

VIEWPOINT

The potential harm of oxygen therapy in medical emergencies

Alexander D Cornet^{*1,3}, Albertus J Kooter^{1,3}, Mike JL Peters^{1,3} and Yvo M Smulders^{1,3}

Abstract

In medical emergencies, supplemental oxygen is often administered routinely. Most paramedics and physicians believe that high concentrations of oxygen are life-saving [1]. Over the last century, however, a plethora of studies point to possible detrimental effects of hyperoxia induced by supplemental oxygen in a variety of medical emergencies. This viewpoint provides a historical overview and questions the safety of routine high-dose oxygen administration and is based on pathophysiology and (pre)clinical findings in various medical emergencies.

Supplemental oxygen in cardiac emergencies

Historical overview

Few controversies benefit more from obtaining historical perspective than that of supplemental oxygen therapy, particularly in the context of cardiac emergencies. More than a century ago, it was first observed that oxygen relieved pain during episodes of angina pectoris [2]. The explanation for this phenomenon came in 1928, when hypoxia of the myocardium was described as the cause of angina [3]. Since then, numerous reports have emphasized the potential benefit of supplemental oxygen in patients with impaired coronary perfusion [4-6]. However, as early as in 1950, it was suggested that oxygen supplementation might be deleterious, as it prolonged electrocardiographic alterations during exercise tolerance testing [7]. In 1964, it was reported that breathing high concentrations of oxygen (85% to 90%) for at least 30 minutes in the first 24 hours after myocardial infarction resulted in decreased heart rate, reduced cardiac output, and increased systemic vascular resistance [8]. In 1965, administration of 40% oxygen for

20 minutes to patients in the first days following myocardial infarction resulted in a 17% decrease in cardiac output and a 5% rise in arterial blood pressure [9]. Three years later, it was confirmed that high-flow oxygen (1-hour exposure) reduced stroke volume and cardiac output and increased arterial pressure and systemic vascular resistance in patients with myocardial infarction [10]. Around the same time, a study showed that hypoxia did not affect the availability of oxygen for myocardial metabolism in normal subjects until arterial oxygen saturation fell to as low as 50% [11]. Only in patients with coronary artery disease, myocardial ischemia was observed in some patients when saturations fell below 85%. Furthermore, no evidence was found that hyperoxia improved myocardial oxygen availability or attenuated myocardial ischemia in patients with coronary artery disease. In fact, in patients with severe triple-vessel disease, administration of 6 minutes of high-flow oxygen was demonstrated to reduce coronary blood flow sufficiently to induce myocardial ischemia [12]. In 1969, Sukumalchantra and colleagues [13] made what might turn out to be a key generic observation: owing to the disproportionate reduction in cardiac output, supplemental oxygen did not increase oxygen transport in patients with arterial oxygen saturations of greater than 90%. Only when oxygen saturations were less than 90%, oxygen administration increased myocardial oxygen delivery [13].

Mechanisms linking oxygen therapy to cardiac and hemodynamic effects

The prime candidate mechanism for unintended hemodynamic effects of supplemental oxygen is coronary and systemic vasoconstriction. As noted previously, signs of vasoconstriction during hyperoxia were observed as early as the mid-1960s [8,9]. It has been postulated that reactive oxygen species (ROS) are responsible for vasoconstriction [14]. This hypothesis was first tested in patients with acute myocardial infarction. Breathing 100% oxygen for 10 minutes increased vascular resistance in the left anterior descending artery by 23%, and this increase could be prevented by co-administration of the antioxidant ascorbic acid. The diameter of the large

*Correspondence: cornet@vumc.nl

¹Department of Internal Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, PO BOX 7075, The Netherlands

Full list of author information is available at the end of the article

conduit coronary arteries was not appreciably affected, suggesting that vasoconstriction occurs at the level of the myocardial microcirculation [15]. A comparable experiment was performed in patients undergoing cardiac catheterization. Administration of 100% oxygen for 15 minutes increased myocardial perfusion resistance by an impressive 41% and consequently decreased coronary blood flow by 29%. Furthermore, the vasodilator response to acetylcholine, an endothelium-dependent vasodilator, was impaired during 100% oxygen, whereas the response to adenosine, an endothelium-independent vasodilator, was unaffected. This suggests that hyperoxia accelerates the oxidative degradation of coronary endothelium-derived nitric oxide by ROS [16]. Several animal models of hyperoxic vasoconstriction suggest that oxygen tension may influence one or more of the endothelium-derived factors responsible for maintaining vascular tone (that is, nitric oxide, endothelin, and prostaglandins) [17,18]. In isolated cardiac myocytes, it was demonstrated that hyperoxia enhances production of angiotensin-I, which is subsequently converted to angiotensin II, which in turn promotes endothelin release, thereby increasing vascular tone [19].

