Balancing the Risks and Benefits of Oxygen Therapy in Critically Ill Adults

G. R. Scott Budinger, MD; and Gökhan M. Mutlu, MD

Oxygen therapy is an integral part of the treatment of critically ill patients. Maintenance of adequate oxygen delivery to vital organs often requires the administration of supplemental oxygen, sometimes at high concentrations. Although oxygen therapy is lifesaving, it may be associated with deleterious effects when administered for prolonged periods at high concentrations. Here, we review the recent advances in our understanding of the molecular responses to hypoxia and high levels of oxygen and review the current guidelines for oxygen therapy in critically ill patients.

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Abbreviations: HIF = hypoxia inducible factor; H₂O₂ = hydrogen peroxide; PEEP = positive end-expiratory pressure; PHD = prolyl hydroxylase; ROS = reactive oxygen species; VEGF = vascular endothelial growth factor

In 1774, Joseph Priestley¹ published his discovery of the substance that Antoine Lavoisier subsequently called “oxygen.” In his original report, Priestley recognized intuitively the double-edged nature of oxygen therapy, writing that “it might be peculiarly salutary to the lungs in certain morbid cases ... but...it might not be so proper for us in the usual healthy state of the body.”¹ Lavoisier confirmed these suspicions when he noted that all guinea pigs placed in “pure” oxygen died with “lungs that were very flaccid but very red” after several days of exposure.² By 1939, an already impressive body of literature suggested that rodents and dogs died with injury to the lungs after several days of exposure to hyperoxia.² Becker-Freyseng and Clamann,³ who were skeptical that these findings were applicable to humans, subjected themselves to 65 h of continuous hyperoxia (90% oxygen).³ After

1 day of exposure, both men complained of progressively worsening paresthesias and dyspnea and developed leukocytoses. By the end of the exposure, one of the men was hospitalized with fever, tachycardia, and a progressive drop in his vital capacity. His examination revealed “fluid in the right thorax and signs of bronchopneumonia” and his vital capacity did not recover until 6 weeks after the exposure. More rigorous confirmation of these findings in subsequent studies has left modern physicians to grapple with concern about oxygen’s toxicity in the face of its obvious clinical benefit.⁴ Detailed guidelines have been published for the monitoring of arterial oxygen saturations and the provision of oxygen therapy in acutely ill adults.⁵ The purpose of this review is to provide a background for the physician prescribing oxygen therapy to better understand the physiologic basis for these guidelines.

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Affiliations: From the Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

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Correspondence to: G. R. Scott Budinger, MD, 240 E Huron St, McGaw M300, Chicago, IL 60611; e-mail: s-budinger@northwestern.edu

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THE CELLULAR RESPONSE TO HYPOXIA

The bulk of cellular oxygen is used by mitochondria as an electron acceptor that allows adenosine triphosphate to be generated from the energy released during the oxidation of carbon in dietary sugars and fats (oxidative phosphorylation).⁶ Oxygen delivery to the mitochondria depends on the arterial oxygen content (primarily determined by the hemoglobin concentration and the oxyhemoglobin saturation), the cardiac output, the vascular supply to the tissue, and the metabolic rate of the tissue. The last is responsible for the observation that

the PO_2 of the tissues is substantially lower than the arterial blood even under normal conditions.⁷ For example, in metabolically active tissues including the liver and the kidney, diffusion gradients between the vasculature and individual cells result in a normal tissue PO_2 as low as 30 torr.⁸ The ability of cells to tolerate these levels of oxygen is explained by the finding that isolated mitochondria do not become substrate limited by oxygen until the PO_2 falls to < 1 torr.⁷ This complex interrelationship between oxygen delivery and metabolism explains how some patients with remarkably low arterial oxygen concentrations can remain clinically “stable” for prolonged periods prior to the initiation of oxygen therapy.⁹ Unlike exposure to hypoxia, ischemia resulting from vascular occlusion interrupts both oxygen and glucose delivery and prevents the clearance of CO_2 and lactate, resulting in tissue, hypoxia, hypercapnia, and acidosis.¹⁰

