>$FIO_2$ from ≤ 0.60 to 1.0 for 10 min</td>
<td>15</td>
<td>Decreased cardiac index: 11%, 2.83 l/min/m$^2$ (0.92) vs 2.52 (0.74, $P&lt;0.025$)</td>
<td></td>
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<tr>
<td><strong>Retrospective studies</strong></td>
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<tr>
<td>Brown⁸⁴</td>
<td>CABG and valve replacement</td>
<td>I $P_aO_2$ 40–47 kPa II $P_aO_2$ 20–33 kPa</td>
<td>19, 17</td>
<td>ICU stay: 38.6 hours (21.5) vs 29 (14.5, $P=0.42$)</td>
<td>Postoperative creatinine: 1.04 mg/dl (0.45) vs 1.01 (0.20, $P=1.0$)</td>
</tr>
<tr>
<td>Sutton⁸⁵</td>
<td>Cardiac surgery*</td>
<td>I $P_aO_2$ ≥40 kPa II $P_aO_2$ 8–40 kPa III $P_aO_2$ &lt;8 kPa</td>
<td>12188, 16452, 54420</td>
<td>Hospital mortality, group I vs II: aOR 0.9 (0.7–1.1)</td>
<td></td>
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</tbody>
</table>

Values are presented as mean (standard deviation) or median (interquartile range). Abbreviations: RCT, randomized controlled trial; CABG, coronary artery bypass graft; CI, cardiac index; CPB, cardiopulmonary bypass; CK, creatine kinase; NS, not significant and exact $P$-value not reported; ND, no difference; AVR, aortic valve replacement; ASD, atrial septal defect. Symbols: *, no further specification of type of cardiac surgery.
and creatine kinase\textsuperscript{18} (Table 3).

Lactate levels, used as a marker for tissue perfusion, were equal during different oxygen regimens\textsuperscript{18,80,81}. Just one (retrospective) study reported postoperative creatinine levels, and did not find differences between hyperoxic and normoxic patients\textsuperscript{84}.

**Inflammation and oxidative stress**

In the nine clinical studies, underlying mechanisms were not well explored. Only two clinical cardiac surgical trials studied the effects of hyperoxia on the inflammatory and oxidative response (Table 3). Normoxic bypass (19 kPa) lowered inflammation compared with hyperoxic cardiopulmonary bypass (53 kPa), as estimated by levels of polymorphonuclear leucocyte elastase (377 vs 171 ng/ml, $P<0.001$)\textsuperscript{18}.

Lower oxygen targets effectively reduced oxidative stress as evidenced by a decrease of malonaldehyde levels by 18–41\%\textsuperscript{8,18} and 40\% higher antioxidant levels\textsuperscript{18}.

**Gas microemboli**

None of the clinical studies reported the effect of hyperoxia on development of gas microemboli. Hyperoxia can reduce emboli by denitrogenation, as gas emboli containing 80\% nitrogen survive approximately ten times longer than emboli consisting of oxygen\textsuperscript{12}, as shown by transcranial Doppler ultrasound\textsuperscript{88}. An effect on neurological outcome was not reported. In a large (n=1018), but retrospective, trial, there was no difference between hyperoxic and normoxic patients in neurocognitive function. Gas microemboli were not investigated in this study\textsuperscript{89}.

Gas microemboli mostly occur during open procedures such as valve replacement (incidence 1.5–10\%)\textsuperscript{90}, where they are generated by cavitation in areas of turbulent flow, by injection of solutions into the circuit or by entrainment of gas from both cannulation sites. Improvement of the components of the bypass circuit has substantially diminished the burden of gas microemboli\textsuperscript{91}. As most of the aforementioned clinical trials excluded patients undergoing valve surgery, the clinical impact of hyperoxia on gas microemboli cannot be determined based on the available literature about different oxygen levels in cardiac surgical patients.
Postoperative infections
None of the nine clinical trials addressed the effect of hyperoxia on postoperative infections in cardiac surgical patients. Studies in colorectal surgery or obstetric surgery\(^{92-97}\) yielded inconsistent results. A recent meta-analysis concluded that perioperative high inspired oxygen therapy was not beneficial for the prevention of surgical site infection\(^ {98}\).

Theoretically, increased reactive oxygen species production could improve oxidative killing by neutrophils, which could be beneficial. However, this is in contrast with a recent study in rats undergoing caecal ligation and puncture and treated by hyperoxia, which showed a greater number of infected samples in the hyperoxic group\(^ {36}\).

Safety of lower oxygen targets
Reduction of oxygen administration during cardiac surgery to an F\(_{\text{I}}\)O\(_2\) of 35\% did not result in hypoxic episodes or an increase in lactate levels\(^ {80}\). None of the studies demonstrated worse outcomes for lower oxygen targets, suggesting that the margin of safety and error seemed large enough. Of note, the lower oxygen targets were still quite high (up to 33 kPa) compared with physiological oxygen values, and even in the lower oxygen groups hyperoxia frequently occurred. The optimal oxygen range might even be more close to physiological values (10–13.3 kPa) than has been investigated to date.

Antioxidative agents
Whether reduction of oxidative stress translates into improved postoperative outcome remains controversial. The aforementioned clinical cardiac surgical studies excluded high-risk patients and had complication rates close to zero. Studies investigating the antioxidative agents N-acetylcysteine\(^ {99,100}\) and vitamin E\(^ {101}\) in cardiac surgery showed, despite reduced oxidative stress, no beneficial effect on biochemical markers of myocardial injury or clinical outcome like length of ICU stay, myocardial infarction or mortality\(^ {102}\). Vitamin C reduced the occurrence of new atrial fibrillation in some, but not all studies\(^ {103}\). However, most of these studies were also performed in low-risk patients with good left ventricular function. Determination of the impact of oxidative stress on clinical outcome for cardiac surgical patients may require inclusion of high-risk patients with low ejection fraction and more complicated surgical
procedures. This is supported by a recent evaluation of randomised clinical trials with the xanthine oxidase inhibitor allopurinol. High-risk CABG patients had more benefit (reduced inotropic and mechanical left ventricle support) with allopurinol compared with low-risk patients.\(^{104}\)

**CONCLUSION**

The present review suggests that hyperoxia may compromise cardiovascular performance in cardiac surgical patients, mainly due to increased oxidative stress. Hyperoxia can induce vasoconstriction, heterogeneity of the microcirculation and diastolic dysfunction, decrease cardiac output and increase myocardial injury. Hyperoxia may thereby hamper oxygen delivery to tissues. Whether these alterations are just a temporary, relatively benign phenomenon or actually impair clinical outcome, remains to be demonstrated. The number of studies and patients included in them were small, the lower oxygen targets were still supraphysiological, and most studies excluded high-risk patients. However, there is extensive evidence from preclinical experiments and clinical studies in other patient groups suggesting harm. No indication of clinical benefit, such as reduction of gas microemboli or postoperative infections, with hyperoxic targets has been reported.

Therefore, especially in cardiovascularly compromised patients, the safety of supraphysiologic oxygen levels is unproven. Current evidence is insufficient to specify optimal oxygen targets. Randomised studies aiming for more physiological oxygen levels and including high-risk patients are needed to identify optimal oxygen targets during and after cardiac surgery.
REFERENCES


34. Rodell TC, Cheronis JC, Ohnemus CL, Piermattei DJ, Repine JE. Xanthine oxidase mediates elastase-induced injury to isolated lungs and endothelium. Journal of Applied Physiology 1987; 63:
2159–63.


98. Togioka B, Galvagno S, Sumida S, Murphy J, Ouanes JP, Wu C. The role of perioperative high inspired oxygen ther-


