OXYGEN supplementation has traditionally been believed to increase blood and tissue oxygenation. However, hyperoxia induces bradycardia and a reduction in cardiac output, which partly offsets the otherwise increased oxygen delivery. Recently, an additional mechanism that could further reduce tissue oxygen delivery has been propounded. Experiments in animals and normal humans have suggested that breathing very high concentrations of oxygen can cause an increase in ventilation.\(^1\)\(^-\)\(^4\) Proposed mechanisms for this include increased production of reactive oxygen species directly stimulating brain stem carbon dioxide chemoreceptors,\(^5\) oxygen disinhibition of an inhibitory input present during normoxia,\(^6\) and increased brainstem partial pressure of carbon dioxide \((P_{CO_2})\) secondary to the Haldane effect. As a result of the observed ventilatory effects of oxygen, it has been speculated that hypocapnia ensuing from hyperoxia-induced hyperventilation can reduce organ blood flow sufficiently to cause hypoxia.\(^7\) This notion is now being used by some clinicians for clinical decision making and has been published in the clinical literature.\(^8\)

During hyperoxia, the solubility of carbon dioxide in blood is reduced. This is known as the Haldane effect and is a result of the displacement of carbon dioxide from hemoglobin by oxygen. As a result, it has been argued that this decrease in carbon dioxide solubility causes \(P_{CO_2}\) in both venous blood and tissue to increase. Hyperventilation should ensue due to increased \(P_{CO_2}\) and proton accumulation in the brainstem, causing stimulation of the central chemoreceptors. It has been hypothesized that this hyperventilation would lead to arterial hypocapnia, and hence vasoconstriction in certain vascular beds, including those in the brain. This hypothesis has been used to suggest that oxygen supplementation can, through reduced tissue blood flow, create tissue hypoxia.\(^7\)

There are multiple flaws in this argument. First, during hyperoxia blood flow is not reduced enough to offset the higher oxygen content, and oxygen delivery is enhanced.\(^9\)\(^,\)\(^10\) Second, if carbon dioxide accumulates in tissue, the resulting acidosis would tend to offset vasoconstriction. Third, although the Haldane effect might be responsible for clinically significant changes in \(P_{CO_2}\) under hypoxic conditions, in normoxia and hyperoxia modeling shows that it accounts for only very small changes in \(P_{CO_2}\) (fig. 1). Fourth, although several investigators have observed that hyperoxia can lead to hyperventilation, the evidence is not at all compelling that this hyperventilation leads to significant arterial hypocapnia as has been suggested.\(^7\) In only one study cited in the development of this hypothesis was arterial \(P_{CO_2}\) \((P_{ACO_2})\) actually measured.\(^1\) In that study, oxygen breathing was associated with a decrease in \(P_{ACO_2}\) in five of six subjects, although the effect was small (mean decrease 2.5 mmHg).\(^1\) In several other published studies, 87–100% \(O_2\) administration caused no significant change in arterial \(P_{CO_2}\) by direct measurement.\(^9\)\(^-\)\(^21\) Even 100% \(O_2\) administration up to 3 atmospheres absolute (ATA) does not cause arterial hypocapnia.\(^10\)\(^,\)\(^22\) In a study of normal volunteers studied while breathing room air at 1 ATA and 100% \(O_2\) at 3 ATA, \(P_{ACO_2}\) was 37 ± 2.9 and 36 ± 2.6 mmHg (mean ± SD), respectively.\(^22\) In other studies at 3.5 ATA, mild hypocapnia (mean decrease 5 mmHg) has been observed\(^14\); however, at such extreme oxygen partial pressure \((P_{O_2})\) values (approximately 2,100 mmHg), hyperventilation due to direct toxic effects is likely.\(^5\)

The evidence for oxygen-induced hypocapnia is based either on observations of increased ventilation only, or on reduced end-tidal \(P_{CO_2}\) \((P_{ETCO_2})\).\(^1\)\(^,\)\(^4\) There are plausible mechanisms that account for these findings that involve the lung directly. For instance, exposure to high oxygen concentrations causes atelectasis, which could cause a decrease in lung compliance and a reflex increase in

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ventilation. Also associated with atelectasis is an increase in the proportion of gas exchange units with low ventilation/perfusion ratios (V̇A/Q̇) or shunt. This would initiate an increase in ventilation to maintain PaCO₂ within the normal range. Indeed, in an investigation of ventilation/perfusion distributions in normal volunteers using multiple inert gas elimination, 100% O₂ breathing caused gas exchange abnormalities consistent with an increase in physiologic dead space (fig. 2), which explained the observed increase in ventilation in the face of unchanged PaCO₂. Rehder et al. did not observe any change in V̇A/Q̇ distribution during 100% O₂ breathing, nor did they observe hyperventilation or hypocapnia.

