ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Understanding the Pathophysiology and Treatment of Acute Respiratory Distress Syndrome in Children

Abdulnasser Ahmed Skheita*

Pediatric Consultant, Head of Pediatric Department, Hotat Bani Tamim General Hospital, Saudi Arabia

***Corresponding Author:** Abdulnasser Ahmed Skheita, Pediatric Consultant, Head of Pediatric Department, Medical Director, Hotat Bani Tamim General Hospital, Saudi Arabia.

Received: September 16, 2021; **Published:** September 28, 2021

Abstract

During the epidemic of Covid-19, we as a doctors faced a more cases of Acute Respiratory Failure, resulted from Acute Respiratory Distress Syndrome ARDS. So, in this article, I will try to give more details about this clinical and pathological identity in order to enhance our understanding and so our management of it.

Most cases of acute respiratory distress syndrome are associated with pneumonia or sepsis.

It is estimated that 7.1 percent of all patients admitted to ICU "Intensive Care Unit" and up to 16.1 percent of all patient on mechanical ventilation develop ARDS.

Keywords: *Pathophysiology; Treatment; Acute Respiratory Distress Syndrome; Children*

Discussion

What is the definition of ARDS?

It is a severe form of Acute Lung Injury, characterized by acute, non-cardiogenic Pulmonary Edema with Bilateral Pulmonary infiltrates on chest x-ray, and a ratio of PaO_2 to FiO_2 of < 200.

American European Consensus criteria for acute lung injury and acute respiratory distress syndrome.

	Acute Lung Injury	Acute Respiratory Distress Syndrome
Timing	Acute onset	Acute onset
Chest Radiograph	Bilateral Pulmonary Infiltrates	Bilateral Pulmonary Infiltrates
Edema	Pulmonary Artery Occlusion pressure ≤18 mmHg, or no clinical evidence of Left Atrial Hypertension	Pulmonary Artery Occlusion pressure ≤18 mmHg, or no clinical evidence of Left Atrial Hypertension
Oxygenation Impairment	PaO_2/ FiO_2 ratio ≤300	PaO_2/FiO_2 ratio ≤200
Adult	17.9-78.9 cases per 100,000/year	14-58.7 cases per 100,000/year
Children	2.95-12.8 cases per 100,000 children/ year	2.2-9.5 cases per 100,000 child/year

Table 1

NB_1: At altitude > 1000m, PaO_2/FiO_2 should be adjusted for local barometric pressure:

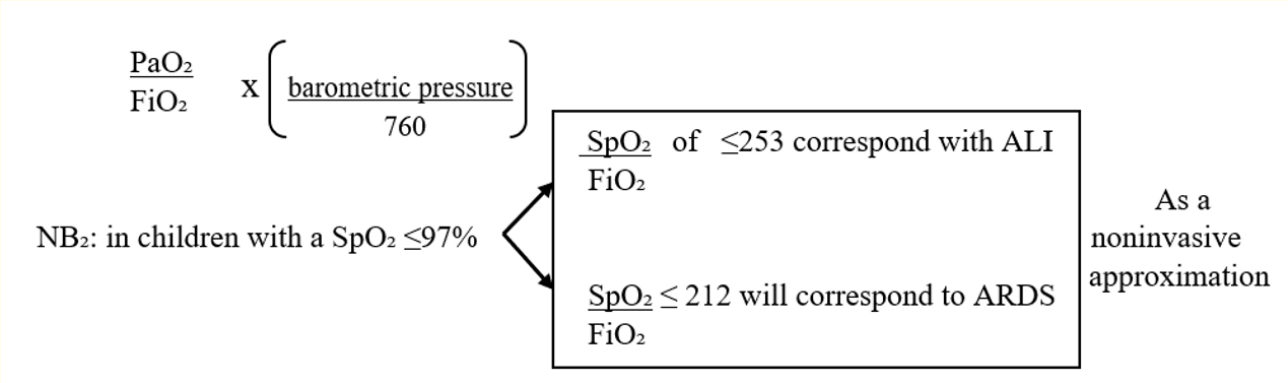

Figure A

Berlin definition of ARDS

- **Timing:** Onset within 1 week of a known clinical trigger, or new/worsening respiratory symptoms
- **Chest imaging (X-ray or CT):** Bilateral opacities not fully explained by effusion, regional atelectasis, or nodules.
- **Origin of edema:** Respiratory failure not fully explained by Cardiac Failure or fluid overload "such as by objective assessment such as echocardiography"
- **Oxygenation impairment:**
    - Mild ARDS: 200 < PaO_2/FiO_2 ≤ 300 with PEEP or CPAP ≥ 5 cm H_2O
    - Moderate ARDS: 100 < PaO_2/FiO_2 ≤ 200 with PEEP ≥ 5 cm H_2O
    - Severe ARDS: PaO_2 ≤ 100 with PEEP ≥ 5cm H_2O
- **Mortality rate:** In mild ARDS 27%, in moderate ARDS 32%, in severe ARDS 45%.

Mechanism of disease and core pathophysiology

Host genetic factors

By linking the presence of specific genetic polymorphisms to the development and/or severity of ARDS. In particular, specific polymorphisms in genes that govern:

- Endothelial barrier function-pro inflammatory and anti-inflammatory cytokine production,

- The transcription regulator nuclear factor-KB (NF-KB) and its inhibitor NF-KBIA,
- Pattern recognition receptors (PRRs) of the innate immune system- oxidant mediated injury,
- Surfactant protein B production-angiotensin-converting enzyme and coagulation cascade have all been associated with either susceptibility to ARDS or the severity of its presentation. Also, there is a genome-wide study that will discover the host genetic factors that have a role in determining disease phenotype.

Initiating factors

Either due to direct or indirect lung injury:

1. **Direct lung injury**
    - Pneumonia } Both are most common
    - Pulmonary aspiration
    - Traumatic pulmonary contusion
    - Fat embolism
    - Submersion injury
    - Inhalational injury
2. **Indirect lung injury:**
    - Sepsis
    - Shock
    - Exposure to cardiopulmonary bypass
    - Transfusion related lung injury.

Each group have a different pathological changes and so a different response to particular therapies, For example:

- Direct injury is suspected of causing regional consolidation from destruction of the alveolar architecture, and the benefit of surfactant use in treatment,
- While Indirect injury is believed to be associated with Pulmonary Vascular Congestion, interstitial edema and less severe alveolar involvement and so benefit from surfactant use in the treatment.

Phases of disease

First: Exudative phase

Characterized by the acute development of decreased pulmonary compliance and arterial hypoxemia, clinically associated with tachypnea, ABG: with hypocarbia and chest x-ray: diffuse alveolar infiltrates from pulmonary edema.

Second: Fibro proliferative phase

Characterized by increased alveolar dead space function, and refractory pulmonary hypertension due to chronic inflammation and scarring of the alveolar-capillary unit.

Third: Recovery phase

Characterized by restoration of the alveolar-epithelial barrier, gradual improvement in pulmonary compliance and resolution of arterial hypoxemia, and eventual return to premorbid pulmonary function in many patients.

Alveolar capillary barrier dysfunction and edema formation

By definition, the edema in ARDS isn't caused by cardiac failure, but results from disruption of the structure components that regulate alveolar fluid balance under normal conditions.