In response to a reduced tissue PO_2 , cells initiate an adaptive program mediated by the transcription factors hypoxia inducible factor (HIF)-1 and HIF-2. The HIFs are heterodimers composed of HIF-1 α or HIF-2 α and HIF-1 β (also known as the aryl hydrocarbon receptor nuclear translocator) (Fig 1).^{11,12} Under normoxic conditions, HIF-1 β can be found in the cytoplasm; however, HIF-1 α is nearly undetectable because it is rapidly targeted for ubiquitin-mediated degradation by its E3 ligase, the von Hippel Lindau protein.^{13,14} For the von Hippel Lindau protein to target HIF-1 α , it must be hydroxylated at specific proline residues by prolyl hydroxylases (PHDs).¹⁴ As the intra-

cellular PO_2 falls below about 30 torr,^{10,11} the activity of the PHDs (primarily PHD2^{15,16}) is inhibited, preventing the hydroxylation and subsequent ubiquitin-mediated degradation of HIF-1.¹⁷⁻²²

Once stabilized, HIFs bind to hypoxic-responsive elements in the genome to induce the transcription of hundreds of genes.²³ Although this HIF-induced program of gene expression varies as a function of cell type, in most cells, HIFs increase the expression of glycolytic genes and angiogenic factors, including vascular endothelial growth factor (VEGF).²⁴ This adaptive program promotes cellular survival and revascularization but often comes at the cost of reducing the function of the cell with respect to the tissue in which it resides (eg, reducing contractile force generation in a cardiac myocyte).²⁵ Prolonged expression of this transcriptional program can even disrupt tissue architecture. For example, the HIF-mediated release of VEGF from hypoxic cells in the retina is implicated in both diabetic retinopathy and the retinopathy of prematurity.^{26,27}

In addition to the HIF-mediated alterations in gene expression, arterial hypoxia causes physiologically important changes in the pulmonary vasculature. In most vascular beds, hypoxia-induced vasodilation increases blood flow to the hypoxic tissue.^{28,29} In contrast, the pulmonary vasculature constricts in response to hypoxia,^{28,29} which allows pulmonary blood flow to be distributed to the better-ventilated regions of the lung and, under normal conditions, ensures a ratio of ventilation to perfusion near unity. In patients with lung disease, large regions of the lung can become hypoxic, causing a significant increase in pulmonary vascular resistance, which can acutely contribute to the development of right-sided heart failure, limiting global perfusion.^{30,31} In these patients, physicians might use supplemental oxygen therapy as a pulmonary vasodilator.³² Because the pulmonary circulation is sensitive to changes in PO_2 as high as 70 to 80 torr,²⁹ the use of oxygen to vasodilate the pulmonary circulation might require the administration of a higher FIO_2 than that required to fully saturate hemoglobin.

FIGURE 1. Stabilization of HIF during hypoxia. During normoxia, HIF-1 α is hydroxylated by cellular PHDs at specific proline residues. The hydroxylated HIF-1 α molecule is recognized by its ubiquitin ligase, the VHL, which targets it for degradation in the proteasome. A fall in the local tissue oxygen concentration inhibits the activity of the PHDs, allowing for the stabilization of HIF-1 α , which forms a complex with HIF-1 β (also known as ARNT), which is translocated to the nucleus, where it binds to HREs in the genome to regulate the expression of hundreds of genes, including VEGF. ARNT = aryl-hydrocarbon nuclear translocator; HIF = hypoxia inducible factor; HRE = hypoxia inducible factor responsive element; OH = hydroxyl; PHD = prolyl hydroxylase; Ub = ubiquitin; VEGF = vascular endothelial growth factor; VHL = von Hippel Landau protein.

HYPEROXIA-INDUCED LUNG INJURY

In 1967, Kistler and colleagues³³ used electron microscopy to conduct detailed morphometric analyses of the lungs from rats exposed to hyperoxia (98.5% oxygen) for 6 to 72 h. They reported that the earliest change induced by exposure to hyperoxia was the accumulation of edema fluid in the lung interstitium, followed by progressive endothelial destruction. Although rodents exposed to hyperoxia had an increase in the number of inflammatory cells within the lungs, depletion of these cells prior to hyperoxia did not attenuate the injury, suggesting that inflammation was a

secondary event rather than a causal factor in the injury.^{34,35} In a seminal study in 1981, Freeman and Crapo³⁶ reported that hyperoxia increased the generation of reactive oxygen species (ROS) within the lungs of rodents, and the administration of an antioxidant alleviated the injury, suggesting a major role for oxidative stress in the pathogenesis of hyperoxia-induced acute lung injury.

