

**Ventilator & Molecular Treatment
of ARDS:
Progress or Standstill?**

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ARDS – What Is It?

- High protein inflammatory permeability edema
- Stereotypical response to a variety of lung &/or systemic insults
- Endothelial &/or epithelial injury results in:
 - Increased alveolar permeability
 - Alveolar inflammation
 - Proteinaceous, RBC-rich pulmonary edema
 - Alveolar procoagulant state – fibrin coagulates into hyaline membranes
- Increased alveolar oxidants and proteases

Why is ARDS Important?

- Residual high mortality (25-50%)
- Relatively common: 22- 64 cases/100K person yrs
- May occur in individuals with little underlying chronic disease
- Very expensive to treat
- Most survivors recover to relatively normal lung function
- Model to understand paradigms of injury and repair of the lung

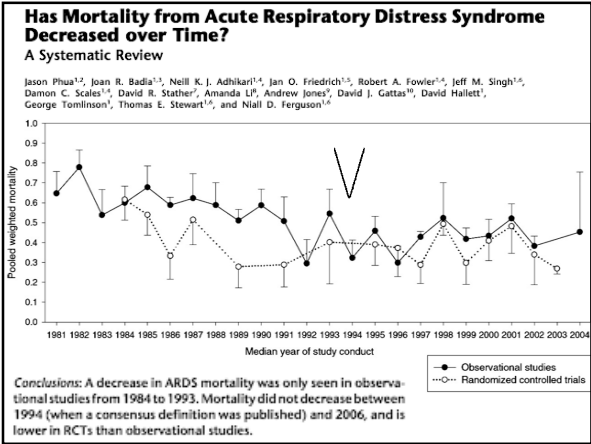
Clinical Associations with ARDS

<p>DIRECT INJURY</p> <ul style="list-style-type: none"> ■ <i>Pneumonia</i> ■ <i>Gastric aspiration</i> ■ Lung contusion ■ Fat emboli ■ Near Drowning ■ Inhalation injury ■ Reperfusion <ul style="list-style-type: none"> ■ Lung transplant ■ Pulm embolectomy 	<p>INDIRECT INJURY</p> <ul style="list-style-type: none"> ■ <i>Sepsis</i> ■ <i>Severe trauma with shock & multi-transfusions</i> ■ Cardiopulm bypass ■ Drug overdose ■ Acute pancreatitis ■ Blood transfusion
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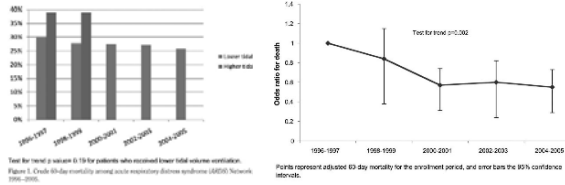
ARDS Pathophysiology Am-Europ Consensus Committee

- “Despite considerable effort, the Committee could not reach a consensus on the order of events in the pathogenesis of ALI. In fact many participants felt that the pathogenesis is different for different precipitating causes of ALI and that our knowledge is neither sufficient to allow an intelligent conclusion about the precise sequence of events nor sufficient to allow a determination of which of these mechanisms are more important.”

Am J Respir Crit Care Med 149: 818, 1994



Recent trends in acute lung injury mortality: 1996-2005.



Erickson, Sara E. MD; Martin, Greg S. MD, MSc; Davis, J Lucian MD; Matthay, Michael A. MD; Eisner, Mark D. MD, MPH; for the NIH NHLBI ARDS Network Critical Care medicine March 25 2009

ARDS – Current Standard Rx

Source Control

- Treat underlying risk factors – infection, DIC, etc

Supportive Care:

- Maintain adequate oxygenation & gas exchange
- Minimize additional lung injury
- Minimize extravascular lung water
- Insure adequate nutrition
- Avoid other iatrogenic ICU complications (VTE, nosomial pneumonia, stress ulcers, ...)

Specific Therapy: ???