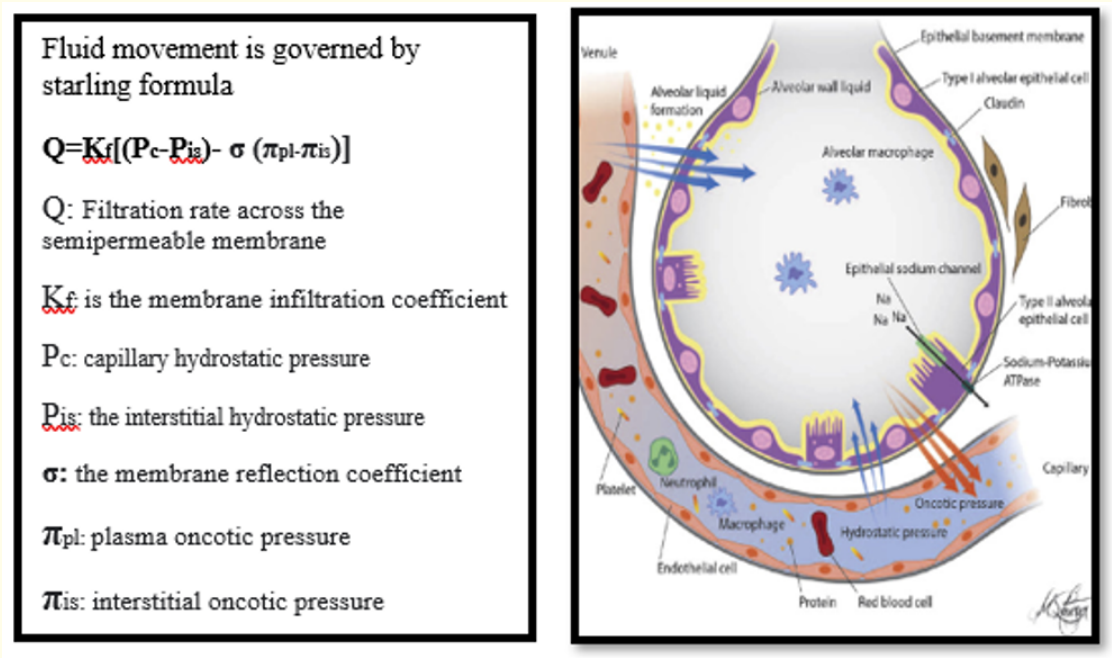

Figure A

Usually, the small amount of fluid that accumulates in the interstitial space can be cleared easily by the pulmonary lymphatic system.

The key pathophysiologic event that distinguishes the orderly regulation of alveolar fluid balance in the normal state from the dysfunction typified by ALI and ARDS is injury to the alveolar epithelium and/or pulmonary capillary endothelium. This injury can occur directly

as the result of parenchymal injury or following a distant or systemic disease that provokes the host immune response causing neutrophil activation and elaboration of pro-inflammatory cytokines.

Either pathway results in the opening of intercellular connections, which causes unregulated leakage of fluid protein, cytokines, and other solutes into the interstitium and the alveolar space impairment of gas exchange through multiple potential mechanisms, soon ensue.

Surfactant dysfunction and alteration of pulmonary mechanics

Injury to the pulmonary surfactant system is one of the more serious consequences of damage to the alveolar epithelium and subsequent alveolar flooding.

Laplace law

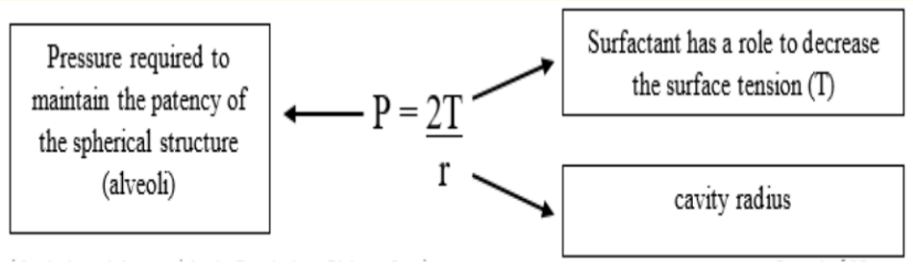

Figure C

So, an increase in surface tension in a small cavity, such as an alveolus will require elevated trans alveolar pressure to achieve and maintain patency.

So, following a lung injury, surfactant production declines due to damage to the alveolar epithelial cells, and also decrease in surfactant activity by alteration in its phospholipid constituents and inactivation by alveolar exudates. The loss of surfactant integrity dramatically alters the mechanical properties of the entire lung.

In normal state:

- **Pulmonary hysteresis:** Produced by interaction between surfactant and the elastic properties of the lung and chest wall.
- **Pulmonary hysteresis:** Allows for the maintenance of Lung volume at lower trans pulmonary pressure during expiration than are required during inspiration.

$$P_{transpulmonary} = P_{airway} - P_{pleura}$$

This will be demonstrated by lung volume- pressure relationships.

Lung compliance: Is the ease with which material can be stretched.

$$\text{Compliance} = \frac{\Delta \text{Volume (L)}}{\Delta \text{ Pressure (cm}H_2O\text{)}}$$

Figure D

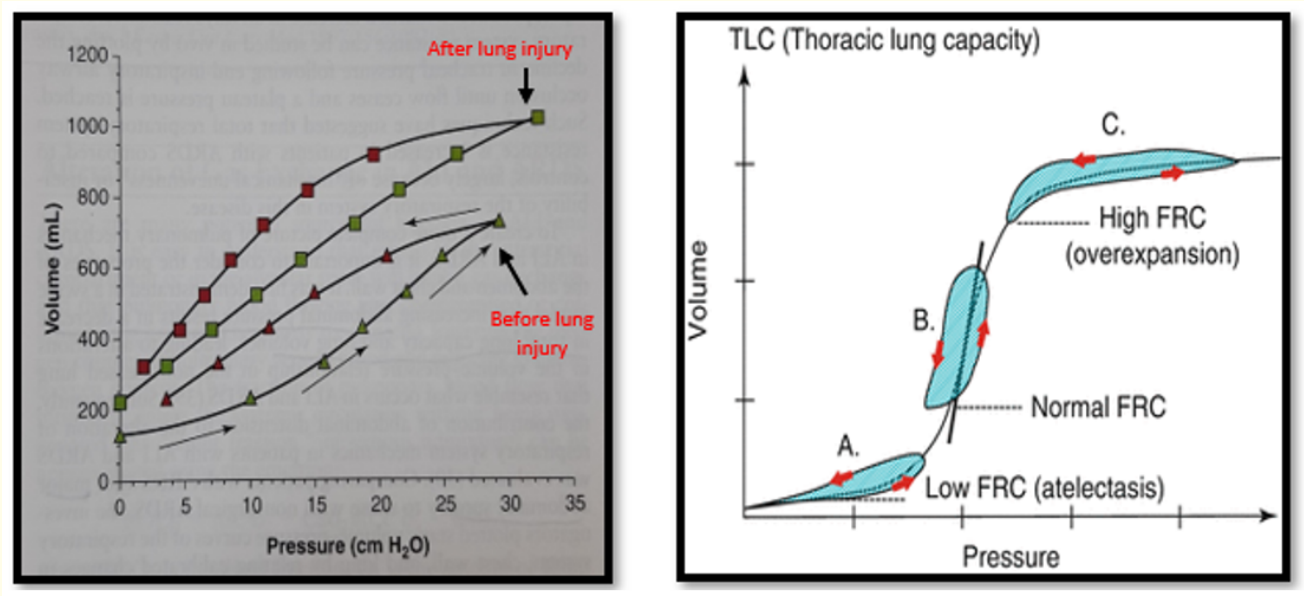

Figure E

The effect of alveolar and small airway collapse on overall airway resistance can be explained by the Hagen-Poiseuille equation describing Laminar Flow in straight circular tubes:

$$R = \frac{8\mu L}{\pi r^4}$$

R=Resistance to flow, μ=Is gas viscosity, L=Tube length, r =Is airway radius.

As long as there is a reduction in airway caliber, from peribronchiolar edema or outright airway collapse, produces a marked increase in airway resistance. And this will be the case in ARDS.

But in surgical (major abdominal surgery) ARDS, we found that a decrease in chest wall compliance is due to an increase in static abdominal pressure which will decrease the total lung capacity and lung volumes, leading to alterations in the volume-pressure relationship.

These observations suggest that ARDS impairs respiratory system mechanics in different ways depending on the underlying etiology, a finding that has significant implications for understanding clinical outcomes in ARDS and for defining subgroups within a large and heterogeneous disease population that may benefit from specific therapies or alternative management strategies.

Mechanisms of alveolar fluid clearance

From the alveolus into the interstitium by:

1. **Alveolar epithelial cell type I:** Which make up about 95% of the alveolar epithelial lining, by their expression of a water transport protein, aquaporin-5 on their apical surface.

2. **Alveolar epithelial type II:** Which account for a much smaller share of the alveolar lining, by trans epithelial ion transport (Na), so once sodium enters through apical channels Na^+/K^+ -ATPase located on the basolateral cell membrane actively transport sodium back into the interstitial space, which creates the gradient for passive movement of water across the alveolar epithelium, and back into the interstitium.

So, the injury to these cells during ARDS will impair the overall alveolar fluid clearance.

The permeability edema that is the defining feature of early ARDS sites the stage for reduced compliance and an EELV "end expiratory lung volume" that decreases below FRC "Functional Residual Capacity" to a point approaching closing capacity creating conditions that favor the development of regional atelectasis, intrapulmonary shunt, and alveolar hypoxia.

