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The medical use of oxygen: a time for critical reappraisal

F. Sjöberg[1,2] & M. Singer[3]

From the [1]Departments of Hand and Plastic Surgery and Intensive Care, Burn Center, Linköping County Council; [2]Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; and [3]Bloomsbury Institute of Intensive Care Medicine, University College of London, London, UK

Abstract. Sjöberg F, Singer M (Departments of Hand and Plastic Surgery and Intensive Care, Burn Center, Linköping County Council, Linköping, Sweden; Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; Bloomsbury Institute of Intensive Care Medicine, University College London, London, UK). The medical use of oxygen: a time for critical reappraisal. (Review). *J Intern Med* 2013; **274**: 505–528.

Oxygen treatment has been a cornerstone of acute medical care for numerous pathological states. Initially, this was supported by the assumed need to avoid hypoxaemia and tissue hypoxia. Most acute treatment algorithms, therefore, recommended the liberal use of a high fraction of inspired oxygen, often without first confirming the presence of a hypoxic insult. However, recent physiological research has underlined the vasoconstrictor effects of hyperoxia on normal vasculature and, consequently, the risk of significant blood flow reduction to the at-risk tissue. Positive effects may be claimed simply by relief of an assumed local tissue hypoxia, such as in acute cardiovascular disease, brain ischaemia due to, for example, stroke or shock or carbon monoxide intoxication. However, in most situations, a generalized hypoxia is not the problem and a risk of negative hyperoxaemia-induced local vasoconstriction effects may instead be the reality. In preclinical studies, many important positive anti-inflammatory effects of both normobaric and hyperbaric oxygen have been repeatedly shown, often as surrogate end-points such as increases in gluthatione levels, reduced lipid peroxidation and neutrophil activation thus modifying ischaemia–reperfusion injury and also causing anti-apoptotic effects. However, in parallel, toxic effects of oxygen are also well known, including induced mucosal inflammation, pneumonitis and retrolental fibroplasia. Examining the available 'strong' clinical evidence, such as usually claimed for randomized controlled trials, few positive studies stand up to scrutiny and a number of trials have shown no effect or even been terminated early due to worse outcomes in the oxygen treatment arm. Recently, this has led to less aggressive approaches, even to not providing any supplemental oxygen, in several acute care settings, such as resuscitation of asphyxiated newborns, during acute myocardial infarction or after stroke or cardiac arrest. The safety of more advanced attempts to deliver increased oxygen levels to hypoxic or ischaemic tissues, such as with hyperbaric oxygen therapy, is therefore also being questioned. Here, we provide an overview of the present knowledge of the physiological effects of oxygen in relation to its therapeutic potential for different medical conditions, as well as considering the potential for harm. We conclude that the medical use of oxygen needs to be further examined in search of solid evidence of benefit in many of the current clinical settings in which it is routinely used.

Keywords: hyperbaric, hyperoxaemia, inflammation, ischaemia–reperfusion injury, prospective randomized trials, vasoconstriction.

Introduction

The current justification for oxygen therapy in emergency medicine derives from the desire to prevent/correct arterial hypoxaemia and any resulting tissue hypoxia. Tissue hypoxia is a common and serious condition in many emergency situations including trauma (e.g. haemorrhagic shock), respiratory distress (e.g. pneumonia and asthma) and circulatory system disorders (e.g. heart failure). Thus, most acute care treatment algorithms recommend early initiation of oxygen, even without first ascertaining whether or not hypoxaemia is present [1, 2]. Most guidelines do not yet recommend dose titration to accomplish normoxaemia as assessed by invasively or noninvasively obtained end-points such as P_aO_2 or SpO_2. As a consequence, many patients become hyperoxaemic (high P_aO_2).

Although this may not cause early and direct tissue damage, increasing evidence suggests that high levels of oxygen may be disadvantageous, especially on normal, nondiseased vasculature, due to decreased local blood flow induced by the well-known vasoconstrictor effect of hyperoxaemia [3] (Fig. 1). Recently, Cornet *et al.* [4, 5] have warned of the potential harm that oxygen therapy may cause when used nonspecifically for medical emergencies in general. This is also described for the administration of hyperbaric oxygen (HBO) [6, 7]. Here, treatment effects are mostly considered to be secondary to cellular effects generated by oxidative stress. Increased production of reactive oxygen (ROS) and nitrogen (RNS) species results in increased growth factor production, collagen synthesis, cell migration, neovascularization events and transient immunosuppression [8, 9].

It is nevertheless important to stress that whilst oxygen may not be advantageous in certain acute medical conditions or disease states, this is not the situation in acute tissue oxygen deficit due to impaired oxygenation of the blood within the lungs and consequent tissue hypoxia. In this case, increasing fractions of inhaled oxygen (F_iO_2) normalizes blood oxygen levels and often rapidly reduces the risk of generalized tissue hypoxia. A classic scenario is the patient with chronic obstructive lung disease who experiences tissue hypoxia from an acute hypoxaemia of pulmonary origin; the beneficial effect of oxygen in this setting, both in the short term and long term, is well documented [10, 11]. Supportive data are, however, less convincing for long-term treatment in patients with a lower level of hypoxaemia [12, 13], although oxygen therapy may reduce the symptoms of dyspnoea even in patients without hypoxia [13].

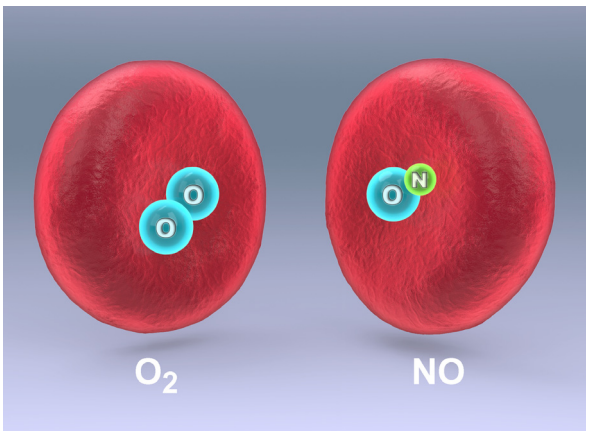

Fig. 1 *Oxygen (O_2) levels, oxygen transport and nitric oxide (NO). The vascular response to changes in arterial oxygen pressure, depicted with red blood cells with haemoglobin as the main transport system, is mediated, particularly during hyperoxaemia, by the effects of oxygen free radicals on local NO levels.*

The aim of this review is to examine the clinical uses of normobaric oxygen (NBO) and hyperbaric oxygen treatment (HBO) therapy in emergency and other acute medical conditions where the use of oxygen therapy has been advocated without the need to titrate dose, and where efficacy has been claimed for many years. We will consider mainly short-term exposure (minutes/hours) or repetitive exposure over several hours. After a brief discussion of the vascular and ventilatory effects of oxygen, we will review specific conditions and outcomes in which oxygen (NBO and/or HBO) has been applied. We will focus on studies supporting level A evidence, that is, randomized controlled trials (RCTs), and on the clinical use of oxygen and its effects on relevant outcome parameters rather than surrogates. For more details of the effector mechanisms of HBO, see the excellent reviews by Thom [8], Crocket *et al.* [9] and Michalski *et al.* [14].

NBO treatment

Oxygen: the molecule of life

It is likely that life started in a nitrogen environment, in which oxygen was first produced by cyanobacteria as a waste product of energy-producing photosynthesis. Rocks, oxidized by this oxygen, have left a geological record that documents fluctuations in the atmospheric oxygen composition. As atmospheric oxygen levels further increased, so did the need to detoxify it and, most importantly, the concomitantly produced oxygen free radicals. Later on, a direct descendent of the cyanobacterium, the mitochondrion, was incorporated into more complex single cells. This organelle could both handle the oxygen radicals and utilize the oxygen to provide much more energy than by glycolysis (anaerobic metabolism) alone. In parallel, other oxygen-detoxifying capabilities were also further developed. These events were important foundations for the evolution of more complex multicellular organisms [15] (Fig. 2). However, these defences can still be overwhelmed, as exemplified by shortened survival times for different species when breathing 100% oxygen: drosophila,

