HARRISON

EDITION 22nd

CRITICAL CARE MEDICINE

Critical Care Medicine

Acute Respiratory Distress Syndrome	Completed
Mechanical Ventilatory Support	Completed
Approach To The Patient With Shock	Completed
Sepsis And Septic Shock	Completed
Cardiogenic Shock And Pulmonary Edema	Completed
Cardiovascular Collapse, Cardiac Arrest And Sudden Cardiac Death	Completed
Nervous System Disorders In Critical Care	Completed

NEET SS Critical Care Medicine Part 1

Acute Respiratory Distress Syndrome (ARDS)

- **Definition**
- A clinical syndrome of severe dyspnea, hypoxemia, and diffuse pulmonary infiltrates leading to **respiratory failure**.
- Caused by diffuse lung injury from medical or surgical disorders.

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TABLE 312-1 Clinical Disorders Commonly Associated with ARDS

DIRECT LUNG INJURY	INDIRECT LUNG INJURY
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma
Pulmonary contusion	Multiple bone fractures
Near-drowning	Flail chest
Toxic inhalation injury	Head trauma
	Burns
	Multiple transfusions
	Drug overdose
	Pancreatitis
	Postcardiopulmonary bypass

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- **Epidemiology**
- Pre-COVID: ~60 cases per 100,000 population annually.
- ICU incidence: ~10% of all ICU admissions.
- Mortality: 30–40% (varies with severity, comorbidities, and management).

TABLE 312-2 Diagnostic Criteria for ARDS Based on 2012 Berlin Criteria

SEVERITY: OXYGENATION[a]	ONSET	CHEST RADIOGRAPH[b]	ABSENCE OF LEFT ATRIAL HYPERTENSION
Mild: 200 mmHg < Pao_2/Fio_2 ≤300 mmHg Moderate: 100 mmHg < Pao_2/Fio_2 ≤200 mmHg Severe: Pao_2/Fio_2 ≤100 mmHg	Acute: Within 1 week of a clinical insult or new or worsening respiratory symptoms	Bilateral opacities consistent with pulmonary edema not fully explained by effusions, lobar/lung collapse, or nodules	Hydrostatic edema is not the primary cause of respiratory failure. If no ARDS risk factor is present, then some objective evaluation is required (e.g., echocardiography) to rule out hydrostatic edema

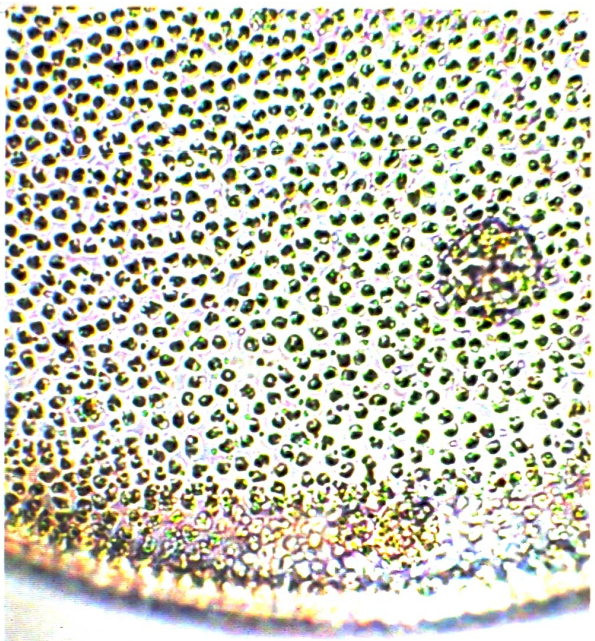
[a]As assessed on at least 5 cmH_2O of positive end-expiratory pressure (PEEP). 2023 proposed updates to the Berlin criteria include: (1) consideration of ARDS in nonintubated patients using Pao_2/Fio_2 ≤300 mmHg or Spo_2/Fio_2 (S/F) ≤315 mmHg (if Spo_2 ≤97% as measured by pulse oximetry) on high-flow nasal oxygen with flow of ≥30 L/min or noninvasive ventilation/continuous positive airway pressure with at least 5 cmH_2O of PEEP; (2) addition of S/F ratios to consideration of ARDS in intubated patients (mild: 235 < Spo_2/Fio_2 ≤ 315 mmHg; moderate: 148 < Spo_2/Fio_2 ≤ 235 mmHg; severe: Spo_2/Fio_2 ≤148 mmHg [if Spo_2 ≤97%]); and (3) consideration of ARDS in resource-limited settings if Spo_2/Fio_2 ≤ 315 mmHg (if Spo_2 ≤97%) without requirement for PEEP, minimum oxygen flow rate, or specific respiratory support devices. It should be noted that pulse oximetry may overestimate the oxygen saturation in patients with darker skin tones, such that correlation with Pao_2 should be considered when feasible. [b]The 2023 proposed update to the Berlin criteria permits ultrasound as an alternative imaging modality, especially in resource-limited settings.

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- **Diagnostic Criteria (Berlin Definition, 2012)**
- **All 4 must be present:**
- **Timing**: Within 1 week of known insult or new/worsening respiratory symptoms.
- **Chest Imaging**: Bilateral opacities on CXR/CT not fully explained by effusions, collapse, or nodules.
- **Origin of Edema**: Respiratory failure not fully explained by cardiac failure or fluid overload (rule out hydrostatic edema).
- **Oxygenation (PaO_2/FiO_2 ratio with PEEP ≥5 cm H_2O)**
  - Mild: 200–300
  - Moderate: 100–200
  - Severe: <100

