

**Acute Respiratory Distress Syndrome
(ARDS)
and Acute Lung Injury (ALI)
Revisited**

**Dr.Dhaher JS Al-habbo
FRCP London UK
Assistant Professor in Medicine
DEPARTMENT OF MEDICINE**

THE EARLY HISTORY OF ARDS

In 1821, Laennec described the gross pathology of the heart and lungs and described *idiopathic anasarca* of the lungs; pulmonary edema without heart failure in “*A Treatise on Diseases of the Chest*” .

Since acute, diffuse, and dense bilateral infiltrates were almost never observed except in patients requiring prolonged mechanical ventilation, many surmised the cause of such infiltrates was the ventilator, hence the term “**Respirator lung**” .

1967: Ashbaugh, et al. described Adult Respiratory Distress Syndrome

Respiratory Distress

Cyanosis

Hypoxemia despite oxygen

Diffuse infiltrates on Chest X-ray.

THE EARLY HISTORY OF ARDS

1988: Murray, et al. expanded the definition of ARDS using a 4- point scale, based on:

Extent of Chest X-ray abnormalities

Severity of Hypoxia : $\text{PaO}_2/\text{FiO}_2$

Amount of PEEP

Search for cause of ARDS

1994: American- European Consensus Conference Committee

Renamed Acute Resp Distress Syndrome

Described ARDS as “syndrome of inflammation and permeability”

Coined the term ALI as a precursor to ARDS

THE EARLY HISTORY OF ARDS

1994: American- European Consensus Conference Committee

Criteria:

A- Acute onset of symptoms

B- Bilateral infiltrates on chest radiographs

C- PAWP \leq 18*

D- ALI: PaO₂/FiO₂ \leq 300

E- ARDS: PaO₂/FiO₂ \leq 200.**

** Pulmonary arterial wedge pressure of 18 mm Hg or less or no clinical signs of left atrial hypertension*

***The ratio of the alveolar partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (FIO₂) of 200 mm Hg or less.*

THE EARLY HISTORY OF ARDS

In 2012, the ARDS Definition Task Force met in Berlin and decided on a new and improved definition of ARDS using 3 mutually exclusive categories of ARDS based on the degree of hypoxemia:

Mild (200 mm Hg $< p_{aO_2}/FIO_2 \leq 300$ mm Hg),

Moderate (100 mm Hg $< p_{aO_2}/FIO_2 \leq 200$ mm Hg),

Severe ($PaO_2/FIO_2 \leq 100$ mm Hg).

ARDS are clinical syndromes characterized by the acute onset (<7 days) of hypoxaemia with bilateral pulmonary infiltrates in the absence of clinical evidence of left atrial hypertension

Predisposing conditions and risk modifiers in ARDS

Hudson et al. Fowler et al. Gong et al and Ferguson et al all agreed that various pulmonary diseases are the top leading predisposing causes for ALI and ARDS.

However sepsis, DIC and multiple transfusions, drug overdose, and multiple fractures, head trauma are also among the high risk factors.

Risk modifiers (obesity, alcohol abuse, diabetes, hypoalbuminemia, acidosis, tachypnea, and oxygen supplementation).

- *Pneumonia (34%)*
- *Sepsis (27%)*
- *Aspiration (15%)*
- *Trauma (11%)*
 - *Pulmonary contusion*
 - *Multiple fractures*

Lung injury prediction score for the emergency department* (EDLIPS)

| NO | Predisposition Risks | EDLIPS Points | NO | Predisposition Risk Modifiers | EDLIPS Points |
|----|----------------------|---------------|----|-------------------------------|---------------|
| 1 | Male gender | 1 | 1 | Diabetes Mellitus | -0.5 |
| 2 | Aspiration | 2 | 2 | Cirrhosis | 1 |
| 3 | Pneumonia | 1 | 3 | Chemotherapy | 2 |
| 4 | Sepsis | 1 | 4 | Obesity(BMI>30) | 1.5 |
| 5 | Shock | 2 | 5 | Acidosis(<7.35) | 2 |
| 6 | Lung contusion | 1 | 6 | FiO ₂ >0.35(>4L/m) | 2 |
| 7 | Smoke inhalation | 1.5 | 7 | Albumin(<3.5) | 1.5 |
| 8 | Long bone fractures | 2 | 8 | SpO ₂ <95% | 1.5 |
| 9 | Brain injury | 2 | | | |
| 10 | Cardiac Surgery | 5 | | | |
| 11 | Aortic surgery | 5 | | | |
| 12 | Spine surgery | 5 | | | |
| 13 | Acute abdomen | 2.5 | | | |

*Trillo-Alvarez C, Cartin-Ceba R, Kor DJ, Kojicic M, Kashyap R, Thakur S, Thakur L, Herasevich V, Malinchoc M,

Gajic O: Acute lung injury prediction score: derivation and validation in a population-based sample. *Eur Respir J* 2011, 37:604-609

Lung injury score according to *CXR* and *PaO₂/FiO₂*

CXR

| |
|-----------------------------|
| A-No consolidation ..0 |
| B-Confined to 1 quadrant..1 |
| C-2 quadrant2 |
| D-3 quadrant3 |
| E-4quadrant4 |

PaO₂/FiO₂

| |
|-----------------|
| A- >300.....0 |
| B-225-2991 |
| C-175-2242 |
| D-100-174 ...3 |
| E-<100.....4 |

Add the sum of each component and divide by the number of components used

0- No lung injury

0.1-2.5 – Mild to moderate lung injury

>2.5 – Severe lung injury (ARDS)

Biomarkers for ARDS

Plasma biomarkers such as (angiopoietin)Ang-2 can improve clinical prediction scores and identify patients at high risk for ALI.

