Can We Optimize Long-Term Outcomes in Acute Respiratory Distress Syndrome by Targeting Normoxemia?

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Abstract

Since its original description in 1967, acute respiratory distress syndrome (ARDS) has been recognized as a devastating condition associated with significant morbidity and mortality. Advances in critical care medicine and ARDS management have led to a substantial increase in the number of ARDS survivors. Long-term cognitive impairment after critical illness is a significant public health concern. ARDS survivors frequently experience long-term cognitive impairment, as well as physical impairment, psychiatric morbidity, and reduced health-related quality of life. At present, no intensive care unit–based intervention has been proven to reduce the risk of long-term cognitive impairment after ARDS. To address the urgent need to identify strategies to preserve long-term health, investigators have advocated the measurement of short- and long-term outcomes in clinical trials. Maintaining

adequate oxygen delivery to preserve organ function is of vital importance in ARDS management. The optimal target range for arterial oxygenation in ARDS remains unknown, due in part to the challenge to maintain adequate tissue oxygenation and to minimize harm, such as oxygen toxicity. An approach targeted to subnormal oxygenation values (partial pressure of arterial oxygen, 55–80 mm Hg) has emerged as a means to accomplish these aims. In this perspective, we critically evaluate this strategy from short- and long-term perspectives, with a focus on the potential long-term cognitive effects of the strategy. We conclude with a proposal to consider resetting the target range for arterial oxygenation higher (85–110 mm Hg) as a potential strategy to improve the long-term outcomes of ARDS survivors.

Keywords: acute respiratory distress syndrome; critical care; oxygenation; cognitive impairment; quality of life

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Since its original description by Ashbaugh and colleagues in 1967, acute respiratory distress syndrome (ARDS) has been recognized as a devastating condition associated with significant morbidity and mortality (1). Advances in critical care medicine and ARDS management (2, 3) have led to a substantial decrease in ARDS-related mortality for the estimated 190,600 annual cases in the United States (4). As a result, an estimated 130,000 to 150,000 ARDS survivors are discharged each year (2–6).

Long-term cognitive impairment after critical illness is a significant public health concern (7), and the broader concept of survivorship is one of the defining challenges of present-day critical care medicine (8, 9). ARDS survivors frequently experience long-term cognitive impairment, as well as physical impairment, psychiatric morbidity, and reduced health-related quality of life (7–16). At present, no intensive care unit (ICU)–based intervention has been proven to reduce the risk of developing long-term cognitive impairment

after ARDS. To address the urgent need to identify strategies to preserve long-term health, investigators have advocated the measurement of short- and long-term outcomes in clinical trials (7, 17). ARDS trials have incorporated long-term outcomes into their trial designs (13–16), although current trials have not yet explicitly targeted long-term outcomes as their primary outcome.

Maintaining adequate oxygen delivery to preserve organ function is of vital importance in ARDS management. The

optimal target range for arterial oxygenation in ARDS remains unknown, due in part to the challenge to maintain adequate tissue oxygenation and minimize harm (e.g., oxygen toxicity) (18–20). An approach targeted to subnormal oxygenation values (PaO_2 , 55–80 mm Hg) has emerged as a means to accomplish these aims (2, 21, 22). In this review, we critically evaluate this traditional strategy from short- and long-term perspectives, with a focus on the potential long-term cognitive effects of the strategy.

The Changing Landscape of Critical Care Trials

By embracing a longitudinal vision that recognizes that ICU interventions may have long-lasting effects (23), clinical investigators have the opportunity to impact both survival and long-term physical and neuropsychological health. The ideal intervention would improve short- and long-term outcomes. However, an intervention may result in short-term benefit at the expense of long-term harm or vice versa. In these instances, intense efforts will be required to modify the intervention to realign short- and long-term outcomes. In the interim, the clinical decision to employ such an intervention at the bedside will be challenging and will require thoughtful deliberation taking into consideration short- and long-term perspectives and the values and preferences of the patient (24).

The Case of Arterial Oxygenation Target in ARDS

As of 2013, to our knowledge, no clinical practice guidelines exist for mechanical ventilation strategies for the management of ARDS. More specifically, no formal guidelines exist regarding the optimal oxygenation target in ARDS. In part, this is due to important, unanswered questions regarding the safety of an approach that permits subnormal oxygenation values.

In the normal state of health, the average PaO_2 at sea level is approximately 100 mm Hg in adults less than 55 years of age (25), and the average brain tissue O_2 level is 25–35 mm Hg (26, 27). In ARDS (28), a common goal is to maintain PaO_2

above 60 mm Hg, based on the classical teaching to defend against the risk of a fall in arterial oxygenation while on the steep portion of the oxygen–hemoglobin dissociation curve (29) so as to avoid oxygenation in the refractory hypoxemia range (Figure 1).

