Goal-Directed Therapy for Severely Hypoxic Patients With Acute Respiratory Distress Syndrome: Permissive Hypoxemia

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Permissive hypoxemia is a lung-protective strategy that aims to provide a patient with severe acute respiratory distress syndrome (ARDS) a level of oxygen delivery that is adequate to avoid tissue hypoxia while minimizing the detrimental effects of the often toxic ventilatory support required to maintain normal arterial oxygenation. However, in many patients with severe ARDS it can be difficult to achieve a balance between maintaining adequate tissue oxygenation and avoiding ventilator-induced lung injury (VILI). A potential strategy for the management of such patients involves goal-oriented manipulation of cardiac output and, if necessary, hemoglobin concentration, to compensate for hypoxemia and maintain a normal (but not supranormal) value of oxygen delivery. Although it has not yet been studied, this approach is theorized to improve clinical outcomes of critically ill patients with severe ARDS. We stress that the goal of this article is not to convince the reader that this approach is necessarily correct, as data are clearly lacking, but rather to provide a basis for continued thought, discussion, and potential research. *Key words: mechanical ventilation; oxygen delivery; cardiac output; hypoxia; shock; acidosis; critical illness; hypoxemia; acute lung injury; acute respiratory distress syndrome; anemia; physiology; hypercapnia.* [Respir Care 2010;55(11):1483–1490.

Introduction

To date, no clinical trial has evaluated the impact of increasing cardiac output while targeting normal—*not* supranormal—oxygen delivery (D_{O_2}) on the clinical outcomes of critically ill patients with refractory hypoxemia. The overall goal of permissive hypoxemia, as a lung-protective strategy, is to minimize the detrimental pulmonary and systemic effects of high ventilatory support (by accepting a relatively low arterial oxygen saturation [S_{aO_2}]), while maintaining adequate D_{O_2} by optimizing cardiac output.

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In general, the strategy of permissive hypoxemia aims for an S_{aO_2} between approximately 82% and 88%. The concept of permissive hypoxemia does not direct a specific S_{aO_2} goal but, rather, a careful balance between the target S_{aO_2} and the ventilatory toxicity required to achieve a higher S_{aO_2}. As ventilatory support is increased beyond the level acceptable to the bedside clinician, the target S_{aO_2} may decrease as long as global D_{O_2} can be maintained. The actual goal S_{aO_2} will probably differ between patients and vary in an individual patient over time. Theoretically, permissive hypoxemia may improve outcomes in pediatric and adult patients with severe acute respiratory distress syndrome (ARDS).

On one hand, randomized controlled clinical trials have demonstrated that maintaining a supranormal D_{O_2} does not improve survival and may actually be detrimental.[1-4] However, other clinical trials have reported favorable outcomes with supranormal D_{O_2}.[5-7] Rivers and co-workers[8] have shown that the concept of early goal-directed therapy reduces mortality for patients with severe sepsis and septic shock. This approach involves adjustments of cardiac preload, afterload, and contractility to balance D_{O_2} with oxygen consumption ($\dot{V}_{O_2}$). The physiologic rationale for a D_{O_2} early-goal-directed-therapy approach is to augment

systemic D_{O_2} to alleviate tissue hypoxia, which can progress to multi-organ failure and death.

In this paper we explore the hypothesis that augmenting cardiac output to supranormal values can normalize D_{O_2}, reduce tissue hypoxia, and allow reduction of ventilator settings in severely hypoxic, critically ill patients. We address this issue by examining the relationship between cardiac output, arterial oxygen content (C_{aO_2}), and D_{O_2}, while emphasizing the role of supranormal cardiac output as a physiologic compensatory mechanism that may prevent tissue hypoxia when C_{aO_2} is reduced. Then we consider the clinical utility of this strategy for the treatment of severe ARDS in patients who remain hypoxic despite high, and potentially injurious, ventilatory assistance, and in those who develop tissue hypoxia while being treated with permissive hypoxemia.