In addition, the early rise of Ang-2 emphasizes the importance of endothelial injury in the early pathogenesis of ALI.

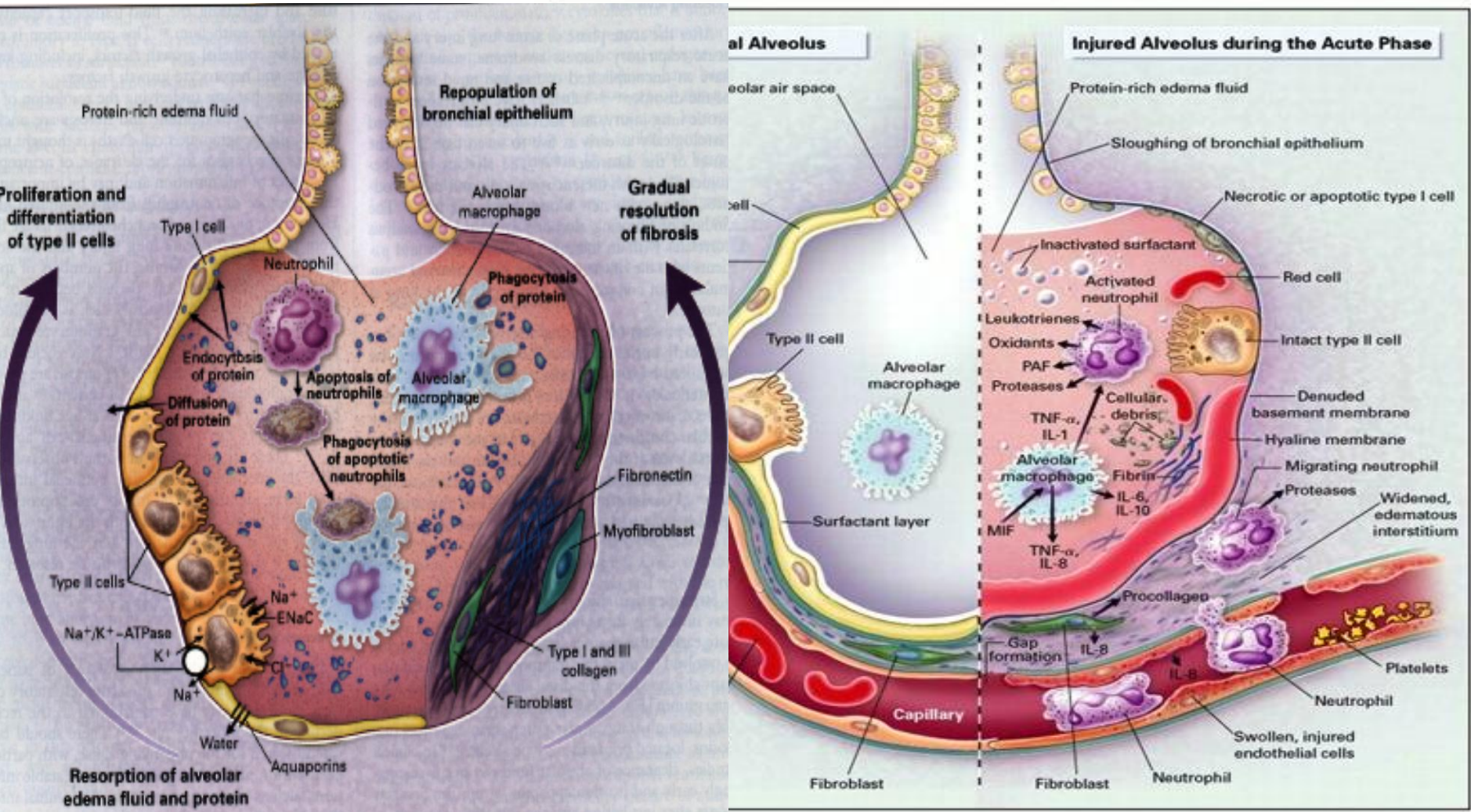
A recent trial in critically ill patients demonstrated that higher levels in plasma of Ang-2 were significantly associated with increased development of ALI (odds ratio (OR) 2.4; 95% CI 1.3-4.2)

*Agrawal A, Matthay MA, Kangelaris KN, Stein J, Chu JC, Imp BM, Cortez A, Abbott J, Liu KD, Calfee CS: Plasma angiopoietin-2 predicts the onset of acute lung injury in critically ill patients.*Am J Respir Crit Care Med* 2013.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY OF ARDS