ARDS Rx
=
High Tech
Babysitting

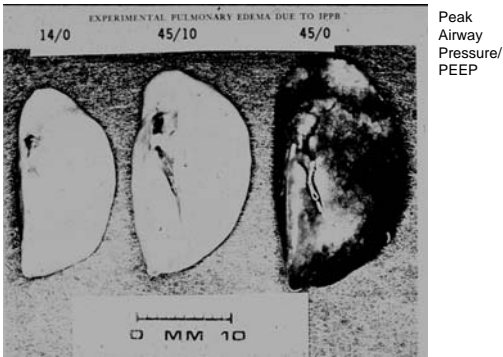
Ventilator-Induced Lung Injury

- Experimental models in normal animals
- Pathology identical to ARDS & O2 toxicity
- Worst damage in dependent lung zones
- Pro-inflammatory cytokine release (human & expt)

Mechanisms:

- "High-End": High volume - overdistention
- "Low-End": Shear forces in re-opening collapsed alveoli

VILI – Rat Model



ARDS Network Low Vt Trial

- Similar demographics: age (51-52); APACHE III (81-84); Non-lung organ failure (1.8); etiologies
- Low Vt group had:
 - Lower Vt (6.2 vs 11.8 mls/kg PBW)
 - Higher PEEP & FiO2, lower P/F at days 1 & 3
 - Lower PEEP & FiO2 at day 7
 - Lower mortality rate (31 vs 40%)
 - Higher # Vent Free Days & days without NLOF
 - Greater fall in plasma IL-6 from day 0 to 3

ARDS Network NEJM 342:1301-8, 2000

ARDS Network Vt Trial

Surprises:

- Low Vt group had normal PaCO2
- Low Vt group had worse oxygenation for first 3 days

Controversies:

- Which is more important: limit Vt or Plateau P?
- What is the optimal Vt?
- What is the proper control group?

ARDS - Other Ventilator Approaches

- Pressure Control Ventilation (PCV)
- High Frequency Oscillation (HFO)
- High Frequency Jet Ventilation (HFJV)
- Airway Pressure Release Ventilation (APRV)
- Negative Pressure Ventilation (NPV)
- Tracheal Gas Insufflation (TGI)
- Recruitment Manuevers

Salvage Therapies for ARDS

Definition:

- Clinical improvements in subgroup (< 1/3)
- No overall mortality improvement

Therapies:

- Inhaled nitric oxide
- High frequency ventilation/oscillation
- Prone positioning
- Partial liquid ventilation
- PCV or APRV
- ECMO or ECCO2R
- Surfactant replacement??

Specific ARDS Therapy			
No Benefit	Probably No Benefit	Uncertain: ? Or Subgroup Benefit	Proven Benefit

Hypothesis

- Attempts to treat ARDS have failed for two reasons:
 - 1) Too many simultaneous pathophysiologic pathways are activated for a single intervention to have major impact
 - 2) Intervention directed at early pro-inflammatory events is too late when clinical Dx is apparent
- Targeting therapy at speeding repair is more likely to be beneficial

Strategies to Augment Repair I.

- Decrease severity of initial or secondary injury
 - Decrease alveolar inflammation
 - Decrease ventilator induced lung injury
- Decrease local or systemic infection
- Increase antioxidant and/or antiprotease defenses
- Cytoprotection

Strategies to Augment Repair II.

- Accelerate alveolar fluid clearance
- Promote repair of epithelial barrier
- Diminish initial provisional matrix & fibrosis
- Inhibit mesenchymal cell migration
- Clear intra-alveolar granulation tissue
- Alter apoptotic pathways

Secondary Amplification of Lung Injury

Many potential contributors:

- Ongoing primary injury source
 - Barotrauma
 - High stretch mechanical ventilation
 - Low end damage from alveolar shear stress
 - Hyperoxia
 - Infection
 - Cytokine production (distant)
- At present can't clinically separate these components from primary ARDS

**Cytoprotection
Heat Shock Protein (HSP-70) Rx of ARDS**

- Adenoviral overexpression of porcine HSP-70
- Model: Rat cecal ligation & double puncture
- Adv alone increased endogenous HSP-70
- Adv-HSP Rx decreased:
 - Alveolar & interstitial edema
 - Alveolar protein and PMNs
 - Mortality at 48 hours by 50%

