Oxygen Therapy in Critical Illness: Precise Control of Arterial Oxygenation and Permissive Hypoxemia*

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Objective: The management of hypoxemia in critically ill patients is challenging. Whilst the harms of tissue hypoxia are well recognized, the possibility of harm from excess oxygen administration, or other interventions targeted at mitigating hypoxemia, may be inadequately appreciated. The benefits of attempting to fully reverse arterial hypoxemia may be outweighed by the harms associated with high concentrations of supplemental oxygen and invasive mechanical ventilation strategies. We propose two novel related strategies for the management of hypoxemia in critically ill patients. First, we describe precise control of arterial oxygenation involving the specific targeting of arterial partial pressure of oxygen or arterial hemoglobin oxygen saturation to individualized target values, with the avoidance of significant variation from these levels. The aim of precise control of arterial oxygenation is to avoid the harms associated with inadvertent hyperoxia or hypoxia through careful and precise control of arterial oxygen levels. Secondly, we describe permissive hypoxemia: the acceptance of levels of arterial oxygenation lower than is conventionally tolerated in patients. The aim of permissive hypoxemia is to minimize the possible harms caused by restoration of normoxemia while avoiding tissue hypoxia. This review sets out to discuss the strengths and limitations of precise control of arterial oxygenation and permissive hypoxemia as candidate management strategies in hypoxemic critically ill patients.

Design: We searched PubMed for references to "permissive hypoxemia/hypoxaemia" and "precise control of arterial oxygenation" as well as reference to "profound hypoxemia/hypoxaemia/hypoxia," "severe hypoxemia/hypoxaemia/hypoxia." We searched personal reference libraries in the areas of critical illness and high altitude physiology and medicine. We also identified large clinical studies in patients with critical illness characterized by hypoxemia such as acute respiratory distress syndrome.

Subjects: Studies were selected that explored the physiology of hypoxemia in healthy volunteers or critically ill patients.

Setting: The data were subjectively assessed and combined to generate the narrative.

Results: Inadequate tissue oxygenation and excessive oxygen administration can be detrimental to outcome but safety thresholds lack definition in critically ill patients. Precise control of arterial oxygenation provides a rational approach to the management of arterial oxygenation that reflects recent clinical developments in other settings. Permissive hypoxemia is a concept that is untested clinically and requires robust investigation prior to consideration of implementation. Both strategies will require accurate monitoring of oxygen administration and arterial oxygenation. Effective, reliable measurement of tissue oxygenation along with the use of selected biomarkers to identify suitable candidates and monitor harm will aid the development of permissive hypoxemia as viable clinical strategy.

Conclusions: Implementation of precise control of arterial oxygenation may avoid the harms associated with excessive and inadequate oxygenation. However, at present there is no direct evidence to support the immediate implementation of permissive hypoxemia and a comprehensive evaluation of its value in critically ill patients should be a high research priority. (*Crit Care Med* 2013; 41:423–432)

Key Words: critical care; hyperoxemia; hyperoxia; hypoxemia; hypoxia; oxygen

*** See also p. 664.**

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The current balance of clinical teaching emphasizes the avoidance of hypoxemia over concerns about the possible harm associated with hyperoxia. This would seem to be a well-founded thesis when considering the necessity of maintaining adequate oxygen delivery to cells to avoid cellular and organ dysfunction. However, in critically ill patients, in whom arterial oxygenation may remain persistently low despite efforts to resolve it, ongoing attempts to restore normoxemia may be more harmful than the acceptance of a degree of hypoxemia. The toxic effects of breathing high concentrations of oxygen and the injury associated with elevated levels of positive pressure ventilation are well recognized (1, 2). However, the balance of benefit and harm at different levels of oxygenation (inspired and arterial), and the interindividual variability in this balance, are not well defined. Successfully balancing the harms associated with hyperoxia and hypoxia may result in improved patient outcomes. We, therefore, propose two novel related strategies for the management of hypoxemia in critically ill patients. Precise control of arterial oxygenation (PCAO) is an approach whereby the arterial partial pressure of oxygen (Pa_{O_2}), or arterial hemoglobin oxygen saturation (Sa_{O_2}), is precisely targeted and significant variation from the target level avoided. Permissive hypoxemia (PH) is an untested concept that describes the tolerance of levels of arterial oxygenation considerably lower than would conventionally be acceptable. If successfully evaluated and implemented, PH could be considered in selected patients in whom tolerance of hypoxemia is expected to be good and maintenance of normoxemia is likely to be associated with harm (3–5).

This review will explore ideas behind the concepts of PH and PCAO in hypoxemic critically ill adult patients. Achieving optimal arterial oxygenation for individual critically ill patients is an ambitious goal due to the complex interaction of multiple harms and benefit. The influences of different underlying disease processes will have dramatic effects on the balance between oxygen supply and demand at a cellular level. The aim of this review is to present the limited clinical evidence base along with useful contributory nonclinical data in order to explore the strengths and limitations of the proposed strategies.

