Phathphysiology of ARDS

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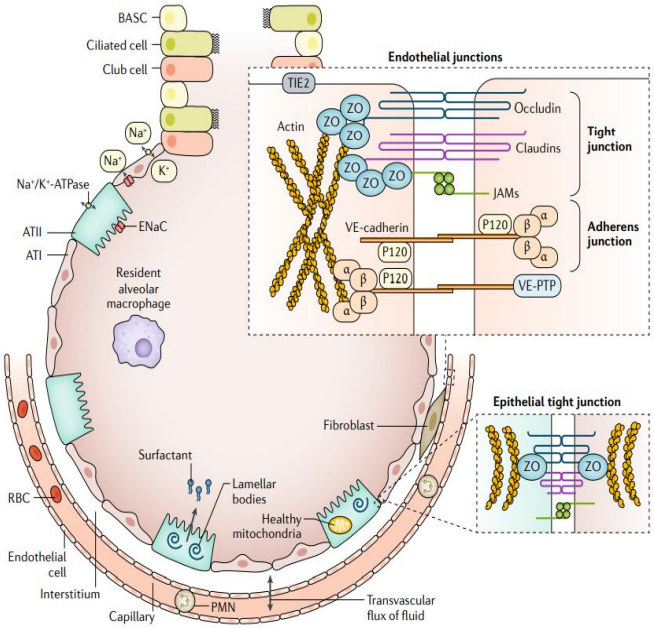
Division of pulmonary

Health alveolus and normal fluid transport



Relativly impermeable epithelium

- Active solute transport
- Surfactant from ATII cells

Regulated endothelial permeability

- Pressure gradient favoring reabsorbtion

Patrolling immune cells

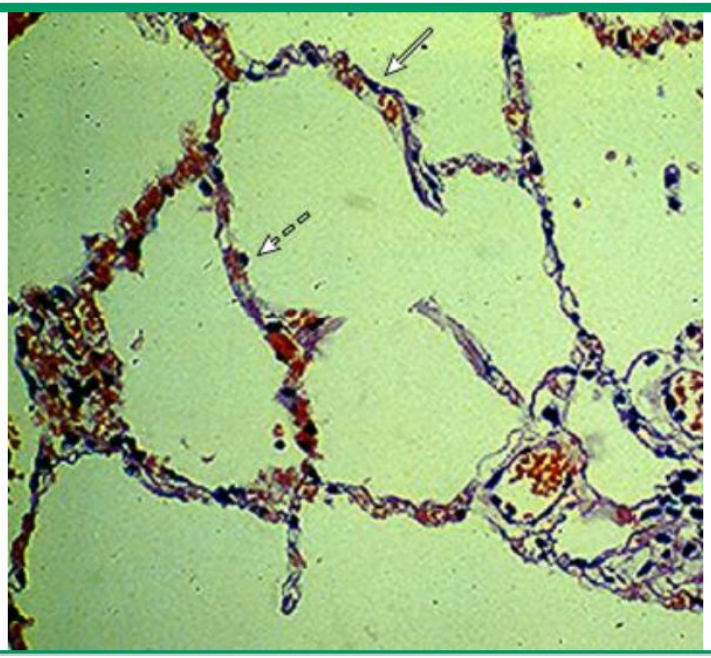
- Macrophages
- Platelets

Michael A. matthay et al .Nature Reviews Disease Primers 2019

UpToDate

Normal lung

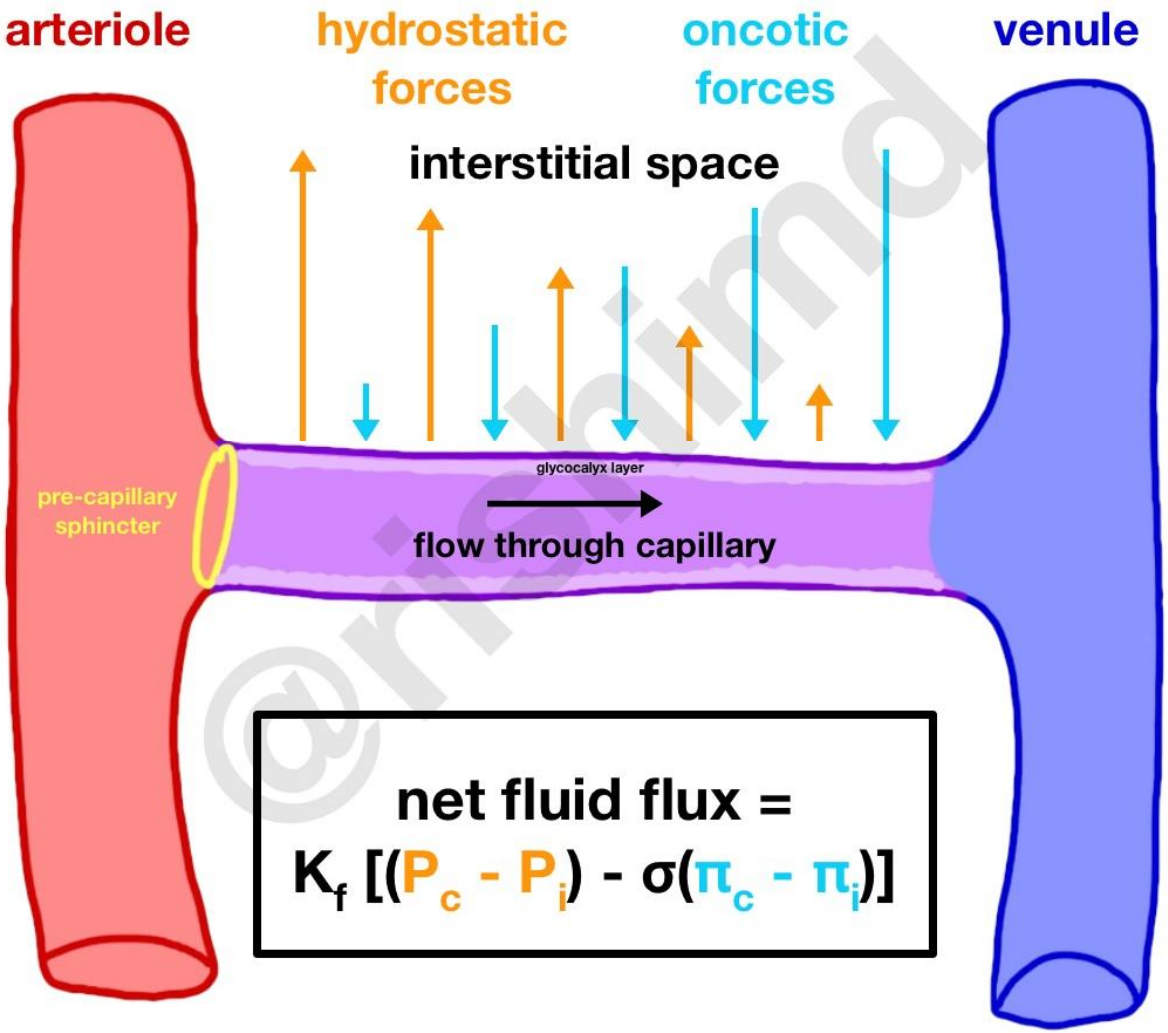
Normal lung



High power photomicrograph shows alveoli containing capillaries within a narrow interstitium. The alveoli are lined with thin, elongated type I pneumocytes (arrow) and smaller numbers of cuboidal type II pneumocytes (dashed arrow).

Courtesy of Steven E Weinberger, MD.

