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REVIEW ARTICLE

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Altering ventilation-perfusion relationships in ventilated patients with acute lung injury

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Introduction

Since its description by Ashbaugh and Petty in 1967, the acute respiratory distress syndrome (ARDS) has been a major research focus in pulmonary and critical care medicine. However, despite rigorous investigation, it remains a common and vexing problem with a high (albeit possibly decreasing) mortality and no specific therapy. The cornerstone of managing patients with ARDS continues to be meticulous supportive care. Severe hypoxemia is a defining characteristic and is usually treated by high fractional inspired oxygen concentrations and the application of positive end expiratory pressure (PEEP). Recently, in response to a better understanding of the mechanisms of hypoxemia, the regional distribution of pulmonary blood flow and ventilation, several additional approaches to improving gas exchange in ARDS have been described. Although studies have not yet been reported to allow comment on whether these new approaches alter measures of clinical outcome, they have the potential to markedly improve our ability to manage these patients.

In this review, the regional ventilation-perfusion ($\dot{V}_A/\dot{Q}$) relationships seen in ARDS are described as well as a number of new interventions designed to alter these in a favorable fashion.

Ventilation-perfusion relationships in ARDS: mechanisms of hypoxemia

ARDS results from a variety of predisposing factors which lead to injury of the pulmonary endothelium and alveolar epithelial membrane [1, 2]. This is manifest clinically in diffuse pulmonary infiltrates and marked hypoxemia with increased venous admixture as calculated from arterial blood gases [1, 3]. The hypoxemia is usually relatively refractory to increasing F_IO_2 but frequently responds in part, to the application of PEEP [4, 5].

Early investigators [3], using the multiple inert gas elimination technique, found that hypoxemia in ARDS is due primarily to intrapulmonary shunt, with an additional contribution from regions of very low $\dot{V}_A/\dot{Q}$ in some patients. These findings are consistent with those seen in experimental models of ARDS [6–8]. A subsequent study [9] confirmed these findings and demonstrated that the application of PEEP reduced shunt and redistributed blood flow to regions of low or normal $\dot{V}_A/\dot{Q}$.

Pulmonary hypertension is described in patients with ARDS and in animal models of the syndrome. The duration in pulmonary arterial pressure is usually modest but is associated with an increased mortality [10, 11]. In animal models the degree of pulmonary hypertension is considerably greater [12] and in the early stages of injury has been attributed to neurohormonal mediators constricting the pulmonary circulation [13]. In humans, it has been difficult to separate vasoconstriction from the effects of PEEP although both seemingly contribute as the degree of pulmonary hypertension changes with titration of PEEP, and intravenous vasodilators reduce pulmonary vascular pressures and improve cardiac output [14, 15, 27, 28]. Unfortunately, this beneficial hemodynamic effect is associated with worsening axygen delivery and increasing shunt (14–16) attributable to attenuation of hypoxic vasoconstriction. Howev-

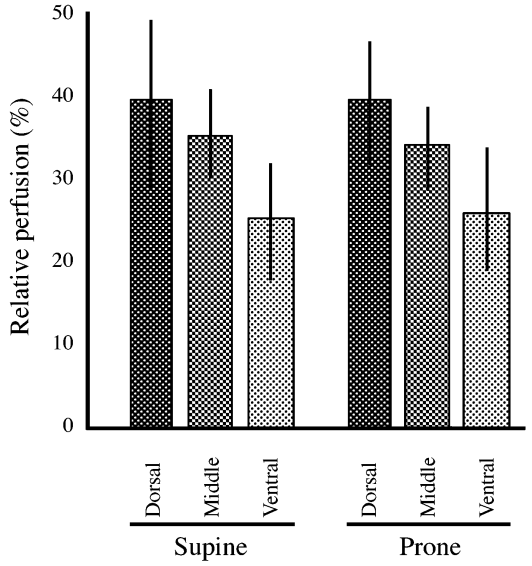

Fig. 1 Effect of body position on regional distribution of perfusion after oleic acid-induced acute lung injury. Note that reversing the gravitational gradient by turning prone has little effect on regional perfusion distribution [60]

