Trauma, inflammatory cells and ARDS

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INTRODUCTION

The adult respiratory distress syndrome (ARDS) was initially described by Ashbaugh as comprising profound hypoxia refractory to oxygen therapy, loss of lung compliance and diffuse radiographic alveolar infiltration (Ashbaugh *et al.*, 1967). The pathophysiological features of ARDS are well established and include reduced functional residual capacity and lung compliance, increased airway resistance, microvascular permeability and severe ventilation/perfusion mismatch (Petty & Fowler 1982; Lloyd *et al.*, 1984; Repine *et al.*, 1992). It is now considered that the process is initiated by a provoking combination of insults, most often distant to the lung, which results in mediator release. This, in turn, initiates a complex sequence of cellular events culminating in breakdown of alveolar/capillary integrity in the lung, leakage of protein-rich fluid into the airspaces, and the clinical manifestations as outlined above.

DISCUSSION

Major trauma is a well recognized predisposing factor for ARDS. It is estimated that such patients run a 5–8% risk (Fowler *et al.*, 1983; Pepe *et al.*, 1982) of developing the full clinical picture of ARDS. In the original description for this disorder (Ashbaugh *et al.*, 1967) a series of 12 patients were described, seven of whom had trauma as their initiating or provoking insult. Mortality in that original series approached 70% and despite improvements in medical facilities in general and intensive care facilities in particular, current mortality remains at 50–70% (Montgomery *et al.*, 1985).

Clinical risk factors per se can give only a poor guide to ARDS progression. However, the incidence of ARDS increases from 6–18% if one clinical risk factor

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is present to 25–59% when multiple factors are involved (Fowler *et al.*, 1983; Pepe *et al.*, 1982). This is also reflected by the correlation between Injury Severity Scores (ISS) and ARDS development (Fowler *et al.*, 1983).

Within the inflammatory process a delicate balance exists between the beneficial effects of inflammation and the potential for the process itself to cause and aggravate tissue injury. There is significant evidence to implicate inflammatory cells and in particular the neutrophil, in the pathogenesis of this disorder. The neutrophil contains more than 30 agents with proven capacity to injure tissues. These include hydrogen peroxide, cationic proteins, collagenase, cathepsin, gelatinase and elastase. The implication of activated neutrophils in the ARDS disease process has evolved from the findings of increased neutrophils (Lee *et al.*, 1981), together with the demonstration of elevated levels of neutrophil protease enzymes such as elastase (Lee *et al.*, 1981) and collagenase (Christner *et al.*, 1985) in lung lavages obtained from ARDS patients. In addition excessive quantities of hydrogen peroxide, believed to be derived from activated inflammatory cells within injured lungs, have been detected in expired air from ventilated patients (Baldwin *et al.*, 1986). Thus activated inflammatory cells, and the neutrophil in particular, have been implicated in full blown ARDS.

However enhanced, inflammatory cell activity alone does not result in ARDS, rather a more complex interplay exists between mediators, inflammatory cells, intercellular adhesive molecules and pulmonary endothelial cells which results in this catastrophic form of acute lung injury. It is well recognized that trauma patients develop a post-traumatic leukocytosis (Hallgren *et al.*, 1984). These neutrophils show enhanced activation as shown by increased elastase secretion (Donnelly *et al.*, 1992). In addition isolated neutrophils from ARDS patients possess the ability to generate increased quantities of potentially toxic oxygen metabolites (Zimmerman *et al.*, 1983). These neutrophils have also been shown to exhibit increased adherence (Seidel *et al.*, 1991).

The fact that neutrophil-mediated endothelial injury does not occur *in vitro* without direct neutrophil adherence, and the observation that neutrophil mediated matrix degradation can still occur in the presence of anti-proteases (Cambell *et al.*, 1982), has led to the concept of a restricted pericellular 'micro-environment' between activated inflammatory cell and the pulmonary endothelium. This 'micro-environment' would physically prevent the action of the large molecular weight protease inhibitors and thus allow the accumulation of excessive quantities of injurious agents such as elastase and reactive oxygen intermediates (ROI's). These agents would then have unrestricted action upon the pulmonary endothelium leading to local destruction. In addition when activated, neutrophils are less able to deform and squeeze through the narrow pulmonary microcirculation. When combined with the activation and upregulation of neutrophil/endothelial adhesive molecules, an increase in the transit time of neutrophils through the lung would occur and lead to prolonged contact of activated neutrophils with the 'at risk' endothelium, enhancing the potential for tissue injury.

Infection, and in particular gram negative septicaemia, has been shown to precipitate the development of ARDS (Pepe *et al.*, 1982). Neutrophils isolated from multiple trauma patients have been shown to have impaired capacity to opsonize pathogenic bacteria shortly after trauma. This impaired ability is more pronounced

in those trauma patients who subsequently progress to develop ARDS (Seidel *et al.*, 1991). Thus these patients will be more susceptible to colonization by Gram negative organisms, which in turn have the potential to initiate the complex cellular and humoral processes necessary for the development of ARDS.

With regard to the development of effective therapies in the future, it would seem logical that the greatest benefit would accrue from giving therapy as soon after the initial traumatic event as is feasible. This would provide the best opportunity of attenuating the cellular processes in their infancy and abort the progression to ARDS. However at the time such patients present to our Accident & Emergency departments, we have no accurate means of predicting which particular major trauma patients are likely to develop ARDS. Thus even if a 'wonder drug' became available, we would be faced with the prospect of being unable to target it to the appropriate major trauma patients. The identification of cellular indicators which can simply and reliably predict a high risk of ARDS, is therefore of paramount importance.

To date many agents have been investigated as to their possible beneficial effects in acute lung injury and ARDS but with disappointing results. Therapy with high dose corticosteroids did not improve outcome in clinical trials (Bernard *et al.*, 1987). Other agents investigated include cyclo-oxygenase inhibitors (non-steroidal anti-inflammatory agents) (van Velzen *et al.*, 1990), oxygen scavenging agents (N-acetylcysteine) (Hanique *et al.*, 1990), vasodilators (prostacyclin) (Radermacher *et al.*, 1990) and methylated xanthines (Pentoxifylline) (Hatherill *et al.*, 1989). Just as the search for a common mediator in ARDS has been disappointing, so has the search for a single 'magic bullet' which would attenuate the ARDS disease process. It would seem more logical that a 'therapeutic cocktail' of agents capable of inhibiting several key processes at specific timepoints in the ARDS disease process, will be the therapeutic strategy of the future.

Mediator and cytokine manipulation is already part of the therapeutic armoury in certain disease states. With regard to sepsis, endotoxin antibodies are currently available commercially and human trials with Interleukin-1 receptor antagonists (Il-1ra) show therapeutic promise. As the cellular basis for ARDS unfolds, combined effective therapy for ARDS should become a reality. In the meantime, appropriate and timely management of the trauma patient in the accident and emergency department is crucial if the risk of developing ARDS is to be reduced. The rapid identification and correction of hypoxia and circulating blood volume deficits will reduce the severity and duration of these insults. Early intubation and mechanical ventilation to correct hypoxia, volume replacement, expert definitive surgery to stop haemorrhage and early fixation of long bone fractures have all been shown to significantly reduce the incidence, severity and mortality of ARDS (Riska *et al.*, 1977; Rhodes *et al.*, 1978; Goris, 1983). With the tools already available to us, the Accident and Emergency specialist is pivotally placed to do most to prevent this serious complication.

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