STARLING EQUATION

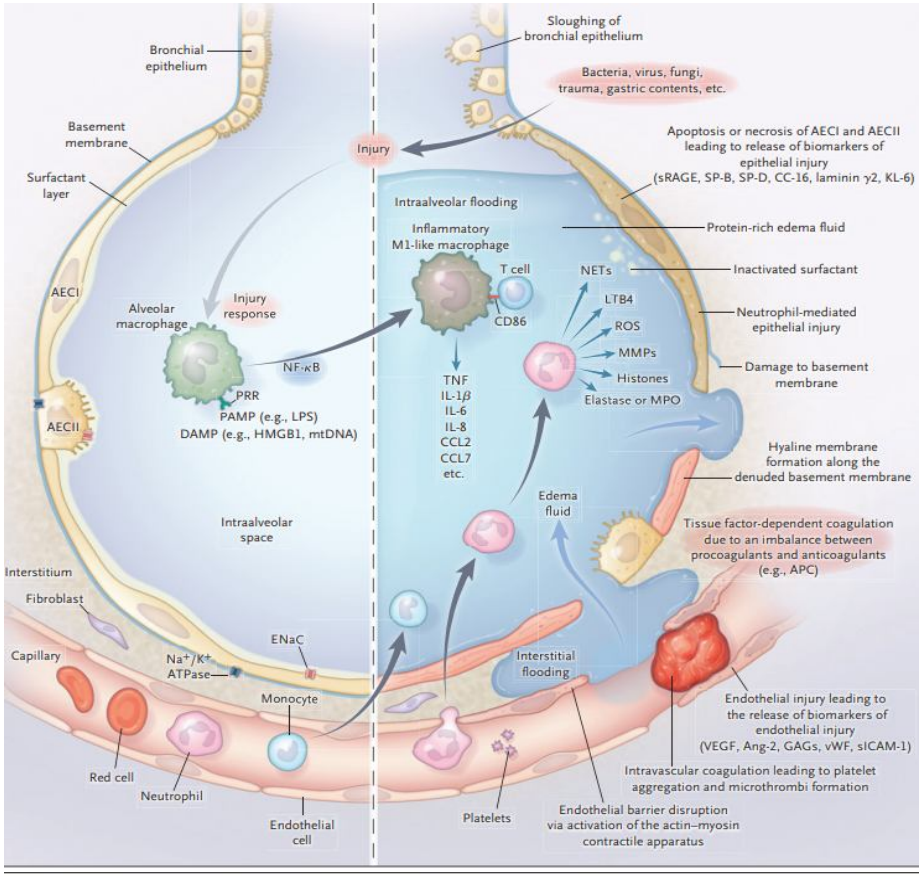


- **Q** :the net transvascular flow of fluid
- **K:** the permeability of the endothelial membrane
- **Pc:** the hydrostatic pressure within the lumen ofthe microvessels
- **Pi:** the hydrostatic pressure in the perimicrovascular space
- **σ :**the reflection coefficient of the capillary barrier
- **πc:** the oncotic pressure in the circulation
- **πi** :the oncotic pressure in the perimicrovascular compartmen

Alveolar injury - ARDS

- Structural/Mechanical
- Immunologic
- Cellular Death / Dysfunction

Alveolar injury - ARDS



n engl j med 377;6 nejm.org August 10, 2017

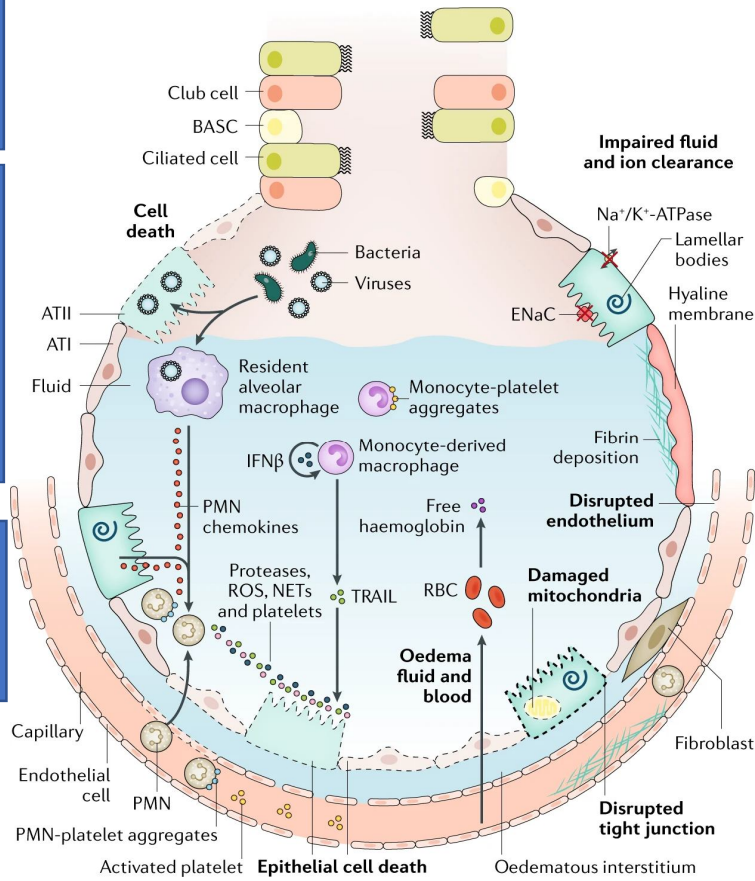
Inflammatory alveolar injury

Pro-inflammatory cytokines
TNFα - IL 1 , 6, 8

Neutrophils-ROIs
Damage capillary
Alveolar epithelium and endothelium

Fluid in interstitium
And
alveoli

Impaired gas exchange
Reduce compliance
Increase PAP



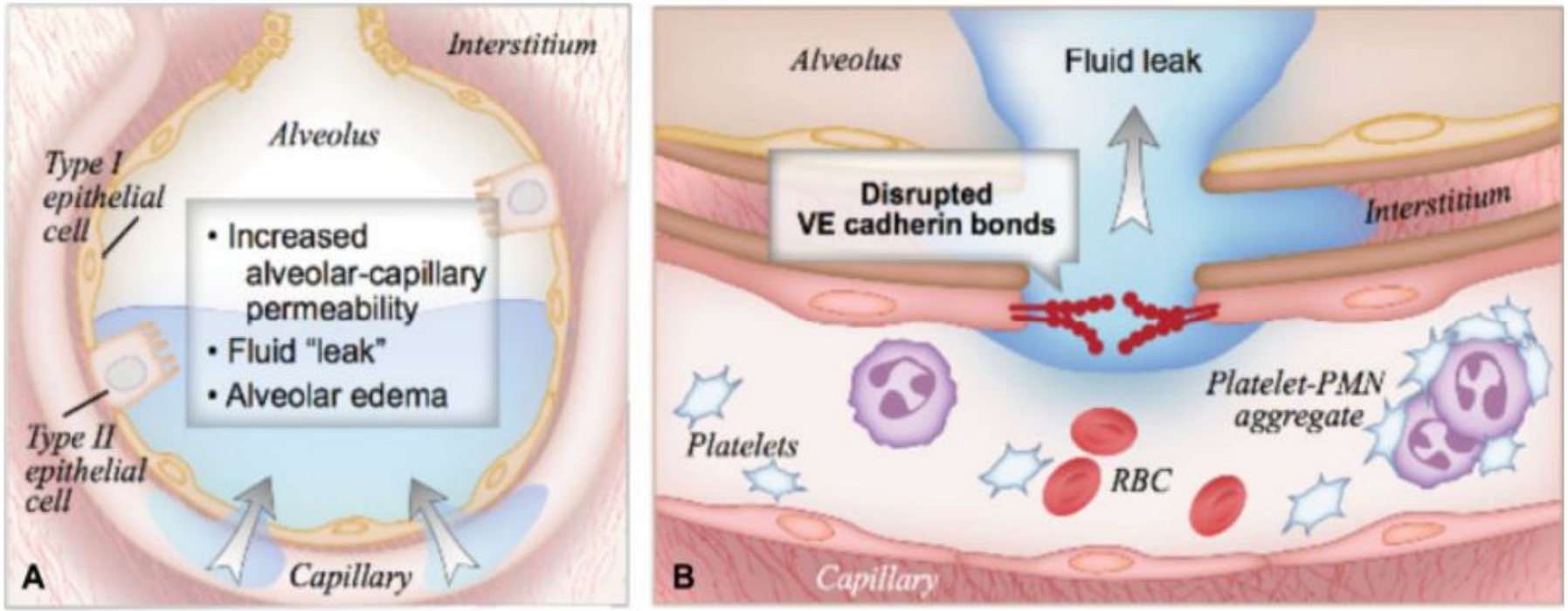


Fig. 1 Increased alveolar endothelial permeability in ARDS. (A) In ARDS, inflammatory molecules disrupt alveolar barrier function, resulting in the accumulation of alveolar edema fluid. (B) Specifically, disruption of VE-cadherin bonds causes increased endothelial permeability, and subsequent leakage of water, solutes, leukocytes, platelets, and other inflammatory molecules into the alveolar space. ARDS, acute respiratory distress syndrome; VE-cadherin, vascular endothelial cadherin.

