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# Acute lung injury/acute respiratory distress syndrome

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# Acute Lung Injury/Acute Respiratory Distress Syndrome

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Reports of pulmonary physiopathological insults following severe trauma resulting in respiratory failure are not new in medical literature<sup>1,2</sup>. In 1967 Ashbaugh and colleagues described a syndrome of acute respiratory distress following a variety of precipitating conditions<sup>3</sup>. Severe hypoxemia, diffuse pulmonary infiltrates, poor lung compliance and absence of left heart failure characterize this condition. Ashbaugh et al<sup>4</sup> subsequently named it as adult respiratory distress syndrome to differentiate it from infant respiratory distress syndrome. It was proposed at that time that both conditions manifest similar physiopathological changes. It was also referred to as “traumatic wet lung”, “congestive atelectasis”, or “Da Nang lung” and had a high mortality rate.

Since these initial reports, researchers focused their attention towards ARDS in order to find out the precipitating factors and therapeutic measures one can take to treat it. From these observations emerged this concept that different systemic conditions and variety of insults to the lung are associated with ARDS clinical syndrome<sup>5</sup> and that it should be regarded as an extreme manifestation of a process called Acute Lung Injury (ALI). Murray quantified the severity of ARDS for determination of prognosis of patients suffering from this clinical syndrome. In 1988, he proposed an ALI score<sup>6</sup> based on four components i.e., the extent of infiltration on patients chest x-ray, degree of hypoxemia, amount of positive end expiratory pressure (PEEP) used to oxygenate the patient and the patients respiratory system compliance when available.

## Definitions and Diagnostic Criteria

In order to resolve the controversy about definitions, precipitating conditions and diagnostic criteria for ARDS, an American European Consensus conference (AECC) was held in 1994. This consensus conference<sup>7</sup> report declared "the difficulty in determining the incidence and outcome of ARDS is largely due to the heterogeneity and lack of definitions for the underlying disease process [and] the lack of definition for ARDS". Despite controversy, the consensus conference ultimately recommended that "acute lung injury" (ALI) be defined as a syndrome of inflammation and increasing permeability. It is associated with a constellation of clinical, radiological and physiologic abnormalities that cannot be explained by, but may coexist with left atrial or pulmonary capillary hypertension and that ARDS be defined simply as a more severe form of ALI. The consensus conference also urged that there should be a return to the original term “acute” rather than “adult” in recognition that ARDS is not limited to adults only.

## AECC members proposed the following diagnostic criteria for ALI and ARDS:

- a) Acute onset
- b) Bilateral chest radiographic infiltrates
- c) Pulmonary artery occlusion pressure of <18 mmHg or no evidence of left atrial hypertension and
- d) Impaired oxygenation regardless of PEEP administration with a PaO<sub>2</sub> / FiO<sub>2</sub> ratio of <300 mmHg for ALI and <200 mmHg for ARDS.

Although debate exists as to the utility of these criteria and the radiographic criteria of bilateral (but not diffuse) chest infiltrates for ALI and ARDS is nonspecific, these criteria are most widely accepted by clinical investigators.

Shuster<sup>8</sup> in 1995 emphasized on the importance of linking structural changes with functional abnormalities; that results in ARDS. He defined ALI to be present when characteristic pathological

abnormalities in the lung result in deterioration of normal lung function, and ARDS to be a specific form of lung injury with diverse causes, characterized pathologically by diffuse alveolar damage and a breakdown in both the barrier and gas exchange functions of the lung, resulting in proteinaceous alveolar edema and hypoxemia.

### **Incidence of ALI and ARDS**

The incidences of ALI and ARDS are not clear. A national institute of health panel in 1972 estimated the incidence of ARDS to be 150,000 cases per year in the United States<sup>9</sup>. Recent prospective studies have shown a much lower incidence of ARDS ranging from 1.5 to 8.4 cases per 100,000 populations per year<sup>10,11</sup>. All of these studies were performed before the AECC definitions were developed. Data on the incidence of either ALI or ARDS using AECC criteria have not yet been published. In ongoing studies of ALI and ARDS at Harborview Medical Center, University of Washington based on AECC criteria the incidence of ARDS is 12.6/1000,000/year and the incidence of ALI and ARDS by AECC criteria is likely to be considerably higher than the recent prospective studies would indicate. However this remains to be confirmed.

### **Risk Factors for ALI and ARDS**

Risk factors or etiologic factors for either conditions are associated with ARDS or markers that occur in conditions known to be associated with ARDS. These associated conditions are direct (primary) i.e. resulting in direct injury to the lung such as aspiration, lung infection, lung contusion or other inhalational injuries. Indirect (secondary) predisposing factors are sepsis, multiple trauma, burns, shock, acute pancreatitis and massive transfusion injuries to the lung through activation of systemic inflammation, presumably related in part to elevated cytokine levels and other biochemical and chemical mediators.

