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Interplay of hypoxia-inducible factors and oxygen therapy in cardiovascular medicine

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Abstract

Mammals have evolved to adapt to differences in oxygen availability. Although systemic oxygen homeostasis relies on respiratory and circulatory responses, cellular adaptation to hypoxia involves the transcription factor hypoxia-inducible factor (HIF). Given that many cardiovascular diseases involve some degree of systemic or local tissue hypoxia, oxygen therapy has been used liberally over many decades for the treatment of cardiovascular disorders. However, preclinical research has revealed the detrimental effects of excessive use of oxygen therapy, including the generation of toxic oxygen radicals or attenuation of endogenous protection by HIFs. In addition, investigators in clinical trials conducted in the past decade have questioned the excessive use of oxygen therapy and have identified specific cardiovascular diseases in which a more conservative approach to oxygen therapy could be beneficial compared with a more liberal approach. In this Review, we provide numerous perspectives on systemic and molecular oxygen homeostasis and the pathophysiological consequences of excessive oxygen use. In addition, we provide an overview of findings from clinical studies on oxygen therapy for myocardial ischaemia, cardiac arrest, heart failure and cardiac surgery. These clinical studies have prompted a shift from liberal oxygen supplementation to a more conservative and vigilant approach to oxygen therapy. Furthermore, we discuss the alternative therapeutic strategies that target oxygen-sensing pathways, including various preconditioning approaches and pharmacological HIF activators, that can be used regardless of the level of oxygen therapy that a patient is already receiving.

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Author contributions

Y.L. and H.K.E. researched data for the article. Y.L., Y.J., X.Y. and H.K.E. contributed to the discussion of its content. Y.L., W.R., Y.J., X.Y. and H.K.E. wrote the manuscript, and all the authors contributed to reviewing and editing the manuscript before submission.

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Introduction

Cardiovascular disease is frequently characterized by hypoxia, a condition in which oxygen is not available in adequate amounts at the tissue level to maintain homeostasis[1]. Hypoxia can be systemic (such as due to impaired oxygenation secondary to heart failure and pulmonary oedema) or localized (such as during myocardial ischaemia after the occlusion of a coronary artery). Oxygen therapy has been widely used in the field of cardiovascular medicine to reverse hypoxia since its introduction in the 1900s, when supplemental oxygen was described as an efficient method to minimize the pain associated with acute coronary thrombosis and as an important adjunct treatment to control the symptoms of severe angina pectoris[2].

Oxygen is an odourless gas comprised of diatomic oxygen that was first discovered in 1771 by the chemist Carl Wilhelm Scheele[3]. Oxygen is continuously restored in the atmosphere by photosynthesis, a process in which green plants use sunlight to produce oxygen from carbon dioxide and water. Since its introduction into medicine in 1885 (ref. 4), supplemental oxygen has been used extensively to treat a myriad of medical conditions, including pneumonia, myocardial infarction and acute exacerbation of chronic obstructive pulmonary disease[5,6]. The use of an oxygen mask for patients with breathing difficulties or chest pain is known to provide comfort and reassurance, but whether oxygen supplementation has a placebo effect is unknown. Given that supplementation of high levels of oxygen does not bring on any symptoms or other immediately obvious consequences, oxygen therapy has traditionally been considered to have a wide therapeutic window.

Although oxygen supplementation is essential for the treatment of hypoxia, excessive oxygen supplementation could lead to harmful effects. Physiologically, hyperoxia (a state of excess supply of oxygen to tissues and organs) can lead to coronary and cerebral vasoconstriction, exacerbate ischaemia–reperfusion (IR) injury, cause central nervous system toxicity, and lead to absorption atelectasis (loss of lung volume caused by the collapse of alveoli) and acute respiratory distress syndrome (ARDS)[7]. At the molecular level, excessive oxygen can promote the generation of reactive oxygen species (ROS) and inflammatory cytokines[8], alter cellular metabolism, and activate several key signalling pathways that lead to hyperoxia-induced enzyme inhibition and cell death. More importantly, hyperoxia inhibits endogenous protective pathways that are under the control of hypoxia-inducible factors (HIFs)[1,9–12].

Investigators in large clinical trials have questioned the excessive and sometimes inadvertent use of high oxygenation levels during oxygen therapy and compared the effects of liberal versus conservative approaches for oxygen therapy to treat cardiovascular disease. A meta-analysis of 25 randomized, controlled trials (RCTs) that included data from >16,000 critically ill patients showed that those who were treated liberally with oxygen had a dose-dependent increase in the risk of death and no improvements in other outcomes compared with patients treated with a more conservative approach[13]. Advances in our knowledge of the molecular mechanisms of oxygen sensing and their relationship to hyperoxia will help us to better understand such clinical findings.

In this Review, we provide an overview of oxygen homeostasis, including a description of the systemic and molecular responses to acute hypoxia. We also outline the consequences of excessive oxygen use and discuss current clinical research that attempts to define different oxygen targets for the treatment of cardiovascular disease. Finally, we highlight numerous alternative therapeutic approaches designed to target oxygen-sensing pathways for the treatment of cardiovascular disease, including various preconditioning approaches and pharmacological HIF activators, which are currently being assessed for the treatment of cardiovascular disease in ongoing clinical trials.

Adaptive responses to hypoxia

During the past three decades, the mechanisms of how cells and tissues sense oxygen and respond to hypoxia were investigated in preclinical studies[14]. These studies reveal a central role of HIFs in the adaptive responses to hypoxia such as the increase in erythropoiesis and the promotion of a glycolytic switch towards more oxygen-efficient pathways, or an increase in the levels of extracellular adenosine production and signalling[15]. Hypoxia signalling is closely linked to oxygen therapy given that high levels of inspired oxygen can directly inhibit these tissue-adaptive responses. Moreover, pharmacological interventions that target the HIF pathway and promote the stabilization of HIFs have been developed and tested in clinical trials to treat anaemia. To understand these responses and their link to oxygen therapy, in this section, we provide an overview of how adaptive responses to hypoxia have evolved on a systemic, cellular, and molecular level and how they have facilitated an adaptive response to fluctuating oxygen levels in humans.

Evolutionary adaptation to oxygen

Changes in atmospheric oxygen levels throughout time have shaped the evolution of eukaryotes, including land mammals[16]. The rise in atmospheric oxygen levels secondary to increased photosynthesis began around 3,000 million years ago and was initially lethal to most unicellular anaerobic life that could not survive the oxidative properties of oxygen[17]. However, eukaryotes developed a tolerance to the toxic effects of oxygen by forming discrete internal, membrane-enclosed compartments and evolved to use oxygen for energy generation efficiently and safely through the process of oxidative phosphorylation[16]. The genetic evolutionary process required to facilitate the adaptation to high levels of oxygen concentration in the atmosphere is essential for evolutionary selection[16] and probably explains the ‘Cambrian explosion’ responsible for the emergence of most modern metazoan phyla. Of note, the oxygen requirement for oxidative phosphorylation in energy generation makes oxygen deficiency a substantial threat to land mammals, which necessitated the evolution of numerous strategies to adapt to low oxygen levels.

Systemic responses to hypoxia

Physiologically, mammals have evolved systemic responses to hypoxia to compensate for the unmet oxygen demand by increasing minute ventilation, cardiac output, and utilization of oxygen reserve and by shifting the oxygen dissociation curve[18]. For example, a decrease in the partial pressure of oxygen in the arterial blood (hypoxaemia) leads to depolarization of the glomus cell membrane found on chemoreceptors in the carotid body. This depolarization activates afferent axons from the carotid body and sends signals to the

nucleus tractus solitarius in the caudal medulla. The signals then project to the respiratory neuronal network and autonomic sympathetic nuclei in the brainstem. From there, the respiratory rate increases and the adrenal medulla is stimulated, resulting in increased catecholamine release to elevate heart rate and blood pressure levels to compensate for the reduced availability of oxygen[19].

Cellular adaptation to hypoxia–oxygen-sensing pathways

At the cellular and molecular levels, oxygen-sensing pathways have evolved to adapt to conditions of limited oxygen availability, with HIFs being at the centre of this response. HIFs were discovered by Semenza et al. in the early 1990s as transcriptional inducers of the erythropoietin promoter during hypoxia[20]. In 2019, Semenza was awarded the Nobel Prize for his discovery, together with Kaelin Jr, who linked HIFs to the pathogenesis of von Hippel–Lindau disease[21], and Ratcliffe, who characterized the molecular mechanisms involved in stabilizing HIFs during hypoxia, including the central role of HIF–prolyl hydroxylases (HIF–PHDs) in this process[14,22] (discussed further below). Subsequent studies found that HIFs can also activate glycolytic enzymes to promote a glycolytic switch from oxidative phosphorylation to glycolysis[23] such as in cancer cells (Warburg effect) or during myocardial IR injury[24]. Furthermore, HIFs are estimated to regulate >1,000 target genes in response to hypoxia[25]. Whereas HIFs typically function as gene inducers, more than half of all HIF target genes have been found to be repressed during hypoxia[26]. Gene repression by HIFs is often an indirect response and involves the transcriptional induction of HIF-dependent microRNAs that subsequently cause repression of a target gene. In addition, microRNAs have also been shown to participate in a feedforward pathway via an increase in HIF responses through PHD1 repression to provide organ protection during IR injury[27] (Fig. 1).