Although PETCO₂ is a good estimate of PaCO₂ under some circumstances, when an intervention (e.g., increased fraction of inspired oxygen) changes the relation between arterial and end-tidal carbon dioxide, the assumption of parity cannot be relied upon. For example, in the setting of increased dead space, PETCO₂ would underestimate PaCO₂.

During oxygen-induced increases in dead space, the addition of carbon dioxide to “normalize” end-tidal carbon dioxide (“normocapnic hyperoxia”) is likely to cause arterial hypercapnia, which will further increase ventilation. In one study carbon dioxide was added to high oxygen breathing mixtures to maintain constant PETCO₂, and not surprisingly, there was a twofold increase in ventilation. As expected, the ventilatory response to hypercapnia in that study correlated linearly with the ventilatory response to “isocapnic” hyperoxia.

Tissue oxygenation in humans is difficult to measure in vitro, but can be assessed by measurement of venous PO₂ and oxygen content and by near-infrared techniques. Direct measurements of both types indicate that breathing high oxygen concentrations increases both venous and tissue oxygenation. Arguments have been proposed suggesting that oxygen breathing has detrimental effects in specific tissues and clinical scenarios. However, the evidence is unconvincing for the following reasons.

**Brain**

Breathing 100% O₂ increases arterial PO₂ and jugular bulb PO₂. In a study of normal volunteers, jugular venous PO₂ and oxygen content measurements (indices of brain PO₂) have been made during air and 100% O₂ breathing under normal and hyperbaric conditions. During 100% O₂ breathing at 1 ATA, jugular venous PO₂ increased from 37 to 40 mmHg (5% increase in O₂ content). Moreover, direct measurements of brain oxygenation indicate that brain PO₂ increases with arterial PO₂. Several other studies demonstrate that oxygen breathing increases cerebral oxygenation. The notion that ox-
ygen breathing causes cerebral hypoxia\textsuperscript{7} was based on two studies, one that indirectly assessed middle cerebral artery velocity and one that did not measure arterial oxygen content\textsuperscript{12} or account for the expected increase in dissolved oxygen (approximately 10% with 100% O\textsubscript{2}). Although oxygen administration results in reduced cerebral blood flow through generation of reactive oxygen species, which deplete nitric oxide,\textsuperscript{29,33} there is overwhelming evidence that the increase in arterial oxygen content more than offsets the decrease in brain perfusion.

The same argument has been made regarding oxygen supplementation causing reduced oxygen delivery during stroke.\textsuperscript{7} Given loss of autoregulation in the ischemic brain, it is unlikely that oxygen or even hypocapnia would reduce blood flow, and there is no evidence that it causes brain hypoxia. In patients with stroke, systematic reviews indicate that supplemental oxygen is beneficial in hypoxemia and is not harmful even in its absence.\textsuperscript{34}

**Fetus**

The bulk of evidence shows that administering up to 100% O\textsubscript{2} during labor and delivery will increase fetal oxygenation and can be used routinely without fear of fetal harm. However, it has been proposed that oxygen breathing by laboring mothers may reduce uterine perfusion and fetal PO\textsubscript{2}.\textsuperscript{7} This is based on the hypothesis that supplemental oxygen results in hypocapnia and reduced uterine perfusion \textit{via} the mechanisms described above. In one study of healthy pregnant women at greater than 35 weeks' gestation, the administration of 100% oxygen caused hyperventilation and a reduced PETCO\textsubscript{2}.\textsuperscript{25} However, in the same study, hyperoxia caused no change in either uterine or umbilical artery pulsatility index, except when the authors added carbon dioxide to their breathing gas to "correct" for decreased PETCO\textsubscript{2}. Furthermore, in several studies of parturients, oxygen administration caused no change in directly measured maternal PaCO\textsubscript{2}.\textsuperscript{11-15,19,16}

