Ventilator Associated Lung Injury

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Origins

- John Fothergill, 1745, on his preference of mouth to mouth lung inflation over that done by the bellows:

  “the lungs of one man may bear, without injury, as great a force as another man can exert; which by the bellows cannot always be determin’d”
But this was John Fothergill..

- Bias?
Mechanisms of VALI

• **Barotrauma**
  • Describes pressure induced lung damage
  • Rats ventilated at higher pressures (45cm H2O vs. 14cms) with no PEEP, developed marked perivascular edema after one hour

• **BUT**
  • Trumpet players will achieve pressures over 150cm H2O without damage
• **Volutrauma**
  
  • Damage done by over distention of lungs
  
  • Rats whose tidal volume was limited by chest straps did not develop injury in response to high peak pressures
  
  • Peak airway pressures are influenced by several variables such as chest wall compliance, airway resistance, lung compliance, etc.
    * So alveolar pressures are not always a reflection of peak airway pressures
Figure 5. Macroscopic aspect of rat lungs after mechanical ventilation at 45 cm H₂O peak airway pressure. Left: normal lungs; middle: after 5 min of high airway pressure mechanical ventilation. Note the focal zones of atelectasis (in particular at the left lung apex); right: after 20 min, the lungs were markedly enlarged and congestive; edema fluid fills the tracheal cannula.

Atelectotrauma

- Lung injury related to repeated recruitment and collapse of alveoli
- Based on studies that have shown high tidal volumes and low PEEP to be more damaging to lungs than low tidal volumes and high PEEP
• **Oxygen Toxic effects**
  • Injury to lungs secondary to a high percentage of inspired oxygen
  • Occur secondary to a chain of events started by the creation of reactive oxygen species
• **Biotrauma**
  
  • Refers to pulmonary and systemic inflammation caused by release of mediators from lungs subjected to injurious mechanical ventilation
Patient Determinants of VALI

• The condition of the ventilated lung is of considerable import in discerning susceptibility to VALI
  • VALI rarely a problem in normal lungs… in ARDS, VALI may be inescapable
• The injured lung

  • Many studies have shown that injured lungs are more susceptible to VALI

  • Uneven distribution of disease leads to regional differences in compliance which leads to uneven inflation and force transduction

  • CT scans of ARDS survivors will show greatest abnormality in the anterior parts of the lung, most likely secondary to injury caused by overdistension
• Injured lungs also may have surfactant deficiencies and dysfunctions
• Injured lungs have pre-existing activated inflammatory infiltrates which may be exacerbated by mechanical ventilation
Manifestations of VALI

- **Pulmonary Edema**
  - A prominent feature in experimental models
  - High protein content suggests increased microvascular permeability
    - Damage occurs at both the alveolar epithelium and vascular endothelium

- **BAL results suggest:**
  - diffuse alveolar necrosis/apoptosis
  - inflammatory cell infiltration

- **Long term fibroproliferative changes**
Mechanisms of VALI

• Barrier Disruption
  • Refers to the interruption of the alveolar-capillary barrier by shear stress and tensile strain
  • Increases capillary endothelial and alveolar epithelial permeability
    • Leads to the formation of alveolar edema
    • Allows easier transfer of inflammatory mediators and even bacteria
• Additional factors in the lung effect force transduction
  • Interdependence
    • Adjacent alveoli share common walls so that forces acting on one lung unit are transmitted to those around it
    • Maintains a uniform alveolar expansion by subjecting each one to a similar transalveolar pressure
    • A collapsed alveoli has traction forces acting on it from surrounding normal lung that promote reexpansion
    • A transpulmonary pressure of 30cm H2O can translate to 140cm H2O of re-expansion pressure
• Recruitment-derecruitment
  • Small airways may become occluded by exudate or apposition of their walls
  • The airway pressure needed to restore patency is much greater than that needed in an unoccluded passage
    • The resulting shear stress may damage the airway, especially if repeated with each breath (about 20,000 times a day)
  • Collapse is favored in injured lungs with surfactant deficiency or weakened interstitial support
A necroscopic study of patients who died with ARDS found expanded cavities particularly around atelectatic areas.
• Surfactant
  • Dysfunction or deficiency amplifies the injurious effects of ventilation
  • Ventilation itself can impair surfactant function
    • Cyclical alterations in alveolar surface area and the presence of serum proteins in the airway lead to a decrease in the functional pool of surfactant
• Surfactant abnormalities lead to VALI in several ways relating to the increase in surface tension
  • Alveoli and airways are more prone to collapse with generation of shear stress as they are opened
  • Uneven expansion of lung units increases regional forces through interdependence
  • Transvascular filtration pressure is increased, leading to edema formation
MALI – Moustache Associated Liver Injury
• **Reduced Airspace Edema Clearance**
  