YG Weiss et al. J Clin Invest 110:801-806, 2002

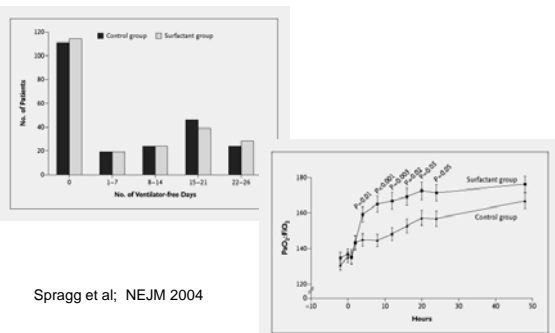
Antioxidant Defenses

- Protein oxidation & nitration products present in lung – SPA, ENaC, Na,K-ATPase
- Prior alcoholism increases risk of ALI due to decreased glutathione
- Rat model of alcoholism:
 - increased lung permeability;
 - decreased cell viability, edema clearance, and surfactant production;
 - increased TGFβ, MMP-9, and fibronectin
- N-acetylcysteine repletion – minor benefit
- Antioxidant vitamins – benefit in SICU
- Extracellular SOD
- Role of an Antioxidant Cocktail ??

Surfactant in ARDS

- Decreased surface tension lowering function
- Change in composition – proteins and lipids
- Replacement therapy:
 - Exosurf: Aerosolized lipids only – no benefit
 - Beef extract with SPB, SPC – suggestive
 - Venticute – human recombinant SPC + PL
 - Surfaxin (KL4) – 21 AA SPB analog
- Immunomodulatory properties of SP-A
 - Decreases lung injury after mouse BMT

ARDS Rx with Surfactant Recombinant SP-C



Alveolar Fluid Clearance in Human Lung Disease

Acute Lung Injury/ARDS (*Ware AJRCCM 163:1376, 2001*)

- 56% of pts impaired fluid clearance (<3%/hr)
- 13% of pts with maximal AFC (>14%/hr)
 - More females & less likely sepsis etiology
 - lower mortality (20% vs 62% for all others)
 - shorter mechanical ventilation time
- AFC not correlated with endogenous Epi & NorEpi

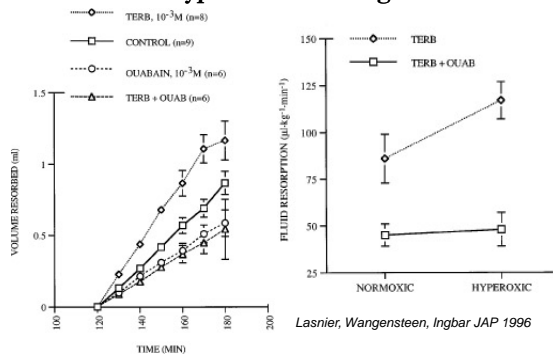
Cardiogenic Pulmonary Edema (*Verghese JAP 87:1301, 1999*)

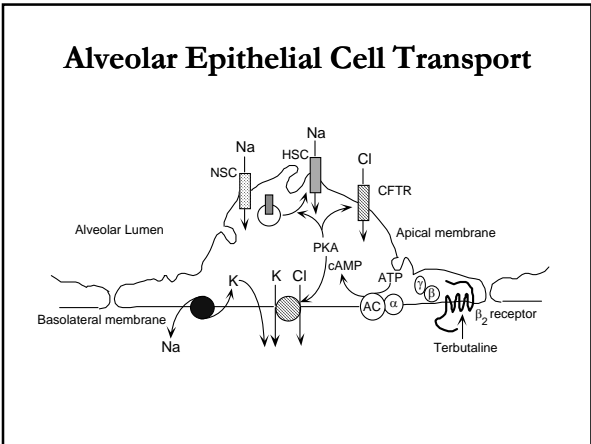
- 75% of pts had intact fluid clearance; 25% decreased
- 38% "maximal" (> 14%/hr)
- Higher AFC assoc with greater increase in oxygenation at 24 hrs & trend to lesser mortality & vent time

Potential Benefits of Augmenting Alveolar Fluid Resorption in ARDS

- Improved gas exchange
- Lower airway pressures
- Less ventilator-induced lung injury
- Less oxygen toxicity
- ? Less surfactant washout
- ? Nosocomial pneumonia

Terbutaline Stimulates AFC in Hyperoxic Rat Lung





Overexpression of Na,K-ATPase β 1 Subunit in Rat Lung Protects Against Hyperoxic Injury

- Intratracheal transfection with Na pump β 1 adenoviral expression construct
- Increased lung Na,K-ATPase activity and β 1 protein level at 1 week
- With hyperoxic exposure of rats
 - Better preservation of fluid resorption
 - Marked improvement in survival
 - Lower wet to dry lung weight

