

FIFTY YEARS OF RESEARCH IN ARDS

Gas Exchange in Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome (ARDS) is characterized by severe impairment of gas exchange. Hypoxemia is mainly due to intrapulmonary shunt, whereas increased alveolar dead space explains the alteration of CO₂ clearance. Assessment of the severity of gas exchange impairment is a requisite for the characterization of the syndrome and the evaluation of its severity. Confounding factors linked to hemodynamic status can greatly influence the relationship between the severity of lung injury and the degree of hypoxemia and/or the effects of ventilator settings on gas exchange. Apart from

situations of rescue treatment, targeting optimal gas exchange in ARDS has become less of a priority compared with prevention of injury. A complex question for clinicians is to understand when improvement in oxygenation and alveolar ventilation is related to a lower degree or risk of injury for the lungs. In this regard, a full understanding of gas exchange mechanism in ARDS is imperative for individualized symptomatic support of patients with ARDS.

Keywords: oxygen partial pressure; carbon dioxide partial pressure; cardiac output; positive end-expiratory pressure; ventilation–perfusion ratios

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Hypoxemia and impaired CO₂ clearance are characteristics of acute respiratory distress syndrome (ARDS) (1–3). Abundant literature has explored the mechanisms of gas exchange abnormalities in ARDS. Because gas exchange remains the main physiological abnormality assessed by the clinician, understanding the complexity of the factors at play remains a cornerstone in the management of ARDS. This article reviews the basic principles of pulmonary gas exchange, the pathophysiology of gas

exchange alterations in ARDS (Table 1), the effects of various therapeutic measures (Tables 2 and 3), and how to use the assessment of gas exchange for individualized symptomatic support.

Pathophysiology of Gas Exchange in ARDS

The Concept of Ventilation-to-Perfusion Ratio

The concept of alveolar ventilation-to-perfusion ratio (V_A/Q) implies that an optimal ratio is necessary to obtain normal gas exchange and that an imbalance in this global and/or regional ratio is one of the few fundamental reasons explaining abnormal gas exchange: low V_A/Q ratios

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Table 1. Main Pathophysiologic Mechanisms of Impaired Gas Exchange in Acute Respiratory Distress Syndrome

Disturbance	Main Mechanisms
Hypoxemia	\dot{Q}_s/\dot{Q}_T Low \dot{V}_A/\dot{Q} Low $P\bar{V}_{O_2}$ Intracardiac shunt (e.g., PFO)
Hypercapnia	Increased V_D/V_T Inhomogeneous distribution of ventilation (high \dot{V}_A/\dot{Q}) Increased V_{CO_2}

Definition of abbreviations: PFO = patent foramen ovale; $P\bar{V}_{O_2}$ = mixed venous O_2 partial pressure; \dot{Q}_s/\dot{Q}_T = intrapulmonary right-to-left shunt.

(i.e., lung regions where perfusion markedly exceeds ventilation) induce hypoxemia, and high \dot{V}_A/\dot{Q} ratios (i.e., lung regions where ventilation markedly exceeds perfusion) induce hypercapnia. Impaired diffusion is another possible mechanism at the blood-gas interface. However, in the ventilated areas in ARDS, because of the high diffusion coefficient of CO_2 and the increased O_2 diffusion gradient induced by the high F_{IO_2} , equilibration of gas partial pressures between the blood and gas phases is complete in a functional gas exchange unit (i.e., alveolus and corresponding capillaries). Consequently, impaired

diffusion across the gas-blood barrier does not appear to play any role in gas exchange abnormalities in ARDS (4, 5). Therefore, for a given F_{IO_2} , total cardiac output (\dot{Q}_T), Hb concentration, and respiratory exchange ratio (RER; the ratio of whole-body CO_2 production to O_2 consumption, $\dot{V}_{CO_2}/\dot{V}_{O_2}$, usually of 0.8 at rest with a normal diet), impaired gas exchange is explained by an altered distribution of alveolar ventilation and perfusion (\dot{V}_A/\dot{Q}) (6–8).

\dot{V}_A/\dot{Q} ratios can vary from 0 (perfused but nonventilated alveoli; gas partial pressures being those of the mixed venous blood), also referred to as shunt, to infinity

(∞) (ventilated but nonperfused alveoli; gas partial pressures being those of the inspired gas), referred to as dead space (Figure 1). In a homogenous lung (i.e., having an ideal $[i]$ \dot{V}_A/\dot{Q} ratio corresponding to the RER), arterial (a) and mean alveolar (A) gas partial pressures equal each other (Figure 1). However, even a healthy lung comprises regions where perfusion exceeds ventilation (i.e., $0 \leq \dot{V}_A/\dot{Q} < i$) and where ventilation exceeds perfusion (i.e., $i < \dot{V}_A/\dot{Q} \leq \infty$). Because arterial blood is the sum of the blood from all gas exchange units, any \dot{V}_A/\dot{Q} inhomogeneity will cause alveolar-arterial (A-a) gas partial pressure differences. The more perfusion exceeds ventilation, the more $P_{(A-a)O_2}$ will fall, creating a $P_{(A-a)O_2}$. To describe the ideal alveolar air and analyze ventilation-perfusion relationships in the lungs, Riley and Courmand described a simple model with three compartments (normal ratio [i.e., $\dot{V}_A/\dot{Q} = RER$], shunt [i.e., $\dot{V}_A/\dot{Q} = 0$], and dead space [i.e., $\dot{V}_A/\dot{Q} = \infty$]), which is displayed in Figure 2 (9). Increasing the \dot{V}_A/\dot{Q} ratio by increasing minute ventilation (\dot{V}_E) cannot compensate for this effect, because of (1) the relatively small contribution to \dot{Q}_T of lung regions where ventilation markedly exceeds perfusion

Table 2. Therapeutic Measures to Correct Hypoxemia

Treatment	Beneficial Effects	Risks
High F_{IO_2}	Increases in P_{AO_2} , P_{aO_2} , and $P\bar{V}_{O_2}$	Resorption atelectasis Oxygen toxicity
PEEP	Alveolar recruitment with decrease in \dot{Q}_s/\dot{Q}_T	Lung overdistension Decreased \dot{Q}_T
Spontaneous breathing (mild-moderate ARDS, postacute phase)	Alveolar recruitment Improved \dot{V}_A/\dot{Q} matching (redirection of pulmonary blood flow to more aerated regions)	Lung overdistension VILI
Recruitment maneuver	Transient recruitment and decreased \dot{Q}_s/\dot{Q}_T	Transient decrease in \dot{Q}_T Barotrauma
Prone position	Homogenization of ventilation distribution (improved aeration in the dorsal regions) Decrease in \dot{Q}_s/\dot{Q}_T (unchanged perfusion, predominantly directed to dorsal regions)	—
Vertical positioning	Alveolar recruitment Increased lung volume	Unpredictable effect Decreased \dot{Q}_T
Inhaled NO	Decrease in \dot{Q}_s/\dot{Q}_T (improved perfusion of aerated lung regions with normal \dot{V}_A/\dot{Q} ratios)	Transient effect Rebound at withdrawal
Inhaled PGI_2	Decrease in \dot{Q}_s/\dot{Q}_T (improved perfusion of aerated lung regions with normal \dot{V}_A/\dot{Q} ratios)	Transient effect Rebound at withdrawal
Intravenous almitrine	Decrease in \dot{Q}_s/\dot{Q}_T (increased pulmonary vascular tone)	Increase in PAP and RV afterload