The transcriptionally active form of HIF consists of a heterodimer comprised of two subunits (HIFα and HIF1β)[28]. Rather than regulation at the transcriptional level, HIF activity is regulated via protein degradation[1,29] (Fig. 1), with the HIFα subunit being targeted for proteasomal destruction during normoxic conditions[1]. This mechanism involves the HIF–PHD set of enzymes[22], which catalyse the hydroxylation of the two conserved proline residues in the oxygen-dependent degradation domain of HIFα[30]. Prolyl hydroxylation promotes the binding of the von Hippel–Lindau gene product to the HIFα subunit, and the subsequent proteasomal degradation of HIFα. Because HIF–PHDs require oxygen as a substrate for their target hydroxylation, PHDs become functionally inactivated during hypoxia and HIFα is stabilized. After this stabilization, HIFα forms a heterodimer with HIF1β, translocates into the nucleus, and binds to hypoxia response elements in the promoter region of hypoxia-responsive genes, thereby promoting their transcriptional induction (Fig. 1). Whereas the stability of HIFα is regulated by the hydroxylation of the proline residues by PHDs, HIF activity is also regulated by hydroxylation of a single conserved asparaginyl residue at the C-terminal transactivation domain by the oxygen-dependent asparaginyl hydroxylase factor inhibiting HIF1 (FIH1). FIH1 provides a direct link between oxygen sensing and HIF-mediated transcription[31].

Of note, HIFs are not cellular oxygen sensors themselves. Oxygen sensing occurs at the HIF–PHD level, with the abundance of oxygen determining their catalytic activity and their stabilization of HIFs. Pharmacological HIF activators stabilize both dominant isoforms of HIFα: HIF1α and HIF2α. These isoforms share a strong homology in their oxygen-dependent degradation domain. HIF2α was initially thought to be expressed predominantly on the vascular endothelium; however, subsequent studies have provided many examples of HIF target genes that are specifically induced by HIF1α or HIF2α[20,23,24]. For instance, the predominant inducer of erythropoietin is HIF2α[20]. HIF1α and HIF2α also differ kinetically, with levels of HIF1α increasing to a greater degree than those of HIF2α during an acute response to hypoxia[32]. In many cases, HIF1α and HIF2α induce the expression of genes that are crucial in adapting tissues to function more efficiently during acute hypoxia or to dampen hypoxia-associated inflammation[23,28,33]. Importantly, HIF–PHDs can function as pharmacological targets for protection against hypoxia-mediated organ damage (Fig. 1). Well-established examples of HIF target genes that are important for cardioprotection from IR injury are summarized in Box 1.

Interestingly, HIFs also have a key role as molecular determinants of oxygen responses in the carotid body[34]. HIF1α and HIF2α have antagonistic functions in the redox regulation of cells of the carotid body, thereby establishing the set point for hypoxic sensing. Mice with a genetic deficiency in *Hif1a* have a blunted carotid body response to hypoxia[35]. By contrast, *Hif2a* deficiency in mice is associated with increased sensitivity of the carotid body to hypoxia, elevated HIF1α and pro-oxidant enzyme activity, and an oxidized intracellular redox state[19,34,36]. These studies highlight the important role of HIFs in eliciting systemic responses to counterbalance hypoxia by altering carotid body function.

Hypoxia and inflammation

Given that the majority of cardiovascular diseases present with increased systemic or local inflammation, the interdependent relationship between hypoxia and inflammation should be highlighted[1,37,38]. Ischaemia-driven hypoxia can further exacerbate inflammatory reprogramming by increasing the expression of Toll-like receptors[39] or by stabilization of nuclear factor-κB[37,40]. Consequently, hypoxia mediates tissue injury by attracting inflammatory cells and promoting uncontrolled inflammation and collateral tissue damage during conditions of sterile inflammation such as in myocardial IR injury[41,42]. Conversely, inflammatory lesions are associated with profound tissue hypoxia owing to thrombosis, vascular occlusion, or increased metabolic demand by infiltrating inflammatory cells or resident tissues, particularly for oxygen[1,38]. However, hypoxia is not simply a bystander of tissue inflammation but elicits adaptive responses through the stabilization of HIFs[1]. HIFs have been shown to activate anti-inflammatory signalling cascades that dampen inflammation, for example, during IR injury[11,24,43,44].

Oxygen toxicity

Discovery of oxygen toxicity

Although organisms have developed complex mechanisms to adapt to hypoxia (such as HIF and HIF–PHD signalling), given that atmospheric oxygen concentrations that are higher

than current levels are rarely encountered, land mammals are less well equipped to adapt to hyperoxia[45]. Joseph Priestley was the first to notice, in 1774, that a candle burned out faster in oxygen than in air and questioned whether this ‘pure air’ also has toxic effects[46]. Subsequently, high concentrations of oxygen were found to cause convulsions or fatal pneumonia in numerous small-animal models[47,48].

Interestingly, less is known about the toxic effects of hyperoxia in healthy individuals or large-animal models given their seemingly better tolerance to hyperoxia[49]. In healthy volunteers, respiratory intake of oxygen concentrations of 96–100% for 48 h did not cause any symptoms of toxicity[49]. In the extreme, 110 h of exposure to pure oxygen (the record time for humans) was not associated with toxicity[50]. However, in contrast to these findings in healthy volunteers, clinical studies of patients with ARDS showed that hyperoxia leads to perturbations in alveolar barrier function, increased alveolocapillary membrane destruction and permeability, and altered immunological responses[51]. These changes might eventually manifest as lung injury or pulmonary fibrosis after prolonged exposure. Together, these studies indicate that, whereas healthy individuals might be able to tolerate hyperoxic conditions without obvious adverse effects, prolonged exposure to hyperoxia in patients with disease can cause lung damage, highlighting the need to define hypoxia thresholds in the context of specific diseases.

Mechanisms of oxygen toxicity

During hyperoxia, excess oxygen levels result in the increased production of ROS[52]. These free radicals are characterized by their readiness to give away or accept electrons to make them chemically neutral or stable, thereby interfering with normal cell function. An increase in ROS production can lead to the inhibition of nucleic acid and protein synthesis, inactivation of cellular enzymes, and increased lipid peroxidation, especially in cell membranes[53]. Mammals have evolved a defence system against oxygen free radicals by forming various antioxidant enzymes such as glutathione peroxidase or superoxide dismutase. However, the excessive production of free radicals in hyperoxic conditions can overwhelm these defence systems, and free radicals can consequently escape inactivation.

Of note, ROS have dual, opposing roles depending on the context. Oxidative burst, the release of ROS mediated by NADPH oxidase, is an important mechanism in neutrophils and macrophages to eliminate invading microorganisms and thereby functions as an inflammatory mediator[54]. When undergoing oxidative burst, neutrophils consume the most oxygen of all cells in the human body and can cause hypoxia-imprinting on adjacent tissues[55]. This microenvironmental hypoxia further stabilizes epithelial cell HIF gene expression and promotes effective inflammatory resolution. Studies in the liver and kidney of animal models of IR injury also showed that ROS can trigger nuclear factor (erythroid-derived 2)-like 2, an essential regulator of antioxidant responses during reperfusion, thereby inducing antioxidant gene expression and protecting the organs from IR injury[56,57]. The seven members of the NOX family of NADPH oxidases are the key producers of ROS in many cells. Mitochondria have an important role in the maintenance of cellular redox status by acting as a ROS and redox sink and limiting NADPH oxidase activity but are also a substantial source of ROS by stimulating NADPH oxidase activity under certain settings[58].

The pathophysiological effect of oxygen toxicity on the vasculature and central nervous system has been assessed[59]. In the cardiovascular system, hyperoxia inhibits endothelial nitric oxide (NO) synthase and NO release from *S*-nitrosothiol[7]. Hyperoxia also leads to excessive ROS production by increasing xanthine oxidase levels[52], which converts available NO to peroxynitrite to promote nitrosative stress. Therefore, NO bioavailability is reduced, leading to increased systemic vascular resistance. In addition, hyperoxia increases parasympathetic tone via the baroreceptor reflex in response to vasoconstriction and central chemoreceptor regulation of respiration, which causes a decline in heart rate and cardiac output[60]. Although different vasculature beds have different reactions to the vasoconstrictive effect of hyperoxia, the cerebral and coronary vasculature has the most pronounced response, which further compromises cerebral and myocardial perfusion and worsens organ injury (Fig. 2).

In addition to the adverse effects of free radicals, excess oxygen levels have also been shown to alter cellular metabolism and activate several key signalling pathways that lead to hyperoxia-induced enzyme inhibition and cell death[61]. For example, in mice, short-term (4 h) exposure to 95% oxygen levels results in a sustained reduction in mitochondrial oxidative phosphorylation in epithelial cells[62]. Hyperoxia also elicited mitochondrial fragmentation in mouse endothelial cells via an increase in mitochondria-derived ROS and phosphorylation of dynamin-related protein 1 (ref. 63) (Fig. 2). Moreover, exposure tooxygen directly triggers the activator protein 1 and mitogen-activated protein kinase signalling pathways, which contribute to hyperoxia-induced death of type II epithelial cells in the lungs of mice[63].

