

## VIEWPOINT

# Supplementary oxygen for nonhypoxemic patients: O<sub>2</sub> much of a good thing?

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### Abstract

Supplementary oxygen is routinely administered to patients, even those with adequate oxygen saturations, in the belief that it increases oxygen delivery. But oxygen delivery depends not just on arterial oxygen content but also on perfusion. It is not widely recognized that hyperoxia causes vasoconstriction, either directly or through hyperoxia-induced hypocapnia. If perfusion decreases more than arterial oxygen content increases during hyperoxia, then regional oxygen delivery decreases. This mechanism, and not (just) that attributed to reactive oxygen species, is likely to contribute to the worse outcomes in patients given high-concentration oxygen in the treatment of myocardial infarction, in postcardiac arrest, in stroke, in neonatal resuscitation and in the critically ill. The mechanism may also contribute to the increased risk of mortality in acute exacerbations of chronic obstructive pulmonary disease, in which worsening respiratory failure plays a predominant role. To avoid these effects, hyperoxia and hypocapnia should be avoided, with oxygen administered only to patients with evidence of hypoxemia and at a dose that relieves hypoxemia without causing hyperoxia.

*... the aim of oxygen therapy should be to increase the delivery of oxygen rather than to reach any arbitrary concentration in the arterial blood.*

EJM Campbell [1]

Is administration of oxygen, the most widely prescribed drug in the formulary, free of risks to nonhypoxemic patients with regional ischemia? Hyperoxia marginally increases the arterial blood oxygen content (CaO<sub>2</sub>),

theoretically increasing tissue oxygen delivery (DO<sub>2</sub>) assuming no reduction in tissue blood flow. However, oxygen causes constriction of the coronary, cerebral, renal and other key vasculatures – and if regional perfusion decreases concomitantly with blood hyperoxygenation, one would have a seemingly paradoxical situation in which the administration of oxygen may place tissues at increased risk of hypoxic stress. Any tissue damage in the course of oxygen administration would plausibly be attributed to the underlying disease process. Ascribing hypoxic damage to oxygen administration is counter-intuitive and is difficult to accept without a receptive mindset. Considering the ubiquity of oxygen therapy, the continued low threshold for its administration, and the widespread belief that its use is justified and safe [2,3], we believe it is important to revisit the arguments made to justify the *status quo*.

Owing to the vasoconstrictor effects on the coronary, cerebral, renal and other key vasculatures, there are many scenarios in which administration of oxygen decreases the perfusion to vital organs to a greater extent than the small increase in CaO<sub>2</sub>, thereby actually reducing DO<sub>2</sub>. The calculated CaO<sub>2</sub> increases with normobaric hyperoxia (assuming all hemoglobin is already saturated) by only 0.03 ml/l per mmHg. With increases in alveolar PaO<sub>2</sub> from 100 to 600 mmHg, CaO<sub>2</sub> increases by 15 ml/l, or about ~7.5% assuming a hemoglobin concentration of 150 g/l.

In healthy adults, hyperoxia decreases cerebral blood flow by 11 to 33% [4,5]. Administration of high oxygen concentrations is therefore likely to decrease brain DO<sub>2</sub>. Despite this known effect of hyperoxia on cerebral blood flow, and the published recommendations [6], patients with stroke – even those with satisfactory arterial saturations – are routinely administered oxygen [4]. Does this matter? Possibly. Although Singhal and colleagues reported transient improvement in patients with ischemic strokes [7], survival at 7 months for patients with mild or moderate strokes is significantly greater in those administered air than in those given 100% oxygen for the first 24 hours after the event [8].