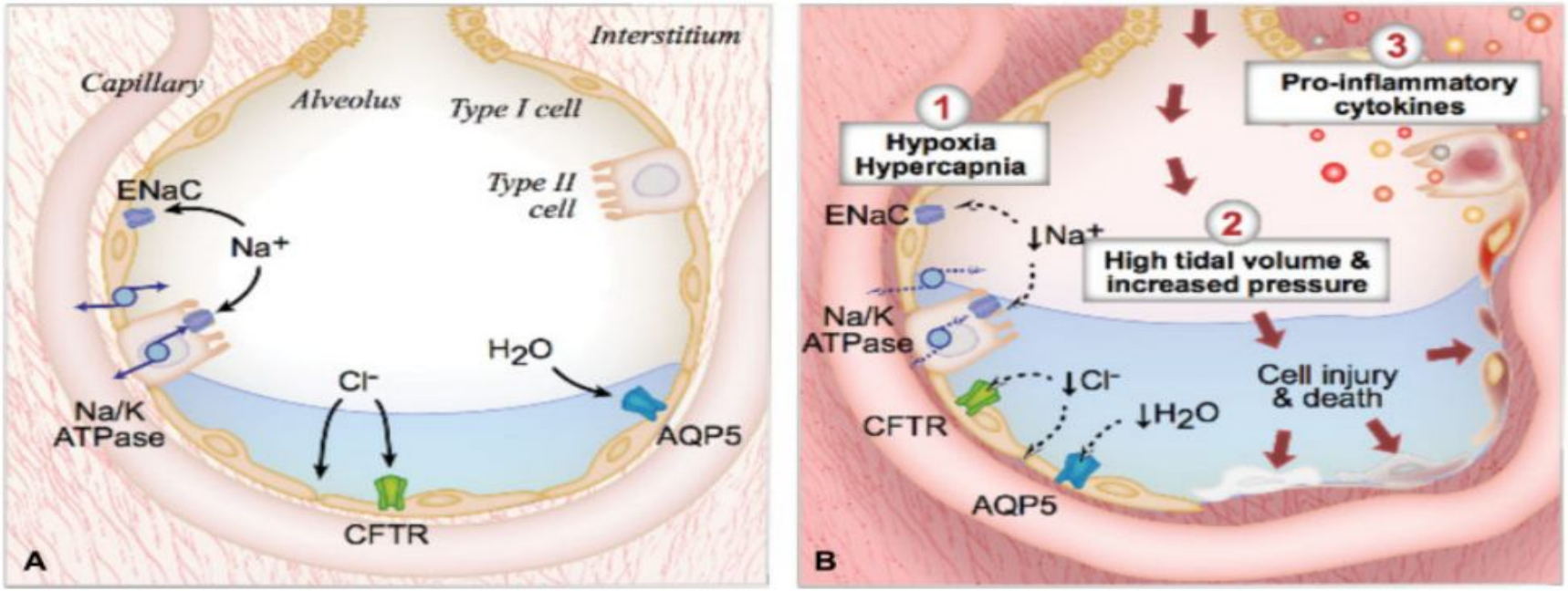
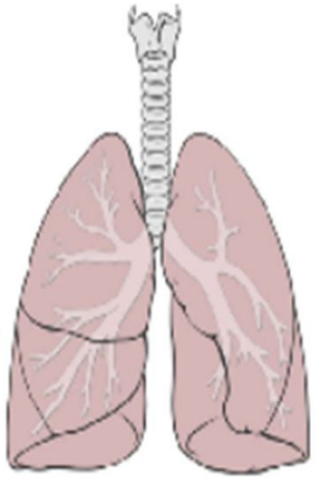


Fig. 2 Alveolar fluid clearance pathways in the uninjured lung versus the lung affected by ARDS. (**A**) In the uninjured lung, fluid is effectively cleared from the alveolar space by vectorial ion transport. Shown are the interstitial, capillary, and alveolar compartments of the lung, with pulmonary edema fluid in the alveolus. Both type I and type II alveolar cells are involved in transepithelial ion transport. Sodium (Na^+) is transported across the apical side of the type I and type II cells through the ENaC, and then across the basolateral side via the sodium/potassium ATPase pump (Na/K-ATPase). Chloride (Cl^-) is transported via the CFTR channel or by a paracellular route. Additional cation channels also transport ions across the alveolar epithelium (not shown). This vectorial ion transport creates an osmotic gradient that drives the clearance of fluid. Specifically, water (H_20) moves down the osmotic gradient through aquaporin channels, such as AQP5 or via an intracellular route (not shown). In the uninjured lung, this vectorial ion transport helps achieve effective alveolar fluid clearance. (**B**) In lungs affected by ARDS, fluid is less effectively cleared from the lungs. First, hypoxia/hypercapnia results in downregulation of ENaC transcription and trafficking and less efficient function of the Na/K-ATPase. Second, high tidal volumes and elevated airway pressures injure the alveolar epithelium, inducing inflammation and cell death. Third, ARDS results in the formation of proinflammatory cytokines, which induce alveolar injury and cause reduced alveolar fluid clearance. ARDS, acute respiratory distress syndrome; AQP5, aquaporin 5; CFTR, cystic fibrosis transmembrane conductance regulator; ENaC, epithelial sodium channel.

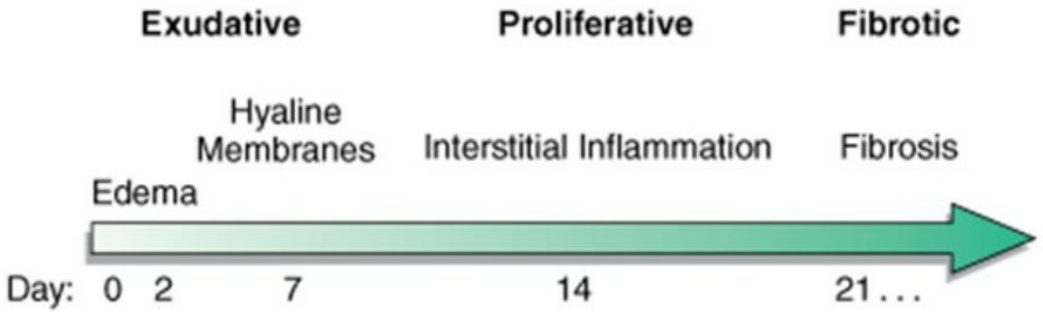
ARDS

Representative Initiating events

- sepsis
- pneumonia
- trauma/shock
- aspiration
- blood transfusion



- Natural history is marked by 3 phases:



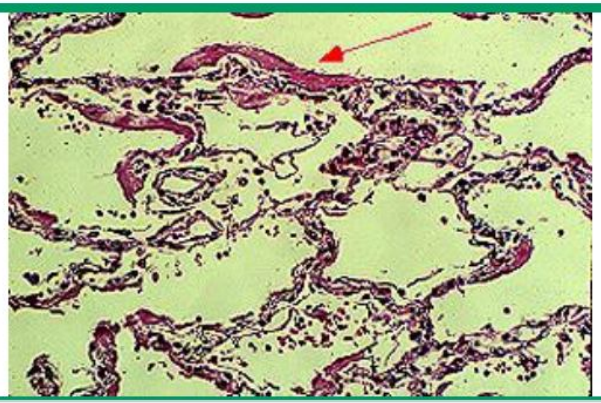
Exudative phase (day 1-7)

- Interstitial and intra-alveolar edema
- Hemorrahge
- Leukoagglutination
- Necrosis
  - Type 1 pneumocyte
  - Endothelial cells
- Hyaline membranes
- Platelet-fibrine thrombi
- Dysnea develops