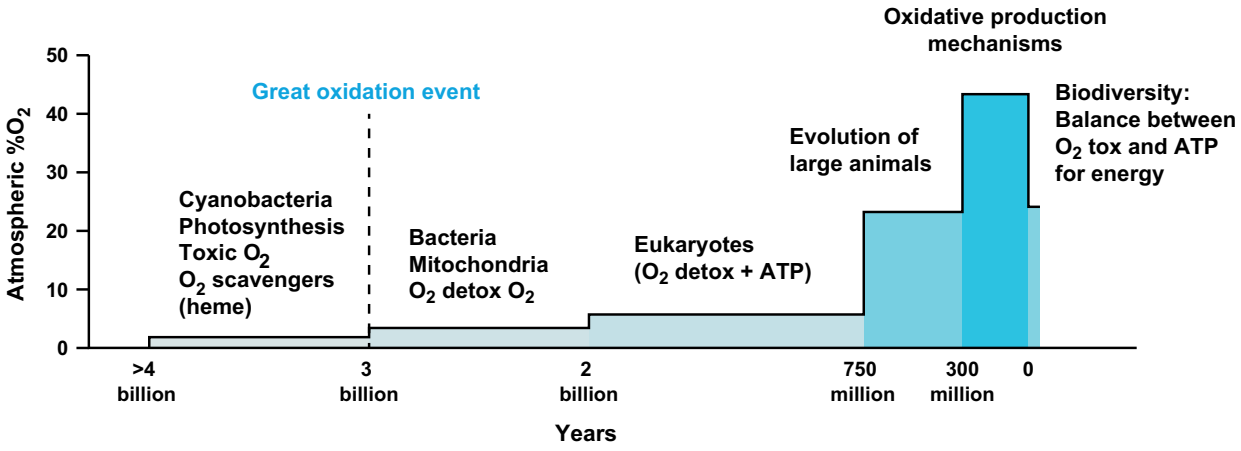

Fig. 2 *Stages of evolution and the associated atmospheric oxygen levels. O_2 detox, oxygen detoxification; tox, toxicity. Modified from Uronis et al.* [13].

168 h; mouse, 77–306 h; cat, 83 h; and monkey, 180–390 h [16]. Oxygen, through its contribution to oxidative stress, has been incorporated into theories of ageing and lifespan determination. Whilst this role holds true for drosophila, recent studies in higher animals such as mice are far less conclusive [17].

Oxygen, human life's most important molecule, was discovered in the late 1700s. Before that, the 'phlogiston theory' proposed that all combustible material contained a substance, phlogiston, that caught fire when matter was heated. Phlogiston had a 'negative mass' as a metal increased in weight during heating. The phlogiston theory predominated until 1777 when the name 'oxygene' (acid forming) was given to the gas released when mercury oxide is heated. It still remains unclear who should be honoured with the discovery: the Swedish chemist Carl Wilhelm Scheele, his French counterpart Antoine Lavoisier or the 'Renaissance man' and British politician Joseph Priestley [18]. In the early twentieth century, Parkinson published the first experiments investigating ventilatory and circulatory effects of oxygen in humans [19]. The induced vasoconstriction and consequent decrease in blood flow [9, 20] and thus became a significant issue when discussing medical uses of oxygen.

The crucial consequence of oxygen uptake by living tissue is 'nature's choice' of oxygen as the terminal electron receptor within the mitochondrial electron transport chain (Fig. 3); oxygen is reduced to water whilst energy is stored by phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Problems arise if insufficient O_2 is present to cope with cellular oxygen demands. An increase in lactate is produced in its stead; though a fuel source in its own right, from an energetic perspective lactate produces much less energy than that generated by hydrolysis of ATP. When conversion of ADP to ATP is prevented, as with conditions of oxygen deficiency (hypoxia), total energy production decreases.

Defining hypoxia

Hypoxia refers to nonspecific oxygen deficiency and is caused by multiple factors, with pulmonary dysfunction and decreased tissue blood flow being the most important. As tissue hypoxia may result from a pathology occurring anywhere along the oxygen transport pathway from lung to mitochondrion, it is essential to determine the site of this defect. The normal partial pressure of oxygen (PO_2) is approximately 20 kPa at sea level. This decreases rapidly in the lung where carbon dioxide, water vapour pressure and some veno-arterial shunting reduce the PO_2 in arterial blood to 13 kPa in young, healthy individuals. Further down the vasculature, more oxygen is lost such that PO_2 within the arterioles is 3–5 kPa, and close to 2 kPa at the level of the capillary. At the inner mitochondrial membrane, where the electron transport chain is located, models have demonstrated that levels are as low as 0.1–1.0 kPa.

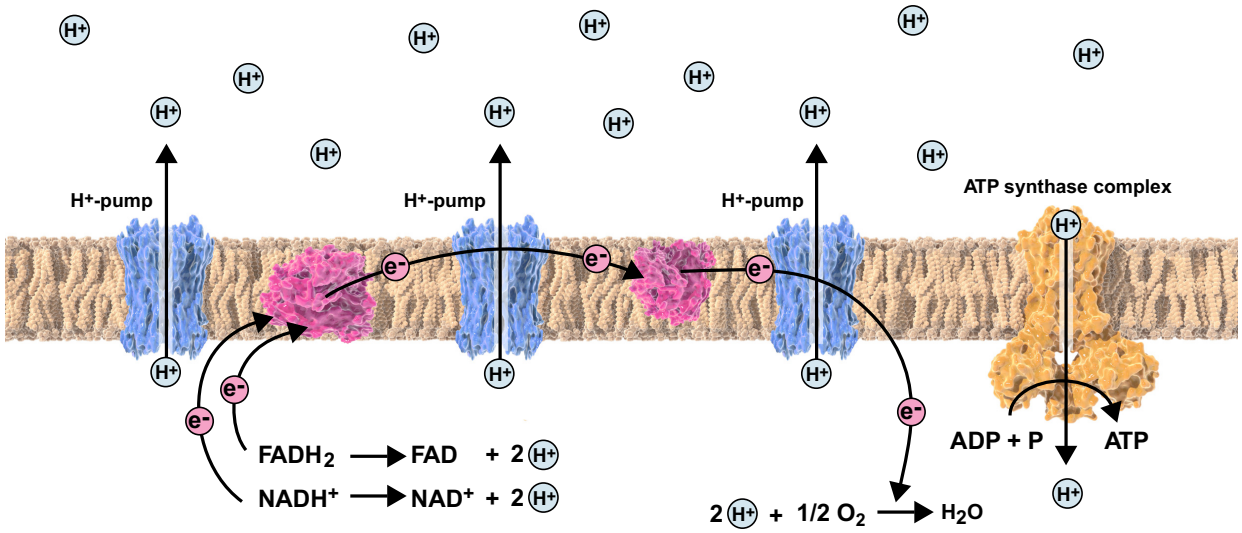

Fig. 3 *The consequences of hypoxia. If there is no oxygen delivered at the end of the electron transport chain (hypoxia) the energy production declines and metabolism is reduced and finally halted. In the later stages, the ion pumps in the cell membranes are inhibited, leading to cell death. Modified from figure by G. E. Kaiser, Baltimore, MD, USA.*

Oxygen levels vary depending on anatomical location. This is due to a combination of arterial blood oxygenation, global and local blood flow, tissue metabolic rate and diffusion distance from blood vessel to cell. The criteria for tissue hypoxia will thus vary from organ to organ. Simply by adding oxygen to an oxygen-deprived lung does not necessarily mean that oxygen increases at the tissue level as these other factors may come into play. One technique that may circumvent this is application of HBO where more oxygen is dissolved within the fluid portion of the blood.

The physiology of oxygen transport

In blood, oxygen is transported predominantly by binding to the four iron atoms within the centre of the haemoglobin molecule. The oxygen saturation of haemoglobin (i.e. how many of the haemoglobin iron atoms are carrying an O_2 molecule, expressed as a percentage) in arterial blood is approximately 98% in young, healthy individuals at sea level. For each gram of haemoglobin, 1.3 mL of oxygen is transported, and thus, approximately 180 mL oxygen is carried per litre of blood with a haemoglobin concentration of 14 g dL^{-1}. Only a small amount of oxygen is dissolved in plasma because oxygen, unlike carbon dioxide, is sparingly soluble (only 0.2 mL O_2 L kPa^{-1}) [21]. At an paO_2 of 12 kPa (normoxaemia), only 3 mL oxygen is carried per litre of plasma. Thus, under normal healthy circumstances, a total of 183 mL oxygen (bound to haemoglobin plus dissolved in plasma) is transported per litre of blood. At normobaric hyperoxia, the amount of oxygen transported rises to 196 mL (182 mL bound to haemoglobin and 14 mL dissolved in plasma) assuming an F_iO_2 of 1.0 and a PaO_2 of 70 kPa [21] (Fig. 4). The difference between breathing oxygen and air in a nonrebreathing system is only 13 mL, representing an increase in approximately 7%. HBO breathing achieves much higher PO_2 values, and thus, the proportion of dissolved oxygen within plasma increases [22]. However, concurrent effects on the circulation may actually decrease the amount of oxygen reaching the cells.

