■ CLINICAL CONCEPTS AND COMMENTARY

Hyperoxia-induced Tissue Hypoxia

A Danger?

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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} (Pa_{CO_2}) actually measured.[1] In that study, oxygen breathing was associated with a decrease in Pa_{CO_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, Pa_{CO_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
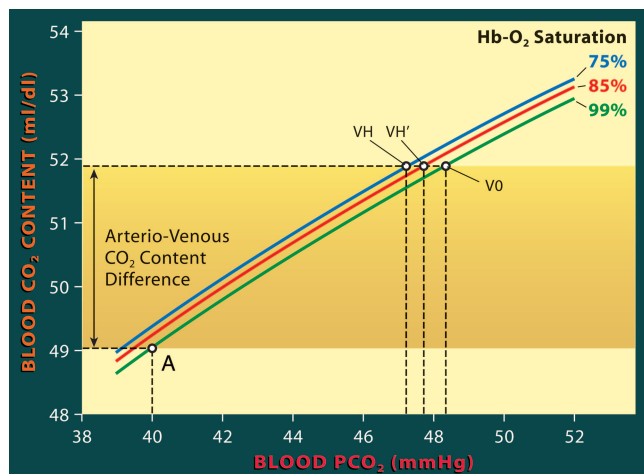
Fig. 1. Haldane effect. Blood carbon dioxide content is drawn as a function of partial pressure of carbon dioxide (P_{CO_2}) for three different oxygen saturations, assuming a hemoglobin concentration of 12 g/dl, cardiac output of 5 l/min, and an arterio-venous carbon dioxide content difference of 2.8 ml/dl. Values are calculated from the equations of Douglas *et al.*[53] and Kelman,[54] assuming $\Delta[H^+] = 0.77 \cdot \Delta P_{CO_2}$.[55] Point *A* represents the arterial blood. Without the Haldane effect, the venous point would be at *V0*, representing a venous P_{CO_2} of approximately 48.3 mmHg. However, because the venous hemoglobin–oxygen saturation ($S\bar{v}O_2$) is lower (approximately 75%), the Haldane effect allows an increase in carbon dioxide capacity of whole blood, resulting in a P_{CO_2} approximately 1.2 mmHg lower than *V0*, shown at venous point *VH*. When breathing 100% O_2, the attenuated Haldane effect should cause an increase in venous P_{CO_2}. However, calculations show that the increase is very small. Assuming that the venous oxygen saturation while breathing 100% O_2 is 85%, with unchanged cardiac output, the blunted Haldane effect would result in only a minor increase in venous P_{CO_2} (shown at point *VH'*) of approximately 0.5 mmHg.
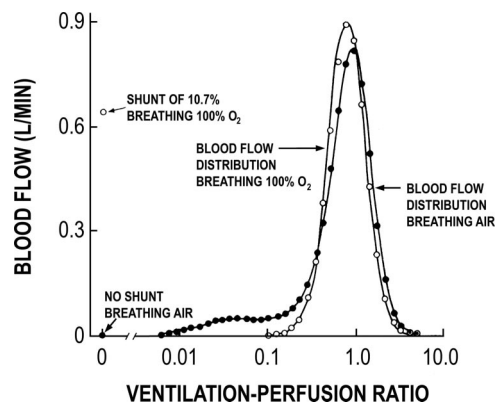

Fig. 2. Effect of 100% oxygen breathing on ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$). Depicted are two curves, each representing the distribution of blood flow as a function of $\dot{V}_A/\dot{Q}$ in a 44-yr-old normal male volunteer. The data are derived from the technique of multiple inert gas elimination, from which a 50-compartment model of $\dot{V}_A/\dot{Q}$ has been derived.[17] The *closed circles* represent the blood flow distribution breathing air, and the *open circles* represent the blood flow distribution breathing 100% O_2. The population of gas exchange units with low $\dot{V}_A/\dot{Q}$ ratios (in the region 0.01–0.1) breathing air has disappeared during oxygen breathing and been replaced by a 10.7% shunt, most likely reflecting blood flow through atelectatic areas. The Bohr dead space/tidal volume ratio increased from 40% to 57%. Redrawn from Wagner *et al.*,[17] with permission.

ventilation.[23] Also associated with atelectasis is an increase in the proportion of gas exchange units with low ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$) or shunt.[24] This would initiate an increase in ventilation to maintain Pa_{CO_2} within the normal range. Indeed, in an investigation of ventilation/perfusion distributions in normal volunteers using multiple inert gas elimination, 100% O_2 breathing caused gas exchange abnormalities consistent with an increase in physiologic dead space (fig. 2),[17] which explained the observed increase in ventilation in the face of unchanged Pa_{CO_2}. Rehder *et al.*[20] did not observe any change in $\dot{V}_A/\dot{Q}$ distribution during 100% O_2 breathing, nor did they observe hyperventilation or hypocapnia.