Permissive Hypoxemia as a Lung-Protective Strategy

Mechanical ventilation is the mainstay of supportive management for most ARDS patients, to prevent life-threatening hypoxemia.[9] Arterial oxygenation can be improved by increasing the F_{IO_2} and/or mean airway pressure (ie, PEEP). However, when treating mechanically ventilated ARDS patients, the benefit of improved arterial oxygenation must be balanced against the potential, and often real, risk of volutrauma, barotrauma, biotrauma, and oxygen toxicity, as well as the adverse cardiovascular effects of increased mean airway pressure on right-ventricular function. Currently the optimal strategy for the management of patients with ARDS is to maintain an "adequate" oxygenation of arterial blood while avoiding VILI. Unfortunately, this may be difficult to achieve in practice, especially in those patients with severe lung disease, as the maintenance of "satisfactory" arterial oxygenation (eg, $S_{aO_2} \geq 90\%$) often requires the use of high and potentially dangerous levels of F_{IO_2} and PEEP (ie, mean airway pressure). This has led to the emergence of the concept of permissive hypoxemia,[10,11] which focuses primarily on the adequacy of tissue oxygenation rather than arterial oxygenation, assuming that clinical outcome is more likely to be determined by the amount of oxygen that actually reaches the tissues than the amount that circulates in the blood.

Permissive hypoxemia is a lung-protective strategy designed to minimize VILI. If measures are not taken to augment D_{O_2} and reduce $\dot{V}_{O_2}$, this approach obviously can lead to tissue hypoxia. A potential strategy for the management of patients with ARDS in whom permissive hypoxemia has been complicated by tissue hypoxia involves goal-oriented manipulation of cardiac output and hemoglobin concentration (if necessary) to compensate for hypoxemia and maintain a normal (but not supranormal) value of tissue D_{O_2}. In the clinical context of ARDS, especially when treated with permissive hypoxemia, augmenting cardiac output can improve tissue oxygenation, minimize tissue hypoxia, and allow for a reduction of ventilator settings to reduce the risk of VILI. A combined strategy of permissive hypoxemia and supranormal cardiac output may, therefore, achieve the ultimate goal of maintaining tissue oxygenation and preventing tissue hypoxia without having to pay the clinical price of increasing P_{aO_2}.

An important question arises regarding the optimal hemoglobin concentration for patients treated with this strategy. A body of evidence supports the restricted use of blood transfusions in critically ill patients. A transfusion threshold of 7 g/dL for most critically ill adult and pediatric patients has been recommended.[12,13] However, those studies were not conducted under conditions of permissive hypoxemia, so a higher transfusion threshold is likely to be more appropriate for ARDS patients treated with permissive hypoxemia, especially if accompanied by tissue hypoxia. A hemoglobin concentration of 9–10 g/dL would seem to be a reasonable option until data from further studies are available. It should be noted that this proposed transfusion threshold is purely speculative, based on clinical experience.

A comprehensive review of the physiology must include the interaction between permissive hypoxemia and permissive hypercapnia. Because of widely used lung-protective strategies that limit delivered tidal volume, many ARDS patients develop hypercapnia and subsequent respiratory acidosis, which shifts the oxyhemoglobin dissociation curve to the right and enhances the unloading of oxygen at the tissue level.[14] Thus, the strategies of permissive hypercapnia and permissive hypoxemia may be viewed as complementary from a physiologic perspective.

As an alternative strategy to permissive hypoxemia we must consider extracorporeal techniques, including veno-venous and veno-arterial extracorporeal membrane oxygenation (ECMO). Although potentially beneficial, ECMO is not without risk. A thorough discussion of ECMO is beyond the scope of this article; however, the advantages/disadvantages and risks/benefits of the possible approaches for a patient with severe hypoxemic respiratory failure must be considered by the clinical care team.

What are the potential risks of permissive hypoxemia? Is permissive hypoxemia equally tolerated by different organ systems? Different organ systems may have different degrees of tolerance to hypoxemia. For example, the healthy brain can generally tolerate hypoxemia better than other organ systems, as long as cerebral perfusion is maintained.[15] However, it should be noted that hypoxemia can lead to long-term cognitive deficits and structural neurologic damage, as observed at extremely high altitude[16-18] and in some survivors of severe ARDS.[19] Furthermore, as the injured brain is extremely sensitive to hypoxemia, a strategy of permissive hypoxemia may not be suitable for patients with traumatic or ischemic brain injury.