Alteration of gas exchange in acute lung injury and acute respiratory distress syndrome

The blood comes from a Pulmonary artery to a compromised or collapsed lung units (due to edema) will pass it and poorly oxygenated. Lowering the oxygen content of pulmonary venous blood and so reducing systemic oxygen content.

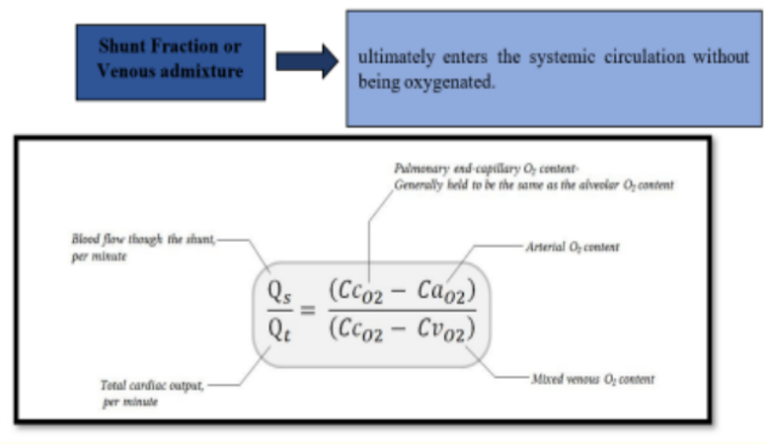

Figure F

Q_s: The amount of shunt flow

Q_t: The total flow

Cco_2: The end-pulmonary capillary oxygen content

Cao_2: Arterial oxygen content

Cvo_2: Mixed venous content.

Shunted blood is low in O_2 and high in CO_2, but intrapulmonary shunt doesn't tend to elevate systemic $PaCO_2$, because chemoreceptors sensitive to acute increases in $PaCO_2$ stimulate respiratory drive, eliminating CO_2 before an increase would be detectable by blood gas analysis.

Therefore, the arteriovenous CO_2 gradient under normal condition is 4 - 6 mmHg.

The phenomenon of "right-to-left" intrapulmonary shunt is ameliorated to some degree by pulmonary vasoconstriction, which redirects blood toward better ventilated lung units. So, in healthy patient 10% of cardiac output doesn't come into contact with alveolar gas.

This called "a physiologic shunt" fraction, as well as blood from bronchial, pleural, and thebesian veins, which returns to the systemic circulation without passing through the pulmonary vascular bed.

In normal lung

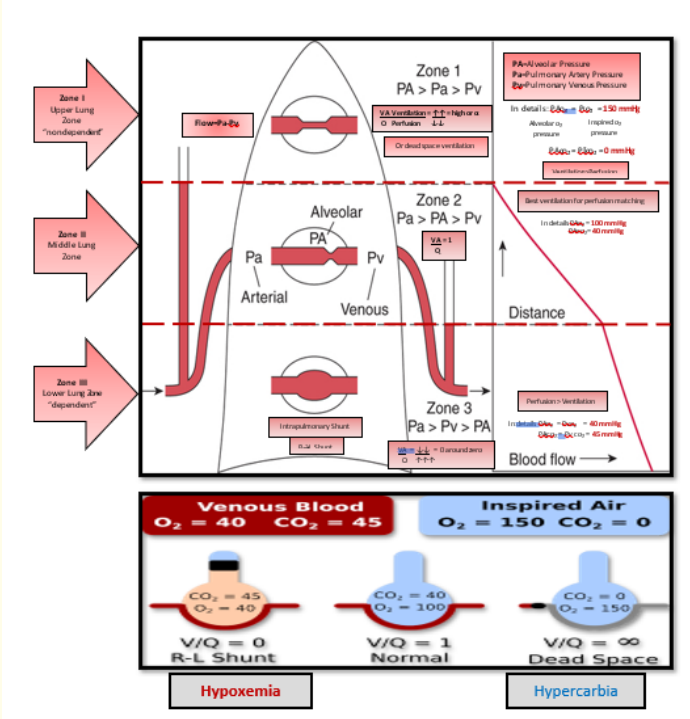

Figure G

Notice: 1. In supine position, pulmonary blood flow was distributed preferentially to the dorsal (dependent) region but make heterogeneity of perfusion existed within tissue planes that were subject to identical gravitational forces. 2. in prone position pulmonary blood flow was also preferentially distributed to the dorsal (now nondependent) region and flow within isogravitational planes was more uniform.

The influence of V/Q imbalance on blood gas tensions is magnified in ARDS consolidation and collapse of the lung units are wide spread and fluid-filled alveoli acts as Low V/Q lung units R→L shunt "intrapulmonary and this leading to elevation in $PaCO_2$. "The most important one". Also, consolidation of disease alveoli creates radial traction forces on neighboring lung units that result in alveolar over distension and pulmonary capillary narrowing, creating a high V/Q areas and adding to alveolar dead space.

Host immune response: Role of cytokines and alteration of hemostasis

- The host immune response plays a crucial role in the pathogenesis of ARDS, by disturbing the balance between pro inflammation and anti-inflammation and pro coagulation and anti-coagulation.
- The cascade of events that characterizes the innate immune response to alveolar injury begins with the engagement of intra and extra cellular PRRs. Pattern Recognition Receptor.

PRR are a family of molecules expressed in (alveolar macrophage, epithelial cells, and intraepithelial dendritic cells).

That recognize:

- Pathogen-associated molecular patterns PAMP.
- Cellular Damage-associated molecular patterns DAMP.
- Also, activate the synthesis of pro-inflammatory cytokines.

There is a similarity between PAMP-triggered and DAMP-triggered inflammatory phenotype due to similarity between bacterial DNA and host mitochondrial DNA both of which can activate the innate immune response through the Toll-Like receptor (TLR) signaling pathway, which is a member of PRR.

TLR are a series of cell surface or endosomal membrane structure that can recruit intermediary adapter molecules to assemble a signaling pathway that ultimately triggers interferon α and β expression and/or NF-kB activation.

NF-kB: Is a transcription factor that controls the expression of proinflammatory cytokines, TNFα, IL-1β, IL-8 a few of the earliest response agents of the innate immune system.

Once expressed TNF-α and IL-1β subsequently stimulate the production of other pro inflammatory interleukins such as IL-6 and potentiate the interaction between β_2 integrin on neutrophils and intracellular adhesion molecule-1 ICAM-1 on vascular endothelial cells. This interaction attaches the neutrophil to the endothelium.

There after IL-8 works together with complement system C_3a, C_5a.

Leukotriene B_4- Platelet activating factor PAF to establish a chemotactic gradient that recruits neutrophils from their endothelial attachments into the alveolar space, where they are capable of elaborating oxygen and nitrogen free radical so the release of Reactive Oxygen Species ROS potentiates additional damage to alveolar epithelial cells, leading to their dysfunction and apoptosis. Then products

of cellular injury serve to perpetuate the cycle of tissue injury by engaging PRRs and renewing the inflammatory response. PRR activity on macrophages and dendritic cells ultimately has a role in influencing T cell behavior during the adaptive phase of the host immune response.

TNFα and IL6 play a part in connecting the inflammatory response with the coagulation cascade, by either promoting coagulation or impairing fibrinolysis.

The role of TNFα:

- Inhibit antithrombin AT.
- Inhibit activated protein C APC.
- Inhibit tissue factor pathway inhibitor TFPI.
- Inhibit fibrin degradation through upregulation of plasminogen activator inhibitor PAI.

The role of IL-6:

- Stimulate the extrinsic coagulation pathway through interaction with tissue factor TF which expressed on the surface of alveolar epithelial cells, activated macrophage, and vascular endothelial cells, and is upregulated in response to inflammatory stimuli.
- Important note by Bastarache., *et al*. the pulmonary edema fluid of mechanically ventilated patients with ARDS, is enriched with TF-bearing, highly procoagulant micro particles, which appear to have a risen from alveolar epithelial cells.

TF+FVII → TF-VIIa activate F Xa → Activate II → IIa which in turn activate Fibrinogen to fibrin.

APC has a role in attenuating the inflammatory response:

1. Coagulation inhibitor as an anti FVa and F VIIIa
2. Inhibit Neutrophil chemotaxis
3. Down regulate production of pro inflammatory cytokines such as IL-6 conversely, conversion of protein C to its activated form is a process that is suppressed in the presence of pro-inflammatory cytokines.