UpToDate

Early diffuse alveolar damage

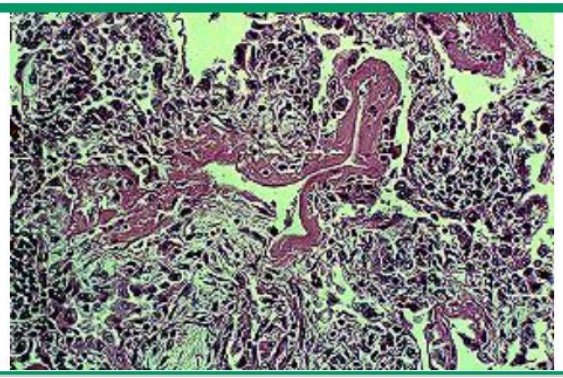
Early diffuse alveolar damage



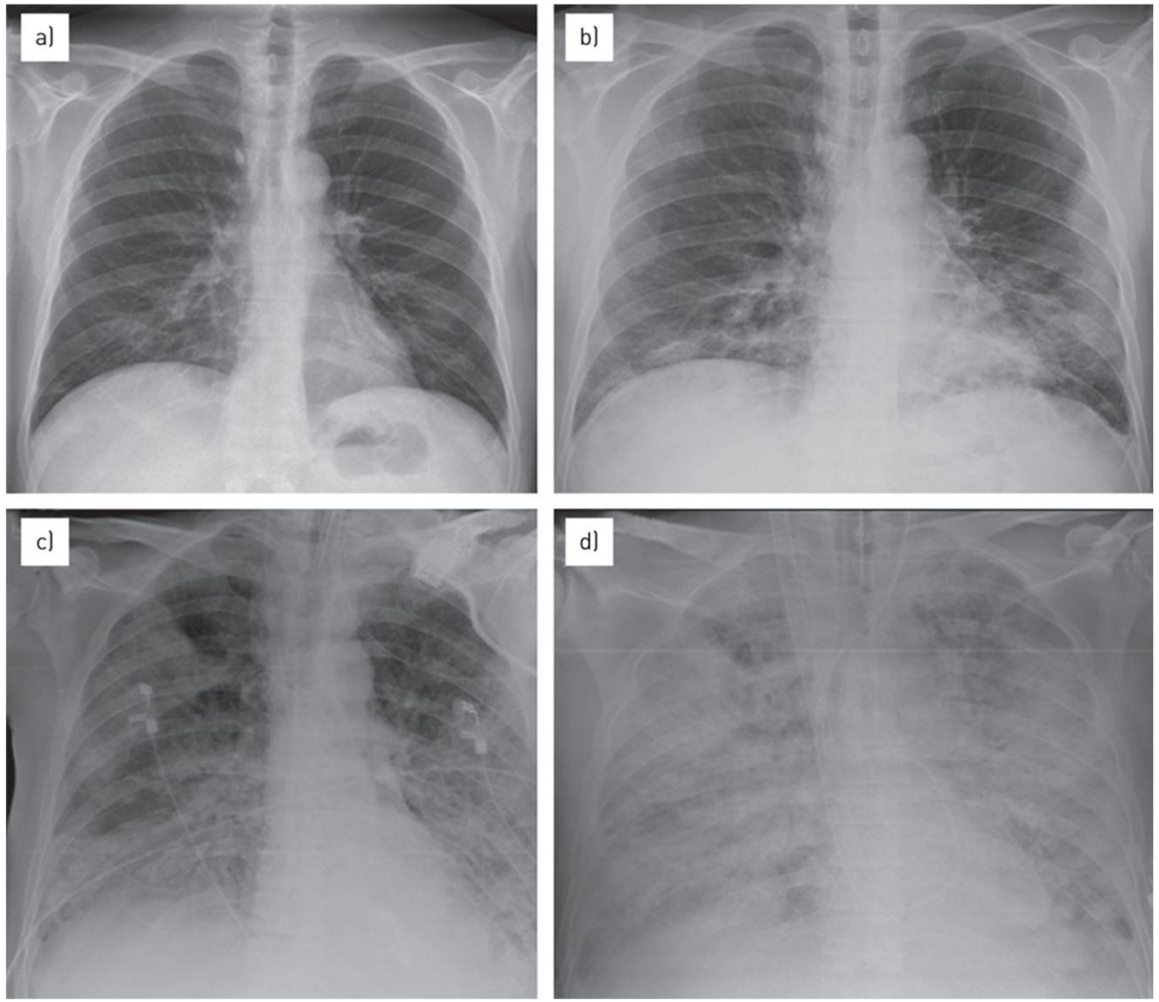
Photomicrograph shows early diffuse alveolar damage with minimal alveolar septal thickening, hyperplasia of pneumocytes, and eosinophilic hyaline membranes (arrow).

Late diffuse alveolar damage

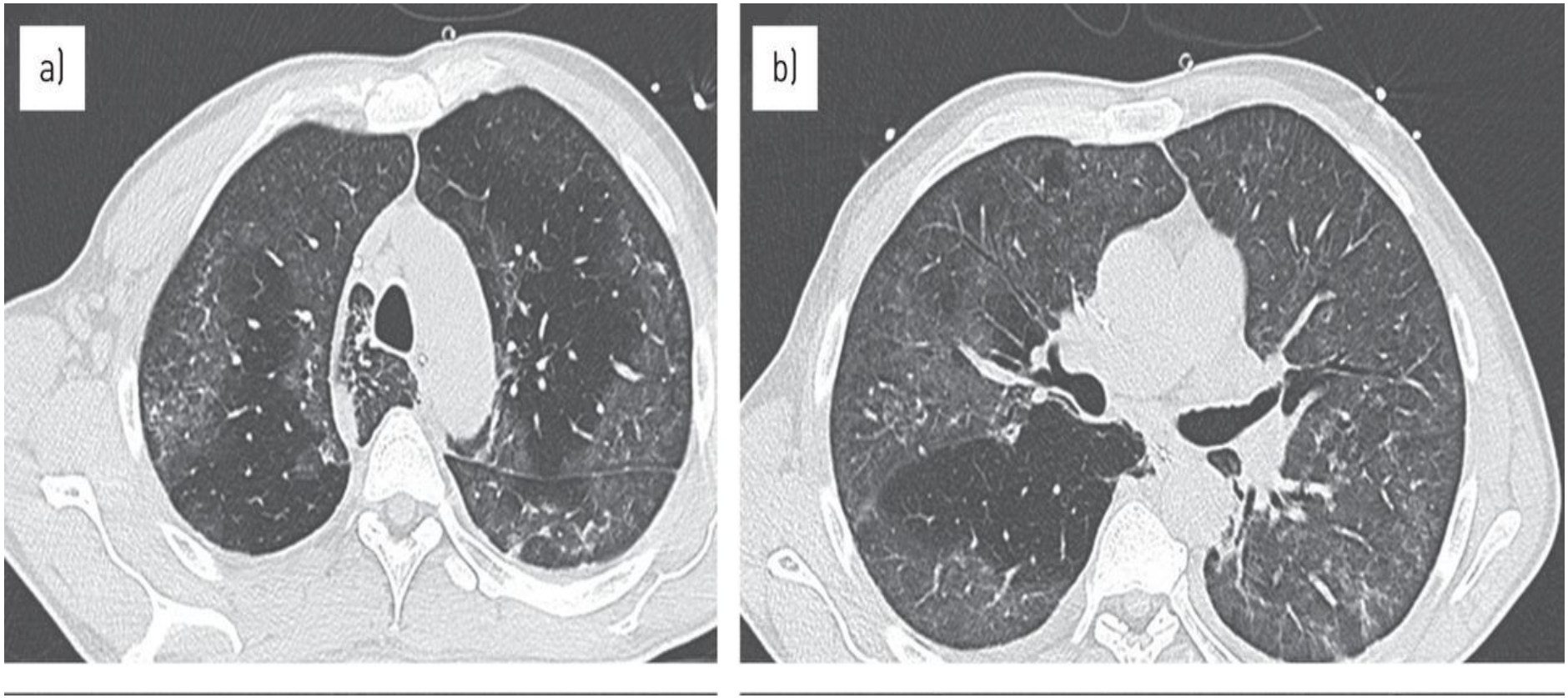
Late diffuse alveolar damage



High power photomicrograph shows changes typical of the proliferative or late stage of diffuse alveolar damage. Although hyaline membranes are still identifiable, the histologic picture is now dominated by thickening and reorganization of interstitial structures due mainly to marked proliferation of mesenchymal spindle cells, including both fibroblasts and myofibroblasts.