- **Pathophysiology & Phases**

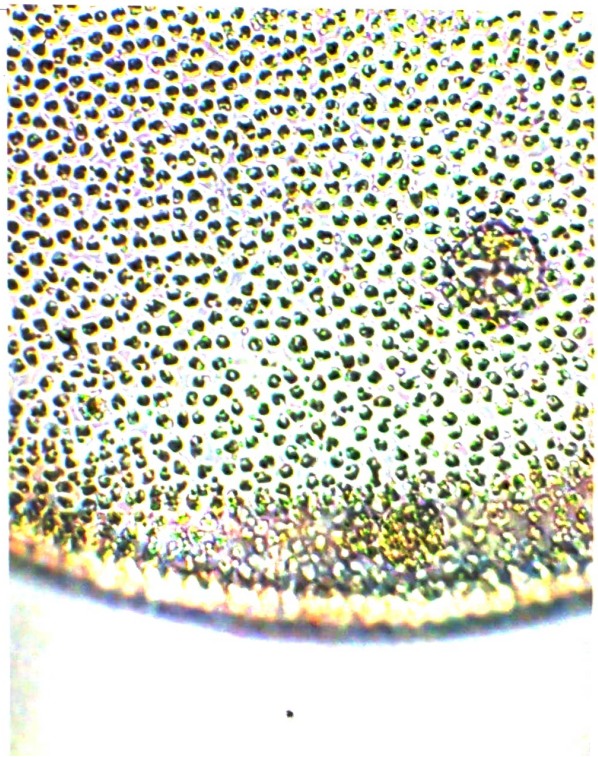
- **1. Exudative Phase (Acute Phase)**
- **Timing**
- First **7 days** after precipitating insult (often onset within **12–36 h**, but can be delayed up to 5–7 days).
- **Pathology & Pathophysiology**
- **Injury to alveolar–capillary barrier** → loss of tight junction integrity.
- **Alveolar type I epithelial cells + capillary endothelial cells** damaged.
- **Protein-rich edema fluid** accumulates in interstitial and alveolar spaces.



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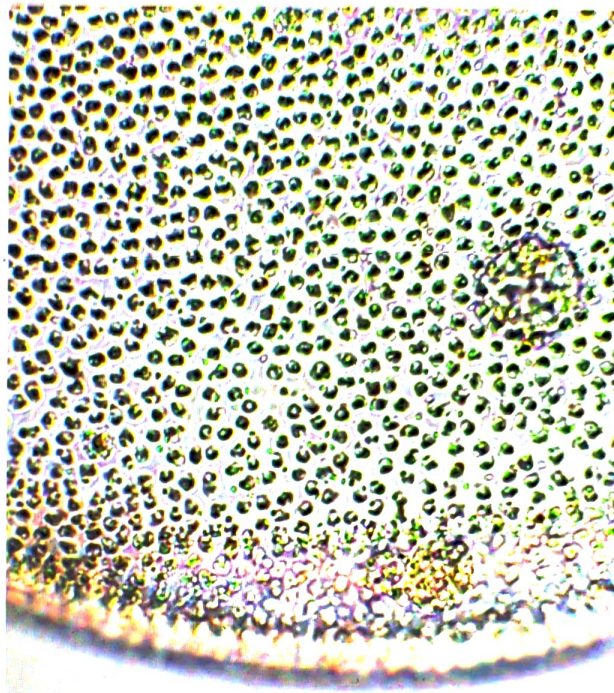
- **Pathophysiology & Phases**

- **Inflammatory mediators:** ↑ IL-1, IL-6, IL-8, TNF-α, leukotriene B4.
- Recruitment of **neutrophils** → further tissue damage.
- **Hyaline membrane formation** (plasma proteins + cell debris + inactivated surfactant).
- **Pulmonary vascular injury**: microthrombi, endothelial damage, fibrocellular proliferation.



- **Pathophysiology & Phases**

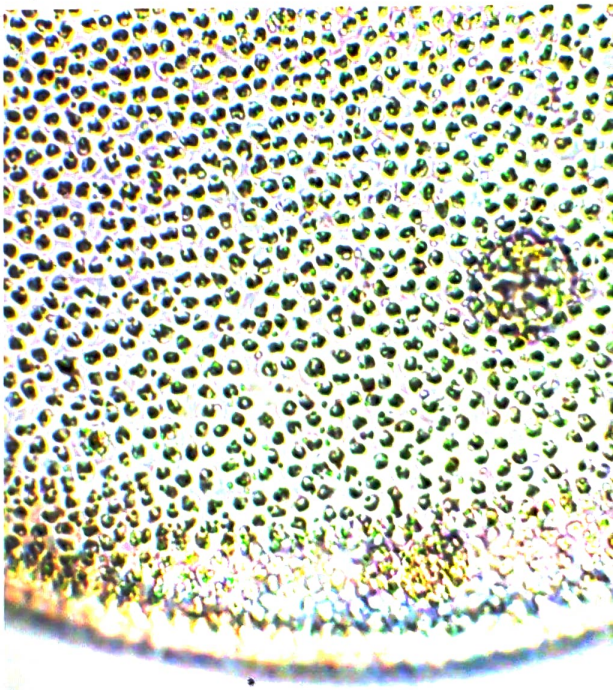
- Edema & collapse → ↓ **lung compliance**.
- **Dependent lung zones** most affected (gravity-dependent consolidation).
- **Intrapulmonary shunting** → severe **refractory hypoxemia**.
- **Microvascular occlusion** → ↑ dead space, pulmonary vascular resistance, pulmonary hypertension.
- Both **hypoxemia + hypercapnia** may be present.
- **Clinical Features**
- Rapid onset **dyspnea, tachypnea, ↑ work of breathing**.
- Respiratory fatigue → respiratory failure.



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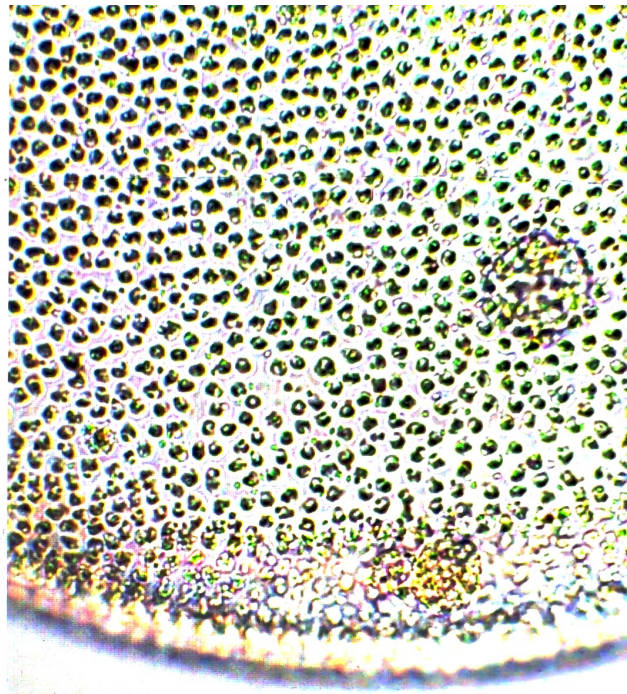
- **Pathophysiology & Phases**

- CXR: **bilateral opacities** involving ≥ 3/4 of lung fields.
  - Resembles pulmonary edema but **without cardiomegaly, pleural effusions, or vascular redistribution**.
- CT: **bilateral, heterogeneous infiltrates** ("patchy involvement").