Intracellular ROS originate as superoxide anions formed by the donation of a single electron to molecular oxygen.³⁷ The bulk of cellular ROS is produced during mitochondrial electron transport or by the nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase complex.^{37,38} The latter is a multiprotein complex that forms in the cellular membrane in response to intracellular signaling events.³⁸ Studies in genetically modified mice have confirmed the importance of both mitochondrial and NAD(P)H oxidase-derived ROS in the pathophysiology of hyperoxia-induced lung injury.^{39,40} Superoxide anions can be dismutated to hydrogen peroxide (H_2O_2) and water by the superoxide dismutases 1 and 2, and H_2O_2 can be converted to oxygen and water by the glutathione peroxidases and

by catalase. H_2O_2 can activate signaling pathways to facilitate cellular adaptation to oxidant stress.⁴¹ However, when present in excess, both the superoxide anion and H_2O_2 are highly reactive and are capable of oxidizing cellular proteins and lipids. In addition, H_2O_2 can react with nitric oxide or its metabolites to generate peroxynitrite and other reactive nitrogen species or can react with water in the presence of iron or other transition metals to form hydroxyl radicals that can damage DNA (Fig 2).⁴²

From transgenic and mouse models, investigators are developing a paradigm to explain the molecular events leading to acute lung injury in response to hyperoxia. Increased oxygen levels drive the generation of ROS from the mitochondria and other sources.^{36,39,40} These ROS directly or indirectly signal the assembly of the NAD(P)H complex at the plasma membrane in a feed forward loop that amplifies ROS generation.⁴³ These ROS also activate signaling pathways designed to defend the lung against oxidant stress. This includes activation of the transcription factor nuclear factor (erythroid-derived 2)-like 2, which induces the transcription of antioxidant genes, including

FIGURE 2. Mechanisms of hyperoxia-induced lung injury. Exposure to hyperoxia results in the generation of $O_2^{\cdot -}$ from the mitochondria and from the NAD(P)H oxidase complex. $O_2^{\cdot -}$ can be converted to H_2O_2 and water in a reaction catalyzed by SOD1, which is localized to the mitochondrial intermembrane space and cytosol, or SOD2, which is localized to the mitochondrial matrix. H_2O_2 is further reduced to oxygen and water by the GPx and by catalase expressed in the cytosol and mitochondria (indicated by *). H_2O_2 can activate adaptive signaling pathways in the cell, but when present in excess, both $O_2^{\cdot -}$ and H_2O_2 can oxidize cellular proteins and lipids or generate $ONOO^{\cdot -}$ and $OH^{\cdot}$ to cause cellular injury. GPx = glutathione peroxidases; H_2O_2 = hydrogen peroxide; NO = nitric oxide; $O_2^{\cdot -}$ = superoxide anions; $OH^{\cdot}$ = hydroxyl radicals; $ONOO^{\cdot -}$ = reactive nitrogen species; Prx(s) = peroxiredoxins; SOD = superoxide dismutase.

the cytosolic and mitochondrial superoxide dismutases and antiapoptotic genes.⁴⁴ Oxidant-dependent activation of the mitogen-activated protein kinase pathways increases the expression of antiapoptotic proteins, induces a cell cycle arrest, and activates a program of autophagy in which the cell consumes its own organelles in an attempt to maintain a sufficient supply of nutrients to survive the ensuing metabolic stress.⁴⁵⁻⁴⁸ The activation of nuclear factor κ B recruits inflammatory cells to the injured lung and further augments the expression of antiapoptotic proteins in the cell.⁴⁹

Despite these measures, the continued production of ROS activates both apoptotic and necrotic pathways to cause epithelial cell death.⁵⁰ Simultaneously, the high concentrations of oxygen prevent the oxidant-mediated inhibition of PHDs that target HIFs for degradation.²⁷ The resulting loss of growth factors, particularly VEGF, contributes to the death of the alveolar endothelium.^{51,52} The loss of alveolar epithelial and endothelial cells contributes to a progressive permeabilization of the alveolar-capillary membrane, allowing the escape of edema fluid and blood into the alveolar space.⁵³ When mechanisms to clear the edema are overcome, hypoxemic respiratory failure and death ensue.