Maurizio Zompatori et al. Eur Respir Rev 2014;23:519-530



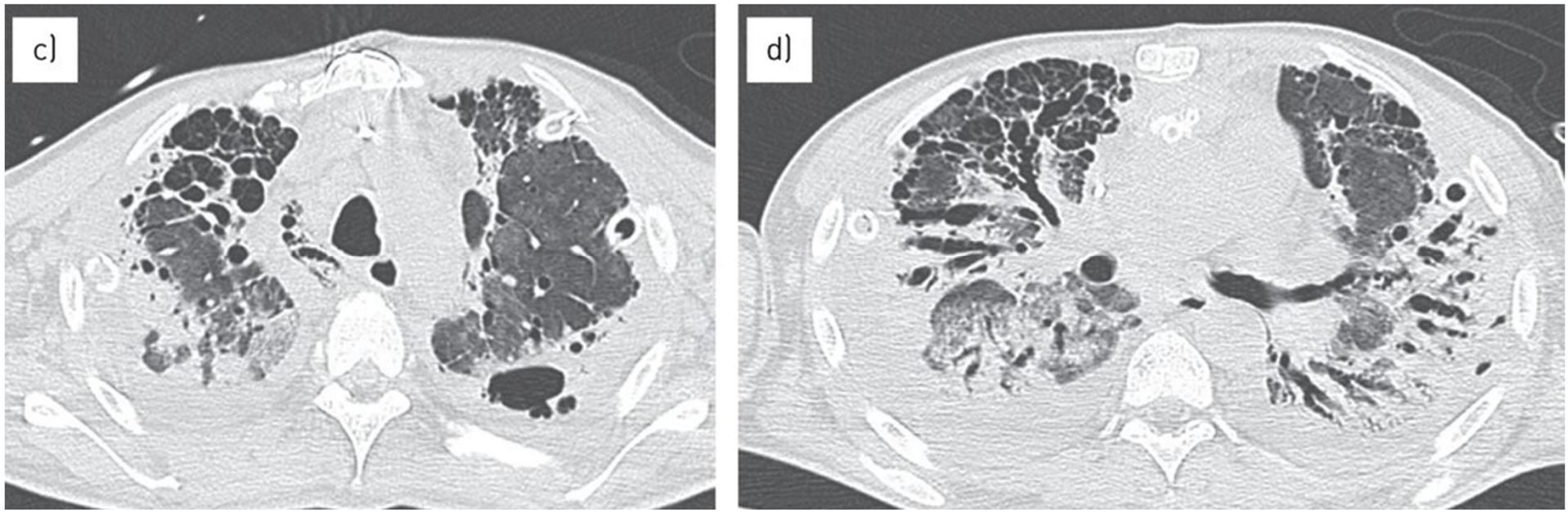
Maurizio Zompatori et al. Eur Respir Rev 2014;23:519-530

Proliferative phase (day 7-21)

- Interstitial myofibroblast reaction
- Lumenal organizing fibrosis
- Paranchymal necrosis
- Type II pneumocyte hyperplasis
- Oblitrative endarteritis
- Macrothrobi
- First sign of resolution
- Most recover rapidly off ventilation

Fibrotic phase (>day 21)

- Fibrotic phase (>day 21)
- Collagenous fibrosis
- Microcystic honey combing
- Traction bronchiectasis
- Arterial toruosity
- Mural fibrosis
- Medial hypertrophy
- Require long –term supporte on mechanical ventilation or supplemental oxygen



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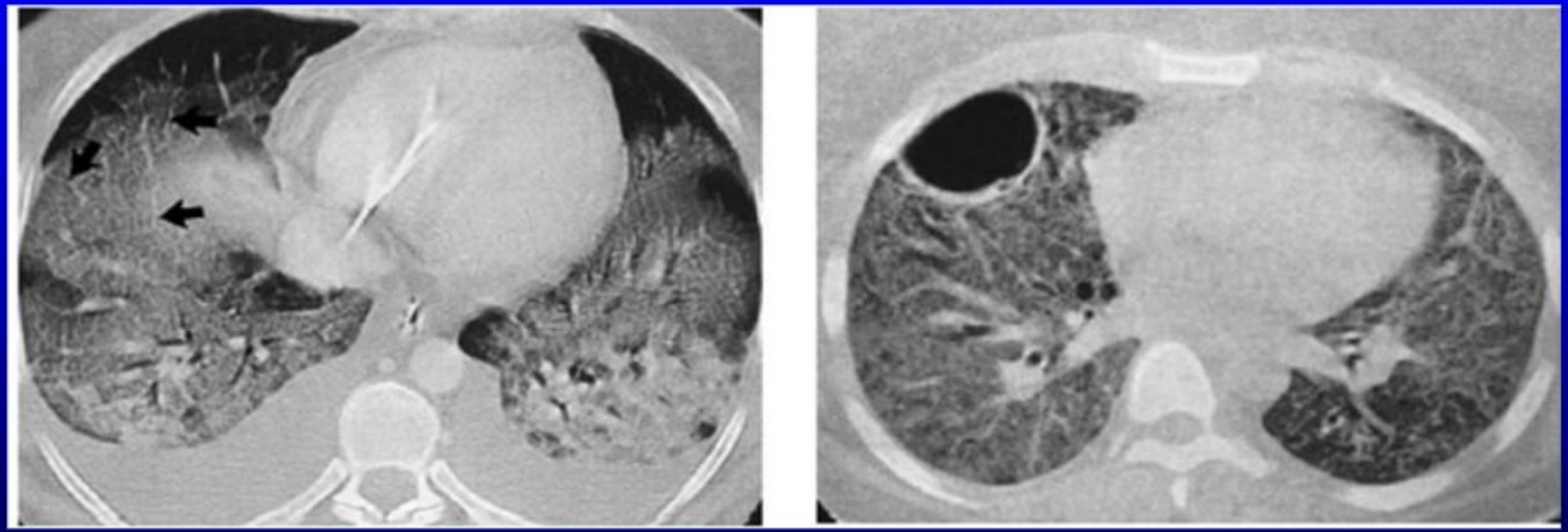
Acute Respiratory Distress Syndrome