PC activation takes place in the surface of alveolar epithelial cells as well as a vascular endothelial cells, in the presence of two entities:

1. Thrombomodulin TM and
2. Endothelial Protein C receptor EPCR in a process intended to modulate coagulation (and inflammation) in the alveolar compartment as well as in the intravascular space.

They found that there is a higher level of soluble EPCR and TM in the alveolar fluid than in plasma of ARDS patients who are mechanically ventilated adults.

Thus, coagulation and fibrin deposition in the alveolar compartment may owe their origin to the metalloprotease-mediated shedding of TM and EPCR from injured epithelia and the resulting reduction in protein C activation capacity.

Whether the individual patient with ARDS expresses, on balance, a predominantly procoagulant or anticoagulant phenotype seems likely to be a function of the interaction between host genetics and the specific inciting factors that leads to disease development. But we noticed that the supportive strategy selected by the clinician can potentially modify this process.

For example, mechanical ventilation using a large tidal volume TV≈20cc/kg seems to be associated with release of PAI-1 and reduced fibrinolytic activity as compared to control animals that ventilated with 6cc/kg TV.

Another group of investigators has reported that patients who were ventilated for 5 hours after an elective surgery.

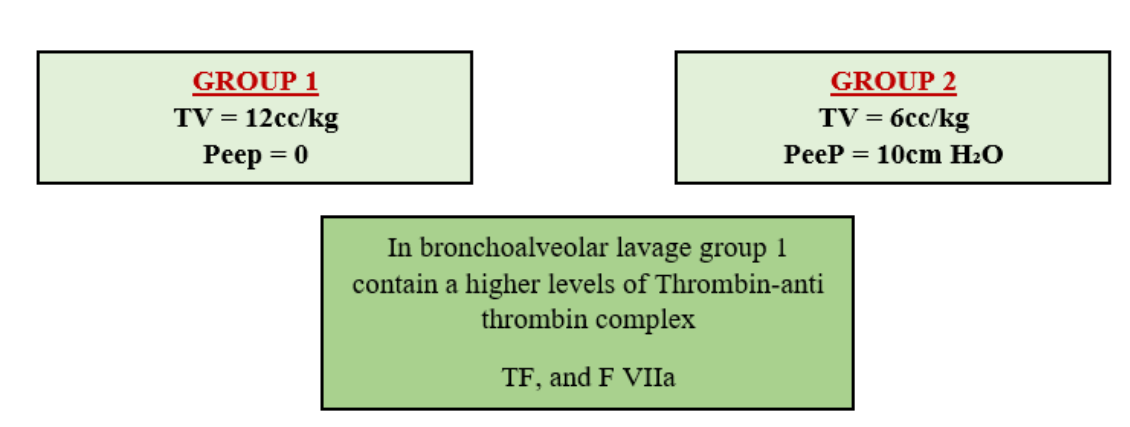

Figure H

In summary

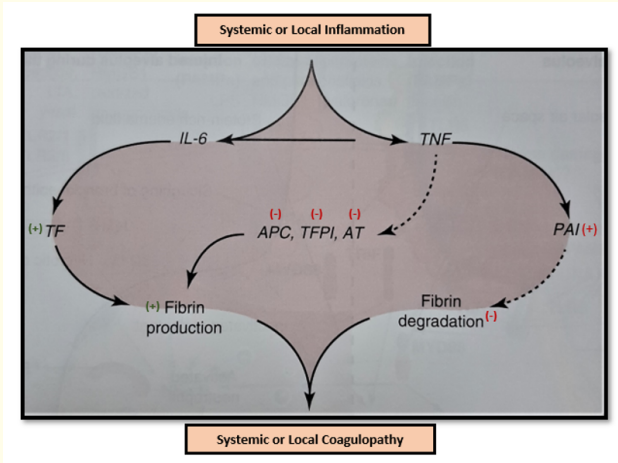

Figure I

In summary

The host inflammatory response concurrently produces its own regulators a phenomenon which may account for the observation that anti-inflammatory therapies can have the undesired effect of interfering with disease resolution.

Innate immune response transitions to a more specific immune response in which activated lymphocytes and monocytes produce anti-inflammatory cytokines: such as tumor growth factor-β which down regulating the effect of their pro inflammatory counterparts on neutrophils and endothelial cells.

Elaboration of extracellular matrix eventually takes place giving way to the Fibro proliferative stage of Disease.

Successful containment of exogenous and/or endogenous triggers of the inflammatory response induces a distinct pro resolution program in host tissue allowing egress and an apoptosis of infiltrating cells and return to premorbid levels of cellular homeostasis.

Dysregulation of this process can actually set the stage for chronic inflammation an observation which may open new avenues for future therapeutic approaches.

Optimally, resolution of acute inflammation in ARDS is mediated by IL-10 an anti-inflammatory cytokine, that attenuates fibrosis and the activity of NF-Kβ, its impact on NF-Kβ helps to induce neutrophil apoptosis and allow for repopulation of bronchial and alveolar epithelium, a process that may involve endogenous stem cell proliferation rather than multiplication of any differentiated cells that remain.

Alteration of cardiovascular function: Effects on pulmonary hemodynamics

The development of permeability edema in the lung, which leads to alveolar hypoxia, thrombotic obstruction of the pulmonary microvasculature, and eventual interstitial fibrosis, each of these pathophysiologic elements has the potential to increase pulmonary vascular resistance [PVR], adding to right ventricular afterload and potentially compromising cardiac output.

PVR is minimal or optimal at the lung volume that corresponds to FRC or normal EELV.

- As EELV increases toward total lung capacity:

  1) Extra-alveolar vascular resistance drops as these vessels become less tortous.

  2) Intra-alveolar vascular resistance escalates very rapidly as alveolar distension begins to compress these vessels.

The net result is an exponential increase in PVR

- As EELV drop towards residual volume:

  1) Extra-alveolar vessels increase as they become more tortuous.

  2) Intra-alveolar vascular resistance decreases as less compress on these vessels.

  3) Hypoxia also causes a pulmonary vasoconstriction which leads to a more increase in PVR.

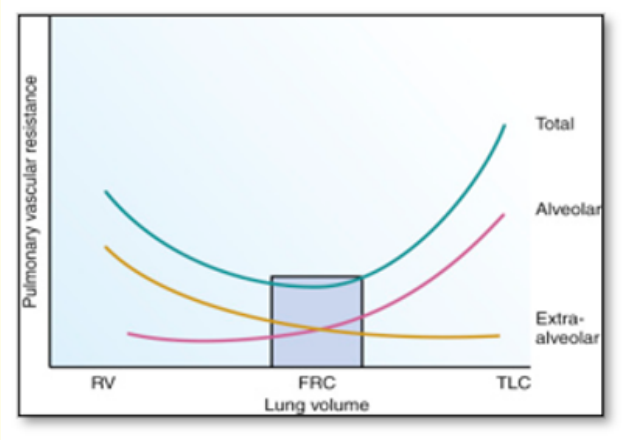

Figure J

An increase in PVR → an increase in RV after load → an increase in end-diastolic volume →in highly complaint RV shifts the interventricular septum towards the left → decrease LV compliance and poor LV Filling.

Clinical presentation

- When fluid accumulate in the interstitial space and exceeds the absorptive capacity of the pulmonary lymphatics, lung compliance declines and tachypnea ensues as the patient attempts to generate adequate minute ventilation in the face of Lower TV with resultant Hypocarbia, however as respiratory muscle fatigue ensues the $PaCO_2$ will further rise.
- The eventual leakage of proteinaceous fluid into the alveolar spaces interferes with native surfactant function, creating conditions that favor regional atelectasis and small airway closure, as well as a decrease in EELV to a point near or below closing capacity especially in small infants and those with highly compliant chest wall (e.g. patient with neuromuscular disease), at this point, hypoxia rapidly worsens and breathing become more labored in an effort to generate trans pulmonary pressures sufficient to maintain alveolar patency.
- On auscultation, the patient will typically demonstrate rales over areas of atelectasis or alveolar congestion, and decrease air entry over areas that are largely consolidated occasionally, it is possible to appreciate wheezes in areas in which intermittent small airways closure is occurring.

Imaging studies

- If you see a Chest X-ray that has bilateral white shadow in the lungs and you suspect ARDS look for the following clues:
    1. The shadows are bilateral, fairly ill defined “difficult to see a clear edge and also it may have the features of consolidation” e.g. air Broncho gram within it.
    2. To distinguish ARDS from LVF:

a. Normal heart size in ARDS.

b. In ARDS shadowing are more peripheral.

c. Kerly B lines are more common in LVF.