Definition of abbreviations: ARDS = acute respiratory distress syndrome; NO = nitric oxide; P_{AO_2} = alveolar oxygen partial pressure; P_{aO_2} = arterial oxygen partial pressure; PAP = pulmonary artery pressure; PEEP = positive end-expiratory pressure; PGI_2 = prostacyclin; $P\bar{V}_{O_2}$ = mixed venous O_2 partial pressure; \dot{Q}_s/\dot{Q}_T = intrapulmonary right-to-left shunt; \dot{Q}_T = cardiac output; RV = right ventricular; VILI = ventilator-induced lung injury.

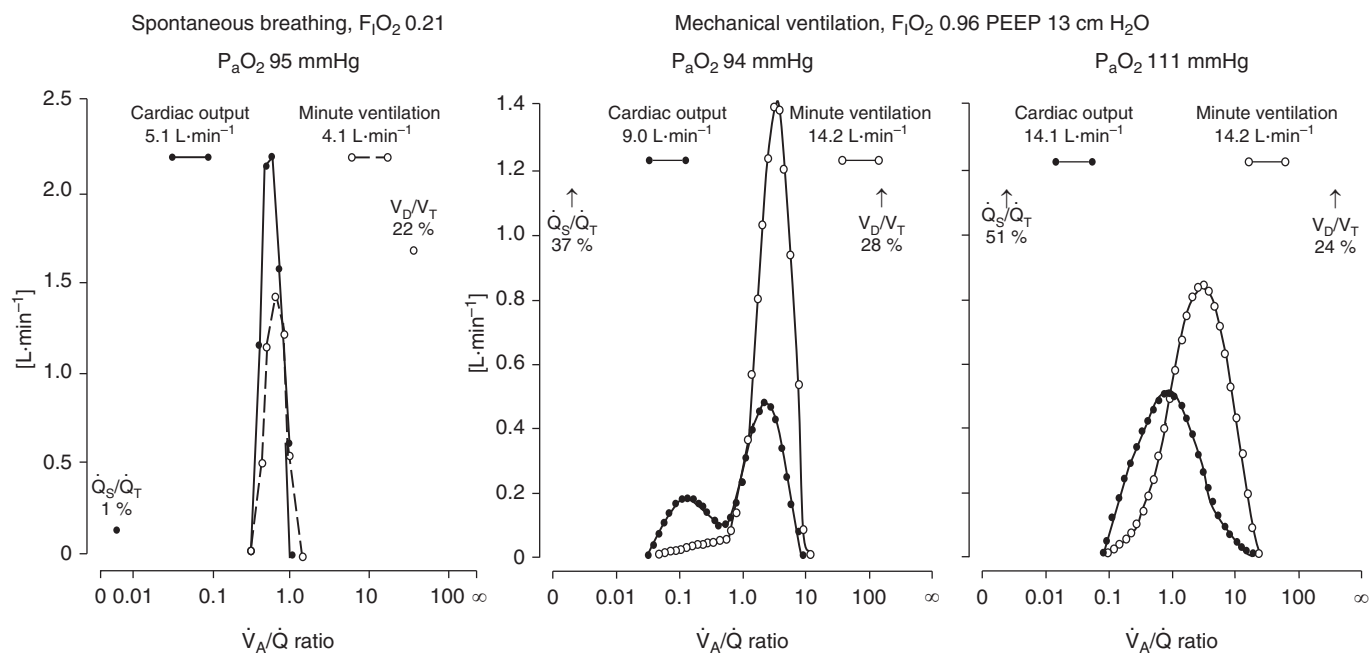


Figure 5. Continuous distributions of alveolar ventilation (\dot{V}_A ; open symbols) and pulmonary blood flow (closed symbols) as assessed using the multiple inert gas elimination technique in a young, healthy volunteer breathing air (left panel) and a patient with severe acute respiratory distress syndrome before (middle panel) and during (right panel) continuous intravenous prostacyclin (PGI_2). In this individual patient, there was a substantial fraction of pulmonary blood flow to lung regions with low \dot{V}_A/\dot{Q} ratios ($0 < \dot{V}_A/\dot{Q} < \text{normal } \dot{V}_A/\dot{Q}$) under baseline conditions, which was markedly reduced owing to increased \dot{Q}_S/\dot{Q}_T during vasodilator infusion. Note that despite the marked increase in \dot{Q}_S/\dot{Q}_T (from 37 to 51% of cardiac output), $P_{a\text{O}_2}$ even increased during the PGI_2 infusion owing to the increase in \dot{Q}_T and the subsequent increase in mixed venous P_{O_2} (see also Figures 7, 8, and 10). PEEP = positive end-expiratory pressure. Middle and right panels adapted by permission from Reference 36.

gravitational lung weight gradients (69, 70), elimination of the compressive force of the heart on dorsal lung regions (71, 72), and the release of the compression of abdominal contents on caudal regions of the dorsal lung (73, 74). The net effect is a homogenization of regional lung inflation, which increases in dorsal lung regions and decreases in ventral regions (75). In addition, both animal and human studies showed that distribution of pulmonary blood flow, which is prevalent in the dorsal lung in the supine position, surprisingly does not change when turning the patient prone (76–79). Thus, the improvement in oxygenation in the prone position is due to a reduction in \dot{Q}_S/\dot{Q}_T resulting from the concomitant increase in the aeration in the dorsal lung regions, with dorsal recruitment being greater than ventral derecruitment, and the persistence of better lung perfusion in these regions.

In sum, there is a pronounced, gravitation-related regional variability of \dot{V}_A/\dot{Q} ratios, with \dot{Q}_S/\dot{Q}_T being particularly present in the dependent lung regions. The beneficial gas exchange effect of prone

position is mainly due to the persistence of higher pulmonary blood flow in regions better aerated in prone position (32).

