Abstracts

Future prospects for pharmacotherapy in the adult respiratory distress syndrome (ARDS)

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Speculation concerning the pathogenesis of ARDS is focused increasingly on the mechanisms leading to the activation of inflammatory cells, particularly the neutrophil; platelets and other clotting factors.[1,2] If effective therapies are to be developed, early interventions aimed at preventing neutrophil and platelet activation, may prove to be more effective than inhibitors of the inflammatory mediators (such as leukotrienes, thromboxane and platelet-activating factor – PAF[3]) that are subsequently released. Neutrophil activation is at least partially dependent upon cytokines, potent inflammatory molecules released from macrophages, which may themselves directly damage vascular endothelial cells.[4] Platelet activation and sequestration in the lungs of patients with ARDS has been described and may be a consequence of, or occur independently of, neutrophil activation, possibly leading to focal endothelial damage and amplifying the effects of neutrophil activation. New experimental evidence obtained from studies aimed at preventing inflammatory cell activation using drugs such as pentoxifylline suggests that this may be a fruitful approach.[5]

References

1. Heffner, J.E., Sahn, S.S. & Repine, J.E. The role of platelets in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1987, **135:** 482–492.
2. Tate, R.M. & Repine, J.E. Neutrophils and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1984, **130:** 552–559.
3. Evans, T.W., Chung, K.F., Rogers, D.F. & Barnes, P.J. Effect of platelet-activating factor on airway microvascular permeability: possible mechanisms. *J Appl Physiol* 1987, **63:** 479–484.
4. Shalaby, M.R., Aggarwal, B.B., Rinderknect, T., Svedersky, L.P., Finkle, B.S. & Palladino, M.A. Activation of human polymorphonuclear neutrophil functions by interferon gamma and tumour necrosis factor. *J Immunol* 1985, **135:** 2069–2073.
5. Mandell, G.L. ARDS, neutrophils and pentoxifylline. *Am Rev Respir Dis* 1988, **138:** 1108–1105.

The inflammatory response to acute lung injury

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The adult respiratory distress syndrome (ARDS) is a form of catastrophic acute lung injury with a mortality approaching 70%, afflicting principally the young and middle-aged. At present there is no means of predicting outcome in individual patients and no specific therapy is available. Although ARDS is associated with many serious medical and surgical conditions, the histological changes observed on open lung biopsy are virtually identical once the patients are hypoxaemic enough to require mechanical ventilation. They include endothelial and epithelial injury, type II pneumocyte proliferation and evidence of an acute inflammatory response.[1] The latter encompasses a protein-rich interstitial and alveolar exudate, often with evidence suggesting the deposition of matrix proteins such as collagen. By the time such changes are apparent it is difficult to envisage favourable therapeutic manipulation of the pathological process and attention has therefore been focused recently on intervention at the earliest possible stage of the disease.

The commonest conditions associated with ARDS are multiple trauma and Gram negative sepsis when a delay or latent period often occurs between the initial insult and the onset of lung problems. This has led to the hope that identification of pathogenic mechanisms in the early stages of the disease will generate specific agents to modulate injury in high risk patients before the onset of frank lung disease. The fact that lung injury often results from insults to other organ systems such as multiple trauma has suggested that it is in part 'humorally-mediated'. Thus, it is now considered that an important early event is pulmonary microvascular endothelial injury caused by the release of injurious agents from inflammatory cells (particularly neutrophils), that have become sequestered within that microenvironment and stimulated by mediators generated by the initial insult. Many attempts have been made to identify a final common mediator, but it is likely that an understanding of how various relevant agents interact in their effects on inflammatory cells will prove to be a more fruitful approach. The role of agents such as endotoxin and activated complement species in ARDS and animal models of acute lung injury and their effects on neutrophils has already furthered our understanding in this respect.[2] Recent work has also suggested that reactive oxygen species and proteolytic neutrophil enzymes are significant factors in neutrophil sequestration in pulmonary microvessels and consequently endothelial injury. The understanding of molecular mechanisms of these events is likely to generate more specific therapeutic approaches which could be employed in patients at a high risk of ARDS in the future.[3]