In certain disease states, such as after an acute myocardial infarction or cardiac arrest, hyperoxia has been shown to exacerbate IR injury[64]. ROS attract neutrophils to the blood–endothelial cell interface and facilitate migration to the surrounding tissues. Neutrophils can increase ROS production, further exacerbating IR injury[64] (Fig. 2). In addition, in the setting of IR injury, vasoconstriction-promoting thromboxanes are synthesized at a much higher rate than vasodilatation-promoting prostaglandins, resulting in microvascular vasoconstriction, microcirculatory failure and the ‘no-reflow’ phenomenon, exacerbating the original injury[65]. Other studies have implicated purinergic signalling events in natural killer T cells in hyperoxic organ inflammation: the $P2X_7$ receptors expressed on invariant natural killer T cells are ion-gated channels activated by ATP and have been shown to prevent invariant natural killer T cell death during hyperoxia[66]. Taken together, although the effects of oxygen toxicity have not been clearly established in healthy individuals, findings from numerous preclinical studies strongly suggest that hyperoxia during acute cardiovascular injury or reperfusion can exacerbate organ injury and should best be avoided.

Failure of HIF stabilization during hyperoxia

HIF stabilization and the downstream signalling pathways have been shown to confer protection against hypoxia-induced tissue damage[9]. For example, several studies demonstrated that HIF is stabilized during myocardial infarction and confers cardioprotection through various signalling mechanisms, such as the induction of glycolytic enzymes, extracellular adenosine signalling or signalling events involving growth hormones (such as amphiregulin)[23,29,43] (Box 1). Therefore, a major concern with the excessive use

of oxygen therapy is the dampening of endogenous adaptive responses that are under the control of HIFs. Furthermore, high levels of inspired oxygen have been shown to prevent the stabilization of HIFs and the induction of HIF target genes. In a study that assessed the effect of hyperoxia on lung development in a newborn rat model, exposure to hyperoxia weakened the stabilization of HIF2α and attenuated HIF2α-dependent induction of vascular endothelial growth factor (VEGF), thereby preventing alveolarization of the lungs[67]. Subsequent in vivo studies in non-human primates demonstrated that the effects of hyperoxia on dampening HIF2α-dependent VEGF responses could be overcome using pharmacological HIF–PHD inhibitors[68]. Similarly, an in vivo study of lung inflammation during polymicrobial sepsis showed that mice exposed to hyperoxia had more severe lung inflammation and a threefold higher risk of death compared with control mice[69]. Importantly, the investigators pointed out that the detrimental effects of hyperoxia were related to the inhibition of adenosine A_{2A} receptor signalling using pharmacological and genetic approaches[70]. In their model, hyperoxia prevented the stabilization of HIFs and the concomitant expression of the gene encoding the adenosine A_{2A} receptor, which is a previously established HIF2α target gene[70]. Similarly, hyperoxia was found to directly inhibit HIF1α and VEGF in a rabbit model of vascular hyperplasia and in human cancer cells[71,72]. Together, these experimental studies demonstrate that hyperoxia is associated with an attenuated HIF response during various inflammatory or injurious disease states (Fig. 1) and is linked to reduced adenosine production and signalling, abolished preconditioning of the heart, inhibition of adaptive metabolic responses, and reduced function of HIFs to dampen inflammation. Moreover, the prevention of HIF target gene induction, which would otherwise promote tissue adaptation and improve ischaemic tolerance, is an important aspect of tissue injury induction associated with excessive oxygen therapy.

Detection of hyperoxia: techniques and limitations

Excessive oxygen use might have harmful effects, especially in certain disease states, as described above. However, the early detection of hyperoxia to prevent any adverse effects is a challenge in clinical practice given that there are currently no non-invasive monitoring modalities that can be used to reliably detect hyperoxia. The most common technique used to measure oxygen levels in clinical practice is pulse oximetry. Although pulse oximetry is a highly effective and reliable monitor to detect hypoxia, it cannot detect hyperoxia because its maximal reading of 100% oxygen saturation (SpO_2) correlates to a partial pressure of oxygen (PaO_2) range of 100 to >663 mmHg. Therefore, pulse oximetry cannot differentiate between a physiological PaO_2 or iatrogenic hyperoxia. As a result, unintentional hyperoxia frequently occurs during oxygen therapy in patients with cardiovascular disease[73,74].

Advances in technology that can enable clinicians to monitor PaO_2 levels would be crucial for the routine non-invasive identification of hyperoxia in patients receiving oxygen therapy. A few emerging techniques have been described. Near-infrared spectroscopy (NIRS) can be used to quantify local SpO_2 levels by measuring the differences in the absorption spectrum between oxyhaemoglobin and deoxyhaemoglobin[75]. NIRS has been proposed as a real-time, continuous and non-invasive technique to measure regional tissue oxygenation. However, most clinical studies demonstrated a bias and wide limits of agreement when comparing the currently available NIRS technology with gold-standard perfusion modalities

such as central venous SpO_2[76]. The Radical-7 Pulse CO-Oximeter (Masimo) is a newly developed, non-invasive device that incorporates a conventional pulse oximeter with the 'oxygen reserve index', which uses the Fick equation, arterial oxygen content and venous SpO_2 to assess real-time PaO_2 levels in the range of 100–200 mmHg. However, in a specific population of patients with brain injuries, the capacity of the oxygen reserve index to diagnose hyperoxia is low (area under the receiver operating characteristic curve to detect PaO_2 of >100 mmHg was 0.567, with a sensitivity of 0.233 and a specificity of 0.909) compared with pulse oximetry[77]. The OxiVenT (SenTec) is another modality developed to continuously monitor the transcutaneous PaO_2. This sensor works by heating the skin to a few degrees above body temperature, causing hyperperfusion owing to increased skin metabolism. This hyperperfusion (also referred to as arterialization) leads to local increases in the blood supply of the skin, which translates to oxygen levels similar to that in the arterial supply. However, a study has shown that transcutaneous PaO_2 is accurate only for patients aged <6 months; the application of this technique in the broader population needs further investigation[78]. In summary, advances in technology to facilitate accurate, non-invasive detection of hyperoxia in a clinical setting continue to be a pressing need for the provision of goal-directed oxygen therapy.

Oxygen therapy in cardiovascular medicine

Acute myocardial infarction

Oxygen supplementation intuitively seems to be beneficial for patients with myocardial ischaemia given that they require increased oxygen supply to ischaemic myocardial tissue. However, the haemodynamic effects of oxygen supplementation in the setting of myocardial infarction are dependent on the concurrent degree of hypoxia. One study showed that an increase in oxygen levels did not increase oxygen transport when the level of arterial SpO_2 was >90% given that reductions in cardiac output (secondary to vasoconstriction from hyperoxia) exceeded the increase in oxygen content[79]. By contrast, in patients with an arterial SpO_2 of <90%, oxygen administration increased oxygen transport due to increased cardiac output and oxygen content[79]. Hyperoxia is likely to impair HIF stabilization and concomitant HIF-mediated organ protection and adaptation to ischaemia. Moreover, hyperoxia might also exacerbate myocardial reperfusion injury in patients undergoing coronary interventions[41].

The 2015 multicentre AVOID trial[80] compared the effects of different levels of oxygen supplementation on acute myocardial injury in 441 patients with ST-segment elevation myocardial infarction (STEMI) by assessing cardiac enzyme activity and the size of the infarct at 6 months (measured via cardiac MRI) (Table 1). Patients were randomly assigned to receive either oxygen supplementation (8 l/min) or room air. Patients in the oxygen supplementation group had increased early myocardial injury and, at the 6-month follow-up, a 55% larger myocardial infarct size compared with patients who did not receive oxygen therapy[80]. However, the study was underpowered to determine hard clinical end points (such as mortality) owing to its small sample size.

In the subsequent registry-based DETO2X-AMI trial[81], 6,629 patients with suspected acute myocardial infarction were randomly assigned to receive either supplementary oxygen (6

l/min for 6–12 h) or room air. Although the oxygen supplementation group had a lower incidence of hypoxia than the control group, no significant differences were found between the two study groups with regards to the primary end point of all-cause mortality at 1 year or the secondary end points of cardiac troponin T levels or rehospitalization for myocardial infarction. The same results were found in the long-term follow-up study (median 2.1 years)[82]. The investigators subsequently extended their analysis with the objective of identifying a subgroup of patients who might benefit from oxygen supplementation but found that all-cause mortality was also not significantly different between treatment groups in patients with diabetes mellitus, normoxic chronic obstructive pulmonary disease or STEMI[83–85]. Therefore, the next question was whether oxygen supplementation could benefit patients with acute coronary syndrome (ACS) who experienced more severe baseline hypoxia compared with patients with less severe baseline hypoxia. The DETO2X-SWEDEHEART trial[86] investigators sought to determine the effect of supplemental oxygen in patients with myocardial infarction while taking into account baseline SpO_2 levels[86]. In total, 5,010 patients with myocardial infarction were classified into low–normal (90–94%) and high–normal SpO_2 (95–100%) subgroups. The investigators identified low–normal baseline SpO_2 or development of hypoxia as an independent marker of poor prognosis. However, if patients were normoxic at baseline, routine oxygen therapy did not offer any clinically relevant benefits, regardless of their SpO_2 levels at baseline. In addition, a subgroup analysis that included data from 144 participants found that supplemental oxygen therapy did not affect the systemic inflammatory response (as evaluated by 92 inflammatory biomarkers)[87]. These findings suggest that supplemental oxygen, when given in a moderate dose for a short duration in patients with acute, non-hypoxic myocardial infarction, does not lead to clinically relevant hyperoxaemic toxicity secondary to excess inflammation.