Hyperoxia-induced decreases in regional DO<sub>2</sub> are not confined to the brain. Normobaric hyperoxia reduces

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coronary blood flow by 8 to 29% in normal subjects and in patients with coronary artery disease or chronic heart failure [9]. The reduction in coronary artery flow is associated with a reduction in myocardial  $\text{DO}_2$  and oxygen consumption [10]. These effects may explain disturbing findings in patients with coronary artery disease. As early as 1950 Russek and colleagues reported that supplemental oxygen failed to reduce electrocardiographic signs of ischemia or reduce anginal pain in patients with myocardial infarction [11]. In 1969 Bourassa and colleagues proposed that hyperoxia-induced decreases in coronary blood flow provoke myocardial ischemia in patients with severe coronary artery disease [12]. Then in 1976, in a double-blind randomized controlled trial, Rawles and Kenmure reported greater serum aspartate aminotransferase levels, indicating increased infarct size, in patients with acute myocardial infarction receiving high-flow oxygen compared with room air [13]. They also observed a nonsignificant tripling of the death rate in those patients.

Given these concerns, the Emergency Oxygen Guideline Group of the British Thoracic Society called for 'large randomised trials of oxygen therapy for non-hypoxaemic patients with acute cardiac and cerebral ischaemia' [14]. Conti, in a recent editorial [15], reminded readers that that there is only level C evidence for the administration of supplemental oxygen to patients with uncomplicated ST elevation in myocardial infarction during the first 6 hours [16]. Based on currently available evidence, the UK National Institute for Health and Clinical Excellence guidelines have recently emphasized that 'supplementary oxygen should not be routinely administered to patients with acute chest pain of suspected cardiac origin, but that oxygen saturation levels should be monitored and used to guide its administration' [17]. Similar cautions have been expressed about the use of oxygen for the treatment of traumatic brain injury [18].

The mechanisms by which hyperoxia causes systemic vasoconstriction remain uncertain. Recent work focuses on the inhibition of vasodilators (prostaglandins, nitric oxide) by reactive oxygen species generated as a result of the hyperoxia [19-23]. Other work suggests that reactive oxygen species activate brainstem respiratory neurons [24], but this suggestion needs to be established as occurring under normobaric conditions. The role of hyperoxia-induced hypocapnia (that is, the reverse Haldane effect) remains contentious [3,25]. Regardless of the underlying mechanism(s), the importance of considering the effects of both  $\text{PaO}_2$  and  $\text{PaCO}_2$  on vascular tone is evident in a study in which both hyperoxia and hypocapnia independently increased cerebrovascular resistance and reduced cerebral blood flow [5]. Indeed, in some situations, the vasoconstrictive effects of hyperoxia may be predominantly due to the concomitant hypocapnia

[25,26]. Positron emission tomography provides similar results: the reduction of cerebral blood flow and the increase in oxygen extraction during inhalation of 100% oxygen is completely reversed when subjects breathe carbogen (5% carbon dioxide, 95% oxygen) [27]. These observations emphasize the importance of independent control of arterial  $\text{PCO}_2$  and  $\text{PO}_2$  – possibly using dynamic forcing of alveolar gases (for example [28]) or sequential gas delivery (for example [29]) – when studying the independent effects of  $\text{PO}_2$  and  $\text{PCO}_2$  on regional perfusions. These observations also suggest that adding carbon dioxide to oxygen may offset the vasoconstriction due to hyperoxia or hypoxia-induced hypocapnia.

There are other clinical situations in which the routine administration of high-concentration oxygen may lead to worse outcomes, although primarily through mechanisms other than changes in regional perfusion. Austin and colleagues recently reported in a randomized controlled trial that patients with acute exacerbations of chronic obstructive pulmonary disease have a twofold to fourfold increased mortality when treated with high-flow oxygen compared with oxygen titrated to result in an arterial oxygen saturation between 88 and 92% [30]. Although several mechanisms may account for these findings [31], worsening respiratory failure is probably the predominant mechanism. Of the patients whose arterial blood gases were measured within 30 minutes of presentation to hospital, those who received high-concentration oxygen were more likely to have hypercapnia (mean difference  $\text{PaCO}_2$  34 mmHg) or respiratory acidosis (mean difference pH 0.12).