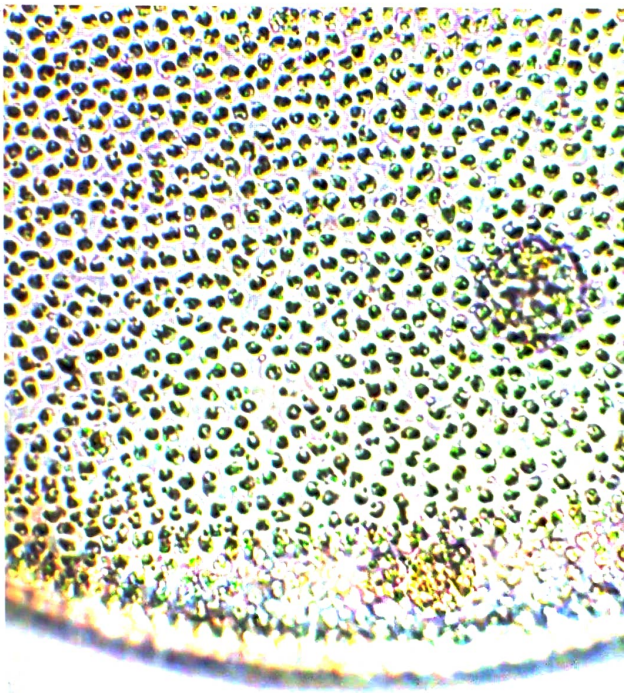
- **Pathophysiology & Phases**

- **Differential Diagnosis**
- Cardiogenic pulmonary edema.
- Bilateral pneumonia.
- Alveolar hemorrhage.
- Others: acute interstitial pneumonitis, hypersensitivity pneumonitis, radiation pneumonitis, neurogenic pulmonary edema.

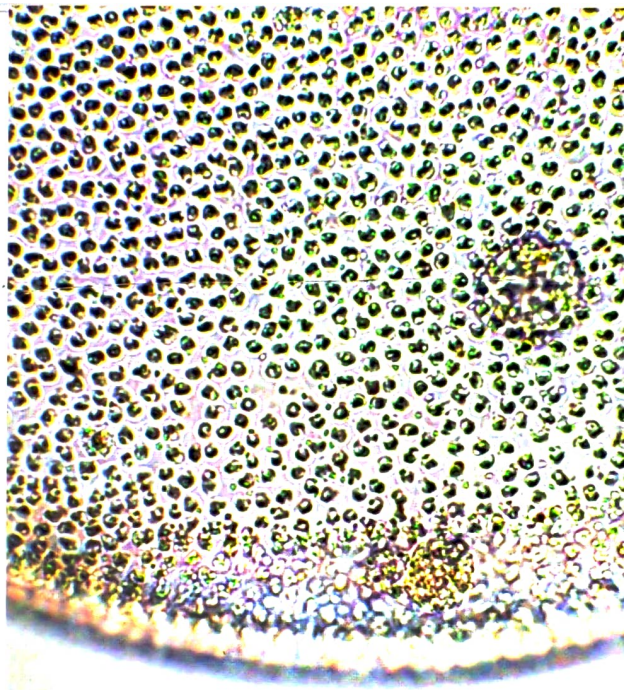


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- **2. Proliferative Phase**
- **Timing**
- Usually **Day 7–21**.
- **Pathology**
- Some patients improve rapidly; others develop **progressive lung injury**.
- **Early fibrosis** can develop in this phase.



- Histologic signs of **resolution**:
  - Resorption of alveolar edema.
  - Proliferation of **type II pneumocytes** (to replace lost type I cells).
  - Infiltration of fibroblasts → early collagen deposition.
- **Clinical Features**
- Dyspnea, tachypnea, persistent hypoxemia may continue.
- Some patients start to **wean from ventilatory support**, others progress to fibrosis.

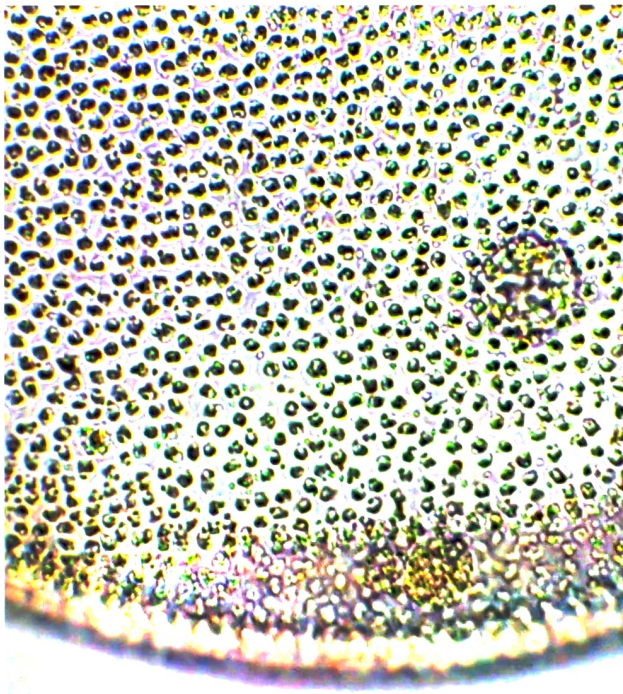


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- **Pathophysiology & Phases**

