Ventilation-Perfusion Mismatch in the Acute Respiratory Distress Syndrome

Subjects: Critical Care Medicine

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Acute respiratory distress syndrome (ARDS) is a heterogenous condition that is characterized by the development of inflammatory pulmonary edema and life-threatening hypoxemia, and it accounts for nearly 25% of patients who require mechanical ventilation. Acute respiratory distress syndrome (ARDS) remains an important clinical challenge with a mortality rate of 35–45%. It is being increasingly demonstrated that the improvement of outcomes requires a tailored, individualized approach to therapy, guided by a detailed understanding of each patient's pathophysiology. In patients with ARDS, disturbances in the physiological matching of alveolar ventilation (V) and pulmonary perfusion (Q) (*V*/*Q* mismatch) are a hallmark derangement. The perfusion of collapsed or consolidated lung units gives rise to intrapulmonary shunting and arterial hypoxemia, whereas the ventilation of non-perfused lung zones increases physiological dead-space, which potentially necessitates increased ventilation to avoid hypercapnia.

Keywords: electrical impedance tomography ; acute respiratory distress syndrome ; ventilation-induced lung injury

1. Genesis of Ventilation-Perfusion Mismatch in the Acute Respiratory Distress Syndrome

Several pathophysiologic derangements give rise to gas exchange abnormalities in patients with ARDS.

1.1. Non-Ventilated Perfused Units (Shunt)

Arterial hypoxemia due to an intra-pulmonary shunt is a hallmark clinical problem. In 1979, Dantzker et al. used multiple inert gas elimination to study 16 patients with severe ARDS and demonstrated that nearly 50% of the cardiac output was distributed to pure shunt or very low *V*/*Q* lung zones, thus entirely explaining the observed hypoxemia [1]. The genesis of these non-ventilated lung zones is multifactorial. Non-aerated lung tissue may arise due to alveolar instability and collapse. Decreased surfactant production and abnormal pressure due to the superimposed weight of the edematous lung [2] contribute to alveolar instability and atelectasis, which have been associated with more severe lung injury and mortality [3]. These derangements are due, in part, to the inflammatory milieu caused by the primary etiologic factor, but mechanical ventilation alone is capable of decreasing surfactant levels in broncho-alveolar lavage fluid obtained from patients even in the absence of lung injury [4]. Such unstable lung units may be "re-opened" (recruited) with increasing airway pressure [5]. Lung units that remain non-aerated at higher levels of airway pressure have traditionally been considered consolidated as they occur due to inflammatory alveolar flooding with protein-rich fluid [6].

On the other hand, ventilation with a high inspired oxygen fraction can worsen shunt in ARDS patients by washing out alveolar nitrogen and promoting atelectasis. This occurs because nitrogen does not cross the alveolar–epithelial barrier and thus acts to maintain end-expiratory lung volume [7][8]. Regardless of the mechanism, the perfusion of poorly ventilated or non-ventilated lung zones is the main cause of arterial hypoxemia [1], and the degree of which is associated with the current definition of ARDS severity and clinical outcomes [9].

The impairment of vasoactive compensatory mechanisms also contributes to the extent of shunt. In normally functioning lungs, decreases in alveolar and/or mixed venous oxygen content trigger local vasoconstriction (hypoxic pulmonary vasoconstriction or HPV), which redirects blood flow towards ventilated lung zones, thereby decreasing functional shunting. Substantial experimental data have demonstrated that HPV is impaired in the setting of lung injury due to factors including endotoxemia [10] and the action of inflammatory mediators such as thromboxane and TNF-alpha [11][12].

Increased blood flow through intrapulmonary arterio-venous anastomoses contributes to shunt physiology. Such shunting is associated with a higher cardiac index and increased hospital mortality and is unrelated to PEEP level [13]. Intra-cardiac shunting through a patent foramen ovale is another cause of shunts in patients with ARDS, occurring in up to 20% of

patients. Intra-cardiac shunting is associated with lower Pa_{O2}/Fi_{O2}, higher pulmonary artery pressure, and increased mortality [14]. It is also important to recall that decreased mixed venous oxygen content, due to reductions in cardiac output, can worsen hypoxemia when a significant concomitant intrapulmonary shunt is present.