HYPOXEMIA

Hypoxemia is a common finding among critically ill patients irrespective of their underlying diagnosis (3, 6). It is defined as a Pa_{O_2} or Sa_{O_2} that falls below what is conventionally considered to be normal. Normal, while breathing air at sea level has been described as a Pa_{O_2} of between 80 and 100 mm Hg (10.7 and 13.3 kPa) (7) and Sa_{O_2} of greater than 94% (8); however, considerable interindividual variability may exist with respect to these quoted values. For example, arterial oxygenation is inversely related to age (9) due to the decline in ventilation–perfusion matching that occurs over time (10). The Pa_{O_2} at which clinicians choose to make a diagnosis of hypoxemia varies widely, but typically is in the range of 60 to 75 mm Hg (8–10 kPa) (11–13). In order to determine its cause, hypoxemia can also been described in relation to fractional inspired oxygen concentration (F_{IO_2}). In this instance the ratio of Pa_{O_2} to F_{IO_2} (Pa_{O_2}/F_{IO_2} or P/F ratio) is used. A P/F ratio of less than 100 (when Pa_{O_2} is measured in mm Hg) or 13.3 (when Pa_{O_2} is measured in kPa) has been suggested for the diagnosis of "refractory hypoxemia" (14) (e.g., a Pa_{O_2} of 60 mm Hg [8 kPa] while receiving 60% oxygen). Perhaps it is the lack of evidence that maintaining normoxemia in critically ill patients is beneficial (15) that explains the wide variation in practice surrounding the management of hypoxemia in these patients (16–18).

The Cause and Time-Course of Hypoxemia

Potential mechanisms leading to hypoxemia should be kept in mind when considering treatment strategies as some causes may respond to specific therapies. Calculation of the alveolar-arterial oxygen partial pressure gradient ($P_{(A\text{-}a)O_2}$) may assist in elucidating the cause of hypoxemia; an example being that hypoventilation with open lungs and no elevation of F_{IO_2} will result in a normal $P_{(A\text{-}a)O_2}$ that responds to simple oxygen therapy; whereas a right-to-left shunt will produce a raised $P_{(A\text{-}a)O_2}$ that will not respond to additional oxygen (**Table 1**).

Regardless of its etiology, hypoxemia may also be defined in terms of the duration of its evolution. However, the precise criteria defining specific categories are open to subjective interpretation. We, therefore, propose a structured approach to defining the time-course of hypoxemia based on the changing physiological responses and adaptations to declining arterial oxygenation that occur over time (**Table 2**). As an example, acute hypoxemia occurring as a consequence of abrupt upper airway obstruction or penetrating chest injury evokes physiological responses that are limited to the immediate augmentation of oxygen delivery through increases in minute volume and car-

TABLE 1. Causes of Hypoxemia and Their Effect on the Alveolar-Arterial Oxygen Difference

Cause of Hypoxemia	Effect on $P_{(A\text{-}a)O_2}$	Comment
Reduced F_{IO_2} (or P_{IO_2})	Unchanged or reduced	Resolved by increasing F_{IO_2} (or P_{IO_2})
Hypoventilation	Unchanged	Causes included pharmacological, neurological, and muscular weakness. Alleviated by increasing F_{IO_2}
Ventilation–perfusion mismatch	Increased	Commonest cause of hypoxemia in the critically ill. Alleviated to some extent by increasing F_{IO_2}
Right-to-left shunt	Increased	Anatomical or physiological. Cannot be alleviated by increasing F_{IO_2}
Diffusion limitation	Increased	Rare cause of hypoxemia that can be alleviated by increasing F_{IO_2}

TABLE 2. Proposed Terms for the Categorization of Hypoxemia Based on Physiological Responses to the Duration of Its Development

Term	Description
Acute hypoxemia	A rapid decline in arterial oxygenation developing over < 6 hrs (e.g., acute upper airway obstruction)
Subacute hypoxemia	Reduced arterial oxygenation occurring in 6 hrs to 7 days (e.g., pneumonia)
Sustained hypoxemia	Reduced arterial oxygenation for 7–90 days (e.g., prolonged acute respiratory distress syndrome, high altitude climbing expeditions)
Chronic hypoxemia	Prolonged reduction of arterial oxygenation for over 90 days (e.g., chronic obstructive pulmonary disease)
Generational hypoxemia	Cross-generational reduced arterial oxygenation (e.g., Tibetan highland residents)

In the absence of any universally accepted terminology describing the time-related differences in responses to hypoxemia, the proposed criteria are based upon human physiological adaptations to hypoxemia.

diac output. Persistence of sublethal hypoxemia results in alternative adaptive mechanisms, predominantly at a cellular level. Critically ill patients tend to fall within the subacute (6 hrs to 7 days) and sustained (7–90 days) categories (Table 2). Sustained cross-generational hypoxic stress occurring in high altitude native populations can lead to modification of the genome. The time-course of hypoxemia may influence decisions surrounding implementation of PCAO and PH for individual patients.