Additionally, permissive hypoxemia can increase pulmonary artery pressure (through hypoxic pulmonary vasoconstriction) and subsequently cause right-ventricular dysfunction, which can adversely affect the clinical outcome of ARDS.[20,21] Permissive hypoxemia (while potentially limiting the adverse hemodynamic, mechanical, and biochemical effects of mechanical ventilation) may increase renal vascular resistance, leading to renal hypoperfusion and a decrease in glomerular filtration rate.[22]

On the other hand, the ultimate goal of permissive hypoxemia is to reduce VILI and its associated biotrauma, a pulmonary inflammatory reaction that can adversely affect the kidneys and other organs and tissues through the systemic release of inflammatory cytokines. Thus, the effects of permissive hypoxemia on renal (and other end-organ) function are unknown and may be variable. Clinical studies are clearly needed to evaluate the safety and efficacy of permissive hypoxemia as a potential strategy to prevent VILI.

Supranormal Cardiac Output as a Physiologic Adaptation to Low Oxygen Content

In many critically ill patients, especially those with severe ARDS, intrapulmonary shunt and ventilation-perfusion abnormalities cause life-threatening hypoxemia, which can in turn compromise D_{O_2} and result in tissue hypoxia, especially when accompanied by low cardiac output, decreased hemoglobin concentration, and/or increased metabolic demand. However, since D_{O_2} is a function of cardiac output and C_{aO_2}, we may hypothesize that cardiac output augmentation with preload optimization, inotropic agents, vasodilators, and, in selected patients, ventricular-assist devices, can maintain a constant D_{O_2} even when C_{aO_2} is substantially reduced. The amount of oxygen delivered to the tissues is described by:

$$D_{O_2}\ (\text{mL/min}) = 10 \times \text{cardiac output (L/min)} \times C_{aO_2} \quad (1)$$

where

$$C_{aO_2} = (1.34 \times \text{hemoglobin} \times S_{aO_2}) + (P_{aO_2} \times 0.003) \quad (2)$$

where 1.34 is the amount of oxygen (in mL) carried by 1 g of hemoglobin, P_{aO_2} is the partial pressure of arterial oxygen, and 0.003 is the solubility of oxygen in plasma.

Accordingly, it may be assumed that cardiac output, S_{aO_2}, and hemoglobin concentration, the 3 major components of D_{O_2}, are physiologically interdependent and that a decrease in one component can be counterbalanced by a compensatory increase in another. Hence, tissue hypoxia may not occur during hypoxemia or anemia if cardiac output is adequately increased. The physiologic rationale for this hypothesis is based on the observation that cardiac output is increased in response to acute hypoxemia and acute isovolemic anemia, in which case supranormal cardiac output may serve as a physiologic adaptive mechanism to prevent tissue hypoxia by maintaining oxygen supply in balance with oxygen demand.

Several animal studies have shown that cardiac output increases in response to acute hypoxemia.[23-28] In an animal model of hypothermic cardiopulmonary bypass, Schultz et al[29] demonstrated that cardiac output augmentation improved the balance between cerebral D_{O_2} and cerebral oxygen consumption, despite the presence of hypoxemia. In birds, which are remarkably tolerant of hypoxia, it has been demonstrated in various studies that increased cardiac output and redistribution of blood flow to the heart and brain play an important role in physiologic adaptation to hypoxia.[30-33]

A number of clinical studies have also demonstrated that cardiac output increases substantially in normal subjects during acute hypoxemia.[34,35] This finding may explain why well trained athletes can tolerate hypoxemia at high altitude remarkably well. Climbers who have reached the summit of Mount Everest without supplemental oxygen can have a P_{aO_2} less than 25 mm Hg without clinically important hyperlactatemia (mean lactate concentration, 2.2 mmol/L).[36] Possibly, these well trained athletes tolerate severe hypoxemia because of their ability to maximize cardiac output and thus ensure an adequate oxygen supply to their tissues.