In 1998, the American–European Consensus Conference on ARDS deliberated on the optimal ventilatory strategy and oxygenation target for ARDS (30). The conference concluded that the appropriate oxygenation target was controversial and, presciently, noted: “the conditions (if any) under which arterial O_2 saturation can be allowed to fall to subnormal values without unacceptable clinical consequences have not yet been delineated” (30). Ultimately, the committee recommended an approach prioritizing aims that may be at odds with one another: “ensure appropriate O_2 delivery to vital organs” and “minimize oxygen toxicity” (30). The inherent tension between these strategies is that an approach aimed at reducing the fraction of inspired oxygen (FiO_2) and mean alveolar pressure to minimize hyperoxia-induced lung injury (18–20) and ventilator-induced lung injury, respectively, may be achieved only by tolerating subnormal oxygenation levels.

In 2000, the National Heart, Lung, and Blood Institute (National Institutes of Health) Acute Respiratory Distress

Syndrome Clinical Trials Network (ARDSNet) published the landmark trial demonstrating that ventilation with lower tidal volumes significantly reduced mortality in ARDS compared with ventilation with traditional tidal volumes (2). The trial, conducted between 1996 and 1999 and based on two pilot studies (31), protocolized an oxygenation target range of 55–80 mm Hg and an oxyhemoglobin saturation of 88–95% (2), effectively prioritizing the avoidance of oxygen toxicity (18–20). This oxygenation target range has been used extensively in subsequent ARDS clinical trials (3, 5, 32, 33) and is advocated in the management of ARDS (34); consideration of targeting even lower levels has been discussed (21).

A Matter of Perspective

The Short-Term Perspective: Survival

The short-term perspective, where the time horizon is limited, prioritizes interventions and the intermediate steps (e.g., reduced duration of mechanical ventilation) required to increase the likelihood of survival. Until more recently, the lone strategy to improve survival in ARDS was the use of lower tidal volume ventilation (2). In more recent trials, the early use of neuromuscular blocking agents and prolonged prone positioning were found to

Figure 1. Distinction between refractory hypoxemia, traditional oxygenation target, and an oxygenation target toward normoxemia to optimize long-term outcomes in the management of acute respiratory distress syndrome. Values for curve derived from the equations developed by Severinghaus (66).

improve 90-day mortality and increase ventilator-free days in moderate-to-severe ARDS (32, 33). In each of these trials, an oxygenation target range of 55 to 80 mm Hg was employed to minimize oxygen toxicity and the potential excessive oxidant stress that may contribute to ARDS pathogenesis (18–20).

In contrast, the long-term effects of these interventions remain unknown. Specifically, despite the potential to improve long-term cognitive outcomes by improving oxygenation (33) or reducing lung stretch (35, 36) in the case of proning or indirectly by shifting the balance between oxygen delivery and oxygen consumption to a more favorable position in the case of neuromuscular blocking agents (32), the effects of these interventions on long-term outcomes remain speculative.

The Long-Term Perspective: Survivorship

The long-term perspective, where the time horizon extends beyond the hospitalization, prioritizes care that results in optimal long-term physical and neuropsychological health. Cognitive impairment, an outcome of vital importance to ARDS survivors and their caregivers (37), is common after ARDS (11, 13, 15, 16). Emerging evidence suggests that mechanical ventilation *per se* may trigger neuronal apoptosis via vagal and dopaminergic pathways (36). In contrast to mechanical ventilation, which is required to support life in ARDS, the selected oxygenation target range may be a potentially modifiable risk factor for long-term cognitive impairment after ARDS.

The brain constitutes 2% of total body mass, yet requires 20% of total body oxygen consumption to supply the energy required to maintain ionic gradients and other diverse, complex cellular functions to preserve cognitive function (26, 38–40). Oxygen delivery to the brain is dependent on cerebral blood flow, oxygen content (hemoglobin-bound and dissolved oxygen), and the cerebral metabolic rate of oxygen consumption. In the normal state of health, approximately 30–40% of the hemoglobin-bound oxygen is extracted by the brain as measured by jugular venous oximetry (26, 41); in contrast, virtually all of the dissolved oxygen content appears to be metabolized (42). As an organ

incapable of storing metabolic fuel, when the oxygen supply is compromised, a complex cascade mediated by excitatory neurotransmitters and calcium influx ensues that culminates in neuronal injury and synaptic dysfunction (26, 38–40). Several compensatory mechanisms exist to mitigate the effects of acute hypoxemia, including increases in cerebral blood flow, glycolysis, oxygen extraction fraction, and erythropoietin production (26, 38–40). Over weeks, hypoxia-inducible factor-1 α induces neovascularization (26). Many of these adaptive response mechanisms, however, are compromised in critical illness.