References

1. Simon, R.H. & Ward, P.A. Adult respiratory distress syndrome. In: Gallin, J.I., Goldstein, I.M., Synderman, R. (eds). *Inflammation: Basic Principles and Clinical Correlates.* Raven Press, New York, 1988, pp. 815–827.
2. Haslett, C., Worthen, G.S., Giclas, P.A., Morrison, D.C., Henson, J.E. & Henson, P.M. The pulmonary vascular sequestration of neutrophils in endotoxaemia is initiated by an effect of endotoxin on the neutrophil in the rabbit. *Am Rev Respir Dis* 1987, **136:** 9–18.
3. Worthen, G.S., Haslett, C., Rees, A.J., Gumbay, R.S., Henson, J.E. & Henson, P.M. Neutrophil-mediated pulmonary vascular injury: synergistic effect of trace amounts of lipopolysaccharide and neutrophil stimuli on vascular permeability and neutrophil sequestration in the lung. *Am Rev Respir Dis* 1987, **136:** 19–28.

Pulmonary physiology in adult respiratory distress syndrome (ARDS)

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When an arm or leg is fractured it is encased in plaster and immobilized for several weeks and rested. When the lung is injured, it is repeatedly stressed with a 'cyclic test to destruction' device (or ventilator) and suffused with one of the most corrosive liquids possible (oxygen). This may not be entirely wise.

Paradoxically, most tests of lung function have been developed for the study of patients fit enough to come to laboratories and participate in vigorous voluntary trials of pulmonary manhood, such that the data-base for most of our understanding of the lung cannot be applied to the acutely ill, until new standards of sub-maximal involuntary tests in recumbent patients have been developed.[1] As a result, most patients with lung damage in intensive care units are managed without quantitative physiological testing. However, it is clear that ARDS is characterized by severe and rapidly changing losses of lung volume and compliance[2] associated with profound loss of surfactant and the influx of protein-rich oedema.[3] Widespread microthrombi cause a rise in pulmonary vascular resistance and consequent pulmonary hypertension. In addition, over-ambitious attempts to reinflate the lungs commonly lead to interstitial mediastinal and more distant tissue emphysema and pneumothorax.

Much of this pattern can be explained by oxygen-radical damage to Type II alveolar cells and the resultant loss of surfactant and uneven distribution of mechanical stresses.

References

1. Prakash, O. (ed.). *Applied Physiology in Clinical Respiratory Care*. Martinus Nijhoff, London, 1982, pp. 480.
2. Brunner, J.X. & Wolff, G. *Pulmonary Function Indices in Critical Care Patients*. Springer-Verlag, London, 1988, pp. 168.
3. Staub, N.C. (ed.). *Lung Water and Gas Exchange*. Marcel Dekker, Basel, 1978, pp. 567.
4. Pritchard, J.S. *Edema of the Lung*. C.C. Thomas, Baltimore, 1982, pp. 436.

Animal experimental models of ARDS

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Experimental lung injury may result in pathophysiological changes very similar to those occurring in ARDS.[1] An understanding of the basic mechanisms of injury is vital if more rational and effective therapies are to be developed. Animal studies have provided useful information about pathogenesis but their clinical relevance is often uncertain. Direct insults to the pulmonary microvascular endothelium in animals using inflammatory agents such as oleic acid or thiourea derivatives may be appropriate in assessing the haemodynamic effects of injury and its consequences for pulmonary mechanics. However, studies addressing pathophysiological aspects require models with clinical relevance, such as those involving the infusion of endotoxin or employing cardiopulmonary bypass.[2] The use of putative mediators of injury (e.g. platelet activating factor, prostanoids and leukotrienes), or neutrophil activation (e.g. phorbol myristate acetate, C_5 derived peptides) has also been widespread. Animal models using both direct and indirect pulmonary insults are useful in the evaluation of methods of defining alveolar capillary integrity. These include measuring the clearance of inhaled isotope-labelled DTPA particles and assessing the rate of protein accumulation in the pulmonary interstitium. Nevertheless, to date no single animal model of acute lung injury accurately replicates the complexity of the human syndrome.[3]

References

1. Staub, N.C. Pulmonary oedema due to increased microvascular permeability. *Ann Rev Med* 1981, **32:** 291–321.
2. Rinaldo, J.E. & Rogers, R.M. Adult respiratory distress syndrome. Changing concepts of lung injury and repair. *N Engl J Med* 1982, **306:** 900–909.
3. Flick, M.R. Mechanisms of acute lung injury: what have we learned from experimental animal models? *Crit Care Clin* 1986, **2:** 444–470.