Defence mechanisms against hypoxia

The body is well equipped with various defence systems designed to deal with hypoxic situations. Sensors that detect oxygen levels are found in both airways (neuroepithelial bodies) and the arterial system (carotid bodies). Moreover, individual cells recognize oxygen levels and may, after activation, increase the synthesis of proteins that aid the oxygen transport process [23]. Once these defences are activated, a chain of physiological processes is triggered, primarily by the sympathetic nervous system. Respiratory rate, depth of breathing,

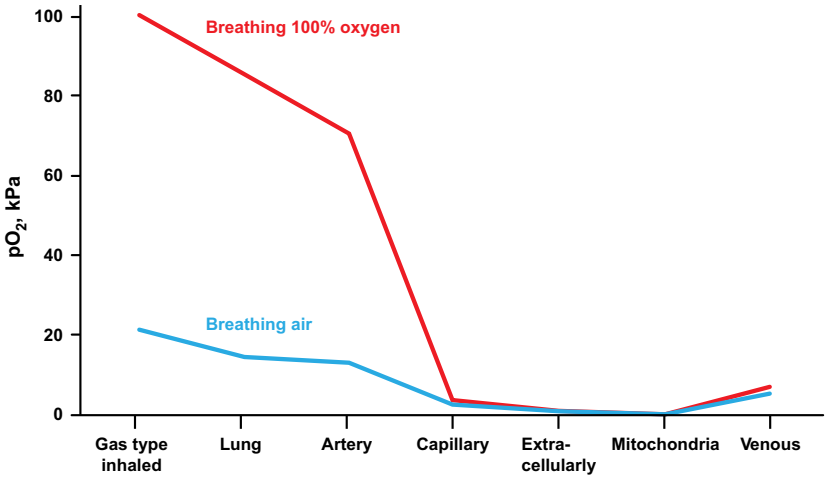

Fig. 4 *The oxygen cascade during normoxia and hyperoxia. Of note, there is a large drop in partial pressure of oxygen (PO_2) from the lung to the tissue, and a small difference in PO_2 in the tissues in normoxaemia and hyperoxaemia. The increase in venous PO_2 (shunting in the microvascular bed) is shown.*

cardiac output and blood pressure all increase [23]. Enhanced production of vasodilator substances also increases local supply of blood and thus oxygen. Cellular effects caused by overt hypoxia include a pro-inflammatory cytokine response with increased capillary leak, increased leucocyte adhesion and prolonged neutrophil survival [24–26].

Effects of increased blood oxygen levels on the circulation

The vascular effects of hyperoxaemia are, in general, the opposite of those of hypoxaemia; whereas hypoxaemia leads to vasodilatation [27], hyperoxaemia causes vasoconstriction [3]. There are two exceptions where the reverse is seen: low oxygen pressures lead to vasoconstriction in lung tissue, and between maternal and foetal blood in the placental circulation, to minimize the mismatch between perfusion and ventilation [28]. Hyperoxaemia-induced vasoconstriction has been described in most vascular beds, for example, in the brain [29, 30], heart [31], skeletal muscle [32], retina [33] and skin [34, 35]. Secondary to this decrease in vessel diameter, there is a reduction in blood flow, except in the kidney [36]. An almost linear inverse relationship is observed between the amount of oxygen in blood and the degree of blood flow reduction. In humans, the maximum decline in blood flow with added oxygen is about 20%, with a fall even being seen at a P_aO_2 of 20 kPa [20].

Acute effects of hyperoxaemia on the central circulation have also been well described. Heart rate is reduced by approximately 10%. Cardiac output falls, but stroke volume remains essentially unchanged [20, 37]. Systemic vascular resistance increases; however, the effect on blood pressure is somewhat unclear [38]. It is currently considered that an increase in blood oxygen concentration leads to peripheral vasoconstriction with an increase in vascular resistance and thereby an increase in blood pressure. Pressure-sensitive baroreceptors sense this increase and, through vagal nerve signalling, heart rate is reduced. With no change in stroke volume, cardiac output is reduced, preventing further blood pressure increases and normalization of pressure (Fig. 5). Additional support for this theory comes from the finding that peripheral vasoconstriction occurs even in patients whose heart and lungs have been disconnected through an extracorporeal circulation [39].

Effects of increased oxygen levels on ventilation

An often-overlooked effect of hyperoxia is a change in ventilation. An early, short-lasting decrease in respiratory rate is followed by a longer period of increased rate [40]. Why this happens is not fully resolved. Decreased cerebral blood flow due to hyperoxia-induced vasoconstriction may be one reason. The reverse of the Haldane effect, whereby oxygenated blood has a reduced capacity for carbon dioxide carriage, could be another. Both lead to relative increases in tissue carbon dioxide and, in turn, compensatory increases in respiratory rate via stimulation of the respiratory centre. A theory proposes that free oxygen radicals directly activate central carbon dioxide-sensitive chemoreceptors within the brainstem [41]. Hyperoxaemia increases formation of oxygen radicals [8, 14, 42, 43], which

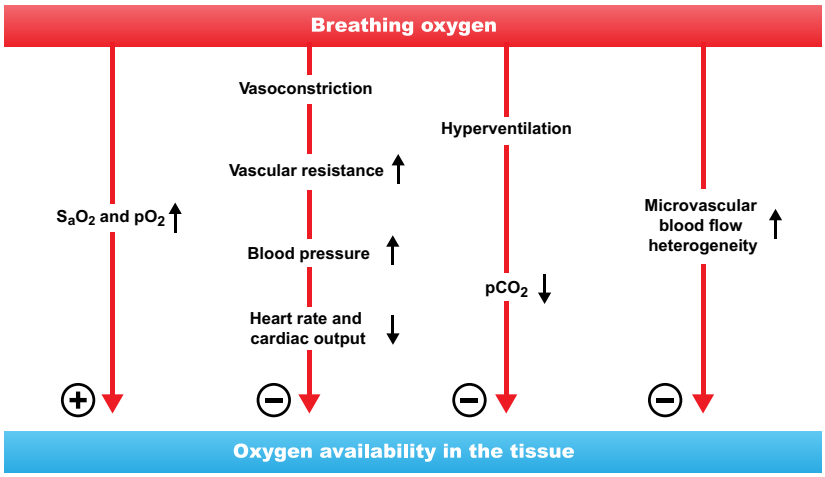

Fig. 5 *Are tissue oxygen levels increased by inhaling increased fractions of oxygen (hyperoxaemia)? Increased oxygen levels in the blood reduce tissue blood flow due to vasoconstriction followed by a decrease in both heart rate and cardiac output. In addition, tissue oxygen availability is also lowered due to microvascular blood flow heterogeneity.*

may explain the hyperventilation. Regardless of the cause, the increase in ventilation decreases P_aCO_2. As carbon dioxide is a potent vasoactive substance, decreased levels will lead to vasoconstriction. There may be synergism, with both hypocapnia and hyperoxaemia contributing to vasoconstriction. Adding carbon dioxide to inhaled gas has been used in hyperbaric medicine to reduce the vasoconstricting effect of oxygen [6].

Effects of oxygen on oxygen uptake

The hyperoxaemia-induced decrease in cardiac output, and vasoconstriction leads to decreases in tissue oxygen delivery and tissue oxygen utilization. Effects on whole-body oxygen consumption are, however, unclear with no effect [20, 21] or a decrease [44] reported.

Mechanisms underlying hyperoxia-induced vasoconstriction

Though there is no clear consensus on the mechanisms leading to vasoconstriction after exposure to hyperoxaemia, there are several plausible theories. First, erythrocyte cellular membrane plasticity may be altered, making these cells more rigid and their passage through the microvascular bed more difficult [45]. Secondly, erythrocytes themselves may sense the PO_2, thereby regulating vascular tone by increasing or decreasing uptake or extrusion of intracellular ATP, which binds to endothelial purinergic P2Y receptors, stimulating local production of nitric oxide [46]. Thirdly, hyperoxia may reduce the availability of the vasodilator prostaglandin PGI_2 [47], or enhance serotonin (5-HT) effects on the 5-HT_2 receptor [48, 49]. However, increased blood serotonin levels were not found in individuals exposed to high oxygen concentrations [50]. Lastly, hyperoxia may reduce the bioavailability of nitric oxide [34, 51]. This latter theory has the most scientific support: hyperoxaemia leads to increased production of oxygen radicals, with the superoxide ion being considered responsible for most of the vascular effects. Superoxide is known to inactivate nitric oxide [52, 53]. Four human studies have investigated the effect of hyperoxia on nitric oxide [34, 38, 51, 54] with two supporting the theory that vasoconstriction occurs via superoxide inactivation of nitric oxide [34, 51]. In both these supporting studies, only short-term oxygen exposure (10–15 min) was evaluated. Causality between hyperoxia, superoxide and nitric oxide inactivation was supported by the lack of vasoconstrictor effect of oxygen after vitamin C administration. This oxygen radical scavenger increases superoxide dismutase activity, which catalyses conversion of superoxide to hydrogen peroxide and oxygen [55], and also lowers superoxide production by inhibiting NADPH oxidase [56].