Clinical "Acclimatization" to Hypoxemia and Cellular Hypoxia

Exposure to subacute and sustained hypoxemia permits a coordinated process of adaptation, which outside of a clinical setting is commonly referred to as acclimatization. For example, at altitude the human response to hypobaric hypoxia is well described and characterized by the restoration of convective oxygen delivery through increases in alveolar ventilation, cardiac output, and red blood cell mass (19, 20). It is unlikely that critically ill patients mount such effective cardiorespiratory countermeasures to increase oxygen delivery as a result of their underlying pathology. However, there may be similarities in tissue and cellular responses to hypoxia between patients and healthy volunteers at altitude (21). In skeletal muscle biopsies of healthy volunteers exposed to sustained hypoxia at high altitude, there is deactivation of mitochondrial biogenesis and down-regulation of mitochondrial uncoupling, possibly resulting in improved efficiency of ATP production (22). Comparable changes in mitochondrial biogenesis also occur in critical ill patients and may reflect similar adaptive responses (23, 24). The difficulty that arises in comparing acclimatization to high altitude and the physiological changes that occur in the critically ill is that the degree of iatrogenic control over the latter group may prevent some aspects of adaptation. For example, patients in whom ventilation is controlled artificially by mechanical means will be unable to mount a hypoxic ventilator response. However, it is unlikely that cellular adaptation to hypoxia via hypoxia inducible factor will be inhibited by such interventions.

Severe and sustained tissue oxygen deprivation results in cellular hypoxia and a decline in ATP production that triggers apoptosis, a regulated energy-dependent process of programmed cell death. The level of cellular hypoxia at which apoptosis is initiated is unclear and almost certainly varies between organs and individuals. In isolated mitochondria, oxidative cellular metabolism fails when the PO_2 falls less than 0.08 to 0.53 mm Hg (0.01–0.07 kPa) (25, 26), while the corresponding values for cultured cells *in vitro* seem to be in the range of 3.00 to 5.25 mm Hg (0.40–0.70 kPa) (25). Cellular oxygen consumption (V_{O_2}) is governed by metabolic activity rather than oxygen supply (27), but this relationship can be modified during conditions of limited oxygen availability. Following exposure to moderately prolonged hypoxia, cultured cells demonstrate a 40 to 60% reduction in V_{O_2} secondary to the down-regulation of "non-essential" cellular processes (28–30). This phenomenon is reversible on re-exposure to normoxia (29) and is not associated with demonstrable long-term cellular harm (28). Termed "oxygen conformance," this reversible reduction in cellular metabolism and ATP production represents a chronic adaptive response to hypoxia not observed during acute hypoxic exposure. The coordinated reduction in V_{O_2} demonstrated by oxygen conformance not only attenuates the depletion of scarce oxygen supplies, but may also render cells less susceptible to hypoxic injury if oxygen delivery continues to fall to a critical level. Strikingly similar mechanisms have been demonstrated during multiple organ failure in critically ill patients, and it has been proposed as an effective cellular survival strategy in this context (31). These processes may be a manifestation of a more generalized adaptive response to hypoxia that facilitates cellular survival under conditions of extreme physiological stress.

POTENTIALLY HARMFUL EFFECTS OF EXCESSIVE OXYGEN AND HYPEROXEMIA

Eponymously named after Paul Bert and James Lorrain Smith, the detrimental effects of hyperbaric oxygen on the central nervous system (32) and pulmonary tissues (33) respectively, were well described in the 19th century. More recently, it has become clear that high concentrations of normobaric oxygen may also be harmful. As the gas exchange interface of the body, it is logical that pulmonary tissue would be one of the tissues at greatest risk of damage from high-inspired oxygen concentrations, and this has been demonstrated in numerous

animal and healthy human volunteer studies (34). The damage caused to pulmonary tissue by excessive oxygen resembles the changes seen in acute respiratory distress syndrome (ARDS); the magnitude of injury is directly related to the concentration of oxygen and duration of exposure (35, 36). Oxygen toxicity is rarely evident when the F_{IO_2} is less than 0.5 (1). As patients with ARDS frequently require an F_{IO_2} greater than 0.5, they are potentially at risk of exacerbating the underlying lung injury. It has been previously reported that positive pressure ventilation with a high F_{IO_2} (0.61–0.93) resulted in specific pathological findings independent of the detrimental effects of the ventilator (37). Clinically, oxygen toxicity can result in decreased mucociliary transport (38, 39), atelectasis (resulting in ventilation–perfusion mismatching), inflammation, pulmonary edema, and eventually interstitial fibrosis (35). These pathologies may result in worsening lung function.

