1. Liquid ventilation

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Introduction

In acute lung injury, capillary permeability to water and large molecules increases. Water and protein are filtered from pulmonary capillary to lung interstitium. The alveolar basement membrane is less permeable to these substances than is the pulmonary circulation, so fluid accumulates in the interstitium. Pulmonary lymphatics drain the interstitium as rapidly as they can, increasing their intrinsic flow rates by a factor of 10 to 20 in an effort to match transudation rates. If this is not sufficient to limit interstitial fluid accumulation, the dam bursts. Interstitial fluid and protein begins to leak into alveoli.

This liquid impairs the function of surfactant in the alveolus, raising alveolar surface tension.

Acute lung injury is not homogeneous. Some alveolar segments are worse affected than others. Those of relatively high surface tension and poor compliance may be virtually unresponsive to positive end-expiratory pressure (PEEP). Other, less affected segments may be readily recruited by PEEP. Yet others, which have been spared or minimally affected, may become overdistended as PEEP is applied and escalated. This sets the stage for massive maldistribution of ventilation, volutrauma and hypoxia.

Perfusion of the lung is, most dramatically, regulated locally, at the alveolar capillary unit. Vessels within those segments that are exposed to high alveolar pressures during the application of PEEP will be compressed. Those segments that fail to oxygenate blood will become hypoxic, and will undergo alveolar hypoxic vasoconstriction. This sets the stage for redistribution, at times maldistribution of perfusion, high V/Q mismatch, and hypercarbia.

Ventilation-perfusion mismatch is the principal impediment to gas exchange in acute lung injury. Until quite recently, the intensivist could only force air into non-receptive lungs, and hope that this ventilator strategy would fortuitously improve ventilation-perfusion (V/Q) matching.

In the past decade, new approaches to V/Q mismatch have improved our approach to RDS in premature and term infants. Efforts to document efficacy of these strategies have been less satisfying in the adult. Nonetheless, the use of exogenous surfactants and nitric oxide as means to modify V/Q matching has opened the door to a new era of respiratory treatment. Perfluorocarbon liquid ventilation and perfluorocarbon associated gas exchange (or partial liquid ventilation) are other methods by which V/Q mismatch may be treated.

Liquid breathing

Fish breathe by extracting oxygen from water that crosses their gills. Though oxygen is sparingly soluble in water (.003 ml O_2/100 ml H_2O/torr pO_2), this method of oxygen uptake suffices, even for fish that you just can't reel in. This reflects the massive volume of water the

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gills can contact per minute. A shark swimming with its mouth open may breathe swimming pool size volumes of water every minute. Mammals, on the other hand, breath in and out through the same set of narrow airways. Minute ventilation is quite limited. The viscosity of liquids raises the time constant of the lung and reduces the volume of fluid to which an alveolus might be exposed during liquid breathing. This would dramatically increase the work of breathing of the normal mammalian lung.

Nonetheless, Clark[1] has shown that mice can spontaneously breathe liquids of high oxygen solubility for periods approaching an hour before exhaustion leads to respiratory failure.

Tidal liquid ventilation (TLV)

For mammals to breathe liquid for longer periods, two requirements must be met : (1) A liquid must be used that possesses high solubilities for oxygen and carbon dioxide, and (2) a ventilator must be used to perform the work of breathing.

Kylstra has shown that dogs can be ventilated, short term, using hyperbarically oxygenated saline[2]. This fluid is associated with carbon dioxide retention. Because surfactants are miscible in water, this process also leaves the animal surfactant deficinet.

Leland Clark first identified perfluorocarbons as a suitable class of compounds for liquid breathing. Numerous impure perfluorocarbons have been studied, but it is only recently that a medical grade liquid suitable for liquid ventilation has become available (perfluorooctyl bromide, LiquiVent^{tm}, Alliance Pharmaceutical Corp, San Diego).

Moskowitz, Shaffer, Wolfson, Fuhrman and Hirschl have developed devices capable of supporting liquid ventilation. Such devices need not be intricate, but do represent a new category of medical device to the Food and Drug Administration (FDA), and are, therefore, intimidating. Yet they are capable of supporting the very immature lung with hyaline membrane disease[3], and can be used at low alveolar pressure[4] without impeding cardiac output[5].

Perfluorocarbon associated gas exchange or partial liquid ventilation

A recent innovation variously termed perfluorocarbon associated gas exchange (PAGE) or partial liquid ventilation (PLV) has simplified the technical aspects of using perfluorocarbons in the lung. It has been shown that it is possible to fill the functional residual capacity of the lungs (FRC) with perfluorocarbon liquid, and to "bubble oxygenate" the liquid in situ (in vivo) using a conventional gas ventilator[6]. This technique (gas ventilation of the fluid filled lung) allows liquid to be used to recruit atelectatic lung and reduce surface tension at the alveolar lining, and provides a reservoir for oxygen during expiration in alveoli that would otherwise collapse and permit intrapulmonary shunting. In inspiration, tidal volumes of gas purge that reservoir of carbon dioxide and replenish the supply of oxygen. Moreover, the inspiratory tidal volume is delivered to a more homogeneous lung during PAGE than during conventional ventilation of the gas filled lung.