How do oxygen radicals affect nitric oxide levels? At least three alternatives have been identified (Fig. 6): (i) reducing levels of the precursor, L-arginine; (ii) inhibiting nitric oxide synthase (NOS); and (iii) reducing nitric oxide unloading from the haemoglobin molecule. Studies reporting no effect of superoxide used long oxygen exposure times (hours). Thus, exposure time is an important factor to consider when investigating oxygen-induced vascular effects [52]. There may be a two-phase vascular change with an initial decrease

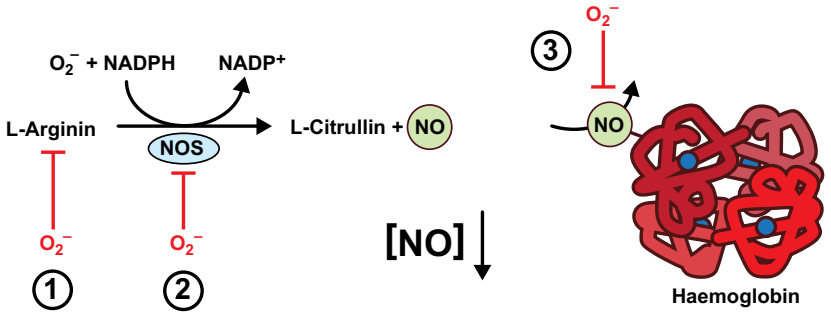

Fig. 6 *The mechanisms by which the superoxide ion (O_2–) reduces the bioavailability of nitric oxide (NO) and thereby induces vasoconstriction by: reducing the L-arginine levels needed for NO production (1); reducing NO oxidase (NOS) function that catalyses conversion of L-arginine to NO (2); and reducing the unloading of NO from the haemoglobin molecule (3).*

in NOS activity followed by a compensatory increase. NOS needs oxygen and L-arginine to produce nitric oxide; hyperoxia increases both [57]. Many unanswered questions remain regarding the interactions between oxygen and nitric oxide.

Effects of HBO

As only a 7% increase in oxygen content is produced by an F_iO_2 of 1.0 at normobaric pressure, and because actual tissue oxygen transport is only due to concurrent vasoconstriction and a fall in cardiac output to a limited degree, other techniques that improve arterial oxygenation have been sought to treat tissue hypoxia. It was reported in *Medicinskt Archiv* (later the *Journal of Internal Medicine*) in its first year of publication in 1863 that administration of HBO increased the dissolved oxygen fraction (see Box below), yet also produce vasoconstriction and reduced blood flow [58].

Many important issues should be considered when examining the evidence for use of HBO in the treatment of tissue hypoxia. Although oxygen transport is enhanced by more dissolved oxygen within plasma, several successful clinical applications of HBO may also rely on direct diffusion of oxygen from the HBO chamber into the tissue at risk. Examples include wounds that are difficult to heal, such as diabetic ulcers, as well as skin damage or osteonecrosis secondary to radiotherapy.

Besides the cardiovascular and respiratory effects of hyperoxia, there may be additional effects related to the hyperbaric pressure alone [61]. However, studies often do not include relevant control groups; for example, pressurizing subjects to the same level but under normoxic conditions, or using a nonpressurized chamber (sham). It is thus difficult to judge whether any effect observed is due to the pressure increase itself, or to a combination of the presence of oxygen and the level of pressure. This is particularly pertinent given the recent renewed interest in wound treatments using hypobaric or negative pressure techniques [62].

Oxygen-induced cellular mechanisms (NBO and HBO)

Positive effects related to oxygen therapy can be due simply to relief of tissue hypoxia, for example, in acute cardiovascular disease, brain ischaemia due to stroke, shock and carbon monoxide intoxication. In these situations, an injurious tissue oxygen deficiency is well established. In other cases, where oxygen therapy is given, often using HBO, such as wound healing, osteonecrosis and compromised flaps and grafts, other mechanisms, mostly cellular, may be responsible [9, 14]. Breathing greater than 1 ATA of oxygen increases production of both reactive oxygen species [8] and nitrogen species [53, 63, 64].

Oxygen increases expression of antioxidant enzymes in both tissues and plasma via an increase in glutathione levels [65, 66]. This reduces the degree of lipid peroxidation [67] and prevents neutrophil activation in response to endothelial damage, thereby modifying ischaemia–reperfusion injury [68, 69] and providing anti-apoptotic effects [70]. The common factor is likely to be induction of protective mechanisms via a lesser degree of oxidative stress [8]. Reactive oxygen species act in conjunction with several redox systems involving

glutathione, thioredoxin and pyridine nucleotides and play central roles in coordinating cell signalling as well as protective antioxidant pathways [71–74]. Oxygen also contributes to the bacteriocidal capacity of leucocytes [75–77].

Cellular effects of HBO

As clinical HBO protocols are relatively brief, it has been claimed that antioxidant defences are adequate such that biochemical stresses are reversible [78–80] (see Fig. 7). The results of animal studies suggest several cellular mechanisms that may explain the positive outcomes of HBO treatment on selected indications [9]. These mechanisms include, first, neovascularization with recruitment and differentiation of circulating stem/progenitor cells [81–83] that can target wounds and accelerate healing [84–86]. This is in part related to elevation of hypoxia-inducible factors (HIF)-1 and hypoxia-inducible factors (HIF)-2 [87, 88]. Secondly, HBO triggers pluripotent mesenchymal stem cells to synthesize placental growth factor that increases cell migratory and tube formation functions [89] and upregulates various protein damage–control pathways enhancing oxidative stress resistance, cell proliferation and tube formation [90]. Thirdly, HBO stimulates synthesis of fibroblasts and transforming growth factor-1 by human dermal fibroblasts [91], angiopoietin-2 by human umbilical vein endothelial cells [92] and basic fibroblast