3. Fibrotic Phase (Late/Chronic Phase)

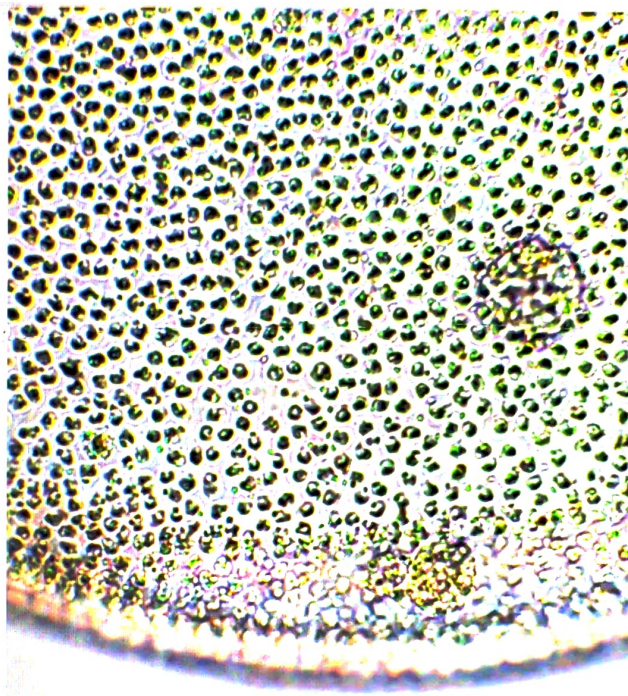
- **Timing:** After **3–4 weeks** in unresolved ARDS.
- **Pathology & Mechanism:**
- Alveolar edema/exudates convert to **interstitial and alveolar duct fibrosis.**
- **Disruption of acinar architecture** → emphysema-like bullae.



- **Pathophysiology & Phases**

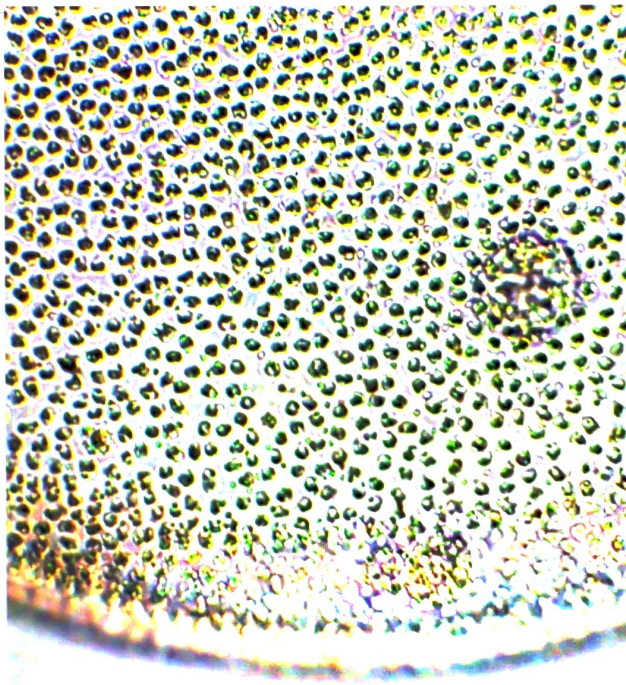
Pulmonary vascular changes: intimal fibroproliferation → vascular occlusion → pulmonary hypertension.

- **Clinical/Physiologic Consequences:**
- ↓ **lung compliance** → stiff lungs.
- ↑ **pulmonary dead space** → hypercapnia.
- ↑ **risk of pneumothorax** (due to bullae + mechanical ventilation).



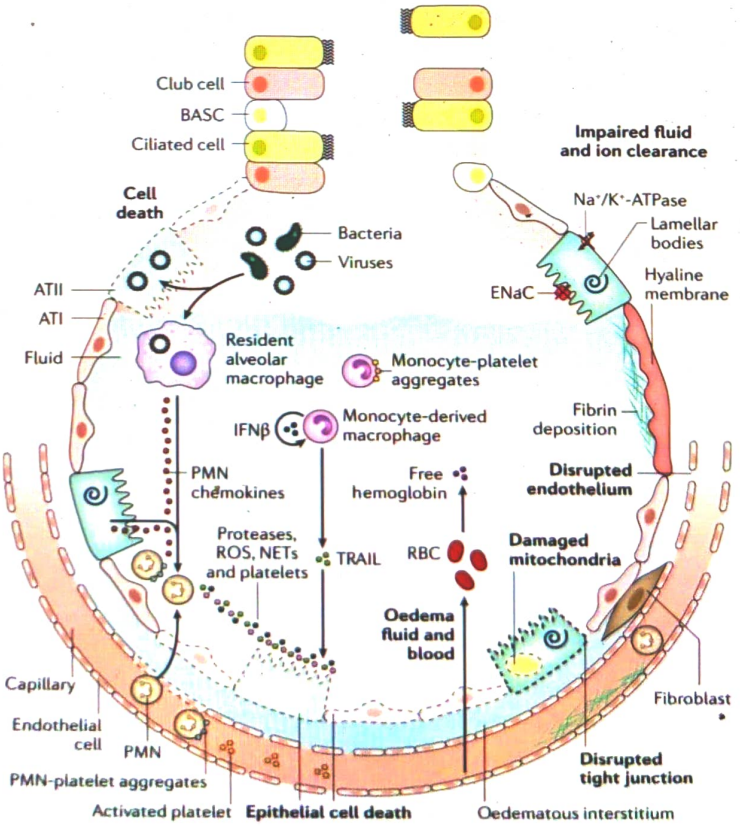
- **Pathophysiology & Phases**

- Persistent need for **mechanical ventilation or oxygen therapy.**
- Lung biopsy evidence of fibrosis → **poor prognosis, higher mortality.**



Clinical Features

- Rapid onset **dyspnea, tachypnea, hypoxemia** not corrected by O_2.
- Bilateral diffuse infiltrates on imaging.
- Severe cases: respiratory acidosis, multi-organ failure (esp. with sepsis).



Pathogenesis of ARDS

1. Initiating Insults

- **Direct injury:** bacteria, viruses, gastric aspiration, toxins, mechanical stretch (ventilator-induced).
- **Indirect injury:** sepsis, trauma, pancreatitis → systemic inflammation affecting the lung.
- These trigger **alveolar epithelial cell (esp. Type II pneumocyte) and resident macrophage activation**.

2. Immune Cell Recruitment & Inflammatory Cascade

- **Toll-like receptor (TLR) activation** on alveolar type II (ATII) cells and macrophages → release of **chemokines**.
- **Chemokines recruit neutrophils, monocytes, and platelets** into alveolar spaces and capillaries.

3. Neutrophil-Mediated Injury

- Neutrophils migrate across injured epithelium.
- They release:
  - **Proteases** → degrade epithelial and endothelial integrity.
  - **Reactive oxygen species (ROS)** → oxidative damage.
  - **Neutrophil extracellular traps (NETs)** → capture pathogens but worsen tissue injury.
- Result → **epithelial + endothelial barrier damage**.