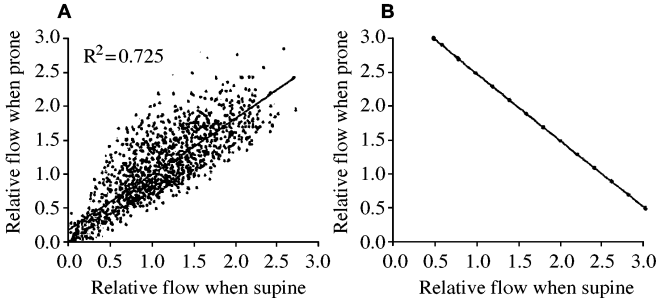

Fig. 2 A, B Relationship of relative flow per 1.9 cm^3 piece of lung measured in the supine and prone positions. **A** Experimental observations demonstrating a strong positive correlation. **B** Theoretical relationship if gravity were the principal determinant of perfusion distribution [61]

er, inhaled agents can circumvent this problem to some extent (see below).

The presence of a variety of vasoactive mediators in ARDS has, both clinically and experimentally, been linked with both vasoconstriction (to explain the pulmonary hypertension) and vasodilation (to explain reductions in hypoxic vasoconstriction). Excess production of vasoactive substances including leukotrienes [17], platelet activating factor [18], prostacyclin [19], and nitric oxide [20] has been identified.

Poorly ventilated, or non-ventilated lung segments in patients with ARDS have generally been attributed to alveolar filling with the cells and proteinrich edema identified on histopathological examination. The extent to which alveolar filling correlates with the parenchymal consolidation seen on chest roentgenograms or CT scans is poor, however. It has been suggested [21] that ARDS is an inhomogeneous condition, based on the fact that regional lung densities seen on chest CT occur predominantly in the dorsal lung. CT scans performed in both the prone and supine positions, have indicated that increased dorsal lung density results from atelectasis rather than focal injury [22]. This idea is supported by the observation made by a number of investigators that prone positioning can increase arterial oxygen tension (PaO_2) and decrease shunt in patients with ARDS. Additional confounding observations are that hypoxemia can occur *prior* to roentgenographic evidence of disease; and it's severity does not correlate with extravascular water content [23, 24].

In summary, the hypoxemia that characterizes ARDS is due primarily to shunt, with a smaller contribution coming from perfusion of low $\dot{V}_A/\dot{Q}$ regions. These findings, together with recent advances in the understanding of the factors governing the regional distributions of both ventilation and perfusion have been used to develop newer strategies to improve gas exchange in patients with ARDS.

Altering regional perfusion distribution

Vasodilators

The rationale for administering vasodilators to patients with ARDS is based on the assumption that decreased cardiac output resulting from excess right ventricular afterload leads to reduced systemic oxygen delivery and potentially exacerbates organ dysfunction. There are numerous potential problems associated with this rationale. Thus, in ARDS pulmonary hypertension is rarely sufficiently seven to decrease right ventricular function to any clinically meaningful extent. In any event, this could be countered by increasing right ventricular filling. Secondly, much of the increase in pulmonary arterial pressures is likely attributable to PEEP rather than active vasoconstriction. Thirdly, vasodilation may counter any potential beneficial effects of hypoxic vasoconstriction on regional lung injury and repair; and, finally, O_2 delivery is generally increased rather than decreased in patients with ARDS.

Not surprisingly, several older clinical trials designed to evaluate the effects of intravenous vasodilators [e.g., nitroglycerin [17], nitroprusside [15], diltiazem [16]] found that pulmonary arterial pressure and pulmonary vascular resistance fall and PaO_2 and systemic O_2 delivery decreased as a result of increased shunt and $\dot{V}_A/\dot{Q}$ heterogeneity. These deleterious effects were presumed to occur secondary to the inhibition of hypoxic vasocon-