  • Edema is both an effect and an amplifier of VALI
  
  • Edema fluid fills distal airways and promotes alveolar collapse
    
    • Leads to greater heterogeneity of lung
    
    • Overdistention leads to greater vascular permeability, and more edema
  
  • High tidal volumes (or regional overdistention) also inactivates Na-K ATPase, which is responsible for active edema clearance
• **Biotrauma**
  • **Inflammation**
    • Stretch and other physical signals may be transduced to biochemical ones via mechanotransduction
    • Signalling events activated by injurious ventilation play a role in VALI
      • High tidal volume, low PEEP strategies lead to higher BAL concentrations of TNF-alpha, IL-1beta, IL-6, and IL-8, lead to neutrophil infiltration into the lung and the activation of lung macrophages
        • Elevations in proinflammatory molecules correlate with increased patient mortality in ARDS
• These mediators do not remain compartmentalized in the lung
  • Injurious ventilation strategies lead to increased cytokine levels in peripheral circulation
• Translocation of Bacteria
  • Overinflation promotes translocation of bacteria from the lung
    • In rat models of high tidal volume/low PEEP, Klebsiella instilled into the airway led to bacteremia after only 180mins
  • Alveolar-capillary barrier disruption also increases lung-systemic translocation of endotoxin
• Circulating proapoptotic factors
  • Injurious ventilation strategies can lead to end-organ epithelial cell apoptosis
    • An in vivo model of aspiration treated with high tidal volume/low PEEP showed epithelial cell apoptosis in the kidney and small intestine
• Suppression of Peripheral Immune Response
  • Hypothesis that local inflammation is accompanied by systemic anti-inflammation
    • Enables the body to concentrate on injured site, while limiting inflammation at uninvolved sites
      • In a study on 12 infants with healthy lungs, TNF-alpha and IL-6 were increased in BAL washings after 2h of ventilation
      • Their peripheral blood lymphocytes, however, showed decreased ability to create interferon gamma and, after LPS stimulation, could create less IL-6
• Oxygen Mediated Lung Injury
  • Damage is mediated by reactive oxygen species (ROS)
    • O2-, OH-, H2O2, HOCL, O
    • NO can also combine with O2 and O2- to form further reactive species
• Damage occurs by:
  • Direct DNA damage leading to strand breaks
  • Lipid peroxidation with formation of vasoactive and proinflammatory molecules such as thromboxane
  • Oxidation of proteins leading to release of proteases
  • Alteration of transcription factors that lead to increased expression of proinflammatory genes
  • Peroxidation of membrane phospholipids, leading to decreased barrier function and increased permeability
  • Oxidative alteration of surfactant, impairing its function
• Neutrophils and macrophages are principle sources of ROSes, in addition to high concentrations of inhaled oxygen
  • An injured lung, which is populated by an increased number of activated neutrophils, is thus more susceptible to the effects of high inhaled O2 and the resulting ROSes
MSOF and Mechanical Ventilation

- Add to this some peripheral immunosuppression, translocation of bacteria from both lung and gut, and you have yourself a real party......
Burden of VALI

- Recent ARDSnet trial
  - 861 patients with ARDS were randomized to either a “traditional” tidal volume (12 ml/kg) or a low tidal volume strategy (6 ml/kg)
  - 39.8% mortality in traditional group, 31% in low tidal volume group
    - AT LEAST 8.8% of mortality due to ARDS is attributable to VALI