Editorial:**Emerging concepts in acute respiratory distress syndrome: implications for clinicians**

The acute respiratory distress syndrome (ARDS) was first described by Ashbaugh and colleagues in 1967.¹ Simply stated, it is a non-cardiogenic pulmonary oedema leading to decreased lung compliance and hypoxia. The Berlin definition classifying ARDS² has helped to bring clarity to the definition based on severity of ARDS. Further, better understanding of the pathophysiology, has led to changing strategies in the approach and management of ARDS.

Several new concepts regarding the aetiology of ARDS have emerged in the last few years. The first is the acknowledgement of the role of genetics in the predisposition to development of ARDS.³ Sepsis is the most important cause of ARDS all over the world, but it is now known that not all patients with sepsis develop ARDS, pointing to unknown host factors. It has been found that epigenetics and gene expression have a major role in the predisposition to ARDS. Measurement of various metabolites in exhaled breath and in bronchoalveolar lavage (BAL) fluid³ have been found to be predisposing to ARDS. In future, epigenetic targets may be identified for prevention of ARDS.

The understanding of pathophysiology of inflammation of alveolo-capillary membrane in ARDS has been redefined in the recent times. The neutrophilic infiltration and their activation leading to alveolar oedema is now known to be reaction to the inflammation rather than the cause. This has been proven by the fact that even neutropenic patients develop ARDS and the administration of granulocyte colony stimulating factor (G-CSF) to ARDS patients does not exaggerate ARDS. The role of angiotensin converting enzyme pathways are known to contribute to the fibrotic and proliferative phase of ARDS.⁴

The various phases of inflammation, proliferation and fibrosis in ARDS have been categorized in the last decade. However ventilatory strategies aimed at different phases of ARDS are still being worked out. With the advent of computed tomography (CT), the infiltrates of ARDS are being clearly defined as generally being posterior and basal, pointing to the heterogeneity of the lung in ARDS. There are areas of normal lung, as well as completely inflamed lung. Ventilation of the normal lung with increased pressures aimed at distending the inflamed lung may lead to over distention and barotrauma.

The concept of the so called “baby lung” evolved over the years to indicate that the normally aerated lung in ARDS probably has the dimensions of the lung of a 5 or 6 year old child.⁵ This diminished capacity of the lung in ARDS was thought to be due to the stiffness and decreased compliance of the involved lung. Such involvement was thought to be permanent and anatomically fixed. However, the CT images of patients with ARDS disproved this. When the patient was put in prone position, the infiltrates moved to the anterior part of the chest showing that the posterior oedematous lung is capable of re-expanding and is not permanently stiff.⁶ This has given more

Online access

http://svimstpt.ap.nic.in/jcsr/oct-dec16_filesedi.16.09.001.pdf

DOI: <http://dx.doi.org/10.15380/22775706.JCSR.16.09.001>

validity for the use of prone-position ventilation as the water-logged lung is allowed to expand and recovery of alveoli is possible.

The next major change in the ventilation strategy in ARDS came with the understanding that ventilation can produce lung injury, the so called “ventilator induced lung injury (VILI)”.⁷ This concept was described by Tierney et al⁸ in rats in 2003. Now it is well known that VILI is due to volutrauma which may be caused by over distension of alveoli. This has been the reason for using low tidal volume ventilation of 6 mL/kg as opposed to 10 mL/kg which was used in earlier years.⁹

Two more types of alveolar trauma have been identified. The first is atelect-trauma due to repetitive opening and closing of alveoli. The application of positive end-expiratory pressure (PEEP) prevents the gross stress and strain on the alveoli, which itself is known to trigger further inflammation. The second measure which allows the driving pressure from the ventilator to be evenly distributed through the inhomogeneous lung is prone position ventilation, thus saving the “baby lung” from excessive distention. Prone positioning removes the weight of the inflamed lung on the posterior alveoli. Both these measures have been shown to be successful in reducing atelect-trauma.¹⁰

Bio-trauma is due to cytokine release from the damaged alveoli. The concept of biotrauma was discovered after it was noted that most patients with ARDS die from multiple organ dysfunction syndrome (MODS) rather than hypoxia.¹¹ This shows that the ARDS afflicted lung may be the source of release of cytokines causing MODS. Several studies have demonstrated the increasing concentrations of tumour necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β) and macrophage inflammatory protein (MIP-2) in BAL fluid especially with increasing volumes during ventilation. This has further strengthened the concept of low tidal volume ventilation and avoiding repeated recruitment of the lung, as a measure to prevent cytokine storm and possibility of MODS.

Probably the most important change in ventilation strategy with the realization of VILI, is the acceptance of lesser arterial oxygen tension (PaO₂) as targets during ventilation. Arterial oxygen saturation measured by pulse oximetry (SpO₂) value of 85% - 90% is enough for survival of patients and haemodynamic stability during the course of ARDS. This concept has led to “gentle lung treatment” and acceptance of lesser oxygenation and to some extent permissive hypercapnia. So understanding of pathophysiology has led to lowering of PaO₂ targets during treatment of ARDS, and low tidal volume, with less distention of alveoli has been implemented.¹² Hopefully, this may have major implications in the lowering of mortality in this condition.

The resolution of ARDS involves the reversal of capillary permeability, the establishment of the integrity of the endothelial membrane and stabilization of the cytoskeleton of the alveolus. Several factors and pathways are involved in this process of reversal. Mesenchymal stem cells which may secrete anti-inflammatory cytokines and growth factors may be useful for therapy in hastening recovery.¹³

ARDS has been associated with 40% -50% mortality in several centres across the world. This has been thought of as due to the severity of the disease itself. However, recent studies have shown that polymorphism of the ACE gene may have a role in the prediction of mortality in Asian populations.¹⁴ After adjusting for several factors, this polymorphism has been shown to definitely affect mortality.

Data about ARDS from developing nations is heavily compromised by the absence of facilities for ruling out cardiogenic pulmonary oedema. In several third world countries, even arterial blood gas assessment is problematic. Keeping this in mind, the Kigali Modifications for the Berlin definition

has been proposed. The ratio of PaO_2 to fraction of inspired oxygen (FIO_2) can be safely replaced by $\text{SpO}_2/\text{FIO}_2$ ratio of less than 315 for the diagnosis and assessment of ARDS. Such modifications may lead to more data from third world countries on this devastating condition.¹⁵

The concepts regarding the etiology of ARDS have shifted focus from environmental factors to host factors. The ventilator strategies have been relooked at with better understanding of the pathophysiology of ARDS after the advent of CT. The recognition of the trauma caused by ventilation has changed the modes of ventilation, the settings for ventilation and the PaO_2 and arterial carbon dioxide tension (PaCO_2) targets. With these concepts, it is hoped that the future will lead to lesser morbidity and mortality for patients with ARDS.

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Received: September 02, 2016; Accepted: September 22, 2016.

Vidyasagar S. Emerging concepts in acute respiratory distress syndrome: implications for clinicians. J Clin Sci Res 2016;5:202-4. DOI: <http://dx.doi.org/10.15380/22775706.JCSR.16.09.001>.

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