4. Monocyte-Mediated Injury

- Monocytes enter alveoli and:
  - Release **TRAIL (TNF-related apoptosis-inducing ligand)** via **IFN-β–dependent pathways**.
  - Induce **epithelial apoptosis** → loss of alveolar lining.

5. Platelet Interactions

Platelets aggregate with neutrophils and monocytes.

Promote NET formation and further inflammation.

Microthrombi formation worsens microcirculation and gas exchange.

6. Red Blood Cell Contribution

RBCs release **cell-free hemoglobin**.

Hemoglobin catalyzes oxidant reactions → amplifies endothelial/epithelial injury.

7. Direct Epithelial Injury

Bacterial toxins (pore-forming toxins).

Mechanical stretch injury from ventilation (VILI).

Mitochondrial dysfunction in alveolar cells.

Result: **plasma membrane disruption** → barrier failure.

8. Consequences of Barrier Injury

Increased alveolar–capillary permeability → leak of proteins, RBCs, and edematous fluid into alveoli.

Airspace flooding → severe **hypoxemia** (shunt physiology).

Alveolar edema → reduced lung compliance.

Vascular injury + alveolar edema → ↓ CO_2 clearance → **hypercapnia**.

9. Vicious Cycle of Edema & Gas Exchange Failure

Hypoxemia and hypercapnia impair **sodium transport** (via ENaC channels).

This reduces alveolar edema clearance → **persistent fluid-filled alveoli**.

Leads to worsening oxygenation and mechanical ventilation requirement.

10. Cellular Players Summary

ATI (Type I cells): structural support, destroyed in ARDS.

ATII (Type II cells): surfactant production + regeneration, but injured and dysfunctional.

BASC (bronchioalveolar stem cells): potential for repair, impaired in ARDS.

Macrophages & PMNs: drive inflammation and tissue damage.

Platelets: microthrombi + immune amplification.

Key Clinical Correlates

Hypoxemia → from shunt physiology (alveoli filled with fluid, not ventilated).

Hypercapnia → from ↑ dead space and impaired clearance.

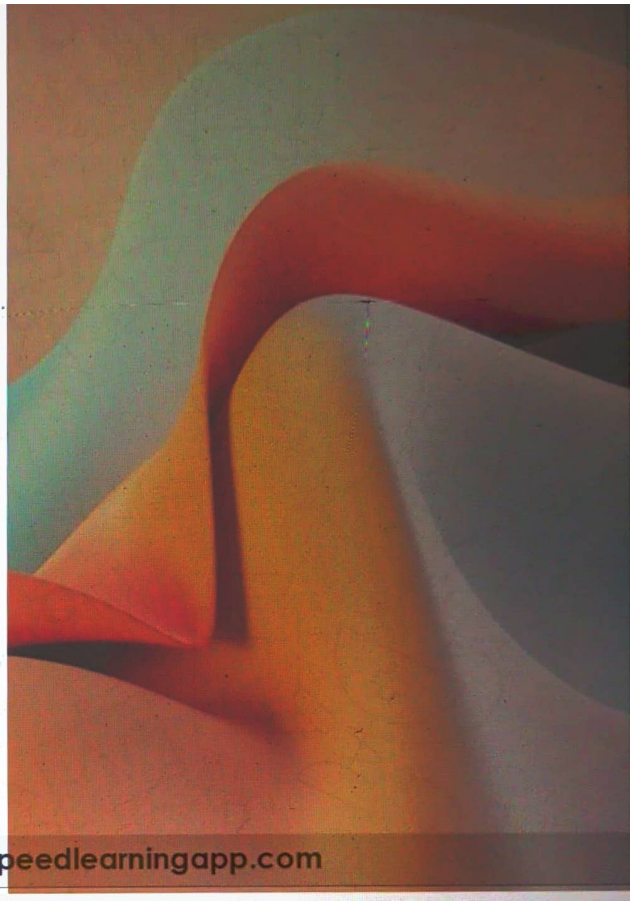
Refractory hypoxemia + hypercapnia → hallmark of ARDS needing advanced ventilatory support.

Clinical Features

- Rapid onset **dyspnea, tachypnea, hypoxemia** not corrected by O_2.
- Bilateral diffuse infiltrates on imaging.
- Severe cases: respiratory acidosis, multi-organ failure (esp. with sepsis).

Treatment of ARDS

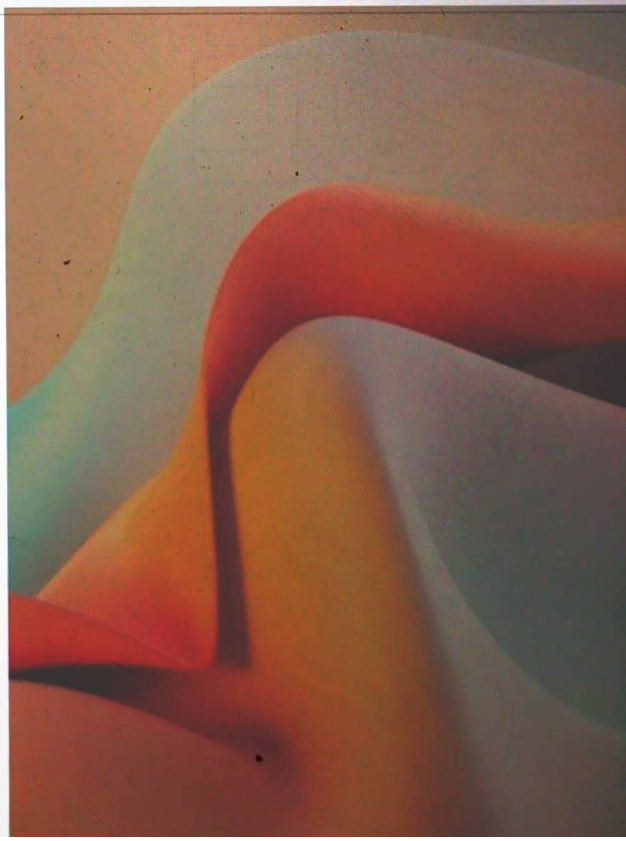
- **General Principles**
- Mortality reduction in ARDS is due to **advances in ICU supportive care** rather than a single curative therapy.
- Five key aspects:
  - Recognition and treatment of **underlying disorder** (e.g., pneumonia, sepsis, aspiration, trauma).
  - Minimize **unnecessary procedures** & ICU complications.



