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1. Adjuncts in the Management of ARDS

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EDITORIAL COMMENTS

Acute respiratory distress syndrome (ARDS) is a relatively common and fatal disorder of diverse etiology. However, the common pathophysiology is almost similar leading to diffuse lung damage and respiratory failure. Earlier, the outcome used to be fatal with mortality rates as high as 70-80%. However with the use of newer ventilatory strategies the survival has improved grammatically. Although ventilatory support is the main stay of treatment various adjuncts has recently been introduced which are thought to be useful in the survival and benefit to these patients.

ADJUNCTS IN THE MANAGEMENT OF ARDS

Since the initial description of ARDS, mortality rates have ranged from 50 to 70%.

Improved understanding of pathogenesis of acute lung injury (ALI/ARDS) has led to important advances in the treatment of ALI/ARDS

Recent reports suggest that the mortality associated with ARDS may be falling, probably because of advances in supporting critically ill patients

In this article we review the modern supportive care to treat ARDS.

ADJUNCTS IN TREATMENT OF ARDS

1. Ventilatory Strategies other than Lung Protective Strategy.
 - Prone ventilation
 - Liquid ventilation
 - High Frequency ventilation
 - Tracheal gas insufflation
 - Extracorporeal gas exchange

2. Hemodynamic management - fluids, vasopressors
3. Selective pulmonary vasodilators
4. Surfactant replacement therapy
5. Anti-inflammatory strategies
 - a) Corticosteroids
 - b) Cyclooxygenase & lipoxygenase inhibitors
 - c) Lisofylline and pentoxifylline.
6. Antioxidants - Procyteine; N-acetylcysteine
7. Anticoagulants

a) Prone Ventilation

Prone ventilation improves oxygenation and allows reduction in FiO₂ and PEEP requirement. The response is variable and not predictable. Overall response to prone ventilation occurs in 50-70% cases of severe ARDS. Proposed mechanism, how it improves oxygenation include

- 1) increase in FRC
- 2) improved ventilation of previously dependent regions
- 3) decrease chest wall compliance
- 4) improvement in ventilation perfusion
- 5) better clearance of secretions
- 6) improved lymphatic drainage

Contraindication to Prone Position Ventilation include

1. Unresponsive cerebral hypertension
2. Unstable bone fractures
3. Left heart failure
4. Hemodynamic instability
5. Active intra abdominal pathology

The frequency, duration and timing of prone positioning has varied among different studies.

Many protocols have described the effect of one time change in position on patients oxygenation. The median length of time, the patients remained in prone position has varied from two hours (interquartile

range 1-4 hrs) to four hours (interquartile range 2-30 hrs). Prone positioning can be achieved by Circ Olectric, bed manual 2 step, light weight portable support frame (Vollman prone positioner).

Several persons (range 3-5) are required to safely implement prone position. Adequate sedation with or without paralytic agents is required to facilitate mechanical ventilation in prone position. Clinical caveats related to prone positioning include repositioning of cardiac monitoring electrodes on to the patient back and anticipating increase bronchial secretions.

Complications

1. Pressure sore
2. Accident removal of endotracheal tube; catheters, arterial / venous lines
3. Arrhythmias
4. Reversible dependent oedema (face, anterior chest wall)

Several randomized control trials have shown that prone positioning improves oxygenation but there is no effect on survival.

b) Partial Liquid Ventilation

In ARDS, there is increased surface tension which can be eliminated by filling the lungs with liquid.

Perflurocarbons are colourless, clear, odourless, inert liquids with high vapour pressure. They are insoluble in water or lipids. The most commonly used perflurocarbon is perfluro octy bromide (Liquivent).

Mechanism of action of perflurocarbon include reduction in surface tension and alveolar recruitment (liquid PEEP). They increase surfactant phospholipid synthesis and secretion. They have anti inflammatory properties which include decrease endotoxin stimulated release of TNF- α ; IL-1; IL-8; decrease production of reactive oxygen species.