Pulmonary Vascular Tone

Pulmonary vascular tone may cause marked regional \dot{V}_A/\dot{Q} differences, in particular as a result of hypoxic pulmonary vasoconstriction (80): local alveolar hypoxia induces regional vasoconstriction and thus reduces perfusion to hypo- and/or nonventilated lung areas, thereby improving gas exchange (31). In patients with ARDS, increasing pulmonary vascular tone improved gas exchange (38, 61–65, 81), whereas reducing pulmonary artery pressure by hyperoxia and/or intravenous vasodilators further aggravated hypoxemia (34–36). In contrast, selective pulmonary vasodilation using inhaled vasodilators improved gas exchange: short-acting inhaled vasodilators (e.g., NO or prostacyclin) are only effective in ventilated lung areas (Figure 6). Consequently, they will redistribute pulmonary blood flow away from unventilated alveoli and thereby attenuate \dot{Q}_S/\dot{Q}_T (39–41, 82). Combining

intravenous pulmonary vasoconstrictors (e.g., almitrine) and inhaled vasodilators even further improved arterial oxygenation in some patients without aggravating right ventricular afterload (83–85).

In sum, augmenting pulmonary vascular tone generally improves \dot{V}_A/\dot{Q} distribution. Selective pulmonary vasodilating using inhaled, short-acting compounds can improve \dot{V}_A/\dot{Q} distributions, because they are only effective in ventilated lung regions (86).

Nonpulmonary Factors

In addition to the degree of low \dot{V}_A/\dot{Q} and \dot{Q}_S/\dot{Q}_T , nonpulmonary factors affect gas exchange, namely $F_{I\text{O}_2}$ (see below “High $F_{I\text{O}_2}$ ”), cardiac output (\dot{Q}_T) and \dot{V}_{O_2} (87). \dot{Q}_T affects gas exchange both indirectly by its effect on O_2 extraction, and thus on $P\bar{V}_{\text{O}_2}$, and directly by modifying \dot{V}_A/\dot{Q} distributions. The complexity is that these factors may have various effects potentially influencing oxygenation in opposite directions. According to the Fick principle

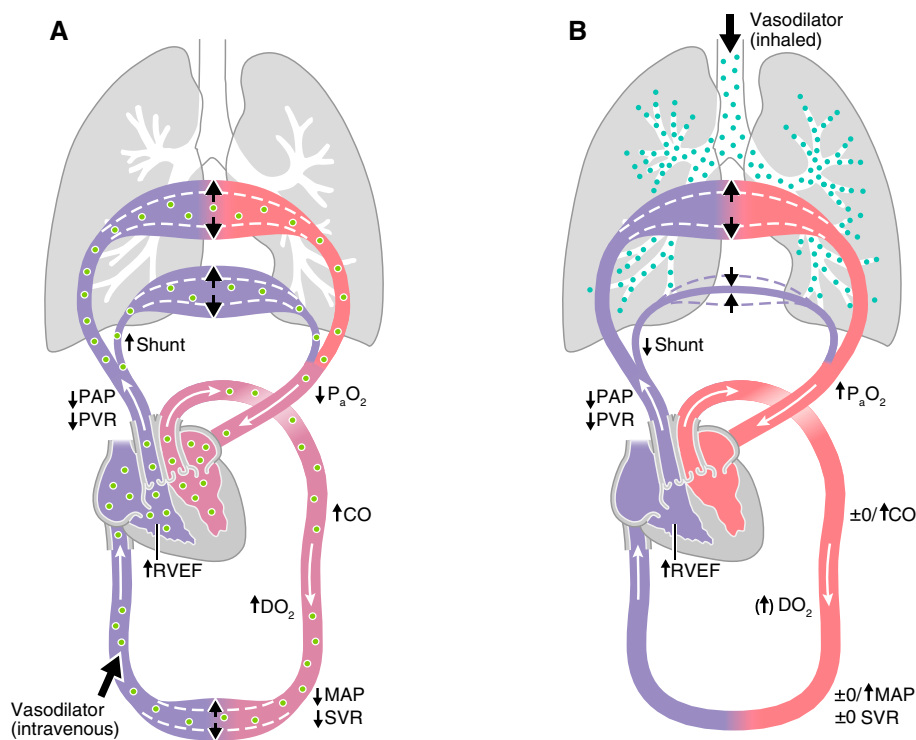


Figure 6. Effects of intravenous (i.v.) (A) and inhaled (B) prostacyclin on systemic and pulmonary hemodynamics and gas exchange in patients with acute respiratory distress syndrome. CO = cardiac output; DO₂ = systemic O₂ delivery; MAP = mean blood pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; SVR = systemic vascular resistance. Illustration by Jacqueline Schaffer.

$$\dot{V}_{O_2} = \dot{Q}_T \cdot (Ca_{O_2} - C\bar{v}_{O_2}) \Leftrightarrow$$

$$C\bar{v}_{O_2} = Ca_{O_2} - \dot{V}_{O_2} / \dot{Q}_T. \quad (11)$$

That is, $C\bar{v}_{O_2}$ and, due to the steep, near-linear shape of the Hb-O₂ dissociation curve, $P\bar{v}_{O_2}$ are directly related to arterial O₂ concentration and \dot{V}_{O_2} and inversely related to \dot{Q}_T . Hence, variations of \dot{Q}_T will directly affect Pa_{O_2} as a result of this interplay between \dot{Q}_T and \dot{V}_{O_2} and $P\bar{v}_{O_2}$. Consequently, for a given \dot{V}_{O_2} and Q_s/Q_T , there is a linear relationship between Pa_{O_2} and the difference between Ca_{O_2} and $C\bar{v}_{O_2}$ (Figure 7) (88, 89). In other words, any increase in $P\bar{v}_{O_2}$ should also increase Pa_{O_2} . In patients treated with extracorporeal CO₂ removal, increasing $P\bar{v}_{O_2}$ by increasing the Fi_{O_2} of the membrane lung was associated with a parallel increase of Pa_{O_2} , whereas whole-body \dot{V}_{O_2} , \dot{Q}_T , Q_s/Q_T , and the \dot{V}_A/\dot{Q} distributions remained unchanged (90). However, under clinical conditions, the magnitude of this effect may depend on the initial level of $P\bar{v}_{O_2}$ and of other factors. Indeed, pharmacological (e.g., inotropic and/or vasoactive drugs) or

nonpharmacologic (positive end-expiratory pressure [PEEP] maneuvers, patient positioning) approaches frequently influence \dot{Q}_T and \dot{V}_{O_2} as well, and, hence, $P\bar{v}_{O_2}$. Moreover, another factor shown both in experimental models and in patients with ARDS is the fact that changes in \dot{Q}_T induce parallel changes in Q_s/Q_T (91–93), including when induced by increasing PEEP or V_T (94). The most likely explanation seems to be an alteration of hypoxic pulmonary vasoconstriction induced by changes in $P\bar{v}_{O_2}$ (95, 96). Variations in $P\bar{v}_{O_2}$ can also directly affect Q_s/Q_T due to changes in pulmonary vascular tone: in patients with ARDS treated with extracorporeal membrane oxygenation, Q_s/Q_T showed a direct, linear dependence on both pulmonary blood flow and calculated pulmonary vascular resistance (91). Consequently, any variation of \dot{Q}_T can affect arterial oxygenation in different directions. Therefore, in an individual patient, the effect of \dot{Q}_T variations on Pa_{O_2} are often unpredictable and will be a consequence of the interplay between effects on Q_s/Q_T , \dot{V}_A/\dot{Q}

distributions, \dot{V}_{O_2} , and $P\bar{v}_{O_2}$ (Figure 8) (86, 87, 97).