- Exudative Phase
 - Neutrophilic Infiltrate
 - Alveolar Haemorrhage
 - Proteinaceous Pulmonary Oedema
 - Cytokines (TNF, IL1,8)
 - » ↑ Inflammation
 - » ↑ Oxidative Stress and Protease Activity
 - » ↓ Surfactant Activity
 - » Atelectasis
- Elastase- induced capillary and alveolar damage
- ↑ Alveolar flooding
- ↓ Fluid clearance
- Capillary thrombosis
 - ↓ Anticoagulant proteins
 - ↑ Procoagulant proteins (Tissue Factor)
 - ↑ Anti- fibrinolytic Protein (Plasminogen Activator Inhibitor)

HISTOPATHOLOGY AND PATHOPHYSIOLOGY OF ARDS



Ware and Matthay, NEJM 2000;341:1334-1349

RESPIRATORY CARE

HISTOPATHOLOGY AND PATHOPHYSIOLOGY OF ARDS

A procoagulant tendency is observed as concentrations of anticoagulant proteins (protein C and S) fall and there is increased expression of procoagulant proteins (tissue factor) and antifibrinolytic proteins (plasminogen activator inhibitor-1) , these changes are probably responsible for thrombosis observed in alveolar capillaries as demonstrated by pulmonary arteriography .

After the exudative stage, a prolonged phase sometimes referred to as fibroproliferative has been reported in some ALI patients during which chronic inflammation, fibrosis, and neovascularization occur

HISTOPATHOLOGY AND PATHOPHYSIOLOGY OF ARDS (The recovery Phase)

Anti-inflammatory cytokines deactivate inciting **neutrophils**, which then undergo apoptosis and phagocytosis.

Type II alveolar cells proliferate and differentiate into **type I cells**, reestablishing the integrity of the epithelial lining and creating an osmotic gradient that draws fluid out of the alveoli and into the pulmonary microcirculation and lung lymphatics.

Simultaneously, **alveolar cells and macrophages** remove protein compounds from the alveoli, allowing the lungs to recover.

Clinical Course

Early findings on the chest radiograph include *normal or diffuse alveolar opacities (consolidation)*, which are *often bilateral and which obscure the pulmonary vascular markings*.

Later, these opacities progress to *more extensive consolidation that is diffuse, and they are often asymmetrical*.

Effusions and septal lines are not usually seen on chest radiographs of patients affected by ARDS, *although these findings are commonly seen in patients with congestive heart failure (CHF)*.

Radiographic findings tend to stabilize (part of the clinical definition of ARDS);

If further radiographic worsening occurs after 5-7 days, another disease process should be considered.

