

---

# Acute Respiratory Distress Syndrome - Pathophysiology -

고려의대 이영석

# CONTENT

**Patient Self-Inflicted Lung Injury**

**Ventilator Induced Lung Injury**

**ARDS Pathophysiology**

**Other issues**

# Cell metabolism

## CELLULAR RESPIRATION

Cellular respiration is the process by which food, in the form of sugar (glucose), is transformed into energy within cells. This energy is stored in ATP molecules, which then power all sorts of cellular processes. Respiration that requires oxygen is known as aerobic respiration; respiration that occurs without oxygen is called anaerobic respiration.



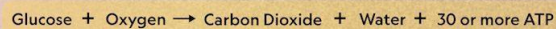
### Aerobic Respiration

① The first stage of aerobic respiration is **glycolysis**, where **glucose** molecules are broken down to create **ATP** in a cell's cytoplasm. Although the process consumes two ATP molecules, it produces four more, as well as two other substances: **pyruvate** and **NADH**.

② In the second stage, which occurs in the **mitochondria** of a cell, pyruvate is used to create **acetyl coenzyme A** and **carbon dioxide**.

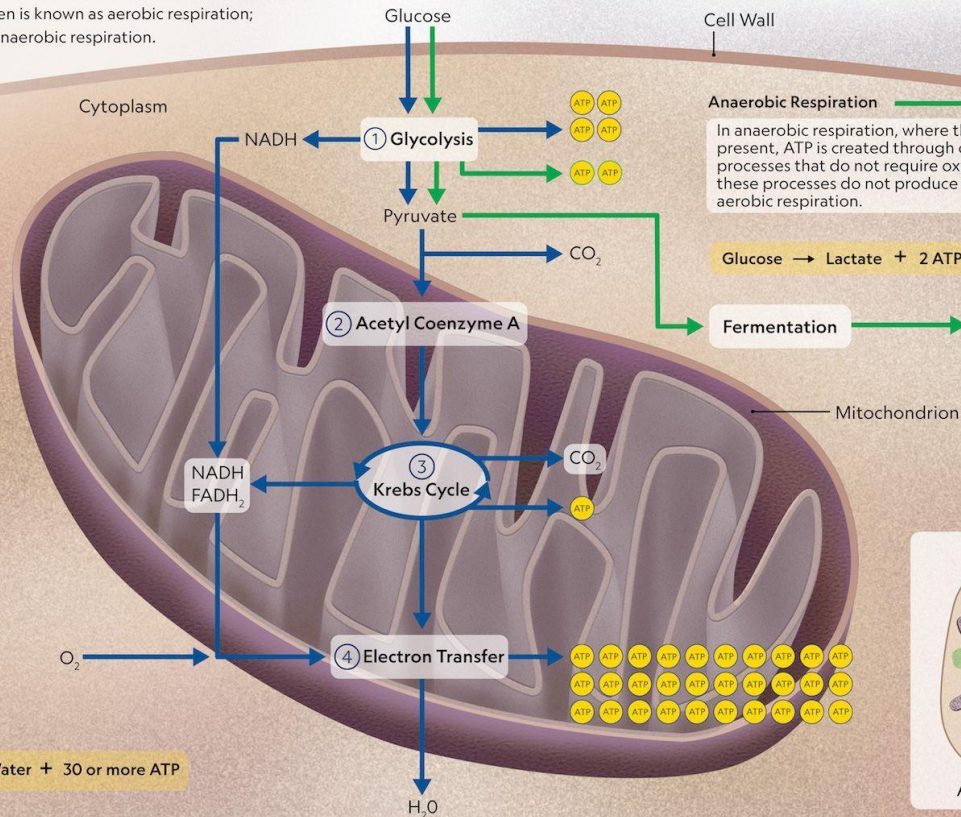
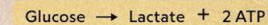
③ The third stage is known as the **citric acid cycle**, or **Krebs cycle**. In this stage, acetyl coenzyme A is used to create more NADH, as well as **FADH<sub>2</sub>**, carbon dioxide, and an additional ATP molecule.

④ In the final stage, NADH, FADH<sub>2</sub>, and **oxygen** are used to create massive amounts of ATP through **electron transfer**. This stage also creates **water** molecules.

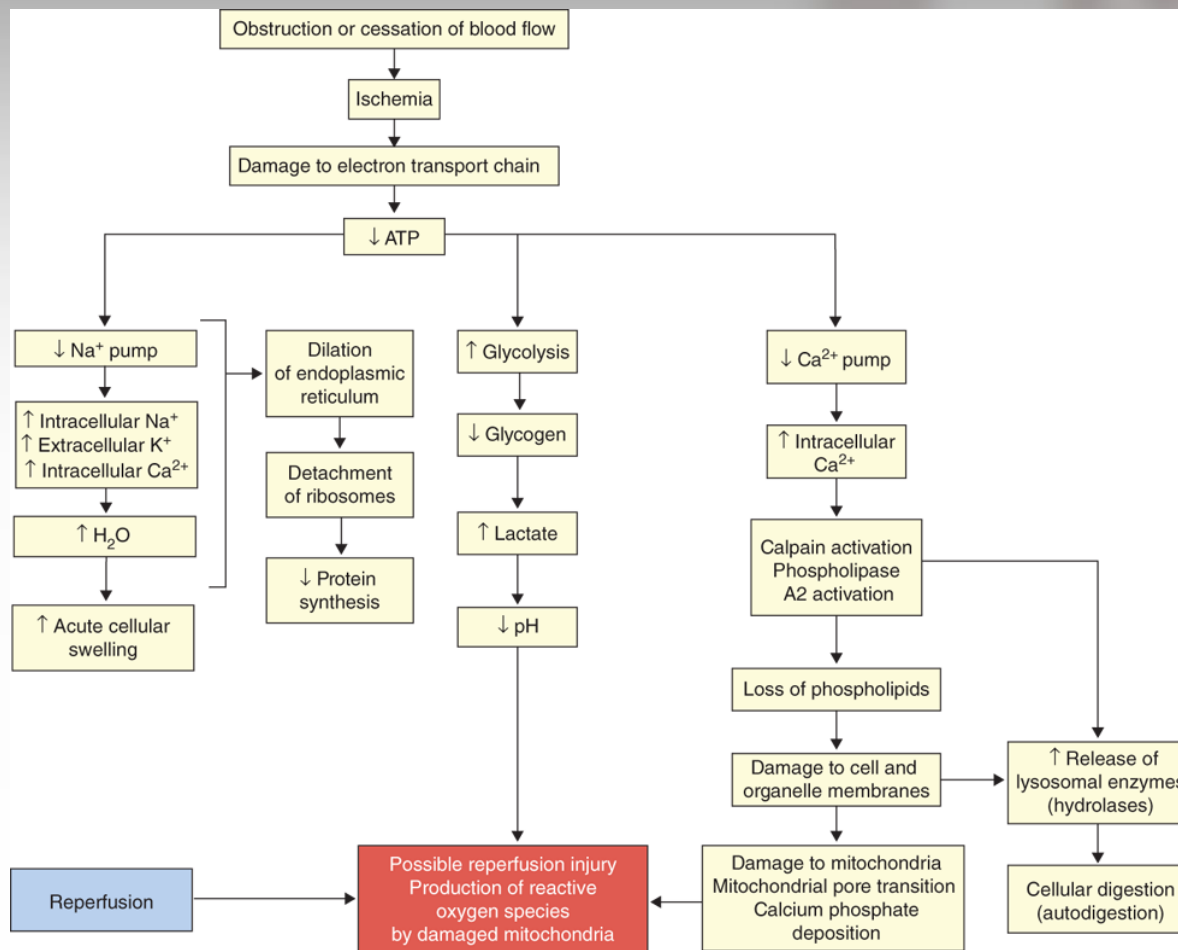


### Anaerobic Respiration

In anaerobic respiration, where there is no oxygen present, ATP is created through other chemical processes that do not require oxygen. However, these processes do not produce as much ATP as aerobic respiration.



# Cell metabolism



Source: Howard M. Reisner  
 Pathology: A Modern Case Study, Second Edition  
 Copyright © McGraw-Hill Education. All rights reserved.

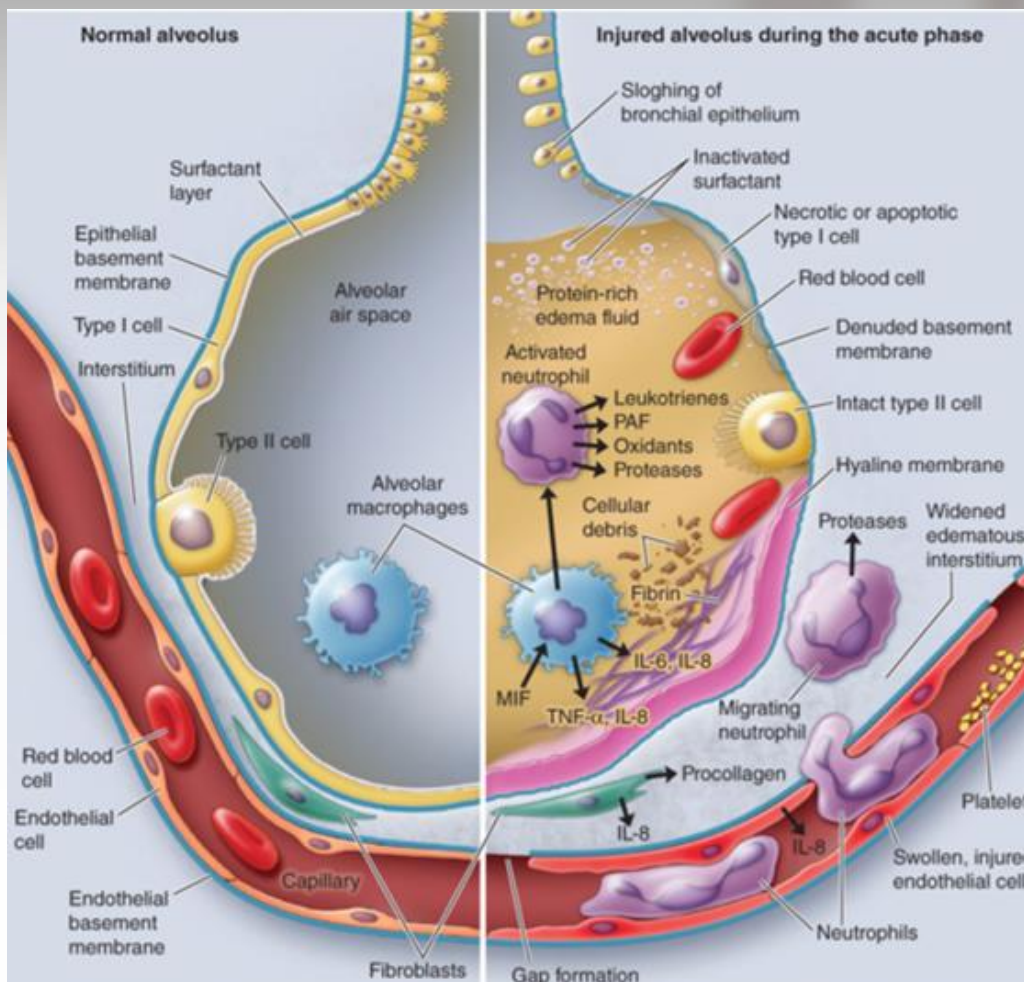
# Organ Dysfunction



# ARDS cause

Direct	Indirect
Bacterial, Fungal, Viral Pneumonia	Sepsis
Aspiration of gastric content	Trauma
Pulmonary contusion	Drug overdose
Inhalation injury	Acute pancreatitis
Fat emboli	Cardiopulmonary bypass

# ARDS



# Berlin Definition

## Acute Respiratory Distress Syndrome

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities-not fully explained by effusion, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	$200\text{mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg}$ with PEEP or CPAP $\geq 5\text{cm H}_2\text{O}$
Moderate	$100\text{mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200\text{mmHg}$ with PEEP $\geq 5\text{cm H}_2\text{O}$
Severe	$\text{PaO}_2/\text{FiO}_2 \leq 100\text{mmHg}$ with PEEP $\geq 5\text{cm H}_2\text{O}$

JAMA 2012;307:2526-2533

# ARDS mortality

ARDS Severity	Mortality (%)
Mild	27
Moderate	32
Severe	45

# ARDS Pathology

Diffuse alveolar damage with protein-rich pulmonary edema, neutrophil, macrophages, and erythrocytes in the alveolar spaces