1.2. Ventilated Non-Perfused Units (Dead-Space)

The other hallmark *V*/*Q* mismatch derangement in patients with ARDS is an increased fraction of physiological dead-space ventilation [15][16]. Patients with more severe lung injury demonstrate higher dead-space fractions [17]. Contributory causes include inflammatory intravascular thrombosis [18], with capillary microthrombi being more common in earlier ARDS stages and larger thrombi occurring throughout the disease course [19]. When present, these lesions are associated with the hypoperfusion of small pulmonary arteries [19]. The ventilation of non- or hypo-perfused lung regions results in impaired CO_2 elimination and requires larger minute ventilation to compensate for hypercapnia. Hyperventilation can lead to the regional overdistension of non-dependent lung units. The compression of alveolar capillaries decreases regional perfusion, thereby generating high *V*/*Q* areas that directly contribute to increasing the global dead-space fraction and may also redistribute blood flow to non-aerated lung zones, which increases shunting (**Figure 1**).

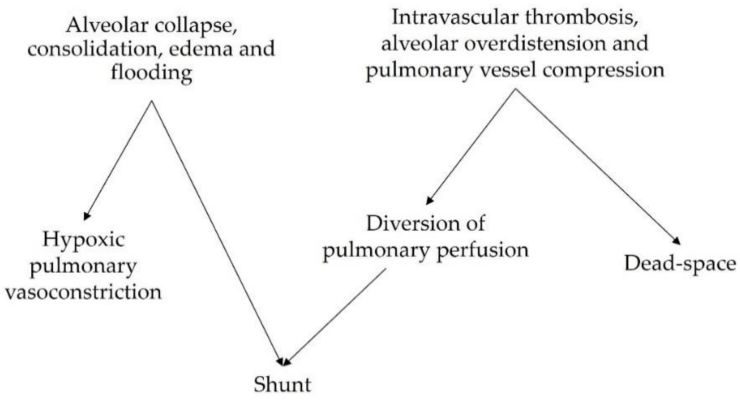

Figure 1. Mechanisms of *V*/*Q* mismatch and their interaction.

2. *V*/*Q* Mismatch as a Marker of Severity in ARDS Patients

2.1. Intrapulmonary Shunt

Although the shunt fraction contributes to the important clinical problem of arterial hypoxemia, its role per se as a potential marker of ARDS severity and adverse outcomes is less established. A modification of the Berggren equation has been related to the risk of developing ARDS in critically ill patients and of increased right ventricular workload [20]. Importantly, the shunt fraction influences dead-space indices [21] and new technologies might increase the feasibility of shunt estimation at the bedside.

2.2. Dead-Space

The Bohr–Enghoff calculation of physiological dead-space has arguably provided one of the strongest indicators of mortality in ARDS patients. The dead-space fraction as determined by volumetric capnography early in the course of ARDS predicts mortality independently of oxygenation, the Simplified Acute Physiology Score II (SAPS-II), and vasopressors [22][23][24]. In the study by Nuckton and colleagues, every 0.05 (i.e., 5%) increase in the dead-space fraction, which was measured a median of 11 h after ARDS diagnosis, was independently associated with a 45% increase in mortality odds [22]. In addition, serial measurements of physiological V_D/V_T by volumetric capnography have been shown to identify patients at increased risk of death up to 6 days after meeting ARDS criteria [23][24]. The use of the threshold value of V_D/V_T as a prognostic tool may differ among different ARDS etiologies, with aspiration and infectious pneumonia having significantly higher V_D/V_T than non-pulmonary sepsis or trauma. Regardless of etiology, V_D/V_T was significantly increased in non-survivors versus survivors [25]. Recently, the prognostic value of physiological dead-space has also been studied in critically ill COVID-19 ARDS patients, showing an interesting association with coagulation. Increased V_D/V_T was associated with higher D-dimer levels and a lower likelihood of being discharged alive. A V_D/V_T above 57% was used to help identify a high-risk subgroup of patients independent of the Pa_{O2}/Fi_{O2} ratio [26].