CLINICAL IMPLICATIONS

In patients with acute hypoxemic respiratory failure, targeting a “normal” arterial oxygen concentration may require the administration of a high FIO_2 . This strategy has several advantages, including the maintenance of tissue oxygen delivery, the prevention of organ dysfunction resulting from anoxic injury to vascular watershed areas, and an improvement in right-sided heart function as a result of pulmonary arterial vasodilation. These benefits come at the cost of an increased risk of oxidant-mediated lung injury. In addition, increased oxygen concentrations in the lung and intentional or unintentional increases in arterial and tissue oxygen concentrations above normal inhibit the activation of HIFs and consequently the transcription of genes including VEGF that promote adaptation to hypoxia as well as lung and tissue repair. To date, there are no randomized data comparing different target arterial oxygen saturation values in the treatment of critically ill patients.⁵ Furthermore, most trials conducted in mechanically ventilated patients do not report compliance with target oxygen saturations. More research is required to determine the optimal targets for oxygen saturation in critically ill patients. For example, higher targets for arterial oxygen might be combined with pharmacologic strategies to manipulate HIF or oxidant signaling to gain

the advantage of increased oxygen delivery while mitigating the associated risks.^{54,55}

OXYGEN THERAPY IN PATIENTS WITH ALVEOLAR FLOODING

Concerns about oxygen toxicity are largely restricted to patients who develop shunt physiology resulting from alveolar flooding (ie, cardiogenic pulmonary edema, ARDS, or alveolar hemorrhage) (Fig 3).⁵⁶ In these patients, the hemoglobin in the mixed venous blood perfusing the shunt can be saturated only by dissolved oxygen carried in the blood perfusing the relatively normal lung regions. Because the oxygen-carrying capacity of blood with a normal hemoglobin concentration is >60-fold higher than that of plasma, high concentrations of oxygen are required to achieve clinically important changes in arterial oxygen content.

Exposure of most mammalian species to an $\text{FIO}_2 > 0.9$ for more than 72 to 96 h is required to induce lung injury, whereas exposure to a lower level of hyperoxia (FIO_2 between 0.8 and 0.85) for more than a week causes lung injury with fibroproliferation.^{33,58,59} Based on these data, most investigators speculate that an $\text{FIO}_2 < 0.7$ is nontoxic, and these recommendations form the basis for most protocols of ventilator management. Similarly, the lowest acceptable level of arterial oxygen saturation is difficult to define because tissue oxygen delivery depends on the arterial oxygen content, the cardiac output, and the health of the vasculature.⁶⁰ In the absence of definitive data, most guidelines define an arterial oxygen saturation of 88% as the lowest acceptable level.^{5,61} In individual patients, these targets might be adjusted based on global measures of perfusion including the mixed venous oxygen saturation and arterial lactate levels.⁶⁰ As an example, the current ARDS Network guidelines for the management of oxygen therapy in patients with ARDS recommend the use of an $\text{FIO}_2 > 0.7$ only in patients who require >12 cm H_2O of positive end-expiratory pressure (PEEP) to maintain an arterial oxygen saturation >88% or a $\text{PaO}_2 > 55$ torr (Table 1).⁶¹⁻⁶³

Although not definitive, the strongest evidence supporting the safety of current recommendations for the use of oxygen therapy in patients with ARDS comes from the National Heart, Lung and Blood Institutes ARDS Network trial of low tidal volume ventilation in patients with ARDS.⁶¹ In that trial, patients were assigned to receive either traditional therapy (tidal volume, 10-12 mL/kg) or to a low tidal volume strategy (tidal volume ≤ 6 mL/kg as required to achieve a plateau pressure ≤ 30 cm H_2O).⁶¹ Patients assigned to the lower tidal volume strategy had lower arterial oxygen saturations despite a higher mean FIO_2 requirement (0.56 vs 0.51 on day 1, lower vs traditional