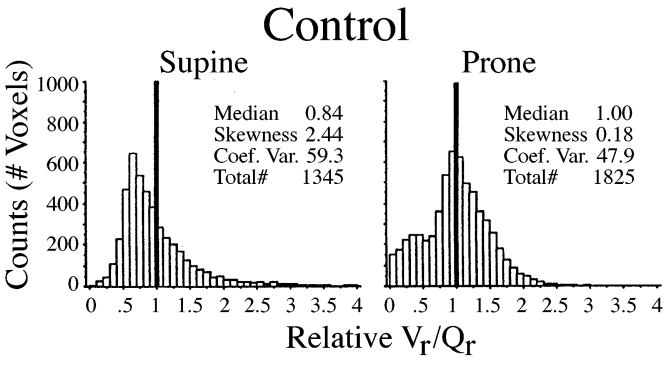

Fig. 3 Frequency distribution of relative regional ventilation-perfusion ratios in a normal dog lung, supine and prone, as determined by SPECT scan. The y-axis represents the number of voxels with a given ventilation-perfusion ratio (x-axis) [78]

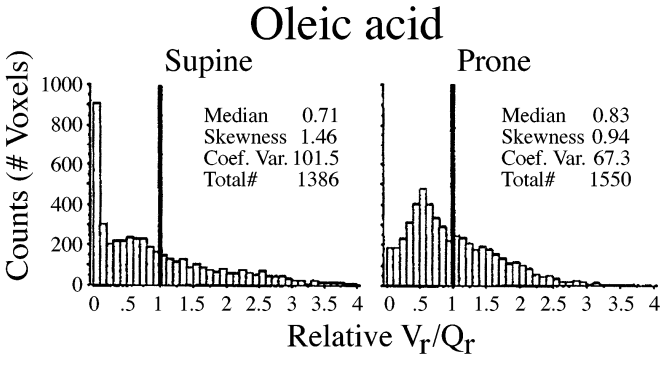

Fig. 4 Frequency distribution of relative regional ventilation-perfusion ratios in a dog lung following oleic acid-induced acute lung injury, supine and prone, as determined by SPECT scan. The y-axis represents the number of voxels with a given ventilation-perfusion ratio (x-axis) [78]

striction by these agents. Examples of vasodilators that have investigated clinically and are worthy of include:

Prostaglandin E_1. Prostaglandin E_1 was thought to be a more promising vasodilator as it did not appear to alter hypoxic vasoconstriction in patients with chronic obstructive pulmonary disease [25]. Furthermore, an early study [26] reported that PGE_1 administration was associated with a significant survival advantage in a subgroup of patients with ARDS but no secondary organ dysfunction. However, subsequent studies [27, 28] found that PGE_1 worsened shunt and had no effect on survival. Accordingly, there seems to be little support for intravenous vasodilator therapy for patients with acute lung injury.

Almitrine. Almitrine bismesylate, a piperazine derivative, has been shown to improve PaO_2 in patients with COPD [29, 30]. Animal data initially attributed this to an increase in minute ventilation (V_E) caused by the effect of the medication on peripheral chemoreceptors [31]. Subsequent measurements of $\dot{V}_A/\dot{Q}$ relationships in patients with COPD indicated that almitrine improved $\dot{V}_A/\dot{Q}$ matching without changing V_E [32–34]. In addition, studies done in isolated rat lungs demonstrated that almitrine enhanced hypoxic vasoconstriction [35].

Almitrine administered to 9 patients with ARDS induced a significant improvement in PaO_2 (78 ± 15 to 140 ± 49 mmHg) and reduction in shunt fraction (29 ± 11 to $17 \pm 11\%$) without altering cardiac output [36]. The effect of almitrine on venous admixture has been found to be similar to that resulting from 10 cm H_2O PEEP [37]. An additive effect on improvements in gas exchange has been seen when almitrine is administered concomitantly with nitric oxide (NO) in patients with ARDS who respond to NO by increasing their $P_aO_2/F_IO_2 > 10$ mm Hg or more [38]. These encouraging improvements in gas exchange have not yet been studied with regard to their ability to alter survival.

Nitric oxide. Nitric oxide (NO) is an endogenous vasodilator and vascular smooth muscle relaxant synthesized in a variety of tissues, including the vascular endothelium, from L-arginine utilizing NO-synthase, and is competitively inhibited by L-arginine analogs [39, 40]. NO-synthase inhibitors enhance hypoxic vasoconstriction in isolated lung preparations [41] and in animal models of acute lung injury [42], suggesting that NO contributes to the attenuated hypoxic vasoconstriction associated with the shunt and low $\dot{V}_A/\dot{Q}$ of ARDS. Inhaled NO has been shown to reverse hypoxemic vasoconstriction in sheep [43] and to redistribute perfusion from poorly ventilated to ventilated lung segments in patients with ARDS [44]. Its effects are limited to the pulmonary (as opposed to the systemic) circulation due to its rapid inactivation by high affinity binding to hemoglobin [45].