- Alveolar epithelium: disrupted and lined by fibrin-rich hyaline membranes

- Capillary endothelium: Injury of glycocalyx
- Capillary lumen: Microthrombi

Fibrosing alveolitis: Lung fibrosis

# ARDS Pathology

## Exudative Phase

- Diffuse Alveolar Damage
- Loss of endothelial and epithelial cells
- Protein rich alveolar edema

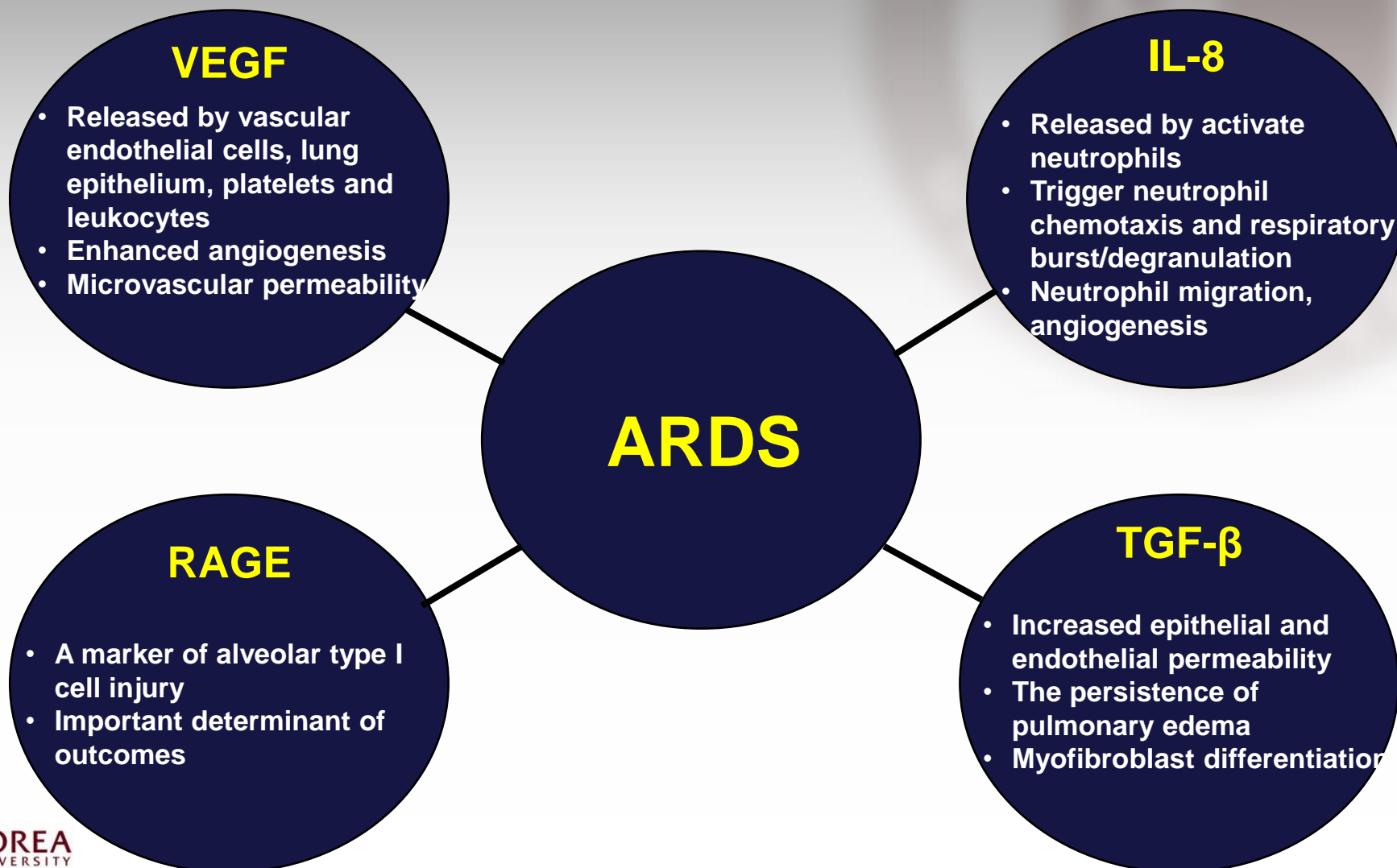
## Proliferative Phase

- Hyaline membrane formation
- Cellular alveolar infiltrates
- Reduced lung compliance and gas exchange

## Fibroproliferative Phase

- Extracellular matrix deposition
- Squamous metaplasia, thromboemboli
- Dense fibrosis and honeycomb change

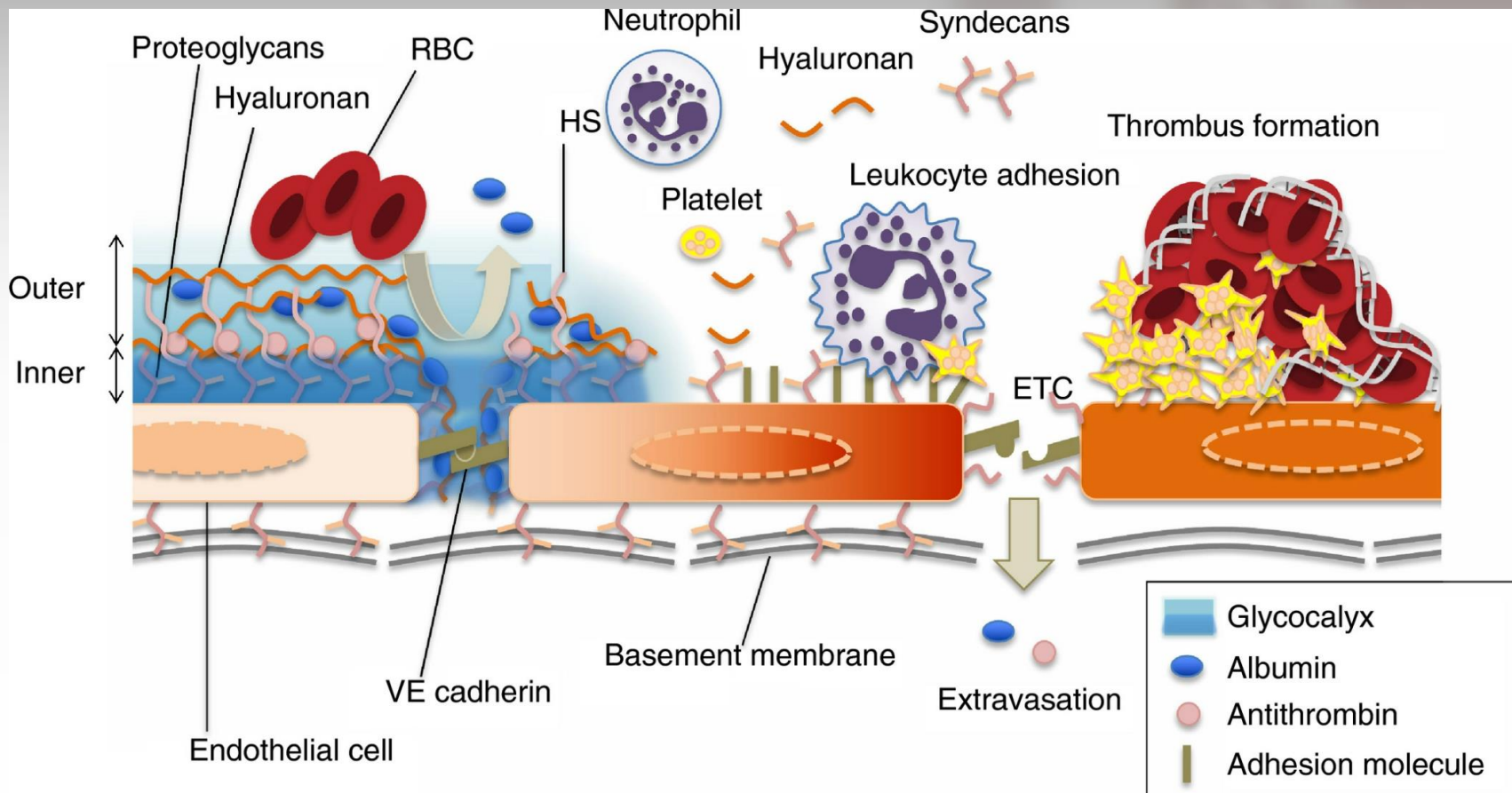
# ARDS Pathology



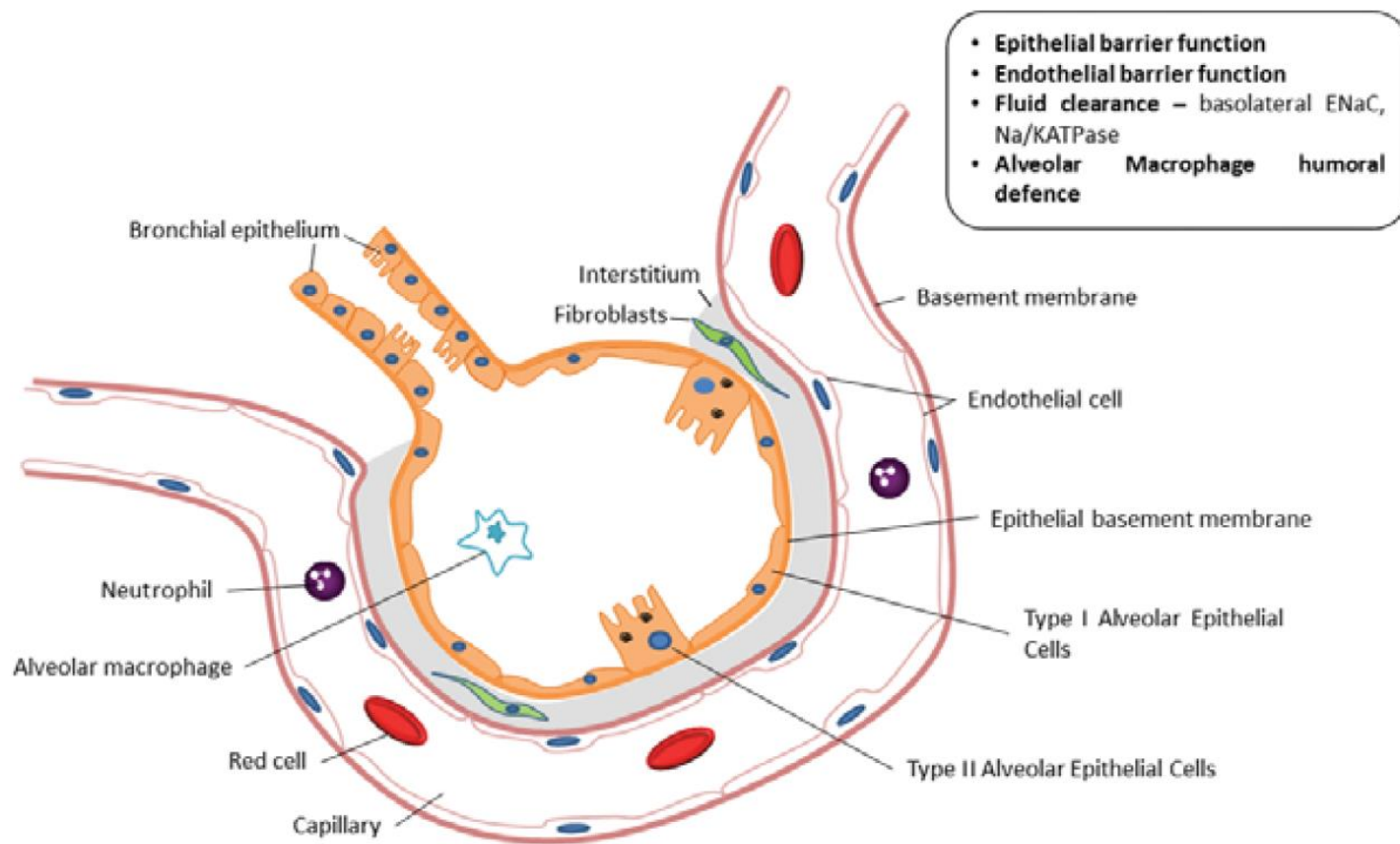
# Endothelial Injury

- **The damage of glycocalyx**
  - **Mechanical cellular stress**
  - **Atrial natriuretic peptide**
  - **Oxygen free radicals**
  - **Endotoxins**
  - **Inflammatory mediators**
  - **Ischemic-reperfusion injury**
  - **Hyperglycemia**