Clinical Course

Acute Phase

Rapid Onset

Exudates

Consolidations

Respiratory failure

Hypoxemia refractory to O₂

Inflammation (even in non-edematous lung) IL-1,6,8,10, Cytokines

Diminished Lung compliance

Patchy infiltrates Coalesce

Air Bronchograms

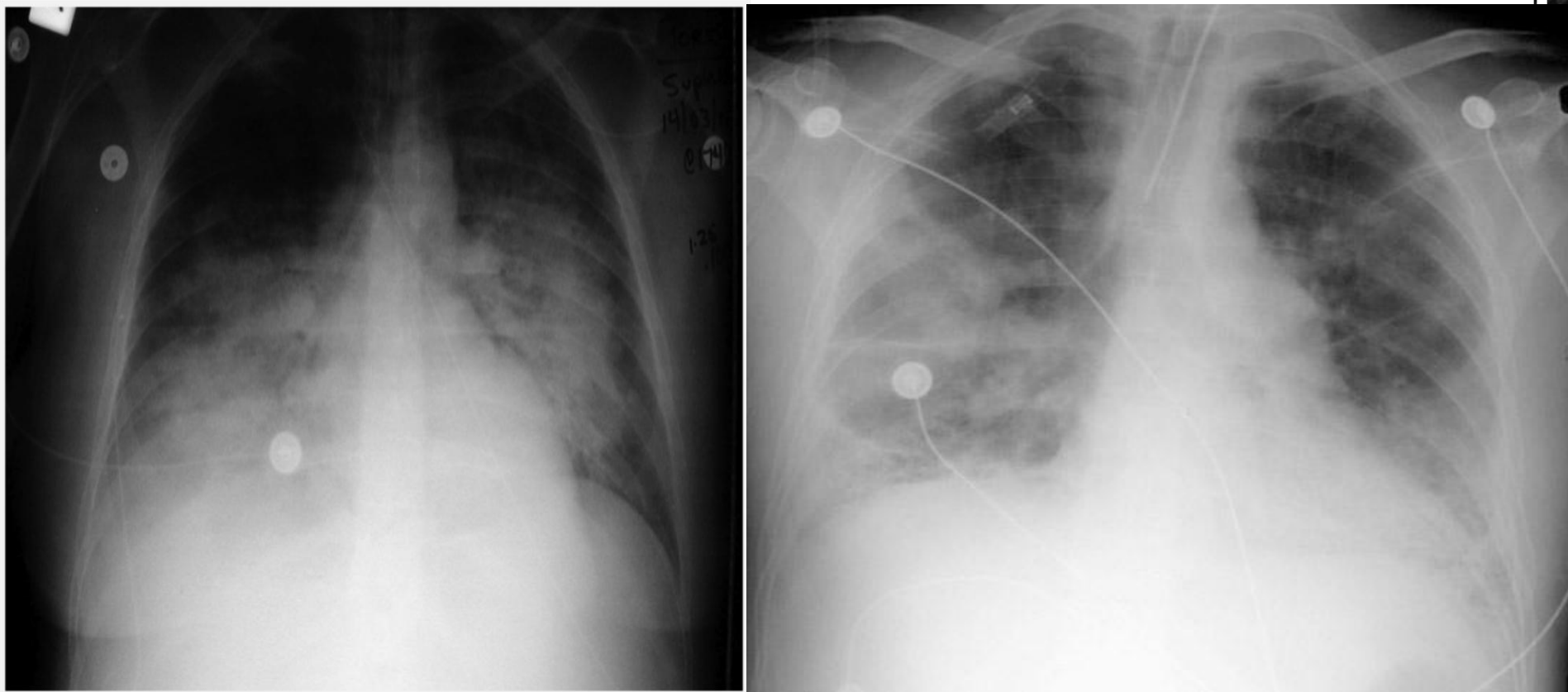
Pulmonary Hypertension

Intrapulmonary Shunting

Endogenous Vasoconstrictors

Hyperadrenergic State

ARDS is characterized by breakdown of the alveolar-capillary barrier, leading to flooding of the alveolar space producing the classical chest radiograph of bilateral pulmonary infiltrates.



Clinical Course

Fibroproliferative phase

Persistent Hypoxia

Pulmonary Fibrosis

Worsening Compliance

Neovascularization

Pulmonary Hypertension

Macrophages clear neutrophils

Chronic Inflammation

Chest xray shows linear opacities consistent with evolving fibrosis.

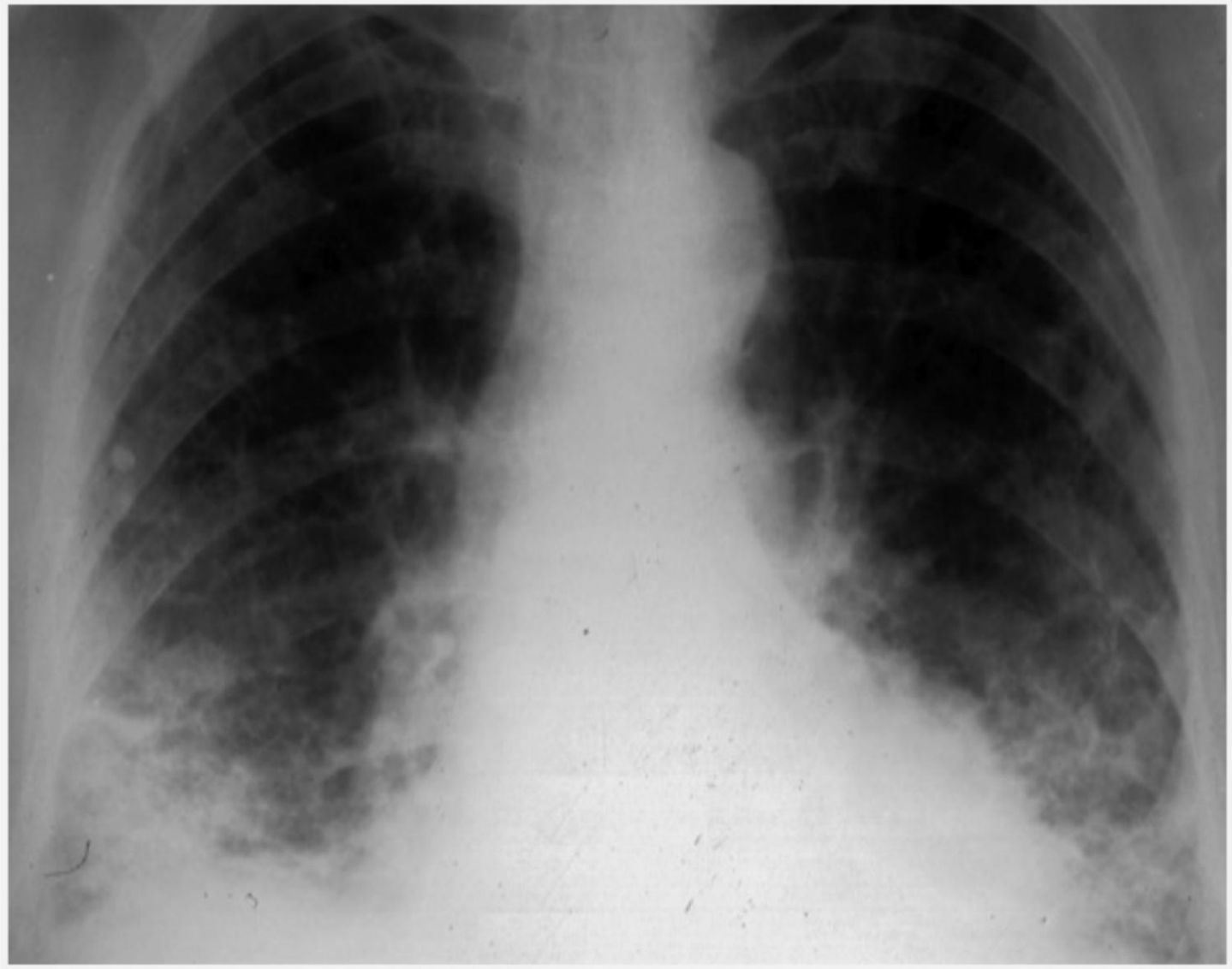
Pneumothorax in 10-13% of patients.