In the systemic circulation, effects similar to those of the coronary circulation have been observed. In 10 patients with stable congestive heart failure (CHF), hemodynamic effects of supplemental oxygen were investigated. Administration of 100% oxygen for 20 minutes was followed by a 16% decrease in cardiac output and stroke volume and a marked increase in systemic vascular resistance [20]. Again, there seems to be an important role for ROS. Both in healthy subjects as well as in patients with CHF, administration of 100% oxygen increased vascular resistance measured in the forearm, and acetylcholine-dependent vasodilation was impaired via a mechanism that could be reversed by ascorbic acid [21]. In other experiments, parameters of ventricular function, such as left ventricular end-diastolic pressure and isovolumetric relaxation, also deteriorated during 100% oxygen, but it is still unclear whether these changes are secondary to the vasoconstrictive effects in the coronary and systemic circulation or relate to direct effects of hyperoxia on the myocardium [22,23]. Additional mechanisms for hyperoxic vasoconstriction have been described in animal studies. It was demonstrated that coronary hyperoxic vasoconstriction is mediated through the closure of ATP-dependent K^+ channels [18]. Furthermore, hyperoxia can induce vasoconstriction by acting directly on L-type calcium channels present on vascular smooth muscle cells [24]. Noteworthy is that all hemodynamic changes seen in patients with CHF (decreased heart rate, cardiac output, stroke volume, and coronary sinus blood flow and increased systemic vascular resistance and left ventricular end-diastolic pressure) also occur in healthy

subjects [22,23,25]. Administration of supplemental oxygen induces a variety of potentially hazardous hemodynamic changes in patients who already are in a compromised cardiac condition.

Clinical trials in cardiac emergencies

Should we refrain from the routine use of supplemental oxygen in cardiac emergencies, or are the considerations outlined above sufficiently outweighed by an intuitive impetus that supplemental oxygen is beneficial? Clinical trials addressing the question of whether oxygen should be administered during acute myocardial infarction are scarce. In 1976, a double-blind randomized controlled trial was performed in 200 consecutive patients (younger than 65 years old) who were admitted with suspected acute myocardial infarction [26]. Patients with CHF, chronic pulmonary disease, or breathlessness from any cause other than acute myocardial infarction were excluded. Patients were randomly assigned to receive either oxygen or compressed air at a flow rate of 6 L/minute for a total of 24 hours. The mean partial arterial oxygen tension (PaO_2) was significantly higher in the group receiving oxygen. In that group, 9 out of 80 (11.3%) patients died as compared with 3 out of 77 (3.9%) in the compressed air group, corresponding with a relative mortality risk of 2.9 (95% confidence interval (CI) 0.8 to 10.3, $P = 0.08$) [26]. A trial similar by design, but open-label, reported that 1 out of 58 (1.7%) patients died in the group treated with oxygen (4 L/minute) versus 0 out of 79 patients in the group receiving ambient air; however, the duration of oxygen exposure is not reported [27]. A recent Cochrane review meta-analyzed available studies on oxygen therapy in patients with acute myocardial infarction. Combining the two aforementioned studies generated a relative risk (RR) of mortality of 3.03 (95% CI 0.93-9.83, $P = 0.06$) [28].

As noted previously, high concentrations of oxygen have significant adverse hemodynamic effects in patients with stable CHF. Although one of these hemodynamic studies had a randomized double-blind design [23], we found no epidemiological studies of supplemental oxygen therapy in CHF with clinical endpoints. In summary, in both acute ischemic cardiac syndromes and CHF, experimental evidence appears to argue against the use of supplemental oxygen therapy.

Oxygen therapy in non-cardiac emergencies **Chronic obstructive pulmonary disease**

In chronic obstructive pulmonary disease (COPD), the dangers of oxygen supplementation, particularly in terms of carbon dioxide retention, are more widely appreciated. Administration of oxygen in patients with COPD may cause hypercapnic acidosis as a consequence of increased ventilation/perfusion-mismatch, the Haldane effect,

resorption atelectasis, and inhibition of hypoxic drive [29]. The number of COPD patients who rely entirely on hypoxic drive is, however, relatively small.

Recently, a randomized trial compared treatment with high-concentration oxygen with titrated oxygen treatment in a pre-hospital setting in 405 patients with a presumed acute exacerbation of COPD. Mortality was significantly lower in patients receiving titrated oxygen rather than high-concentration oxygen (RR 0.42, 95% CI 0.20 to 0.89). In the subgroup of patients with confirmed COPD (n = 214), mortality reduction was even stronger (RR 0.22, 95% CI 0.05 to 0.91) [30].