FIGURE 3. Correction of arterial hypoxemia in patients with alveolar flooding (shunt). The lungs of a patient with an alveolar flooding process (eg, ARDS, cardiogenic pulmonary edema, and so forth) are represented by two alveoli. When the patient is breathing room air ($F_{IO_2} = 0.21$, black numbers), the $C_v O_2$ is determined primarily by the amount of oxygen carried on hemoglobin (about 15 mL O_2 /dL) with a nearly negligible contribution from dissolved oxygen (about 0.15 mL O_2 /dL). Hemoglobin in the blood flowing through the normal alveoli (unshaded) is fully saturated (about 20 mL O_2 /dL on Hg and 0.3 mL O_2 /dL dissolved); however, the oxygen content of the mixed venous blood flowing through the fluid-filled alveoli (shaded) is not changed. With a $\dot{Q}_s/\dot{Q}_T$ of 0.5 as shown, the resulting arterial oxygen content in room air is 17.5 mL O_2 /dL, corresponding to an $S_a O_2$ of about 89%. Supplemental oxygen therapy can only improve $S_a O_2$ by increasing the levels of oxygen dissolved in the plasma. Because these levels are negligible until F_{IO_2} levels approach 1.0 (an F_{IO_2} of 0.3 is shown as an example, italic numbers), shunt physiology is often recognized clinically by the failure to respond to low-flow oxygen or by a reduction in the P_{aO_2}/F_{IO_2} ratio. $S_a O_2$ in these patients can be improved (black arrows) by increasing the F_{IO_2} to values near 1 (bold numbers), reducing the shunt or increasing the $C_v O_2$. $C_v O_2$ (mL O_2 /dL) = $\%sat \times [Hg](g) \times (1.34 \text{ mL } O_2/g \text{ Hg}) + P_{O_2} (\text{torr}) \times \text{solubility of oxygen in plasma}$ (0.003 mL O_2 /torr). $C_v O_2$ = mixed venous oxygen content; $\dot{Q}_s/\dot{Q}_T$ = shunt fraction; $S_a O_2$ = arterial oxygen saturation. (Adapted with permission from Leff and Schumacker.⁵⁷)

tidal volume strategy).⁶¹ Nevertheless, these patients had a significant reduction (about 8%) in mortality.

Less direct evidence supporting the safety of current oxygen therapy guidelines comes from trials of therapies designed to improve oxygenation in patients with ARDS. As can be seen in Figure 3, arterial oxygen content for a given F_{IO_2} can be increased by strategies that recruit functioning alveoli (ie, reduce the shunt fraction) or by strategies that improve mixed

venous oxygen content.⁵⁷ The best-studied therapies to reduce the shunt fraction in patients with ARDS are those that increase the mean airway pressure through the application of PEEP, intermittent applications of CPAP ("recruitment maneuvers"), high-frequency oscillatory ventilation, airway pressure release ventilation, or pressure control ventilation with prolonged inspiratory times.⁶³⁻⁷¹ In prospective trials that compared different combinations of these strategies

Table 1—Combinations of Oxygen and PEEP for the Treatment of Patients With ARDS as Recommended by the ARDS Network

Lower PEEP/Higher FiO_2		Higher PEEP/Lower FiO_2	
PEEP	FiO_2	PEEP	FiO_2
5	0.3	5	0.3
5	0.4	8	0.3
8	0.4	10	0.3
8	0.5	12	0.3
10	0.5	14	0.3
10	0.6	14	0.4
10	0.7	16	0.4
12	0.7	16	0.5
14	0.7	18	0.5
14	0.8	20	0.5-0.8
14	0.9	22	0.8
16	0.9	22	0.9
18	0.9	22	1.0
18-24	1.0	24	1.0

The combination of PEEP and FiO_2 should be increased if the PaO_2 is <55 torr or the SpO_2 is $<88\%$ and decreased if the PaO_2 is >55 or the SpO_2 is $>95\%$. PEEP = positive end-expiratory pressure. (Adapted with permission from The Acute Respiratory Distress Syndrome Network,⁶¹ Wiedemann et al,⁶² and Brower et al.⁶³)

with standard care, most notably the Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI),⁶³ Lung Open Ventilation Study (LOVS),⁶⁴ and Expiratory Pressure (ExPress)⁶⁵ studies, investigators observed an improvement in oxygenation associated with the increase in mean airway pressure (defined as a lowering of the $\text{PaO}_2/\text{FiO}_2$); however, mortality and other important ICU outcomes were unchanged. In a meta-analysis of these trials, Briel et al⁷² suggested that the negative results were misleading in that mortality was improved in the subgroup of patients with ARDS and increased in those without ARDS; however, these results have not been validated in prospective trials.