The wet lung: matching man and machine

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Mechanical ventilation for acute lung injury is primarily supportive rather than therapeutic. It relieves respiratory distress and can permit sufficient control of life-threatening hypoxaemia to 'buy time' for resolution. No technique of ventilation is clearly superior to all others, but the objectives can be summarized thus: (a) to optimize tissue oxygen delivery, (b) to minimize lung damage.

In ARDS the lungs behave as though small and stiff; this may be a generalized phenomenon or the consequence of ventilating only a small volume of relatively normal lung.[1] Intermittent positive pressure ventilation with positive end-expiratory pressure is conventional,[2] but high tidal volumes which distend the lungs beyond the limit of elasticity are dangerous.

Alternatives which have been explored include high frequency ventilation,[3] inverse ratio ventilation,[4] differential ventilation[5] and methods of extracorporeal gas exchange.[6,7] Haemodynamic consequences warrant concern[8] as well as effects on pulmonary function and intrapulmonary gas exchange.

References

1. Gattinoni, L., Pesenti, A., Avalli, L. *et al.* Pressure–volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis* 1987, **136:** 730–736.

2. Weisman, I.M., Rinaldo, J.E. & Rogers, R.M. Positive end-expiratory pressure in adult respiratory failure. *N Engl J Med* 1982, **307:** 1381–1384.
3. McCulloch, P.R., Forkert, P.G. & Froese, A.B. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *Am Rev Respir Dis* 1988, **137:** 1185–1192.
4. Cole, A.G.H., Weller, S.F. & Sykes, M.K. Inverse ratio ventilation compared with PEEP in adult respiratory failure. *Intensive Care Med* 1984, **10:** 227–232.
5. Hedenstierna, G., Baehrendtz, S., Klingstedt, C. *et al.* Ventilation and perfusion of each lung during differential ventilation with selective PEEP. *Anesthesiology* 1984, **61:** 369–376.
6. Dorrington, K.L. Extracorporeal gas exchange in acute respiratory failure. *Br Med J* 1988, **296:** 151.
7. Egan, T.M. *et al.* Ten-year experience with ECMO for severe respiratory failure. *Chest* 1988, **94:** 681–687.
8. Sibbald, W., Driedger, A.A., Myers, M.L., Shori, A.I.K.L. & Wells, G.A. Biventricular function in the adult respiratory distress syndrome: haemodynamic and radionuclide assessment, with special emphasis on right ventricular function. *Chest* 1983, **84:**126–134.

Fluid balance in adult respiratory distress syndrome (ARDS)

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Significant progress has been made towards a better understanding of the mechanisms underlying the acute lung injury associated with a variety of serious clinical illnesses. Eventually this knowledge will yield improved management strategies and possibly drugs that may ameliorate or even reverse the inflammatory component. Recent clinical series evaluating outcome in ARDS[1] have reported virtually identical mortality to that observed when the syndrome was first described some twenty years ago.[2] Currently, there is no magic bullet for ARDS, nor is there any prospect of one in the offing. Some extravagant success has been reported following the use of extracorporeal support techniques,[3] but the mainstay of clinical practice is still strict attention to fluid balance. The principal aim is to minimize pulmonary capillary pressure to reduce oedema formation and promote resolution before extensive infection or fibrosis is established. This aim should take precedence over concern about nutrition. The increasing availability of haemofiltration techniques offers the opportunity to optimize fluid balance, to specifically enhance pulmonary oedema resolution without sacrificing nutrition to any extent.[4,5]

References

1. Bauman, W.R., Jung, R.C., Koss, M. *et al.* Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. *Crit Care Med* 1986, **14:** 1.
2. Ashbaugh, D.G., Bigelow, D.B., Petty, T.L. & Levine, B.E. Acute respiratory distress in adults. *Lancet* 1967, **ii:** 319–323.
3. Gattinoni, L., Pesenti, A., Mascheroni, D. *et al.* Low frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. *JAMA* 1986, **256:** 881–886.
4. Sivak, E.D., Tita, J., Meden, G. *et al.* Effects of furosemide versus isolated ultrafiltration on extravascular lung water in oleic acid-induced pulmonary oedema. *Crit Care Med* 1986, **14:** 48–51.
5. Morgan, J., Morgan, C.J. & Evans, T.W. Pump-assisted haemofiltration after cardiopulmonary bypass. *Int J Cardiol* 1988, **21:** 259–267.