CT: diffuse interstitial opacities and bullae.

Histologically, fibrosis, mesenchymal cells, vascular proliferation, collagen and fibronectin accumulation.

Can start 5-7 days after symptom onset.

Not present in every patient with ARDS, but does portend poorer prognosis



RESPIRATORY CARE

Management of ARDS

Ventilator Strategies

A-Lung recruitment maneuvers

B-Prone positioning

C-High-frequency oscillatory ventilation
(HFOV)

Initial ventilator set up and adjustments

STEP 1- Calculation of ideal body weight (IBW):

- For males, $IBW(kg) = 50 + 2.3 \{height(inch) - 60\}$
Or $IBW(kg) = 50 + 0.91 \{height(cm) - 152.4\}$
- For females, $IBW(kg) = 45.5 + 2.3 \{height(inch) - 60\}$
Or $IBW(kg) = 45.5 + 0.91 \{height(cm) - 152.4\}$

Ideal body weight is used, not actual weight (the lungs don't get any larger).

STEP 2- Oxygenation

- Initially high F_{iO_2} given (1.0) to correct hypoxia
- F_{iO_2} and PEEP adjusted to the lowest level compatible with the oxygenation goals

STEP 3

Higher positive end-expiratory pressure values (12 cm H_2O or more) are associated with decreased mortality compared with lower values of 5 to 12 cm H_2O (number needed to treat = 20).

Positive End-Expiratory Pressure (PEEP)

Clinical practice guidelines recommend maintaining Oxygen saturation of 88 to 95 percent and a plateau pressure of 30 cm H₂O or less to avoid barotrauma. Also to maintain arterial pH of 7.30 to 7.45, although patients in some research trials have tolerated permissive hypercapnia and a pH as low as 7.15.

- PEEP is to decrease FiO₂
 - Goal sat 88% with FiO₂ <60%
 - Minimize oxygen toxicity
 - PEEP can improve lung recruitment and decrease end-expiratory alveolar collapse (and therefore right-to-left shunt)
 - Can also decrease venous return, cause hemodynamic compromise, worsen pulmonary edema
- ARDSnet PEEP trial of 549 patients show no difference in mortality or days on ventilator with high vs low PEEP

Positive End-Expiratory Pressure (PEEP)

PEEP level separation at various F_{iO_2} levels was in the range of 6 cm H_2O (mean of 14 versus 8 cm H_2O) .

The use of 6 ml/kg PBW tidal volume strategy and PEEP– F_{iO_2} scale as a starting point for ventilation is recommended but routine use of recruitment maneuvers is not.

However, it would be reasonable to reserve higher levels of PEEP and/or recruitment maneuvers for patients with refractory hypoxemia in an attempt to improve oxygenation when severity of the oxygenation defect is the most immediate threat to survival.

| | | | | | | | | | | | | | | |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| FIO2 | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0 |
| PEEP | 5 | 5 | 8 | 8 | 10 | 10 | 10 | 12 | 14 | 14 | 14 | 16 | 18 | 20-24 |

Lung Recruitment

A-To open the collapsed alveoli

B-A sustained inflation of the lungs to higher airway pressure and volumes

Potentially recruitable (PEEP 5 → 15 cmH₂O)

- Increase in PaO₂:FiO₂
- Decrease in PaCO₂
- Increase in compliance

Sensitivity : 71%

Specificity : 59%

The effect of PEEP correlates with the percentage of potentially recruitable lung.

The percentage of recruitable lung correlates with the overall severity of lung injury.

NEJM 2007; 354: 1775-1786

RESPIRATORY CARE

Strategy for Recruitment

Administer 40cm H₂O of PEEP for 90s

Set the ventilator to an effective rate of zero (with no machine breaths) and then immediately raise the PEEP to 40cm H₂O for a carefully timed period of one and a half minutes. Then re-institute ventilation as before.

Wait and recheck the ABG

Wait for a period of five minutes, leaving the patient in the prone position, and obtain a blood gas analysis. If the PaO₂ is under 300mmHg, then consider repeating the maneuver at PEEPs of 45mmHg and (if this fails) 50mmHg, also for ninety seconds.

Prone Position advantages and disadvantages

Mechanisms to improve oxygenation:

a-Increase in end-expiratory lung volume

b-Better ventilation-perfusion matching

c-More efficient drainage of secretions

d-Improve oxygenation in about 2/3 of all treated patients

e-No improvement on survival, time on ventilation, or time in ICU

f-Might be useful to treat refractory hypoxemia

g-Optimum timing or duration ?

h-Routine use is not recommended

Prone Position advantages and disadvantages

Investigators randomized 474 patients at 26 French ICUs (and one in Spain) with severe ARDS (PaO₂:FiO₂ ratio of <150 mm Hg, PEEP >5, FiO₂ > 0.60) to receive standard care, or to also be “proned” (turned face-down) for 16 hours a day, every day for up to 28 days (or longer if their doctors so chose).