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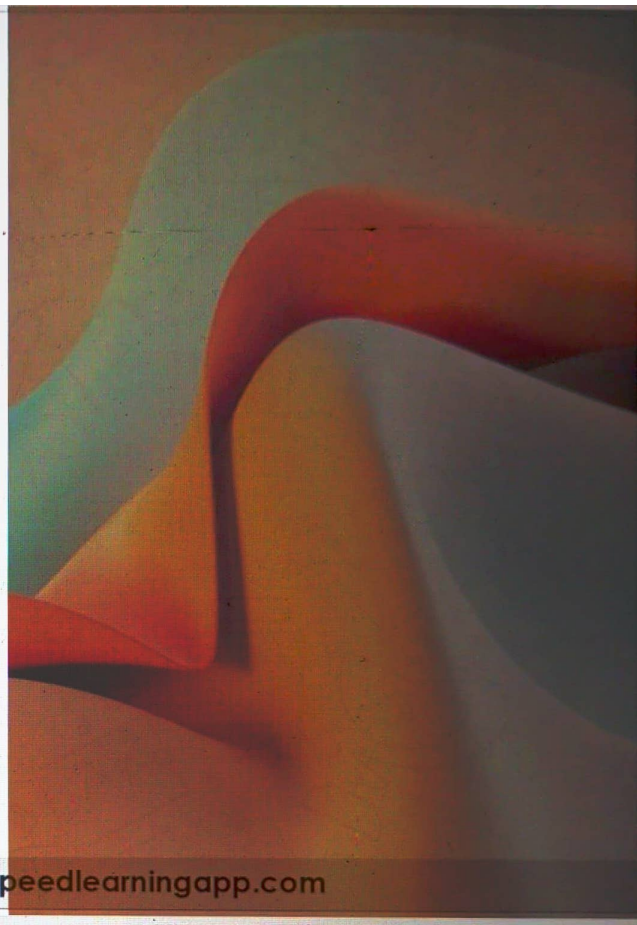
Treatment of ARDS

- Use **bundled care**: prophylaxis against VTE, GI bleed, stress ulcers; early enteral nutrition; prevent nosocomial infections.
- Avoid **iatrogenic injury** (e.g., ventilator-induced, fluid overload).
- Early provision of **enteral nutrition** when feasible.



Treatment of ARDS

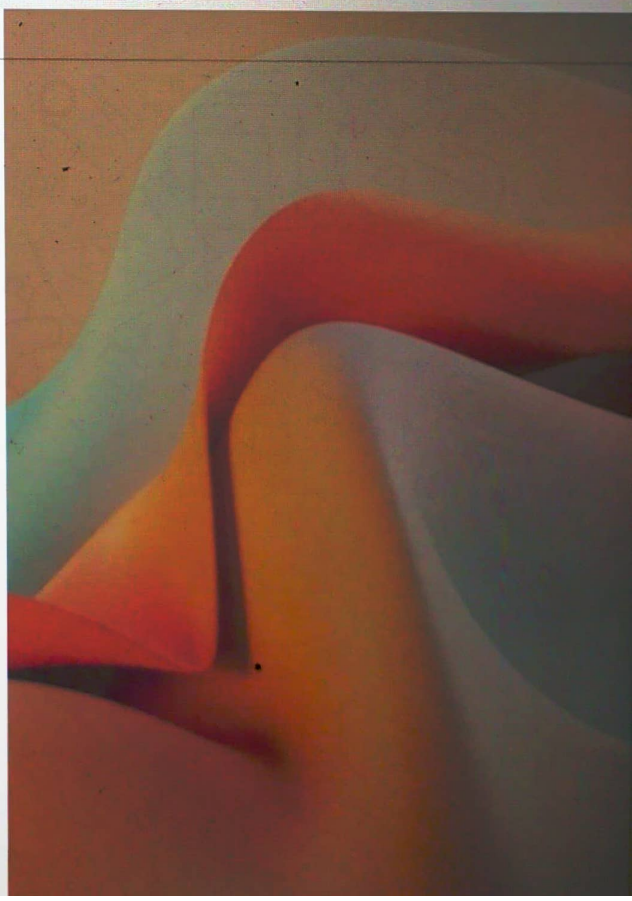
- **Mechanical Ventilation: Cornerstone of ARDS Management**
- **1. Low Tidal Volume Ventilation (Lung Protective Strategy)**
- **Target:** 6 mL/kg predicted body weight.
- Maintain **plateau pressure ≤30 cm H_2O**.
- Reduces volutrauma, barotrauma, atelectrauma.
- Mortality benefit shown in ARDS Network trial.



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Treatment of ARDS

- **2. PEEP (Positive End-Expiratory Pressure)**
- Prevents alveolar collapse (atelectrauma).
- Improves oxygenation by recruiting alveoli.
- **Individualised titration** needed:
  - Too low → derecruitment, hypoxemia.
  - Too high → overdistension, ↓ venous return, hypotension.
- Strategies: PEEP-FiO_2 tables, or esophageal pressure monitoring to optimize transpulmonary pressure.



Treatment of ARDS

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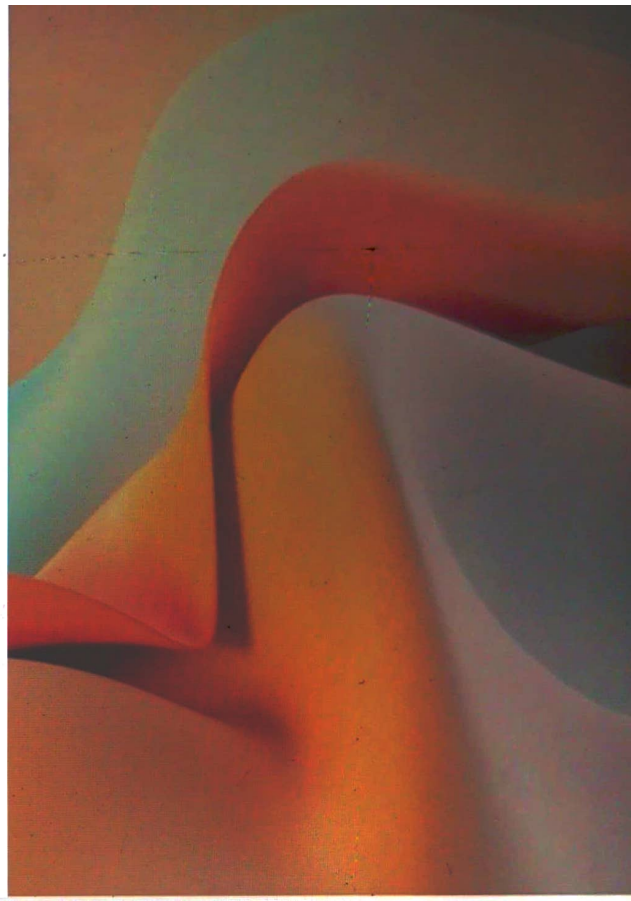
Treatment of ARDS

