Hyperoxia-Induced Hypocapnia*
An Underappreciated Risk

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Abbreviation: CBF = cerebral blood flow

Administration of supplementary O₂ is considered to be safe, as exemplified by one editorial comment¹: “Oxygen should be used as soon as possible, in as near 100% as possible in all resuscitation situations, and for the early management of injury and illness. Its use will never disadvantage [our emphasis] a patient under these circumstances.” We believe this claim merits examination.

The rationale for administering O₂ is that it increases the O₂ content of blood and, therefore, O₂ delivery to tissues. In a healthy person, hemoglobin is nearly saturated, and switching from air to pure O₂ at sea level will increase O₂ content by <10% due almost exclusively to the increase in O₂ dissolved in the plasma. In these people, the more influential determinant of O₂ delivery is tissue perfusion that is determined by perfusion pressure and local tissue vascular resistance. Vascular resistances in the brain, heart, and placenta are affected by the P₃CO₂ in arterial blood.

At issue is the existence of a strong link between hyperoxia and arterial P₃CO₂. Oxygen has long been known, but seldom recognized, to be a respiratory stimulant resulting in hypocapnia in adults²–⁶ and infants,⁷–⁹ a result confirmed by more recent work.¹⁰ While oxygen may not have this effect in patients with a limited ability to increase ventilation because of disease,¹¹ it can be expected to cause at least some hyperventilation in the vast majority of patients. This raises the possibility that hyperoxia-induced hypocapnia would cause vasoconstriction of CO₂-responsive vascular beds and paradoxically exacerbate ischemia there, if present. Furthermore, the hypocapnia increases the affinity of hemoglobin for O₂, reducing O₂ unloading to tissues. These effects are known from basic physiologic principles but are seldom emphasized in clinical texts or taken into account when O₂ administration is prescribed.

The link between hyperoxia and hyperventilation can be explained by the Haldane effect. Oxygenated hemoglobin binds less CO₂ (the Haldane effect); therefore, CO₂ transport must be maintained by increases in bicarbonate and dissolved CO₂, the latter increasing local tissue P₃CO₂. In most tissues, this is of no consequence; but in the brainstem, the location of the central chemoreceptors responsible for most of the respiratory drive,¹² the increased P₃CO₂ and, more importantly, H⁺ stimulate these receptors, increasing ventilation. This increase is greater if not blunted by the resulting arterial hypocapnia.¹⁰,¹⁵ Figure 1 illustrates this effect in a typical subject breathing sequentially air, O₂, and O₂ with P₃CO₂ returned to and maintained at control values. We now briefly discuss several clinical situations in which hyperoxia-induced hypocapnia may paradoxically not improve—or even worsen—tissue oxygenation.

Labor

Maternal hyperoxia does not necessarily improve oxygenation of the fetus.¹⁶,¹⁷ In women receiving mechanical ventilation during cesarean deliveries, increases of inspired O₂ > 50% either do not improve¹⁸ or decrease¹⁹ the Po₂ in the umbilical vein and artery; O₂ decreases uterine perfusion regardless of the woman’s clinical status.²⁰,²¹ The decline in fetal PO₂ is related to the degree of maternal hypocapnia²² despite maternal hyperoxia.²³ Most impor-
CO POISONING

Pure O₂ is the recommended acute treatment for CO poisoning. However, Takeuchi and colleagues²⁵ demonstrated that CO-exposed subjects breathing pure O₂ hyperventilate, decreasing end-tidal PCO₂ by an average of 2.8 mm Hg, a reduction that would, in the absence of any effect of CO on cerebrovascular resistance, decrease cerebral blood flow (CBF) by approximately 7% in adults and 30% in infants.²⁶,²⁸ A follow-up study²⁹ from the same laboratory showed that hyperoxia did reduce CBF and thereby cerebral O₂ delivery in CO-exposed subjects. This raises questions about the current recommended therapy, normobaric hyperoxia, for CO poisoning. Hyperbaric hyperoxia also decreases PCO₂ and CBF,³⁰–³² an effect to which the hyperoxia contributes.³³ This reduction in CBF has not been taken into account when assessing the efficacy of hyperbaric O₂ in treating CO poisoning. The risk of viewing O₂ treatment as benign (i.e., “it can’t hurt”) may result in ignoring its potential contribution to morbidity and attributing all adverse sequelae to CO alone.

STROKE

Hyperoxia, but not hyperventilation,³⁴,³⁵ continues to be advocated for treatment of strokes³⁶ but no consideration has been given to the effects of hyperoxia-induced hypocapnia. As discussed above with respect to CO poisoning, any hypocapnia-induced decrease in CBF could offset any increase in blood O₂ content and reduce actual O₂ delivery. To our knowledge, there have been no studies in man of the effects of CO₂ on the efficacy of hyperoxia in the management of stroke. However, animal studies³⁷ suggest that hypercapnia better preserves cerebral oxidative metabolism and reduces the extent of posts ischemic atrophy.

MYOCARDIAL ISCHEMIA

Breathing 100% O₂ impairs left ventricular relaxation, increases end-diastolic pressure, and decreases coronary sinus blood flow in subjects with either heart failure or normal left ventricular function.³⁸ No measurements were made of PCO₂, so it is premature to attribute these effects to hypocapnia. Nevertheless, because arterial PCO₂ affects the resistance of coronary vessels, there may be little benefit, but considerable risk, in treating myocardial ischemia with hyperoxia without measures to prevent hypocapnia. In patients with congestive heart failure, hypocapnia may explain the detrimental effects of hyperoxia on some cardiovascular parameters.¹¹

WOUND HEALING

In 2000, Greif and colleagues³⁹ described an approximate 50% reduction in the incidence of postoperative infection in patients administered 80% O₂ during and for 2 h after an operation vs those receiving 30% O₂. Tissue and wound PO₂, however, depend not just on the inspired concentration of O₂ but also on perfusion; this, in turn, is affected by the arterial PCO₂. In humans, “the skin blood flow measured on the chest decreased by an average of 8% during hyperventilation; blood flow on the hand (thenar eminence) decreased by 60%; and blood flow on the foot decreased by 51%.”⁴⁰ In contrast, hypercapnia increased tissue PO₂. This raises the question, would maintenance of normocapnia, or even slight hypercapnia, reduce wound infections or improve perfusion to ischemic chronic leg ulcers in diabetics? Hyperbaric O₂ is a useful form of treatment for chronic infections and leg ulcers,⁴¹–⁴⁴ but availability and cost limit its use⁴⁵ and are likely to do so even more as the numbers of such patients increase. For the reasons given above, preventing a fall in PCO₂ when breathing O₂, whether normobaric or hyperbaric, may increase perfusion and thereby, one hopes, aid in tissue healing.
CONCLUSION

Supplementary O₂ is typically administered without knowledge of its effect on CO₂ levels. Even when CO₂ levels can be monitored, physicians are concerned, perhaps unnecessarily, about hypercapnia and do not consider the potentially detrimental effects of hypocapnia. Moreover, simple breathing circuits to control PCO₂ during O₂ administration, such as those introduced by Severinghaus and colleagues and Banzett and colleagues, could be adapted to clinical use. The next challenge is to determine whether maintaining normocapnia, or even slight hypercapnia, during the many clinical situations in which O₂ is administered to relieve hypoxia in CO₂-responsive vascular beds confers additional benefits and improves clinical outcomes.

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