It remains unclear, however, if increased cardiac output in response to hypoxemia can reduce tissue hypoxia in the critically ill patient. Several studies have demonstrated that patients with acute isovolemic anemia have high cardiac output secondary to increased myocardial contractility and reduced blood viscosity.[37-40] Again, this emphasizes the importance of supranormal cardiac output as a physiologic compensation to anemia, and may explain the findings of Hebert et al[12] and Lacroix et al,[13] that a hemoglobin concentration as low as 7 g/dL is well tolerated by critically ill patients. *How can these patients tolerate a 50% reduction of C_{aO_2} without developing tissue hypoxia, multi-organ failure, and death*? In addition to a compensatory increase in cardiac output, other, possibly less important, adaptive mechanisms include a rightward shift of the oxyhemoglobin dissociation curve, increased oxygen extraction by the tissues, and improved microcirculatory flow.[41]

Supranormal cardiac output can be considered an important compensatory mechanism by which sufficient oxygen can be delivered to the tissues during hypoxemia or anemia. It is likely that critically ill patients can tolerate

mild to moderate degrees of hypoxemia or anemia if tissue oxygenation is adequately maintained. This should prompt us to redirect our attention to the adequacy of D_{O_2} rather than to the numeric values of its components, such as S_{aO_2} and hemoglobin concentration (the so-called *tissue-oxygenation-oriented strategy*). Understanding the role of supranormal cardiac output as a physiologic adaptation to low C_{aO_2} may have a therapeutic implication for the management of hypoxic patients, especially those with severe ARDS.

Does Constant Oxygen Delivery Predict Constant Oxygen Uptake?

Cardiac output is the most important component of D_{O_2}, and can compensate for decreased C_{aO_2} to maintain an adequate oxygen supply to the tissues.[42] However, it remains unclear whether an augmented cardiac output can maintain a constant $\dot{V}_{O_2}$ in clinical conditions characterized by low C_{aO_2}, such as substantial anemia or hypoxemia.

What determines $\dot{V}_{O_2}$? We must attempt to answer this question to better assess the potential role of permissive hypoxemia in the clinical setting of severe ARDS. Is it the capillary P_{O_2} that represents the driving force for oxygen diffusion from capillary to mitochondria? Or is it the total amount of oxygen delivered to the tissues that determines $\dot{V}_{O_2}$, regardless of the presence of anemia, hypoxemia, or low cardiac output?

Unfortunately, the medical literature provides conflicting data, mostly from animal studies, regarding the ability of an augmented cardiac output to maintain a constant $\dot{V}_{O_2}$ during hypoxemia and isovolemic anemia. In an animal study that compared low-flow/high-C_{aO_2} and high-flow/low-C_{aO_2} conditions, while maintaining D_{O_2} constant, Hogan et al[43] reported that high cardiac output failed to compensate for low C_{aO_2}, and that maximal $\dot{V}_{O_2}$ ($\dot{V}_{O_{2max}}$) was lower during the high-flow/low-C_{aO_2} condition. They also noted that for the same D_{O_2}, capillary P_{O_2} is lower during hypoxemia than during anemia, and muscle $\dot{V}_{O_{2max}}$ is decreased more if the reduction in D_{O_2} is caused by hypoxemia than by anemia.[44] Those authors suggested that with decreased D_{O_2} (as in hypoxemia, for example), capillary P_{O_2} is decreased and $\dot{V}_{O_{2max}}$ declines because of the reduced pressure gradient for oxygen diffusion. They concluded that D_{O_2} is important in determining $\dot{V}_{O_{2max}}$, primarily because of its role in determining capillary P_{O_2} (the so-called *diffusion limitation hypothesis*). The importance of capillary P_{O_2} in determining $\dot{V}_{O_{2max}}$ is illustrated in the following equation:

$$\dot{V}_{O_2} = D_{O_2} (\text{capillary } P_{O_2} - \text{mitochondrial } P_{O_2}) \quad (3)$$