3. Prone Positioning

- Shown to improve survival in **moderate–severe ARDS** (PaO_2/FiO_2 <150).
- Duration: **≥16 h/day**.
- Improves V/Q matching, oxygenation, lung homogeneity.
- Requires trained team → risk of dislodging tubes/lines if not careful.



Treatment of ARDS



4. Other Ventilation Strategies

- **Recruitment maneuvers:** transient ↑ airway pressures to reopen alveoli. Can improve oxygenation but no consistent survival benefit.
- **Alternative modes:** High-frequency oscillatory ventilation (HFOV), airway pressure release ventilation (APRV) → not proven superior to conventional ventilation.
- **ECMO (Extracorporeal Membrane Oxygenation):** Rescue therapy in refractory hypoxemia (PaO_2/FiO_2 <80 despite optimal care).

Adjunctive Therapies

Fluid Management

- ARDS = leaky capillaries → risk of worsening pulmonary edema.
- Conservative fluid strategy (after hemodynamic stabilization):
- Improves lung mechanics.
- Decreases ventilator days & ICU stay.
- Avoid aggressive fluid resuscitation once shock is stabilized.

Neuromuscular Blockade

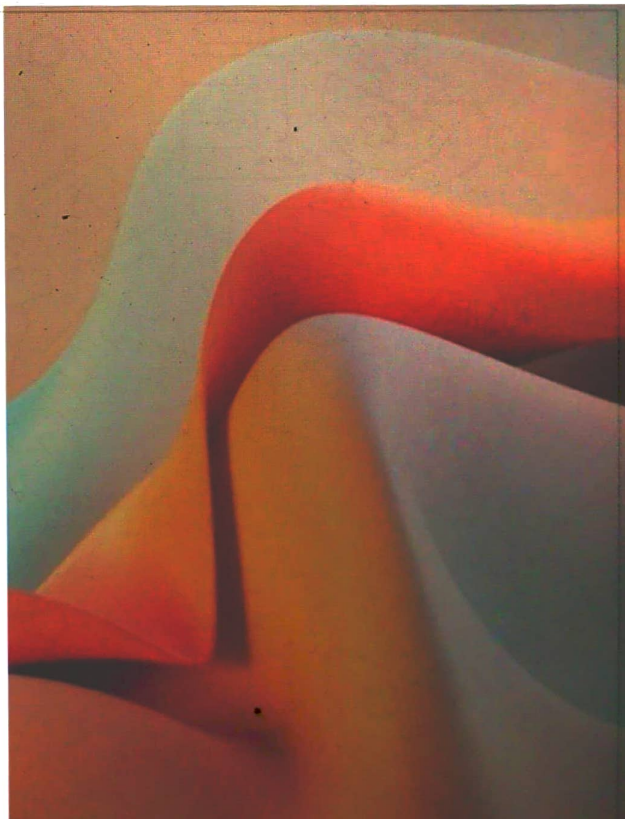
- Short course (e.g., cisatracurium 48h) in early severe ARDS:
- Improves ventilator synchrony.
- Reduces oxygen consumption, risk of barotrauma.
- No consistent mortality benefit in all studies.

Key Goals & Limits in Ventilation

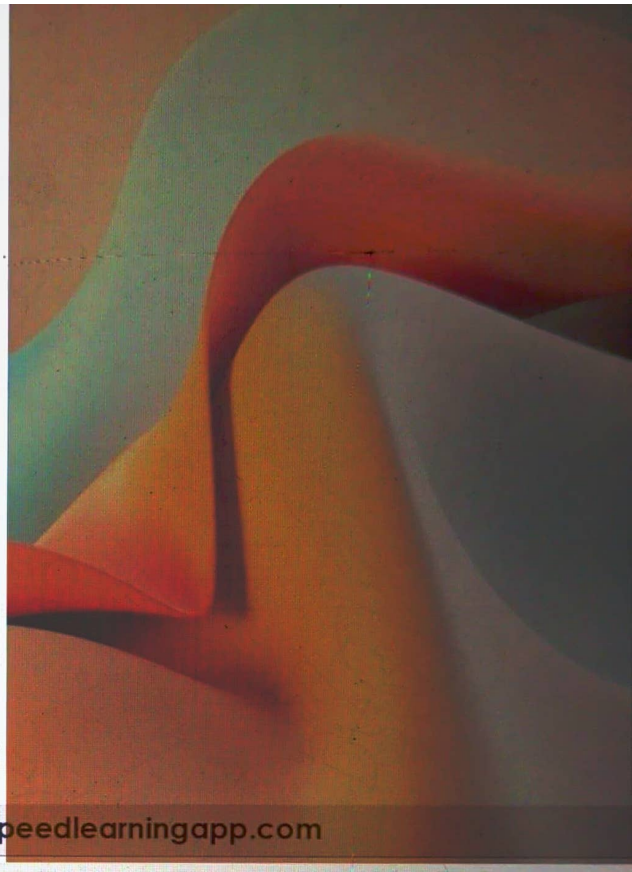
- Tidal volume: 6 mL/kg predicted body weight.
- Plateau pressure: ≤30 cm H_2O.
- Respiratory rate: ≤35/min (adjust for permissive hypercapnia if tolerated).
- Maintain adequate oxygenation: PaO_2 55–80 mmHg or SpO_2 88–95%.

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- **Adjunct Therapies in ARDS**
- **Glucocorticoids**
- Aim: reduce pulmonary inflammation.
- Evidence: mixed, no consistent mortality benefit.
- Routine use **not supported**.
- Possible role:
  - Low-dose hydrocortisone in septic shock + ARDS.
  - Patients with community-acquired pneumonia with ARDS.

