Liquid Ventilation for Neonatal Respiratory Failure

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I. Description: Liquid ventilation refers to the process of enhancing pulmonary function through the instillation of perfluorocarbon liquid into the lungs.
   A. Partial liquid ventilation (PLV): the achievement of gas exchange through the delivery of gas tidal volumes to lungs which have been filled with perfluorocarbon liquid
   B. Total liquid ventilation (TLV): the achievement of gas exchange through the delivery of tidal volumes of perfluorocarbon liquid to the lungs using a specialized mechanical liquid ventilator

II. Physiology of Perfluorocarbon Ventilation
   A. Perfluorocarbons (PFC): inert liquids which are produced by the fluorination of common organic hydrocarbons. The carbon chain length and any additional atom give unique properties to each perfluorocarbon molecule.
   B. Physical properties of perfluorocarbons
      1. Density: denser than hydrocarbon counterparts with levels approaching twice that of water (1.75–1.95 g/mL at 25 °C).
      2. Surface tension: have weak intermolecular forces and remarkably low surface tensions (15–20 dyn/cm at 25 °C).
      3. Respiratory gas solubility: solubilities of the respiratory gases in perfluorocarbons are significantly greater than their corresponding solubilities in water or non-polar solvents.
         a. O_2 solubility at 37 °C = 44–55 mL gas/100 mL liquid
         b. CO_2 solubility at 37 °C = 140–210 mL gas/100 mL liquid
      4. An ideal PFC for respiratory application should have the properties of high gas solubility and moderate vapor pressure and viscosity. These properties, however, might not be found in a single pure perfluorocarbon. Thus, recent studies are focusing on PFC combinations that may optimize the fluid properties to better suit a particular application.
      5. Vapor pressure: perfluorocarbons are relatively volatile (vapor pressures range from 11 to 85 Torr at 37 °C). This property is important because it governs the evaporation rate of perfluorocarbons from the lungs during and after both types of liquid ventilation; high vapor pressure liquid would need more frequent supplementation than a low vapor pressure one.

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C. Basis for the use of liquid ventilation in neonatal ventilator-dependent respiratory failure
   1. Gas exchange
      a. Dependent portion of the lungs tends to be collapsed or filled with inflammatory exudate during severe pulmonary inflammation leading to ventilation-perfusion (V/Q) mismatching and hypoxemia.
      b. The high densities of perfluorocarbon liquids facilitate their distribution to the dependent portions of the lungs where atelectatic lung appears to be recruited.
      c. Perfluorocarbons have also been shown to redistribute pulmonary blood flow to the better-inflated, non-dependent segments.
      d. These effects, combined with the high respiratory gas solubilities of perfluorocarbons, lead to improvements in V/Q matching and arterial oxygenation.
   2. Pulmonary compliance
      a. Perfluorocarbons lead to an increase in pulmonary compliance secondary to their density-related recruiting effect on collapsed, inflamed alveoli. However, during PLV an increase in the perfluorocarbon dose can be associated with a reduction in compliance. This is related to the heterogeneous distribution of gas in the partially liquid-filled lungs.
      b. Perfluorocarbons act as an artificial surfactant and increase the stability of small airways.
      c. The regions of the lung that are filled with perfluorocarbon liquid (all regions for TLV, the dependent regions for PLV) exhibit a reduction of the gas–liquid interface in the distal airway which also reduces surface active forces tending to alveolar collapse.
      d. The result of these effects is enhanced alveolar recruitment at lower inflation pressures.
   3. Reduction of lung injury
      a. Effects may relate to improved alveolar inflation and better displacement and lavage of inflammatory mediators and debris from the affected portions of the lungs or to a limitation of excessive ventilator pressures from improvements in compliance.
      b. Perfluorocarbons have been shown to have in vitro anti-inflammatory activities, such as reduction in neutrophil chemotaxis and nitric oxide production, as well as decreased LPS-stimulated macrophage production of cytokines. Neutrophil infiltration also appears to be reduced following lung injury in liquid ventilated animals. In vivo evaluation has shown a reduction in the release of TNF-α, IL-1, and IL-6 in human alveolar macrophages in perfluorocarbon exposed lungs.