According to this diffusion limitation hypothesis, when capillary P_{O_2} is decreased (as in hypoxemia), $\dot{V}_{O_2}$ can no longer be maintained constant, even though D_{O_2} is adequately maintained. This hypothesis was subsequently tested by Dodd et al,[45] who compared the effects of reduced D_{O_2} with anemia, hypoxemia, and ischemia on $\dot{V}_{O_{2max}}$ in skeletal muscle in dogs. That follow-up study demonstrated that, for the same D_{O_2}, $\dot{V}_{O_{2max}}$ was equivalent, although capillary P_{O_2} was greater, during anemia than during hypoxemia. Thus, capillary P_{O_2} was lower while $\dot{V}_{O_{2max}}$ remained the same during hypoxemia, as compared to anemia. It might be speculated that the decreased capillary P_{O_2} in hypoxemia is counterbalanced by enhanced oxygen unloading, which favors the release of oxygen into the tissues.[46]

The relationship between oxygen delivery and oxygen consumption can also be illustrated by an equation that does not take into account capillary P_{O_2} as a determinant of $\dot{V}_{O_2}$:

$$\dot{V}_{O_2} (\text{mL } O_2/\text{min}) = 10 \times \text{cardiac output (L/min)} \times (C_{aO_2} - C_{vO_2}) \quad (4)$$

where C_{vO_2} is the mixed venous oxygen content. From that equation it is apparent that D_{O_2}, but not capillary P_{O_2}, is the principal determinant of $\dot{V}_{O_2}$. Cain[47] studied low-D_{O_2} states produced by anemia and hypoxemia in anesthetized dogs and demonstrated no difference in critical D_{O_2} (the level below which $\dot{V}_{O_2}$ falls and tissue hypoxia develops) in either the anemic or hypoxic group. He concluded that $\dot{V}_{O_{2max}}$ is dependent on the absolute quantity of oxygen delivered to the tissues, and not on the capillary P_{O_2}. This finding is supported by various animal studies,[48-50] which demonstrated that the limitation in $\dot{V}_{O_{2max}}$ is dependent on the absolute level of D_{O_2}, and not on the method by which D_{O_2} is reduced.

In those studies, experimental animals developed lactic acidosis when D_{O_2} was reduced below a critical D_{O_2} level, regardless of being anemic, hypoxic, or ischemic, which suggests that D_{O_2} as a whole is more important than the absolute values of hemoglobin, S_{aO_2}, or cardiac output in maintaining $\dot{V}_{O_{2max}}$ and preventing tissue hypoxia. It should be noted, however, that the determinants of tissue hypoxia may be different in critically ill patients, in whom alterations of microvascular blood flow are frequent.[51] Moreover, since the data from those animal studies do not truly reflect the type of therapy proposed in this article, clinical studies are needed to explore the relationship between oxygen delivery and oxygen consumption in *clinical* conditions associated with high cardiac output and low oxygen content. Until such studies are performed to better understand the potential implications of permissive hypoxemia

in the intensive care unit setting, caution should be exercised when extrapolating the results of these animal studies to clinical practice. For each individual patient the risks and benefits of such an approach must be carefully considered by the clinical care team.

Risks and Benefits of Maximizing Cardiac Output

As previously mentioned, cardiac output can compensate to provide adequate tissue oxygen supply when the oxygen content of arterial blood is reduced. For example, an ARDS patient with an S_{aO_2} of 80% and a hemoglobin concentration of 10 g/dL would still have normal D_{O_2} if his/her cardiac index were increased to 4.5 L/min/m^2 (calculated D_{O_2} is 480 mL/min/m^2, normal value is 400–650 mL/min/m^2). On the contrary, another patient with ARDS who has a cardiac index of 3 L/min/m^2 and a hemoglobin concentration of 10 g/dL may suffer from tissue hypoxia despite having an S_{aO_2} of 90% (calculated D_{O_2} is 360 mL/min/m^2). Interestingly, increasing the cardiac index from 3 L/min/m^2 to 4.5 L/min/m^2 would increase tissue D_{O_2} much more than raising S_{aO_2} from 80% to 90%. This can obviate aggressive attempts to correct hypoxemia by increasing the F_{IO_2} and/or airway pressure, which can increase the risk of VILI and oxygen toxicity. This clinical example illustrates the central role of cardiac output in physiologic compensation for hypoxemia and provides a theoretical basis for the use of supranormal cardiac output in the treatment of patients with severe ARDS, especially those who remain hypoxic despite maximal ventilatory support. However, supranormal cardiac output can be difficult to achieve in many patients with critical illness. In a large multicenter trial with approximately 11,000 critically ill patients, a supranormal cardiac index (defined as $>$ 4.5 L/min/m^2) was reached in only 45% of patients.[1]