Albeit to a lesser degree due to the small difference between arterial and mixed venous levels, the same is true for any effect of \dot{Q}_T and $P\bar{v}_{CO_2}$, respectively, on Pa_{CO_2} : theoretically, any increase in \dot{Q}_T should result in a decrease of Pa_{CO_2} . However, the effects of \dot{Q}_T variations on Pa_{CO_2} can also work in different directions; for example, the expected fall of Pa_{CO_2} resulting from a vasodilator-induced increase in \dot{Q}_T may be offset by the simultaneous rise in Q_s/Q_T and, in particular, \dot{V}_D/\dot{V}_T . The latter can be caused by the vasodilator-induced reduction in pulmonary arterial pressure, which may result in “derecruitment” of the pulmonary vasculature: as mentioned above, pulmonary vascular resistance and, consequently, the distribution of pulmonary blood flow depend on the relation between intravascular (i.e., arterial [Pa], venous [Pv], and alveolar [PA]) pressures (58). Any fall in intravascular pressure can transform “zone II” regions of the lung (with $Pa > PA > Pv$) into so-called “zone I” regions of the lung, which are nonperfused because $PA > Pa$ (58).

Nonpulmonary factors, namely Fi_{O_2} , cardiac output (\dot{Q}_T), \dot{V}_{O_2} , and, as a result of the $P\bar{v}_{O_2}$, will also directly affect Pa_{O_2} .

Extrapulmonary Shunt

Intracardiac shunt via a patent foramen ovale (PFO) may also contribute to compromised gas exchange in ARDS. Under normal conditions, a PFO does not affect gas exchange, because the gradient between left and right atrial pressure precludes significant blood transfer from the venous to the arterial side. However, pulmonary artery hypertension is a common phenomenon in patients with ARDS and can lead to acute cor pulmonale (98–100). Prevalence of a PFO during ARDS has been reported in between 15 and 19% of patients and is often associated with acute cor pulmonale (101, 102). Frequently, in the presence of a moderate to large PFO shunting, there is a poor oxygenation response to PEEP. High PEEP may further increase the right atrial pressure, thereby increasing the occurrence and severity of right-to-left shunting due to PFO (60, 101, 103, 104). Lowering PEEP and/or inhaled NO may reduce pulmonary hypertension, thus decreasing or abolishing right-sided shunting in some patients ($\approx 14\%$), thereby improving oxygenation (103, 104).

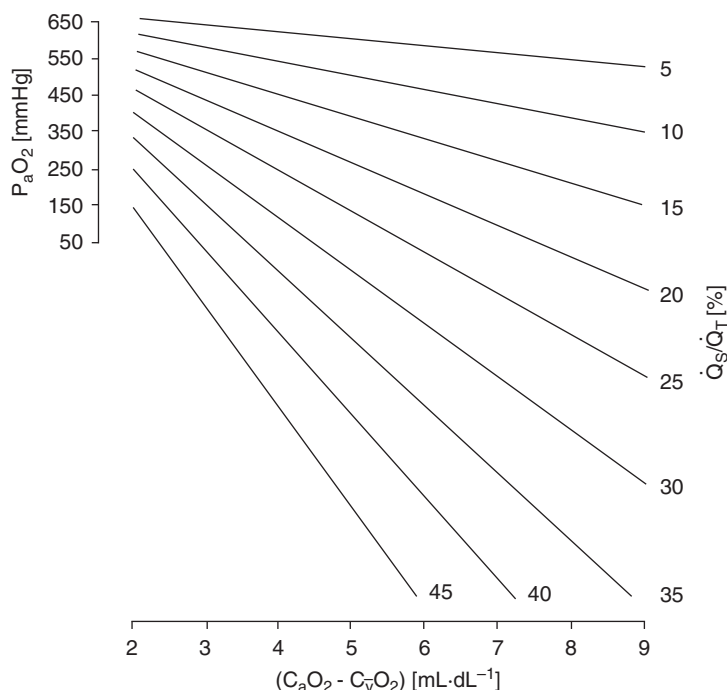


Figure 7. Arterial P_{aO_2} during pure O_2 breathing, plotted as a function of the arterial–mixed venous O_2 concentration difference (in mL/dl) for incremental \dot{Q}_s/\dot{Q}_T (in percentage of total pulmonary blood flow) levels. Note that for any given \dot{Q}_s/\dot{Q}_T level, the higher the arterial–mixed venous O_2 concentration difference, the lower the mixed venous P_{O_2} and, consequently, the lower the P_{aO_2} . Ca_{O_2} = arterial O_2 concentration; Cv_{O_2} = mixed venous O_2 concentration. Adapted by permission from Reference 249.

Clinical Applications

There is a real difficulty for the clinician at the bedside to accurately interpret gas exchange abnormalities in ARDS. In particular, different maneuvers can influence gas exchange through various

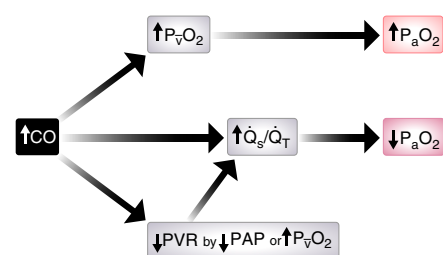


Figure 8. Effect of an increase in cardiac output (CO) on P_{aO_2} . Note that increasing cardiac output may lead to an increase in P_{aO_2} due to the increase in Pv_{O_2} (see also Figures 5, 7, and 10). On the other hand, any increase may even cause a decrease in P_{aO_2} as a result of an increase in right-to-left shunt (\dot{Q}_s/\dot{Q}_T), either directly (91–93) and/or due to the decrease in pulmonary vascular tone (34–41). PAP = pulmonary artery pressure; Pv_{O_2} = mixed venous P_{O_2} ; PVR = pulmonary vascular resistance. Illustration by Jacqueline Schaffer.

mechanisms; for example, improved oxygenation can reflect a pure redistribution of blood flow (see inhaled vasodilators), a change in mixed venous O_2 concentration, and/or a reopening of previously nonaerated lung units (see recruitment). Therefore, the same effects on gas exchange may indicate a real change in lung function due to a specific maneuver or to the natural resolution of the disease, a simple “cosmetic” effect without alteration in lung function, or even a worsening of lung distension with a reduction in cardiac output and consequently of shunt. Therefore, a careful interpretation merits a multimodal clinical approach and a careful reasoning.