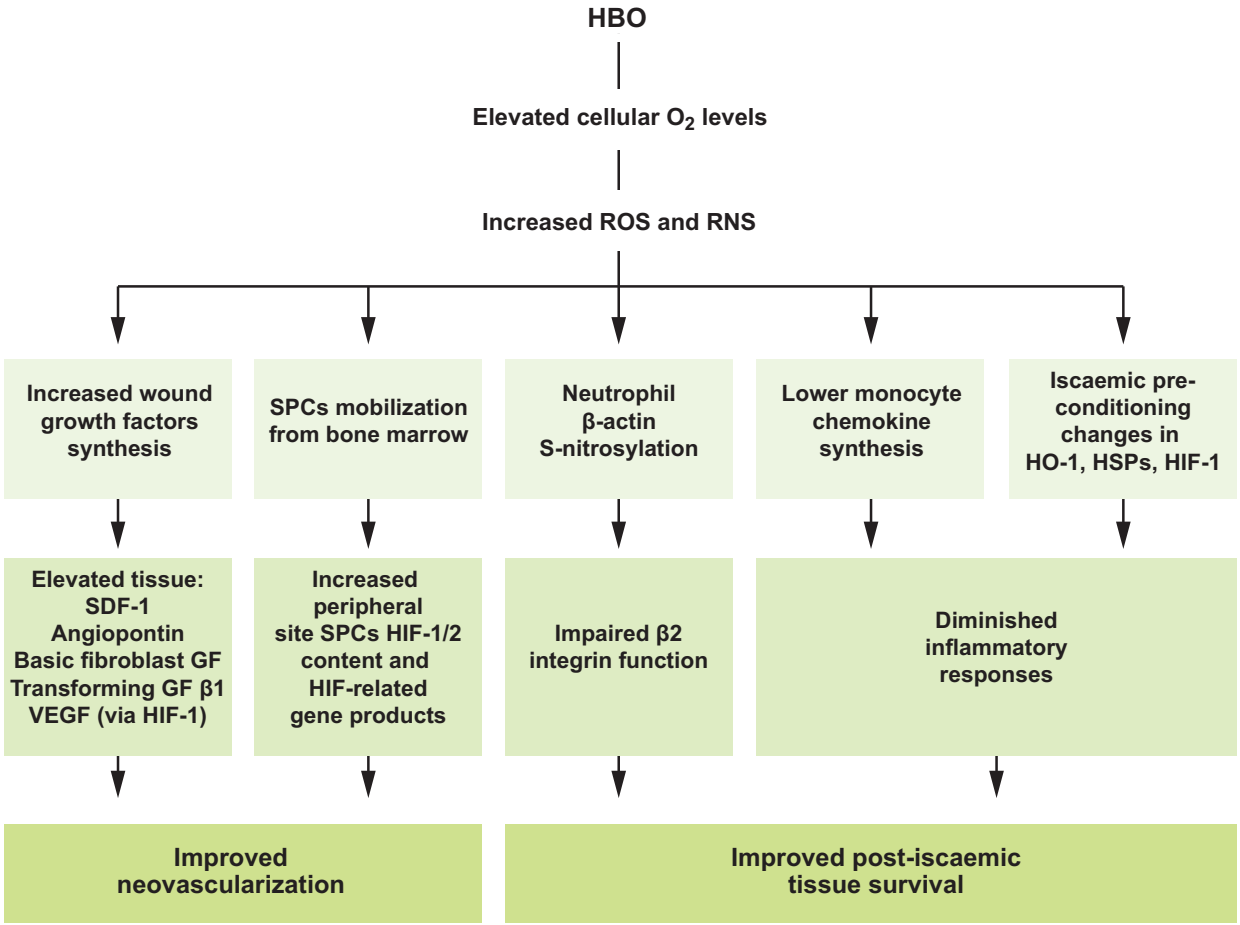

Fig. 7 *Overview of therapeutic mechanisms of hyperbaric oxygen (HBO) related to elevations of tissue oxygen tensions. The initial effects that occur due to increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their consequences are outlined. GF, growth factor; VEGF, vascular endothelial growth factor; HIF, hypoxia-inducible factor; SPCs, stem/progenitor cells; HO-1, haeme oxygenase-1; HSPs, heat shock proteins; SDF-1, stromal cell-derived factor 1. Modified from Thom [9].*

growth factor and hepatocyte growth factor in ischaemic limbs [93]. Fourthly, HBO may inhibit neutrophil-2 integrin adhesion, which has been shown to ameliorate reperfusion injuries in many organs (reviewed in [9]). Fifthly, HBO may reduce pro-inflammatory cytokine production by monocytes and macrophages [94]. Finally, HBO experimentally augments ischaemic tolerance of the brain, spinal cord, liver, heart and skeletal muscle by mechanisms involving induction of antioxidant enzymes and anti-inflammatory proteins in the different organs [9, 95].

Oxygen toxicity and side effects

As disturbances in oxygen transport can take place at different levels, indications for oxygen therapy differ even if the goal remains the same, namely to maintain tissue oxygenation and/or induce the desired cellular effects of hyperoxic therapy [9]. Oxygen is usually provided to counteract pulmonary-related hypoxaemia (due to abnormal lung mechanics or diffusion), circulatory hypoxia (due to pulmonary and cardiovascular diseases) affecting the great vessels, or tissue hypoxia related to microvascular abnormalities such as diabetes and sepsis. Oxygen is also given prophylactically for short-term (<10 min) procedures, such as induction of anaesthesia, to eliminate nitrogen gas from the lung and create an oxygen reservoir that can be utilized in case of difficulty in maintaining an airway or performing endotracheal intubation. Even in this setting, adverse effects of oxygen therapy, such as development of atelectasis, have been reported [96]. After prolonged oxygen exposure (hours), other adverse effects are recognized including inflammatory changes in the mucous membranes [97, 98]. Direct lung damage causing pneumonitis is another well-known effect of prolonged exposure to high oxygen concentrations (>60%). Some countries have adopted a more restrictive approach to medical oxygen therapy; however, care should be taken to ensure that, through fear of its harmful effects, the amounts of oxygen provided are not inadequate [99].

The negative effects of hyperoxia may be avoided if hypoxia is confirmed before oxygen therapy is initiated. However, from the findings of a recent meta-analysis, it was concluded that oxygen resuscitation of asphyxiated neonates led to increased mortality compared with control groups treated with air [100]. The authors of this analysis were the first to state that oxygen may be disadvantageous or even harmful despite a prevalent respiratory-induced hypoxia. Nevertheless, in one of the defining studies included in the meta-analysis, oxygen was actually given as back-up therapy in 25% of the neonates initially treated with air. Thus, the conclusion of a Cochrane review was that more studies are needed, especially as long-term follow-up was lacking [101].

HBO exposure with pressures >3 ATA can cause overt problems such as seizures; these were vividly described by Donald in the 1940s [102, 103]. More recently, experiments in rats demonstrated brain-protective vasoconstriction during HBO treatment as oxygen toxicity was more clearly seen when concurrent vasodilatation (e.g. by carbon dioxide inhalation) was produced [7]. Harmful effects have also been recently reported for one of the mainstay indications for HBO, namely carbon monoxide intoxication [104], where a dose-related increase was seen in neurological sequelae [105]. Likewise, HBO treatment of cyanide intoxication has been debated; the conclusion of a Cochrane report from 2011 was that there was no reduction in neurological sequelae [106].

Oxygen treatment in diseased states

The most investigated indications are reviewed below, with particular consideration of:
(i)whether there was any documented oxygen deficit that was adjusted for;

(ii)whether an explanatory theory was given for any effect observed; and

(iii)how the oxygen was provided, that is, *ad libitum* or in a controlled manner, and normobaric or hyperbaric.

Ischaemic heart disease

NBO is widely recommended for patients with acute myocardial infarction (AMI), though there have been suggestions that it causes more harm than good. Potentially deleterious mechanisms include reductions in coronary artery blood flow and increased coronary vascular resistance [107, 108], reduced stroke volume and cardiac output [38], increased systemic vascular resistance [20] and a greater degree of reperfusion injury [20]. In recent systematic reviews, including numerous animal studies of the effects of NBO and HBO dating back to the 1960s, it was concluded that

there is insufficient evidence to determine the impact of oxygen on myocardial ischaemia or infarct size [109, 110]. In the 2010 Cochrane review [111], a lack of conclusive RCT data, including effects on pain relief or mortality reduction, was found to justify the routine use of inhaled oxygen in patients with acute AMI. The authors of the review recommended that such studies are urgently needed, especially given the ubiquitous place of oxygen therapy in clinical practice guidelines [112]. O'Driscoll and colleagues recently argued in the *British Medical Journal* that practitioners should 'maintain normoxaemia until more evidence is available' [113]. However, in a recent pilot study, no deleterious effects of hyperoxia were found in patients with ST segment-elevated AMI [114]. Several ongoing trials are examining normobaric oxygen administration, including two in Sweden and one in Australia [*Air Versus Oxygen In myocarDial Infarction Study* (AVOID); http://www.clinicaltrials.gov/ct2/show/study/NCT01272713] that is due to complete in 2013.

With respect to HBO in AMI, the findings of small trials ($n = 6$; 665 patients; pooled data) suggest a reduced risk of death, reduction in the volume of damaged muscle and an improved left ventricular ejection fraction. Outcomes were also improved in terms of the risk of major adverse coronary events, re-infarction, dysrhythmia and time to relief from ischaemic pain. In view of the modest number of patients, methodological shortcomings and poor reporting, these results should be interpreted cautiously. Again, an appropriately powered trial of high methodological rigour is required to define those patients (if any) who can be expected to derive most benefit from HBO. At present, its routine application cannot be justified [115].

Focal brain ischaemia including stroke and traumatic brain injury

Focal brain ischaemia, most often related to ischaemic or haemorrhagic stroke, is an extensive clinical and societal problem worldwide. In the USA, 700 000 people are affected annually and, with 150 000 deaths, stroke constitutes the third leading cause of mortality [116, 117]. Traumatic brain injury (TBI) also carries a significant socioeconomic burden, as exemplified by 50 000 deaths per year in the USA [118]. As these conditions are likely to be significantly influenced by brain hypoxia, there is a rationale for a positive treatment effect from oxygen [14]. Direct cerebral effects of NBO and HBO have been summarized in various reviews [59, 119–124].

In preclinical studies, both NBO and HBO have predominantly beneficial effects [14], including normalization of extracellular homoeostasis, reduced levels of excitotoxic metabolites such as glutamate, pyruvate and lactate [119, 122, 125, 126], blood–brain barrier (BBB) stabilization [127] with decreased permeability [128], reduced free levels of laminin 5 (a tissue breakdown marker) and downregulation of matrix metalloproteinase (MMP)-9, an enzyme associated with basal lamina degradation [122, 129–131]. NBO or HBO also have anti-apoptotic effects [119, 122, 132–134] and various anti-inflammatory properties, including decreasing cyclooxygenase-2 and myeloperoxidase activities, and reducing expression of ICAM-1 [122, 135, 136]. Decreased expression of ICAM-1 results in reduced binding of leucocytes to the endothelial surface and decreased leucocyte infiltration into stroke-affected tissue [137, 138]. Neuronal plasticity is also positively influenced by HBO [139, 140]. As similar mechanisms are invoked in the pathophysiology of TBI, the need to evaluate oxygen application during focal brain ischaemia is highly relevant.