   Kerly B lines: caused by edema of the interlobular septa, they are horizontal non branching, white lines best seen at the periphery of the lung just above the cost phrenic angle.

d. Pleural effusion much more common in LVF.

e. Look at old films.

ARDS and CT

1. Always bilateral lung changes.
2. The most common abnormalities are ground glass shadowing and consolidation.
3. Interstitial thickening "Linear opacities" due to fibrosis.
4. As a general role: Asymmetrical distribution of shadows is more likely to be due to pulmonary disease mostly pneumonia.

A symmetrical distribution due to extra-pulmonary disease like sepsis.

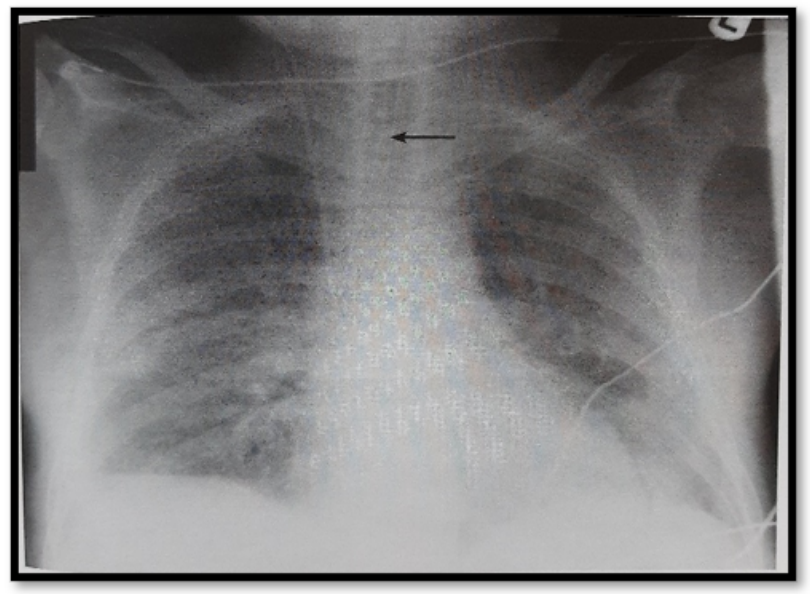

Figure 1

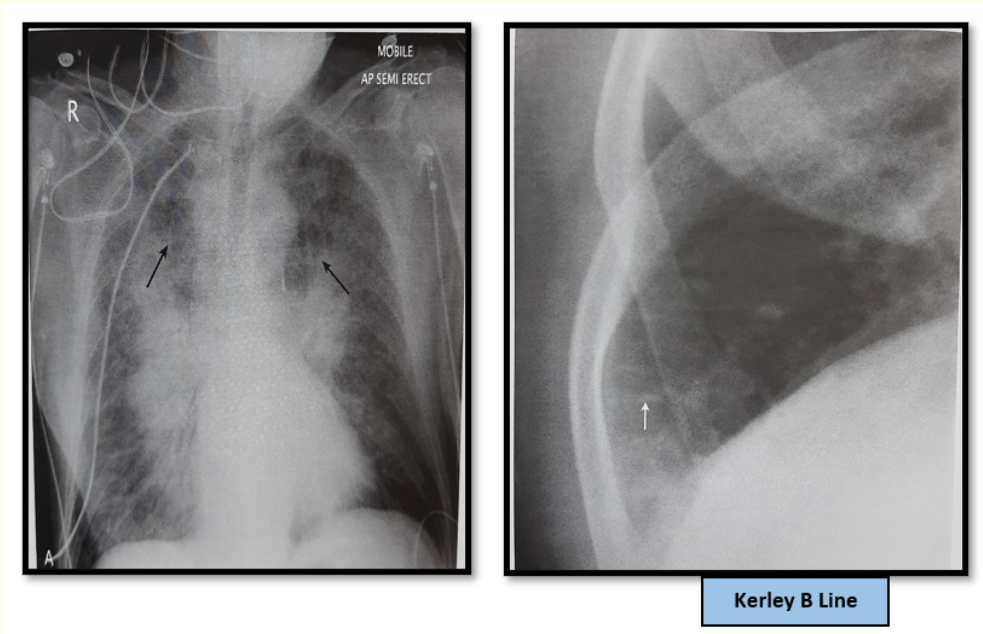

Figure 2

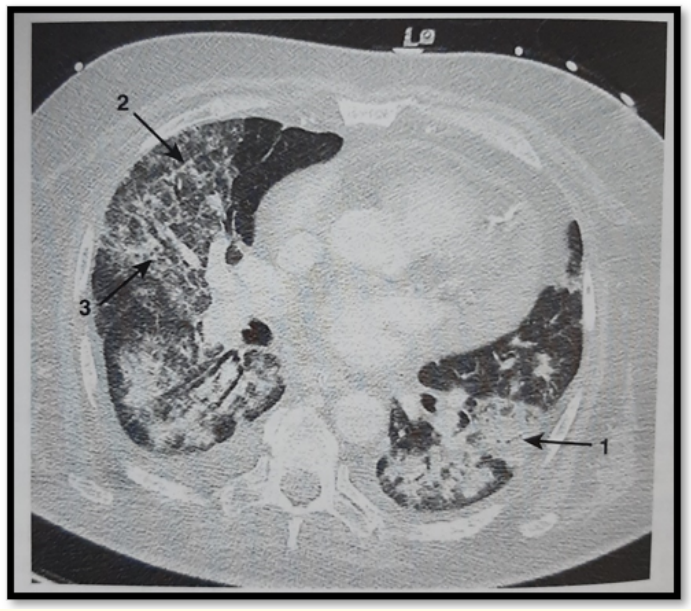

Figure 3

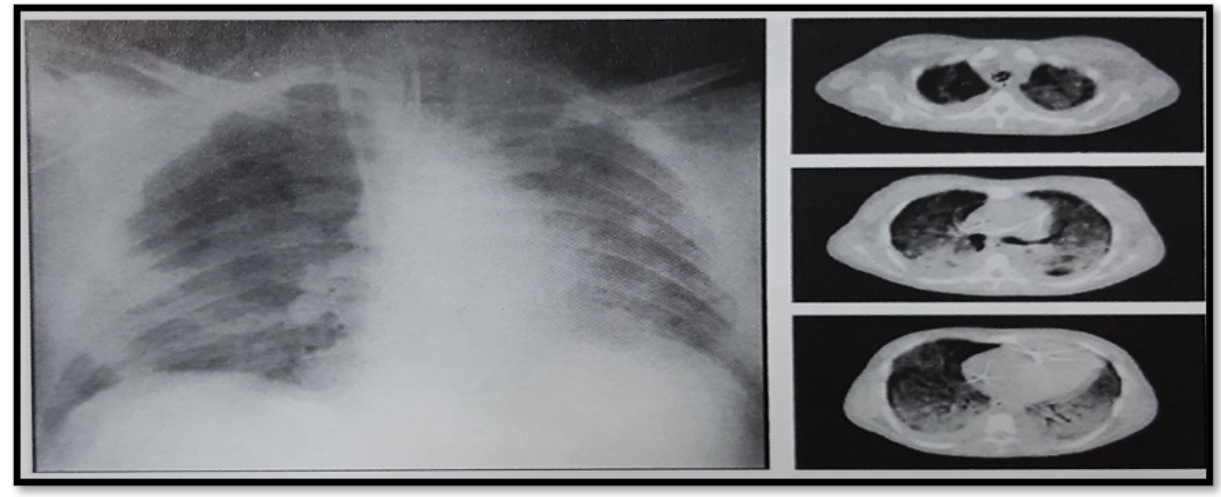

Figure 4

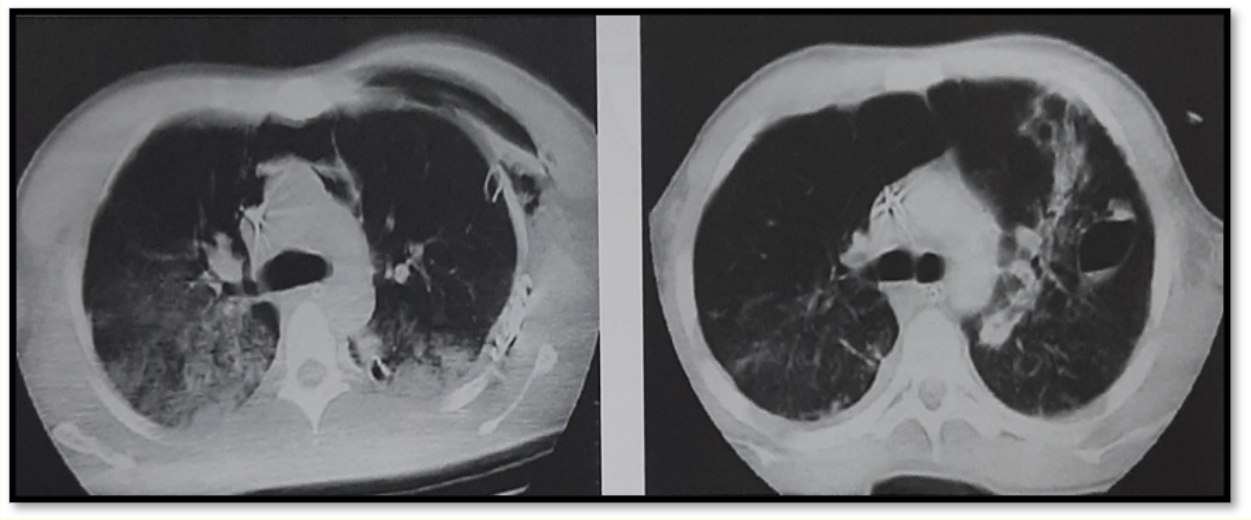

Figure 5

Principles of clinical management

The mainstay of therapy remains supportive care, of which a critically important component is the application of positive pressure ventilation.

Positive pressure ventilation

Hypoxia mainly due to breakdown of the alveolar-capillary barrier and V/Q mismatch which is refractory to the provision of Supplementary oxygen alone. Also in humans the O_2 Supplement with FiO_2 > 0.5 long time can itself causes a lung injury.

The importance of PeeP in reversing Hypoxia is by redistributing extravascular lung water and restoring EELV toward FRC. Also limit the development of ventilator-associated injury.

Also it is important to recognize the potential for Peep to augment anatomical dead space by distending large airways, and potentially adding to alveolar dead space as well.

Also take into account the effect of PPV on cardiovascular function.

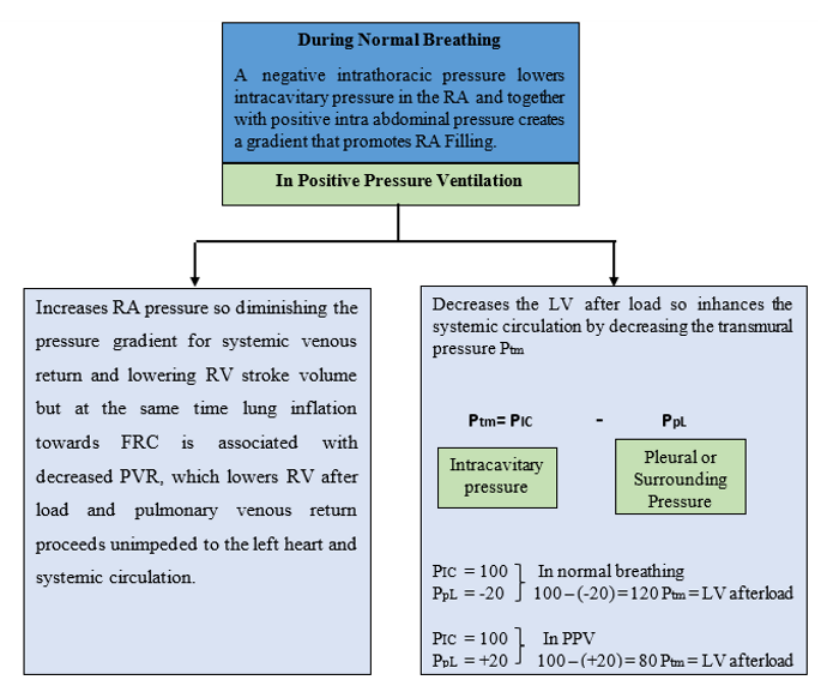

Figure K

In a summary, A sound physiologic basis supports the expectation that titrating PeeP in a way that achieves alveolar recruitment, avoids alveolar over distention, and optimizes the relationship of ventilation to perfusion will provide adequate gas exchange, while limiting the possibility for exposure to additional lung injury and potentially adverse cardiovascular effects.