Diagnosis and Assessment of Severity

Hypoxemia is a central component of the diagnosis of ARDS. Several indices have been proposed to characterize hypoxemia, such as Q_{VA}/\dot{Q}_T , $P(A-a)O_2$, the oxygenation index, and the P_{aO_2}/F_{IO_2} ratio. These indices are influenced by many factors, such as ventilator settings (V_T , respiratory rate, PEEP) and hemodynamics (\dot{Q}_T and Pv_{O_2}).

Due to its simplicity, the P_{aO_2}/F_{IO_2} ratio has been adopted for routine practice and is used to characterize the severity of ARDS (1). The use of the P_{aO_2}/F_{IO_2} ratio is underlined by the necessity to assess hypoxemia independently from F_{IO_2} . Unfortunately, due to the complex mathematical relationship between the Hb level, the Hb- O_2 dissociation curve, and the arterial–mixed venous O_2 concentration difference, the relationship between P_{aO_2}/F_{IO_2} and F_{IO_2} is nonlinear and depends on the underlying \dot{Q}_s/\dot{Q}_T (105, 106) (Figure 9).

Thus, no matter the possible effect of F_{IO_2} on \dot{Q}_s/\dot{Q}_T *per se* (denitrogenation atelectasis), any change in F_{IO_2} may also modify P_{aO_2}/F_{IO_2} . This variability of P_{aO_2}/F_{IO_2} suggests that its use be cautioned in an individual patient with ARDS, when ventilator settings are modified. Despite these limitations, classification of patients with ARDS in three categories of severity according to P_{aO_2}/F_{IO_2} (“mild” for $300 \leq P_{aO_2}/F_{IO_2} < 200$, “moderate” for $200 \leq P_{aO_2}/F_{IO_2} < 100$, and “severe” for $P_{aO_2}/F_{IO_2} \leq 100$ mm Hg) allows the identification of patients with different duration of mechanical ventilation and mortality (1, 107). Furthermore, the P_{aO_2} during pure O_2 ventilation was shown to be strongly correlated with the computed tomography (CT)-quantified percentage of nonaerated lung (108). Finally, this simple index appears to be useful for identifying patients who could benefit from additional therapeutic interventions, such as high PEEP, prone positioning, and/or neuromuscular blockade (109–111). As shown by Villar and colleagues, the prognostic value of P_{aO_2}/F_{IO_2} depends greatly on the time and conditions of its measurement, the better stratification of the risk of death being obtained with $PEEP \geq 10$ cm H_2O and $F_{IO_2} \geq 0.5$ after 24 hours of protective ventilation (112, 113).

The ratio of transcutaneous arterial Hb- O_2 saturation (Sp_{O_2}) to F_{IO_2} (Sp_{O_2}/F_{IO_2}) was suggested as a screening tool for ARDS when arterial blood gases are not available (114). Unfortunately, due to its poor accuracy, this noninvasive method cannot be used to assess the effects of therapeutic interventions on oxygenation (115). Finally, it was recently suggested that a nonlinear equation gave a more reliable estimate of the P_{aO_2}/F_{IO_2} ratio (116).

Impaired CO_2 elimination is also a hallmark of ARDS. In patients with ARDS

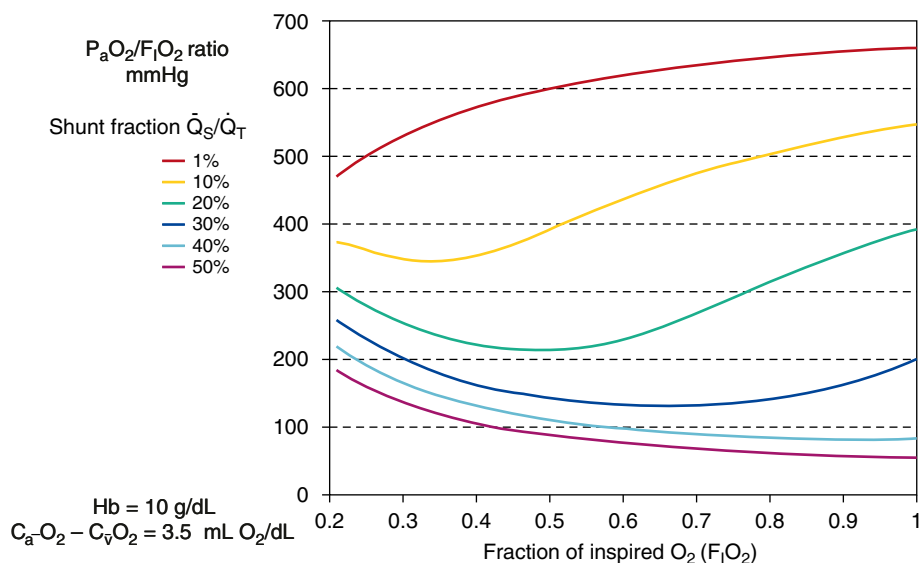


Figure 9. The ratio P_{aO_2}/F_{iO_2} plotted as a function of F_{iO_2} ranging from 0.21 (air) to 1.0 (pure O_2) for \dot{Q}_s/\dot{Q}_T values ranging from 1 to 50% at a constant Hb concentration = 100 g/L and an arterial-mixed venous O_2 concentration difference = 3.5 ml/dl. C_{aO_2} = arterial O_2 concentration; C_{vO_2} = mixed venous O_2 concentration. Adapted by permission from Reference 106.

of variable severity, V_D/V_T measured on PEEP of 5 cm H_2O was highly correlated with CT scan quantification of lung aeration inhomogeneity, suggesting that V_D/V_T could be useful for individual assessment of the risk of ventilator-induced lung injury (VILI) (117). In line with this observation, V_D/V_T measured in standardized conditions at the early or the intermediate phase independently predicted mortality (3, 118). Calculation of V_D/V_T with the Enghoff formula requires the determination of $P_{E_{CO_2}}$ and/or $F_{E_{CO_2}}$, which is not routine clinical practice. Several methods have been proposed for V_D/V_T estimation without measuring $F_{E_{CO_2}}$, or for the calculation of indices reflecting ventilatory efficiency: \dot{V}_E standardized at a P_{aCO_2} of 40 mm Hg ($\dot{V}_{E_{corr}} = \dot{V}_E \cdot P_{aCO_2}/40$) (119), ventilatory ratio = $(\dot{V}_E \cdot P_{aCO_2})/(\text{predicted } \dot{V}_E \cdot 37.5)$ with predicted $\dot{V}_E = 100 \text{ ml} \cdot \text{kg}^{-1}$ predicted body weight (PBW) $\cdot \text{min}^{-1}$ (120). Retrospective analysis of the ARDS network databases suggests that both V_D/V_T , using the Harris-Benedict calculation of energy expenditure, and the ventilatory ratio are predictive of mortality (121–123). Although not mandatory for the diagnosis, assessment of the impaired CO_2 elimination using either V_D/V_T and/or calculation of a surrogate index should be part of the initial evaluation of ARDS severity.