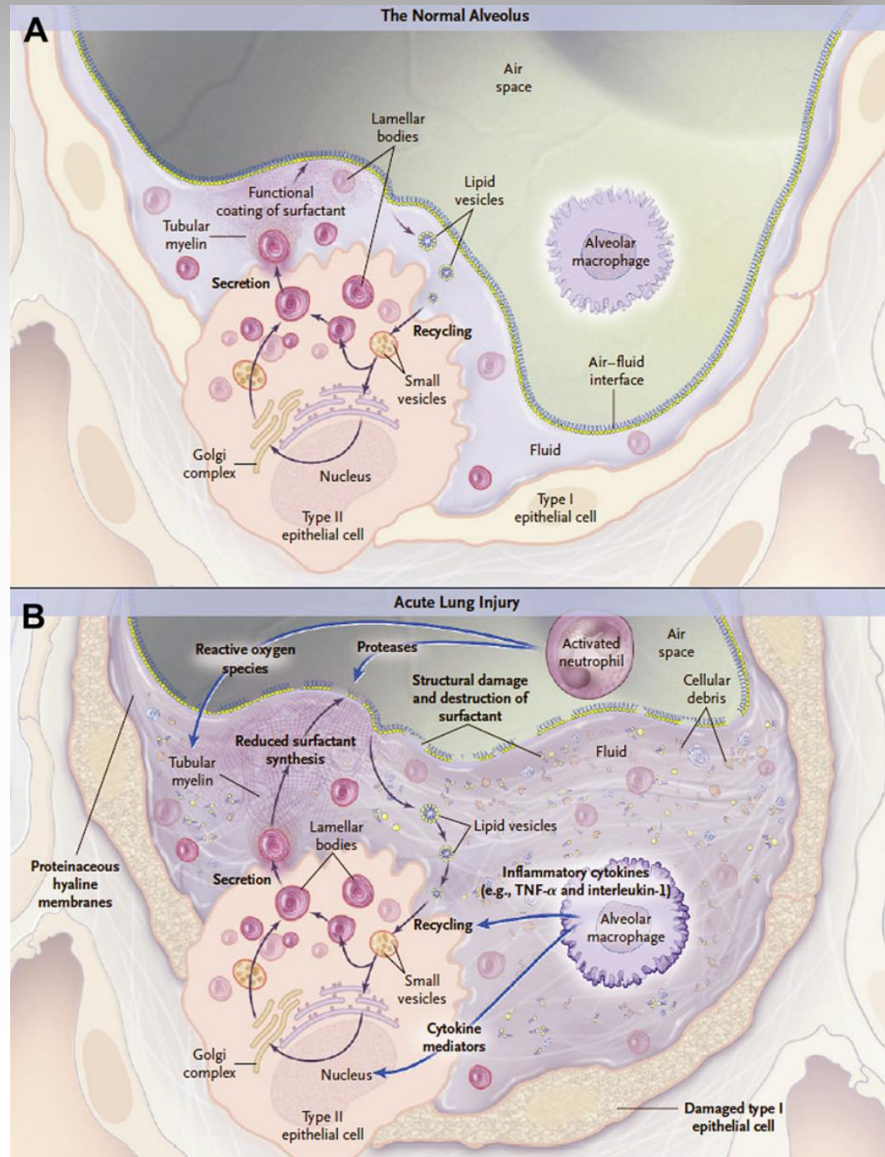
# Endothelial Injury



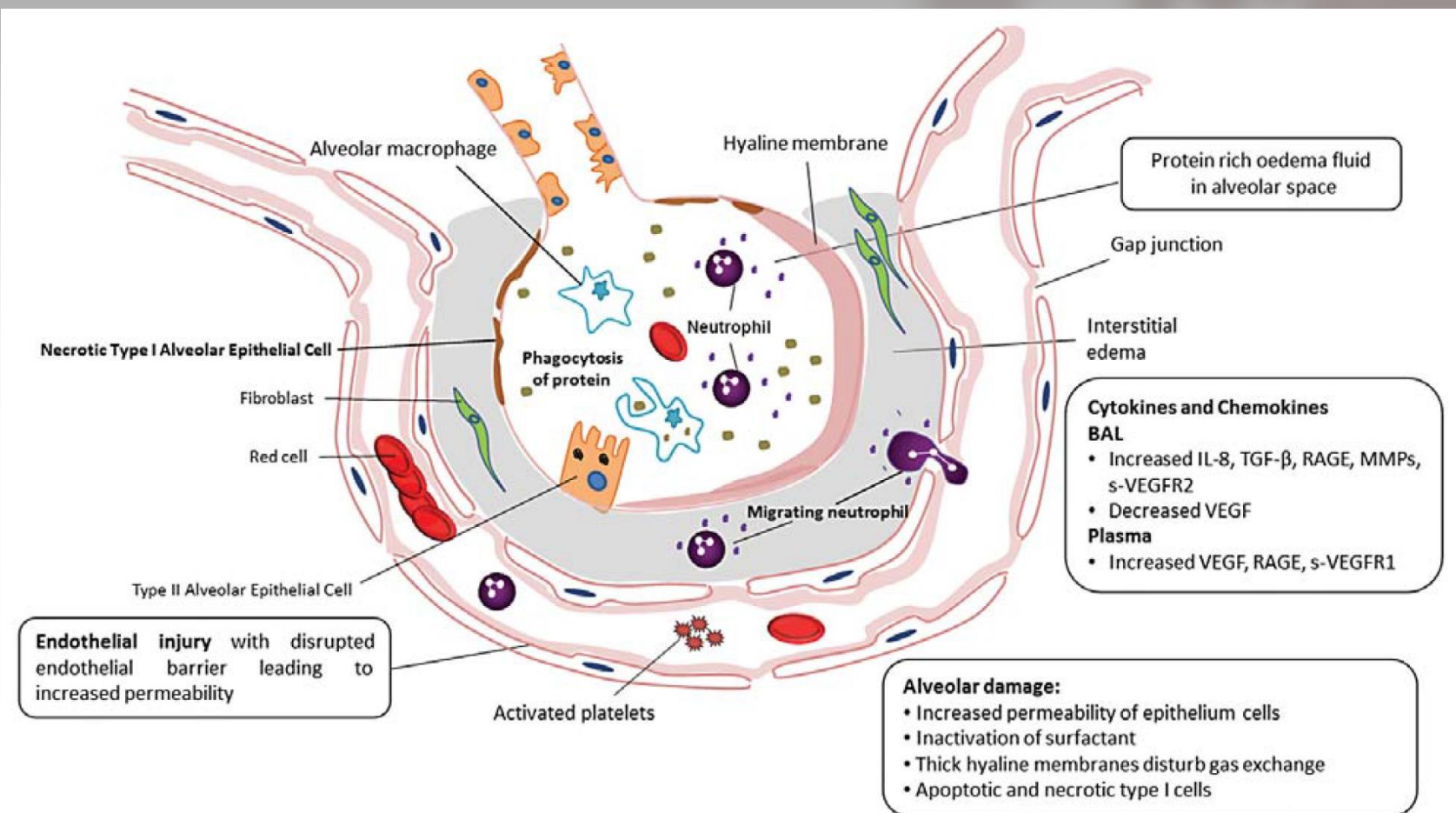
# Epithelial Injury



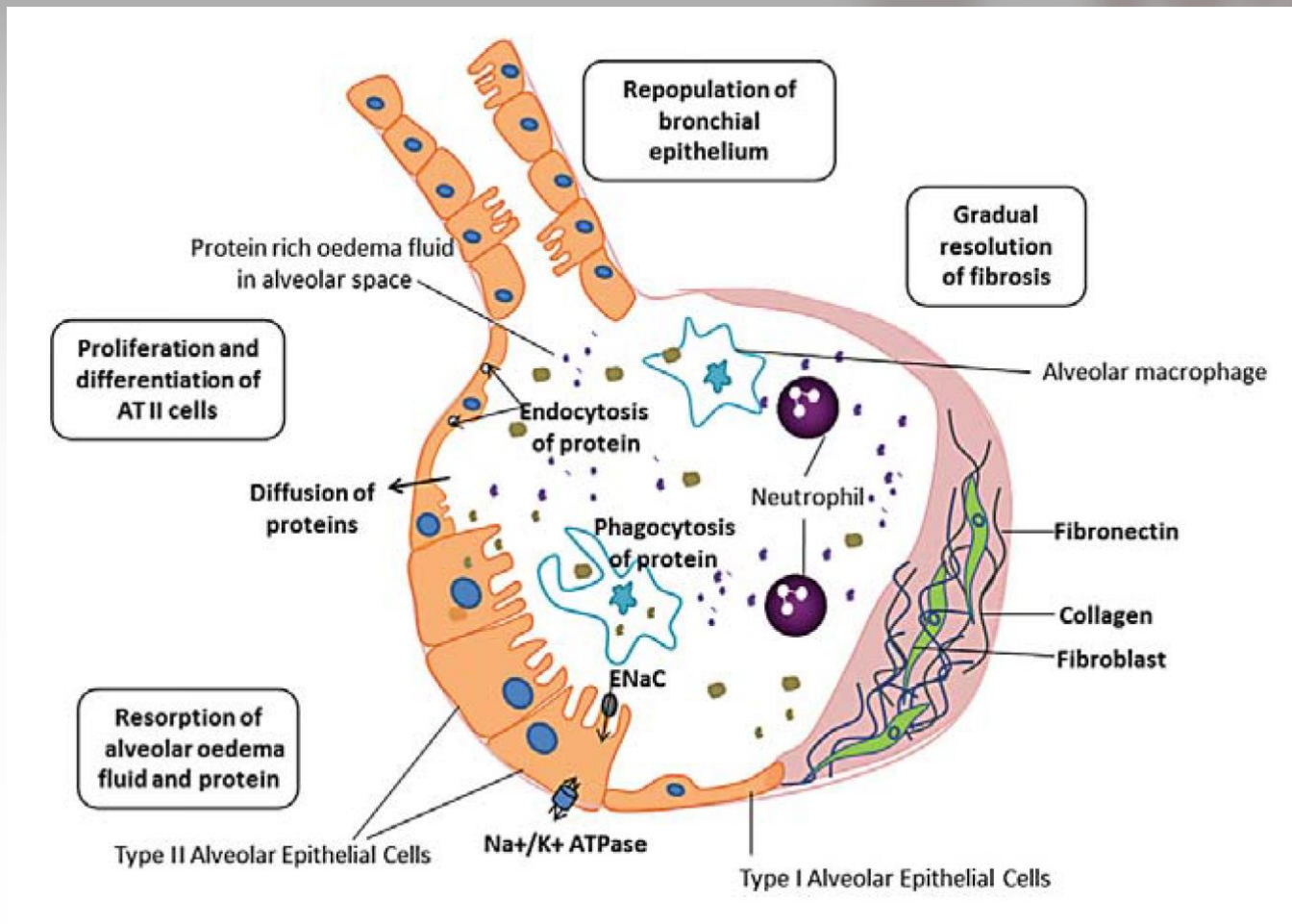
# Epithelial Injury



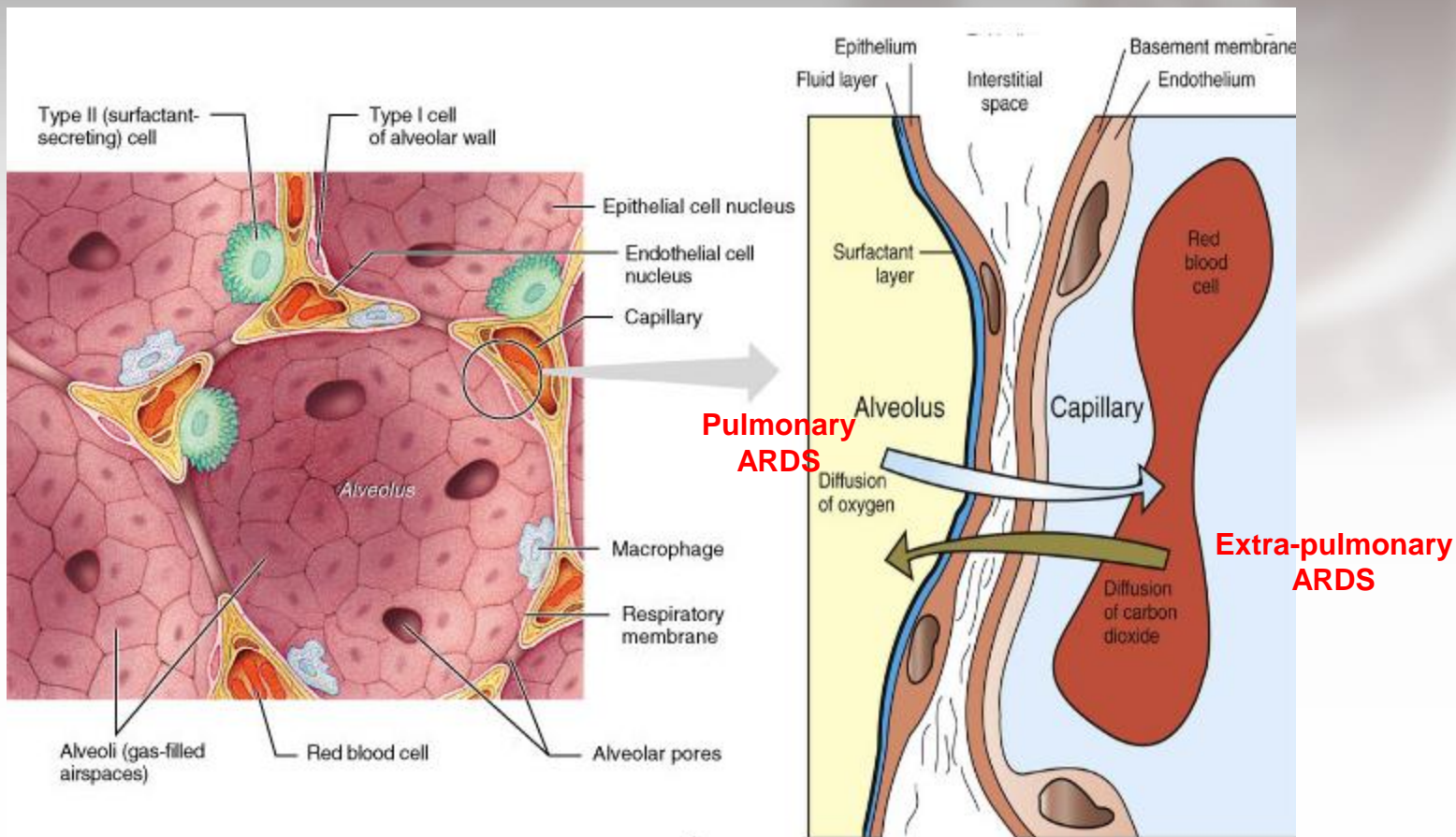
# Exudative phase



# Recovery Phase



# Pulmonary vs. Extrapulmonary

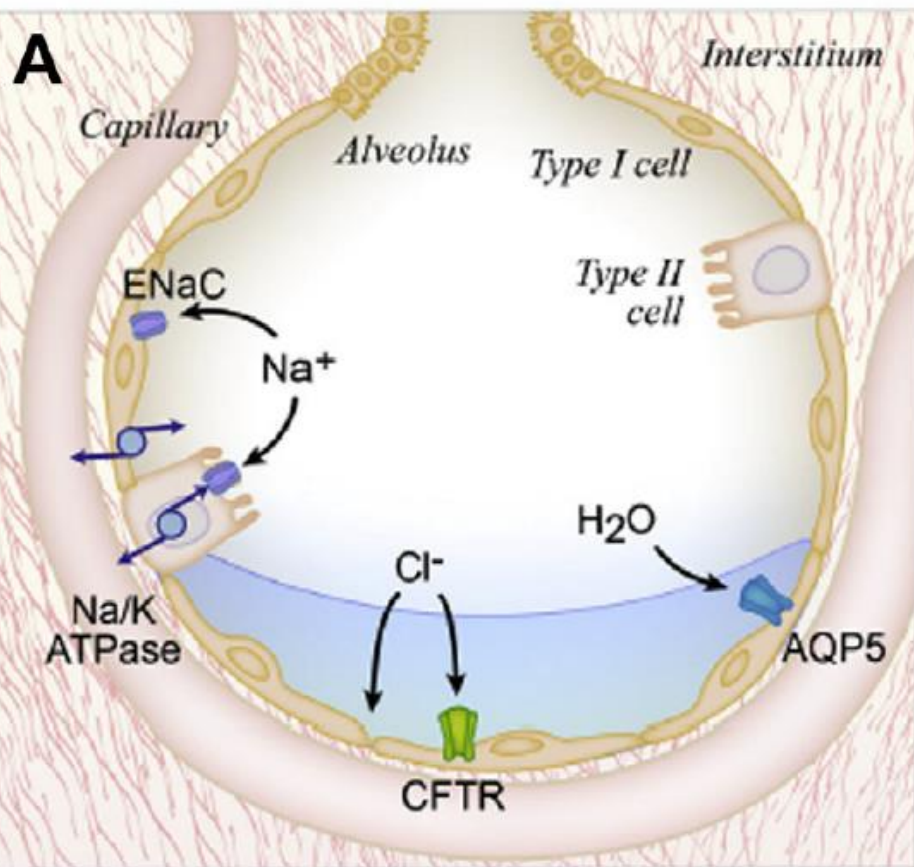


# Pulmonary vs. Extrapulmonary

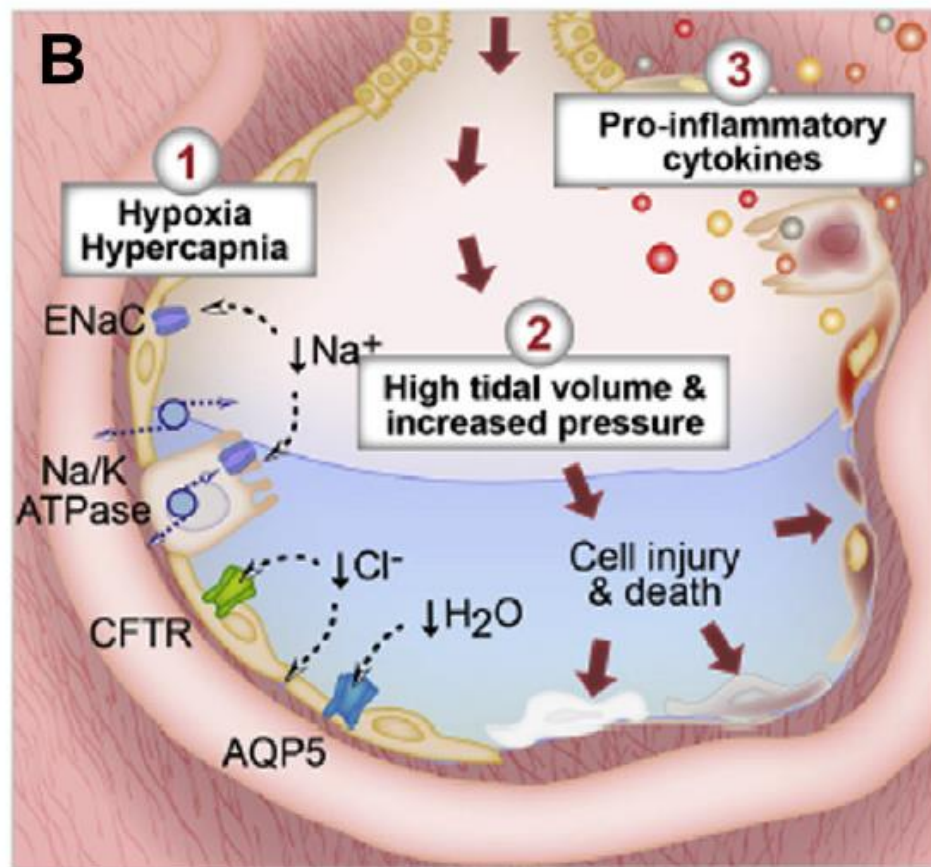
Histological and biochemical alterations in pulmonary and extrapulmonary acute respiratory distress syndrome

	ARDS <sub>p</sub>	ARDS <sub>exp</sub>
<b>Alveoli</b>		
Alveolar epithelium	↑↑ Damage	Damage
Altered type I and II cell	↑↑ Damage	Normal
Alveolar neutrophils	Prevalent	Rare