A logical strategy suggests stepwise escalation of Peep in 3→5 cm H_2O increments until arriving at the minimum Peep that allows for a PaO_2 in the range of 55 - 80 mmHg with SpO_2 of 88 - 95%, using an FiO_2 of 0.5 - 0.6.

Relating tidal volume "TV"

Evidence indicate that limiting phasic changes in lung volume and preventing alveolar over distension at end-inspiration will reduce the risk of ventilator associated lung injury.

Exposure to a large TV ventilation strategies have been associated with the development of ALI in patient with previously normal pulmonary mechanics and exposure to high volume/low PeeP strategies has been associated with rapid enhancement of inflammatory cytokine expression in plasma or BAL Fluid samples in adult with and without ARDS.

Both observations implicate physical forces imposed by mechanical ventilation in the pathogenesis of ALI.

Acute injury makes the lung particularly susceptible to ventilator-induced stress and strain wounds

Mechanical stress

The force per unit area that develops in response to a force applied in the opposite direction.

Stress is analogous to trans alveolar distending pressure which is determined by PeeP and plateau pressure.

Strain

Strain is related to the ratio of a structures change in length, to its length at rest (of course in response to an applied force)

Strain is analogous to phasic alveolar stretch which is determined by end-inspiratory lung volume (TV).

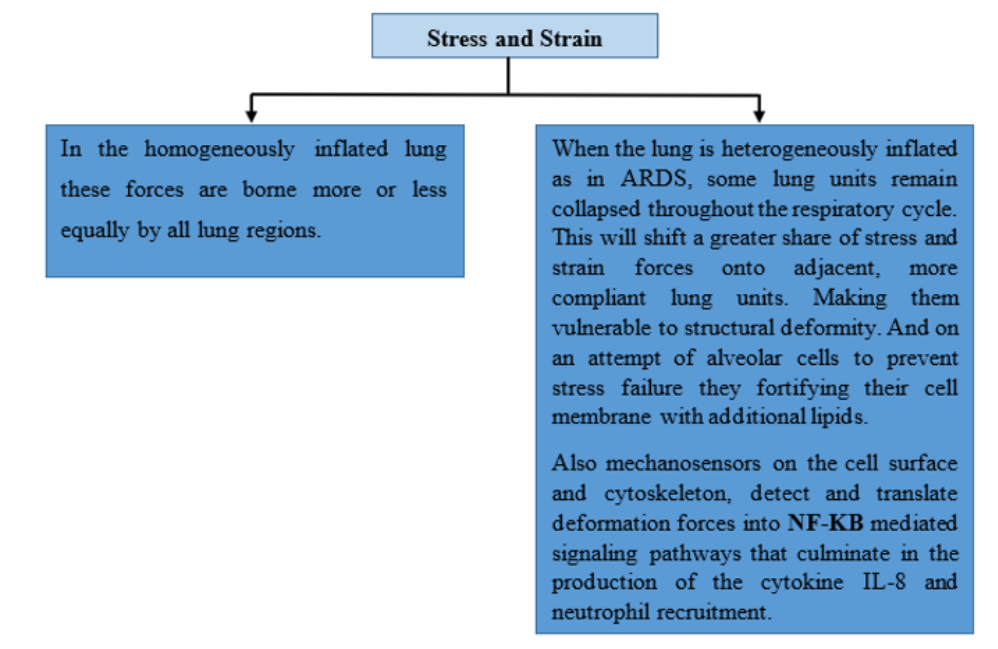

Figure L

So many trials said that limiting TV could result in significantly decrease mortality in ARDS with a lower plasma levels of IL-6.

And many studies conclude that reducing the magnitude of phasic stretch during mechanical ventilation influences patient outcomes by attenuating the systemic inflammatory response.

Mechanically the salutary effects of limiting trans alveolar pressure (i.e. plateau pressure) and limiting phasic stretch through TV reduction maybe related to reduction in alveolar stress and strain forces.

Also, some studies concluded that higher PeeP conferred 4% absolute reduction in mortality.

HFOV: Better suited for patients with diffuse alveolar disease that is coupled with increased chest compliance "a condition that commonly coexist in infant and young children with ARDS especially if applied early in the course of disease.