### **Pathogenesis**

Regardless of whether the primary etiology originates within or outside the lung, a systemic inflammatory response accompanies and may determine the progression of ALI. Chemotaxis and activation of leukocytes lead to the release of cytotoxic free radicals and cytokines such as tumor necrosis factor and the interleukins. The expression of leukocyte adhesion molecules and proteases contribute to epithelial and endothelial injury<sup>12</sup>. A number of homeostatic systems are activated: the complement and kinin system, the coagulation cascade, the cyclo-oxygenase and leukotrienes pathway and the NO- elevated cytokine levels and other biochemical and chemical mediators.

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### **Phases of ALI / ARDS**

#### **Initial Phase**

During the first 3-5 days of respiratory failure, there is an increase in the permeability of the endothelial and epithelial barriers of the lung with accumulation of protein rich edema fluid in the interstitial and air spaces of the lung<sup>13</sup>. This results in severe defect in oxygenation, a reduction in lung compliance and bilateral pulmonary infiltrates<sup>14</sup>. Some of the studies have shown that during this phase there is either production of abnormal surfactant or inactivation of surfactant by the protein rich edema

fluid<sup>15,16</sup>. The edema fluid contains a variable quantity of red blood cells, white blood cells, hyaline membranes, (which consists of albumin, immunoglobulin, fibrin, fibrinogen and other proteins)<sup>17</sup>. This has been given the name of diffuse alveolar damage. Some patients recover from this insult where as others pass into a sub-acute or chronic phase of lung injury<sup>18</sup>.

### **Sub-acute Phase**

This phase, which develops 5-7 days after the onset of lung injury, is characterized physiologically by an increase in alveolar dead space, necessitating a high minute ventilation to achieve a normal or near normal PaCO<sub>2</sub>. There is also a persistent oxygenation defect as well as decrease in the lung compliance.

There is evidence of interstitial fibrosis with proliferation of alveolar type 2 cells and both obstruction and destruction of portions of microcirculation of lungs<sup>19-21</sup>. During this phase there are usually persistently large unchanging bilateral infiltrates on chest X-ray.

### **Chronic Phase**

When the patient survives these phases there is a gradual transition to a chronic phase of lung injury with persistently low lung compliance and a markedly elevated dead space fraction. There is pathological evidence of extensive pulmonary fibrosis with obliteration of normal alveolar architecture and progressive development of emphysematous region of the lungs including the development of discrete emphysematous bullae, which can be observed by CT Scan only<sup>22</sup>.

### **Management**

The management of ARDS is complex. It consists of supportive management that supports the physiologic abnormalities and returns them towards normal but which has no fundamental effect on the underlying mechanism of lung injury, and that, which is definitive, i.e. which affects the mechanism of injury. A large number of management strategies have been proposed in the literature mostly involving animal models. Some of the management strategies that have been evaluated in humans over the last 10-15 years shall be reviewed here.

### **Ventilatory Management**

Many new forms of mechanical ventilatory support for patients with ARDS have been proposed.

The goals of ventilatory management<sup>23</sup> in patients with ARDS are to:

Ensure appropriate oxygen delivery to vital organs along with sufficient CO<sub>2</sub> removal

#### **Minimize oxygen toxicity**

Recruit alveoli

Minimize high airway pressure

Prevent atelectasis

Use sedation and paralysis judiciously

In order to achieve the above-mentioned goals of ventilatory management, a number of ventilatory strategies have been proposed and these are:

#### **Permissive Hypercapnia**

Low tidal volume strategy has shown beneficial effects in patients with ALI/ARDS<sup>24</sup>. Here the tidal volume is reduced to between 5-7 ml/kg of the body weight. The PaCO<sub>2</sub> is slowly allowed to rise giving the time to the body to compensate for this respiratory acidosis. It is suggested that pH as low as 7.15 or 7.2 may be well tolerated in the absence of significant cardiac or central nervous system abnormalities<sup>25</sup>. One recent study in animal model has shown that therapeutic Hypercapnia protects against ALI<sup>26</sup>.

#### **Pressure Controlled Ventilation**

In order to minimize the high airway pressure in patients with ALI/ARDS, pressure controlled ventilation is currently the most favoured mode used by intensivists all over the world. In the pressure control mode, the pre set time factors trigger gas flows that continues until a predetermined pressure is

achieved in the proximal airway. The pressure controlled mode provides very rapid initial flows that later on decelerate. The theoretical advantage of this rapid initial flow includes better gas mixing and improved patient synchrony. Assuming an adequate inspiratory time, the delivered tidal volume will be determined by the pre set airway pressure and the pulmonary compliance. Therefore if there is a significant decrease in the compliance of patients lung than the tidal volume delivery can decrease.