Although P_{ETCO_2} is a good estimate of Pa_{CO_2} 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, P_{ETCO_2} would underestimate Pa_{CO_2}.

During oxygen-induced increases in dead space, the addition of carbon dioxide to "normalize" end-tidal carbon dioxide ("normocapnic hyperoxia")[25] 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 P_{ETCO_2}, and not surprisingly, there was a twofold increase in ventilation.[1] 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 vivo*, but can be assessed by measurement of venous P_{O_2} and oxygen content[26,27] 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.[7] However, the evidence is unconvincing for the following reasons.

Brain

Breathing 100% O_2 increases arterial P_{O_2} and jugular bulb P_{O_2}. In a study of normal volunteers, jugular venous P_{O_2} and oxygen content measurements (indices of brain P_{O_2})[27] have been made during air and 100% O_2 breathing under normal and hyperbaric conditions.[14] During 100% O_2 breathing at 1 ATA, jugular venous P_{O_2} increased from 37 to 40 mmHg (5% increase in O_2 content).[14] Moreover, direct measurements of brain oxygenation indicate that brain P_{O_2} increases with arterial P_{O_2}.[28] Several other studies demonstrate that oxygen breathing increases cerebral oxygenation.[28-31] The notion that ox-

ygen breathing causes cerebral hypoxia[7] was based on two studies, one that indirectly assessed middle cerebral artery velocity and one that did not measure arterial oxygen content[32] or account for the expected increase in dissolved oxygen (approximately 10% with 100% O_2). Although oxygen administration results in reduced cerebral blood flow through generation of reactive oxygen species, which deplete nitric oxide,[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.[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.[34]

Fetus

The bulk of evidence shows that administering up to 100% O_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_2.[7] This is based on the hypothesis that supplemental oxygen results in hypocapnia and reduced uterine perfusion *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 $Petco_2$.[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 $Petco_2$. Furthermore, in several studies of parturients, oxygen administration caused no change in directly measured maternal $Paco_2$.[11–13,15,16]

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_2 in umbilical vein[35,36] and artery[36] as a function of maternal inspired oxygen concentration. In both, umbilical Po_2 increased up to 50–65% inspired oxygen, but the incremental effect of higher concentrations could not be established because of poor maternal Pco_2 control and insufficient statistical power. However, most studies have shown that peripartum administration of oxygen increases fetal oxygenation.[11–13,15,16,37] Furthermore, with increasing maternal inspired oxygen concentration up to 100%, there is evidence of a dose related increase in fetal oxygenation
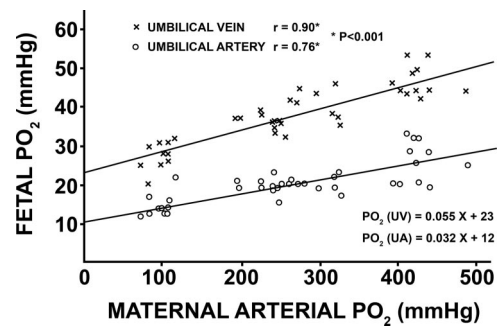

Fig. 3. Umbilical artery and vein blood gas values as a function of maternal inspired oxygen concentration. Administration of oxygen (fractional concentration of oxygen 0.21, 0.47, 0.74, or 1.0) to women undergoing elective cesarean delivery during epidural anesthesia resulted in a dose-related increase in partial pressure of oxygen (Po_2) in both the umbilical vein (UV) and artery (UA). Maternal partial pressure of carbon dioxide (Pco_2) values were, at the four inspired oxygen concentrations, respectively, 27.6 ± 1.2, 29.3 ± 0.8, 29.2 ± 1.05, and 28.6 ± 0.5 mmHg (mean ± SEM). Graph redrawn from Ramanathan *et al.*,[16] with permission.