Therapeutic Targets

Arterial P_{O_2} . Although prevention of death from hypoxemia is a major goal of mechanical ventilation in patients with ARDS, very few studies addressed the question of the optimal target for oxygenation. There is ample evidence from studies outside the field of ARDS suggesting that hyperoxemia ($P_{aO_2} > 120\text{--}150$ mm Hg) should be avoided in critical illness (124, 125). In most of the large randomized controlled trials on symptomatic support in ARDS, the recommended targets for oxygenation were a P_{aO_2} of 55 to 80 mm Hg and/or an Sa_{O_2} of 88 to 95%. Interestingly, the data reported in these studies show that mean values for P_{aO_2} were mostly close to or even higher than the upper target limits (111, 126–130). This observation is well in line with data from observational studies showing that high P_{aO_2} and/or Sa_{O_2} values are frequently observed in critically ill patients and suggests that investigators do not feel comfortable with lower P_{aO_2} and/or Sa_{O_2} values. This was probably due to much more concern about the risk of hypoxia than that of pulmonary O_2 toxicity and/or deleterious effects of hyperoxia (131). The safety of moderate levels of oxygenation has been questioned by the observation of an association between lower levels of oxygenation and long-term neuropsychiatric impairment in a subgroup

of survivors from ARDS (132). Nevertheless, in ARDS the “optimal” Sa_{O_2} and P_{aO_2} level remains undetermined, because experimental data suggest that hyperoxia can worsen VILI (133), and mechanical ventilation with F_{iO_2} of 0.6 or greater for 3 or more days was associated with increased thickness of the air–blood barrier and endothelial cell injury (134). Moreover, a retrospective analysis demonstrated that the number of days with hyperoxemia as defined with a P_{aO_2} greater than 120 mm Hg was an independent risk factor for ventilator-associated pneumonia (135). More evidence for the toxicity of hyperoxemia was provided by the randomized controlled trials O2-ICU (Optimal Oxygenation in the Intensive Care Unit) and HYPER2S (Hyperoxia and Hypertonic Saline in Septic Shock) (136, 137). The O2-ICU trial compared P_{aO_2} targets of 120 (“conventional”) versus 75 (“conservative”) mm Hg in 434 general ICU patients with an expected length of stay greater than 72 hours: the conservative approach was associated with a 50% reduction of overall mortality (11.6 vs. 20.2%; $P = 0.01$); the authors concluded that the findings must be considered preliminary because of the early trial termination due to difficult patient enrollment. Moreover, only 67% of the patients were mechanically ventilated at inclusion (136). The HYPER2S trial comparing target Sa_{O_2} 88 to 95% versus pure O_2 ventilation during the first 24 hours in patients with septic shock was preliminarily stopped for safety reasons after enrollment of 442 patients (137). In this study, 50% of the patients had ARDS with P_{aO_2}/F_{iO_2} less than 200 mm Hg at baseline. Mortality did not significantly differ at Days 28 and 90, but hyperoxia was associated with a significantly higher incidence of serious adverse events, with a clinically relevant higher number of patients with ICU-acquired weakness and atelectasis.

Arterial P_{CO_2} . Experimental studies have shown that hypercapnia and/or respiratory acidosis may have numerous beneficial cellular and physiological effects, such as attenuated pulmonary inflammation, protection against VILI and oxidant-induced lung injury (138–140), improved \dot{V}_A/\dot{Q} distribution through enhanced hypoxic pulmonary vasoconstriction (141), increased \dot{Q}_T and O_2 delivery secondary to catecholamine

related to surfactant perturbation. Although not definitively demonstrated in patients, it is likely that this phenomenon may play a role in explaining the effect of PEEP on lung recruitment (164). Albeit questioned (165), several studies reported a direct relation between the improvement in oxygenation and PEEP-induced lung recruitment (159, 161, 166, 167). However, this correlation may be too weak to allow, in an individual patient, assessment of PEEP-induced recruitment by its effect on oxygenation. The lack of a bedside method to quantify recruitment induced by PEEP has always limited the interpretation of oxygenation as a marker of recruitment. Some studies suggested that PEEP may protect against the development of pulmonary edema (168–171), partly because of a concomitant reduction in Q_T (172). Although an increase in lung volume is the main mechanism for PEEP-induced changes in oxygenation, a small decrease in Q_T also reduces Q_S/Q_T and may thereby improve Pa_{O_2} (94). Many studies showed that PEEP in reality does not reduce extravascular lung water but mostly redistributes edema (173, 174). By recruiting nonaerated alveoli and stabilizing airways, PEEP may also influence the regional distribution of tidal ventilation (175–177): when the predominant effect of PEEP is recruitment, alveolar ventilation is expected to become more homogeneous, particularly in the dependent zones, and confer a protective effect against VILI. Patients subjected to increased PEEP while receiving dopamine to maintain the same cardiac output exhibited significant reductions in Q_S/Q_T , suggesting that alveolar recruitment, rather than reduced Q_T (94, 178), was the predominant mechanism for improved oxygenation from increased PEEP (179).

The effects of PEEP on V_D/V_T and CO_2 elimination are complex. On the one hand, PEEP-induced alveolar recruitment may decrease physiological V_D/V_T due to a more homogeneous distribution of V_T and thereby decreased Q_S/Q_T (26, 27, 156). However, on the other hand, PEEP may favor overdistension of previously well-aerated alveoli, resulting in increased physiological V_D/V_T (10, 174). Overall, the impact of PEEP on V_D/V_T and Pa_{CO_2} is usually modest (180–183). Increases in Pa_{CO_2} may indicate predominant hyperinflation.

Recruitment maneuvers. Recruitment maneuvers can improve oxygenation in many patients with ARDS (184). These maneuvers are integral part of the “open lung strategy” that aims at maximizing recruitment (184). However, the safety of these maneuvers is debated and, moreover, unless combined with increased PEEP levels, their effect is usually very transient, lasting 15 to 20 minutes (185). Some authors showed that most of the effect is obtained after 10 seconds, before side effects occur, suggesting that these maneuvers could be aborted rapidly (185).

Ventilatory mode. It has been suggested that, due to a more homogeneous distribution of V_T , the decelerating flow characteristic of pressure-targeted ventilation could result in improved gas exchange compared with the square wave flow usually used in volume-targeted modes (186). However, several studies demonstrated that, when the main settings (V_T , PEEP) are comparable, pressure- and volume-controlled ventilation have similar effects on gas exchange (187, 188).