Exudative phase

Proliferative phase

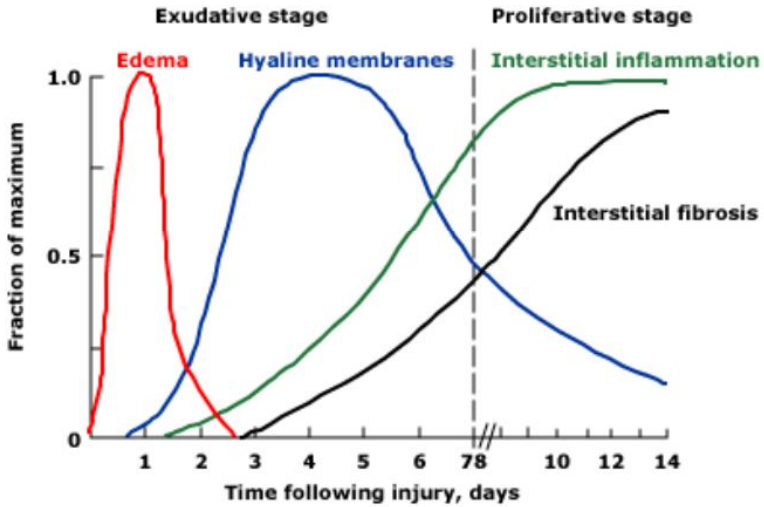
Fibrotic phase

Diffuse alveolar damage

UpToDate

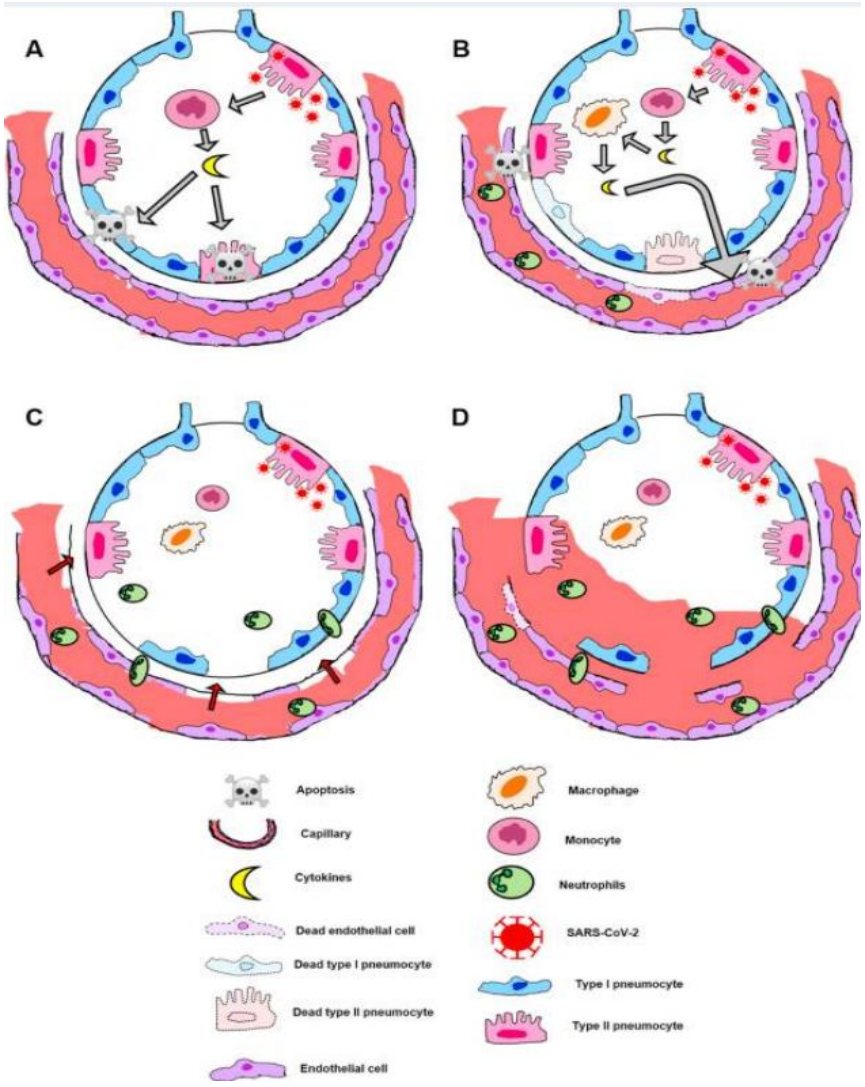
Time course of acute respiratory distress syndrome (ARDS)

Time course of acute respiratory distress syndrome (ARDS)



Schematic representation of the time course of the acute respiratory distress syndrome (ARDS). During the early (or exudative) phase, the lesion is characterized by high permeability pulmonary edema followed by the formation of hyaline membranes. After seven to ten days, a proliferative phase may develop, with marked interstitial inflammation, fibrosis, and disordered healing.

Scheme of SARS-COV-2 inflammatory response. The host's immune system is activated after SARS-CoV-2 binding to ACE2 receptor on type II pneumocyte surface



A - Recruited monocytes secretes pro-inflammatory cytokines, inducing pneumocytes apoptosis

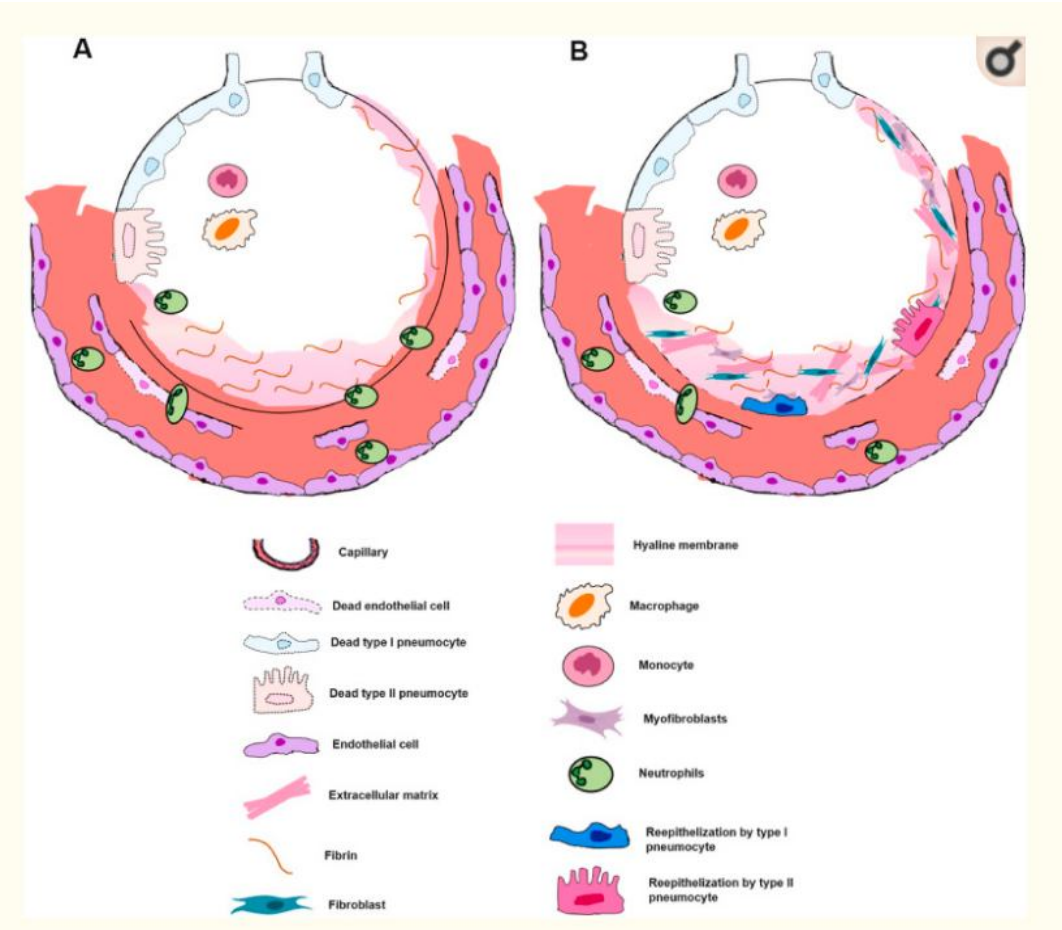
B - Recruited macrophages releases other cytokines causing capillary permeability increase and consequent neutrophils recruitment

C - Neutrophils migrate into the interstitial/alveolar space and degranulate, culminating in permanent damage to pneumocytes and endothelial cells, resulting in alveolar-capillary barrier disruption

D - Interstitial and alveolar edema due to transmigration of blood proteins.

Sabrina et al .Respir Med. 2021

Schematically representation of the two histopathological phases of DAD



A - The first or exudative phase constitutes alveolar edema, neutrophil infiltration in the intra-alveolar space and mainly by hyaline membrane formed by fibrin polymerization contained in the plasma liquid that leaked into the interstitial/alveolar space, being recognized as DAD hallmark

B - The second or proliferative phase is described essentially by an intense fibroblast/myofibroblast recruitment and proliferation, with subsequent extracellular matrix deposition. Over time and together with the fibrotic deposition, there is also the reepithelization by type I and II pneumocytes

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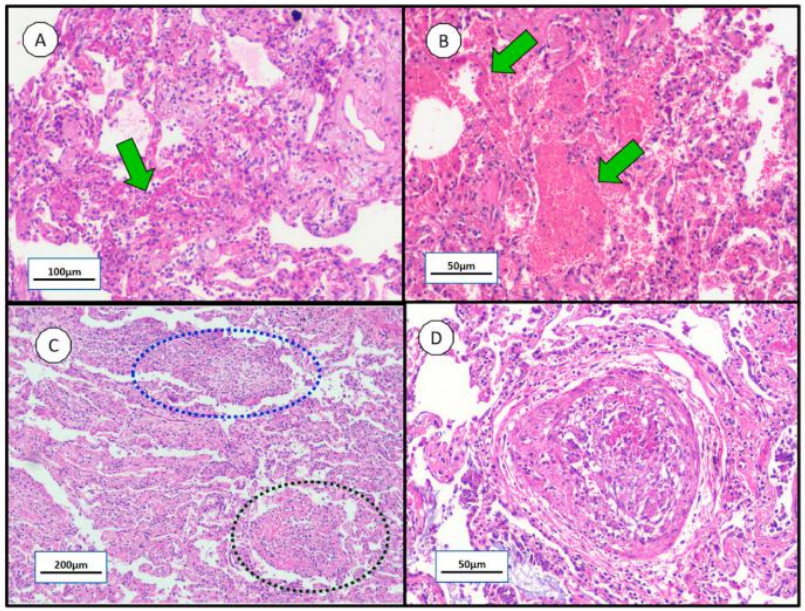
Histopathological findings in COVID-19 lungs by minimally invasive autopsy.