Apoptotic neutrophils	Prevalent	Rare
Fibrinous exudates	Present	Rare
Alveolar collapse	↑↑ Increased	Increased
Local interleukin	Prevalent	Rare
<b>Interstitial space</b>		
Interstitial oedema	Absent	High
Collagen fibres	↑↑ Increased	Increased
Elastic fibres	Normal	Normal
Capillary endothelium	Normal	↑↑ Damage
<b>Blood</b>		
Interleukin	Increased	↑↑ Increased
TNF- $\alpha$	Increased	↑↑ Increased

# Alveolar fluid clearance

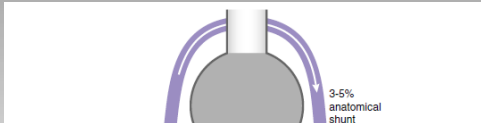


Normal alveolus



Injured alveolus

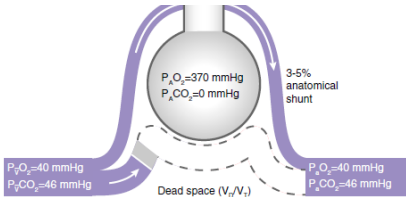
# V<sub>A</sub>/Q abnormality



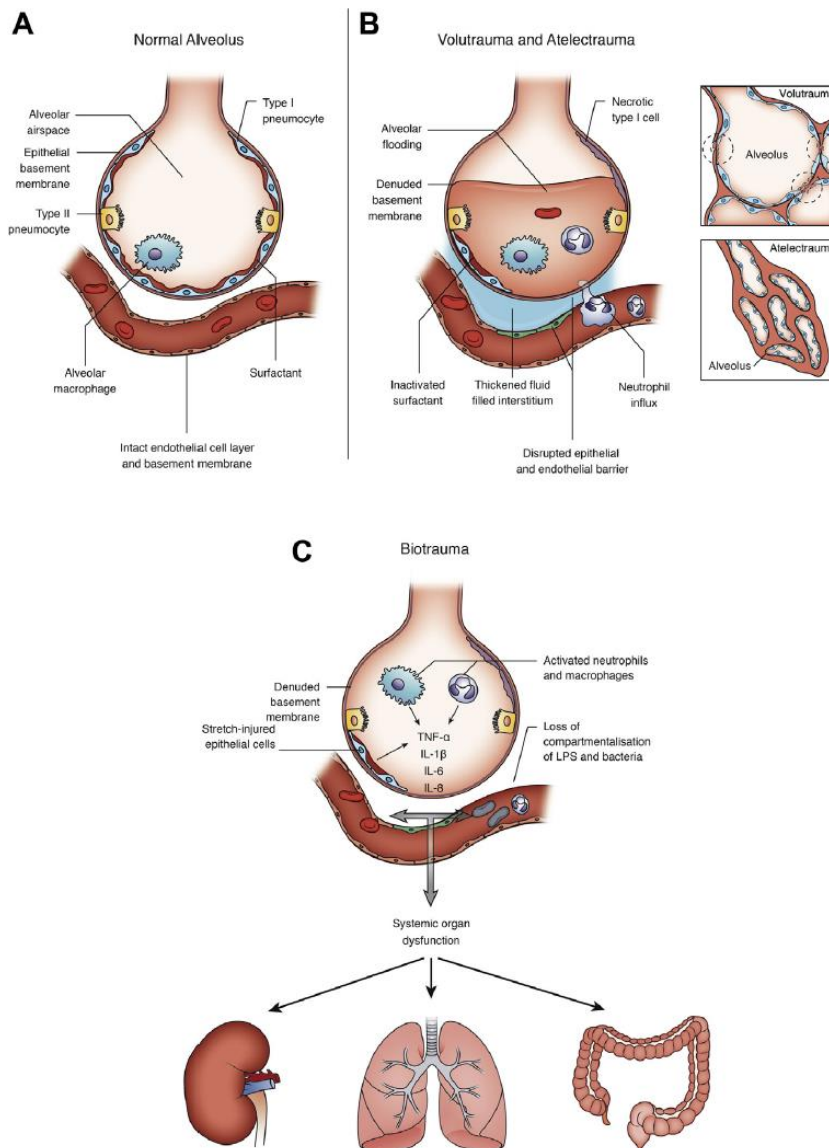
**Table 1.** Main Pathophysiologic Mechanisms of Impaired Gas Exchange in Acute Respiratory Distress Syndrome