	Total liquid ventilation	Partial liquid ventilation
1. Ventilator	Liquid	Conventional
2. Tidal volume is delivered of	Oxygenated PFC	Gas
3. Lungs are filled	Completely by PFC	Filled till FRC by PFC
4. Feasibility	Experimental	Yes
5. Disadvantage	Technically difficult	Loss of gas by evaporation, high cost

PFC-perflurocarbon, FRC-functional residual capacity

Technique of liquid Ventilation :

1. Total liquid ventilation
2. Partial liquid ventilation

The recommended dose of Perfurocarbon is - 20 ml/kg. Beyond this dose there is decrease in cardiac output. More clinical trials are required to demonstrate its efficacy.

c) Tracheal Gas Insufflation (TGI)

In ARDS, there is increase physiological dead space and open lung strategy to ventilate such patients lead to hypercapnia.

During conventional ventilation bronchi and trachea are filled with alveolar gas at end exhalation which is forced back into the alveoli during next inspiration.

In tracheal gas insuffalation stream of fresh air is insufflated (4 to 8 L/min) through small catheter or

through a small channel in the wall of ET into lower trachea flushing CO₂ laden gas.

Complications include

- 1) Dissection of secretions
- 2) Airway mucosal injury
- 3) Nidus for accumulation of secretions
- 4) Auto - PEEP

d) High Frequency Ventilation

It utilizes small volume (<VD) and high respiratory rat(100 b/min) It avoids over distention (VILI). Mechanism of action include alveolar recruitment, enhances gas mixing and improved ventilation perfusion.

Complications include

1. Necrotizing tracheobronchitis
2. Shear at interface of lung
3. Air trapping

Comparison of conventional versus high frequency

	JET	Oscillator	Conventional
Frequency available	Upto 600 b/min	300-3000 b/min	2-60 b/min
Tidal vol delivered	<or> V _D	< V _D	>> V _D
Expiration	Passive	Active	Passive
Potentiatiion of intrinsic PEEP	3+	2+	1+
VT x f product for effective V _A	>> Conv	>> Conv	
P _{PK}	< Conv	< Conv	
P mean	<or> conv	<or> conv	

VD - dead space

Pmean - mean airway pressure

VILI - Ventilator induced lung injury

P_{PK} - Peak airway pressure

b/min - breaths per minute

Conv - Conventional

ET - Endotracheal tube

e) Extracorporeal Membrane Oxygenation

Extra corporeal membrane oxygenation is an adaptation of conventional cardiopulmonary bypass technique. It oxygenate blood and remove carbondioxide extracorporally.

Types of ECMO

1. High-flow venoarterial bypass system.
2. Low-flow venovenous bypass system.

Criteria for treatment with extracorporeal gas exchange

Fast entry criteria

$PaO_2 < 50$ mmHg for > 2 h at $FiO_2 1.0$; PEEP > 5 cmH₂O

Slow entry criteria

1. $PaO_2 < 50$ mmHg for > 12 h at $FiO_2 0.6$; PEEP > 5 cmH₂O maximal medical therapy > 48 h
2. $Q_s / Q_t > 30\%$; CTstat < 30 ml/cmH₂O*

Complications of ECMO

Mechanical	Patient related Problem
1. Oxygenator failure	1. Bleeding
2. Circuit disruption	2. Neurological complications
3. Pump or heat exchanger malfunctioning	3. Additional organ failure
4. Cannula placement/removal	4. Barotrauma
	5. Infection

2) Hemodynamic Management

The management is controversial because restriction of fluid has been found to be beneficial in various observational studies. It has been observed

to decreased pulmonary edema formation, increased lung compliance and improved survival.

Net positive balance < 1 litres in first 36 hours. is associated with improved survival, decrease length of ventilation, ICU stay and hospitalization.

On the other hand restriction of fluids may be detrimental because most patients have associated sepsis which is associated with ineffective circulatory volume. Restriction of fluid in these patients can reduce cardiac output and tissue perfusion.

The goal is to correct volume deficit and thus promote oxygen delivery.

This is achieved by adequate Central venous pressure (CVP) (- 8-12 mmHg) or Pulmonary artery occlusion pressure (PAOP) (-14-16 mmHg).

The oxygen demand can be reduced by adequate sedation, analgesia, neuro-muscular blocking agents, treatment of hyperpyrexia and early institution of mechanical ventilation.

There is no role for supraphysiological oxygen delivery.