Excess oxygen administration is thought to damage tissue through the production of reactive oxygen species (ROS). These oxygen-containing molecules that form covalent bonds with other molecules through their unpaired electrons are produced by the mitochondria during oxidative phosphorylation and serve a number of important biological functions. In excessive concentrations, ROS-mediated oxidative stress can lead to cellular necrosis or apoptosis. Paradoxically, hypoxia can also result in an increase in ROS production (40), and ROS are thought to be key players in the pathobiology of reperfusion injury (41). An important feature of pulmonary oxygen toxicity is that it is almost impossible to distinguish from damage caused by other lung injury processes (42). Consequently, it is unclear whether deterioration of lung function during high concentration oxygen therapy is due to worsening of the primary disease process or to oxygen-free radical-induced damage; the administration of high concentration oxygen may be perpetuating lung injury in some patients.

Supranormal arterial oxygenation is also associated with a number of cardiovascular responses such as reduced stroke volume and cardiac output (43, 44), increased peripheral vascular resistance (43), coronary artery vasoconstriction, and reduced coronary blood flow (45, 46), which may be undesirable in critically ill patients.

A growing body of clinical evidence points to the potential harm of using high concentrations of inspired oxygen in clinical situations where classical teaching and physiological intuition might suggest a beneficial response. A number of examples are outlined below:

1. Acute myocardial infarction. Two recently published systematic reviews of the use of supplemental oxygen during the management of acute myocardial infarction came to the same conclusion; there is no evidence that oxygen therapy (when compared to air breathing) is of benefit in this setting (47), and it may in fact be harmful, resulting in greater infarct size and increased mortality (48). While the small number of included studies limited the interpretation of these reviews and none of the original studies obtained a statistically significant result (49), they highlight provocative data that merits further urgent investigation. The AVOID (Air Verses Oxygen In myocarDial infarction) study (NCT01272713) is currently recruiting patients in order to answer this crucial clinical question (50).
2. Acute ischemic stroke. Clinical trial data evaluating the effects of different inspired oxygen levels are even more sparse in acute ischemic stroke. Oxygen therapy may be of benefit if administered within the first few hours of onset, but evidence also exists that it may result in increased harm (higher 1-yr mortality) with continued administration (51).
3. Neonatal resuscitation. During the past decade, the practice of resuscitating neonates with 100% oxygen has been challenged and many are now advocating that air should be used for initial resuscitation (52). Several studies have demonstrated that the use of 100% oxygen during the resuscitation of human neonates may increase mortality, myocardial injury and renal injury, and even be associated with a higher risk of childhood leukemia and cancer (53). Furthermore, in a manner comparable to an ischemia-reperfusion injury, the use of 100% oxygen in the new born following an asphyxiating perinatal event (54) is thought to result in cerebral damage. Such is the evidence base that resuscitation guidelines in neonates now advise that the initial gas administered for ventilation should be air, and that oxygen should be titrated into the mixture according to clinical response so as to avoid hypoxemia (55).
4. Adult resuscitation following cardiac arrest. In a retrospective cohort study of more than 6,000 patients following resuscitation from cardiac arrest, hyperoxemia (defined as a Pa_{O_2} > 300 mm Hg [40 kPa]) was associated with a significantly worse outcome than both normoxemia (60–300 mm Hg [8 to 40 kPa]) and hypoxemia (< 60 mm Hg [8 kPa]) (56). The authors of this article concluded that excessive oxygen has harmful potential during adult resuscitation post cardiac arrest, possibly via ischemic reperfusion damage to central nervous tissue.
5. Critical illness. Limited data are available describing the relationship between arterial oxygenation, morbidity, and mortality in critically ill patients. The complexity of separating "signal" from "noise" in this heterogeneous patient cohort makes this task challenging. Among acute medical emergency admissions there is evidence that low Sa_{O_2} is an independent predictor of mortality (57); however, this relationship is more complicated in established critical illness with sustained hypoxemia. Likewise, the degree to which a reduction in arterial oxygenation can be tolerated in the critically ill is difficult to determine and remains unclear (58).