### **Inverse Ratio Ventilation**

Inverse ratio ventilation is an alternative method of limiting excessive airway pressures. In inverse ratio ventilation the inspiratory time is prolonged thereby increasing mean airway pressure while maintaining peak airway pressures<sup>27</sup>. Selecting an inspiratory / expiratory ratio greater than 1:1 may allow for recruitment of non compliant, surfactant deficient alveoli and more homogeneous gas delivery. The maximal benefit of inverse ventilation on gas exchange may take several hours to achieve, which supports the hypothesis that sustained inspiratory pressure is one mechanism of benefit with its use. Based on clinical experience it has been shown to improve gas exchange in patients with ARDS who failed to maintain oxygenation with conventional ventilation using PEEP<sup>28</sup>. However a recent randomized, cross over study failed to show any improvement with inverse ratio ventilation<sup>29</sup>. As it has not been well studied and is uncomfortable for the patient requiring high dose of sedation or neuromuscular blockade, it is currently not recommended as the initial ventilatory approach in all patients with ALI/ARDS. However it can be considered in patients with refractory hypoxaemia requiring high FiO<sub>2</sub>, or when the use of PEEP is associated with excessive peak air way pressures.

### **Positive end expiratory pressure (PEEP)**

PEEP has a definite role in recruiting and stabilizing injured alveoli<sup>30</sup>. This improves ventilation perfusion mismatch and lung compliance. Acute lung injury is a heterogeneous condition so PEEP applied to the patient may be appropriate in one region of the lung but may cause over distention in the other. It may be sub-optimal in the third region. It is therefore of paramount importance to select best PEEP in the patients with ARDS to avoid the deleterious effects. PEEP in the range of 5-15 cms H<sub>2</sub>O has been found to provide a reasonable balance between these effects<sup>31</sup>. One can increase the PEEP above 15 cms H<sub>2</sub>O, but this usually will result in over distention of already recruited alveoli. For this reason PEEP level >20 cms of H<sub>2</sub>O or PEEP levels associated with plateau pressure of >35 cms of H<sub>2</sub>O are generally avoided<sup>32</sup>.

### **Fluid Management**

There has always been a controversy regarding optimal fluid management in patients with ARDS. This controversy revolves around which fluid to use and whether to use fluid or not. There are few who advocate keeping the patient with ARDS relatively dry either by diuretics or restricting fluids whereas others favor fluid administration to maintain DO<sub>2</sub>, cardiovascular and renal function<sup>33</sup>. Those who favour fluid restriction base their arguments on theoretical, experimental and clinical data. Experimental studies have indicated that pulmonary functions and outcome are better in patients who achieve a negative fluid balance where as positive fluid balance results in worse outcome<sup>34-36</sup>. Recommendations are to maintain a lower pulmonary artery wedge pressure by either restricting fluid or by using diuretics especially during the first few days of onset of ARDS<sup>37</sup>. However at a later stage fluid restriction is of no benefit specially when fibrosis has occurred. One should be careful about aggravating renal function and to avoid problems from fluid restriction a pulmonary artery wedge pressure monitoring is essential<sup>38</sup>.

### **Prone positioning**

The infiltrates in the lungs of patients with ALL / ARDS are not evenly distributed therefore by changing the position of patient one can get improvement in gaseous exchange<sup>39</sup>. If there is more involvement of one lung, then the lateral decubitus position may benefit the patient. The patient should be in a position in which the less diseased lung is dependent in order to match ventilation and

perfusion. Prone position to improve oxygenation in patients with ARDS has been proposed in many studies<sup>40</sup>. The prone position is beneficial because it generates a transpulmonary pressure sufficient to exceed airway-opening pressure in dorsal lung regions where atelectasis, shunt and ventilation perfusion mismatch occurs<sup>41</sup>. This approach should be used only in centers experienced with it because of the problems and complications associated with prone position<sup>42</sup>. A randomized controlled trial which was done in 35 Italian intensive care units showed an improvement in oxygenation of 85% after 6 hours of prone positioning<sup>39</sup>.