The findings of experimental studies indicate greater effectiveness of HBO compared to NBO [14], with dose dependency at higher pressures (2.5 and 3.0 ATA). The greatest benefits were observed when HBO was initiated early (within 3 h, and partially up to 6 h) after the onset of focal cerebral ischaemia. HBO is more effective in transient models, whereas permanent artery occlusion is the commonest cause of stroke in humans. Oxygen is not commonly used in acute cerebral ischaemia-related transient ischaemic events [14].

NBO therapy also offers promising results for the management of focal ischaemic brain injury, and its routine application is far easier than that of HBO. At least four clinical studies [120, 141–144] have addressed the use of NBO therapy in stroke, albeit two from the group of Singhal, partly including the same data [120, 141, 142], and the other two also from one research group: Roffe *et al.* [143, 144]. In the first study [120], a positive effect was seen with NBO at 4 h, whilst the second study, also be Singhal's group [141, 142], showed a decrease in tissue lactate using voxel-based analysis. The authors proposed that NBO could possibly extend the window for thrombolysis by resuscitating

acutely ischaemic tissue [120]. Of note, the latest study by the same group investigating the effect of NBO in acute ischaemic stroke (http://www.clinicaltrials.gov/ct2/show/NCT00414726) was recently terminated, after inclusion of 85 patients, because of an 'imbalance in deaths favouring the control arm'. The third study, conducted by Roffe *et al.* [143], demonstrated a small but significant positive effect from supplementary oxygen provided during the first 24-h poststroke; however, baseline data in the control and treatment groups were not fully comparable. In a similar study, in patients with ongoing stroke, the same group found that respiratory-induced hypoxia was not uncommon and could be improved by supplemental oxygen [144]. In summary, there is currently minimal evidence either to support or to refute the use of NBO in acute focal ischaemic brain injury and stroke; therefore, further studies are urgently needed.

More studies have been undertaken in patients with TBI, boosted by the early finding that normobaric hyperoxia significantly increases brain tissue pO_2, and possibly rescuing aerobic metabolism as judged by decreased extracellular lactate levels [145, 146]. A further five studies also using the cerebral tissue microdialysis technique similarly demonstrated favourable metabolic outcomes in brain tissue of TBI patients treated with hyperoxia. Support for beneficial local metabolic effects (tissue oxygenation) was also demonstrated by near-infrared spectroscopy [147]. Of note, using Xenon-enhanced computed tomography and specific intra-parenchymal oxygen sensors, Hlatky *et al.* [148] reported that 'at-risk' peri-lesional brain tissue, which is most likely to benefit from oxygen, was paradoxically the least likely to receive it due to vasoconstriction in noninjured vessels. This finding is in line with the physiological vasoconstricting effect of oxygen, especially in noninjured vessels [20].

There are, as yet, no RCT data with relevant patient-reported outcome measures to fully support or not the use of NBO in brain ischaemia, including stroke or TBI. Based on knowledge gained from preclinical studies, HBO appears to have more potential than NBO, but the only three available clinical RCTs failed to show efficacy [149–151]. Firm conclusions cannot be drawn because of major shortcomings in these clinical studies. In addition, only HBO pressure levels of 1.5 ATA have been examined and one of the trials was prematurely discontinued as outcomes in the HBO treatment arm were worse than in controls. There is also no evidence of benefit of HBO for vascular dementia [152]. For a definitive clinical study of HBO in stroke, very large sample sizes have been advocated; however, realization has been hampered by cost, availability of facilities and a lengthy enrolment period [14]. This paucity of evidence currently prevents any possibility of HBO becoming a routine treatment in acute ischaemic stroke. Further preclinical research is needed, especially for HBO, to explore the likely mechanisms of benefit and interactions with key factors such as MMP and HIF-1alpha.

The use of oxygen to treat infections

The two most important indications for the use of oxygen in treating infection are peri-operative administration of NBO to reduce postoperative infections [153, 154], and the adjunctive use of HBO in extensive necrotizing fasciitis [155, 156]. Some of the physiological effects of oxygen, especially HBO, indicate a possible benefit in treating infections. Infected necrotic tissue with a disrupted vasculature is oedematous and hypoxic [77, 157], but tissue PO_2 has seldom been assessed during treatment sessions. HBO was reported to increase tissue PO_2 in necrotizing fasciitis wounds, thereby salvaging critically ischaemic areas [158]. Hyperoxia also potentiates antibiotic efficiency, improves the efficacy of leucocyte killing and has anti-inflammatory effects, all of which may improve outcome of severe infection [155, 156, 159–163].

Outcomes relating to prevention of postoperative infections have varied markedly. Some early RCTs showed statistically significant reductions in surgical site infection when high-concentration inspired oxygen therapy was used [154, 164, 165]. This led to two meta-analyses showing evidence to support the use of peri-operative oxygen [166, 167]. However, subsequent RCTs were unable to confirm this benefit [168–170]. In a more recently published meta-analysis [171], the authors stated that 'Peri-operative high inspired oxygen therapy overall was not found to be beneficial for preventing surgical site infection'. Nevertheless, they did find a positive result in two subgroup analyses (general anaesthesia and colorectal surgery groups) and concluded that additional studies were needed to clarify the situation. Two recent RCTs showed either no effect on reducing infection in abdominal, gynaecological

and breast surgery [172], or a positive result in vascular surgery patients [173], albeit based on a very small patient sample and only for infections at the groin incision site. Oxygen-related complications were not seen, even in high-risk groups [174], but neither study addressed this question properly. An unexpected and difficult to explain outcome in the recent PROXI study was an increase in 30-day mortality in patients undergoing cancer surgery who received oxygen therapy with an FiO_2 of 0.80 [175]. This finding also merits further investigation.

Necrotizing fasciitis is a rare soft tissue infection characterized by rapidly progressive necrosis of fascia and subcutaneous tissue with relative sparing of the underlying muscle [176]. It was first described in the scrotum and penis by Fournier in 1883 and, subsequently, by Meleney in patients with streptococcal disease [177, 178]. HBO has been used as an adjunctive treatment to early aggressive surgery and prompt initiation of antibiotic therapy in necrotizing soft tissue infections since the 1960s when its use for treating mainly anaerobic infections was first proposed [179]. However, evidence supporting the use of HBO is conflicting; a significant reduction in mortality has been demonstrated in some retrospective cohort studies [180–183], whereas others have shown no effect [184–186]. An increased risk has also been proposed due to the potential delay in surgery resulting from transferring affected patients to hyperbaric facilities. As a result, clinical practice varies widely. Some centres use HBO as an integral part of their standard treatment regimen whilst nonusers highlight the importance of a short time to initial surgery [181, 187, 188]. Acknowledging the lack of RCTs to support the use of HBO for this condition, the Cochrane group presented a protocol for review in 2009 but, due to the lack of RCT data, a review has not yet been carried out [189].

Oxygen administration during or after cardiopulmonary resuscitation for cardiac arrest (adults, children and neonates)

Oxygen used to be an integral part of most resuscitation algorithms [2], not least for cardiopulmonary resuscitation (CPR). The more recent CPR protocols, such as the 2010 American Heart Association (AHA) guidelines, do not stress the need for oxygen supplementation in either the early stage of resuscitation or in the postarrest phase. The AHA guidelines state: 'On the basis of increasing evidence of potential harm from high oxygen exposure after cardiac arrest, once spontaneous circulation is restored, inspired oxygen should be titrated to limit the risk of hyperoxemia' [190]. The guidelines cite evidence from nonrandomized studies of the importance of minimizing interruptions in chest compressions, recommending that survival from out of hospital cardiac arrest may be improved by the initial emergency medical services provider delivering continuous chest compressions even without initial assisted ventilations [191, 192]. It is also stated that CPR may be initially effective without rescue breathing as blood oxygen levels remain adequate for the first several minutes after cardiac arrest. In addition, many cardiac arrest victims exhibit gasping or agonal gasps, and gas exchange allows for some oxygenation and carbon dioxide elimination [193–196]. It is unknown whether 100% inspired oxygen (FIO_2 of 1.0) is beneficial or whether titrated oxygen is better. Although prolonged exposure to 100% inspired oxygen has potential toxicity, there is insufficient evidence to indicate that this occurs during brief periods of adult CPR [197–199]. In one prospective RCT, ventilation with either 30% or 100% oxygen for the first 60 min after return of spontaneous circulation was compared. In this small trial, no differences in serial markers of acute brain injury, survival to hospital discharge or the percentage of patients with good neurological outcome at hospital discharge were detected; however, the study was inadequately powered to detect important differences in survival or neurological outcomes [200]. At some time, during prolonged CPR, supplementary oxygen with assisted ventilation is necessary [190]. The precise interval for which the performance of hands-only CPR is acceptable remains uncertain [193–196, 201–204].