D. Uptake, biodistribution, elimination, and toxicology
   1. Uptake: absorbed in small quantities from the lungs during liquid ventilation, reaching a steady state at 15–30 min of liquid breathing
   2. Biodistribution: have preferential distribution to tissues with high lipid content. These compounds are cleared most quickly from vascular, lipid-poor tissues such as muscle.
   3. Elimination: do not undergo significant biotransformation or excretion. PFCs are primarily eliminated by evaporation from the lungs and are scavenged by macrophages in both the lungs and other tissues.
   4. Toxicology: pulmonary, metabolic, hematologic, and clinical effects of liquid ventilation have been studied extensively in laboratory animals with no significant pulmonary or systemic toxicity noted. Clinical studies have identified transient hypoxemia during PFC dosing and the development of pneumothorax as potential short term complications of PLV in humans.

III. Partial Liquid Ventilation
  A. A hybrid method of gas exchange, achieved through the delivery of conventional gas tidal volumes to perfluorocarbon-filled lungs
    1. Methods
      a. Lungs are filled with PFC liquid to an estimated fraction of FRC (approximately 5–30 mL/kg, depending on disease process, age, and weight) and conventional ventilation superimposed to achieve gas exchange.
      b. Adequate filling of the lungs is judged by the presence of a fluid meniscus in the endotracheal tube at a PEEP of 0, by the opacification of the dependent portions of the lungs on lateral chest radiography, and by the adequacy of gas tidal volumes. Fluid may be added or withdrawn.
    2. Theoretical basis for use of PLV in RDS
      a. PLV has relative simplicity as the need for a complex mechanical liquid ventilator is eliminated.
      b. The presence of dense perfluorocarbon fluid in the dependent regions of the lungs allows the recruitment of severely inflamed airways for the purpose of gas exchange. Oxygenation during PLV can occur either by the gas ventilation of these airways directly or by the oxygenation of the liquid as it equilibrates with the inspired gas.
      c. Carbon dioxide elimination is enhanced by increased gas tidal volumes.
      d. Compliance is enhanced secondary to alveolar recruitment and the surfactant-like activity of the perfluorocarbons. Because the gas–liquid interface is not completely eliminated during PLV, compliance improvement is not as dramatic as that seen during TLV and can actually deteriorate if the lungs are overfilled with perfluorocarbon liquid.
  B. Clinical studies of PLV in neonatal ventilator-dependent respiratory failure
    1. Leach reported significantly improved gas exchange and pulmonary compliance during PLV in 13 premature infants (24–34 weeks' gestation at birth) with refractory RDS as part of a multicenter, non-controlled trial. Significant complications occurring during the trial were limited to the development of Grade IV intraventricular hemorrhage in one patient. Of the ten patients completing at least 24 h of PLV, survival to a corrected gestational age of 36 weeks was 60 %.
    2. Pranikoff evaluated the use of PLV in four newborn patients maintained with extracorporeal life support for respiratory failure secondary to congenital diaphragmatic hernia (CDH). During 5–6 days of PLV therapy, patients exhibited significant increases in arterial oxygen tension and static pulmonary compliance compared to pretreatment values. The therapy was well tolerated and significant complications were limited to the development of pulmonary hemorrhage in one patient 4 days after the final dose of PFC.
    3. Migliori et al. evaluated the use of high-frequency PLV in two infants with chronic lung disease and severe respiratory failure. Both patients showed improved gas exchange with reduction in oxygen indices.

IV. Total Liquid Ventilation
  A. Lungs are completely filled with perfluorocarbon and a liquid tidal volume is perfused into and drained from the lungs for the purpose of gas exchange using a specialized mechanical liquid ventilator.
  B. Clinical studies of TLV
    1. The feasibility and potential of liquid ventilation as treatment for severe respiratory distress was reported in 1990 by Greenspan.
    2. Liquid ventilation was performed in 3 preterm neonates in whom conventional treatment had failed.

3. Improvement of pulmonary mechanics without hemodynamic impairment was reported in all three neonates.
4. The severity of pulmonary injury before the initiation of liquid ventilation precluded a successful outcome.

V. Perfluorocarbon-induced lung growth (PILG)
   A. Different studies have demonstrated the effectiveness of perfluorocarbon to induce lung growth in neonates with CDH on ECMO.
   B. A multicenter, prospective, randomized pilot study showed a higher mortality for the PILG group (75 %) compared to patients treated with conventional ventilation (40 %), though the number of patients in the study was very small.

VI. *At present*, *liquid ventilation is not yet an approved therapy for clinical use and remains investigational*.

Suggested Reading

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