Disturbance	Main Mechanisms
Hypoxemia	$\dot{Q}_s/\dot{Q}_T$ Low $\dot{V}_A/\dot{Q}$ Low $P\bar{V}_{O_2}$ Intracardiac shunt (e.g., PFO)
Hypercapnia	Increased $V_D/V_T$ Inhomogeneous distribution of ventilation (high $\dot{V}_A/\dot{Q}$ ) Increased $\dot{V}_{CO_2}$

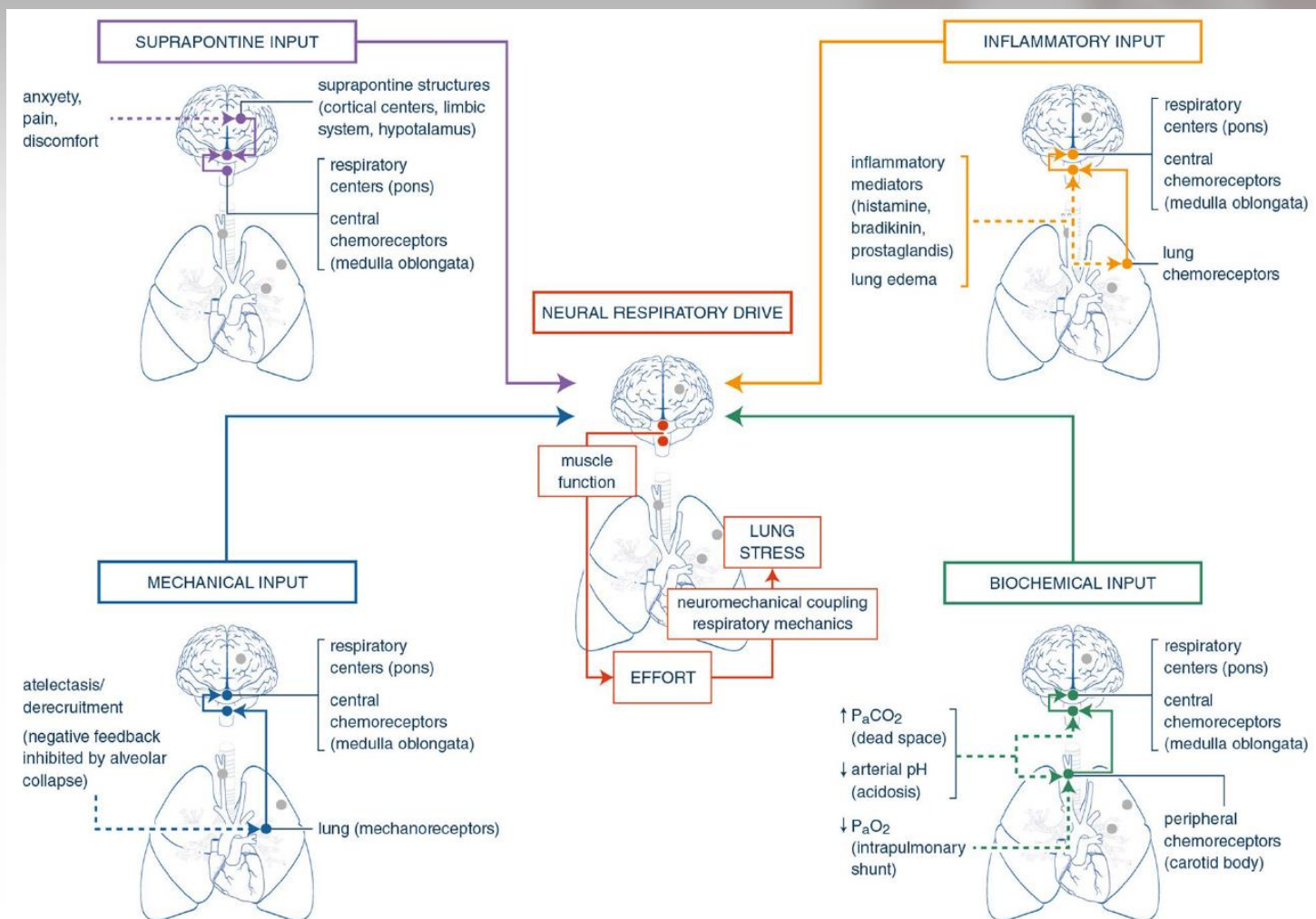
*Definition of abbreviations:* PFO = patent foramen ovale;  $P\bar{V}_{O_2}$  = mixed venous O<sub>2</sub> partial pressure;  $\dot{Q}_s/\dot{Q}_T$  = intrapulmonary right-to-left shunt.



# Ventilator Induced Lung Injury



# Patient Self-Inflicted Lung Injury

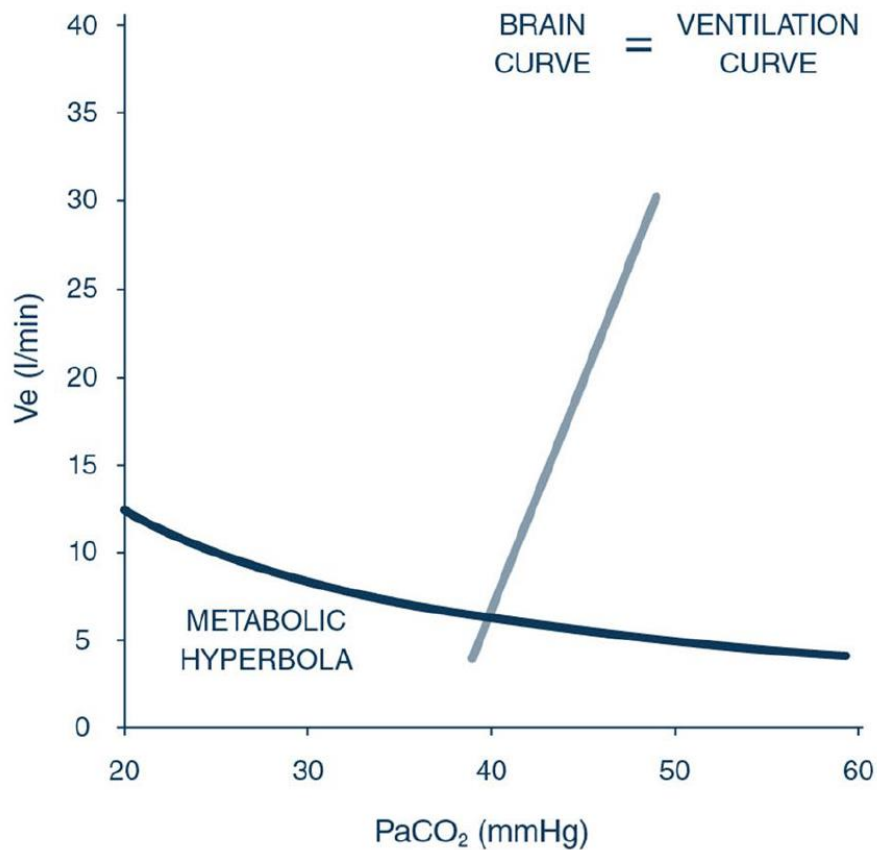


# Patient Self-Inflicted Lung Injury

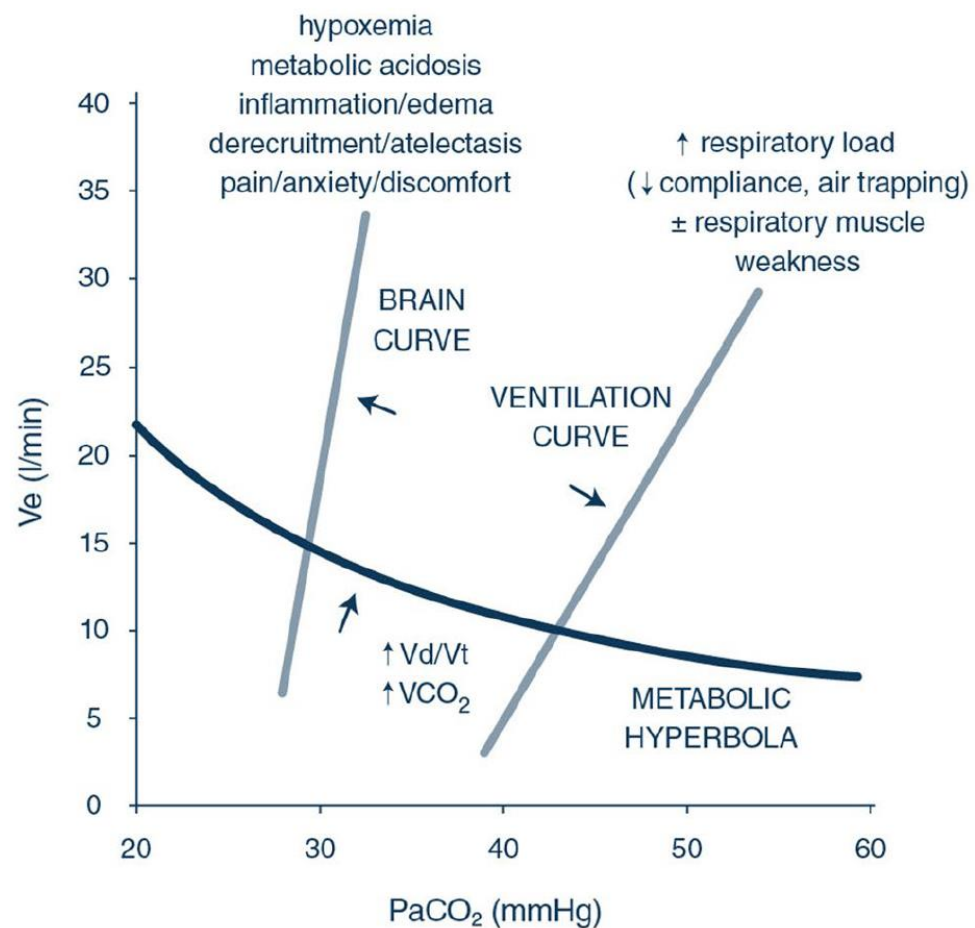
	Upward/Left Shift	Downward/Right Shift
Brain curve	<ul style="list-style-type: none"> <li>Metabolic acidosis</li> <li>Hypoxemia</li> <li>Interstitial lung edema</li> <li>Brain pathology (cortical)</li> </ul>	<ul style="list-style-type: none"> <li>Metabolic alkalosis</li> <li>Hyperoxemia</li> <li>Sedation</li> <li>Brain pathology (brainstem)</li> </ul>
Ventilation curve	<ul style="list-style-type: none"> <li>Mechanical ventilation</li> <li>Partial or full recovery from disease that affects inspiratory–flow generation pathway (upward shift from disease state, toward normal)</li> </ul>	<ul style="list-style-type: none"> <li>Upper motor neuron disease</li> <li>Diseases affecting nerve conduction (Guillain-Barré syndrome)</li> <li>Diseases affecting neuromuscular junction (myasthenia gravis)</li> <li>Respiratory muscle weakness/injury</li> <li>Impaired diaphragm length–tension relationship</li> <li>Increased airway resistance</li> <li>Decreased respiratory system compliance</li> </ul>
	<b>Upward Shift: Increased <math>V_D/V_T</math> or Increased <math>\dot{V}_{CO_2}</math></b>	<b>Downward Shift: Decreased <math>V_D/V_T</math> or Decreased <math>\dot{V}_{CO_2}</math></b>
Metabolic hyperbola	<ul style="list-style-type: none"> <li>Low <math>V_T</math> (<math>V_D/V_T</math>)</li> <li>Rapid shallow breathing (<math>V_D/V_T</math>)</li> <li>Increased <math>V_D</math>: lung pathology (<math>V_D/V_T</math>)</li> <li>Increased <math>V_D</math>: ventilator circuit (<math>V_D/V_T</math>)</li> <li>Agitation/shivering (<math>\dot{V}_{CO_2}</math>)</li> <li>Fever (<math>\dot{V}_{CO_2}</math>)</li> <li>Strenuous breathing (<math>\dot{V}_{CO_2}</math>)</li> </ul>	<ul style="list-style-type: none"> <li>High <math>V_T</math> (<math>V_D/V_T</math>)</li> <li>Sedation (<math>\dot{V}_{CO_2}</math>)</li> <li>Hypothermia (<math>\dot{V}_{CO_2}</math>)</li> </ul>