Two studies cited in support of the notion of fetal hypoxia induced by maternal hyperoxia were in mechanically ventilated women undergoing cesarean delivery. Both studies reported the PO\textsubscript{2} in umbilical vein\textsuperscript{35,36} and artery\textsuperscript{36} as a function of maternal inspired oxygen concentration. In both, umbilical PO\textsubscript{2} increased up to 50-65% inspired oxygen, but the incremental effect of higher concentrations could not be established because of poor maternal PO\textsubscript{2} control and insufficient statistical power. However, most studies have shown that peripartum administration of oxygen increases fetal oxygenation.\textsuperscript{11-15,19,16,37} Furthermore, with increasing maternal inspired oxygen concentration up to 100%, there is evidence of a dose related increase in fetal oxygenation

**Myocardium**

Although the increase in systemic vascular resistance associated with oxygen breathing can have adverse effects in patients with impaired left ventricular function, in most patients with myocardial ischemia or infarction, the overall effect of supplemental oxygen is beneficial. In a physiologic study in dogs, oxygen administration (PO\textsubscript{2} = 0.6 and 3.0 ATA) caused an increase in arterial and coronary sinus oxygen content with no adverse effect on myocardial function.\textsuperscript{40} In a study of humans with and without coronary artery disease, administration of 10-15 l/min oxygen caused a significant increase in coronary artery and coronary sinus oxygen content (mean increase 2.1 vol% in subjects without coronary disease and 2.9 vol% in subjects with coronary disease).\textsuperscript{41} Published evidence supports the use of oxygen supplementation for myocardial infarction or ischemia.\textsuperscript{41-44} Based on systematic reviews of the evidence, both American and European guidelines recommend it as first aid treatment for all patients with acute coronary syndromes.\textsuperscript{45,46}

**Carbon Monoxide Poisoning**

A major mechanism of carbon monoxide toxicity is tissue hypoxia due to binding of carbon monoxide to hemoglobin, myoglobin, and other hemoproteins, and inhibition of electron transport at cytochrome a,a\textsubscript{3}. Tis-
sue damage or death results from hypoxia, oxidative stress, and other secondary mechanisms. Very high oxygen displaces carbon monoxide from heme-protein binding sites. Hyperbaric oxygen is the definitive treatment for carbon monoxide poisoning. However, proponents of the “oxygen decreases PO2” idea have argued that reduced cerebral blood flow caused by oxygen supplementation may contribute to morbidity. On the contrary, oxygen breathing shortens the half-life of carbon monoxide-bound hemoglobin and has other beneficial pharmacologic effects including the attenuation of oxidative stress. It has been suggested that carbogen (oxygen-carbon dioxide mixtures) may be superior to pure oxygen because the addition of carbon dioxide to the breathing mixture would normalize the PCO2. However, there is no evidence that oxygen administration to patients with carbon monoxide poisoning would exaggerate the hypocapnia already present during carbon monoxide hypoxia. The observation that carbogen administration facilitates carbon monoxide elimination relative to oxygen alone is an old one, an effect attributable to both stimulation of respiration by hypercapnia and reduction of carbon monoxide-hemoglobin affinity due to the decrease in pH.

Conclusions

In summary, the evidence is overwhelming that administration of supplemental oxygen to either normal subjects or patients augments blood and tissue oxygenation (fig. 4). Although normobaric hyperoxia within the clinical range can cause hyperventilation, the most plausible mechanism is related to atelectasis and the consequent ventilation/perfusion mismatching. The resulting increase in venous admixture has the effect of increasing physiologic dead space. Moreover, it is possible that the change in lung compliance produced by atelectasis could precipitate reflex-induced hyperventilation. The ensuing decrease in PETCO2 is not associated with significant arterial hypocapnia and does not cause either ischemia or hypoxia. Although there can be small effects of oxygen breathing on PaCO2, there is a consistent lack of evidence for any significant change in numerous studies using direct measurement. In the few observations supporting a decrease in PaCO2, the magnitude is small and unlikely to be of clinical significance. Clinicians can rest assured that short-term appropriate administration of high oxygen concentrations will have no adverse effects on tissue oxygenation.

References

HYPEROXIA-INDUCED TISSUE HYPOXIA

Anesthesiology, V 106, No 5, May 2007

27. Tenney SM: A theoretical analysis of the relationship between venous blood and mean tissue oxygen pressures. Respir Physiol 1974; 20:283–96
38. Cogliano MS, Graham AC, Clark VA: Supplementary oxygen administration for elective caesarean section under spinal anaesthesia. Anaesthesia 2002; 57:66–9
42. Kelly RF, Hursey TL, Parrillo JE, Scharl GC: Effect of 100% oxygen administration on infant size and left ventricular function in a canine model of myocardial infarction and reperfusion. Am Heart J 1995; 130:957–65