Extracorporeal gas exchange

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The feasibility of long-term use of an extracorporeal lung in adult respiratory distress syndrome (ARDS) was first demonstrated in 1972 and subjected to a prospective randomized trial comparing the technique with conventional ventilation in 1979.[1] Extracorporeal membrane oxygenation (ECMO) had no significant effect on a mortality of 90% and more recent limited experience is similarly disappointing.[2] By contrast, the application of ECMO in the newborn has accelerated markedly in the USA since 1984.[3] In adults, the technique of veno-venous low-flow extracorporeal CO_2 removal ($ECCO_2R$) has shown greater promise than ECMO.[4] Furthermore, benefits seen in laboratory experiments[5,6] have been encouraging. Meanwhile, the results of a prospective randomized trial of $ECCO_2R$ in the USA are awaited.

References

1. Zapol, W.M., Snider, M.T., Hill, J.D. *et al.* Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979, **242:** 2193–2196.
2. Egan, T.M., Duffin, J., Glynn, M.F.X. *et al.* Ten-year experience with extracorporeal membrane oxygenation for severe respiratory failure. *Chest* 1988, **94:** 681–687.
3. Klein, M.D. Neonatal ECMO. *Trans Am Soc Artif Internal Organs* 1988, **34:** 39–42.
4. Gattinoni, L., Pesenti, A., Mascheroni, D. *et al.* Low-frequency positive pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. *JAMA* 1986, **256:** 881–886.
5. Kolobow, T., Borelli, M., Spatola, R., Tsuno, K., Prato, P. Single catheter veno-venous membrane lung bypass in the treatment of experimental ARDS. *Trans Am Soc Artif Internal Organs* 1988, **34:** 35–38.
6. Dorrington, K.L., McRae, K.M., Gardaz, J.P., Dunnill, M.S., Sykes, M.K. & Wilkinson, A.R. A randomized comparison of total extracorporeal CO_2 removal with conventional mechanical ventilation in experimental hyaline membrane disease. *Intensive Care Med* 1989, **15:** 184–191.

Monitoring in adult respiratory distress syndrome

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Modern management of ARDS hinges on the realisation that there are multiple cardiorespiratory interactions,

such that respiratory and haemodynamic monitoring cannot be separated. Furthermore, it has been demonstrated repeatedly that ARDS results in a central pulmonary defect in oxygen across the alveolar membranes, together with a defect in oxygen uptake by the cells at the periphery.[1] However, the application of traditional monitoring techniques and the maintenance of an adequate arterial oxygen tension has not prevented progressive multi-system organ failure and death in these patients.

Patients with ARDS and/or sepsis require high levels of oxygen delivery (Do_2) in order to maintain the supranormal levels of oxygen consumption (VO_2) needed to optimize optimal survival rates.[2] Ventilation with positive end expiratory pressure (PEEP) can be particularly hazardous, because it frequently reduces cardiac output and thereby Do_2. PEEP may not reduce blood pressure and may increase Pao_2, but this engenders a false sense of security, as PEEP actually lowers Do_2 causing tissue hypoxia and organ failure. Additionally, indices of pulmonary function based on calculations such as respiratory index and alveolar–arterial oxygen gradient are not as accurate as measuring shunt fraction using samples of arterial and mixed venous blood.[3,4]

Important equations:

Oxygen delivery = cardiac output × arterial oxygen content (ml/min)

Oxygen consumption = cardiac output × (arterial – mixed venous oxygen content) (ml/min)

References

1. Shoemaker, W.C. Relation of oxygen transport patterns to the pathophysiology and therapy of shock states. *Intensive Care Med* 1987, **13:** 230–243
2. Danek, S.J., Lynch, J.P., Weg, J.G. & Dantzker, D.R. The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1980, **122:** 387–395.
3. Cane, R.D., Shapiro, B.A., Templin, R. & Walther, K. Unreliability of oxygen tension-based indices in reflecting intrapulmonary shunting in critically ill patients. *Crit Care Med* 1988, **16:** 1243–1245.
4. Edwards, J.D. Optimum levels of oxygen transport in critically ill patients. In: Vincent, J.L. (ed.) *Update in Intensive Care and Emergency Medicine*, 8. Springer-Verlag, Berlin, 1989.