Finally, a large pragmatic, cluster-randomized, crossover trial investigated the effect of high-flow supplementary oxygen on 30-day mortality in 40,872 patients with confirmed or suspected ACS[88]. The patients were randomly assigned to the oxygen supplementation group (6–8 l/min via a face mask) or the control group (who received oxygen only when SpO_2 levels fell below 90%, with a target SpO_2 of <95%). At 30 days, high-flow oxygen supplementation did not significantly affect mortality in either treatment group. Taken together, clinical evidence indicates that oxygen supplementation offers no benefit and, in some settings, might even be potentially harmful, such as in patients with acute ischaemic heart disease without hypoxia. Therefore, the 2017 ESC guidelines recommend supplementing oxygen in patients with STEMI only if their SpO_2 level is <90%[89]. Moreover, the 2015 AHA guidelines recommend withholding oxygen supplementation in normoxic patients with suspected or confirmed ACS in the prehospital, emergency department and hospital settings[90] (Fig. 3).

Cardiac arrest and resuscitation

Oxygen therapy has also received much attention for the treatment of patients after a cardiac arrest event. Hyperoxia increases parasympathetic tone and reduces heart rate, leading to decreased cardiac output. Hyperoxia also leads to vasoconstriction, especially in the coronary and cerebral vasculature, reducing the chance of return of spontaneous

circulation and neurological recovery. Additionally, hyperoxia could exacerbate myocardial injury during the reperfusion phase of cardiopulmonary resuscitation[41].

To date, most of the evidence on the role of oxygen therapy during cardiac arrest and resuscitation originated from retrospective studies and small RCTs. A 2010 multicentre, retrospective analysis compared the effect of hyperoxia versus normoxia in the first 24 h of admission to an intensive care unit (ICU) on in-hospital mortality in patients with non-traumatic cardiac arrest[91]. Compared with patients with normoxia (PaO_2 60–300 mmHg; n = 1,171), patients with hyperoxia (PaO_2 >300 mmHg; n = 1,156) had significantly increased in-hospital mortality (45% versus 63%)[91]. Further analysis revealed that every 100-mmHg increase in PaO_2 was associated with a 24% increased risk of death[92].

A 2020 meta-analysis of seven RCTs that included a total of 429 participants who had cardiac arrest demonstrated that a conservative oxygen therapy approach was associated with a significant reduction in mortality compared with a liberal oxygen therapy approach. However, inconsistencies in the oxygen therapy protocols that were used in the different trials limit the certainty of the findings[93]. In the multicentre EXACT trial[94] involving 428 patients with out-of-hospital cardiac arrest, an SpO_2 target of 90–94% in the early phase of post-resuscitation care did not significantly improve survival until hospital discharge compared with an SpO_2 target of 98–100%. Indeed, mortality tended to be higher among patients assigned to the low-oxygen target group (61.7%) compared with patients in the high-oxygen target group (52.1%). Of note, this trial was terminated early due to the COVID-19 pandemic and, therefore, the primary outcome could not be adequately assessed owing to the small sample size. In addition, participants underwent active titration of their oxygen intake throughout the study period whereas, in clinical practice, inadvertent oversupply of oxygen is common, especially during the active resuscitation phase before return of spontaneous circulation[95]. Furthermore, a subanalysis of the TTM2 trial[95] showed that both hypoxaemia and hyperoxaemia during the first 72 h of mechanical ventilation in patients with an out-of-hospital cardiac arrest were independently associated with increased mortality but not with poor neurological outcome at 6 months after the cardiac arrest. Of note, mortality significantly increased when PaO_2 levels were <69 mmHg or >195 mmHg (ref. 95).

In summary, numerous observational studies have identified an association between post-arrest hyperoxia (PaO_2 >300 mmHg) and poor neurological outcome in patients with non-traumatic cardiac arrest. As such, the 2015 AHA guidelines recommend the use of titrated and individualized oxygen therapy (with an SpO_2 target of 94–98%) instead of the previously recommended liberal oxygen therapy strategy after return of spontaneous circulation[96] (Fig. 3). On the basis of RCT findings[94], a lower SpO_2 target of 90–94% is not recommended for patients with out-of-hospital cardiac arrest.

Heart failure

Given that the essential function of the cardiovascular system is to provide oxygen and nutrients to the tissues and organs when cardiac function is compromised during heart failure, oxygen delivery largely relies on an increase in oxygen content in the blood. Therefore, supplemental oxygen therapy would seem to be intuitively beneficial

for patients with heart failure. However, oxygen is carried predominantly bound to haemoglobin in red blood cells (approximately 20 ml of oxygen per 100 ml of blood with a haemoglobin concentration of 15 g/dl), with a small amount of oxygen dissolved in plasma (approximately 0.3 ml of oxygen at a physiological PaO_2 of 100 mmHg but up to 1.8 ml under conditions of hyperoxia with an intake of 100% oxygen and a PaO_2 of 600 mmHg)[97]. When haemoglobin is saturated with oxygen, further oxygen supplementation will only increase the amount of oxygen dissolved in the blood, and the increase in oxygen delivery is minimal. Of note, excess oxygen dissolved in blood will lead to excessive production of ROS.

Physiological studies in patients with acute heart failure with reduced ejection fraction have confirmed that oxygen supplementation increases systemic vascular resistance and reduces heart rate, stroke volume and cardiac output, even in patients with hypoxia (baseline SpO_2 of 92%)[98,99]. A 2021 propensity-matched analysis involving 2,922 patients with normoxaemia and acute heart failure found that routine supplemental oxygen did not reduce all-cause in-hospital or ICU mortality but was instead associated with longer length of stay in the ICU and in hospital[100]. Therefore, the 2021 ESC guidelines recommend oxygen therapy for patients with acute heart failure and SpO_2 <90% or PaO_2 <60 mmHg to correct hypoxaemia, but state that oxygen should not be used routinely in patients without hypoxaemia[101]. Well-designed, prospective RCTs are needed to determine whether oxygen therapy is beneficial in different subgroups of patients such as in those with hypoxia or normoxia, with acute or chronic heart failure, or with heart failure with reduced or preserved ejection fraction.

Cardiac surgery and cardiopulmonary bypass

Cardiac surgery with cardiopulmonary bypass is characterized by a profound systemic inflammatory response, which could be secondary to surgical trauma, contact of blood with artificial surfaces of the bypass circuit or IR injury after discontinuing bypass[102]. Hyperoxia can exacerbate inflammation-induced organ injury through the generation of ROS and should therefore be discouraged during cardiac surgery. Furthermore, hyperoxia should be avoided during cardiopulmonary bypass for several other reasons. First, cardiac output, which is a crucial determinant of oxygen supply, can be readily adjusted during cardiopulmonary bypass by changing the pump flow to meet demand. Second, a study has shown that hyperoxia causes an increase in vascular resistance, a decrease in surface oxygen tension and an increase in the heterogeneity of the oxygen distribution profile in the skeletal muscles of individuals undergoing cardiopulmonary bypass[103]. These findings indicate that paradoxical tissue hypoxia might take place in the setting of arterial hyperoxia.

A 2022 RCT involving 100 patients undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass found that intraoperative hyperoxygenation (fraction of inspired oxygen (FiO_2) of 100% in the hyperoxia group versus 40% in the normoxia group) delayed extubation after surgery and was associated with worse late-term cognitive function[104]. By contrast, another similar RCT involving elderly patients (median age of 71 years) did not find any significant difference in neurocognitive function between the intraoperative normoxia and hyperoxia groups[105]. Although hyperoxia is generally not recommended for patients during CABG surgery with cardiopulmonary bypass, an

oxygenation target for patients undergoing the procedure has still not been established. The ongoing prospective ROCS trial[106] aims to determine whether physiological oxygenation during cardiac surgery can decrease oxidative damage and acute kidney injury compared with hyperoxia. The results from this trial will hopefully shed some light on the optimal oxygenation target for patients requiring cardiopulmonary bypass.

Discrepancies between preclinical and clinical studies

On the basis of the above clinical evidence, oxygen therapy, although convenient and affordable, does not have a universally safe dose range for the treatment of different diseases. Hyperoxia resembles an oxygen overdose and is likely to be harmful in many clinical settings such as in acute myocardial infarction. However, the harmful effects of hyperoxia observed in preclinical studies have not been confirmed by data from large-scale clinical trials. Three important reasons might underlie this discrepancy. First, preclinical studies usually test in an actual hyperoxic environment (FiO_2 70–100% and PaO_2 >300 mmHg) to examine the harm associated with hyperoxia, whereas the majority of clinical trials use a few litres of oxygen supplementation (estimated FiO_2 30–45% and variable levels of PaO_2) to determine the benefits of oxygen supplementation in clinical practice. As such, the test environment and aims of the studies are different between preclinical and clinical studies. Second, current technology limits our ability to detect excess oxygen supply in tissues given that peripheral oximetry is not capable of detecting iatrogenic hyperoxia. Therefore, most clinical trials might not have achieved true hyperoxia if a non-invasive peripheral pulse oximeter was used alone to monitor oxygen levels. Finally, the true threshold for a harmful oxygen level is still unknown. The only clinical study that was designed to define a harmful ‘threshold’ involved patients with cardiac arrest in which a PaO_2 threshold of 300 mmHg was identified, but this study was retrospective and other confounders could not be excluded[91]. More importantly, perhaps, from the perspective of individual cells, the terms ‘hypoxia’ and ‘hyperoxia’ are relative and context dependent. In this respect, ‘normoxia’ is defined as an oxygen level that provides optimal conditions for typical physiological processes in the cell. Any disturbances in this homeostatic balance can result in pathology. As such, without knowing the actual ‘harmful threshold’ for different disease conditions, any clinical study will be in vain.