An L-arginine analog has been shown to induce pulmonary vasoconstriction in a canine oleic acid model of acute lung injury [46], although $\dot{V}_A/\dot{Q}$ relationships were unchanged and the effects were reversed with inhaled NO at 40 PPM without effecting systemic vascular resistance (SVR). Gas exchange improved via a redistribution of blood flow away from poorly ventilated lung units. These beneficial effects were augmented by the application of continuous positive airway pressure (CPAP), presumably due to the recruitment of atelectatic gas exchange units [47]. A subsequent study demonstrated that NO-induced increases in P_aO_2 were proportional to the baseline pulmonary vascular resistance index in patients with acute, hypoxemic respiratory failure in whom the application of 10 cm H_2O PEEP resulted in alveolar recruitment [48].

Prostacyclin (PGI_2) has also been administered via the inhaled route with similar results [49, 50]. Inhaled

prostaglandin E1 has been found to be ineffective [26–28].

Although these results are encouraging, it remains to be seen whether inhaled interventions will translate to improved outcome in patients with ARDS, who rarely die of hypoxemia. Accordingly, therapeutic interventions aimed solely at improving oxygenation are unlikely to alter mortality. On the other hand, if improvements in oxygenation allow reductions in F_IO_2, PEEP, the necessity for mechanical ventilatory support and/or the need for invasive monitoring, improvements in mortality resulting from ventilator-induced lung injury or the sepsis syndrome might be observed.

Altering regional ventilation distribution

Prone position

Numerous investigators have reported that PaO_2 improves in patients with ARDS when they are turned from the supine to prone position (mean increases of 28 to 69 mm Hg) [51–55]. Although only 50–75 % of patients respond, the degree of improvement can be marked (up to 140 mm Hg increase in PaO_2 on the same PEEP and F_IO_2) allowing major reductions in PEEP and F_IO_2 (e. g., as much as 17.5 cm H_2O and 0.5, respectively). Improvements can be sustained for up to seven days [51].

Initially, investigators observing the prone position-induced improvements in gas exchange hypothesized that they might result from the redirection of perfusion (Q) from dorsal to ventral lung regions on turning prone [52]. This would, of necessity, require that regional lung injury also be preferentially localized to the dorsal lung regions. Subsequent studies have questioned both assumptions.

Pulmonary blood flow (Q) distribution has been described by the zonal model [56] for over 40 years. In this model, Q increases from non-dependent to dependent regions (to approximately three-fourths of the way down the lung, after which it decreases) [57, 58]. Factors thought to account for these differences include the relationship between intravascular hydrostatic pressures and alveolar pressure at a given gravitational level (Zones 1 and 2), the distensibility of the pulmonary vasculature (Zone 3) and the potential effects of regional differences in interstitial edema and/or lung weight on alveolar volume in the most dependent regions (Zone 4).

A gravitational Q gradient has been described in the upright, head down, supine and lateral decubitus positions [59, 60]. Although a gravitational gradient has also been observed in the prone position of humans and several animal species, the gradient has always been found to be markedly reduced (i. e., a more uniform Q distribution compared to that seen in the other positions) [60].

A strong gravitational Q gradient was indeed identified in supine dogs with oleic acid-induced acute lung injury, but Q distribution changed very little when the animals were turned prone (Figure 1), suggesting the role played by gravity in determining this gradient is small [61]. Subsequent studies using microsphere technology, examined Q on a much smaller scale than was previously possible and found that flow distribution in supine animals was strongly correlated ($R^2 = 0.725$) to that found in the prone position; exactly the *opposite* to that predicted by the gravitational model [62].

A number of investigators have now found that Q is preferentially distributed to the dorsal lung regions *regardless* of body position and have suggested that the large majority of Q heterogeneity (> 90 %) can be accounted for by a fractal model of dichotomous vascular branching in which the distribution of flow between daughter branches is constant at each branch point [63–65].

