Ischaemia/reperfusion, inflammatory responses and acute lung injury

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The 1994 American-European consensus conference recommended that acute lung injury be defined "as a syndrome of inflammation and increased permeability . . .".[1] Thirty years on from Ashbaugh's original paper[2] this definition reflects the current understanding of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) as the pulmonary manifestations of a systemic inflammatory response. Recognised risk factors for this response have long included diverse entities such as trauma, sepsis and surgery, all of which induce transcription of several inflammatory cytokines. Earlier efforts to improve our understanding of the pathophysiology of acute lung injury have included studies of groups of patients undergoing oesophagectomy or cardiopulmonary bypass where an assessment of the inflammatory response and pulmonary capillary permeability have been made.[3 4] Ischaemia/reperfusion is another more recently recognised cause of both local and systemic inflammatory responses which can progress to cause acute lung injury. Aortic vascular surgery is a major cause of ischaemia/reperfusion of the lower limb and there is increasing evidence to support its role as an initiator of similar mechanisms leading to acute lung injury including the production of proinflammatory cytokines, neutrophil chemoattraction within the lung, and local release of neutrophil-derived proteases and oxygen radicals which mediate pulmonary capillary endothelial injury.

In this issue of *Thorax* Raijmakers and colleagues[5] describe an increase in microvascular permeability both in the lung and in the skin following aortic surgery. To assess microvascular permeability they used a variant of the double isotope method described by Gorin *et al*[6] to determine protein accumulation within the lung. An early assessment of this method[7] demonstrated a high sensitivity and specificity for the detection of pulmonary oedema associated with pulmonary vascular injury. Subsequent clinical studies confirmed its bedside utility and supported the concept of ALI/ARDS as variably severe pulmonary vascular responses to a systemic inflammatory response, in which neutrophil activation and capillary permeability were related[8] and in which an increase in capillary permeability was a major determinant of the severity of lung injury.[9] Variants of the double isotope method have been used to study patients undergoing cardiopulmonary bypass[4 10 11] or aortic surgery.[5 12] Increased pulmonary vascular permeability has been observed in the absence of clinically significant lung injury in most of these patients. An increase in intestinal permeability after cardiopulmonary bypass has also been reported[4] and Raijmakers and colleagues have described an increase in skin permeability in their clinical model of ischaemia/reperfusion.[5] This lends further support to the concept of a more widespread abnormality of capillary function in the systemic inflammatory response following both cardiopulmonary bypass and aortic vascular surgery.[5 12–15]

In addition to increases in lung and skin capillary permeability Raijmakers *et al* also report increases in circulating levels of IL-8[5 12] and its relation to the intensity of the permeability changes in the lung. What does this tell us about mechanisms of acute lung injury in man? Clamping and release of the aorta subjects the vascular endothelium to damage by processes involving production of toxic oxygen radicals. Cellular hypoxia is a recognised stimulus for induction of IL-8 gene expression[16] and there is some evidence to link the intensity of the IL-8 response to the duration of aortic clamping.[17] Interleukin-8 is a proinflammatory cytokine released in response to inflammatory stimuli by several cell populations. It possesses many properties compatible with an important role in the genesis of acute lung injury. It is a potent neutrophil activating and chemotactic factor and also plays a regulatory role in the transendothelial migration of neutrophils. A role for IL-8 in the development of lung injury is suggested by several clinical studies[18–20] and there are animal studies to suggest that early treatment with an antibody to IL-8 reduces severity and mortality of acute lung injury.[21] Miller and colleagues have recently demonstrated increased levels of IL-8 in bronchoalveolar lavage (BAL) fluid in patients with sepsis/ARDS compared with those with non-septic ARDS and congestive cardiac failure.[22] Levels of IL-8 in BAL fluid of patients at risk have been related to disease progression and/or survival with a better outlook for patients with lower BAL fluid levels of IL-8.[18 23 24] The level of IL-8 rises consistently after cardiopulmonary bypass where there is evidence for upregulation of IL-8 mRNA expression in heart and skeletal muscle.[25] Aortic surgery with ischaemia/reperfusion is also associated with evidence of increased IL-8 production and systemic neutrophil activation. As a consequence of these processes, neutrophils slow down as they tumble along vessel walls. Endothelial cells express various adhesion molecules or selectins which bind to complementary sites on neutrophils. Interleukin-8 plays an important role in increased expression of neutrophil cell surface receptors (integrins) – for example, CD11a/CD18, CD11b/CD18, CD11c/CD18 – and is also thought to exert control over downregulation of endothelial cell adhesion molecules (selectins) as the process of neutrophil/endothelial adhesion progresses. Following adhesion, neutrophils migrate through the endothelial barrier and subsequent release of their injurious granule contents and toxic oxygen radicals mediates the endothelial damage of acute lung injury. In most patients who undergo cardiac and vascular surgery this process is short lived and reversible. If this process progresses, the increased pulmonary capillary permeability allows transudation of plasma into the alveoli where surfactant is inactivated, further compounding the tendency to early airway closure in the supine patient, dependent pulmonary oedema, worsening regional ventilation/perfusion mismatching, and the progression from ALI to ARDS.

Whilst our knowledge of cellular and humoral events underlying ARDS has improved, our attempts to alter its course by using various anti-inflammatory strategies have been quite unsuccessful. This underlines the importance of developing a better understanding of the interaction between components of the systemic inflammatory response. Raijmakers *et al* have shown that increased lung and skin permeability are part of the systemic inflammatory

response that occurs in patients after aortic surgery. Whilst their study included only 11 patients, it provides support for the rationale to study groups of homogeneous patients in whom a predictable systemic inflammatory response can be demonstrated and in whom therapeutic intervention might be used to determine whether or not we can reduce the intensity and duration of these responses. Ultimately, this approach has the potential to provide benefit to future patients with acute lung injury of more diverse aetiology.

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