Dead-space estimation based on resting energy expenditure has been proposed as a bedside index capable of predicting mortality based on secondary analyses of two prospective studies [27] but other analyses have failed to demonstrate improved outcome prediction when added to measures of oxygenation and respiratory mechanics [28][29]. Nevertheless, the estimated and measured dead-space fractions had a similar ability to predict the extent to which extracorporeal CO_2

removal reduced driving pressure (DP) when ultra-protective ventilation was applied, but only the measured dead-space was associated with mortality [30]. Of note, compared to other empirical dead-space formulae, a direct estimate based on the least angle regression of physiological variables proposed by Beitler and colleagues (direct estimation) seems relatively less biased and may retain some potential for prognostication [29][31].

The ventilatory ratio is an index that relates a patient's measured minute ventilation and $PaCO_2$ to the predicted minute ventilation required to achieve a $PaCO_2$ of 37.5 mmHg.

$$\text{Ventilatory ratio}: \frac{\text{Minute ventilation } (\text{mL}/\text{min}) \times \text{Pa}_{\text{CO}\,2}\ (\text{mmHg})}{\text{Predicted body weight } (\text{kg}) \times 100\ (\text{mL}/\text{kg}/\text{min}) \times 37.5\ (\text{mmHg})} \quad (1)$$

This is an easy-to-use bedside calculation that operates as an outcome predictor in a way that is strikingly similar to the measured physiological dead-space fraction. Higher values indicate greater ventilatory inefficiency and a higher dead-space fraction [32]. It has been shown to be capable of predicting mortality independently of oxygenation, shock status, vasopressor use, and Acute Physiology and Chronic Health Evaluation III (APACHE-III) scores [33][34][35], with odds ratios comparable to those of Nuckton and colleagues [33], thereby outperforming empirical estimates, except with respect to direct estimation [29]. The trajectory of ventilatory ratios during the early stages of ARDS has also been associated with survival and may prove valuable when tracking a patient's clinical course [29][36].

Interestingly, in a recent secondary analysis of the large (*n* = 927) PRoVENT-COVID study cohort, none of the previously discussed formulae for dead-space estimation, nor the ventilatory ratio, were found to be independent predictors of mortality in an adjusted base risk model. Only direct estimation—when measured early at the start of ventilation, but not on the following day—retained additional prognostic value. The researchers also argued that in patients with COVID-19, dead-space might be regarded more as a marker of ARDS severity rather than as an independent prognostication factor. Despite its apparent simplicity, the $P_{ET}CO_2/PaCO_2$ ratio was the only index in this cohort to be independently associated with outcomes both at the start of ventilation and on day one [28] and has been recently validated as a predictor of mortality in a large retrospective cohort [37].

2.3. Assessment of V/Q Mismatch by EIT

The sum of the percentages of non-perfused ventilated and perfused non-ventilated lung units (unmatched units) obtained by superimposing EIT-derived ventilation and perfusion maps has recently been shown to be capable of independently predicting mortality in ARDS patients. A value of 27% unmatched units predicted mortality with a positive predictive value of 67% and a negative predictive value of 91%. The percentage of only perfused units (i.e., an estimate of a shunt) was significantly inversely correlated with the Pa_{O2}/Fi_{O2} ratio and the dorsal fraction of ventilation [38]. These findings represent an additional means to assess ARDS severity at the bedside and lay the foundation for more advanced analyses. EIT imaging offers the potential to differentiate between dead-space and shunt fractions, potentially bridging the gap between bedside measures and respiratory pathophysiology.