ARDS exemplifies how the synergistic effects of critical illness and impaired oxygen delivery may contribute to long-term cognitive impairment (7). First, ARDS is characterized by dysregulated inflammation, excessive oxidant stress, and coagulation and endothelial dysfunction (43), factors that have been implicated in the pathogenesis of critical illness–associated cognitive impairment (44). Furthermore, inflammation impairs erythropoietin production (45), and hypoxia itself perpetuates and amplifies inflammation (46) and may exacerbate neuroinflammation after brain injury (47, 48). Second, hypoxia, a cardinal feature of ARDS, is associated with neuronal loss, cerebral atrophy, and ventricular enlargement (38, 40). These neuroanatomical changes have been observed in ARDS survivors (49) and are consistent with hippocampal and temporal lobe atrophy and loss of white matter tract integrity. These regions of the brain are especially vulnerable to hypoxia (49) and localize to cognitive domains frequently impaired in ARDS survivors, that is, memory and executive function (11, 13, 16). Third, anemia and ischemia frequently coexist in ARDS (2, 3, 5, 6, 50) and may further impair oxygen delivery at the macrocirculatory level, and hypotension in particular has been implicated in the development of cognitive impairment after ARDS (51). At the microcirculatory level, alterations in red blood cell deformability (45), cerebral microcirculation (52), and impaired tissue oxygen extraction (53) may further impair brain tissue oxygenation in critical illness.

In ARDS, the threshold, in terms of severity and duration of subnormal oxygenation values, at which the brain is

injured and cognitive function impaired is unknown. Evidence suggests that the noninjured brain can tolerate tissue oxygen levels significantly lower than normal values for short periods before injury results, as long as perfusion is maintained (54–56). In contrast, brain tissue hypoxia (< 20 mm Hg) is associated with poor outcomes in the severely injured brain and oxygen-directed strategies may improve outcomes (27, 56, 57). Although the optimal strategy to restore brain tissue oxygen tension to normal levels after brain injury is unknown, guidelines recommend targeting oxygenation values toward or within normal limits (58, 59). In practice, based on the observation that brain tissue oxygen tension appears to be highly dependent on diffusion of dissolved oxygen (60), a common, albeit controversial, strategy in treating patients with traumatic brain injury is to use high FiO_2 to achieve supraphysiological PaO_2 values to restore brain tissue oxygen levels (57).

Although the neuropathology of ARDS is unclear, for the above-described reasons, inadequate oxygenation has been implicated as playing a central role in the development of long-term cognitive impairment. Inadequate oxygenation was first identified as a potentially modifiable risk factor for long-term cognitive impairment in ARDS survivors in 1999 (11). Using extensive, serial pulse oximetry measurements, Hopkins and colleagues found that the amount of time spent well below normal saturation values (e.g., < 90%) correlated with decreased cognitive performance in the domains of attention, memory, mental processing speed, visuospatial skills, executive function, and intelligence (11). The association between lower oxygenation values and long-term cognitive impairment and executive dysfunction was confirmed in survivors from the ARDSNet Fluid and Catheter Treatment Trial (FACTT) (13). In survivors with cognitive impairment at 12 months, which constituted 55% of those examined, the average daily PaO_2 values (measured closest to 8:00 A.M.) were significantly lower compared with nonimpaired survivors (71 mm Hg [interquartile range, 67–80 mm Hg] vs. 86 mm Hg [interquartile range, 70–98 mm Hg]; $P = 0.02$) (13). In the most recent ARDSNet trial, long-term cognitive impairment was observed in 25% of survivors at 12 months (15, 16). Compared

with prior trials (2, 3), the latest trial enrolled a greater proportion of subjects with mild ARDS (15, 16). Although the relationship between severity of hypoxemia and long-term cognitive impairment was not examined formally in these studies (15, 16), and other potential explanations exist, it serves as additional, indirect evidence for the association. Although these associations do not establish causation and the severity of hypoxemia may serve as a marker of illness severity, the collective evidence suggests that, in ARDS, the brain may not tolerate subnormal oxygenation values.