Far more prone-positioned patients survived their ARDS: 16% mortality at 28 days (38 deaths in 237 patients) vs. 33% in the supine group (75 of 229 patients), with a very low p-value, < 0.001. That’s a staggering 17% absolute risk reduction. The benefit was only slightly smaller at 90 days.

Claude Guérin et al’s PROVESA study (May 20, 2013 New England Journal of Medicine)

Prone Position advantages and disadvantages

Side effects of Prone Position

A-Facial edema, Airway obstruction Skin lesions

B-Difficulties with enteral feeding, Hypotension

C-Transitory decrease in oxygen saturation. Arrhythmias

D-Loss of venous accesses and probes,

E-Increase need for sedation.

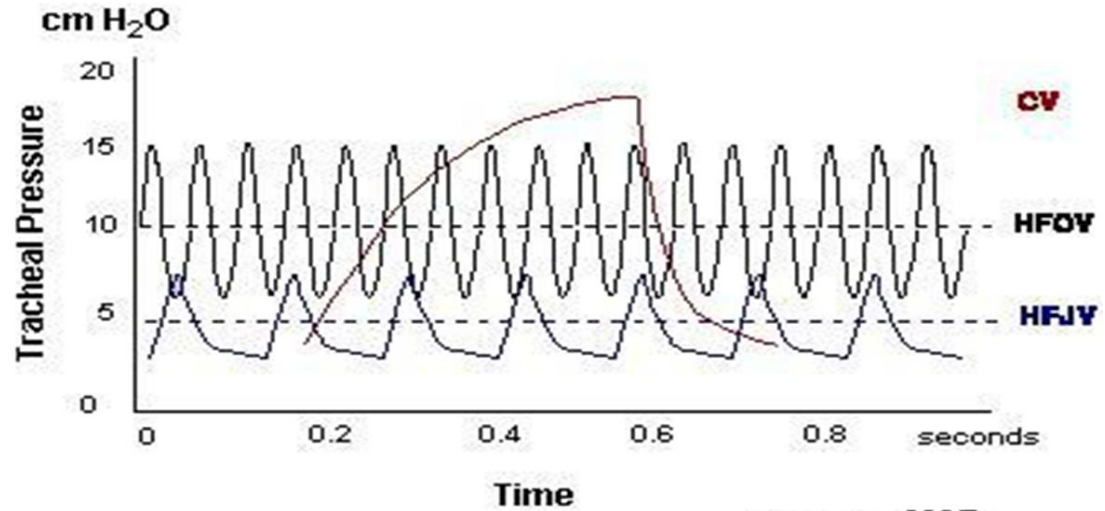
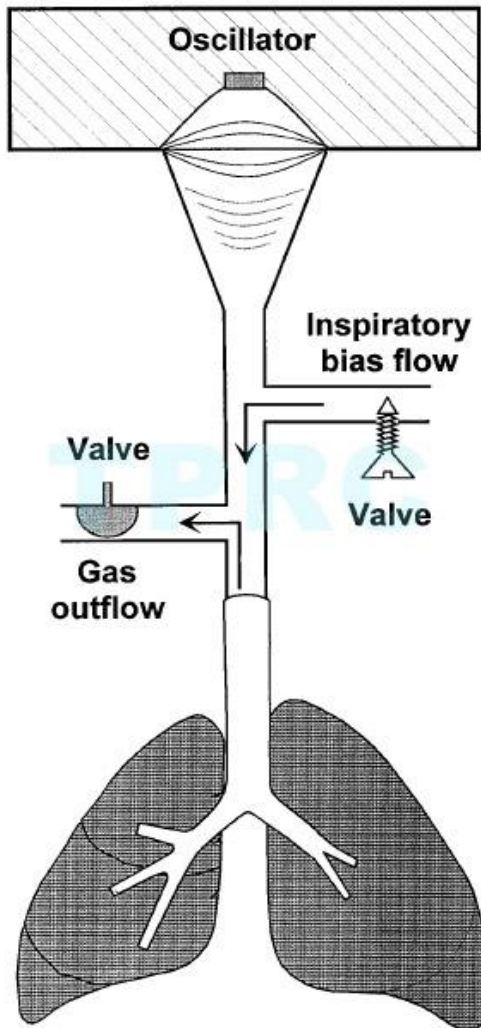
F-Loss of dialysis drains and catheters, Accidental extubation.

G-Apical atelectasis due to incorrect positioning of the tracheal tube

Video 1

RESPIRATORY CARE

High-Frequency Oscillatory Ventilation (HFOV)



Frequency: 180-600 breaths/min (3-10Hz)

Chest 2007; 131:1907-1916

- High frequency oscillatory ventilation shown no benefit over low tidal volume ventilation
 - 30 day mortality not statistically significant (37% vs 52%, p=0.10)
 - Earlier recovery from hypoxia

Adjunctive Therapy

Steroid therapy

The use of corticosteroids is controversial.