3. Hypoxic Pulmonary Vasoconstriction and *V/Q* Mismatch as Mechanisms of VILI

Beyond causing impairments in gas exchange, *V/Q* mismatch and the physiologic responses to mismatch have been implicated in the development and progression of lung injury in patients with ARDS. A summary of the corresponding explanatory mechanisms is presented in **Table 1**.

Table 1. *V/Q* mismatch as a mechanism of lung injury.

	Mechanisms of Injury	Reference
Shunt (perfused non-ventilated lung units)	**Redistribution of perfusion due to hypoxic pulmonary vasoconstriction: hypo-perfused lung zones with locally decreased oxygen and nutrient delivery and lung ischemia.**	**[39]**
	Decreased size of aerated lung with increased risk of overdistension and barotrauma in the ventilated lung.	**[40][41][42]**
Dead-space (ventilated non-perfused lung units)	**Local alveolar hypocapnia: altered surfactant system, alveolar instability, apoptosis, and hemorrhagic infarction.**	**[43][44][45][46][47][48][49][50][51]**

Mechanisms of Injury	Reference
Local bronchoconstriction with diversion of ventilation to perfused lung zones resulting in hyperventilation and hyperperfusion in diverted zones.	**[52][53]**

3.1. VILI Related to Perfused Non-Ventilated Lung Units

The perfusion of low *V*/*Q* and shunted lung zones in healthy lungs is counterbalanced by hypoxic pulmonary vasoconstriction (HPV), a physiological response to alveolar hypoxia and/or to decreased mixed venous oxygen content that diverts pulmonary blood flow from poorly ventilated to more normally ventilated lung zones [54], thereby improving *V*/*Q* matching and gas exchange. HPV has been extensively investigated in experimental studies. In ARDS models induced by E. Coli endotoxin and oleic acid infusion, HPV appeared to be inhibited [39][40][55][56], contributing to increased shunt and worsening oxygenation. In other models, induced mainly by oleic acid infusion, HPV was preserved [41]. In ARDS patients, the effectiveness of HPV might vary depending on etiology, hemodynamic status, the administration of medications, and preexisting pulmonary conditions. However, both experimental [42] and clinical [43] observations of worsening acute pulmonary hypertension induced by hypoxemia and acidosis, and of the hypoxemic effects of intravenous vasodilators, suggest that HPV is preserved in most ARDS patients.

The observation that intrapulmonary shunting and physiological HPV redistribute pulmonary perfusion has shed light on the potentially deleterious effects of hypo-perfused lung zones in the genesis and/or progression of lung injury in ARDS. Studies of healthy lungs demonstrated that HPV optimizes gas exchange but may also limit the supply of oxygen and nutrients to shunted lung zones [44]. In the presence of atelectasis, the size of the aerated lung is decreased, thus increasing the risk of overdistension and barotrauma of the ventilated areas and, consequently, promoting inflammation [45]. SPECT analysis of pigs undergoing one-lung ventilation (OLV) for 90 min followed by two-lung ventilation (TLV) showed hyperinflation and hyperperfusion of the ventilated lung, which caused diffuse damage to the alveolar compartment [46]. However, most studies of OLV models in the literature were performed for only a few hours and focused on the development of lung injury after TLV was restored (ischemia-reperfusion injury). Recently, the impact of OLV with a higher and lower V_T for 24 h without restoration of TLV was studied in pigs by group [47] (**Figure 2**).