Additionally, oleic acid-induced lung injury (as manifested by regional wet/dry ratios) was shown to be uniformly distributed in the dog lung [61]. Accordingly, there is no support for the idea that turning from the supine to prone position improves oxygenation by redirecting Q to ventral regions and other explanations were needed.

Since the distribution of Q does not change to any meaningful extent, yet shunt improves, attention was turned to potential explanations by which the prone position could improve regional alveolar ventilation.

There is a gravitational gradient of regional lung volume resulting in greater expansion of non-dependent versus dependent lung regions at functional residual capacity (FRC) and all volumes above FRC until total lung capacity (TLC) is reached [66]. This relationship has been observed in normal lungs in the supine, upright, and both lateral decubitus positions [66–71], and results in preferential distribution of alveolar ventilation to more dependent lung regions [72–77]. Differences in regional pleural pressure (P_{pl}) account for this phenomenon.

Recently, several studies have shown that the relatively steep P_{pl} gradient seen in the supine position (i. e., more negative in non-dependent areas) becomes much more uniform when prone. This observation can explain older findings that alveolar ventilation is more uniform, and the slope of phase III on a single breath oxygen test is flatter [78] in the prone versus supine position.

The more uniform P_{pl} gradient in the prone position is attributed to the fact that, while gravity still has an effect on P_{pl} and alveolar volumen when prone, it is offset by positional differences in the forces generated within the thoracic cavity [72] in part a result of the weight of the heart and in differences in the shape and attachment

of the diaphragm to the dorsal compared with the ventral chest wall [79].

Lamm and colleges [79] measured positional variations in regional ventilation/perfusion ratios with single photon emission computed tomography (SPECT scanning) in dogs before and after oleic acid-induced acute lung injury. Prior to injury regional V_E/Q increased from dorsal to ventral regions (slope = 0.12, $p < .001$ versus slope of zero) when the animals were supine. Turning them prone eliminated the gravitational V_E/Q gradient (slope = 0.00, $p < 0.05$ versus supine slope), increased the median V_E/Q ratio of from 0.8 to 0.94 ($p < 0.05$) and generated a more Gaussian V_E/Q distribution (Figure 2).

After acute lung injury, supine animals exhibited a lower median V_E/Q ratio (0.77), an increased gravitational gradient (slope = 0.22) and a large fraction of shunt that were located almost exclusively in the dorsal (i.e., dependent) lung regions (Figure 3). When turned prone, the median V_E/Q ratio increased to 0.94, the gravitational gradient disappeared (slope = – 0.02, $p < 0.05$ versus supine slope) and regions of shunt decreased (Figure 4). Interestingly, small areas of shunt only rarely developed in the ventral (i.e., dependent) regions on turning prone, supporting the fact that the P_{pl} gradient did not simply reverse. Accordingly, the generally fixed preferential distribution of Q to dorsal regions, together with markedly improved dorsal lung ventilation that occurs in the prone position produces a more homogeneous V_E/Q relationship accounting for the improvement in gas exchange. As with the vasodilator studies cited above, the effect of the prone position on morbidity or mortality has not yet been studied.

Exogenous surfactant

Dysfunction of the surfactant system is well documented both in patients with ARDS (1,80) and those at risk of developing the syndrome (80). The loss of its surface tension lowering properties may enhance the development of atelectasis in concert with the mechanisms described above and may contribute to the gas exchange derangements observed. The rationale for exogenous surfactant therapy has been supported by observed improvements in both gas exchange and survival in several animal models of ARDS (81), and in neonates with a primary surfactant deficiency, i.e., the respiratory distress syndrome [82, 83].

Initial studies administering mammalian surfactant extracts to animals and patients with ARDS were associated with encouraging improvements in ventilatory requirements and gas exchange [84–86]. Unfortunately, the first multicenter, randomized, controlled trial of surfactant therapy in patients with ARDS found no statistically significant differences in physiologic function, or clinical outcome, defined by length of mechanical ventilation, days in intensive care or 30 day mortality [87]. Explanations for this lack of benefit may relate to the fact that only patients with sepsis-associated ARDS were studied, the synthetic surfactant used contained no surfactant-associated proteins (these may have considerable therapeutic importance) and/or administering surfactant via aerosol might have been inefficient such that lung phospholipid pools might not have been adequately replaced.