A summary of important published and ongoing clinical trials aimed at assessing a liberal versus a conservative oxygen therapy approach for cardiovascular and other diseases are presented in Tables 1 and 2. Additional clinical studies are needed to define the optimal oxygenation targets for different disease states. Moreover, efforts must be made in the design and execution of these clinical studies to achieve the desired oxygen targets so that an accurate interpretation of the study results and their implications for clinical care can be achieved. In settings of unclear benefits or harm, hypoxia and excessive hyperoxia should be avoided when using oxygen therapy.

Alternative therapies targeting oxygen-sensing pathways

Oxygen therapy was introduced to cardiovascular medicine to overcome the detrimental effects of tissue hypoxia and to prevent ischaemic injury during myocardial infarction, cardiac arrest and resuscitation, or other types of acute organ injury. Ironically, however, the

clinical studies performed in the past decade that were discussed above did not demonstrate the desired benefits of oxygen therapy in these clinical scenarios. By contrast, several studies showed that liberal use of oxygen therapy can actually worsen outcomes in patients with IR injury or during critical illness[80,92,104]. Therefore, alternative therapeutic strategies that focus on promoting organ resistance to IR injury have been explored, including various preconditioning approaches.

These experimental approaches target oxygen-sensing pathways and converge in the stabilization of HIFs, with the concomitant induction of crucial HIF target genes[9–11,107]. Importantly, however, even though an increase in HIF expression is possibly beneficial in the short term, chronic overexpression might activate autonomous pathways that lead to cardiomyopathy in the setting of increased mechanical load and ageing[108]. This effect is partially mediated by the regulation of immune-related cells during physiological or pathophysiological hypoxia[109]. Importantly, pharmacological preconditioning with HIF activators can be applied independently of the level of inspired oxygen concentration delivered to a patient. Therefore, this strategy can be used in patients with severe systemic hypoxia who require high levels of inspired oxygen concentrations to maintain adequate oxygen delivery to different organs.

Preconditioning and postconditioning approaches

Although the level of tolerable hypoxia in various clinical settings has yet to be identified, short bursts of hypoxia or ischaemia are usually well tolerated and have been used as a therapeutic strategy known as ischaemic preconditioning[110]. The cardioprotection offered by ischaemic preconditioning has been directly linked to the stabilization of HIF1α and its effects on gene expression (such as via increased production of the extracellular signalling molecule adenosine[111], which subsequently activates the adenosine A_{2B} receptor)[11,29] (Fig. 4). Activation of adenosine A_{2B} receptor signalling also leads to the stabilization of the transcriptional repressor period circadian protein homologue 2 (PER2). The increase in PER2 signalling results in increased glycolytic capacity of the cardiomyocytes and improved ischaemia tolerance[24,43].

In clinical practice, ischaemic preconditioning is rarely feasible because the majority of acute myocardial infarction events are not predictable. However, ischaemic postconditioning is a more feasible strategy that can be used in the clinic. Similar to preconditioning, preclinical findings have highlighted a crucial role of HIF stabilization in providing cardioprotection during ischaemic postconditioning[112]. Ischaemic postconditioning can be achieved by repetitive brief interruptions of coronary blood flow before the final complete reperfusion. Investigators in the DANAMI-3-iPOST trial[113] assessed the effect of ischaemic postconditioning on all-cause mortality and hospitalization for heart failure (composite primary end point) in 1,234 patients with STEMI undergoing percutaneous coronary intervention (PCI). The study demonstrated that routine ischaemic postconditioning during primary PCI did not reduce the composite primary outcome, but a post hoc analysis of patients who were not treated with thrombectomy showed that ischaemic postconditioning reduced the short-term composite primary outcome[113]. At the long-term follow-up

(median 4.8 years), ischaemic postconditioning decreased cardiovascular mortality and hospitalization for heart failure in patients treated with PCI without thrombectomy[114].

An alternative approach to ischaemic postconditioning is remote ischaemic postconditioning (RIPC)[10,115]. RIPC is achieved by repetitive ischaemia and reperfusion to a limb (typically using inflation and subsequent deflation of a non-invasive blood-pressure cuff) and has been evaluated as a strategy to protect against organ damage[116]. Mechanistically, RIPC can exert remote organ protection against IR injury via three different pathways: humoral, neuronal and systemic pathways[117] (Fig. 4). For example, RIPC stabilizes HIF1α in the peripheral musculature, leading to increased expression of the HIF target gene *IL10*. The release of IL-10 from remote tissue exposed to hypoxia-mediated ischaemia subsequently activates the IL-10 receptor on cardiomyocytes and mediates cardiac protection against ischaemic injury[118]. Other mediators involved in this humoral pathway include adenosine, erythropoietin and various microRNAs[119]. Numerous studies demonstrated that an intact neural pathway is essential for the protective effect of RIPC. RIPC activates the production of autacoids, such as adenosine and bradykinin, in the remote preconditioned organ, which stimulates afferent nerves and relays the neural signal to the myocardium via the efferent nerve fibres. Denervation of the neural pathway in the remote organ has been shown to abolish RIPC protection[120,121]. Finally, RIPC triggers a systemic response by modulating inflammatory cells either post-transcriptionally or through transcriptional regulation. In a study that involved a microarray analysis of blood samples from healthy individuals subjected to forearm preconditioning, preconditioning suppressed the expression of genes involved in regulating cytokine production and leukocyte chemotaxis, adhesion and migration, and upregulated the expression of anti-inflammatory genes[122].

The protective effect of RIPC has been the focus of several clinical trials. In a 2015 trial that enrolled 240 patients undergoing cardiac surgery who were at increased risk of acute kidney injury, patients who received RIPC had a significantly lower incidence of acute kidney injury (37.5%) compared with control patients (52.5%)[123]. Similarly, fewer patients in the RIPC group received renal replacement therapy compared with the control group (5.8% versus 15.8%)[123]. However, a large multicentre RCT involving 1,403 patients undergoing elective cardiac surgery with cardiopulmonary bypass did not find any significant differences in the rate of the primary end point (composite of death, myocardial infarction, stroke or acute renal failure until the time of hospital discharge), nor any of the individual secondary end points, between the RIPC group and the sham group[124]. Furthermore, another trial performed at the same time also showed that RIPC did not improve clinical outcomes in patients undergoing elective on-pump CABG surgery with or without valve surgery[125]. Taken together, these studies show that the therapeutic effect of RIPC on perioperative outcomes is yet to be established. Future studies might focus first on optimizing the RIPC protocol and validating the efficacy of RIPC by measuring various mediators, such as IL-10 or HIF target genes, before addressing clinical outcomes[115].

Pharmacological HIF activators

As outlined above, a major concern with a liberal oxygen therapy strategy is its inhibition of the protective effect of HIF stabilization. Similarly, HIF stabilization is central to the

different preconditioning and postconditioning approaches, including RIPC. Therefore, pharmacological HIF activators could be used to directly stabilize HIFs without the potential risk of exacerbating injury secondary to hyperoxia. Findings from several animal studies indicate that HIF activators protect against IR injury in different organs, including the heart[11,24], kidneys[126] and liver[27]. Similarly, HIF activators have also been shown to protect the lungs during ARDS[127,128], and an ongoing trial is examining HIF activators for ARDS prevention[129]. Pharmacological approaches to promote the normoxic stabilization of HIFs have also been assessed. In the PRO2TECT study[130], the oral HIF–PHD inhibitor vadadustat was non-inferior to darbepoetin alfa with regards to haematological efficacy but did not meet the prespecified non-inferiority criterion for cardiovascular safety in patients with non-dialysis-dependent chronic kidney disease. When relevant safety concerns have been addressed, it is conceivable that pharmacological HIF activators could be developed as an alternative approach to oxygen therapy to attenuate IR injury independent of inspired oxygen concentrations.

Conclusions

Findings from RCTs suggest that preventing hyperoxia is an essential clinical strategy for oxygenation management in cardiovascular medicine, including for acute myocardial infarction and post-cardiac arrest resuscitation. In other disease contexts, such as heart failure, more evidence is needed on optimal oxygenation targets. Nevertheless, regardless of clinical setting, a balanced oxygen treatment regimen to prevent systemic hypoxia and simultaneously avoid excessive hyperoxia is needed. Although hypoxia can be readily detected with pulse oximetry, hyperoxia is more challenging to monitor. As such, novel non-invasive means to identify hyperoxic levels of oxygen in the blood of patients would be highly desirable to guide clinicians on the safe use of oxygen therapy.