The assumption that a higher Pa_{O_2} is correlated with improved long-term survival in critically ill patients has no robust evidence in its support (15). A retrospective study of arterial oxygenation in Dutch intensive care patients who were mechanically ventilated within 24 hrs of admission demonstrated a biphasic relationship between Pa_{O_2} and in-hospital mortality (59). Mean Pa_{O_2} in this cohort of more than 36,000 patients was 99.0 mm Hg (13.2 kPa), yet the nadir for unadjusted hospital mortality was just below 150 mm Hg (20 kPa). A similar study of patients in Australia and New Zealand reported

a mean Pa_{O_2} of 152.5 (±109.5) mm Hg (20.3 kPa), representing supraphysiological levels of oxygenation, with 49.8% of the 152,680 cohort being categorized as hyperoxemic (Pa_{O_2} > 120 mm Hg [16 kPa]) (60). In contrast to the Dutch cohort, an association between progressive hyperoxemia and in-hospital mortality was not found after adjustment for disease severity, although hypoxemia was associated with elevated mortality. These conflicting data are limited by the methods used: both studies evaluated the association between the single "worst" (lowest P/F ratio) blood gas within the first 24 hrs of admission to an intensive care unit with in-hospital mortality, without quantifying oxygenation during the rest of the patients' critical illness. The difficulty in inferring a clear message from these studies may, therefore, reflect discordance between the severity of acute hypoxemia and subsequent changes in oxygenation along with the consequent adaptive responses that may occur in critically ill patients. Using arterial blood gas data beyond the first 24 hrs of admission may help more clearly define any association between oxygenation and outcome.

Oxygenation in ARDS

The assumption that elevating arterial oxygenation improves outcomes in patients with hypoxemia secondary to ARDS underpins many studies in this field (61). However, data from clinical trials in patients with ARDS challenge this assumption and frequently oxygenation and long-term outcome seem unrelated (62–64). While some studies have reported a relationship between arterial oxygenation and mortality, a systematic review of 101 clinical studies of ARDS concluded that P/F ratio was not a reliable predictor of outcome (65). A variety of interventions including high frequency oscillatory ventilation, prone positioning, inhaled nitric oxide, and extracorporeal membrane oxygenation have been shown to improve arterial oxygenation in patients with ARDS without yielding an outcome benefit (14, 66). Furthermore, different strategies of mechanical ventilation have led to 1) improved oxygenation but unchanged outcome (67–69), 2) improved outcome but unchanged oxygenation (70), and 3) deterioration in oxygenation but unchanged outcome (71). Taken together, these data do not support the assumption that improved oxygenation has a causative relationship with improved clinical outcomes in patients with ARDS.

Three important considerations relate to this discussion. First, supplemental oxygen is a supportive intervention serving to correct a consequence of the underlying pathophysiology, rather than to treat a cause or reverse a disease process. Second, cellular hypoxia is not a prominent feature of ARDS. Third, death in these studies is rarely due to intractable hypoxemia or respiratory failure, but commonly from the underlying cause of ARDS (e.g., systemic inflammation due to sepsis) (72, 73). Taken together, these data suggest that the underlying assumption that merits testing through adequately powered well-designed clinical trials.

POTENTIALLY HARMFUL EFFECTS OF HYPOXEMIA

Severe hypoxemia can result in cellular hypoxia, organ dysfunction, and death. The degree of organ dysfunction is determined by the rapidity of onset, severity, and duration of hypoxemia and individual susceptibility. An extreme example of ischemia-hypoxia tolerance is iatrogenically induced hypothermic circulatory arrest during cardiothoracic surgery. Sudden exposure to severe atmospheric hypoxia will cause rapid unconsciousness secondary to cerebral hypoxia (74), while gradual acclimatization to a comparable level of hypoxia can be well tolerated (75). In a report detailing 22 clinical cases of profound hypoxemia (Pa_{O_2} < 20.3 mm Hg [2.7 kPa]), 13 of the patients survived, ten of whom were seemingly unaffected by the event (76). The lowest reported Pa_{O_2} was 7.5 mm Hg (1.0 kPa), in a 20-yr-old male patient breathing room air following a heroin overdose yet he made an unremarkable recovery (76).

Much of the concern regarding extreme hypoxemia is focused upon recovery of neurological function. It is difficult to attribute cognitive deficits occurring after critical illness directly to hypoxemia, when other factors such as hypotension, infection, electrolyte abnormality, and drug effects may have contributed. Whether hypoxemia reduces long-term cognitive function after sustained exposure to extreme high altitude is disputed (77–80). In a study of healthy volunteers breathing 7% oxygen, no electroencephalogram abnormalities were detectable (81). Furthermore, postmortem examinations of young adults following severe and prolonged hypoxemia prior to death from sudden cardiac failure revealed no specific pathological cerebral changes that might be attributed to hypoxia (82). Hypoxemia tends to increase blood flow to tissues (83) ensuring an adequate oxygen supply for metabolism, and this has been clearly demonstrated in the severely hypoxemic brain (83). Thus, when untangling the literature it is important to differentiate the subtle but important differences between hypoxemia and ischemia. "Hypoxic brain injury" in the absence of hypoperfusion is a much-feared consequence of a prolonged reduction in arterial oxygenation, yet there is little evidence for its existence and it should not be mistaken for ischemic cerebral injury that occurs post cardiac arrest.