Fluid management

- Decades ago, laboratory evidence from large animal models of ALI indicated that lower cardiac filling pressures and intravascular pressure could limit extravascular lung water accumulation without impairing tissue oxygenation.
- And a recent laboratory evidence offers new insight into the mechanism behind this observation by suggesting that hydrostatic pressure elevation in post capillary pulmonary venules may in fact be capable of triggering (or exacerbating) the inflammatory response.
- But take care that the contemporary lung-protective strategies of mechanical ventilation that have recently proven to reduce mortality in ARDS, often call for high levels of PeeP to stabilize alveolar volume, and intravascular volume supplementation may be necessary in this context to optimize V/Q relations and improve the overall cardiac output.
- Also conservative strategy (of fluid) was associated with an improvement in oxygenation index and a significant increase in ventilator free days during the first 28 days of therapy, although it didn't seem to increase the incidence of renal failure or need for dialysis, but mortality was similar between the conservative group and liberal group.

Adjuvant therapies in ALI and ARDS

Prone positioning:

- In ARDS alveolar consolidation occur along the gravitational axis and because pulmonary blood flow is distributed preferentially to dorsal lung regions so it is logical to speculate that V/Q relationship in mechanically ventilated injured lung can be improved by manipulating body position.
- Also one could imagine that placing a patient prone might reduce chest wall compliance, thus transmitting airway pressure to the alveoli more efficiently, stabilizing alveolar volume, and distributing stress and strain forces over a large portion of previously no aerated lung units.
- Also in many studies they found a significant mortality benefit from prone position especially in those with TV > 12 cc/kg.
- Although existing data don't support the routine use of prone positioning for infants and young children with ARDS, the strong scientific basis for this intervention may prompt clinicians to use it in individual patients whose specific underlying physiology suggests that their gas exchange efficiency may improve as a result. In such cases improvement in gas exchange are occasionally

substantial enough to allow weaning from potentially injurious inflation pressures and/or fractional inspired oxygen concentrations.

Surfactant

- Analysis of Broncho alveolar Lavage BAL fluid from post mortem lung specimens demonstrated alterations in the lipid-to-protein ration of endogenous surfactant and an overall increase in surface tension in ARDS, compared to healthy controls.
- The results of many trials suggest a possible benefit of surfactant in pediatric population, but it is not clear if this finding is due to the intrinsic superiority of Calfactant compared to other preparations, or to other issues with the study design.
- In the Calfactant trial as well, post hoc analysis revealed that patients with direct forms of lung injury experienced a greater mortality benefit than those with indirect forms of injury.

Despite the evidence for surfactant and dysfunction in ARDS, outcome benefits associated with the use of surfactant in this relatively heterogeneous patient cohort have not come close to those reported in association with its use in surfactant-deficient neonates with the neonatal respiratory distress syndrome.

It is logical to speculate that the mechanical ventilation strategy used for ARDS may confound the effects of exogenous surfactant in these diseases, because such patients generally require mechanical ventilation support for a longer period of time than do newborn with neonatal respiratory distress syndrome.

Although the data have yet to identify a clear indication for the use of surfactant in ARDS, arriving at the "ideal" surfactant dose and composition as well as the timing of its administration, will ultimately depend on understanding its interaction with the chosen mechanical ventilation strategy.

Corticosteroids

- Using corticosteroids is appealing for several reasons:
    - **First:** Limit transudation of plasma across the capillary endothelium.
    - **Second:** Exert anti-inflammatory effects by downregulating expression of steroids responsive genes coding for pro inflammatory cytokines.
    - **Third:** Upregulate genes encoding for anti-inflammatory cytokines such as IL-10.
- Studies that evaluated short courses of high-dose corticosteroids administered early in ARDS were not able to demonstrate an outcome benefit, although the data on the use of corticosteroids in persistent ARDS are thought to be more encouraging.
- Methylprednisolone was not associated with an increase infectious complications, but we did identify a higher incidence of neuromuscular weakness in the treatment group.
- The most recent corticosteroid trial leaves open a number of questions, including how best to address hyperglycemia and other collateral effects of corticosteroid administration in critically ill patients.
- Moreover, future studies must incorporate the evolving evidence base of BEST PRACTICES with regards to mechanical ventilation strategy and metabolic hemodynamic and sedation management.

Inhaled nitric oxide

Known as "endothelium-derived relaxing factor" that couples with cGMP system to mediate vasodilation by local smooth muscle relaxation and to modify immune function and PLT aggregation.

In the lung Nitric Oxide is produced by the endothelium, airway smooth muscle cells, inflammatory cells, platelets, epithelial cells, and fibroblasts as a product of the conversion of L-arginine to citrulline by the enzyme Nitric Oxide synthase, Nitric Oxide binds readily with hemoglobin, resulting in its own inactivation and the production of nitrosyl-hemoglobin and methemoglobin.

Nitric Oxide can also interact with O_2 to form NO_2, which has been associated with provoking the host inflammatory response in laboratory animals exposed to ambient concentration as low as 1.5 ppm (parts per million).

Nitric Oxide could serve a selective pulmonary vasodilator if administered exogenously (iNO inhaled Nitric Oxide).

In summary, the data don't support routinely offering iNO to nonseptic patients with ARDS, but of course some individuals suspected of having particularly reactive pulmonary vasculature may yet benefit from this therapy.

In cases in which the clinician elects to use iNO as an adjuvant therapy in ARDS, its dose-response behavior should be considered.

After a few days of exposure to iNO at a constant dose, ARDS patients appear to become more sensitive to its effects.

Clinicians should also consider potential strategies for optimizing iNO delivery to the alveoli.

Post hoc analysis of the original iNO study data reported that delivering iNO in combination with HFOV appeared to produce greater improvement in oxygenation than either therapy alone.

These findings suggest that ventilation strategies that incorporate sustained alveolar recruitment may be more likely to potentiate any favorable effect of iNO.

Activated protein C

We know that the inflammatory and coagulation systems interact to alter the hemostatic balance in inflammatory states.

Activated Protein C is a naturally occurring anticoagulant that reduces the tendency toward thrombosis by inhibiting coagulation factors Va and VIIIa, which decreases thrombin formation.

It is also capable of downregulating production of proinflammatory cytokines, such as IL-6 and inhibiting neutrophil chemotaxis.

Protein C activation has long been known to take place the actions of the thrombin-thrombomodulin complex and the protein c receptor both located on the surface of vascular endothelial cells, which is impaired during the systemic inflammatory response, owing in part to widespread endothelial injury.

Evidence supporting a role for APC in the mitigation of both local "alveolar" and systemic coagulation and fibrin deposition in ARDS.

Also interpreting the adult APC trials in light of this information raises the possibility that APC exerts important local effect, rather than generalized systemic effects in patients with severe sepsis, and one such benefit includes modulation of fibrin turnover in the lung.

At this point, it appears that the APC chapter may have closed with the withdrawal of recombinant human APC from the market in 2011.

Modifying alveolar fluid clearance

- Studies that related impairment of alveolar fluid clearance to increased mortality in ARDS suggest that attention to this aspect of care in these conditions should 'in theory' offer the promise of reduced mortality.
- Since the local cellular mechanisms of alveolar fluid accumulation and clearance as potential therapeutic targets with less apparent risk of provoking unwanted systemic effects.
- Airway epithelial ion and fluid transport is reduced by alveolar hypoxia and recent data indicate that this phenomenon can be reversed by re oxygenation as well as through stimulation of β_1 and β_2 adrenergic receptors found on alveolar epithelial cells.

For instance, alveolar fluid clearance appears to be stimulated by β-receptor agonists administered IV or instilled directly into the alveolar space.

The β-agonist-mediated increase in alveolar fluid clearance is reversible by amiloride, suggesting that β-agonists are upregulating transepithelial Na transport. It appears that the adrenergically mediated increase in Na Flux is triggered by IC movement of Cl⍰ through the cystic fibrosis transmembrane regulator CFTR located in the apical surface of alveolar type II cells.

In addition, β-agonists are suspected of having other potentially favorable effects, such as inhibiting:

- Endotoxin-induced pro inflammatory cytokine release.
- Endotoxin-related coagulation and pro-inflammatory neutrophil activity.

But even β_2 agonists could be delivered reliably to injured alveoli, the alveolar epithelium in some lung units may be denuded as to be unable to respond to them.