# Patient Self-Inflicted Lung Injury

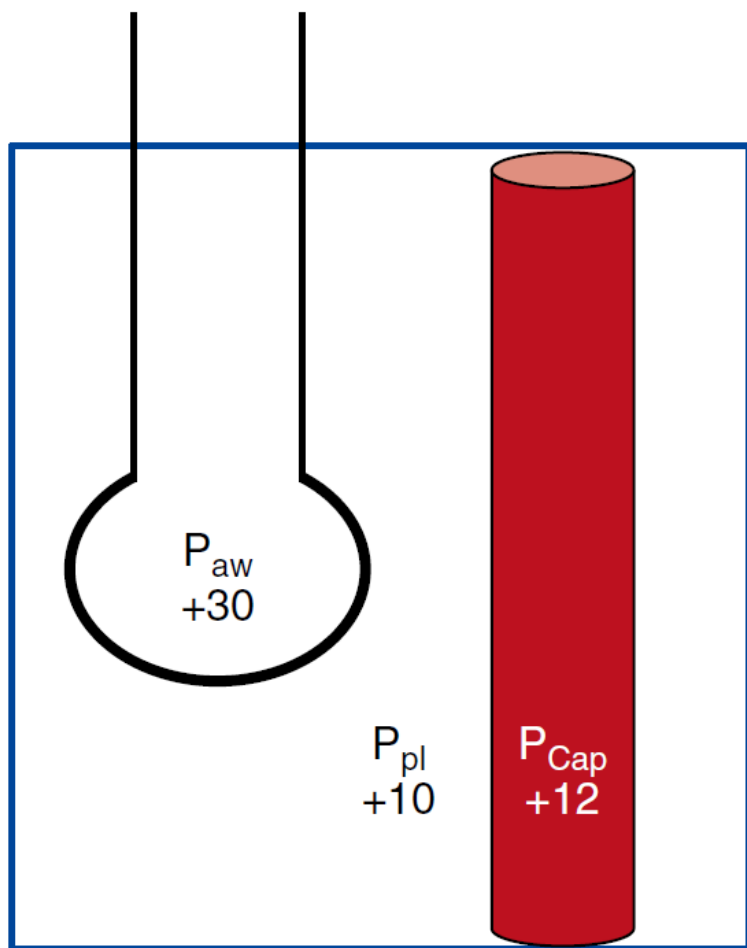
HEALTHY LUNGS



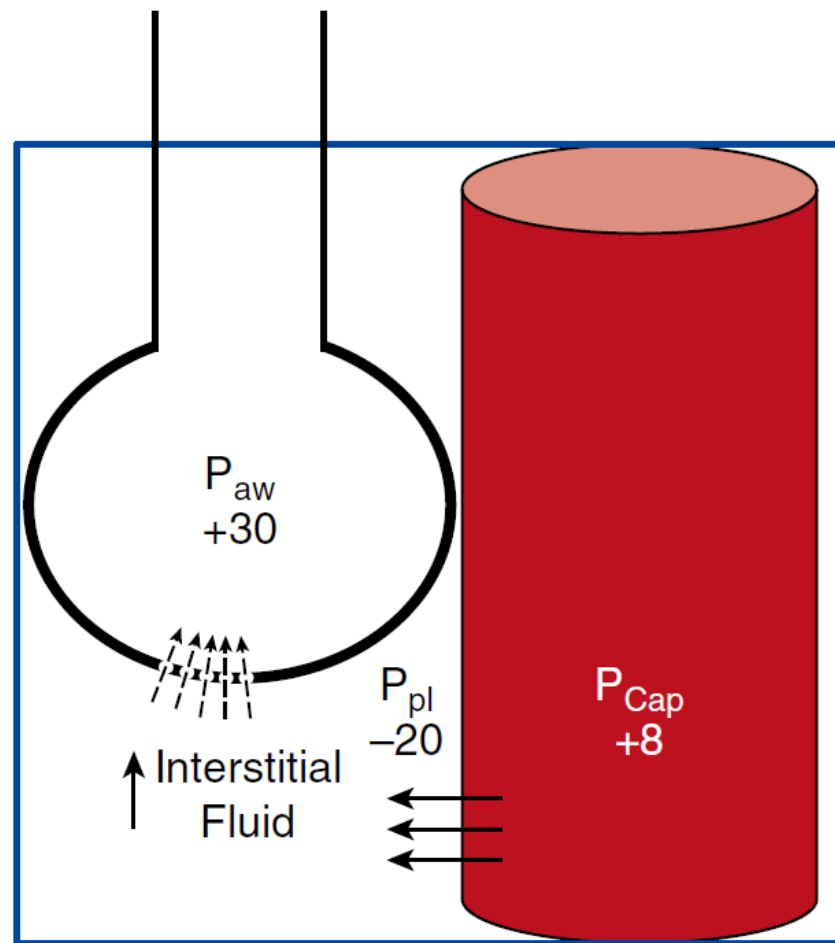
ARDS



# Patient Self-Inflicted Lung Injury

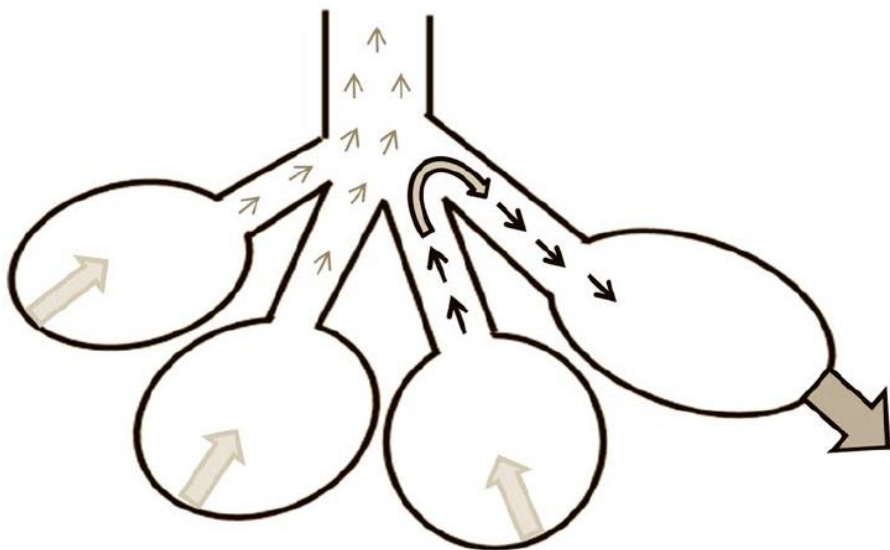


Sedation

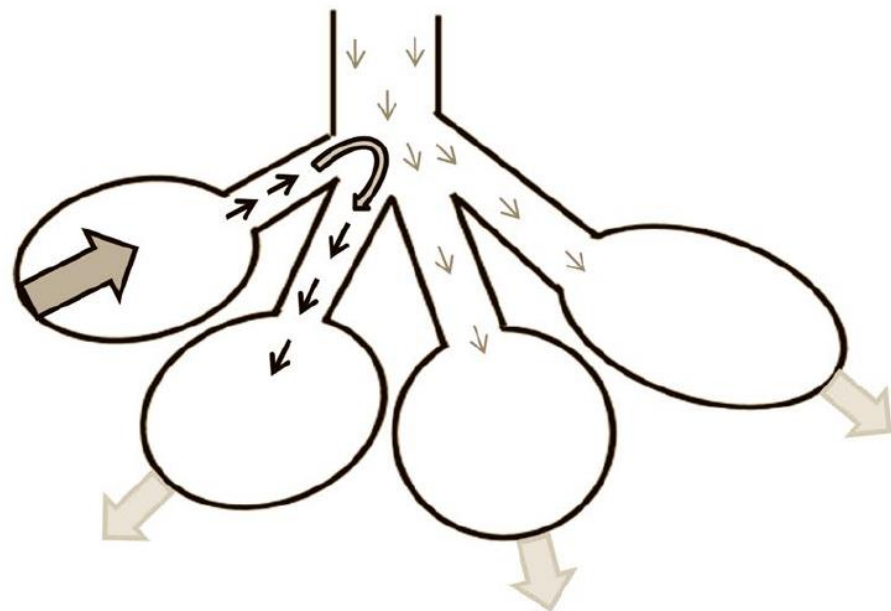


Spontaneous breathing

# Patient Self-Inflicted Lung Injury



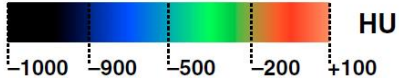
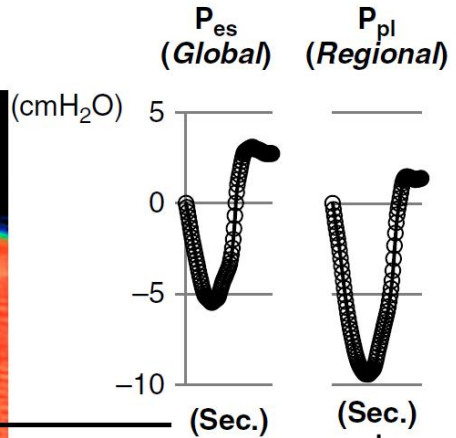
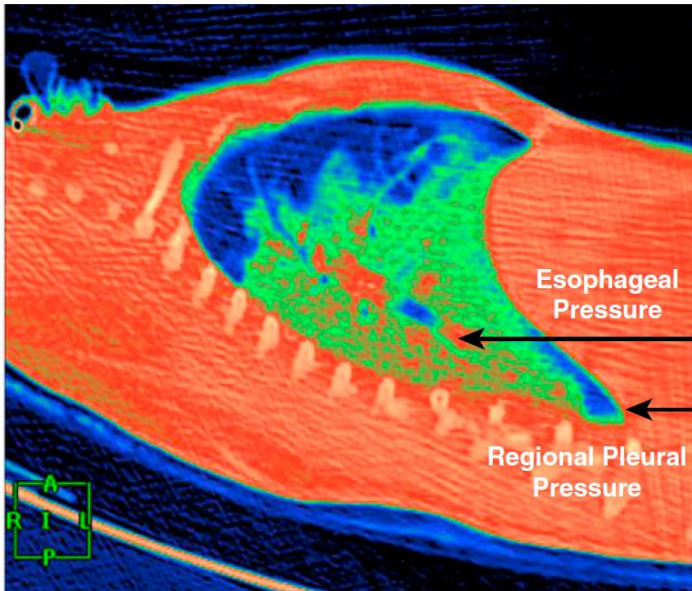
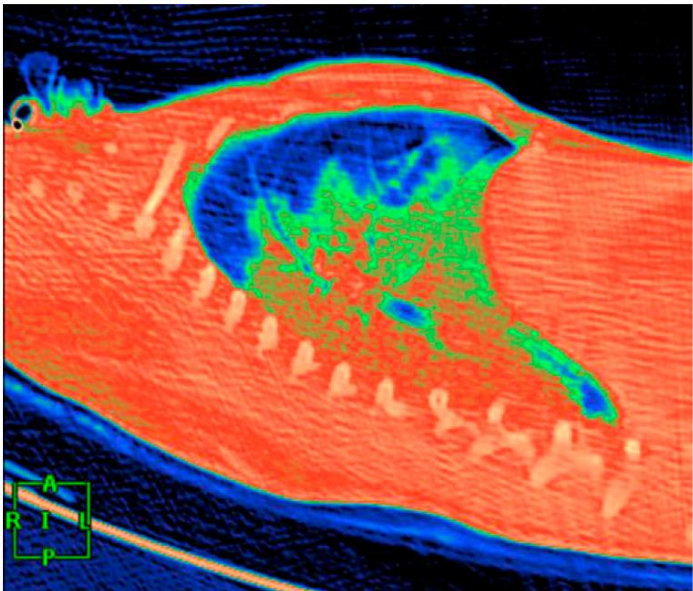
Expiration