Lengthening inspiratory time to increase mean airway pressure without increasing peak alveolar pressure has been considered an attractive approach to improve oxygenation and lower the risk of barotrauma (189, 190). Inverse ratio ventilation (i.e., an inspiratory-to-expiratory time ratio > 1) was therefore proposed as an alternative to conventional ventilation in ARDS. Several uncontrolled studies reported improved oxygenation with inverse ratio ventilation (191, 192). Controlled studies, however, did not find advantages for inverse ratio over conventional ventilation in terms of oxygenation when total end-expiratory pressure was kept constant (187, 188, 193). Extending inspiratory time by lengthening the duration of inspiratory pause slightly decreases V_D/V_T and thereby Pa_{CO_2} due to improved end-inspiratory gas mixing between alveoli and airways (194–196). Although usually of small magnitude, this effect may allow the decrease of V_T , and thus plateau pressure, with unchanged Pa_{CO_2} (196). A prolonged inspiratory time may also increase right ventricular afterload (193).

High-frequency oscillation has been proposed as an alternative to conventional ventilation in patients with severe ARDS (197). In this mode, oxygenation depends mainly on mean airway pressure and Fi_{O_2} ,

whereas CO_2 elimination depends on the frequency, the amplitude of oscillations, and the inspiratory time on expiratory time ratio. The negative results of two large randomized controlled trials have led to a discontinuation of the use of this technique in adults with ARDS (198, 199). Whether the hemodynamic effects of a high intrathoracic and mean airway pressure explain these negative results has been questioned (200).

V_T and \dot{V}_E . Low V_T is a key element of lung-protective ventilation to decrease mortality (126). In the ARMA trial, the low V_T arm was associated with a lower level of oxygenation than the high V_T arm (126). When compared with “conventional” V_T at unchanged respiratory rate and PEEP, reducing V_T increases Pa_{CO_2} due to decreased \dot{V}_E and increased Q_S/Q_T resulting from increased Q_T and derecruitment of poorly ventilated respiratory units (units with very low \dot{V}_A/Q ratios) (201). Due to the concomitant increase in $P\bar{V}_{O_2}$ associated with increased Q_T , the increase in Q_S/Q_T associated with the reduced V_T results in an inconstant and small decrease in Pa_{O_2} (141, 201). Reducing V_T is associated with decreased V_D , usually resulting in unchanged V_D/V_T (141, 201). Due to the high V_D/V_T , the \dot{V}_E required to obtain normocapnia is abnormally high (3). When using a V_T of $6 \text{ ml} \cdot \text{kg}^{-1} \text{ PBW}$, a respiratory rate of $25 \text{ to } 35 \cdot \text{min}^{-1}$ is therefore usually necessary to achieve a Pa_{CO_2} with arterial pH of 7.30 to 7.45 (126).

Reduction of dead space. In mechanically ventilated patients, instrumental dead space contributes to total V_D/V_T . Because $V_A = V_T - V_D$, the impact of instrumental dead space on Pa_{CO_2} or on the required \dot{V}_E is especially significant when using low V_T . Several clinical studies have shown that in patients with ARDS ventilated with a low V_T , reducing the instrumental dead space by replacing the heat and moisture exchanger by an active humidifier significantly decreased Pa_{CO_2} (202, 203).

Tracheal gas insufflation consists of a continuous or an expiratory injection of fresh gas into the central airways via an endotracheal catheter, to flush CO_2 from airway dead space and thereby to decrease anatomical dead space (204). Several studies have shown that tracheal gas insufflation significantly reduced Pa_{CO_2} and/or allowed reducing V_T at constant Pa_{CO_2} (205, 206). Due to safety issues and

technical difficulties (increased intrinsic PEEP, inaccurate or difficult measurements of V_T and airway pressure, humidification of the insufflated fresh gas, monitoring of the position of the catheter, tracheal lesions), this technique has been difficult to apply in daily practice and has progressively lost interest. De Robertis and Jonson developed a technique of aspiration and flushing of airway dead space during expiration that allowed them to significantly decrease ventilatory requirements without increasing intrinsic PEEP (207, 208). This technique requires a specific device synchronized with the ventilator, and, hence, is not yet available for clinical use.

Spontaneous breathing versus muscle paralysis. Although muscle paralysis and controlled mechanical ventilation have been classically used in patients with ARDS, allowing spontaneous breathing during mechanical ventilation gained increased interest during recent years. During assisted mechanical ventilation, the patient's inspiratory effort triggers the start of gas-flow delivery by the ventilator, which is maintained until a predefined termination criterion is met. Conversely, during nonassisted spontaneous breathing, the patient breathes freely in a continuous or demand-flow system without any specific assistance of inspiratory efforts (i.e., during continuous positive airway pressure or airway pressure release ventilation, APRV).

Experimental (209–213) and clinical (214–217) studies demonstrated that spontaneous breathing during mechanical ventilation can improve oxygenation. Two mechanisms have been postulated for the possible beneficial effect of additional spontaneous breathing on gas exchange: (1) alveolar recruitment of atelectatic regions, mainly in the dependent portions of the lung, eased by the preserved contraction of the diaphragm; and (2) shifting of pulmonary blood flow toward lung regions with higher \dot{V}_A/\dot{Q} ratios (215, 218). When spontaneous breathing is preserved during mechanical ventilation, the pressure generated by the respiratory muscles adds to the pressure delivered by the ventilator, thus magnifying transpulmonary pressure (219, 220). In addition, local overstretch in dependent lung regions may occur, when a local increase in transpulmonary pressure causes alveolar air shift from nondependent to dependent parts of the lung (i.e., pendelluft) (221). Through these

mechanisms, spontaneous breathing may increase the risk of VILI. Thus, three points should be considered when allowing spontaneous breathing during mechanical ventilation: (1) the severity of ARDS, (2) the evolution phase of the disease, and (3) the degree of synchronization between ventilator assistance and the patient's inspiratory effort. Most of the studies suggesting benefits of spontaneous breathing were performed in patients with mild to moderate ARDS with only moderate ventilatory demands and/or after the acute phase of the disease. In patients with severe ARDS, the use of a neuromuscular blocking agent during the first 48 hours improved oxygenation and, ultimately, survival (111). Finally, the synchronization between ventilator assistance and the patient's inspiratory effort also determines the gas exchange effects of spontaneous breathing. When comparing the effects of pressure support (fully synchronized pressure-targeted assisted ventilatory mode) and APRV (nonsynchronized pressure-targeted ventilatory mode allowing unassisted spontaneous breathing) to pressure-controlled ventilation, Putensen and colleagues showed in patients with ARDS that APRV increased \dot{Q}_T and improved oxygenation due to better \dot{V}_A/\dot{Q} matching resulting from decreased Q_s/\dot{Q}_T and V_D/V_T . Pressure support did not have beneficial effects (215). Interestingly, these beneficial effects of unassisted spontaneous breaths during APRV were obtained despite a quite small spontaneous breathing activity.