A - alveolar hyaline membrane (green arrow)
B - alveolar-capillary barrier injury with hemorrhage (green arrows)
C - acute fibrinous organizing pneumonia (dark blue circle) and organizing pneumonia (dark green circle)
D - pulmonary intravascular thrombotic events.

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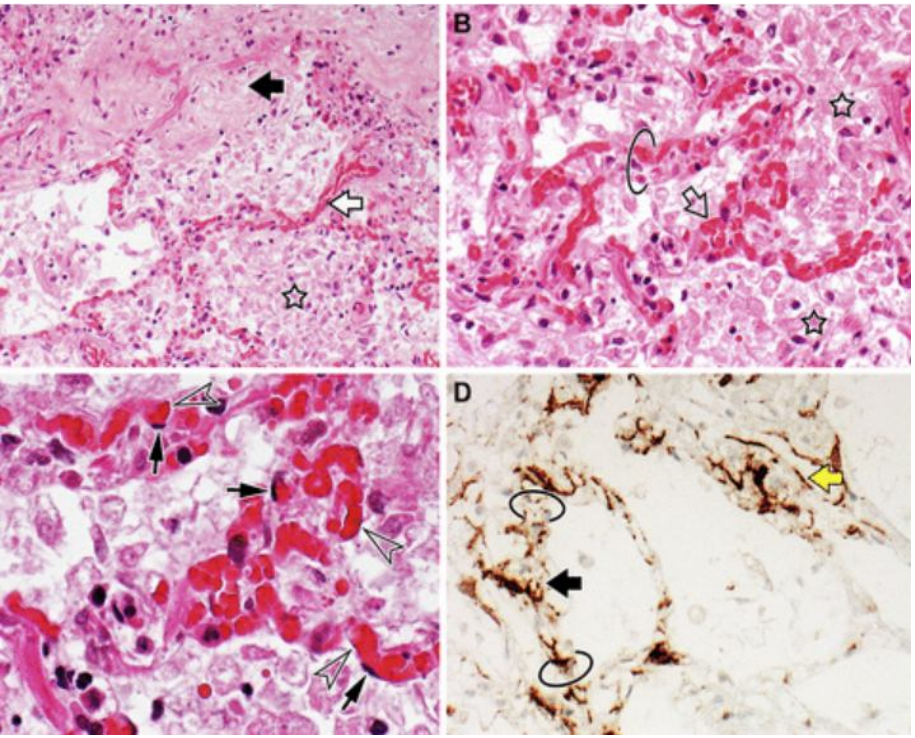


analysis of postmortem lung tissue from patients with COVID-19.

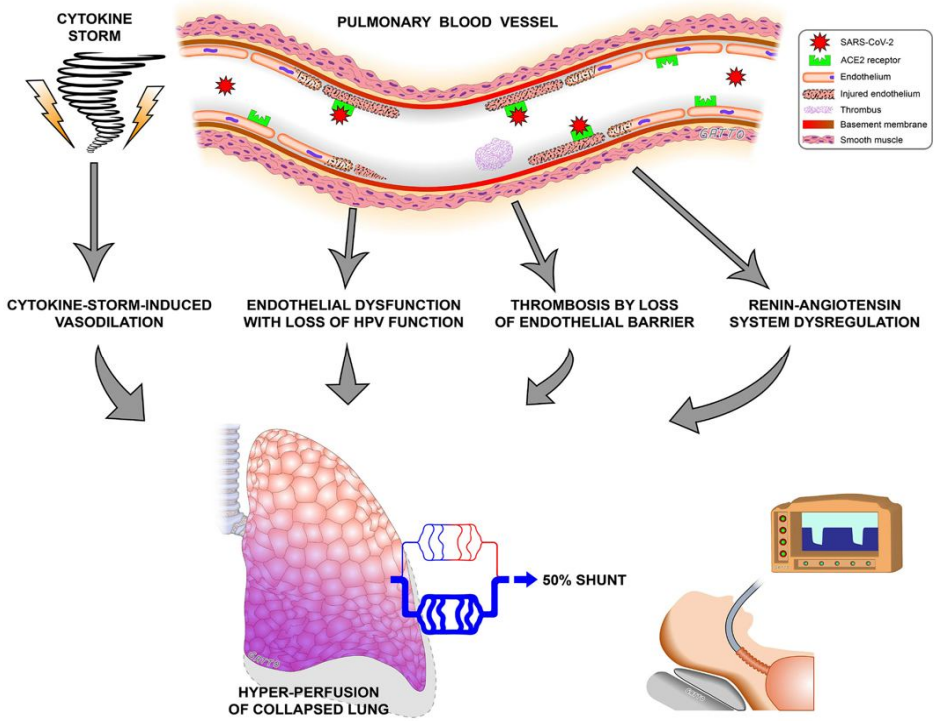
A: Organizing pneumonia pattern of fibrosis (black arrow). Congested alveolar capillaries (white arrow) in area of atelectasis (star) (hematoxylin and eosin ×100)

B: Collapsed alveolar walls (circled) in area of atelectasis (star). Alveolar capillaries show marked congestion (arrow) and are packed with red blood cells (hematoxylin and eosin ×200)

C: Detailed view of alveolar capillaries showing endothelial cell nuclei (arrows) and the presence of cytoplasmic accretions (arrowheads) indicative of endothelial involvement (hematoxylin and eosin ×400)

D: postmortem SARS-CoV-2 lung immunohistochemistry showing alveolar walls (circled) with ACE2 receptor expression in alveolar epithelial cells (black arrow) and endothelial cells (yellow arrow) (immunoperoxidase ×200)

Radiological and pathological studies report increased rates of micro- and macrovascular thrombosis with alveolar capillary microthrombi nine times as prevalent in patients with SARS-CoV-2 versus those with influenza



The mechanisms causing alterations in pulmonary perfusion could be caused by some combination of

1) Renin-angiotensin system dysregulation
2) Thrombosis caused by loss of endothelial barrier
3) Endothelial dysfunction causing loss of hypoxic pulmonary vasoconstriction perfusion control
4) hyperperfusion of collapsed lung tissue

Nader M. Habashi et al. Journal of Applied Physiology 2021

Hypoxia without Lung Collapse

Gattinoni et al. have referred to these phenotypes as SARS-CoV pneumonia type “L” and type “H”

“L”

low elastance, V/Q ratio, lung weight, and recruitability

“H”

High elastance, right to left shunt, lung weight, and recruitability

However, the LUNG-SAFE (Large Observational Study to Understand the Global Impactof Severe Acute Respiratory Failure) and ESICM (European Society of Intensive Care Medicine) Trials Groups have shown that 13% of the mechanically ventilated non-COVID-19 ARDS patients have the type-L phenotype. Other studies have shown that CARDS and ARDSrespiratory mechanics overlap and that standard ventilation strategies apply to these patients.