Although outcomes after compression-only CPR have been described in many studies, these rarely address additional techniques to improve ventilation or oxygenation. In two comparative studies [191, 192, 205] and two *post hoc* analyses [192, 206] of passive ventilation airway techniques during cardiac arrest, a similar protocol was used that included insertion of an oral airway and administration of oxygen with a nonrebreathe mask, with interposed ventilations versus passive insufflation of oxygen during minimally interrupted chest compressions. These studies did not demonstrate any overall improvement in outcome measures. For hands-only CPR by laypersons, evidence is insufficient to support a recommendation for the use of

any specific passive airway or ventilation technique.

In pregnant women presenting with cardiac arrest, oxygen administration is recommended as Cheun and Choi [207] reported that desaturation occurred significantly faster in pregnant than in nonpregnant patients during apnoea. Bag-mask ventilation with 100% oxygen is, therefore, considered important [208, 209]. Under special conditions such as trauma and acute exacerbations of asthma, the 2010 AHA guidelines also recommend oxygen administration despite the fact that evidence to support this is lacking [209].

Several cases of fires being ignited by sparks from poorly applied defibrillator paddles in the presence of an oxygen-enriched atmosphere have been reported [210–212]. Fires have also been reported when ventilator tubing is disconnected from the endotracheal tube and then left adjacent to the patient's head, blowing oxygen across the chest during attempted defibrillation [211, 212]. It may be reasonable for rescuers to take precautions to minimize sparking during attempted defibrillation by avoiding it in oxygen-enriched atmospheres.

The AHA paediatric guidelines recommend oxygen administration during CPR as present evidence is based only on data from resuscitation during the newborn period. Until additional information becomes available, it is recommended that 100% oxygen be used during resuscitation. Once the circulation is restored, oxygen saturation should be monitored and, when appropriate equipment is available, oxygen administration should be titrated to maintain an oxyhaemoglobin saturation >94% [213].

When advanced paediatric resuscitation is being performed under special conditions such as hypovolaemia (trauma) and sepsis, the guidelines make no mention of additional inspired oxygen, despite recommendations to optimize the circulation in order to improve tissue oxygen delivery [214]. For particular paediatric disorders, such as a single ventricle, oxygen saturation should be targeted in the hypoxic range (80%), whereas for other emergencies, such as intoxications, the recommendation is to provide oxygen to maintain saturations >94%.

In the case of neonates, the findings of two meta-analyses suggest harmful effects from oxygen resuscitation, despite it being applied to asphyxiated neonates [100, 215]. There have also been concerns regarding the liberal administration of oxygen in the early postdelivery setting as healthy term babies start with an oxygen saturation <60% and take 10 min to reach saturation levels >90% [216, 217]. Hyperoxia may be considered toxic, particularly to the preterm infant and, perhaps, particularly to the brain [218]. For babies born at term, resuscitation should be initiated with room air rather than 100% oxygen. One study in preterm infants, however, showed that initiation of resuscitation with a blend of oxygen and air resulted in less hypoxaemia or hyperoxaemia, as defined by the investigators, than when resuscitation was initiated with either air or 100% oxygen followed by titration with an adjustable air–oxygen mixture [219]. In the absence of studies comparing outcomes from neonatal resuscitation initiated with other oxygen concentrations or targeted to various oxyhaemoglobin saturations, babies resuscitated at birth, whether born at term or preterm, should be targeted to achieve an oxygen saturation value in the interquartile range of preductal saturations (see Table 1) [216]. These targets may be achieved by initiating resuscitation with air, or a blended oxygen–air mix, and titrating the oxygen concentration to achieve an SpO_2 in the target range as described earlier using pulse oximetry. If blended oxygen is not available, resuscitation should be initiated with air. Recent data support a targeted early goal in a higher range (SaO_2 91–94%) rather than 85–89% [220]. Ongoing trials are addressing the issue of what level of oxygen mixture should be recommended for the preterm infant [221].

Any long-term supplementary oxygen administered in the postresuscitation period to hypoxic babies should be regulated by blending oxygen and air, using oximetry to guide titration of the blend delivered [190]. The findings of recent reviews suggest that it is prudent to avoid saturation levels as low as 85–89% [222]. It has also been suggested that hyperoxia may further aggravate oxidative injuries in the preterm infant, especially when combined with parenteral nutrition [223].

There is not enough evidence to support the use of prophylactic oxygen therapy for women in labour, or to evaluate its effectiveness for foetal distress. In view of the widespread use of oxygen during labour and the possibility that it may be ineffective or even harmful, there is an urgent need for randomized trials (RTCs) to assess its effects [224].

Table 1 *Summary of randomized controlled trials (RCTs) of normobaric (A) and hyperbaric (B) oxygen treatment in the indications described in the text*

Indication	Outcome	Recommendation
(A)		
Ischaemic heart disease	No RCTs: (though studies ongoing)	More studies needed
Focal brain ischaemia (stroke)	RCTs: 2 with positive outcome for oxygen, 1 negative; 1 inconclusive	More and better powered studies needed
Traumatic brain injury	Studies only using surrogate end-points; no RCTs	Studies needed
Postoperative infections	2 meta-analyses suggesting positive oxygen effect; 1 meta-analysis suggesting no effect; 2 new RCTs – no effect	More and better designed studies needed
CPR cardiac arrest (adult)	Underpowered RCT (no effect)	RCTs needed
CPR neonates	2 meta-analyses – poor outcome in oxygen groups	Oxygen harmful
During labour	No RCTs conducted	RCTs needed
Carbon monoxide intoxication	No RCTs conducted	RCTs needed
Cluster headache	RCT some evidence of improvement	Further studies suggested
(B)		
Ischaemic heart disease	6 RCTs: Positive results but only 665 pooled patients	Interpretation difficult – cumbersome experiments (?)
Focal brain ischaemia (stroke)	3 RCTs; no effects found	The size and number of patients may exclude further studies
Necrotizing fasciitis	No RCTs	RCTs needed
Wound healing	Meta-analysis – positive effect of hyperbaric oxygen treatment	Short-term positive effects – long term not yet evaluated
Sprain or ligament injury	Meta-analysis – effect uncertain based on 9 underpowered trials	Better RCTs needed
Burns	Meta-analysis (based on 2 RCTs with inadequate methodology – no conclusion)	Better RCTs needed
Carbon monoxide intoxication	7 RCTs; 2 positive, 4 negative or no effect; largest RCT suggests harm – dose related	Further RCTs needed – presently no treatment recommendation can be made
Cancer/tumour sensitization – radiotherapy	19 RCTs (in total 2000 patients)	Conclusion: cautious interpretation due to methodological inadequacies
Idiopathic sudden sensorineural hearing loss and tinnitus	7 RCTs – 25% hearing improvement in pooled data (NNT = 5)	No effect on chronic hearing loss or tinnitus
Headache	9 RCTs – some evidence for early improvement in migraine – no effect for prophylaxis	
Multiple sclerosis	9 RCTs – 2 positive, 7 no effect	No further trials justified
Autism	2 early RCT´s positive effect; 3 subsequent RCT´s showed no effect	
Facial palsy	One RCT of poor quality	More studies needed

Normoxia, normal oxygen partial pressure; normoxaemia, normal oxygen partial pressure in blood; hyperbaric, high air pressure (above 1 AT); hypoxia, low-oxygen partial pressure; hypoxaemia, low-oxygen partial pressure in blood; hyperoxia, high-oxygen partial pressure; hyperoxaemia, high-oxygen partial pressure in blood; NNT, number needed to treat.