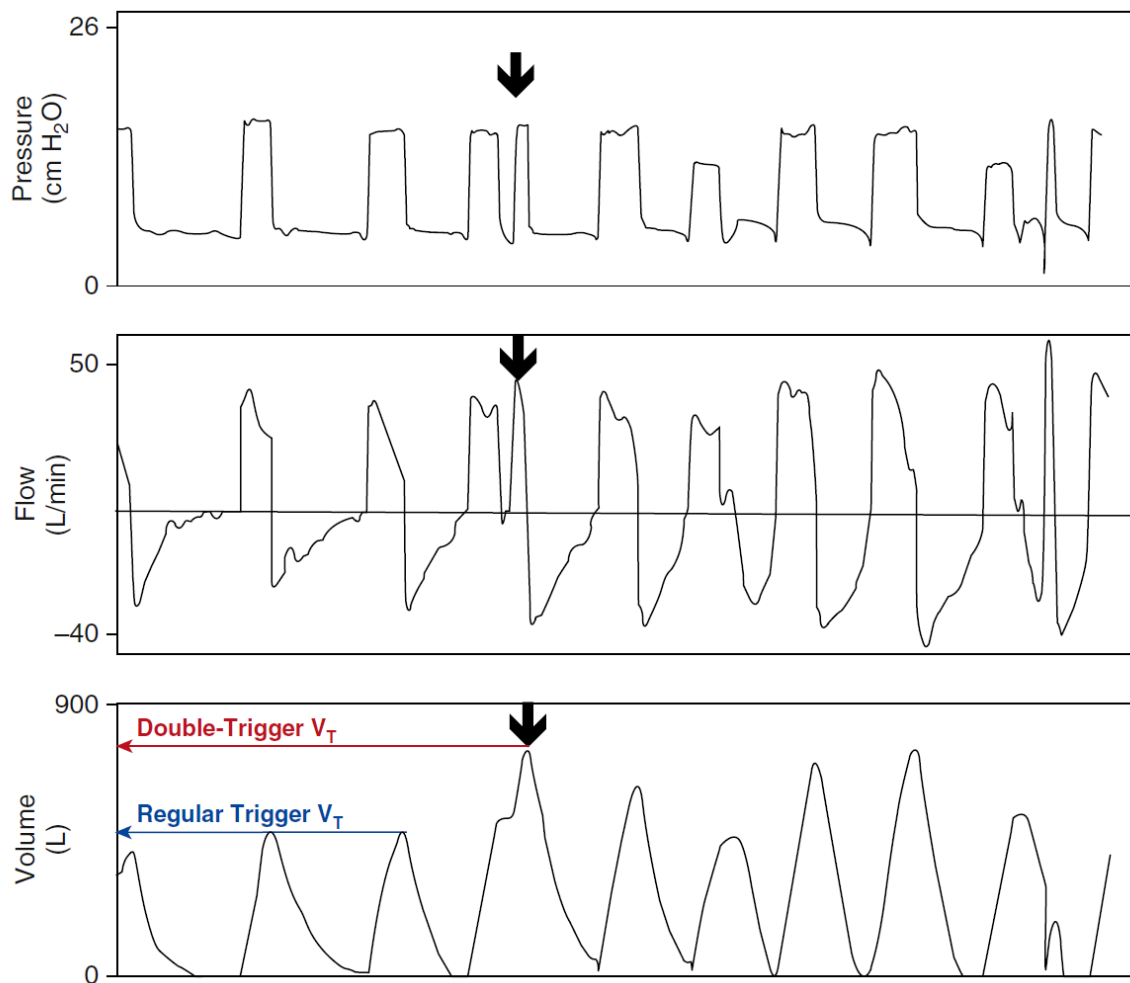
Inspiration

## Pendelluft Phenomenon

# Patient Self-Inflicted Lung Injury

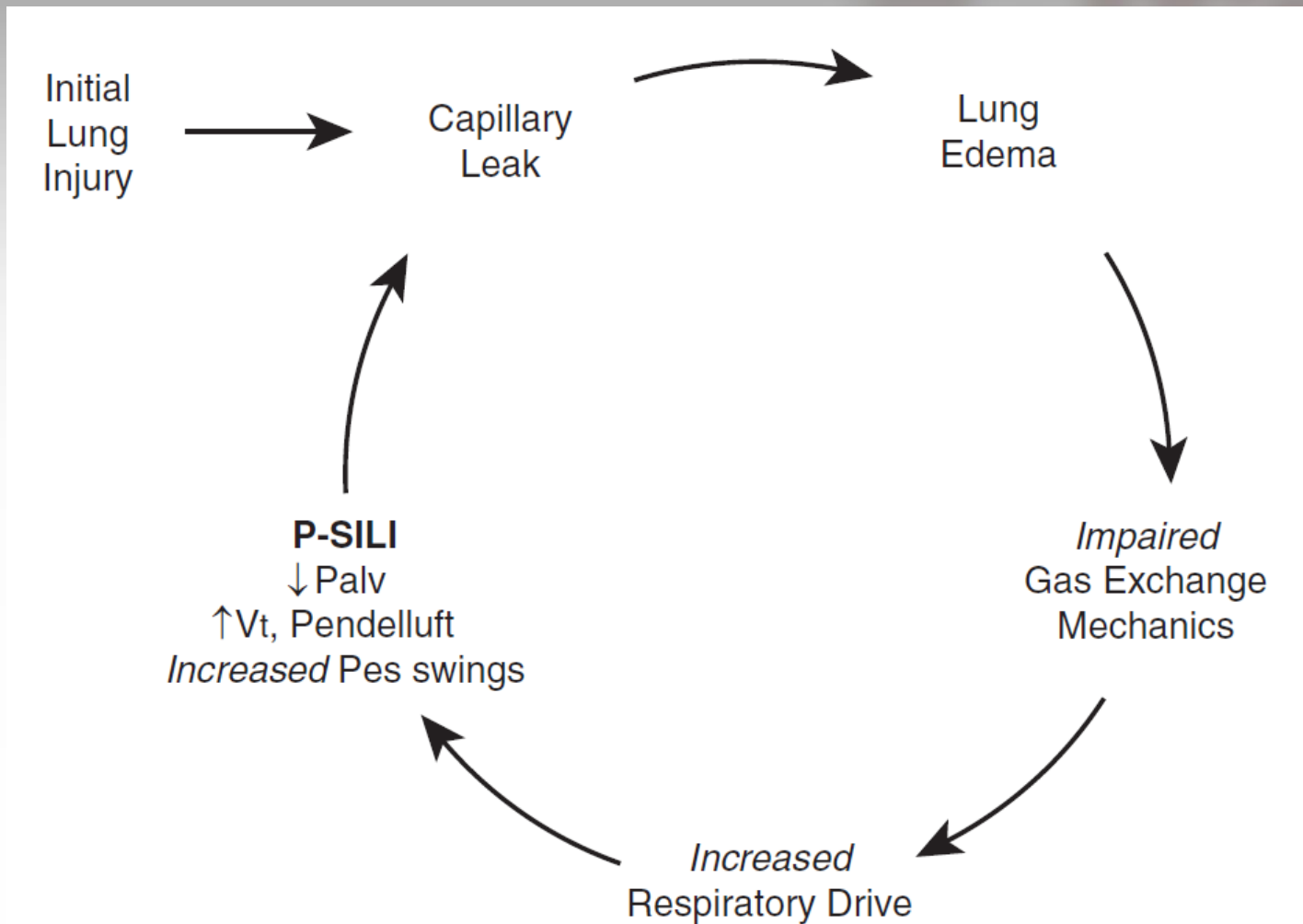


# Patient Self-Inflicted Lung Injury



Am J Respir Crit Care Med 2017;195:985-992

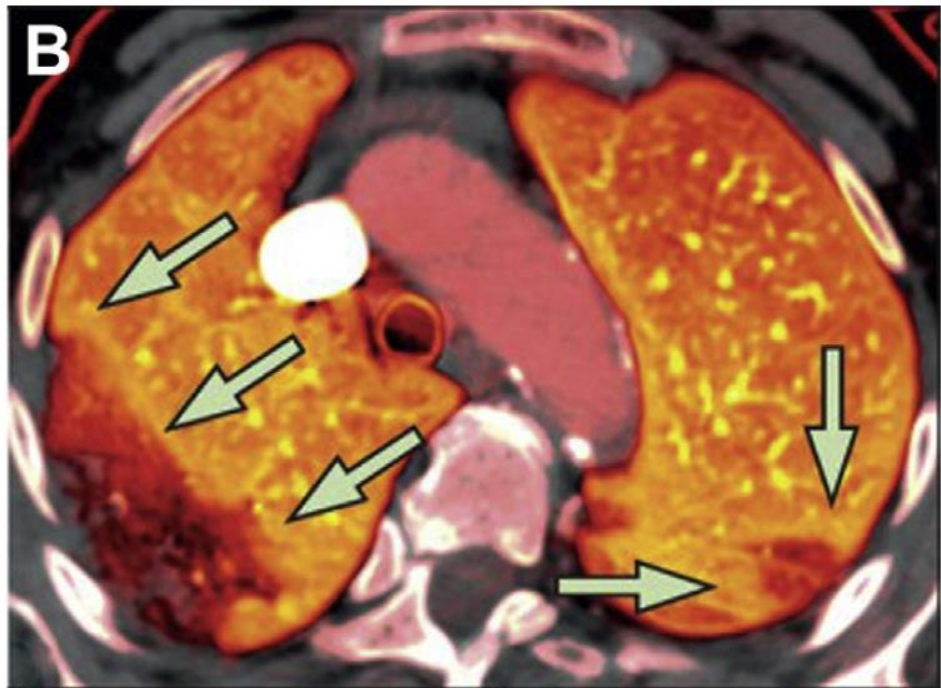
# Patient Self-Inflicted Lung Injury



# COVID-19 lung injury vs. ARDS

Comparisons between pathophysiology of COVID-19 lung injury and acute respiratory distress syndrome		
	COVID-19 Lung Injury	Acute Respiratory Distress Syndrome
Onset	8–12 d	< 7 d (Berlin definition)
Cause	SARS-CoV-2 (agent of COVID-19) via direct viral and immune response-mediated-injury	Multiple pulmonary and nonpulmonary (systemic) causes, both infectious and noninfectious
Histologic features	<ul style="list-style-type: none"> <li>• DAD</li> <li>• Organizing pneumonia</li> <li>• More severe vasculopathy                             <ul style="list-style-type: none"> <li>- Thromboembolism</li> <li>- In situ microthrombi</li> <li>- Capillary dilatations</li> <li>- Endothelial damage</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• DAD                             <ul style="list-style-type: none"> <li>- Exudative phase</li> <li>- Proliferative phase</li> <li>- Fibrotic phase</li> </ul> </li> <li>• Vascular changes                             <ul style="list-style-type: none"> <li>- Thromboembolism</li> <li>- In situ microthrombi</li> <li>- Capillary dilatations</li> <li>- Endothelial damage</li> </ul> </li> </ul>
Imaging	<ul style="list-style-type: none"> <li>• Peripheral and basilar ground-glass opacities in early disease</li> <li>• Progression to typical consolidation as in ARDS</li> </ul>	<ul style="list-style-type: none"> <li>• Consolidations, often patchy and dependent</li> </ul>
Respiratory mechanics	<ul style="list-style-type: none"> <li>• <math>C_{ST}</math> range: 20–90 mL/cmH<sub>2</sub>O</li> <li>• Compliance and oxygenation often improved with increased PEEP or prone positioning</li> </ul>	<ul style="list-style-type: none"> <li>• <math>C_{ST}</math> range: 10–78 mL/cmH<sub>2</sub>O</li> <li>• Compliance and oxygenation often improved with increased PEEP or prone positioning</li> </ul>
Pulmonary vasculature	<ul style="list-style-type: none"> <li>• Mild-moderate pulmonary hypertension</li> <li>• Unknown whether HPV intact or impaired</li> <li>• Vasculature responsive to almitrine and inhaled NO</li> </ul>	<ul style="list-style-type: none"> <li>• Mild-moderate pulmonary hypertension</li> <li>• HPV intact</li> <li>• Vasculature responsive to almitrine, calcium channel blockers, nitrates, PDE-5 inhibitors, and inhaled NO</li> </ul>
Gas exchange	<p><math>V_A/Q</math> mismatching:</p> <ul style="list-style-type: none"> <li>• Hypoxemia due to low <math>V_A/Q</math> and shunt</li> <li>• No evidence for diffusion limitation</li> <li>• Hypercapnia due to permissive hypoventilation, and all forms of <math>V_A/Q</math> mismatch</li> </ul>	<p><math>V_A/Q</math> mismatching:</p> <ul style="list-style-type: none"> <li>• Hypoxemia due to low <math>V_A/Q</math> and shunt</li> <li>• No evidence for diffusion limitation</li> <li>• Hypercapnia due to permissive hypoventilation, and all forms of <math>V_A/Q</math> mismatch</li> </ul>
Alveolar epithelial fluid clearance	Likely reduced due to alveolar type I and II cell damage, but not formally tested	Reduced due to alveolar type I and II cell damage; unresponsive to beta-adrenergic therapy