Randomized controlled trials and cohort studies tend to support early use of corticosteroids (with dosages of methylprednisolone [Solu-Medrol] ranging from 1 to 120 mg per kg per day) for decreasing the number of days on a ventilator

MATTHEW FARGO, MD, MPH, Dwight D. Acute Respiratory Distress Syndrome: Diagnosis and Management. Am Fam. Physician. 2012 Feb 15;85(4):352-358.

Adjunctive Therapy

Steroid therapy

A-Increase the number of ventilator-free and shock-free days during the first 28 day

B-Improve oxygenation, compliance and blood pressure

C-No increase in the rate of infectious complications

D-Higher rate of neuromuscular weakness

E-Routine use of steroid is not supported

F-Starting steroid more than 14 days after the onset of ARDS may increase mortality

Supportive treatments

Fluid Management

- Central venous pressure guided therapy – 10-14 mmHg (*ARDS Network Trial 2003*)
- Study of conservative vs liberal fluid management⁵
 - 60 day mortality: 25.5 vs 28.4% $p=0.30$
 - 1st 28 days ventilator free: 14.6 vs 12.1 $p<0.001$
 - 1st 28 days ICU free: 13.4 vs 11.2 $p<0.001$
 - Difference in organ failure and need for dialysis not statistically significant
 - No specific mention of CVP/ PAOP levels which to aim for
 - Conservative = 4mmHg Liberal = 10-14mmHg CVP

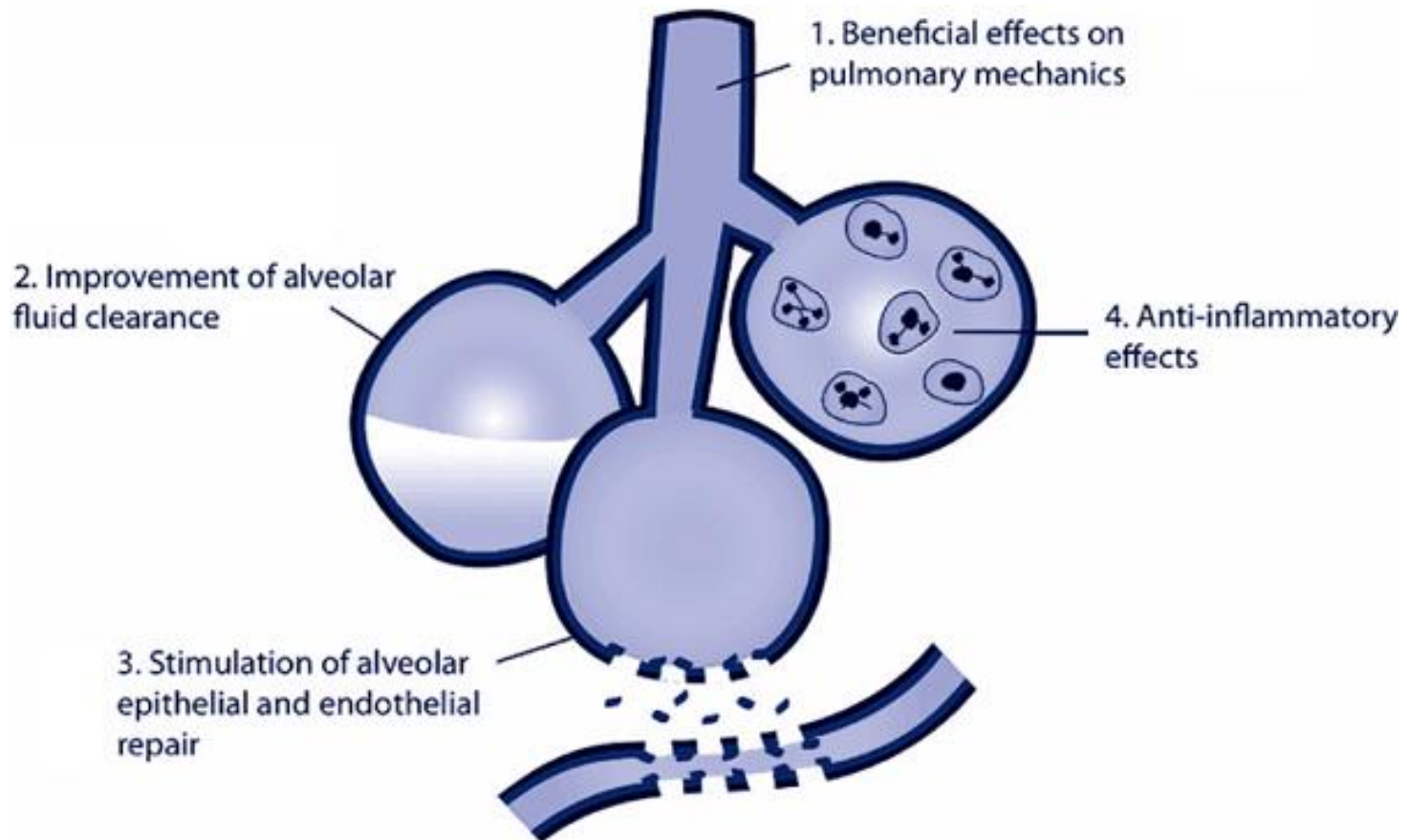
Supportive treatments

A variety of coagulation inhibitors have been tested including heparin, antithrombin, tissue factor pathway inhibitor, factor VIIa, activated protein C, and thrombomodulin in animal models and/or humans with either sepsis or ALI .