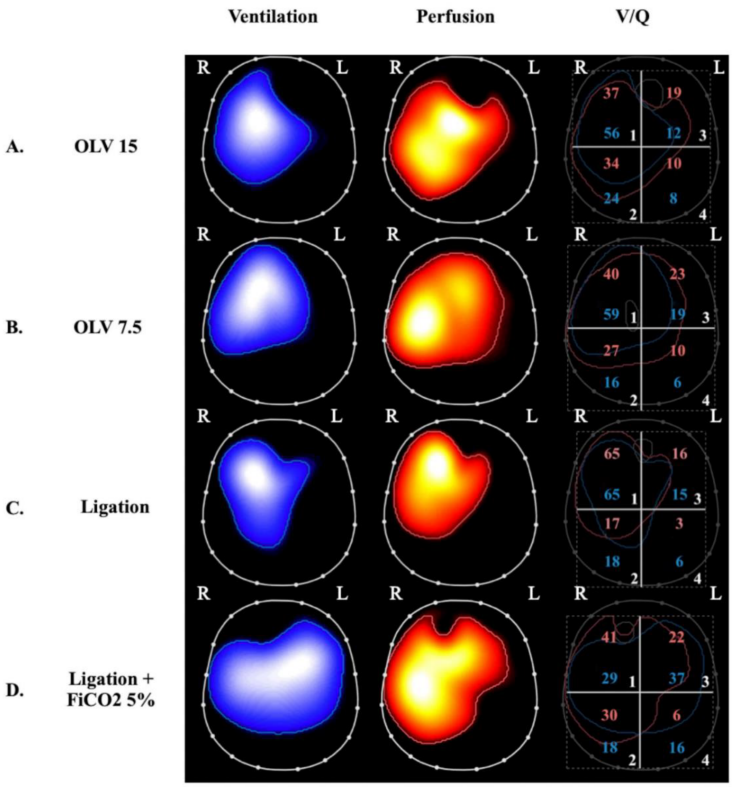

Figure 2. Ventilation, perfusion, and ventilation-perfusion matching via electrical impedance tomography in 4 experimental swine study groups. Images on the left display regional ventilation, middle images depict regional perfusion and were obtained by administering a hypertonic saline bolus under apneic conditions (see text), and images on the right depict ventilation-perfusion matching, which is expressed as the superposition of the ventilation and perfusion maps. The percentages of ventilation and perfusion to each of the four quadrants are annotated as blue and red numbers, respectively, on the right-side panels. The letters R and L indicate the right and left lung, respectively. (Panels **A** and **B**) were obtained during one-lung ventilation (OLV) with exclusion of the left lung and a tidal volume of 15 mL/kg (panel **A**)

and 7.5 mL/kg (panel **B**) [47]. At both tidal volumes, there is no ventilation of the left lung and perfusion appears to be redistributed to the ventilated lung. OLV at higher tidal volume (panel **A**) caused bilateral lung injury (lung histological score 5 ± 2 in the right lung and 10 ± 2 in the left lung); this was compared to two-lung-ventilated controls (lung histological score 3 ± 1 in right lung and 3 ± 1 in left lung). Interestingly, lowering tidal volume to 7.5 mL/kg (panel B) attenuated inflammation and lung injury (lung histological score 3 ± 1 in the right lung and 7 ± 1 in the left lung) despite an absence of change in the overall distributions of ventilation and perfusion (ANOVA $p \leq 0.01$ for the right lung and $p \leq 0.001$ for the left lung). (Panels **C** and **D**) were obtained from a study of selective left pulmonary artery ligation [48]. (Panel **C**) represents ligation alone whereas (panel **D**) represents ligation + 5% inhaled CO_2. The two groups differ significantly both for ventilation and perfusion distributions: In the ligation group, perfusion is only present in the right lung, ventilation is also diverted to the right lung, and total lung histological score was 11 ± 3. In the ligation + inhaled CO_2 group, there is a more homogeneous distribution of ventilation and perfusion in both lungs and total lung histological score decreased to 4 ± 2 (ANOVA $p \leq 0.0001$). The occurrence of perfusion to the ligated lung with inhaled CO_2 is thought to transpire due to increased flow through bronchial circulation.

OLV caused bilateral lung injury and, interestingly, lowering V_T prevented injury to the ventilated lung, but this protection was only partial in the non-ventilated lung. EIT analyses demonstrated that lung stress (classical VILI mechanism) was the main mechanism of injury in the ventilated lungs but collapse and hypoperfusion were implicated in the non-ventilated lungs. Notably, inflammation measured in the non-ventilated lung was dampened by reducing V_T to the contralateral ventilated lung, indicating the possible role of inflammation-based crosstalk between the lungs.