The effect of oxygen on any biological system goes beyond its direct involvement in metabolism and energy generation. Since the discovery of the hypoxia signalling pathway in the early 1990s, for which Kaelin Jr, Ratcliffe and Semenza were awarded the 2019 Nobel Prize in Physiology or Medicine, the knowledge of oxygen sensing, regulation of metabolism, and many other physiological and pathophysiological processes related to cellular oxygenation continues to expand at an extraordinary pace. Strategies such as direct or remote preconditioning or the use of pharmacological HIF activators are examples of alternative approaches to oxygen supplementation that target oxygen-sensing mechanisms to provide organ protection independent of the amount of oxygen that a patient receives. Although some of the initial clinical studies are very encouraging, data from RCTs will be necessary to make these alternative approaches an integral part of the treatment plan for patients with cardiovascular disease.

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Box 1 HIF target genes implicated in cardioprotection

Hypoxia-inducible factors (HIFs) have a central role in tissue adaptation to limited oxygen availability (hypoxia). These transcription factors are stabilized during hypoxic conditions such as in myocardial ischaemia–reperfusion (IR) injury[43]. When the HIFα subunit is stabilized, it forms a heterodimer that translocates into the nucleus and activates the transcription of hypoxia-responsive target genes[29]. Several studies have shown that HIFs and their target gene expression have an important role in cardioprotection. For example, mice with a partial deletion[143], an induced deletion[42,144] or silencing RNA-mediated repression[11] of the *Hifa* isoforms (*Hif1a* or *Hif2a*) have more severe myocardial IR injury in vivo than control mice. Moreover, targeting cardiac *Hif1a* prevents the cardioprotective effects exerted by ischaemic preconditioning[110]. Pharmacological interventions that stabilize HIFs have also been shown to precondition the myocardium and protect it against damage[11]. This cardioprotection involves the direct induction of specific target genes. For example, HIFs have been shown to induce glycolytic enzymes, allowing cells to adapt their carbohydrate metabolism during hypoxia[23]. This response has an important role during myocardial IR injury because it promotes a more oxygen-efficient utilization of carbohydrates[24]. Another group of known HIF target genes involved in cardioprotection relates to the extracellular production and signalling of adenosine. Adenosine is produced from precursor nucleotides via the ectonucleotidase CD73 (conversion of AMP to adenosine)[145] and can signal through four distinct adenosine receptors[146]. Whereas the heart rate-slowing effects of adenosine are mediated predominantly via the adenosine A_1 receptor[147], the adenosine A_{2A} and A_{2B} receptors are known HIF target genes that are crucial for cardioprotection[29,43,148]. An additional HIF1α target gene implicated in mediating the cardioprotective effects of HIF1α encodes the neuronal guidance molecule netrin 1 (ref. 44). Levels of this protein are increased in the blood of patients with myocardial infarction or in mice exposed to myocardial IR injury[149]. Other studies implicate HIF1α in mediating the protective effects of remote ischaemic preconditioning, whereby short periods of limb ischaemia (for example, by inflation of a tourniquet) could protect against myocardial or kidney injury[115]. Moreover, in vivo studies in mice have shown that IL-10 levels are increased after remote ischaemic preconditioning[118]. *IL10* has been identified as an HIF1α target gene and crucial for the cardioprotective effects mediated by remote ischaemic preconditioning. Finally, in addition to HIF1α, the cardioprotective effects of HIF2α have also been demonstrated during IR injury. Mice with an induced *Hif2a* deletion in cardiomyocytes had increases in infarct size compared with wild-type mice[12]. An unbiased microarray analysis identified the epidermal growth factor amphiregulin as a mediator of HIF2α-induced cardioprotection. Taken together, these studies have laid the groundwork for using HIF–prolyl hydroxylase inhibitors in ongoing clinical trials for cardioprotection.

Key points

- Patients with cardiovascular disease frequently experience hypoxia, which can be systemic or localized.
- Hypoxia causes the stabilization of hypoxia-inducible factor (HIF) transcription factors, which promote adaptive responses to limited oxygen availability, precondition the heart and increase resistance to acute ischaemia.
- In the past 12 decades, oxygen therapy has been used extensively in patients with cardiovascular disease to treat or prevent hypoxia but often leads to unintended high oxygen levels (hyperoxia).
- Hyperoxia is associated with the excessive production of reactive oxygen species and also dampens endogenous adaptive responses to hypoxia, including HIF stabilization, thereby exacerbating organ injury.
- The findings from several clinical trials from the past 10 years support a more conservative and vigilant approach to oxygen therapy in specific cardiovascular disease contexts, including myocardial infarction, cardiac arrest, heart failure or cardiac surgery.
- Alternative approaches targeting oxygen-sensing pathways include preconditioning approaches or newly developed pharmacological agents that promote the stabilization of HIFs; these therapeutic interventions are being developed for the treatment of cardiovascular disease and can be applied independently of the level of oxygen therapy that a patient is receiving.

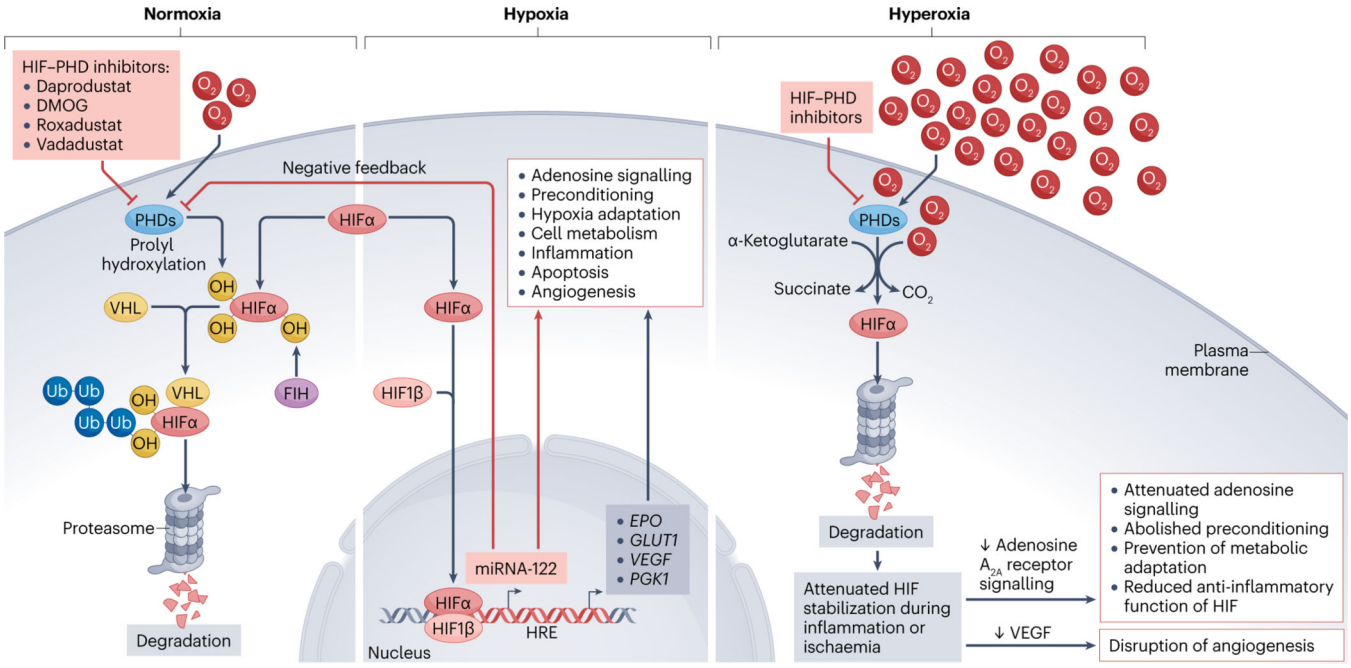

Fig. 1 |. Responses of HIFs to hypoxia or hyperoxia.

Under normoxic conditions, hydroxylation at two proline residues by prolyl hydroxylases (PHDs) promotes the association between hypoxia-inducible factor-α (HIFα) and the von Hippel–Lindau (VHL) gene product, leading to HIFα destruction via the ubiquitin–proteasome pathway[21,22,131]. During hypoxia, this process is suppressed due to the lack of oxygen as a substrate for PHDs, allowing the HIFα subunit to escape proteolysis. After stabilization, HIFα dimerizes with HIF1β, and the heterodimer translocates to the nucleus to activate the transcription of target genes that contain hypoxia response elements (HREs) in their promoter[20]. These target genes control essential physiological functions such as hypoxia adaptation, cell metabolism, inflammation, apoptosis and angiogenesis. Importantly, gene repression by HIFs frequently occurs as an indirect response that involves the transcriptional induction of HIF-dependent microRNAs (miRNAs) and the subsequent repression of target gene expression[132–135]. Furthermore, miRNAs have also been shown to participate in a feedforward pathway via an increase in HIF responses through PHD1 repression to provide organ protection during ischaemia–reperfusion injury[27]. HIF stabilization by HIF–PHD inhibitors (such as daprodustat, dimethyloxalylglycine, roxadustat and vadadustat) might be a potential therapeutic approach for acute cardiovascular disease[27,130]. In addition, HIF activity is also regulated by hydroxylation of a single conserved asparaginyl residue at the C-terminal transactivation domain by the oxygen-dependent asparaginyl hydroxylase factor inhibiting HIF1 (FIH1). During hyperoxia, high oxygen levels prevent the hypoxic inhibition of PHDs during conditions such as inflammation, ischaemia or metabolic imbalance. Attenuated HIF stabilization can dampen adaptive responses, such as angiogenic responses, or cardioprotection by adenosine generation and signalling (for example, through decreased adenosine A_{2A} receptor signalling). As such, hyperoxia is associated with attenuated adenosine production and signalling, abolished preconditioning of the heart, suppression of adaptive metabolic responses, and reduced capacity of HIFs to dampen inflammation. Of note, given that

HIF–PHD inhibitors will still be functional in stabilizing HIFs, even during hyperoxia, HIF activators can be considered as a cardioprotective strategy that works independently of the level of oxygen therapy that a patient receives. DMOG, dimethyloxalylglycine; OH, hydroxylation; Ub, ubiquitination; VEGF, vascular endothelial growth factor.