Factor & Sznajder, J Clin Invest 1999; Hum Gene Therapy 2000

Stimulation of Alveolar Fluid Clearance – Ingbar & O’Grady Labs

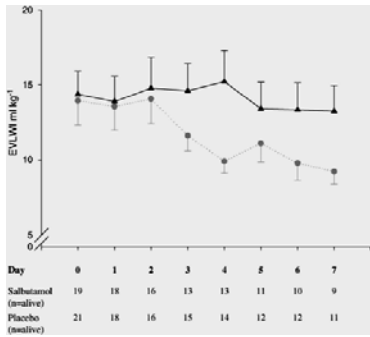
Multi-Pronged Approach

- Beta adrenergic agonists
- T3 stimulation of Na,K-ATPase and ? other transporters
- Glucocorticoid stimulation of AFC and Na,K-ATPase transcription
- Stimulate Cl channel / Na transport using combination of beta adrenergic agonists and selective phosphodiesterase isoenzyme inhibitors (PDE 3 and 4)

**BALTI: IV Salbutamol for ARDS
(Beta Agonist Lung Injury Trial)**

- Single center DBRPCT of iv salbutamol Rx for ARDS for 7 days in 40 adult patients
- Salbutamol treated pts had:
 - Lower extravascular lung water (EVLW)
 - Lower plateau airway P
 - More SVT
- No difference in mortality, oxygenation, vent times

BALTI – Serial EVLW Changes



**When Should We Launch
Clinical Trials?**

- Confirmation of benefit in large animals
- ? Standardized fluid management
- Way to measure physiologic effect
- What endpoints to use??
 - Mortality
 - Ventilator-free days
 - Oxygenation
 - Lung extravascular water

Lung Repair in ARDS

Observations:

- Variable clinical course of patients
- After 2 weeks relatively little ongoing mortality
- Most surviving patients recover much of their pulmonary function, even with severe prolonged injury

Questions:

- How do some patients recover rapidly after weeks/months of little progress?
- Why the wide dispersion in rates of recovery?
- How is recovery possible from severe injury?
- What is the role of genetic predisposition?

Epithelial Repair

Concept:

- If preserved alveolar basement membrane, then restoration of normal architecture is possible

Components:

- type II cell proliferation,
- type II cell migration to reform barrier
- reform alveolar basement membrane (if necessary)
- clearance of epithelial space – type II cell apoptosis?
- differentiation into type I cells

Type II Cell Proliferation

Is there a stem cell population??

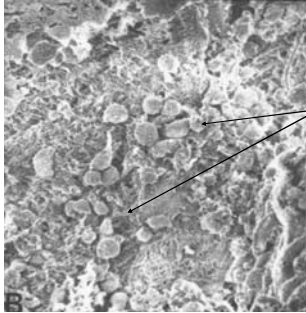
Type II cell turnover: slow in normal lung (~ 30 days); much faster with injury

Type II Cell Mitogens:

- KGF
- EGF*
- TGF α *
- Insulin
- Hepatocyte growth factor*
- Heparan binding protein
- Inhibited by TGF β

Injury increases p21 (WAF1), decreases TGF β

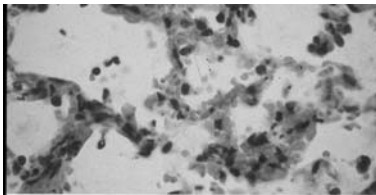
Scanning EM of Alveolar Surface
Human Dying of ARDS



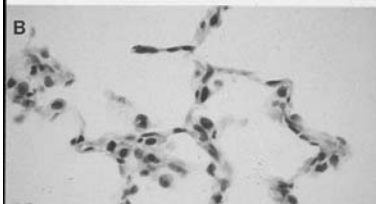
Alveolar
Type II
Cells

**Keratinocyte Growth Factor
(KGF) and ARDS**

- KGF has multiple potential benefits:
 - Increased fluid resorption, Na transporters
 - Epithelial cytoprotectant
 - Increased surfactant lipid/apoprotein secretion
 - Preserved alveolar barrier with type II hypertrophy
- Preinjury treatment with KGF improves lung injury and survival in many models – hyperoxia, radiation, bleomycin, acid aspiration
- Low dose systemic KGF pre-BMT improves survival and lung injury