In addition to improving D_{O_2} and alleviating tissue hypoxia, supranormal cardiac output can also improve arterial oxygenation. *How would high cardiac output raise* S_{aO_2}? First, improving oxygen supply to hypoxic tissues through manipulation of cardiac output decreases tissue oxygen extraction and increases mixed venous oxygen saturation (S_{vO_2}) and, hence, S_{aO_2}. This is particularly relevant in ARDS, because in the presence of increased intrapulmonary shunting (a hallmark of ARDS), alterations in mixed venous oxygenation will influence arterial oxygenation.[52,53] Second, because of hypoxic pulmonary vasoconstriction, increased blood flow secondary to high cardiac output is more likely to be diverted away from the consolidated or collapsed alveoli toward normally functioning lung units, thereby improving ventilation-perfusion matching, pulmonary gas exchange, and arterial oxygenation.

It must be noted that, on the other hand, supranormal cardiac output increases pulmonary blood flow and decreases capillary transit time, which may worsen hypoxemia if the flow rate is too high.[54] Supranormal cardiac output can also decrease the red cell transit time in systemic circulation and impair oxygen unloading to the tissues.[55] Moreover, it must be noted that by increasing metabolic demand, inotropic agents used to augment cardiac output may unfavorably alter the balance between oxygen delivery and oxygen consumption and thus exacerbate tissue hypoxia, especially if these agents fail to improve cardiac output and D_{O_2}.[56] It also must be cautioned that inotropic agents may provoke arrhythmias and ischemia, especially in patients with preexisting coronary artery disease, by creating an imbalance between myocardial oxygen supply and demand.[57]

Probably, the most important benefit of cardiac output augmentation, and the underlying principle behind permissive hypoxemia (as discussed in more detail in the next section), is to maintain a constant, adequate D_{O_2} in severely hypoxic ARDS patients while avoiding ventilator-induced complications that may develop when high ventilator settings are used to treat refractory hypoxemia. To be thorough in this discussion of augmenting cardiac output, it should be noted that increased cardiac output may elevate pulmonary vascular pressure and/or pulmonary blood flow and give rise to shearing stresses within the vascular endothelium, which can initiate or exacerbate endothelium-epithelium injury at the alveolar-capillary junction.[58-60] Dreyfuss and Saumon[61] demonstrated that ventilation with negative pressure caused more severe lung damage than that caused by positive pressure, suggesting the involvement of increased pulmonary blood flow in VILI. They also noted that rats administered dopamine to increase cardiac output suffered increased albumin leak when ventilated with high pressure, providing further evidence that increased pulmonary vascular pressure resulting from maximized cardiac output may accentuate a tendency toward VILI.[62] Another important point to consider is that under high-permeability conditions of early ARDS, even minor increases in pulmonary microvascular pressure can dramatically increase edema formation.[58] Therefore, the potential benefits of supranormal cardiac output—as a strategy to maintain D_{O_2} by targeting cardiac output rather than arterial oxygenation—should be carefully weighed against the possible risks associated with this strategy.

Tissue Hypoxia: Diagnostic and Therapeutic Challenges

Tissue oxygenation reflects the balance between D_{O_2} and $\dot{V}_{O_2}$. Tissue hypoxia can develop if there is a decrease in cardiac output (ischemic hypoxia), hemoglobin concentration (anemic hypoxia), or oxygen saturation (hypoxic hypoxia), or an increase in the metabolic demands of the body.[63] In sepsis, tissue hypoxia is secondary to disordered distribution of regional blood flow despite a high tissue

D_{O_2}.[64] Sepsis is also characterized by mitochondrial dysfunction, impaired oxygen extraction capability, and abnormal tissue oxygen utilization (cytopathic hypoxia).[64,65] Thus, cardiac output augmentation cannot be expected to correct regional or global tissue hypoxia in sepsis (a common cause of ARDS) unless sepsis has induced myocardial depression and a low cardiac output state. Tissue hypoxia, however, can be reduced if tissue oxygen demand/consumption is reduced by cooling febrile patients[66] and administering sedation, and, if necessary, neuromuscular blockade.[67]

