National Heart and Lung Institute Workshop Series

Acute Lung Injury

Proceedings of the third National Heart and Lung Institute
Workshop, held on 5 May 1989 at the National Heart and Lung Institute, London SW3 6LY

Adult respiratory distress syndrome: time for re-appraisal?

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The term adult respiratory distress syndrome (ARDS) defines a group of patients with refractory hypoxaemia, decreased lung compliance and radiological evidence of pulmonary oedema proven to be non-cardiogenic in origin. The term was first coined in 1967, when lung biopsies taken from such patients were shown to be histologically similar to those seen in the infantile distress syndrome.¹ ARDS is responsible for up to 50,000 deaths per annum in the USA alone and may be precipitated by a wide variety of serious medical and surgical problems, most of which do not directly involve the lung. The associated mortality approaches 60% and may be as high as 80% in some circumstances, particularly those involving sepsis.² Little progress has been made towards the development of therapies aimed at interrupting or reversing the pathophysiology underlying ARDS. However, recent advances in cell biology have increased our understanding of the aetiology of the increased pulmonary vascular permeability that characterizes the syndrome, suggesting that new interventions may not be far away. Furthermore, the growing recognition that ARDS is a complex disorder of peripheral oxygen utilization has led to a number of developments in the field of ventilatory and circulatory support, making this an opportune time to reassess progress in management.

Speculation regarding the aetiology of ARDS has focused increasingly on the role of the neutrophil and the mechanisms leading to its activation by cytokines such as tumour necrosis factor (TNF) and interleukin-1, which are released from macrophages and which can themselves damage vascular

endothelial cells.³ Both substances can mimic the haemodynamic and metabolic consequences of septic shock when administered to experimental animals and therapies aimed at preventing cytokine–neutrophil interaction have produced promising preliminary results. Thus the advent of anti-TNF antibodies for clinical use may follow evidence that it can substantially reduce mortality from septic shock in experimental animals. The methylxanthine pentoxifylline has been shown to block cytokine-induced neutrophil adherence to endothelial cells *in vitro* and to attenuate the mortality associated with experimentally-induced haemorrhagic shock.⁴

Studies carried out in animal models of ARDS have been useful in defining the pathophysiology of the condition and have enabled the development of techniques for assessing the integrity of the alveolar-capillary membrane. These have varied from measuring the transfer of radiolabelled albumin from the vascular compartment to tracheal aspirate, to more sophisticated dual isotope techniques quantifying the leak of transferin across the endothelial barrier.⁵ The increasing awareness that changes in pulmonary vascular permeability may represent the end-stage of a complex inflammatory cascade suggests that such tests may not be useful in the clinical management of patients with ARDS, but they have an important role in the evaluation of new and potentially potent interventions.

It is in the field of respiratory and circulatory support that most advances have been made in the management of ARDS. The conventional approach has involved the application of continuous positive airways pressure (CPAP) to the spontaneously breathing patient and tidal volume-preset, controlled mandatory ventilation with

positive-end expiratory pressure (PEEP) and an inspiratory to expiratory time (I:E) ratio of less than one in those requiring mechanical assistance. However, the delivery of a preset volume of gas regardless of the compliance of the respiratory system may result in high peak airways pressure, haemodynamic compromise and an increased potential for barotrauma. In ARDS, optimizing cardiac performance and hence oxygen delivery involves minimizing these adverse effects of positive-pressure ventilation whilst maximizing the recruitment of 'unstable' alveoli and preventing their subsequent collapse. This has been attempted through the use of inverse ratio ventilation in which I:E ratios in excess of 1:1 are applied, such that alveoli are recruited but the brief period of expiration, although sufficient for carbon dioxide (CO₂) clearance, prevents their collapse.⁶ The use of ultra high frequency jet ventilation, in which frequencies in the range of 5–7 Hz are applied has a similar effect on alveolar recruitment and may reduce mean airway pressures compared with conventional techniques.⁷ The results of randomized, prospective controlled trials in patients with ARDS are eagerly awaited.

In patients with established ARDS there is much debate regarding the correct approach to fluid and electrolyte balance. The increased permeability of the alveolar capillary membrane suggests that a policy involving a reduction in circulating volume through the use of diuretics or haemofiltration is logical. Any reduction in cardiac performance consequent upon reduced filling pressures can be countered through the use of inotropic agents. Feeding is usually contraindicated in the acute phase for the same reason. Furthermore, the contribution of lipids in exacerbating ventilation-perfusion mismatch remains controversial, although fat metabolism results in a lower CO₂

production when compared to glucose, thus favourably affecting respiratory quotient.⁸

The potential for supporting patients in respiratory failure using extra-corporeal membrane oxygenation (ECMO) has been realized since the advent of cardiopulmonary bypass techniques some 20 years ago and is now an accepted and effective practice in neonatal respiratory distress syndrome. Nevertheless, controlled trials comparing ECMO with conventional techniques of ventilation in established ARDS have been disappointing, although subsequent advances in membrane technology have re-awakened interest in the technique. Currently, removal of CO₂ using small cannulae and low blood flow rates (20–30% of cardiac output) is favoured, combined with 'apnoeic' or low frequency pressure limited ventilation permitting oxygenation via the patient's own lungs.⁹ Despite encouraging early results using this approach, extra corporeal support in ARDS remains controversial, but may have a role as a bridge to cardiopulmonary transplantation.

Monitoring in ARDS has become increasingly invasive and the flow-directed, balloon-tipped pulmonary artery catheter has become an important tool in both the diagnosis and management of patients with ARDS. The calculation of pulmonary and systemic vascular resistances and the appropriate use of inotropic agents to maximize oxygen delivery can best be achieved in this way. It has also led to the realization that the relationship between oxygen delivery and uptake may differ significantly from the norm in critically ill patients.¹⁰

The progress in patients with ARDS remains poor, but the increase in understanding of the mechanisms underlying the condition coupled to increasingly effective means of cardiopulmonary support suggests that real progress in reversing this trend may not be far away.

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