In summary, spontaneous breathing can improve oxygenation in ARDS, but this approach should probably be limited to patients not exhibiting strong inspiratory efforts, after improvement of the acute phase or even in the early phase of mild or moderate ARDS (222). During pressure-targeted, assisted ventilator modes, monitoring of V_T is mandatory to estimate the inspiratory effort and, thereby indirectly, transpulmonary pressure (220). The use of a nonsynchronized mode may prove useful to limit V_T and transpulmonary pressure. Finally, excessive ventilator efforts leading to an increase in respiratory muscle metabolic rate and thus to an increase in ventilator requirements should be avoided.

Patient positioning. Prone positioning has been used to improve oxygenation in

patients with ARDS since the 1970s (223, 224). Several studies demonstrated that prone positioning improves oxygenation (defined as an increase in $Pa_{O_2} \geq 20\%$ or $Pa_{O_2}/Fi_{O_2} \geq 20$ mm Hg, as compared with supine) in approximately 75% of patients (110, 225–227). By recruiting the lung and homogenizing alveolar ventilation, prone position should theoretically decrease Pa_{CO_2} and V_D/V_T as well (228, 229). The effect of prone position on Pa_{CO_2} , however, is less predictable and has mostly been considered less important than the effect on oxygenation. Nevertheless, the decrease in Pa_{CO_2} , rather than the increased Pa_{O_2}/Fi_{O_2} , is associated with improved recruitment and better outcome with prone position (230, 231). Besides the effects on gas exchange, prone position decreases lung stress and strain and prevents VILI (232–234). Hence, it seems to improve outcome of the patients with the most severe ARDS (110, 130, 235, 236).

Limited data suggested that vertical positioning can also improve oxygenation (237, 238). Richard and colleagues showed that, as compared with supine position, upright positioning (trunk elevated at 45° and legs down at 45°) improved oxygenation in 11 of 16 patients with ARDS (237). The improved oxygenation was associated with an increased lung volume, suggesting an increase in lung recruitment. By relieving abdominal compression on lung bases, verticalization may, hence, allow caudal displacement of the diaphragm and thereby promote recruitment of dependent lung areas. These results were confirmed by Dellamonica and colleagues, who found that vertical position improved oxygenation, increased end-expiratory lung volume, and decreased lung strain in 13 of 40 patients with ARDS (238). However, the individual oxygenation response to verticalization was unrelated to changes in lung volume, suggesting that mechanisms other than recruitment, for instance changes in cardiac output, also contributed to the improved oxygenation with vertical positioning.

Pharmacological manipulation of \dot{V}_A/\dot{Q} distribution. Inhaled NO decreases Q_s/\dot{Q}_T due to regional vasodilatation of well-ventilated respiratory units (39). In most patients with ARDS, concentrations of 1 to 10 ppm are sufficient to achieve an NO effect on oxygenation (239). These low concentrations of inhaled NO allow avoiding formation of harmful NO_2

concentrations and the occurrence of methemoglobinemia. The inhaled NO-related improvement of oxygenation is usually transient (≤ 72 h) (240), and the risk of rebound necessitates a progressive withdrawal (241). Finally, this transiently improved oxygenation was not associated with improved outcome (242). Aerosolized prostacyclin is an alternative to inhaled NO resulting in similar improvement in oxygenation (40, 41, 82, 86). By enhancing hypoxic vasoconstriction, intravenous almitrine, a selective pulmonary vasoconstrictor, redistributes blood flow from shunt units to ventilated units and may thereby improve oxygenation (83, 85). Low-dose intravenous almitrine ($4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) increased Pa_{O_2} comparable to 5 ppm inhaled NO, the combination of the two drugs eventually resulting in additive effects (83–85). Interestingly, the association of inhaled NO allows offsetting of the increase in pulmonary arterial pressure induced by almitrine (84).

Individualized Adjustment of Ventilator Settings

Currently, strategies proposed for V_T adaptation are mainly based on P_{BW} and/or indices of lung stress, such as plateau pressure, transpulmonary pressure, or driving pressure. Reducing V_T is accompanied by a decreased V_D (201, 243). The resultant effect on CO_2 elimination efficiency assessed by V_D/V_T is variable. A decreased V_D/V_T has been suggested to be indicative of attenuated overinflation (140). However, changes in V_D/V_T secondary to changes in V_T are usually quite small

(201, 243), and the clinical impact of a strategy including measurement of V_D/V_T for individual settings of V_T has not been evaluated so far.

Reducing V_T at constant PEEP levels increases Q_s/Q_T due to alveolar derecruitment and increased Q_T (141, 201, 244, 245). As mentioned above, the net effect on Pa_{O_2} depends on the respective magnitudes of the changes in Q_s/Q_T and $\text{P}\bar{V}_{\text{O}_2}$. Any increase in Q_s/Q_T induced by V_T reduction is easily counterbalanced by increasing PEEP (160).

Although the effect of PEEP on oxygenation cannot be considered an accurate estimate of its effect on alveolar recruitment (159, 165), data from physiologic studies and from large randomized controlled trials suggest that oxygenation should be taken into account for individual PEEP titration (109). Studies from Gattinoni's group assessing the effect of PEEP using CT scan clearly demonstrate a relationship between $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ measured on low PEEP (5 cm H_2O) and the quantity of lung tissue that can be recruited and protected from tidal opening and closing with high PEEP, this quantity being much more important in patients with a $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ less than 150 mm Hg on PEEP 5 cm H_2O than in patients with less severe hypoxemia (174, 245). In line with this finding, an individual meta-analysis of the three large randomized clinical trials comparing high PEEP to moderate PEEP in patients with ARDS ventilated with a low V_T (127–129) demonstrated that impact of high PEEP on mortality varies according to $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ (109). High PEEP was associated with decreased mortality in

patients with a $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ less than 200 mm Hg (moderate or severe ARDS), whereas a tendency for an opposite effect was observed in the less severely hypoxemic patients ($200 < \text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} < 300$ mm Hg). Another argument for taking into account oxygenation for PEEP setting was provided by Goligher and colleagues, who retrospectively analyzed the results of the LOVS (Lung Open Ventilation Study) and ExPress (Expiratory Pressure Study) trials (246): the effect of increasing PEEP on oxygenation was highly variable, and the magnitude of the PEEP-induced increase in $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ was strongly associated with decreased adjusted odds ratio for death.

Measurement of V_D/V_T has been proposed as a tool for determination of the optimal level of PEEP (155), but the magnitude of the changes of Pa_{CO_2} secondary to PEEP is usually too small to allow an easy identification of an optimal PEEP level (181, 182). Finally, Caironi and colleagues reported that the best combination of physiological parameters predicting more pronounced recruitment as measured by CT scan was $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ on PEEP 5 cm H_2O less than 150 mm Hg, together with increased compliance of the respiratory system and a decreased V_D/V_T when PEEP was increased from 5 to 15 cm H_2O (247).

Altogether, these findings strongly suggest that individual titration of PEEP in patients with ARDS should take into account effects on both oxygenation and CO_2 elimination. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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