End points used to confirm that tissue oxygen supply is adequately maintained include normalized values for S_{vO_2}, blood lactate, base deficit, and arterial pH.[68] S_{vO_2} can be measured either intermittently via repeated blood withdrawal, or continuously via a fiberoptic catheter.[69] Mixed S_{vO_2} is probably the best single indicator of the adequacy of oxygen transport, since it represents the amount of oxygen remaining in the systemic venous blood after passing through the tissues.[52] Mixed S_{vO_2} reflects the balance between oxygen supply and demand and is a surrogate for cardiac output as a target for goal-oriented hemodynamic therapy.[1] Central S_{vO_2} can be used as a surrogate for S_{vO_2} for the assessment of the adequacy of tissue oxygenation.[70]

The oxygen-extraction ratio may be preferable to mixed S_{vO_2} (and central S_{vO_2}) as an indicator of global tissue hypoxia, because arterial hypoxemia per se can reduce S_{vO_2} without necessarily indicating oxygen debt (ie, the oxygen-extraction ratio can be normal while S_{aO_2} and S_{vO_2} are proportionally reduced). S_{vO_2} has limitations in monitoring regional tissue hypoxia, especially in patients with sepsis, because marked alterations of microcirculatory blood flow reduce the sensitivity of global markers of tissue hypoxia to detect regional abnormalities of tissue oxygenation.[52,71] Moreover, since tissue hypoxia in sepsis is largely due to impaired $\dot{V}_{O_{2max}}$ and utilization, S_{vO_2} may be normal or even high despite severe tissue hypoxia.[64,65] Thus, in such situations, serial monitoring (via arterial blood gas analysis) of blood lactate and/or base deficit can be extremely helpful.

A pulmonary artery catheter can provide important data regarding hemodynamic and oxygen-transport parameters, including pulmonary artery pressure, cardiac output, and S_{vO_2}. However, randomized trials of high-risk surgical patients,[72] patients with ARDS and sepsis,[73] and those with general critical illness[74,75] showed lack of benefit from pulmonary artery catheters. Trials that compared pulmonary artery catheters to central venous catheters demonstrated that pulmonary-artery-catheter-guided therapy does not improve survival and is associated with more complications than central-venous-catheter-guided therapy.[76,77] In most clinical situations in which permissive hypoxemia is employed, pulmonary artery catheters are generally not needed as long as some combination of oxygen-extraction ratio, mixed S_{vO_2}, cerebral oxygen saturation, serum lactate, and arterial blood gases are serially monitored. If desired, cardiac output can be monitored with noninvasive or minimally invasive means, including transthoracic electrical bioimpedance,[78] electrical velocimetry,[79] transesophageal Doppler ultrasonography (which measures blood flow velocity in the descending thoracic aorta),[80,81] or transthoracic echocardiography.[82,83]

Conclusions

We hypothesize that augmenting cardiac output may adequately maintain tissue oxygen supply despite moderate hypoxemia and allow for the reduction in the amount of ventilatory support, to reduce the risk of VILI. Theoretically, this approach may be particularly helpful for ARDS patients who are more prone to lung damage, especially as high F_{IO_2} and airway pressures are used to correct hypoxemia. Although the physiologic principles presented in this paper would support permissive hypoxemia with supranormal cardiac output as a lung-protective strategy, it is important to note that this approach has not been studied and thus remains speculative. The potential risks of augmenting cardiac output to supranormal values, especially in patients with coronary artery disease, must be strongly considered. Prospective randomized clinical trials in both pediatric and adult patients are needed to evaluate the safety and efficacy of supranormal cardiac output (while targeting a normal D_{O_2}) as a therapeutic option for severely hypoxic patients with ARDS. Thus, the goal of this article is not to convince the reader that this approach is necessarily correct, as data are clearly lacking, but, rather, to provide a basis for continued thought, discussion, and potential research.

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