Hyperoxia



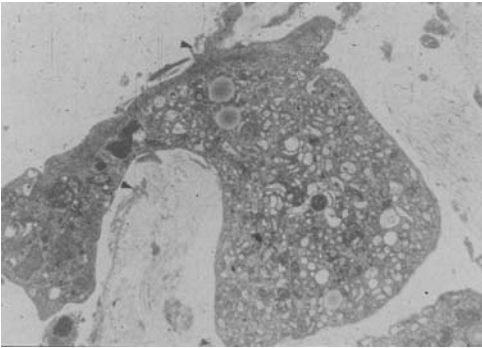
Hyperoxia +
KGF

Panos et al
JCI

KGF Rx for ARDS

- Ongoing experimental human studies for prevention/Rx of post-BMT mucositis
- Why not yet studied?
 - Cost of lung toxicology
 - ? Route/dosing for lung effect
 - ? Efficacy of rescue therapy
 - ARDS & Sepsis are “Graveyard of clinical trials”

Mesenchymal Cell Migration into the Alveolar Space



Conversion to Chronic Phase ARDS

- Early : Hyaline membranes = cross-linked fibrin
- Intra-alveolar clot becomes scab with fibroblast & endothelial influx into provisional matrix
- Prevents gas exchange & oxygenation
- Intra-alveolar and interstitial collagen deposition
- Very stiff lung

Therapeutic Manipulation of Alveolar Coagulation System ?

Experimental Results:

- Overexpression of fibrinolytic enzymes reduced pulmonary fibrosis after bleomycin;
- PAI overexpression increased fibrosis with bleo

Potential Therapeutic Strategies

- Replete activated protein C to inactivate V & VIII
- Increase tissue factor pathway inhibitor (TFPI)
 - TFPI increases survival in sepsis/endotoxemia models
- Augment antithrombin III to inhibit IXa, Xa and thrombin
- Inhibit pro-coagulant cytokines: IL-1 β and TNF α

Apoptosis in ARDS

- 1993 – first description of apoptosis in ARDS human lung biopsy specimen
- BALF from chronic phase ARDS patients who went on to recover induced apoptosis of endothelial cells and fibroblasts; early ARDS and non-survivor BALF lacked this activity
- What factors induce apoptosis?
- Now appreciated as common in lung injury of many types
- Occurs during selected times of lung development

Cell Death

Good

- Eliminate inflammatory cells
- Eliminate granulation tissue in airspace
- Remove excess type II cells to allow type I cells to spread

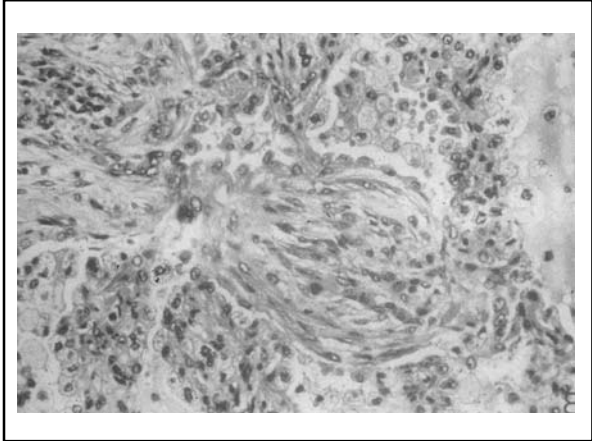
Bad

- Eliminate vital structures
Capillaries
Epithelial barrier

Apoptosis in Early ARDS

- Oxidants (NO, H₂O₂), TNF, Fas-Fas Ligand and other cytokines can induce apoptosis of epithelial and endothelial cells
- BALF from ARDS patients, but not at risk patients, activates AEC apoptosis
- Elevated TNF levels are common in ARDS
- Human lung specimens show alveolar epithelial cell apoptosis with increased expression of p53, WAF-1, and BAX

Preliminary conclusion: apoptosis probably contributes to early lung injury, especially of epithelium



Apoptosis in Chronic Phase ARDS

- Excess/dying neutrophils cleared from lung by apoptosis. Macrophages specifically recognize & engulf apoptotic PMNs
- Apoptosis is likely mechanism to remove granulation tissue – especially intra-alveolar fibrosis
- Eliminates excess hyperplastic type II cells, leaving room for some cells to differentiate into type I cells

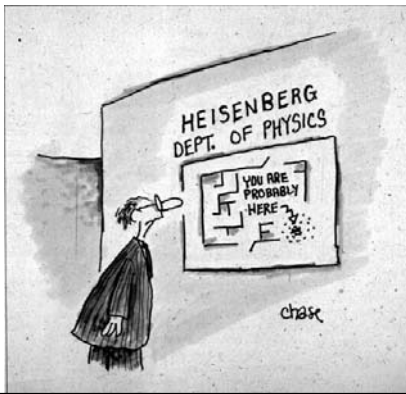
Can We Manipulate Apoptosis for Therapeutic Purposes?