Adverse outcomes with hyperoxia have also been reported in critically ill patients admitted to the intensive care unit; a high  $\text{PaO}_2$  in the first 24 hours after admission is independently associated with in-hospital mortality [32]. In this study a U-shaped curve of mortality with  $\text{PaO}_2$  was observed, illustrating the risks of both hypoxia and hyperoxia. Kilgannon and colleagues recently reported that patients administered high-concentration oxygen resulting in hyperoxia ( $\text{PaO}_2 >300$  mmHg) following cardiac arrest have increased in-hospital mortality, a finding they attributed to increased oxidative stress associated with hyperoxia [33]. However, because a subsequent study was unable to replicate these findings [34], randomized controlled trials will be required to resolve the clinical uncertainty.

Neonatal resuscitation is the clinical situation in which administration of 100% oxygen has most clearly been demonstrated to increase the risk of death [35,36]. This has resulted in a radical change in practice whereby room air rather than oxygen is now the recommended resuscitation regime [36].

Considering the ubiquity of the administration of supplemental oxygen, there are surprisingly few

randomized clinical trials that demonstrate its beneficial role when hypoxemia is absent. This may reflect the fact that its usage is so embedded in clinical practice that it is accepted as safe [2]. Nevertheless, there are some situations in which supplemental oxygen administration is useful: treatment of cluster headache [37], reducing the oxidative stress associated with colon surgery [38], and the prevention of desaturation during endoscopy [39,40]. Supplemental oxygen administration can, however, have the unintended side effect of delaying recognition by oximetry of hypoventilation [41,42]. Until recently many studies had indicated that supplementary oxygen reduced postoperative nausea and vomiting, but the current status is ambiguous (for example [43-46]). Similarly, oxygen was thought to reduce postsurgical infections – but more recent studies (see [47] for a partial summary) have cast doubt on the original findings. Moreover, ventilation with high inspired oxygen concentrations during surgery leads to subsequent impairment of pulmonary gas exchange [48-50] that may be of clinical significance [50]. Traumatic injury and compartment syndrome may appear to be obvious applications for supplementary oxygen – an increased PO<sub>2</sub> would help overcome the reductions in perfusion – but hyperbaric rather than normobaric oxygen is the treatment of choice [51-53]. Oxygen is used for the treatment of carbon monoxide poisoning [54], but this is probably less effective than it should be if the accompanying hypocapnia is not prevented [26]. In the case of breathlessness, which has long been treated with supplementary oxygen, a recent randomized double-blind controlled trial established that nasal oxygen was no better than air in relieving breathlessness and improving quality of life in palliative care patients with refractory breathlessness [55].

In conclusion, NASA managers demanded in 1986 that their counterparts at Martin-Thiokol prove that it was not safe to launch the Space Shuttle Challenger despite concerns expressed by engineers about the integrity at low temperatures of the O-rings joining the segments of the solid rocket boosters [56]. The correct question would have been: can you prove that it is safe? In the case of supplementary oxygen, failure to ask the right question reinforces complacency about its use in patients who may have regional hypoxia or ischemia but are not hypoxemic.

#### Abbreviations

CaO<sub>2</sub>, arterial blood oxygen content; DO<sub>2</sub>, oxygen delivery; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; PaO<sub>2</sub>, arterial partial pressure of oxygen; PCO<sub>2</sub>, partial pressure of carbon dioxide; PO<sub>2</sub>, partial pressure of oxygen.

#### Competing interests

SI and JAF have participated in the development of devices suitable for increasing the efficiency of oxygen delivery. The protection of the related intellectual property and distribution of income from sales (if any) follow the guidelines set by the University Health Network.

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Published: 30 June 2011

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doi:10.1186/cc10229

Cite this article as: Iscoe S, et al.: Supplemental oxygen for nonhypoxemic patients: O<sub>2</sub> much of a good thing? *Critical Care* 2011, **15**:305.