Wound healing (HBO)

The findings of a recent meta-analysis of diabetic wound care suggested that HBO both decreased the risk of a major amputation for refractory wounds and improved healing [225]. The authors of a Cochrane meta-analysis conducted in 2004 concluded that only four patients needed to be treated with HBO to prevent one amputation [226]. Two additional groups have since confirmed the benefits of HBO use [227, 228]. The benefit of HBO for radiation injury has also been shown in RTCs [229, 230]. However, it should be emphasized that a prospective randomized study in patients with mandibular osteoradionecrosis was terminated prematurely due to worse outcomes in the HBO group [231]. For both diabetic wounds and radiation injuries, HBO should be used in conjunction with standard wound care management techniques; HBO is likely to be ineffective in the absence of appropriate surgical care [232]. In the setting of acute surgical and traumatic wounds (including burns, see below), the findings of a Cochrane review are less conclusive [233], whereas those of another contemporary review tend to be more positive [234]. The latest Cochrane review, although including a positive effect of HBO on difficult to heal wounds in the short term, did raise concerns regarding the lack of evidence to support HBO use for long-term treatment, especially as the underlying illness causing the wound is unlikely to be affected by the treatment itself [235].

There was also insufficient evidence to establish any benefit from HBO in ankle sprain or acute knee ligament injury, or in experimentally induced closed soft tissue injury (nine small trials involving 219 patients). Some evidence suggested that HBO may even increase interim pain. Any future use of HBO for such injuries requires carefully conducted RCTs to demonstrate effectiveness [236].

HBO has also been used in the treatment of burn injuries. In a Cochrane review (conducted in 2004 and updated in 2009 and 2013), only two studies satisfied the quality criteria [237]. However, these were still considered to be of poor methodological quality so firm conclusions cannot be drawn. One of these trials demonstrated no difference in mortality, number of operations or length of stay between control and HBO groups after adjustment for severity [238], whereas the other showed shorter mean healing times in patients exposed to HBO [239]. Further research is thus needed to better define the role, if any, of HBO in the treatment of thermal burns as well as acute and traumatic wounds.

Carbon monoxide poisoning (NBO/HBO)

Carbon monoxide poisoning is an important cause of accidental and intentional injuries worldwide; between 1000 and 2000 individuals die each year in the USA alone [240]. Based on the underlying mechanism that carbon monoxide blocks oxygen transport and mitochondrial respiration, both NBO and HBO have been proposed to reduce the neurological sequelae caused by this intoxication. This hypothesis was strengthened by several early, nonrandomized, nonblinded trials, the results of which suggested that HBO, in particular, reduced the development of late neurological sequelae, leading to the widespread use of HBO for this indication [106]. NBO is generally recommended on the basis that it significantly reduces the half-life of carboxyhaemoglobin; scientific support for the use of NBO is otherwise scarce (http://www.ameriburn.org/ablshandbook.php).

With regard to HBO, seven RCTs of varying quality were identified in a recent review [106]. Six studies involving 1361 participants evaluated clinical outcomes; two demonstrated a beneficial effect of HBO in reducing neurological sequelae at 1 month, whereas the other four did not. Although the findings of a pooled random effects meta-analysis did not suggest benefit from HBO, there was significant methodological and statistical heterogeneity. Of note, no effect of HBO on transiently unconscious patients was found in one of the largest studies whereas, for comatose patients, there was a suggestion of harm from HBO which was dose dependent [105]. Additional research is urgently needed to better define the role, if any, of HBO in the treatment of carbon monoxide poisoning.

Other specific disease entities (HBO)

Cochrane reviews have addressed the effects of oxygen in several other diseases in which mainly hyperbaric treatment has been used. This treatment showed promise for some indications but, in general, the number and quality of the underlying trials were considered insufficient to draw definite conclusions.

Cancerous tumour sensitization to radiotherapy (HBO)
Based on a recent Cochrane review and meta-analysis of data from 19 trials and almost 2000 patients [241], there is some evidence that HBO improves local tumour control and mortality, mainly for cancers of the head and neck, and local tumour recurrence in cancers of the head and neck (in some cases up to 5 years) and the uterine cervix. It is claimed that the benefits are observed with unusual fractionation schemes. In these studies, HBO was associated with significant adverse effects including oxygen toxic seizures and severe tissue radiation injury. The methodological and reporting inadequacies of the studies included, therefore, call for cautious interpretation. More research is needed regarding HBO therapy in head and neck cancer, but its use for bladder cancer is probably not justified. There is little evidence available concerning malignancies at other anatomical sites on which to base recommendations [241].

Idiopathic sudden sensorineural hearing loss and tinnitus (HBO)
Idiopathic sudden sensorineural hearing loss (ISSHL) is a common disorder that has a significant effect on quality of life. Bennett and colleagues conducted reviews in 2007 and 2012 [242, 243], with seven trials (with a total of 392 participants) included in the latter [243]. The studies were in general small and of poor quality. Pooled data from two trials did not show any significant improvement in the chance of a 50% increase in hearing threshold on pure-tone average with HBO but did show a significantly increased chance of a 25% increase in pure-tone average. There was a 22% greater chance of improvement with HBO, and the number needed to treat to achieve one extra good outcome in the short term was five. There was also an absolute improvement in average pure-tone audiometric threshold following HBO treatment. The significance of any improvement in tinnitus could not be assessed. There were no significant improvements in hearing or tinnitus reported for chronic presentation (6 months) of ISSHL and/or tinnitus. There is no evidence of a beneficial effect of HBO on chronic ISSHL or tinnitus and therefore this treatment is not recommend for this purpose [243].

Headache (NBO and HBO)
Based on nine RCTs included in a Cochrane review in 2009 [244], it was concluded that there is some evidence that HBO may effectively terminate an acute migraine headache, but the practical problems involved in the delivery of therapy suggest that HBO should be reserved for those resistant to standard pharmacological therapies, and therefore, there is insufficient evidence of efficacy to recommend HBO as routine or prophylactic therapy for migraine. There is also insufficient evidence from RTCs to establish the effects of HBO on cluster headache although some effect was noted in a small trial of the effect of NBO on cluster headache. The findings of two small RTCs suggest that the administration of NBO to treat acute cluster headache is likely to be effective in more than 70% of cases, and given the safety and ease of administration of NBO, its use may continue. There is no evidence to support the use of NBO as a prophylactic measure. To our knowledge, no new studies in this area have been conducted, other than case reports, since the Cochrane review in 2009.

Multiple sclerosis
In a Cochrane review by Bennett and Heard in 2011, 10 reports of nine RCTs were found including 504 participants in total [245]. Amongst these, two trials demonstrated positive results, whilst the remaining seven showed generally no evidence of a treatment effect. Three analyses (of 21) did indicate benefit of treatment. It was, therefore, concluded that there was no consistent evidence to confirm a beneficial effect of routine use of HBO therapy in multiple sclerosis. Because of the small number of analyses suggestive of benefit, it is difficult to attribute biological plausibility and well-designed trials would be needed in future for the confirmation of an effect of treatment in this disorder. However, such trials are not justified by the results of this Cochrane review.

Autism (HBO)
Autism spectrum disorders (ASDs) are characterized by the presence of impaired development in social interaction and communication and several studies have demonstrated oxidative stress and inflammation in individuals with autism, both of which have been shown to be improved by HBO. In 2007, Rossignol and co-workers showed a decrease in inflammation (as C-reactive protein levels) and anecdotal improvement in several domains of autism in a small case series [246]. Two years later, the same authors conducted a double-blind multicentre RCT in 62 children and showed significant improvements in overall functioning,

receptive language, social interaction, eye contact and sensory/cognitive awareness compared with children who received slightly pressurized room air [247]. It should be noted that both these studies involved only mild HBO pressure treatments (1.3 ATA). Subsequently, a similar RCT but using a higher HBO pressure level (1.5 ATA) was conducted: improvements were seen in both the treatment and control (sham air) arms but no difference could be seen between groups. However, other RCTs have been unable to show beneficial effects of HBO in ASD [248, 249].

Facial palsy (HBO)

Very low-quality evidence from one trial suggests that HBO therapy may be an effective treatment for moderate to severe Bell's palsy. However, this study was excluded from the latest Cochrane review as the outcome assessor was not blinded to treatment allocation; it was concluded that further RCTs are needed [250].

Conflict of interest statement

No conflicts of interest were declared.

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Box
HBO is defined as breathing 100% oxygen at a pressure greater than that at sea level, which represents 1 atmosphere absolute (ATA; [14, 59]). Based on the oxygen transport equation, 0.3 vol% is dissolved in plasma during normobaric hyperoxaemia (breathing 100% oxygen) compared with 3.26 vol% at 1.5 ATA and 5.62 vol% at 2.5 ATA. P_aO_2 increases from 90 mmHg in room air at 1 ATA to 1053 mmHg in 100% oxygen at 1.5 ATA, to >2000 mmHg in 100% oxygen at 2.5 ATA [59, 60].

Correspondence: Folke Sjöberg, MD, PhD, Department of Anesthesiology and Intensive Care, Linköping University Hospital, 581 85 Linköping, Sweden. (fax: +46 (0)70-5571820; e-mail: folke.sjoberg@liu.se).