NOVEL CLINICAL STRATEGIES FOR OXYGEN PRESCRIPTION

Moving away from targeting normal values as physiological goals (84) for oxygen therapy in critically ill patients is consistent with recent paradigm shifts in relation to other interventions. These include hemoglobin concentration ([Hb]) (85) and arterial partial pressure of carbon dioxide (86). For oxygen therapy, consideration of how the balance of benefit and harm alters over time may also be important. For example, specific oxygen delivery targets seem to be effective in the resuscitation of acutely injured patients (87–90), whereas elevating systemic oxygen delivery above normal does not improve outcome in established critical illness and may cause harm (91–93). The same may be true for maintenance of Pa_{O_2} as critical illness develops with time.

Precise Control of Arterial Oxygenation

PCAO involves targeting of Pa_{O_2} or Sa_{O_2} to individually specified values, and avoiding significant fluctuation outside of a

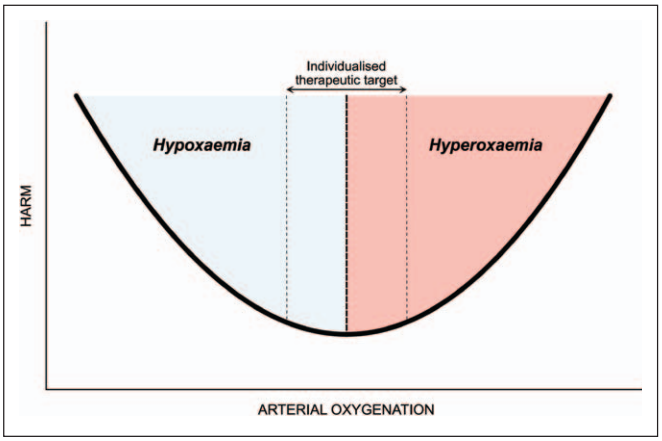

Figure 1. Schematic diagram of the precise control of arterial oxygenation concept. A target arterial partial pressure of oxygen or arterial hemoglobin oxygen saturation is selected for each patient (*thick dashed, arrowed line* in the center of curve) around which tight boundaries are delineated that create the therapeutic target range for oxygenation (*thin dashed lines*). Harm is possible if oxygenation strays outside of this selected range. The optimal range for individuals will be dependent upon their specific clinical situation.

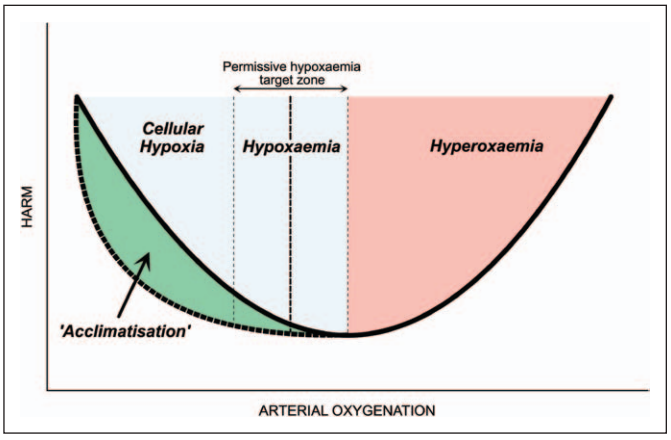

Figure 2. The precise control of arterial oxygenation concept demonstrating the potential risk reduction presented by permissive hypoxemia. Shifting the therapeutic target range for oxygenation (*area between thin dashed lines*) to the left on this conceptogram could potentially reduce harm to selected patients by tolerating increasing degrees of hypoxemia and avoiding interventions that pursue normoxemia or lead to hyperoxemia. Cellular and organ "acclimatization" may occur during subacute and sustained hypoxemia that facilitates survival without increased harm, which occurs during prolonged ascent to high altitude.

tightly defined range, thereby minimizing the potential harms associated with hyperoxemia and hypoxemia (unnecessarily high or low Pa_{O_2} and/or P_{IO_2}). The traditional clinical approach to oxygen therapy has been to prioritize the avoidance of hypoxemia while being relatively tolerant of hyperoxemia. The possibility that "too much" oxygen may be as harmful as "not enough" should (94) lead to a pragmatic rethinking of the practice of oxygen administration. Observational data suggests that current practice tends to hyperoxemia (59, 60). This may be an inevitable consequence of the widespread use of pulse oximetry that effectively detects hypoxemia but cannot be used to differentiate between normoxemia and hyperoxemia (ceiling effect). The result of PCAO should be oxygenation values that fall within a considerably narrower range than is currently common, the midpoint of which is appropriately targeted for a specific patient. Prescription of an achievable range (e.g., "60 to 75 mm Hg" or 8 to 10 kPa) might replace the more commonly observed prescription of "> 60 mm Hg" (8 kPa).