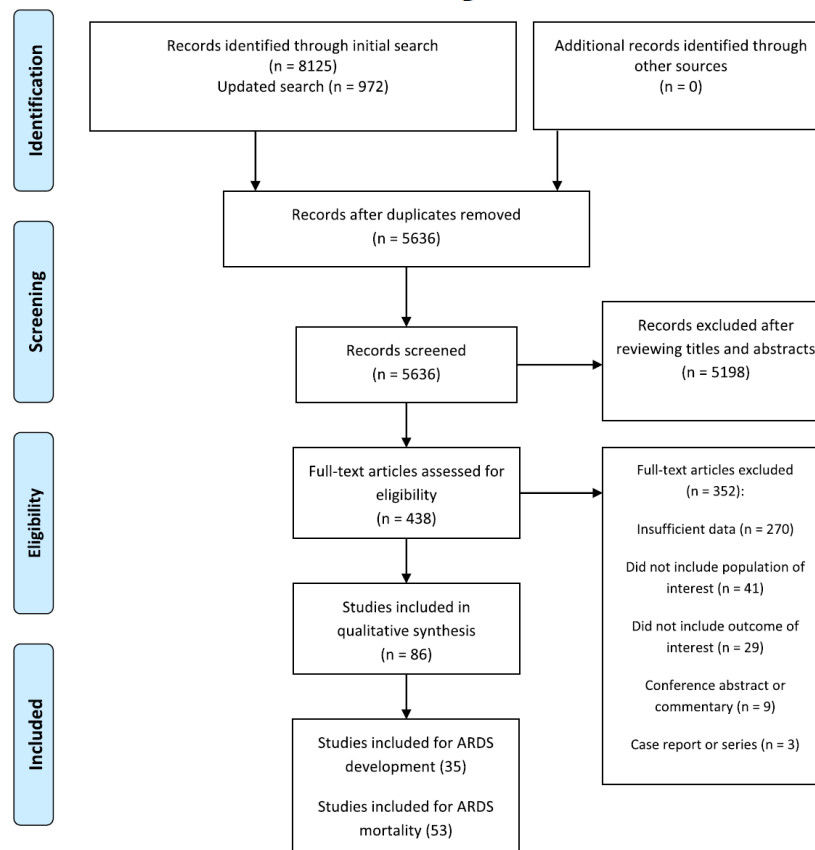
# COVID-19 lung injury vs. ARDS



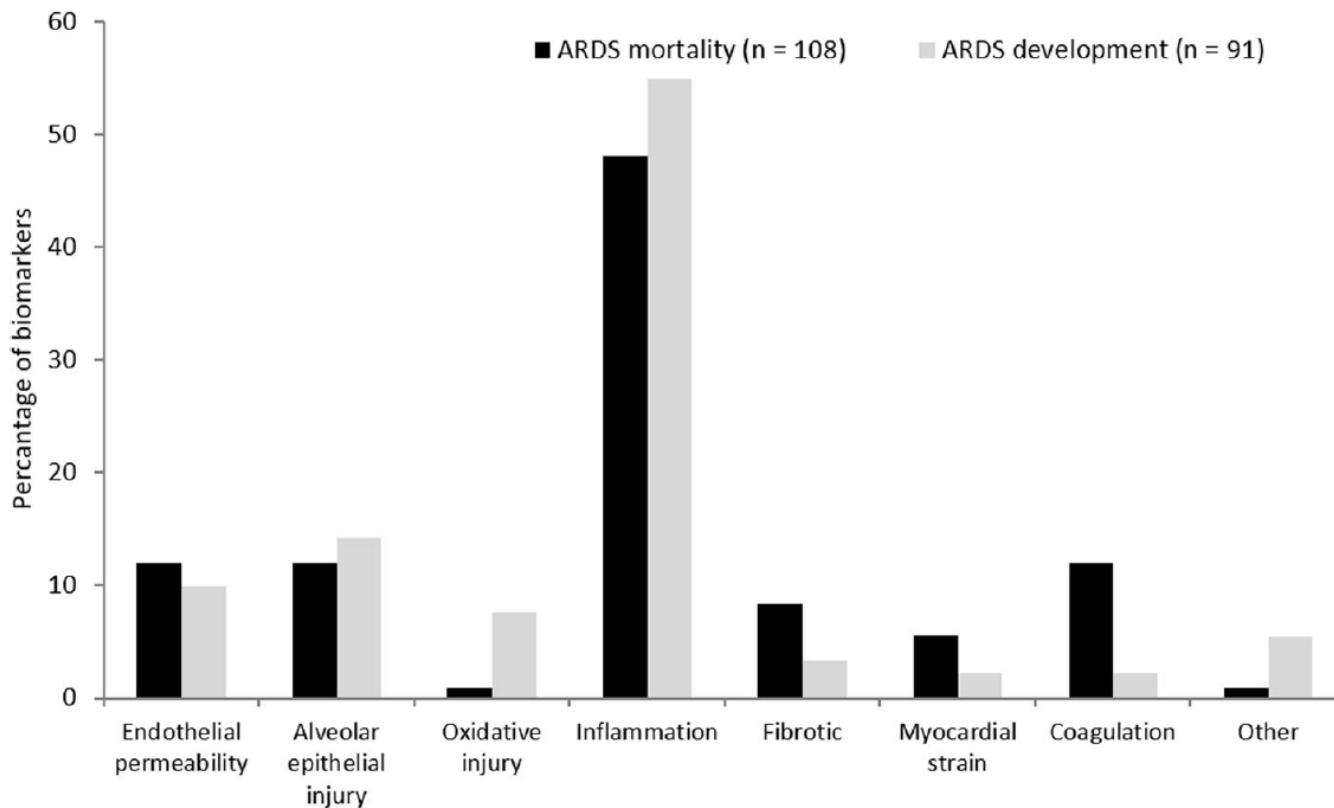
Lancet Infect Dis 2020;20:1365-1366

# Biomarkers

## A systematic review of biomarkers multivariately associated with acute respiratory distress syndrome development and mortality



# Biomarkers



Biomarker role in ARDS pathophysiology

# Biomarkers

**Data extraction and synthesis:** We included 35 studies for ARDS development (10,667 patients at risk for ARDS) and 53 for ARDS mortality (15,344 patients with ARDS). These studies were too heterogeneous to be used in a meta-analysis, as time until outcome and the variables used in the multivariate analyses varied widely between studies. After qualitative inspection, high plasma levels of angiopoietin-2 and receptor for advanced glycation end products (RAGE) were associated with an increased risk of ARDS development. None of the biomarkers (plasma angiopoietin-2, C-reactive protein, interleukin-8, RAGE, surfactant protein D, and Von Willebrand factor) was clearly associated with mortality.

**Conclusions:** Biomarker data reporting and variables used in multivariate analyses differed greatly between studies. Angiopoietin-2 and RAGE in plasma were positively associated with increased risk of ARDS development. None of the biomarkers independently predicted mortality. Therefore, we suggested to structurally investigate a combination of biomarkers and clinical parameters in order to find more homogeneous ARDS phenotypes.

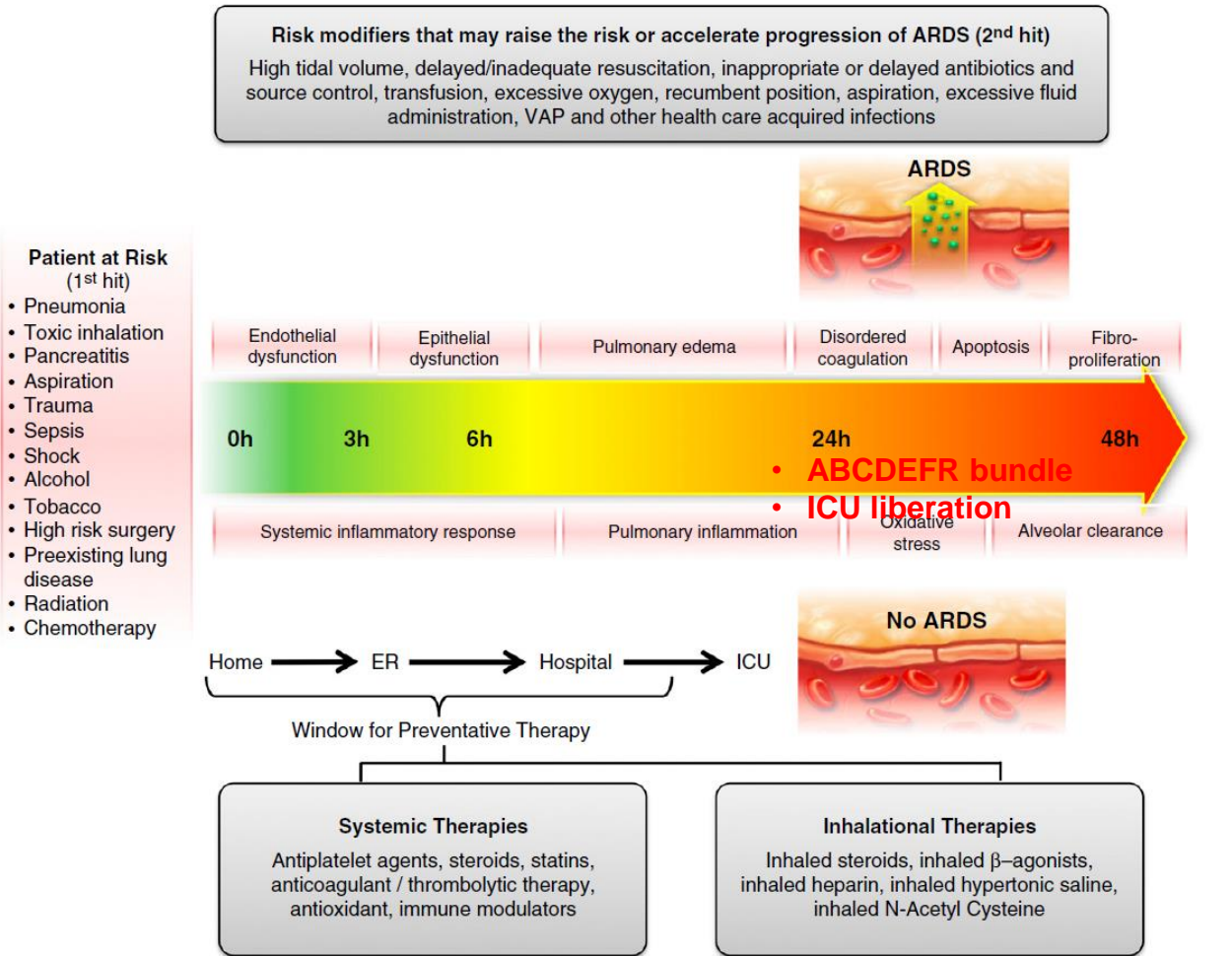
Angiopoietin-2: Increased endothelial permeability  
RAGE: Alveolar epithelial injury

# Prevention

CLIP Element	Best Practice
Adequate empiric antimicrobial treatment and source control	According to suspected site of infection, health care exposure, and immune suppression
Lung-protective mechanical ventilation	$V_T < 6-8$ ml/kg predicted body weight Plateau pressure $< 25$ cm H <sub>2</sub> O PEEP $\geq 5$ cm H <sub>2</sub> O, Minimize F <sub>I</sub> O <sub>2</sub> (target Sp <sub>O</sub> <sub>2</sub> = 88–92% after early shock)
Aspiration precautions	Rapid sequence intubation supervised by experienced providers Elevated head of the bed Oral care with chlorhexidine Gastric acid neutralization Early reassessment of noninvasive ventilation to prevent delayed intubation
Limiting fluid overload	Modified ARDS Network FACTT protocol after early shock
Restrictive transfusion	Hemoglobin target $> 7$ g/dl Male-predominant plasma donor pool
Assess readiness for extubation	Limit continuous sedation and perform spontaneous breathing trial as soon as feasible

# Prevention

Wi



F

---

# THANK YOU