A subsequent multicenter trial enrolled 59 patients with ARDS and a variety of risk factors for the syndrome and instilled a bovine surfactant extract which contains surfactant-associated proteins B and C directly into the airways [88]. Significant reductions in F_IO_2 at 120 hours and a trend toward improved survival (18.8 % versus 43.8 %, $p = 0.075$) were observed in those treated with 4 doses of 100 mg phospholipid/kg. While these results suggest a possible role for surfactant replacement in the treatment of ARDS, further studies are needed to address issues such as optimal dosage, route of delivery and the preparation's precise composition.

Partial liquid ventilation

The ability of mammals to sustain gas exchange while breathing liquid perfluorocarbons was first described in 1966 [89]. The technique of partial liquid ventilation (PLV); instilling perfluorocarbon liquid into the lungs with subsequent tidal breaths of gas delivered by standard positive pressure ventilation, has recently been proposed for use in treating infants and adults with acute lung injury.

Perfluorocarbons are biologically inert, high density, low surface tension compounds capable of dissolving large amounts of O_2 and CO_2 at atmospheric pressure [89]. The rationale suggesting that they might be useful in treating acute lung injury stems from their potential ability to re-expand areas of atelectatic lung due to its density and low surface tension (i.e., "liquid PEEP"), and/or as a result of their high density, by redirecting perfusion to more non-dependent lung retions [99].

Recruitment of previously non-ventilated alveoli and improved surface tension should increase lung compliance and FRC and may improve $\dot{V}_A/\dot{Q}$ matching [90]. As predicted, there is a marked increase in end-expiratory lung volume with liquid versus gas re-expansion in normal animal lungs and in those in which surfactant has been altered or depleted [91]. Furthermore, some investigators have suggested that endogenous surfactant production may increase during liquid ventilation [92, 93] and at least one of the perflurocarbons (Perflubron Liquivent®, Alliance Pharmaceutical Corp., San Diego) may possess anti-inflammatory properties [94, 95].

Although encouraging improvements in oxygenation and lung mechanics have been seen in animal models of acute lung injury and animals and humans with the respiratory distress syndrome, there is minimal experience in humans with acute lung injury. A recent uncontrolled trial enrolled 13 premature infants with severe respiratory distress syndrome (RDS) unresponsive to exogenous surfactant replacement to be treated with PLV. Significant improvements were noted in both dynamic compliance (61 % increase) and P_aO_2 (138 % increase); and 8 of 10 patients who completed the study survived to 36 weeks corrected gestational age [96]. Similar results have been observed in pediatric patients with acute respiratory failure [97, 98].

The results of a phase II randomized, controlled trial comparing PLV with conventional gas ventilation in 90 adult patients with acute, hypoxemic respiratory failure were recently reported [100]. No significant differences in physiologic variables or indices of clinical outcome were observed by a trend toward reduced mortality and fewer ventilator days was seen in patients under 55 years of age treated with PLV. PLV was also associated with more frequent transient hypoxia and bradycardia. Plugging of the endotracheal tube with secretions and a rather frequent incidence of pneumothorax has also been described [96]. A phase III trial is currently planned.

Conclusion

ARDS is a common clinical problem with an associated mortality of 36 to 50 %. Management remains primarily supportive. Recent insights into the physiologic explanation for the observed gas exchange abnormalities suggest that shunt is primarily the result of Q being directed primarily to the dorsal lung regions where atelectasis develops when the patients are supine. Ventilation, and the relationship between V_E and Q become more homogeneous when patients are turned prone due to the effect of forces generated within the thorax manifest as a change in the P_{pl} gradient.

Several promising interventions designed to alter the distribution of pulmonary blood flow (e. g., inhaled NO and intravenous almitrine) and/or ventilation (exogenous surfactant, PLV, prone position) are emerging which may be added to the available management armamentarium pending an evaluation of their effect on morbidity and mortality.

Of the interventions discussed, prone positioning is the most intriguing as it improves $\dot{V}_A/\dot{Q}$ without the added expense and potential complications associated with pharmacological interventions and can be easily and safely accomplished in virtually any critical care setting.

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