Other therapies designed to reduce the shunt fraction in patients with ARDS include a conservative fluid strategy that minimizes the generation of edema fluid by hydrostatic mechanisms,⁶² prone positioning,⁷³⁻⁷⁸ the administration of an inhaled vasodilator (nitric oxide),⁷⁹⁻⁸⁴ and the intratracheal administration of surfactants^{85,86} or perfluorocarbons with high oxygen solubility (liquid ventilation).⁸⁷ The mixed venous oxygen content can be increased by blood transfusion,^{22,23} paralysis,⁸⁸ control of fever,⁸⁹ and extracorporeal membrane oxygenation.⁹⁰⁻⁹² Again, many of these strategies resulted in transient or sustained improvements in the $\text{PaO}_2/\text{FiO}_2$ ratio in patients with ARDS; however, only the induction of paralysis (in a single trial awaiting confirmation) was associated with improved survival, and mortality data with respect to extracorporeal membrane oxygenation are conflicting (Table 2).^{88,90-92}

Insufficient evidence exists to reach firm conclusions about the safety of exposing patients to an $\text{FiO}_2 > 0.7$ for short periods of time. In retrospective analyses, investigators have failed to identify an association between a short (< 24 h) duration of exposure to hyperoxia and mortality in critically ill patients and patients admitted to the ICU after a cardiac arrest.^{97,98} Experimental studies in animals suggest that the effect of hyperoxia depends on several factors, including the species, the strain of animal, and its health status, age, and history of oxygen exposure, and that the risk of oxygen toxicity may be reduced in the injured lung.⁹⁹ In the absence of definitive data, these results cannot be used to justify a more liberal oxygen strategy in some critically ill patients.¹⁰⁰

Premature infants ventilated with hyperoxic gas mixtures are at high risk of the development of retinopathy of prematurity and bronchopulmonary dysplasia.¹⁰¹⁻¹⁰³ The retinopathy of prematurity has been hypothesized as resulting from an initial hyperoxia-induced inhibition of the PHDs, which prevents the stabilization of HIF. The resulting loss of VEGF and other HIF target genes impairs development of the retinal vasculature. As the nonvascular tissue in the retina develops and becomes increasingly metabolically active, the imbalance between oxygen demand and supply causes local tissue hypoxia and excessive HIF-mediated release of VEGF, which induces the neovascularization characteristic of the retinopathy of prematurity.^{54,55} In support of this hypothesis, the risk of retinopathy is increased both by exposure to hyperoxic gas mixtures and by large fluctuations in arterial oxygen saturation, and both restrictive and liberal oxygen saturation targets in neonates have been associated with adverse long-term outcomes.¹⁰² Determining optimal strategies for oxygen therapy in these patients remains an active area of investigation.¹⁰⁴

OXYGEN THERAPY IN PATIENTS WITH ALVEOLAR HYPOVENTILATION

The reduction in minute ventilation that can occur in patients with drug overdoses, brainstem dysfunction, neuromuscular diseases, and chest wall abnormalities can result in alveolar hypoventilation.⁵⁶ When this occurs, the steady-state whole-body CO_2 production and oxygen consumption cause the alveolar PaCO_2 to rise and the alveolar (and, therefore, arterial) PO_2 to fall.¹⁰⁵ This relationship is described by the alveolar gas equation (Fig 3). In patients with obstructive airway diseases,^{106,107} interstitial lung diseases,¹⁰⁸ and pulmonary vascular diseases including venous thrombembolism,^{109,110} relative alveolar hypoventilation results from impaired ventilation-perfusion matching and increased physiologic dead space ventilation, even when the total minute ventilation is