An Alternative Approach to Oxygenation in ARDS: Resetting the Target toward Normoxemia

Because the evidence suggests that a strategy in which oxygen is titrated to subnormal levels may contribute to long-term cognitive impairment in ARDS survivors, it seems plausible that raising the target range for arterial oxygenation to 85–110 mm Hg and 94–98% oxyhemoglobin saturation (25) may reduce the risk of long-term cognitive impairment in ARDS survivors (Table 1 and Figure 1). An oxygenation strategy that more closely approximates the normal state of health (25), combined with lower tidal volume ventilation (2) and precise oxygen titration to avoid hyperoxia (sustained FI_{O_2} in excess of 80%) and hyperoxemia (18–20, 22), has the potential to improve both short- and long-term outcomes in ARDS.

Admittedly, oxygen delivery to brain tissue is more complex than the arterial oxygen content alone, and vigilance to

maintain adequate cardiac output and perfusion pressure is critical to any approach aimed to preserve cognitive function after ARDS. Theoretically, strategies to augment cardiac output and improve oxygen carrying capacity through transfusion would increase oxygen delivery. However, a complicated relationship exists between macrohemodynamics and the microcirculation (61); transfusions may not increase oxygen transport in the manner predicted (62, 63); and the use of intravenous fluids (64), vasoactive agents (65), and transfusions (45) has each been associated with adverse consequences. An alternative approach would be to reduce the cerebral metabolic rate of oxygen consumption through targeted temperature management or pharmacologic coma. To avoid the complexities and potential harm of these alternatives, we have taken the approach to reconsider the oxygenation target while simultaneously prioritizing the maintenance of adequate perfusion pressure.

The ideal approach to achieve the higher oxygenation target range safely remains unknown. To attenuate the risk of hyperoxia-induced lung injury (18–20), the optimal strategy would incorporate direct means, such as increased FI_{O_2} , and indirect means, such as positive end-expiratory pressure and prone positioning (33). Ultimately, while basic science investigations and carefully designed observational studies are required to better understand the relationship between oxygenation and long-term cognitive impairment in ARDS, a randomized trial comparing the traditional approach titrated to a target Pa_{O_2} of 55–80 mm Hg to a higher target range would be necessary to test the hypothesis. The question could be

tested directly (i.e., Pa_{O_2} target range of 55–80 vs. 85–110 mm Hg), or, alternatively, a trial could be designed to test an intervention (e.g., early, prolonged proning) and different oxygenation targets in a factorial design. A strategy in which oxygen is titrated toward normoxemia could result in prolonged duration of mechanical ventilation, and therefore extended length of stay, by delaying extubation if one used a protocolized target of FI_{O_2} and positive end-expiratory pressure to commence weaning (i.e., potential for short-term harm, long-term benefit). To combat this potential disadvantage and related adverse effects (i.e., sedation), a transient deescalation of support when approaching liberation would be necessary.

Conclusions

The short- and long-term morbidity and mortality associated with ARDS remain substantial. For many, cognitive impairment is a life-altering consequence of ARDS that impacts the day-to-day lives of survivors and their caregivers. Although advances have been made to improve short-term outcomes, there is an urgent need to identify novel strategies to preserve neuropsychological health after ARDS. Whether resetting the oxygenation target toward normoxemia within a lung-protective ventilation strategy, as an example of a potential neuroprotective intervention, would be effective remains unknown.

For now, as clinicians begin the process of critically evaluating the long-term effects of critical care practice, they are left with many of the same questions that were posed by the Consensus Conference in 1998: “Under which condition(s) is a subnormal Pa_{O_2} tolerable? How is adequacy of tissue O_2 delivery best assessed? What are the acceptable limits for pH, Pa_{CO_2} and Pa_{O_2} ?” (30). Until these questions are answered, the team assembled at the bedside of a patient with ARDS will need to consider both the short- and long-term perspectives when selecting an oxygenation target. ■

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Table 1. Comparison of two target ranges for arterial oxygenation in acute respiratory distress syndrome: potential advantages and disadvantages

	Traditional Target	Toward Normoxemia
Oxygenation target	55–80 mm Hg	85–110 mm Hg
Potential advantages	<ul style="list-style-type: none"> ● Mitigate risk of hyperoxia-induced lung injury ● Reduce duration of mechanical ventilation 	<ul style="list-style-type: none"> ● Mitigate risk of long-term cognitive impairment
Potential disadvantages	<ul style="list-style-type: none"> ● Increase risk of long-term cognitive impairment 	<ul style="list-style-type: none"> ● Increase risk of hyperoxia-induced lung injury ● Increase duration of mechanical ventilation

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