- Yes – statins
- Yes – small molecules designed to have specific effects on translational machinery



- Yes – activate cell surface receptors: integrins; RHAMM; others

So now where are we?



ARDS: Why have almost all interventions failed thus far?

- Wrong targets
- Treatments ineffective on specific target
- Studies not well designed
- Treatment initiated too late
- Treating one aspect is too little to alter clinical outcome

Conclusions

- Stimulating repair is likely to be useful alternate to early intervention with single agents
- Clinically approved, safe agents are available that stimulate repair in animal models
 - Statins for fibroproliferation
 - β -Adrenergic agonists for fluid resorption
 - Recombinant human KGF – multifactorial
 - Pro-fibrinolytic therapies – APC, TFPI, ATIII
- Prior to human trials we need to:
 - Understand mechanisms
 - Prove efficacy in large animal trials

ARDS Rx: My Biases

- Successful intervention will require combination therapy a la combination chemoRx
- Don't discard potential of a treatment just because it doesn't work in isolation
- Need to have both supportive interventions and those that alter the disease process.

The molecular intensivist of the new millenium

Check the vitals, get me an 8.0 ET tube, a central line set up, and... start the Apo - neb



ARDS Treatment of 2015 ?

Supportive Treatments:

- Optimize mechanical ventilation
- Supplement lung antioxidants & antiproteases

Specific Therapies

- Cytoprotection – keratinocyte growth factor
- Promote resolution of inflammation – induce PMN apoptosis
- Pro-epithelialization therapy
- Pro-fibrinolytic therapy
- Pro-apoptotic therapy late

Mixed Approaches

- Surfactant replacement
- Increased alveolar fluid resorption

Pathology of ARDS = Diffuse Alveolar Damage

Overlapping of 3 components

Phase I: Pulmonary edema

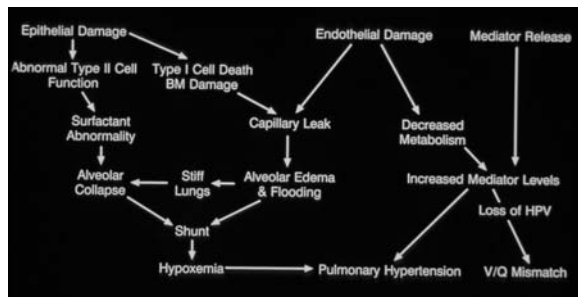
- Exudative neutrophilic protein rich edema
- Epithelial and endothelial injury

Phase II: Proliferative phase (“Subacute”)

- Alveolar type II cell hyperplasia
- Ingrowth of mesenchymal cells on intra-alveolar provisional fibrin matrix

Phase III: Fibrotic phase (“Chronic”)

ARDS Pathophysiology



Beta2-Adrenergic Receptor Overexpression

- Adenoviral overexpression of BAR in rat lungs
- Increases beta adrenergic responsive fluid clearance
- Increases responsiveness to endogenous catecholamines
- In A549 cells, BAR overexpression prevents homologous receptor desensitization
- Increases rodent survival with hyperoxic lung injury

*P Factor, et al. JACI 110:S242-6, 2002
Circ Research 2002*

ARDS Network Low Vt Trial

- 861 ARDS Pts at 10 Centers 1996-99
- Excluded high mortality groups
- Randomized to:
 - Traditional Vt group: start at 12 ml/kg PBW and allow high airway Pplateau
 - Low Vt group: start at 6 ml/kg PBW and keep Pplat <30
- Endpoints: Death; # ventilator free days; Non-lung organ system failure

Pulmonary Edema

Old View

- Major barrier = endothelium
- Edema determined by Starling forces across capillary
- Hydrostatic edema has normal barrier

New View

- Major barrier = alveolar epithelium
- Active ion transport by epithelium is critical
- High intravascular P or high stretch damage barrier