### **Nitric Oxide**

Nitric oxide is a potent pulmonary vasodilator. When given by inhalation in small doses, it causes vasodilatation of ventilated areas. Blood is directed from the poorly or non-ventilated areas to better ventilated areas of lung and improvement in ventilation perfusion mismatch and reduction in intrapulmonary shunting occurs. The nitric oxide is blended with oxygen and administered to the patient in parts per million. The optional dose of nitric oxide inhalational therapy is not determined but response may be patient specific or related to the severity of ARDS. Side effects of high concentration of nitric oxide are methemoglobinemia, acute pulmonary edema and acidemia but the likelihood of toxicity from prolonged inhalation of Nitric oxide (2-20 ppm) is minimal<sup>43</sup>. There are published data that indicates that nitric oxide reduces pulmonary artery pressure and shunt. It also increases PaO<sub>2</sub>/FiO<sub>2</sub> ratio without affecting cardiac output or systemic arterial pressure. However a recent randomized trial of 177 patients using 4 doses of nitric oxide failed to show any improvement in oxygenation or duration of mechanical ventilation<sup>44</sup>. Other clinical trials in adults have failed to show any benefit on mortality or on mechanical ventilation requirements<sup>45</sup>. Nitric oxide can be considered a rescue therapy in patient with ARDS refractory to conventional modes of ventilation and gas exchange support.

### **Corticosteroids**

The ability of corticosteroids to attenuate host inflammatory response has provided the rationale for their use in ARDS. Large prospective studies in the mid 80s failed to demonstrate increased survival when high dose steroids were used in early phases of ARDS<sup>46</sup>.

In refractory or late ARDS corticosteroids improve important physiological values. Criteria that investigators used for prescribing steroids for late ARDS were:

- No improvement for at least 72 hrs with maximum ventilatory support
- When no other therapeutic options were available
- Progressive respiratory failure with worsening lung injury score
- No evidence of active infection.

There has been only one prospective randomized trial<sup>47</sup> a pilot study of 24 patients, which suggests that this therapy may be beneficial corticosteroids may have an important role in patients with late ARDS<sup>48</sup>. Large prospective trials are needed to determine specific target patient characteristic, timing of the start of therapy and optimal dosage and duration of therapy.

### **Surfactant Replacement Therapy**

In ALI surfactant becomes dysfunctional because of altered composition and disruption of the continuity of the surfactant layer by pulmonary edema fluid and neutrophilic infiltration<sup>49</sup>. Surfactant replacement therapy has been evaluated in the infant respiratory distress syndrome with recognized benefits<sup>50</sup>.

Exogenous surfactant administration in adult human has been investigated in many studies that have shown trends towards increased survival but no difference in other measured parameters were noted<sup>51</sup>. A prospective, multicentre, double blind, randomized, placebo controlled study involving more than 700 patients with sepsis induced ARDS has failed to show any benefit of exogenous surfactant administration by continuous aerosol<sup>52</sup>. However one of the recently published study concluded that the pulmonary response to exogenous surfactant after mechanical ventilation is experimental. ALI is

improved when a ventilatory strategy with high PEEP is used<sup>53</sup>.

Surfactant still may show promise in specific subgroups of ARDS, or may have a role in the treatment of patients with high risk of syndrome. Dosage, mode of delivery, timing of therapy and its use in combination with other agents are areas where it deserves prospective trials before final decisions can be made to eliminate it from the treatment options for ARDS.

### **Outcome**

Factors associated with mortality include risk factors and age. Patients developing ARDS secondary to sepsis have a considerably higher mortality than most other common risk factors<sup>54</sup>. Older patients greater than 65 years of age have an increased mortality rate<sup>55</sup>.

The severity of ARDS at the time of first diagnosis as measured by oxygenation abnormality (PaO<sub>2</sub>/FiO<sub>2</sub>) has generally not been associated with differing outcomes. Krafft et al<sup>56</sup> in a meta analysis of 102 publications on ARDS found no correlation between PaO<sub>2</sub>/FiO<sub>2</sub> and mortality. The most common cause of death in patients with ARDS is sepsis and multiple organ failure rather than hypoxia<sup>57,58</sup>.

### **Conclusion**

ALI/ARDS is a complex response of the lung to direct and indirect insults. Treatment of ALI/ ARDS is mainly supportive at the moment. Ventilatory management is the mainstay of supportive therapy and many new ventilatory strategies have been proposed. Attention has been turned to prevention of iatrogenic lung damage by use of pressure controlled ventilation and permissive hypercapnia, thus limiting the rise in peak airway pressure. For those with refractory hypoxaemia, inverse ratio ventilation, use of nitric oxide and prone position do offer some improvement in oxygenation. Most of the deaths in patients with ALI/ARDS is secondary to multiple organ failure. There is therefore a need to evolve strategies to prevent the development of non-pulmonary organ dysfunction in these patients.

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