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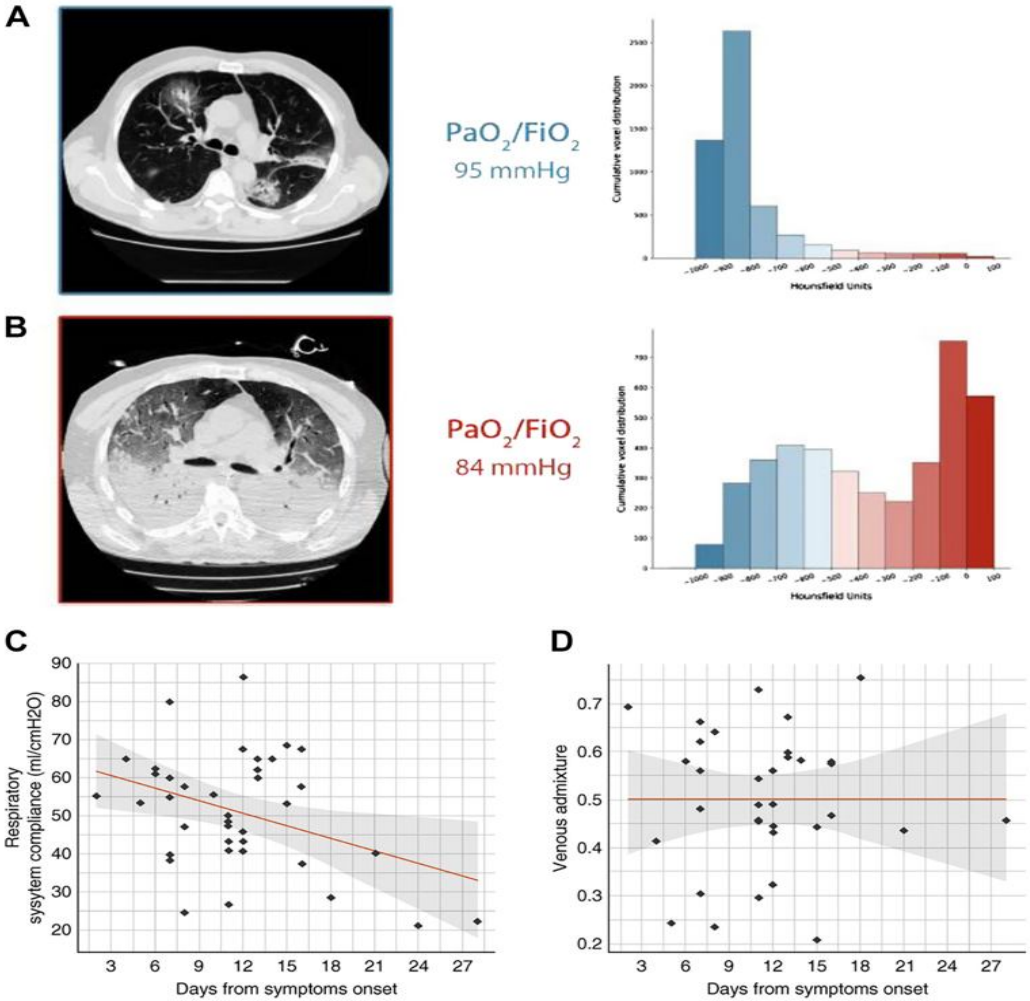

A: CT scan from patients with SARS-CoV-2 during spontaneous breathing. Blue bars are color coded for less dense, and red bars are color coded for denser. FIO2 on a venturi mask was 80% with a PaO2/FIO2 ratio of 95 mmHg

B: CT scan taken on mechanical ventilation at end-expiration with a PEEP of 5 cmH2O. The CT scan is shifted to the right (nonaerated compartment), while the aerated compartments are greatly reduced. FIO2 was 70% with a PaO2/FIO2 ratio of 84 mmHg

C: in a series of 28 patients, there was a strong correlation of a fall in respiratory system compliance with an increase in number of days from symptom onset

D: no correlation between the number of days from symptom onset and venous admixture .

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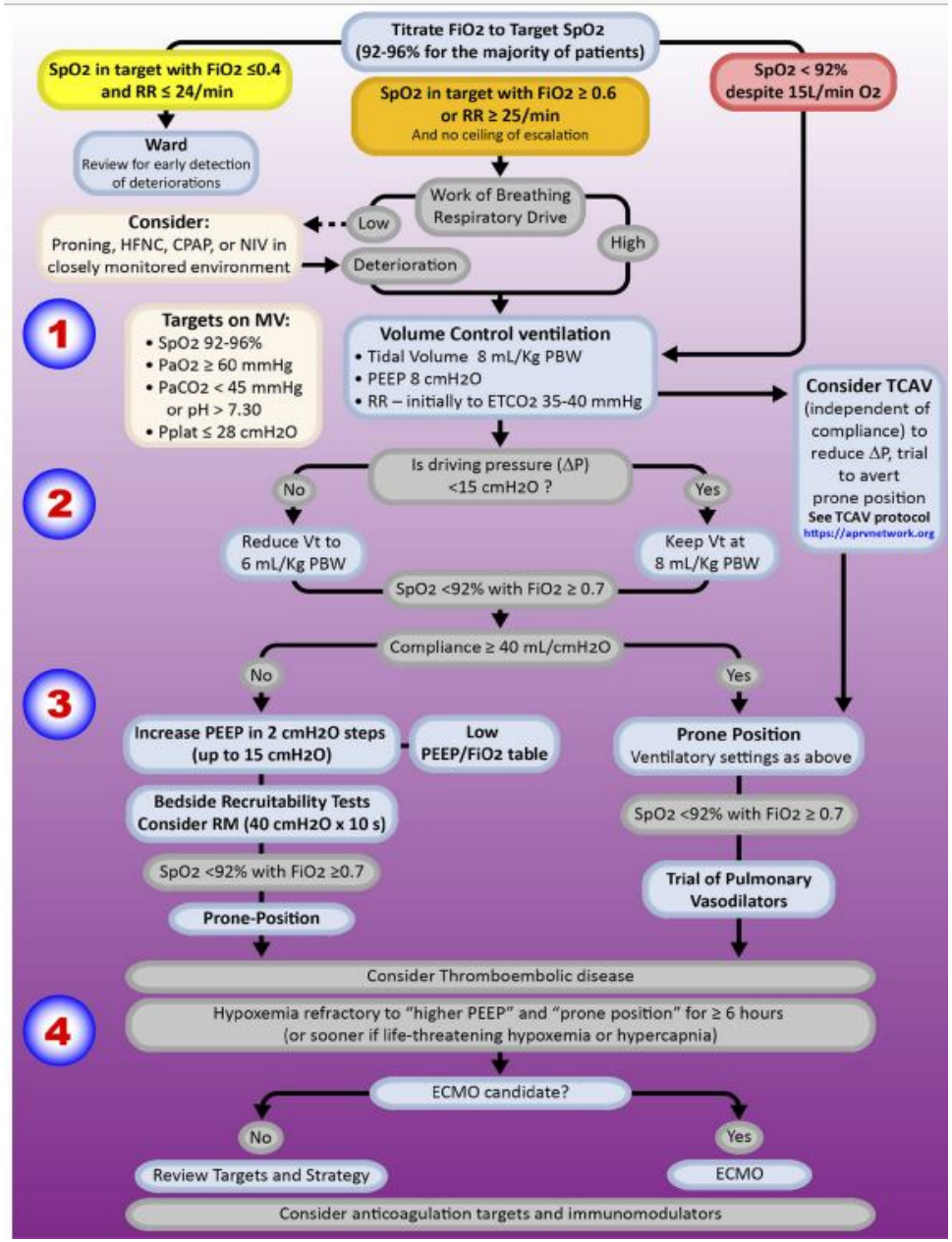
Titrate FiO2 to Target SpO2
(92-96% for the majority of patients)
SpO2 in target with FiO2 ≤0.4 and RR ≤ 24/min
Ward
Review for early detection of deteriorations
SpO2 in target with FiO2 ≥ 0.6 or RR ≥ 25/min
And no ceiling of escalation
SpO2 < 92% despite 15L/min O2
Work of Breathing Respiratory Drive
Low
High
Consider:
Proning, HFNC, CPAP, or NIV in closely monitored environment
Deterioration
1
Targets on MV:
• SpO2 92-96%
• PaO2 ≥ 60 mmHg
• PaCO2 < 45 mmHg or pH > 7.30
• Pplat ≤ 28 cmH2O
Volume Control ventilation
• Tidal Volume 8 mL/Kg PBW
• PEEP 8 cmH2O
• RR – initially to ETCO2 35-40 mmHg
Consider TCAV (independent of compliance) to reduce ΔP, trial to avert prone position
See TCAV protocol
https://aprvnetwork.org
2
Is driving pressure (ΔP) <15 cmH2O ?
No
Yes
Reduce Vt to 6 mL/Kg PBW
Keep Vt at 8 mL/Kg PBW
SpO2 <92% with FiO2 ≥ 0.7
Compliance ≥ 40 mL/cmH2O
3
No
Yes
Increase PEEP in 2 cmH2O steps (up to 15 cmH2O)
Low PEEP/FiO2 table
Prone Position
Ventilatory settings as above
Bedside Recruitability Tests
Consider RM (40 cmH2O x 10 s)
SpO2 <92% with FiO2 ≥0.7
Prone-Position
SpO2 <92% with FiO2 ≥ 0.7
Trial of Pulmonary Vasodilators
Consider Thromboembolic disease
4
Hypoxemia refractory to "higher PEEP" and "prone position" for ≥ 6 hours
(or sooner if life-threatening hypoxemia or hypercapnia)
ECMO candidate?
No
Yes
Review Targets and Strategy
ECMO
Consider anticoagulation targets and immunomodulators

با تشکر