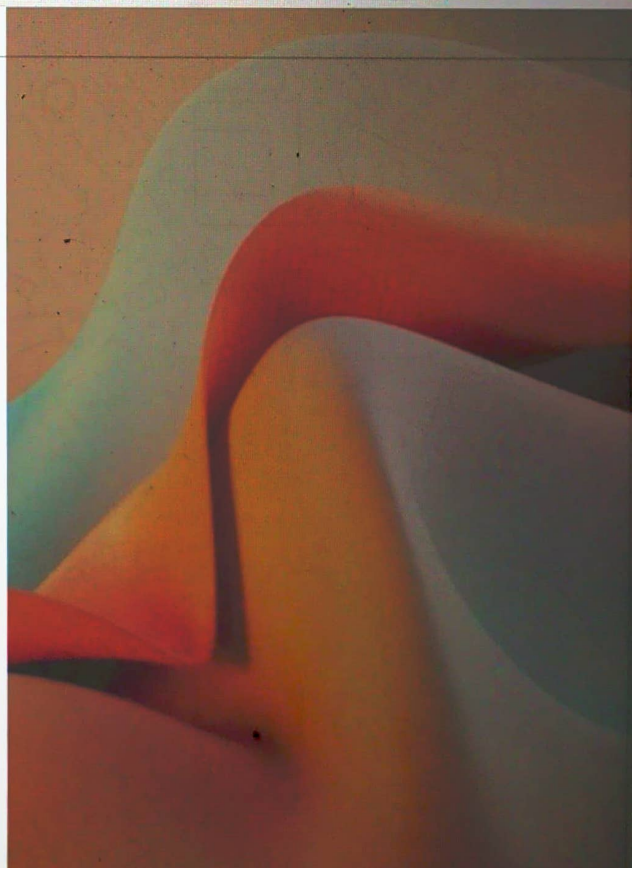


- **Other Therapies**
- **Inhaled vasodilators (NO, prostacyclin):**
  - Transiently improve oxygenation.
  - No proven mortality benefit.
- **Surfactant replacement, anti-inflammatory drugs (NSAIDs, ketoconazole, prostaglandins):**
  - No clear benefit.
- **Routine ECMO:** reserved for **refractory severe ARDS** only.

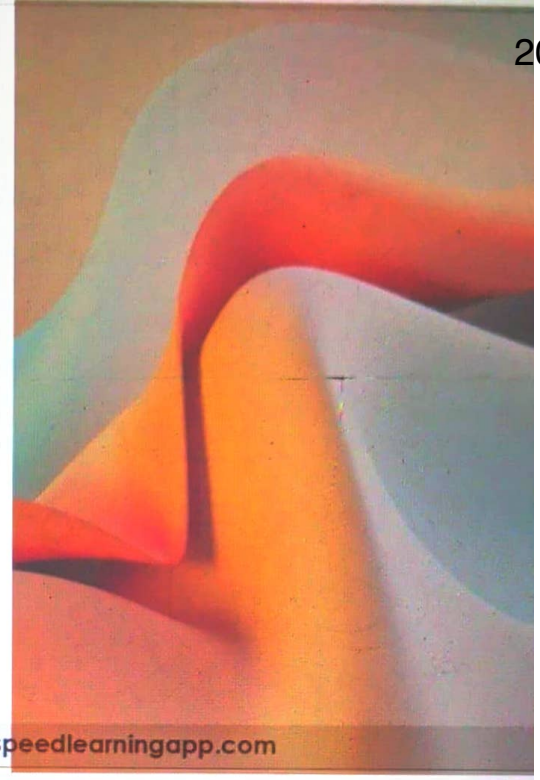


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- **Prognosis of ARDS**
- **Mortality**
- **LUNG SAFE trial:**
  - Mild ARDS: ~35%
  - Moderate ARDS: ~40%
  - Severe ARDS: ~46%
- **Sepsis + multiorgan failure** → mortality >80%.

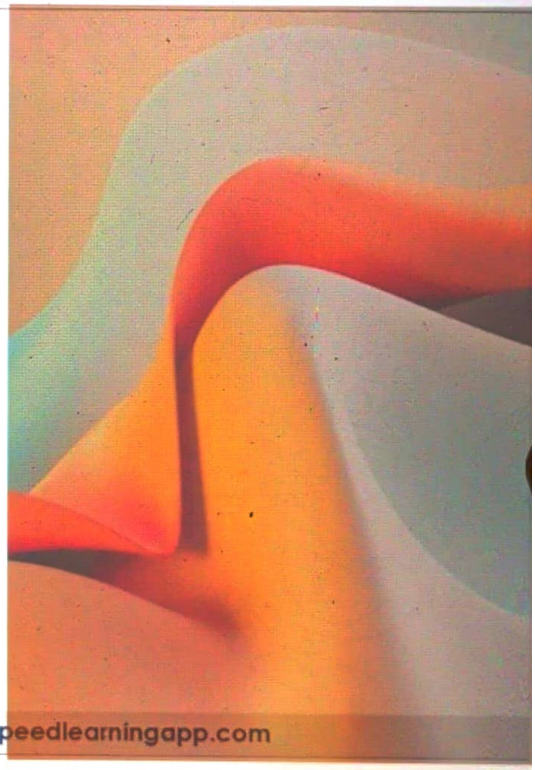


- **Prognosis of ARDS**
- Mortality influenced by:
  - Age (>75 yrs: ~60% vs <55 yrs: ~24%).
  - Cause (trauma/surgery-induced ARDS → better survival).
  - Underlying comorbidities (cirrhosis, chronic lung disease, malignancy, immunosuppression).
  - Severe physiologic derangements (low compliance, high dead space, extensive consolidation on imaging).



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- **Functional Recovery in Survivors**
- Most survivors regain **near-normal lung function** within 6 months.
- 1 year after extubation:
  - Majority → normal spirometry, near-normal gas exchange.
  - Some → mild reduction in DLCO (diffusion capacity).



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- **Functional Recovery in Survivors**
- Persistent issues:
  - ICU-acquired weakness, neurocognitive deficits.
  - Reduced quality of life due to muscle wasting, psychological trauma.
- Predictors of poorer recovery: advanced age, comorbidities, prolonged mechanical ventilation.