Table 2—Strategies to Improve Oxygenation in Patients With ARDS

Objective/Study	Strategy	Improved Oxygenation	Improved Mortality
Reduce shunt fraction			
Gattinoni et al, ⁷³ Guerin et al, ⁷⁴ Voggenreiter et al, ⁷⁵ Taccone et al, ⁷⁶ Mancebo et al, ⁷⁷ and Fernandez et al ⁷⁸	Prone positioning	Yes	No ^a
Wiedemann et al ⁶²	Conservative fluid management strategy	Yes	No
Troncy et al, ⁷⁹ Michael et al, ⁸⁰ Cuthbertson et al, ⁸¹ Dellinger et al, ⁸² Gerlach et al, ⁸³ and Lundin et al ⁸⁴	Inhaled nitric oxide	Yes	No
Anzueto et al ⁸⁵ and Spragg et al ⁸⁶	Inhaled surfactants ^b	Conflicting results	No
Kacmarek et al ⁸⁷	Liquid ventilation	No	No
Increase mean airway pressure			
Brower et al, ⁶³ Meade et al, ⁶⁴ and Mercat et al ⁶⁵	PEEP	Yes	No ^c
Derdak et al, ⁶⁶ Bollen et al, ⁶⁷ and Ip et al ⁶⁸	High-frequency oscillatory ventilation	Yes	No
Brower et al, ⁶³ Meade et al, ⁶⁴ Mercat et al, ⁶⁵ and Pelosi et al ⁷¹	Recruitment maneuvers	Yes	No
Putensen et al ⁶⁹ and Varpula et al ⁷⁰	Airway pressure release ventilation	Yes	No
Increase Cvo₂			
Papazian et al ⁸⁸	Paralysis	Yes	Yes
Fernandes et al ⁹³ and Parsons et al ⁹⁴	RBC transfusion	Unknown	Unknown
Peek et al, ⁹⁰ Zapol et al, ⁹¹ and Morris et al ⁹²	Extracorporeal oxygenation	Yes	Conflicting results

The PaO₂/FIO₂ ratio in patients with ARDS can be improved by reducing the shunt fraction or increasing the Cvo₂. Although several strategies have been shown to improve the PaO₂/FIO₂ ratio, very few have been shown to improve mortality. Cvo₂ = mixed venous oxygen content. See Table 1 legend for expansion of other abbreviations.

^a Mortality benefit has been suggested in the subgroup of patients with ARDS with severe hypoxemia.⁹⁵

^b Demonstrated mortality benefit in infants with respiratory distress syndrome.⁹⁶

^c Unconfirmed meta-analysis of these trials suggests a mortality benefit.⁷²

normal or increased. With progressive hypoventilation, the alveolar PO₂ approaches the PO₂ in the mixed venous blood. Unlike in patients with alveolar flooding, however, even the small increases in alveolar PO₂ achieved after the administration of low concentrations of supplemental oxygen in patients with alveolar hypoventilation result in marked increases in oxyhemoglobin saturation, reflecting the avidity with which hemoglobin binds oxygen in this range of PO₂ (Fig 4).⁵⁷

Decades ago, investigators recognized that the administration of supplemental oxygen therapy to some patients with COPD caused an increase in arterial PaCO₂.¹¹¹ In many patients, the magnitude of this increase is relatively small and clinically insignificant; however, some patients develop a symptomatic respiratory acidosis if the oxygen therapy is not administered carefully.⁵ Several groups of investigators have shown that this increase in PaCO₂ is attributable primarily to a worsening of ventilation and perfusion matching within the lung, likely secondary to impaired hypoxic pulmonary vasoconstriction, with relatively smaller contributions from the Haldane effect and an oxygen-induced reduction in overall minute ventilation.¹¹²⁻¹¹⁶ Similar increases in PaCO₂ have been observed in response to oxygen administration in patients with neuromuscular disease¹¹⁷ and obesity hypoventilation syndrome,¹¹⁸ in whom a reduction in minute ventilation may play a more important role.