Vasopressors should be used following fluid resuscitation with the goal to achieve mean arterial pressure (MAP) > 65 mmHg.

Inotropes should be added if cardiac output is low.

3) Selective Pulmonary Vasodilators

In ARDS there is reduced pulmonary vasoconstriction in hypoxic shunt areas along with vasoconstriction in well ventilated areas. There is pulmonary arterial hypertension because of vasoconstriction and insitu thrombosis. Pulmonary arterial hypertension aggravates edema by increasing inflow pressure hence, role of pulmonary vasodilators.

Selective Pulmonary Vasodilators include:

- a. Inhaled Nitric oxide (INO)
- b. Intravenous almitrine with/without INO
- c. Aerosolized prostacyclins
- d. Inhibition of cyclic nucleotide phosphodiesterase
- e. Inhalation of endothelin receptor antagonists

a) Inhaled Nitric Oxide

It improves oxygenation by selective vasodilatation of vessel associated with better ventilation thus improves ventilation perfusion mismatch. There is reduction in the pulmonary artery pressure. NO also inhibits platelet aggregation and neutrophil adhesion. Selectivity of iNO is because of rapid inactivation on contact with hemoglobin.

About sixty percent of patients respond to INO by increase in arterial oxygenation more than twenty percent.

Maximal improvement in oxygenation is usually achieved by 1-2 ppm and occurs at less than 10 ppm in most. Maximum reduction in pulmonary artery pressures is achieved by 10-40 ppm. Intra-individual variation in response is due to lung recruitment, coexistent pathology and resolution of inflammation. Response to INO is not a static phenomenon.

There is no mortality benefits associated with inhaled NO.

Side-effects are minimal and include

1. Rebound pulmonary hypertension & hypoxemia
2. Met-hemoglobinemia
3. Toxic Nitrous & Nitric Acid

The side effects can be prevented by decreasing the contact time and concentration of gas.

b) Almitrine

It potentiates hypoxic vasoconstriction, thus decreasing shunt and improves oxygenation. It has additive effect with INO and prone ventilation.

c) Aerosolized Prostacyclin

Inhaled prostacyclin selectively vasodilates the well perfused areas. The selectivity is in dose of 17-50 ng/kg/min.

d) PDE -5 Inhibitors

Basal pulmonary vascular tone is believed to be influenced by the balance between cGMP production and PDE - dependent degradation. The PDE - 5 specifically hydrolysis cGMP. Selective PDE-5 inhibitors include dipyridamole and sildenafil.

e) Inhalation of Endothelin receptor antagonist

Endothelins are increased in lungs of patients with ARDS. Stimulation of ETA₂ receptors induces sustain vasoconstriction revealing the potential of ETA₂ receptor antagonist. Non Selective ET antagonist include bosentan and Selective ETA₂ antagonist include sitaxsentan and ambrisentan.

4) Surfactant Replacement Therapy

In ARDs there is deficiency and functional abnormality of surfactant. There is decreased production (injury to type-2 pneumocytes), abnormal composition (decrease phosphatidyl choline, phosphatidylglycerol, Sp. A & Sp. B) and inhibitors of surfactant function (TNF- α , reactive oxygen species peroxynitrite, neutrophil elastases). Impaired surfactant function leads to atelectasis / collapse and increase edema formation so rationale of exogenous surfactant replacement therapy. Sufficient dose of the surfactant should reach alveolar environment to have its beneficial effects. Surfactant therapy should be introduced as early as possible. There is little benefit at 3 to 5 days because fibrosis sets in at this time.

Surfactant delivery techniques include instillation, lavage and aerosolization.

5) Anti-inflammatory Strategies

a) Glucocorticoids in ARDS

Two meta analysis of short course (48hr) of high dose methyl pred. (30mg/kg/d) in early sepsis and ARDS found no evidence of beneficial effects.

In a recent randomized control trial of low dose prolonged administration of methyl prednisolone in patients with unresolving ARDS was associated with improved lung injury score, multiorgan dysfunction score and mortality.