Stroke

Hyperoxia can cause vasoconstriction of the carotid and downstream cerebral arteries. In healthy humans, administration of 100% oxygen during 10 to 15 minutes is associated with a 20% to 33% decrease in cerebral blood flow independently of arterial partial pressure of carbon dioxide (PaCO₂) [31,32]. Routine administration of supplemental oxygen to patients with stroke has been questioned. A randomized trial suggested that hyperbaric oxygen therapy in acute ischemic stroke may be harmful as measured by stroke severity scores [33]. In a Cochrane analysis on the effects of hyperbaric oxygen in acute ischemic stroke, no effects on mortality or functional disability could be demonstrated [34]. With regard to normobaric oxygen treatment in ischemic stroke, three randomized trials were performed. An Indian trial showed no benefit in clinical performance scores or outcome [35]. Secondly, a Scandinavian trial found lower survival at 1 year (odds ratio (OR) 0.45, 95% CI 0.23 to 0.90) in non-hypoxic patients with mild or moderate strokes who had received supplemental oxygen as part of the initial treatment [36]. Thirdly, because excess mortality was found in the hyperoxia group (40% versus 17%, *P* = 0.013 (own calculation), a randomized trial was terminated in 2009 after 85 patients with acute ischemic stroke were enrolled [37]. Although an external monitor considered the excess mortality to be unrelated to oxygen treatment, these results are important as this is the largest randomized trial investigating oxygen treatment for ischemic stroke. In our opinion, they do not support the use of oxygen for this condition. It is remarkable that these results have not been published (yet). Guidelines from the American Stroke Association do not support the use of supplemental oxygen for most patients with acute ischemic stroke [38].

Cardiopulmonary resuscitation

Patients receiving cardiopulmonary resuscitation are often given 100% oxygen, in accordance with the 2010 guidelines for adult advanced life support [39]. To the best of our knowledge, this recommendation is not based

on epidemiological evidence. Actually, only months before this guideline was published, an observational study in 6,326 patients showed that post-resuscitation hyperoxia, defined as PaO₂ of greater than 300 mm Hg, was independently associated with a higher in-hospital mortality as compared with normoxia (OR 1.8, 95% CI 1.5 to 2.2) [40]. There is no information on the duration of high-dose oxygen exposure in this study. In a secondary analysis of these data, all patients with hypoxia (PaO₂ of less than 60 mm Hg) or severe oxygenation impairment (highest PaO₂-to-fraction of inspired oxygen ratio of less than 200 mm Hg) were excluded in order to focus on a population of patients in which oxygen exposure could potentially be reduced [41]. In this analysis, it was found that the association between supranormal oxygen tension and increased mortality was not limited to hyperoxia. A PaO₂ increase of 25 mm Hg was associated with a 6% increase in RR of death, and an increase of 100 mm Hg was associated with a 24% increase in RR of death. A threshold for harm from supranormal oxygen tension was not apparent [41]. Comparable results have been found in patients treated with mild therapeutic hypothermia after cardiac arrest [42]. Finally, in New Zealand and Australia, a comparable cohort study enrolling 12,108 patients was performed. Again, the hyperoxia group displayed a higher mortality than the normoxia group (OR 1.2, 95% CI 1.1 to 1.6) [43]. When Cox proportional hazards modeling of survival was applied, hyperoxia was not independently associated with mortality. However, no beneficial effects of hyperoxia were found [43].

In the post-resuscitation phase, there is evidence that patients surviving initial resuscitation may be managed more safely with 30% oxygen than with 100% oxygen, resulting in lower levels of neuron-specific enolase [44]. Clinically, hyperoxia is associated with poor neurological outcome following resuscitation [41,42].

Septic and hemorrhagic shock

It can be hypothesized that peripheral vasoconstriction, induced by hyperoxia, may be beneficial in septic and hemorrhagic shock, reducing the need for intravenous volume resuscitation and vasopressor requirements. Furthermore, hyperoxia exerts anti-inflammatory effects and may even have antimicrobial properties in humans [45]. To date, however, no studies have shown benefits of reaching supranormal oxygen levels. In fact, hyperoxia may impair oxygen delivery in patients with sepsis [46]. Moreover, hyperoxia decreases whole-body oxygen consumption in critically ill patients [47]. The Surviving Sepsis Campaign guidelines recommend that peripheral oxygen saturation be maintained between 88% and 95% in sepsis patients with acute respiratory distress syndrome and do not advocate hyperoxia [48]. In

hemorrhagic shock, increasing the fraction of inspired oxygen does not affect survival but does compromise hemodynamics [49].