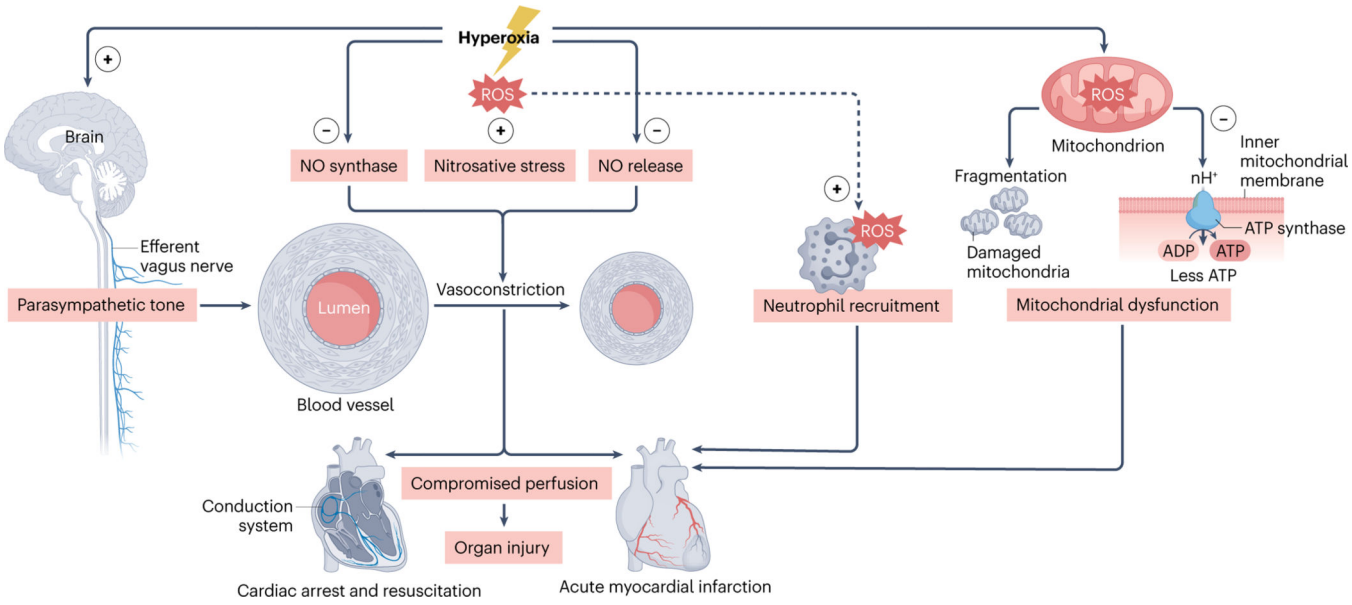

Fig. 2 |. Pathophysiological effects of hyperoxia on the cardiovascular system.

Hyperoxia inhibits endothelial nitric oxide (NO) synthase and NO release from *S*-nitrosothiol, thereby reducing NO bioavailability and promoting vasoconstriction in cerebral and coronary arteries. Hyperoxia also increases the production of reactive oxygen species (ROS)[59]. An increase in ROS converts available NO to peroxynitrite, which leads to nitrosative stress. In addition, hyperoxia increases parasympathetic tone, resulting in a reduction in heart rate. As a consequence of this vasoconstrictive effect, hyperoxia reduces cardiac output, compromises organ perfusion and exacerbates organ injury. Moreover, ROS facilitate the migration of neutrophils to the blood–endothelial cell interface and the surrounding tissues, further exacerbating ischaemia–reperfusion injury[64,65]. Finally, hyperoxia can also directly mediate mitochondrial dysfunction at the cellular level, thereby contributing to cell death[62,63,136].

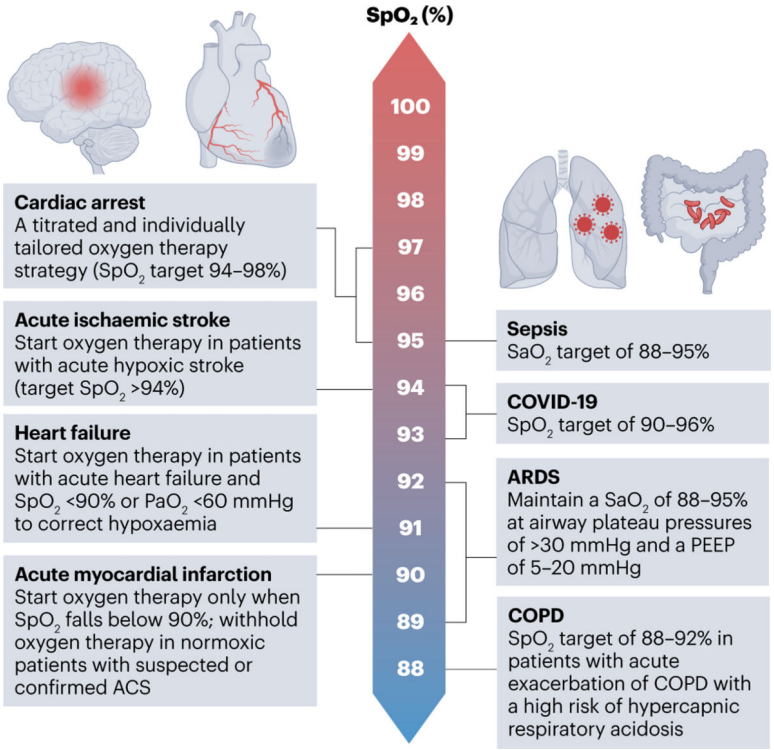

Fig. 3 |. Oxygen targets during cardiovascular disease and acute illness.

Guidelines have recommended different oxygen targets for treating specific diseases on the basis of current clinical evidence. However, regardless of the disease entity, there is a general agreement to avoid hypoxia and excessive hyperoxia. In patients with acute myocardial infarction, the 2017 ESC guidelines recommend supplementing oxygen only when oxygen saturation (SpO_2) levels fall below 90%[89]. The 2015 AHA guidelines recommend withholding oxygen supplementation in normoxic patients with suspected or confirmed acute coronary syndrome (ACS) in the prehospital, emergency department and hospital settings[90], and a titrated and individualized oxygen therapy strategy for patients after cardiac arrest with a target SpO_2 of 94–98% after the return of spontaneous circulation[96]. For patients with heart failure, the 2021 ESC guidelines recommend oxygen therapy for patients with acute heart failure and SpO_2 of <90% or partial pressure of oxygen (PaO_2) of <60 mmHg to correct hypoxaemia, and that oxygen should not be used routinely in patients without hypoxaemia[101]. For patients with acute ischaemic stroke, the 2018 AHA guidelines recommend providing oxygen therapy to maintain an oxygen saturation level of >94%[137]. For patients with acute respiratory distress syndrome (ARDS), the ARDS Network recommends a target SpO_2 level of 88–95% with an airway plateau pressure of <30 mmHg and a positive end-expiratory pressure (PEEP) of 5–20 mmHg (ref. 138). For patients with sepsis, the Surviving Sepsis Campaign guidelines recommend an arterial haemoglobin oxygen saturation (SaO_2) target of 88–95%[139]. In addition, for patients with ARDS related to COVID-19, a target SpO_2 of between 90% and 96% is recommended[140]. Finally, for patients with chronic obstructive pulmonary disease (COPD), the British Thoracic Society, the Global Initiative for Chronic Obstructive Lung Disease, the American Thoracic Society and the European Respiratory Society recommend titrating oxygen therapy to alleviate

hypoxia while avoiding hyperoxia to maintain SaO_2 levels of between 88% to 92% in patients with acute exacerbation of COPD and a high risk of hypercapnic respiratory acidosis[141,142].