Proposed mechanism of action of steroids in early ARDS include inhibition of transcriptional activation of various cytokines, synthesis of phospholipase A₂, cyclooxygenase, reduced production of prostanoids, Platelet activating factor (PAF), nitric oxide, fibrinogenesis.

b) Cyclooxygenase Inhibitors

Thromboxane A₂ and prostaglandins are produced from arachidonic acid by cyclooxygenase pathway.

They cause neutrophil chemostaxis and adhesion, bronchoconstriction, increased vascular permeability and platelet aggregation.

Ketoconazole is a specific inhibitor of thromboxane synthetase. It also inhibits 5 - lipoxygenase.

NIH ARDS Network trial, 1997, enrolling 234 ALI/ARDS patients, did not show any mortality benefit with ketoconazole.

c) Lisophylline and Pentoxifyline

They are Phosphodiesterase inhibitors. They inhibit neutrophil chemostaxis and activation. Lisophylline inhibit release of free fatty acids from cell membranes under oxidative stress.

6) Antioxidants

There is convincing evidence that reactive oxygen metabolites derived from neutrophils, macrophages and endothelial cells play a major role in mediating injury to the endothelial barrier. Oxidants include super oxide ion (O₂⁻), hydrogen peroxide (H₂O₂), hypochlorous acid (HOCl) and hydroxyl radical (OH). They interact with proteins, lipid and DNA and denature them.

Various antioxidant drugs (N-acetyl cysteine, procysteine, vitamin C and E, precursors of glutathione etc) have been attempted to restore depleted levels of anti oxidants in an attempt to protect the lung from increased free oxygen radical injury.

7) Anticoagulant Therapy in ALI/ARDS

In lungs fibrin deposition intra-alveolar and interstitial is the hallmark of early ARDS.

Local procoagulant activity and reduced fibrinolysis constitute the rationale for anti coagulant use in ALI/ARDS.

Fibrin is a potent inhibitor of surfactant. It along with fibrinectin lays matrix on which fibroblast aggregate. It is a potent chemotactic agent for neutrophils.

a) TF Pathway Inhibitors and Factor VII ai

TF levels are elevated in early ARDS and levels correlate with lung injury score, reduced platelet count and disseminated intravascular coagulation (DIC), score.

In a phase II study there was 20 % relative risk reduction in 28 days, all cause mortality and improvement in organ dysfunction in patients with severe sepsis.

b) Heparin

Its effectiveness in blocking fibrin deposition is debatable. In experimental animals large doses of unfractionated heparin reduced fibrin deposition; prevent extra vascular lung volume and improved PaO₂/FiO₂. Human data is lacking.

c) Antithrombin (AT)

It is broad spectrum serine protease inhibitor. AT inhibits thrombin by forming thrombin-AT complex which is removed from the circulation by reticulo-endothelial system. It also inactivates TF - VIIa complex. It also stimulates prostacyclin release.

AT reduces vascular injury; leukocyte accumulation and vascular permeability.

In the large kybersept trial, there was no reduction in 28 days, all cause mortality but excess rate of bleeding events in patients receiving concomitant heparin prophylaxis.

Possible explanation for this adverse effects includes i) AT levels below expected levels. ii) Heparin prophylaxis could have influenced efficacy. There was improvement in 90 days survival rate in patients receiving antithrombin without heparin.

d) Activated protein- C (APC)

The protein-C pathway plays a major role in the regulation of thrombin formation.

Protein-C when converted to activated protein-C by thrombomodulin complex inactivates Va & VIIa. Thus limit thrombin generation. It also inhibits PAI-1 activity and promotes fibrinolysis. It also inhibits apoptosis.

In the PROWESS study APC administration improved survival in patients with severe sepsis.

7) Enhanced Resolution of Alveolar Edema

Alveolar clearance of edema depends on active sodium/potassium triphosphate pump. Beta 2 adrenergic (Salmeterol, Dopamine, Dobutamine) stimulation markedly increases alveolar fluid clearance.

8) Enhanced Repair

One of the hallmark of ALI/ARDS is disruption of alveolar epithelial with necrosis or apoptosis of alveolar Type I cells. As a part of the repair process, alveolar epithelial Type II cells proliferate and provide a provision of new epithelial barrier. Studies suggest that mitogens for Type II pneumocytes include hepatocyte growth factor and keratinocyte growth factor.

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