Also, there is a competing challenges of delivering β_2 agonist agents to injured alveoli while avoiding systemic toxicity [tachycardia, arrhythmias and lactic acidosis].

Nutritional support in ARDS

- Over the past several years, a number of reports support the concept that enteral rather than parenteral nutrition can preserve functional integrity of the gastrointestinal mucosal barrier and decrease the potential for intestinal bacterial translocation and systemic infection.
- There is evidence supporting a critical role for fatty acid metabolism in the inflammatory cascade, specifically:
    - Linoleic, α Linolenic acid are essential fatty acids that are converted after ingestion to cell membrane associated lipids, such as:
    - Arachidonic acid, eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA] which possess a central role in host immunity.
- For inflammation pathway.

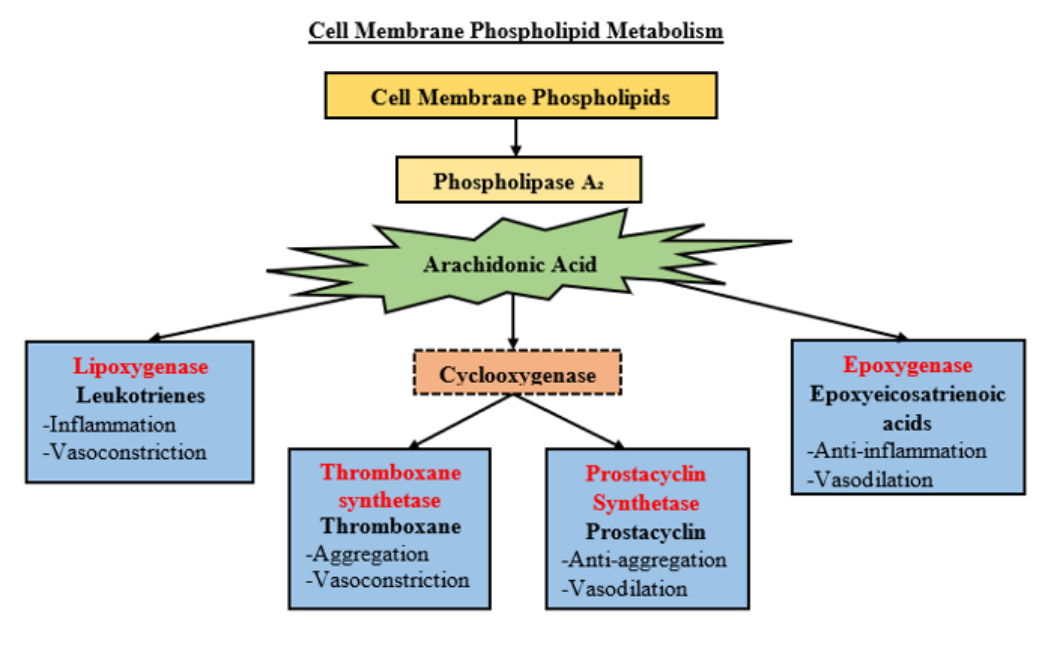

Figure M

The central role of the arachidonic acid pathway in inflammation results from the ubiquity of its parent compound Linoleic Acid, in the human diet, leading to its over-representation as a cell membrane constituent relative to compounds in the α-Linoleic acid family.

- [Leukotrienes E_4 is a product of arachidonic acid metabolism].
- [Leukotrienes E_5 is a product of EPA and DHA metabolism].

Not surprisingly, increases in arachidonic acid metabolites have been documented in ARDS, Leukotrienes, prostaglandins, thromboxane have been identified in plasma urine and BAL Fluid.

And are believed to be accountable for many undesired collateral effects of the host immune response, such as vasoconstriction, platelet aggregation and increases airways resistance.

Administration of arachidonic acid precursors to patient with ARDS seems to increase thromboxane A_2 production, while inhibiting cyclooxygenase activity seems to improve gas exchange, relieve vasoconstriction, and decrease airway resistance.

Thus, the ultimate constituents of cell membranes reflect the balance of ingested fatty acids, and dietary manipulations can influence the characteristics of the host inflammatory response.

One of the early studies was a prospective RCT in 146 ARDS patients that showed an increased EPA to -AA ratio in plasma, and a reduction in BAL fluid neutrophil content, intensive care unit stay, development of new organ failures, and duration of mechanical ventilator support among patients receiving enteral feeds supplemented with Omega-3 Fatty acid EPA, αLinoleic acid, and antioxidants.

But at this time it remains uncertain whether enteral supplementation with less inflammatory fatty acids can reliably produce a shift in cell membrane phospholipid in critically ill ARDS patients to a degree that would produce a mortality benefit.

Role of extracorporeal membrane oxygenation in pediatric ARDS

- In any case the best outcome can be expected from patients with reversible lung injury who are identified as failing conventional therapy before they begin to develop non pulmonary organ failures.
- A growing amount of data indicate that the trend in oxygenation index OI a measurement that characterizes oxygenation as a function of the intensity of ventilator support, is a reliable indicator of a patient's prospect for responding to a course of mechanical ventilation for severe ARDS and serial measures may assist the clinician in identifying patients who may benefit from ECMO before the transition into a syndrome of irreversible multi organ dysfunction.

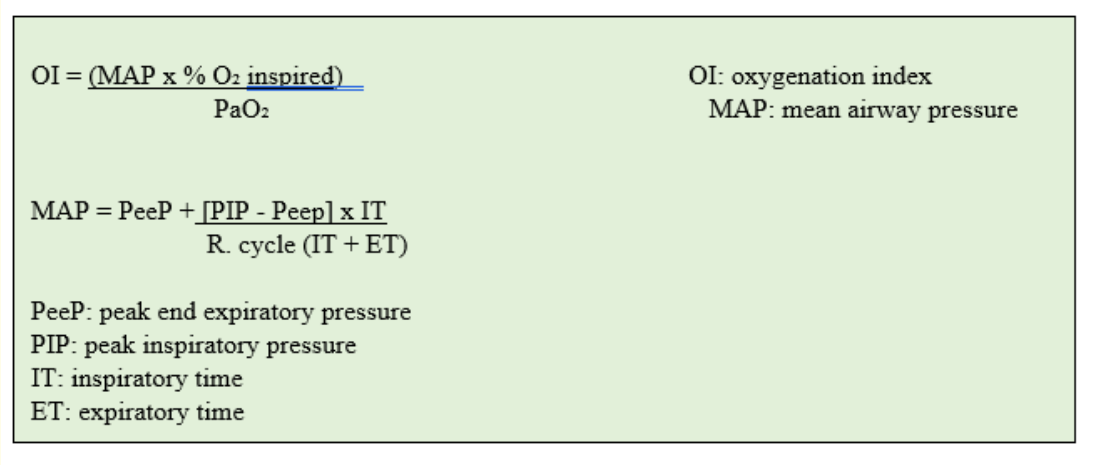

Figure N

The higher the OI the more severe lung injury.

Example: A term newborn + OI ≥ 40

A very severe lung pathology and it is an indication for ECMO.

Outcomes in pediatric ARDS

Recent data indicate that mortality in pediatric ARDS seems to be decreasing.

And it has long been suspected that death from ARDS rarely occurs as a result of refractory impairment of gas exchange, but that is more often occurs in association with development of multiorgan dysfunction.

Thus, one mechanism by which a non-injurious mechanical ventilation strategy impact ARDS outcomes may involve its interference with the development of non-pulmonary organ dysfunction [1-3].

Conclusion

The only interventions that have proven to result in a significant mortality benefit among patients with ARDS are simple variations on a form of therapy that is applicable to all patients with this disease regardless of etiology, namely Low Tidal Volume Ventilation and mechanical ventilation in the prone position.

But still we have to evaluate ARDS prevention strategies for patients requiring extended courses of MV.

And by refining the diagnostic criteria in ways that make them capable of distinguishing clinically relevant subgroups of ARDS patients.

Bibliography

1. Ashok P Sarnaik., *et al.* "Respiratory Distress and Failure". Nelson Textbook of Pediatric (2020): 583-601
2. Kathleen M Ventre and John H Arnold. "Acute Lung Injury and Acute Respiratory Distress Syndrome". Roger's Textbook of Pediatric Intensive Care (2018): 766-790.
3. Jonathan Corne and Maruti Kumaran. "Acute Respiratory Distress Syndrome. Chest X-ray made easy" (2017): 74-76.

Volume 10 Issue 10 October 2021
© All rights reserved by Abdulnasser Ahmed Skheita.