Discussion

This viewpoint designates detrimental effects of routine administration of high-dose supplemental oxygen in a variety of medical emergencies. Not only is supplemental oxygen often part of routine practice, many guidelines support its use in several medical emergencies. For example, the US task force on decompensated CHF recommends oxygen therapy to maintain a normal oxygen saturation (at least 95% in non-COPD patients, class I recommendation, level of evidence C) [50,51]. Similarly, in patients with acute myocardial infarction, oxygen therapy is recommended not only for patients with arterial hypoxia (oxygen saturation of less than 90%) but also for those with subjective respiratory distress or high-risk features for hypoxemia [51]. The British Thoracic Society guideline for emergency oxygen use in adult patients recommends immediate administration of high-concentration oxygen in all critically ill, hypoxic non-COPD patients to achieve a target peripheral oxygen saturation of 94% to 98% [52]. These guidelines do, however, underscore that there is little or no evidence to support the recommendations.

Despite its relatively small weight (2% of total body weight), the human brain accounts for approximately 20% of the body's oxygen consumption, rendering it vulnerable to hypoxemia. Even modest hypoxemia is associated with enduring cognitive sequelae [53]. When PaO₂ falls to below 60 mm Hg, hypoxic vasodilatation occurs as a part of cerebral autoregulation [54]. Hyperoxia, on the other hand, is associated with vasoconstriction and therefore hampers cerebral perfusion [32,33]. Even mild levels of hyperoxia are associated with a decrease in perfusion of grey matter [55]. Both hyperoxia and hypoxia may be detrimental for cerebral oxygenation. A recent retrospective study in patients with traumatic brain injury showed hyperoxia and hypoxia to be equally detrimental to both mortality and functional outcomes [56].

Why would one want to provide supplemental oxygen in the first place? Firstly, if hemoglobin is fully saturated, additional oxygen only marginally increases oxygen transport capacity. For example, increasing PaO₂ from 100 to 150 mm Hg increases blood oxygen content from 200 to 201.5 mL/L [57]. Secondly, many physicians believe that oxygen administration automatically relieves the sense of breathlessness. However, hypoxemia itself hardly causes breathlessness [58]. Breathlessness is caused predominantly by hypercapnia and pulmonary mechanoreceptor stimulation, each of which shares causes with hypoxemia. Accordingly, in patients with chronic

hypoxemia, a consistent effect of supplemental oxygen inhalation on breathlessness has not been demonstrated [59,60]. In acute conditions, however, hypoxemia may lead to hyperventilation, which subsequently triggers mechanoreceptor stimulation, and thus a sense of breathlessness. Relief of breathlessness by oxygen in such acute conditions thus cannot be ruled out but awaits empirical evidence. Taking these data together, we subscribe to the words of Sir William Osler, who was skeptical of the overall benefit of oxygen but who said that oxygen supplementation 'does sometime seem to give transitory relief and to diminish cyanosis' [61]. We must acknowledge that there is a lack of well-designed, large-scale randomized clinical trials. On the other hand, the existing literature is remarkably unequivocal and certainly informative. Given the data we have, would there be absolute ethical objections to randomized clinical trials? We believe this is not the case, but the design of such trials should ensure avoidance of marked hyperoxia, unless under careful monitoring. Also, it seems prudent to study normoxia versus only moderate hyperoxia first and to move on to trials of marked hyperoxia only if moderate hyperoxia suggests benefit. Only then can we safely come to evidence-based recommendations that will tell us when to start, and particularly when to stop, administration of supplemental oxygen.

Conclusions

There are potential dangers of routine use of supplemental oxygen in patients with medical emergencies. High-dose oxygen is associated with a variety of hemodynamic alterations that may increase myocardial ischemia and impair cardiac performance. This viewpoint outlines that supplemental oxygen therapy may also be associated with adverse outcomes in several non-cardiac emergencies. The literature to date is sufficiently convincing to recommend appropriate caution in applying supplemental oxygen. Severe hypoxemia should be treated promptly but slowly with stepwise increases in oxygen concentration, avoiding arterial hyperoxemia. It appears reasonable to aim at a peripheral oxygen saturation of 90% to 94%, particularly if the clinical condition of the patient is stable at that point. More precise titration of oxygen is obviously facilitated by arterial blood gas analysis.

Abbreviations

CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; PaO₂, partial arterial oxygen tension; ROS, reactive oxygen species; RR, relative risk.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ADC and MJLP helped to conceive and design the study; to acquire, analyze, and interpret data; to draft the manuscript; to critically revise the manuscript

for important intellectual content; and to provide administrative, technical, and material support. AJK helped to conceive, design, and supervise the study; to acquire, analyze, and interpret data; to draft the manuscript; and to critically revise the manuscript for important intellectual content. YMS helped to conceive, design, and supervise the study; to draft the manuscript; and to critically revise the manuscript for important intellectual content. All authors read and approved the final manuscript.

Author details

¹Department of Internal Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, PO BOX 7075, The Netherlands. ²Department of Intensive Care Medicine, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, PO BOX 7075, The Netherlands. ³Institute of Cardiovascular Research, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, PO BOX 7075, The Netherlands.

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