(fig. 3).[15,16] Supplemental oxygen is associated with either no significant change in maternal or umbilical vessel Pco_2[13,38] or a slight increase in umbilical vein and artery Pco_2,[16] and no negative effect on fetal outcomes.[13,16,38,39]

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_2 = 0.6 and 3.0 ATA) caused an increase in arterial and coronary sinus oxygen content with no adverse effect on myocardial function.[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).[41] Published evidence supports the use of oxygen supplementation for myocardial infarction or ischemia.[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.[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_3. Tis-

AIR

	Carotid Artery	Jugular Vein
PO_2	100	37
PCO_2	40	50
pH	7.40	7.34
HbO_2	96%	65.5%

	Arterial	Mixed Venous
PO_2	100	40
PCO_2	40	44
pH	7.40	7.37
HbO_2	97%	72%

	Umbilical Artery	Umbilical Vein
PO_2	15	28
PCO_2	44	35
pH	7.33	7.37
HbO_2	26%	65%

100% OXYGEN

	Carotid Artery	Jugular Vein
PO_2	500	40
PCO_2	38	51
pH	7.40	7.34
HbO_2	100%	68.5%

	Arterial	Mixed Venous
PO_2	500	50
PCO_2	38	42
pH	7.40	7.38
HbO_2	100%	84%

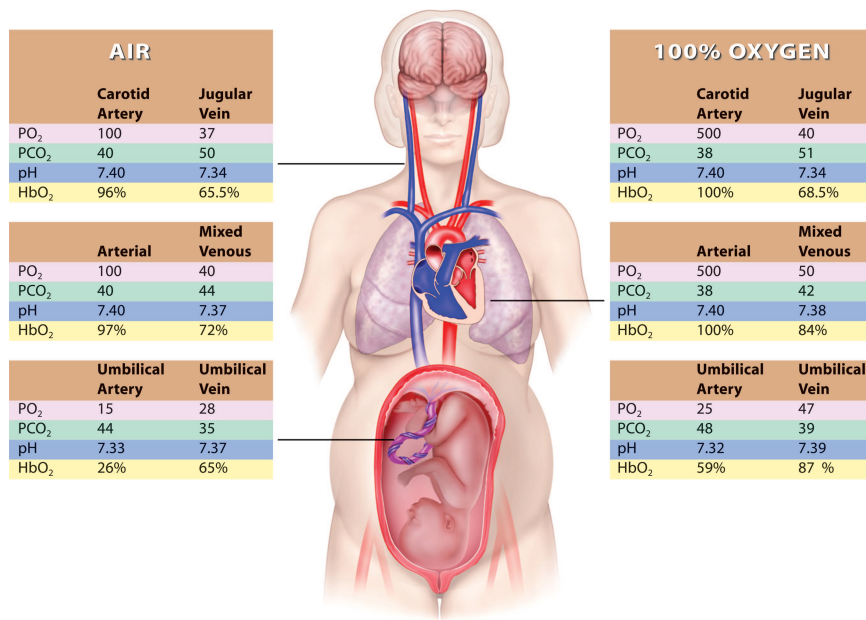|	Umbilical Artery	Umbilical Vein
PO_2	25	47
PCO_2	48	39
pH	7.32	7.39
HbO_2	59%	87 %

Fig. 4. Typical arterial and venous blood gas values. Typical values have been taken from published data[9,10,14,16] and clinical observations. Umbilical artery and vein blood gas values are from Ramanathan *et al.*[16] Note that in that study, maternal arterial partial pressure of carbon dioxide (PCO_2) was lower than the typical adult value shown above (mean 27.6 mmHg while breathing air, 28.6 mmHg while breathing 100% O_2). PO_2 = partial pressure of oxygen; HbO_2 = hemoglobin–oxygen saturation.

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.[47] However, proponents of the "oxygen decreases PO_2" idea have argued that reduced cerebral blood flow caused by oxygen supplementation may contribute to morbidity.[7,32] On the contrary, oxygen breathing shortens the half-life of carbon monoxide–bound hemoglobin[48] and has other beneficial pharmacologic effects including the attenuation of oxidative stress.[49,50] 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 PCO_2.[7] However, there is no evidence that oxygen administration to patients with carbon monoxide poisoning would exacerbate 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,[51,52] 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.[23] The ensuing decrease in $PETCO_2$ 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 $PaCO_2$, 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 $PaCO_2$, 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.

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