This increase in PaCO₂ is often clinically undetectable and transient and improves when the FIO₂ is reduced. Therefore, concern about this complication should not preclude the prompt use of supplemental oxygen to achieve an adequate oxygen saturation in hypoxemic patients.⁵ As discussed earlier, the definition of “adequate” is not clear. In patients with COPD, the British Thoracic Society Guidelines recommend the administration of oxygen sufficient to achieve saturations between 88% and 92%,⁵ based on expert opinion. Although many centers use higher oxygen saturation targets in appropriately monitored settings, judicious use of oxygen to exclude CO₂ retention in these patients is prudent in the absence of blood gases. A similar strategy should be employed in patients with asthma,¹¹⁹ neuromuscular disease,¹¹⁷ and obesity hypoventilation syndrome.¹¹⁸

OXYGEN ADMINISTRATION

Oxygen provided by nasal cannula forms a reservoir in the nasopharynx that is entrained during inspiration. The concentration of oxygen in the trachea can be increased progressively by creating a larger reservoir for oxygen outside the nasopharynx.¹²⁰ Examples include venturi masks and “nonbreather” masks, which are equipped with an expiratory valve to prevent CO₂ rebreathing. With any reservoir system, the tracheal FIO₂ decreases with higher minute ventilations and

For CO₂: IN = OUT - PRODUCED

$$0 = \dot{V}_A \times P_a\text{CO}_2 - \dot{V}\text{CO}_2$$

For O₂: IN = OUT + CONSUMED

$$F_{\text{I}}\text{O}_2 \times (P_{\text{atm}} - P_{\text{H}_2\text{O}}) \times \dot{V}_A = P_{\text{A}}\text{O}_2 \times \dot{V}_A + \dot{V}\text{O}_2$$

$$P_{\text{A}}\text{O}_2 = F_{\text{I}}\text{O}_2 \times (P_{\text{atm}} - P_{\text{H}_2\text{O}}) - P_{\text{a}}\text{CO}_2 / R$$

FIGURE 4. Correction of arterial hypoxemia in patients with alveolar hypoventilation. The difference between the inspired PO₂ and the alveolar PO₂ is defined by the alveolar gas equation, which is a statement of the conservation of mass for CO₂ and oxygen around the alveolus in steady state. Alveolar hypoventilation can result from a fall in minute ventilation or ventilation-perfusion mismatching with increased dead space ventilation. As a result, the alveolar PO₂ can approach mixed venous values (an obstructed alveolus with a PO₂ similar to the mixed venous is shown). Low-level oxygen therapy results in small increases in the alveolar PO₂; however, because hemoglobin binds avidly to oxygen in this range of PO₂, these changes are usually sufficient to correct the arterial hypoxemia (an F_IO₂ of 0.3 is shown in italic numbers). CaO₂ = arterial oxygen content; Patm = atmospheric pressure; P_{H₂O} = water vapor pressure. See Figure 3 legend for expansion of other abbreviations. (Adapted with permission from Leff and Schumacker.⁵⁷)

higher inspiratory flow rates.¹²⁰ This can be overcome partially by increasing the flow rate of the inspired oxygen. For example, tight-fitting external masks with high flow rates can deliver an F_IO₂ near 1.0 to the trachea and can be combined with PEEP valves to provide continuous positive airway pressure. Some newer systems for nasal cannula oxygen delivery use very high flow rates, which actively replenish the nasopharyngeal reservoir during inspiration and generate modest continuous positive airway pressure.¹²¹ Conventional mechanical ventilators use centralized oxygen supplies, which have no flow rate limitation, allowing for precise control of the inspired F_IO₂. In

contrast, many systems for noninvasive ventilation rely on the entrainment of oxygen into the ventilator tubing and oropharyngeal mask, resulting in limitations to oxygen delivery similar to those of the nasal cannula or simple mask delivery systems. This is typically not a problem because noninvasive ventilation has a high failure rate in patients with acute hypoxemic respiratory failure due to noncardiogenic causes, and is used infrequently.¹²² However, in selected patients, higher oxygen concentrations can be achieved during noninvasive ventilation using specifically designed noninvasive ventilators or standard mechanical ventilators with tubing adapted to fit noninvasive masks.^{123,124}

SUMMARY AND CONCLUSIONS

The administration of supplemental oxygen is a lifesaving therapy for patients with critical illness. As with many interventions in the ICU, supplemental oxygen therapy can cause toxicity and should be administered at the lowest level that achieves an arterial oxygen saturation appropriate for a given patient. Further research is needed to understand the risks and benefits of oxygen therapy in patients with different types of respiratory failure. In the future, targeted pharmacologic therapies that alter the stabilization of HIF or the expression or activity of its transcriptional targets, as well as antioxidants targeted to specific cellular compartments, may allow physicians to more favorably balance the risks and benefits of oxygen therapy in specific critically ill populations.

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