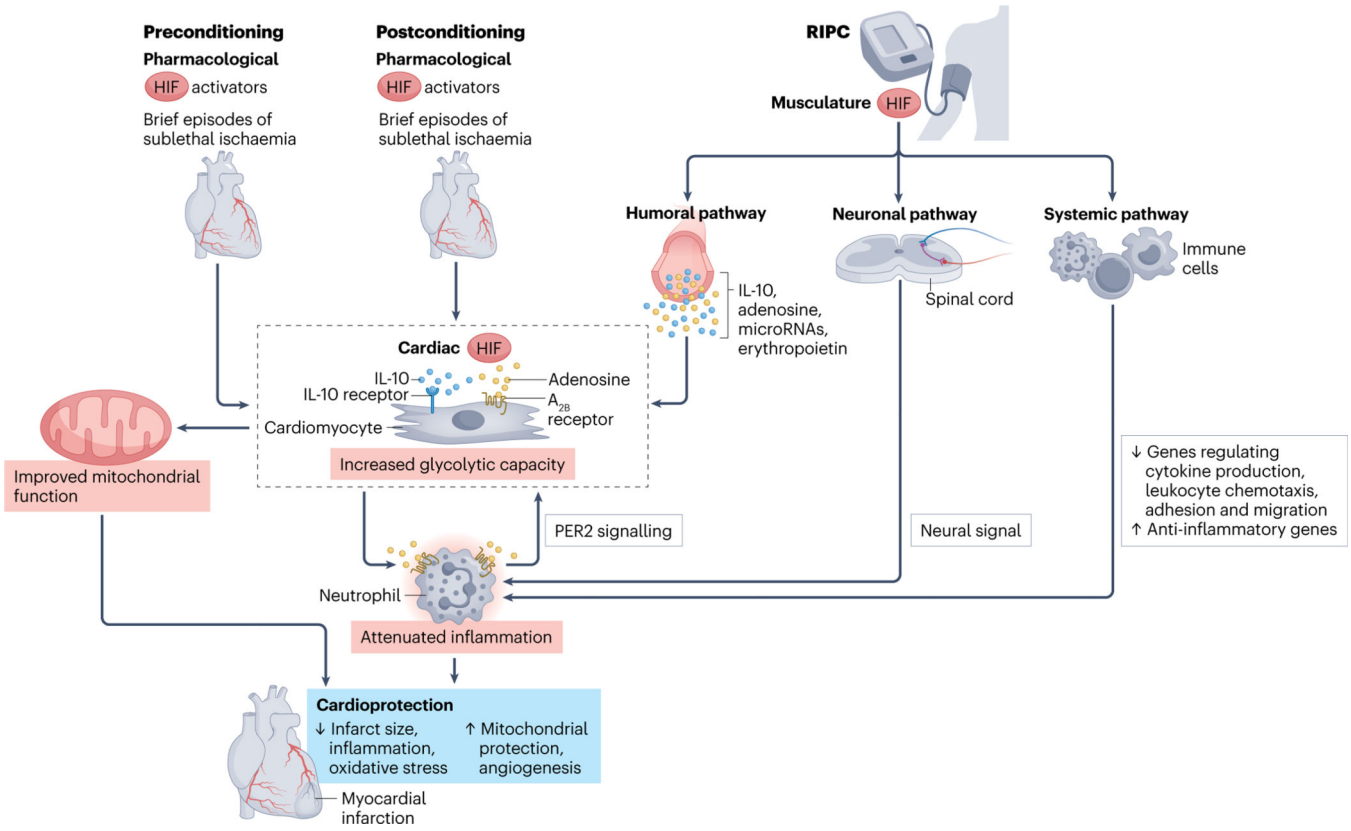

Fig. 4 |. Molecular mechanisms of preconditioning, postconditioning and RIPC for cardioprotection.

During ischaemic preconditioning, short episodes of myocardial ischaemia provide cardioprotection during a subsequent prolonged ischaemic event, whereas ischaemic postconditioning is achieved by repetitive brief interruptions of coronary blood flow before final complete reperfusion. Remote ischaemic postconditioning (RIPC) can be achieved by repetitive cycles of ischaemia and reperfusion to a limb via inflation and subsequent deflation of a non-invasive blood-pressure cuff. All three experimental approaches target oxygen-sensing pathways and converge on the stabilization of hypoxia-inducible factors (HIFs), with the concomitant induction of crucial HIF target genes[111]. For example, the extracellular signalling molecule adenosine and its subsequent activation of the adenosine A_{2B} receptor are central to ischaemic preconditioning-mediated cardioprotection. Activation of the adenosine A_{2B} receptor also stabilizes circadian protein homologue 2 (PER2), which results in amplified PER2 signalling and improved glycolytic capacity of the cardiomyocytes and ischaemic tolerance[24]. This increase in ischaemic tolerance leads to myocardial protection via attenuated inflammation and oxidative stress, reduced myocardial infarct size, and improved mitochondrial function. RIPC can protect organs against ischaemia–reperfusion injury via three different pathways: the humoral, the neuronal and the systemic pathways[117]. RIPC stabilizes HIF1α in the peripheral musculature, leading to the elevated expression of the HIF target gene *IL10*. The release of IL-10 from the remote tissue exposed to hypoxia-induced ischaemia subsequently activates the IL-10 receptor on cardiomyocytes and protects the heart against ischaemic injury[118]. Other mediators involved in this humoral pathway include adenosine, erythropoietin and various microRNAs[119]. Second, RIPC

activates the production of autacoids, such as adenosine and bradykinin, in the remote preconditioned organ, which stimulates afferent nerves and relays the neural signal to the myocardium via the efferent nerve fibres. Denervation of the neural pathway in the remote organ abolishes RIPC protection[120,121]. Third, RIPC provokes a systemic response by suppressing genes involved in regulating leukocyte chemotaxis and cytokine production, adhesion, and migration and upregulating anti-inflammatory genes[122]. Pharmacological HIF activators or prolyl hydroxylase inhibitors have been shown to have similar preconditioning and cardioprotective effects to those of ischaemic preconditioning[11].

Table 1 |

Selected large-scale RCTs comparing a liberal versus a conservative oxygen therapy approach in CVD

Clinical setting	Trial name (year)	Patient population	*n*	Intervention	Outcomes	Ref.
MI	AVOID (2015)	ST-segment elevation MI without hypoxia	441	Oxygen supplementation (8 l/min) versus room air	Increased myocardial injury and larger myocardial infarct size at 6 months in patients in the oxygen supplementation group compared with patients in the control group	80
	DETO2X-AMI (2017)	Suspected MI without hypoxia	6,629	Oxygen supplementation (6 l/min for 6–12 h) versus room air	No significant difference in the primary end point (all-cause death at 1 year) nor in secondary end points (rehospitalization with MI and cardiac troponin T levels)	81
	Stewart et al. (2021)	Suspected acute coronary syndrome	40,872	Oxygen supplementation (6–8 l/min) versus oxygen supplementation only if SpO_2 was <90%, with a target level of <95%	High-flow oxygen was not associated with a significant change in 30-day mortality	88
Cardiac arrest	EXACT (2022)	Out-of-hospital cardiac arrest	428	Oxygen saturation target of 90–94% versus a target of 98–100% after return of spontaneous circulation and until admission to the intensive care unit	The low oxygen target did not significantly improve survival to hospital discharge compared with the high oxygen target	94
CABG surgery	Onur et al. (2022)	Elective CABG surgery	100	FiO_2 ≥40% to maintain PaO_2 of 100–180 mmHg versus FiO_2 of 100% to maintain PaO_2 ≥180 mmHg	Hyperoxaemia during CABG surgery delayed extubation and was associated with worse postoperative, late-term cognitive function compared with normoxaemia	104
	Shaefi et al. (2021)	Aged ≥65 years undergoing CABG surgery with cardiopulmonary bypass	100	FiO_2 ≥35% or to maintain a PaO_2 >70 mmHg versus FiO_2 of 100% throughout the surgery	Intraoperative normoxia did not reduce postoperative cognitive dysfunction compared with intraoperative hyperoxia	105

CABG, coronary artery bypass graft; CVD, cardiovascular disease; FiO_2, fraction of inspired oxygen; MI, myocardial infarction; PaO_2, partial pressure of oxygen; RCT, randomized controlled trial; SpO_2, oxygen saturation.

Table 2 |

Ongoing clinical trials comparing liberal versus conservative oxygen strategies for treatment of adult patients

Trial name	Clinical trial number	Patient population	Purpose of study
REOX	NCT01881243	Adult patients resuscitated from cardiac arrest	To determine whether the degree and duration of hyperoxia after return of spontaneous circulation from cardiac arrest is associated with the degree of neurological disability at hospital discharge
HOBIT	NCT02407028	Patients with traumatic brain injury	To determine whether hyperoxia improves the outcome of patients with acute traumatic brain injury
ROCS	NCT02361944	Patients undergoing cardiac surgery with cardiopulmonary bypass	To determine whether maintenance of normoxia during cardiac surgery (physiological oxygenation) reduces kidney injury and oxidative damage compared with hyperoxygenation
O2-ICU	NCT02321072	Patients admitted to ICU with ≥2 positive criteria for SIRS and an expected ICU stay of >48 h	To determine the short-term and long-term effects of two different PaO_2 targets (75 mmHg and 120 mmHg) on circulatory status, organ dysfunction and outcomes
HO2T or NO2T	NCT02378545	Adult patients with sepsis presenting to the emergency department by ambulance	To determine whether delivery of high-flow oxygen (hyperoxic oxygen therapy) compared with titrated oxygen therapy (normoxic oxygen therapy) reduces mortality at 90 days
ROXAMI	NCT04803864	Patients with acute ST-segment elevation myocardial infarction	To determine the efficacy and safety of early and short-term administration of roxadustat (a HIF activator) for the treatment of acute ST-segment elevation myocardial infarction

HIF, hypoxia-inducible factor; ICU, intensive care unit; PaO_2, partial pressure of oxygen; SIRS, systemic inflammatory response syndrome.