Founded upon physiological first principles, one can construct a theoretical schema that depicts a patient's target oxygenation zone (**Fig. 1**). The choice of values for a specific patient will depend upon their age, the clinical setting, underlying disease (and its chronicity), and other comorbidities. Agreed target values may be suitable for cohorts of patients, for example postoperatively or following a myocardial infarction. This approach to PCAO can be compared to other well-founded, evidence-based practices in critical care medicine; for example, the administration of intravenous fluids to optimize intravascular volume status (95) is now commonly guided by measurable end points such as stroke volume. In this instance, increased risks are encountered if physiological goals are ignored and fluid is administered in a uniformly prescriptive style (e.g., volume per hour or kilogram) rather than being tailored according to individual's requirements (96). Tight control of blood glucose again endorses this approach, having a significant impact on mortality and morbidity in the critically ill (97).

Permissive Hypoxemia

The concept of target defined arterial oxygenation described above (PCAO) is echoed in a recently published guideline for acutely ill patients which suggests normal or near normal oxygenation as the goal for oxygen therapy rather than unrestricted administration of oxygen to hypoxemic patients (8). However, while targeting normoxemia may be the best practice in acute situations, it may be neither achievable nor beneficial in critically ill patients exposed to subacute or sustained hypoxemia. In patients who have had sufficient time to be adapting or adapted to a subacute or sustained hypoxemia (Table 2), a strategy of PH may improve outcomes because of the marginal benefit (and potential increased harm) that arises from increasing arterial oxygenation to normal. In other words, the goal of PH is to reduce morbidity and mortality in selected hypoxemic patients who have had sufficient time to adapt this state, by targeting lower levels of arterial oxygenation than are currently acceptable. Conceptually, this can be presented as a shift to the left of the PCAO curve in Figure 1 (lower Pa_{O_2}), with the consequence that the zone of "optimal outcome" lies within the sector conventionally described as hypoxemia: hence PH (**Fig. 2**). The corollary of this is that normoxemia may be associated with worse outcome in these individuals. Within the oxygenation target zone (left of center) in Figure 2, adaptation to hypoxemia may facilitate a reduction of risk, in a similar way to the acclimatization process that occurs on ascent to high altitude permits continued functioning even under conditions where inspired oxygen is profoundly reduced (75). This rationale for PH is in part a reflection of the fact that humans posses a variety of effective adaptive mechanisms that support hypoxia tolerance,

whereas hyperoxia seems to be consistently harmful due to the absence of known defensive adaptations.

The two proposed strategies (PH and PCAO) could be used in combination; the application of PH without PCAO risks the unintended consequence of unacceptably low Pa_{O_2}.

Individualizing Oxygen Therapy in Critical Illness

There is wide variability in human responses to a hypoxic stimulus, strikingly demonstrated by dramatic interindividual differences in performance at high altitude (98). Prediction of an individual's response to hypoxemia is very poor, and neither isolated variables relating to an ability to improve oxygen transport (e.g., hypoxic ventilatory response), nor measures of physiological reserve relating to overall oxygen flux (e.g., peak oxygen consumption), are predictive of subsequent hypoxia tolerance (21). That said, predictor variables for acute mountain sickness were recently identified in a large cohort of subjects ascending to high altitude, and these consisted of marked desaturation and low ventilatory response to hypoxia during exercise (99). Comparable predictor variables in critically ill patients are largely unknown, and although individual risk stratification according to exercise capacity perioperatively is now commonplace (100), a "one-size fits all" approach is still commonly adopted.

The etiology and time-course of hypoxemia will affect the optimal level of arterial oxygenation for an individual patient (Table 2). Our current understanding of the transition from acute response to a more adapted phenotype is limited in critically ill patients and there is likely to be substantial interindividual variation in the magnitude and time-course of these processes. For example, the targets for arterial oxygenation, [Hb] and blood pressure in a patient with a traumatic chest injury may well be different from those in a patient with long-standing multiple organ failure secondary to sepsis. Clinical decisions should be driven by a pragmatic approach to individual patients guided by the best available clinical evidence.

Patient Selection for PCAO and PH

Although most patients are likely to benefit from PCAO, not all patients will tolerate profound hypoxemia. Hypoxemia is currently contraindicated in patients with severe brain injuries and evidence exists that increasing systemic oxygenation with supplemental oxygen following major surgery reduces postoperative wound infection rates (101). Given that even in these patients excessive oxygenation is likely to be harmful, and PCAO is likely to be beneficial, the identification of "susceptibility" biomarkers for hypoxia tolerance or intolerance is imperative and would facilitate individualized implementation of PCAO and PH to patients. Such biomarkers might include physiological variables, biochemical signals in plasma or other compartments, genetic loci, and epigenetic modifications (102). Rapid diagnostic technologies currently being developed might permit bedside characterization of the likely rate and degree of adaptation to hypoxemia and thereby guide management.