To date only activated protein C has been proven useful in severe sepsis, though it is not clear that it directly improves lung function

Pharmacological treatments in ARDS

β -adrenoceptor agonists (β -agonists) are well established in the treatment of airflow obstruction. In addition to actions as bronchodilators, they have anti-inflammatory properties, promote the clearance of alveolar fluid, and promote epithelial and endothelial repair((15 $\mu\text{g}/\text{kg}/\text{h}$)



Pharmacological treatments in ARDS

Neuromuscular blockade (NMB) may permit lower-pressure, lower-tidal volume ventilation with a consequent reduction in ventilator-induced lung injury.

Neutrophil elastase inhibitors

Neutrophil elastase (NE) Excessive NE is capable of degrading endothelial basement membrane, and has been implicated in the pathogenesis of ARDS. Neutrophil elastase inhibitor, was investigated in an international randomized, double-blind, placebo-controlled, multi-center phase III trial (STRIVE) .

The study was stopped prematurely due to an increase in 180-day all-cause mortality. A more recent meta-analysis of eight clinical trials (including STRIVE) investigating silvestat has shown it to have no effect on short-term mortality, and a worse outcome for 180-day mortality .

Andrew James Boyle, Rob Mac Sweeney and Daniel Francis McAuley. *Pharmacological treatments in ARDS; a state of the art update. BMC Medicine* 2013, 11:166 doi:10.1186/1741-7015-11-166

Pharmacological treatments in ARDS

Statins, Heparin, Aspirin, Angiotensin converting enzyme inhibitors/angiotensin receptor blockers. Stem cell therapy, Growth factors, vitamin D and interferon- β (IFN- β).

Prone Position



RESPIRATORY CARE

A new strategy for Recruitment

Select an appropriate patient

Ideal patients for recruitment maneuvers are patients with putative ARDS in the early phase of the disease (before the onset of fibro-proliferation). Patients should be poorly oxygenated on a high FiO_2 . Pre-existing focal lung disease that may predispose to barotrauma should be regarded as a relative contra-indication to the maneuver (for example extensive apical bullous lung disease). Patients with 'secondary' ARDS (following on, for example, abdominal sepsis) are thought to be more likely to respond favourably to the maneuver than patients with 'primary' lung disease and acute lung injury.

A new strategy for Recruitment

Recruitment maneuvers (RM) can be defined as a voluntary strategy to increase the transpulmonary pressure (P_L) transiently with the goal to reopen those alveolar units that are not aerated or poorly aerated but reopenable.

Position the patient prone

This is easily done (after some initial resistance from nursing staff)! An important component of prone positioning for recruitment is to have a pillow under the upper chest, and another beneath the pelvic area, so the abdomen hangs down somewhat in between the two pillows. Continue appropriate mechanical ventilation.

A new strategy for Recruitment

The patient must be fully monitored

Monitoring should include (at least) invasive arterial blood pressure monitoring, pulse oximetry and ECG. The patient must also be completely paralysed with non-depolarising neuromuscular blockade, to prevent attempts at respiration during the maneuver. A baseline arterial blood gas analysis (ABG) should be obtained after the FiO_2 has been increased to 100%.

A new strategy for Recruitment

Administer 40cm H₂O of PEEP for 90s

Set the ventilator to an effective rate of zero (with no machine breaths) and then immediately raise the PEEP to 40cm H₂O for a carefully timed period of one and a half minutes. Then re-institute ventilation as before.

Wait and recheck the ABG

Wait for a period of five minutes, leaving the patient in the prone position, and obtain a blood gas analysis. If the PaO₂ is under 300mmHg, then consider repeating the maneuver at PEEPs of 45mmHg and (if this fails) 50mmHg, also for ninety seconds.

A new strategy for Recruitment

Prevent 'de-recruitment'

The patient should now be maintained on a PEEP of 15 cmH₂O. Often, the patient can be turned back to a supine position without substantial worsening of oxygenation. Ventilation should continue with a strategy that minimises additional alveolar trauma (for example, inverse ratio pressure-control ventilation, with every attempt to keep trans-alveolar pressure to under 35cm H₂O). Ventilator tidal volumes should perhaps be limited to approximately 6 ml/kg.

A new strategy for Recruitment

Rationale

The rationale behind the above maneuver is that prone ventilation splints the thoracic cage, especially the anterior portion and the area around the upper lobes. If diaphragmatic excursion is promoted (by freeing up the abdomen) then preferential ventilation of the lower lobes is encouraged, and overdistension of the upper lobes is prevented.

Sustained pressures of 40 to 50 cm H₂O are applied to the airway for a sufficient time to distribute pressure to collapsed lung areas, and promote recruitment. Once adequate recruitment has been achieved, high PEEP is used to prevent recurrent airway collapse.

POINTES TO REMEMBER

{ Ibsen in (1954) first used cuffed endotracheal tubes and positive pressure ventilation, which clearly moved ARDS from a nearly universally fatal form of “double pneumonia” to treatable disease. Roentgen describes X-rays in 1896. Early chest X-rays required exposure time of 20 min and were not considered useful until the 1920s }