In normal piglets, PLV can be instituted without elevating airway pressure, and consistently provides adequate ventilation and oxygenation[4]. PLV has been shown effective over prolonged treatment periods, and recovery back to gas breathing has been demonstrated in normal piglets[7] and baboons[8]. Hernan has shown that inspiratory oxygen fraction can be adjusted during PLV to achieve desired arterial pO_2 without impairing hemodynamics or accumulating nitrogen foam in the lungs[9].

Large animals have only recently been studied. Sheep weighing up to 70 kg can be support-

ed by PLV[10]. Oxygenation has been found to be tidal volume dependent in that model. This has not been observed in smaller animals.

PLV in models of lung disease

Lachmann has shown that rabbit lungs, lavaged with saline to induce surfactant deficiency, exchange gas more efficiently during PLV than during conventional gas ventilation[11]. Leach has shown this to be the case in premature lambs with hyaline membrane disease as well[12]. Wilcox has studied lambs with surgically induced left diaphragmatic hernia, and has shown that this lesion (which is complicated by surfactant deficiency) is amenable to treatment by PLV[13]. In all of these models, lung compliance was dramatically improved by the presence of LiquiVenttm in the lung.

This technique has also been applied to piglets after intratracheal instillation of meconium[14]. In this model, oxygenation and six-hour survival were both substantially improved. Meconium is thought to impair surfactant function, but also obstructs distal airways. Improvement in gas exchange was less striking in this model than in surfactant deficiency.

Several models of acute lung injury have been studied. Papo has shown that lung injury induced by intravenous oleic acid infusion is ameliorated by PLV[15]. Nesti has shown that gastric acid pneumonitis ARDS is improved by PLV[16]. In both of these studies, there is histologic evidence of diminished inflammation, suggesting that there might be an antiinflammatory effect of the perfluorocarbon in the lung. Hernan has recently shown that PLV also improves gas exchange in large sheep injured by acid aspiration.

In normal lung, instillation of perfluorocarbon consistently decreases pO_2 by about 100 torr. The normal gas filled lung clearly functions more effectively than the normal lung filled with liquid. This has been attributed to limitations of oxygen solubility and diffusivity. In essence, PLV does not improve on nature in the normal lung. However, in a wide variety of animal models of lung disease, PLV using LiquiVent^{tm} has improved gas exchange. This poses a strong argument that PLV improves ventilation-perfusion matching in these abnormal lungs.

We have noted that PLV with LiquiVent^{tm} yields pO_2's in several models of lung disease that are comparable to those achieved by PLV in normal lungs[17]. This coupled with histologic evidence of diminished inflammation in several models of inflammatory lung disease suggests that perfluorooctylbromide may have an antiinflammatory effect.

Steinhorn has shown that alveolar macrophages are less readily stimulated to generate free radicals and hydrogen peroxide after exposure to perfluorooctylbromide[18]. This perfluorocarbon may quench inflammation in the lung, thereby ameliorating inflammatory lung disease.

PLV combined with other modalities in lung disease

Lambs with surgically induced left diaphragmatic hernia do not respond to inhaled nitric oxide without other treatment to recruit atelectatic lung. Nitric oxide is, however, effective after institution of PLV.

Leach has studied compatibility of LiquiVent^{tm} PLV with exogenous surfactant, and has found the treatments to be compatible and probably synergistic.

Clinical trials of PLV

The FDA has approved clinical trials of LiquiVent^{tm} PLV to prove its efficacy in ARDS.

The first study under this IND involved premature infants with hyaline membrane disease. Candidates for study failed all conventional therapies, including multiple doses of surfactant, and were expected to die if not offered experimental therapy. Thirteen infants were enrolled in this trial. Seven neonates had prolonged survival, and are alive and at home. All but two infants had improvement in oxygenation, and most, in whom lung mechanics were measured, showed improved lung compliance.

Phase I/II clinical trials in adults have also been completed. Of nine patients enrolled, 7 were alive at day 28 (78%). In a Phase I/II clinical trial in children, 10 were enrolled and 8 survived (80%).

Adult and pediatric Phase I/II ARDS trials have addressed the patient with high risk of mortality. Entry criteria were geared toward patients at 50% or greater presumed risk of mortality. Unfortunately, historical data do not make it easy to identify such patients. Moreover, ARDS is associated with multiple organ systems failure. Mortality in ARDS, therefore, often reflects extrapulmonary disease. Etiology is a further confounding problem, in that certain causes of ARDS are themselves highly lethal, eg sepsis, trauma, and malignancy. Clinical trials will have to cope with this complicating factor if efficacy is to be established on the basis of improved survival.

Safety has been adequately demonstrated by Phase I/II studies to justify randomized, controlled clinical trials. Such a study is now underway in adults with ARDS, and will soon be undertaken in children with ARDS. These trials will further address the issues of safety and efficacy.

Conclusion

PLV improves lung function by enhancing uniformity of lung inflation, and does not merely force air into the diseased lung.

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