3.2. VILI Related to Ventilated Non-Perfused Lung Units

The other extreme of *V*/*Q* mismatch is represented by areas with high and infinite *V*/*Q* (dead-space), which have been studied in experimental settings mostly by intravascular occlusion or the surgical ligation of the pulmonary arteries. Alveolar hypocapnia in ventilated non-perfused alveoli seems to be responsible for local lung injury, which is, in part, mediated by alterations of the surfactant system [49] that lead to alveolar damage due to instability [50][51][52][53][57][58] and apoptosis [59]. Non-perfused ventilated areas can develop hemorrhagic infarction, as shown in a model of cardiopulmonary bypass and preserved ventilation [60]. Healthy swine lungs undergoing regional pulmonary vascular occlusion were studied to assess the local diversion of V_T from nonperfused to perfused areas via computed tomography. This diversion of ventilation appeared to be a compensatory mechanism that effectively limits *V*/*Q* mismatch [61] but also an indirect mechanism of lung injury due to overdistention and injury to perfused ventilated regions (**Table 1** and **Figure 2**, panel C). As with HPV for perfusion, hypocapnic bronchoconstriction can divert ventilation, improve *V*/*Q* matching, and optimize gas exchange by redistributing V_T to better-perfused lung areas [62][63]; on the other hand, it may contribute to the development of injury in these areas due to concomitant hyperventilation and hyperperfusion [64]. In a model of pulmonary hypertension induced by E. Coli endotoxin in sheep, it was shown that there is no threshold for edema formation when capillary permeability was increased; any increase in pulmonary blood flow or pressure increased edema [65]. This finding supports the hypothesis that an increase in regional lung perfusion in conditions of local injury (for example, due to increased lung stress from hyperventilation) can result in further injury due to edema formation. Furthermore, mild bilateral lung injury that develops in dogs after unilateral pulmonary artery occlusion is characterized by endothelial abnormalities and perivascular edema [66]. Broccard et al. observed that the dependent distribution of VILI in supine large animals ventilated with high V_T might be explained by regional differences in blood flow and vascular pressure, suggesting that differences among ventilatory patterns may be due, at least partially, to differences in hemodynamics [67].

Since the 1960s, the role of alveolar hypocapnia in the development of lung injury in non-perfused ventilated lung units has been demonstrated by studying the impact of inhaled CO_2 in unilateral pulmonary artery ligation (UPAL) models. Edmunds et al. first found a significant reduction in atelectasis in the ligated lung and a local increase in ventilation induced by inhaled CO_2, which led them to hypothesize that there was a direct effect of CO_2 or [H+] on bronchiolar alveolar cells and surfactant [68]. Kolobow et al. observed a reduction in hemorrhagic infarction and decreased alveolar and capillary injury in spontaneously breathing lambs during total cardiopulmonary bypass coupled with inhaled CO_2. The effect of high PCO_2 inhalation was also studied in preterm lambs; the result was an increase in lung gas volume and a reduction in histological damage and inflammation [69]. Recently, the group described a significant reduction in bilateral lung injury due to left-sided UPAL by administering 5% inhaled CO_2 during controlled mechanical ventilation [48] (**Figure 2**). The findings confirmed the protection of the ligated lung but also highlighted the protective role of inhaled CO_2 in the non-ligated lung, which was less overdistended due to a more homogenous distribution of ventilation as assessed by EIT. The group also investigated the question of whether the protective effects of inhaled CO_2 in the setting of bilateral lung injury caused by UPAL were due to increased $PaCO_2$ or to the local effects of CO_2 inhalation. Researchers demonstrated that inhaled CO_2 allows for more effective bilateral lung protection compared to plasmatic hypercapnia obtained through other methods [70].

In summary, in the presence of an elevated dead-space fraction, ventilated non-perfused units can be damaged by the inhibition of surfactant production and function, the induction of apoptosis, local ischemia, and inflammatory crosstalk from the residual hyperventilated and hyperperfused lung.

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