Patient Responses and Targeting of Treatments

Should a distinct group of "response" biomarkers be identified that indicate hyperoxic or hypoxic tissue damage, they could also be used to monitor treatment and modify therapeutic strategies for individual patients. Markers of cellular damage (e.g., S100) (103), beneficial adaptation (nitrogen oxides) (104), or oxidative stress (105) may be useful for this purpose. In addition , continuous monitoring of tissue oxygenation to provide a real-time readout of the balance between oxygen delivery and consumption is also likely to be imperative to successful PH. Technologies such as near infrared spectroscopy (106), real-time *in vivo* speckle laser (107), Clarke electrodes, microdialysis, and fluorescence quenching (108) offer the potential of monitoring oxygenation in a variety of tissues and the potential for generating organ-specific oxygen toxicity profiles. It is difficult to pinpoint the threshold for oxygen-related tissue damage in humans; the precise F_{IO_2} is likely to differ between individuals and depend upon their degree of underlying lung injury. The consequences of ROS-mediated oxidative damage due to high F_{IO_2} in the lung may be identified through analysis of pulmonary surfactant with characterization of phospholipid oxidative damage using high precision modern diagnostics such as bedside mass spectrometry. The identification of such markers is an unmet research need with the potential to improve the safety and efficacy of oxygen therapy.

Taken further, perhaps the ultimate goal, as with other contexts in medicine where precise control of a monitored variable is required, would be the introduction of "servo control" systems to permit the automated control of arterial oxygenation. With appropriate monitoring and safety structures in place, systems based on high quality input variables, such as that derived from a reliable pulse oximetry source or continuous intra-arterial oxygen tension monitoring (109), could be linked to variable oxygen administration systems, to allow real-time management of hypoxemia.

Oxygen Delivery and PH

When implementing PH, it may necessary to manipulate [Hb] and cardiac output in subgroups of patients to ensure adequate convective oxygen delivery to tissues (5). Patients with reduced oxygen delivery due to low [Hb] (e.g., Jehovah's Witness post surgery) or low cardiac output (e.g., end-stage heart failure) may therefore not be suitable candidates for PH but may still benefit from modified target values for Pa_{O_2}. Determination of the precise thresholds for [Hb] and cardiac output in the context of a selected oxygenation target will depend on basal metabolic oxygen requirements and should be guided by the use of biomarkers and monitors of tissue oxygenation/hypoxia. While it may be necessary to reduce metabolic requirements in patients in whom hypoxemia is severe and oxygenation targets are low, for example through the use of sedatives, muscle relaxants, or therapeutic hypothermia, tissue oxygen extraction

SUMMARY

- The safe lower limit of arterial oxygenation in critically ill patients is unknown, but may be less than accepted in clinical practice.
- High fractional inspired concentrations of oxygen cause pulmonary damage, possibly more so in patients with injured lungs, but this damage is difficult to identify clinically and knowledge of safety thresholds for oxygen administration are unclear.
- Precise control of arterial oxygenation in critically ill patients is a novel treatment strategy that we propose may improve outcomes by reducing the harm associated with unnecessary extremes of arterial oxygenation.
- For selected critically ill patients, permissive hypoxemia (the tolerance of lower arterial oxygenation levels) may better balance the harms and benefits of oxygen therapy than attempting to achieve normoxemia.
- Clinical evidence supporting permissive hypoxemia is not currently available and robust studies are required to evaluate safety and efficacy before implementation can be advocated.

might also be amenable to manipulation via matching of microvascular blood flow to local tissue demands (110).

CONCLUSIONS

The selection of optimum arterial oxygenation goals is essential if cellular hypoxia and unnecessarily excessive oxygenation (and ventilation) are to be avoided. It is imperative that balancing the risks associated with hypoxemia and hyperoxemia forms part of the daily assessment of critically ill patients. Oxygen administration should be considered in the same way as other drugs, being titrated to a measured end point to avoid excessive and inadequate dosage. While the signs of excessive oxygen administration are often difficult to tease apart from a patient's underlying lung injury, limiting the dose administered and the mechanical means to achieve oxygenation may reduce harm in some individuals. There are no generally acceptable thresholds for the lower limit of oxygenation that can be tolerated and individual evaluation is crucial when determining prescribed targets. The development of new technologies and biomarkers may aid patient selection, and provide an umbrella of safety with regards to tissue oxygenation.

At present, any immediate change in clinical practice toward PH is not justified in the absence of experimental data in critically ill patients. However, greater attention to both the concentration of oxygen received by patients and the arterial oxygenation achieved is likely to be beneficial. Implementation of the PCAO method of oxygen prescription may assist in this process, providing a safe oxygenation range for the patient.

The weight of clinical experimental data coupled with observational and basic science studies suggest that a comprehensive evaluation of PH in critically ill patients should be a high research priority.

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