The pulmonary physician in critical care • 6: The pathogenesis of ALI/ARDS

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An understanding of the pathogenesis of ARDS is essential for choosing management strategies and developing new treatments. The key mediators involved in the inflammatory and fibroproliferative responses are reviewed and the mechanisms which regulate these responses are highlighted.

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Lung injury is the term used to describe the pulmonary response to a broad range of injuries occurring either directly to the lung or as the consequence of injury or inflammation at other sites in the body. Acute respiratory distress syndrome (ARDS) represents the more severe end of the spectrum of this condition in which there are widespread inflammatory changes throughout the lung, usually accompanied by aggressive fibrosis.[1–5] The pathogenesis of lung injury is not well understood.[1 5] We do not know why some people progress to ARDS while others who sustain indistinguishable injuries remain relatively unaffected.[6] ARDS is unique among pulmonary fibrotic conditions in that the fibrosis resolves almost completely in many cases; once again the mechanisms for this are not understood.[7] It is now well recognised that some of the damage is created and exacerbated by mechanical ventilation.[8] However, mortality from ARDS has improved in certain centres over the last 10 years,[9 10] predating major changes in ventilatory practice; the reasons for this improvement in mortality are thus also not clear.

ARDS often occurs as part of a wider picture of multiorgan dysfunction syndrome (MODS).[11] Central to the pathogenesis are an explosive inflammatory process and the reparative responses invoked in an attempt to heal this. This review will outline the pathological processes which occur during ARDS and their evolution as our understanding of the inflammatory, immune, and fibroproliferative responses has grown. It will describe the underlying cellular and molecular processes, correlate these with the clinical picture, and highlight how such insights can lead to novel therapeutic approaches.

DEFINITIONS

Lung injury (acute lung injury (ALI) and ARDS) is currently defined clinically by gas exchange and chest radiographic abnormalities which occur shortly after a known predisposing injury and in the absence of heart failure.[1] The definition and range of predisposing conditions are discussed by Atabai and Matthay in a previous article in this series.[12]

The pathophysiology of ARDS is driven by an aggressive inflammatory reaction. Indirect injury occurs as part of a systemic inflammatory response syndrome (SIRS), which can be due to infective or non-infective causes such as pancreatitis or trauma; when SIRS is caused by infection it is called sepsis. SIRS with organ dysfunction is called severe sepsis and, in the presence of significant hypotension, septic shock.[13] ARDS can thus occur in conjunction with failure of other organs, the multiorgan dysfunction syndrome (MODS). A number of endogenous anti-inflammatory mechanisms are also initiated to counterbalance the effects of such an aggressive inflammatory response and this is termed the compensatory anti-inflammatory response syndrome (CARS), although these responses too may be excessive and contribute to a state of immunoparesis.[14 15]

PATHOLOGY

Lung injury is an evolving condition and the pathological features of ARDS are typically described as passing through three overlapping phases (table 1)—an inflammatory or exudative phase, a proliferative phase and, lastly, a fibrotic phase.[2–5] These phases are complicated by other variables—for example, episodes of nosocomial pneumonia and the deleterious effects of ventilator induced lung injury. Moreover, the initiating insults themselves may influence the pathophysiological picture. Radiographic differences have been identified between patients with ARDS arising from direct pulmonary injuries compared with those from indirect injuries.[16] Likewise, a small study has suggested greater areas of alveolar collapse and oedema in patients dying with ARDS from direct rather than indirect injuries.[17] Although these differences may translate into differences in outcome, no clear mechanistic differences between these groups have been identified.[18] A recent study has suggested, however, that lung cyclo-oxygenase-2 (COX-2) gene expression (a gene implicated in the early proinflammatory response) is only induced by indirect mechanisms related to the systemic response to endotoxin rather than directly in response to inhaled endotoxin.[19]

Exudative phase

Typically, this lasts for the first week after the onset of symptoms. The histological changes are termed diffuse alveolar damage.[5] At necroscopic examination the lungs are heavy, rigid and, when sectioned, do not exude fluid because of its high protein content. Bachofen and Wiebel were among the first to study the histopathological

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Table 1 Summary of some histopathological changes in ARDS

	Exudative phase	Proliferative phase	Fibrotic phase
Macroscopic	• Heavy, rigid, dark	• Heavy, grey	• Cobblestoned
Microscopic	• Hyaline membranes • Oedema • Neutrophils • Epithelial>endothelial damage	• Barrier disruption • Oedema • Alveolar type II cell proliferation • Myofibroblast infiltration • Neutrophils • Alveolar collapse • Alveoli filled with cells and organising matrix • Epithelial apoptosis • Fibroproliferation	• Fibrosis • Macrophages • Lymphocytes • Matrix organisation • Deranged acinar architecture • Patchy emphysematous change
Vasculature	• Local thrombus	• Loss of capillaries • Pulmonary hypertension	• Myointimal thickening • Tortuous vessels

changes in detail in patients who died with ARDS.[20] An acute stage commencing within the first 24 hours of symptoms was marked by significant proteinaceous and often markedly haemorrhagic interstitial and alveolar oedema with hyaline membranes. The hyaline membranes are eosinophilic containing fibrin, immunoglobulin, and complement. The microvascular and alveolar barriers have focal areas of damage and the alveolar wall is oedematous with areas of necrosis within the epithelial lining, although the basal lamina is intact initially. The early endothelial lesions are more subtle, containing areas of necrosis and denuded spaces usually filled with fibrin clot. Neutrophils are found increasingly during the initial phases in capillaries, interstitial tissue, and progressively within airspaces.[21]

Proliferative phase

Typically occupying the second 2 weeks after the onset of respiratory failure, the proliferative phase is characterised by organisation of the exudates and by fibrosis.[2–5 20 22] The lung remains heavy and solid, and microscopically the integrity of the lung architecture becomes steadily more deranged. The capillary network is damaged and there is a progressive decline in the profile of capillaries in tissue sections; later, intimal proliferation is evident in many small vessels further reducing the luminal area. The interstitial space becomes grossly dilated, necrosis of type I pneumocytes exposes areas of epithelial basement membrane, and the alveolar lumen fills with leucocytes, red cells, fibrin, and cell debris. Alveolar type II cells proliferate in an attempt to cover the denuded epithelial surfaces and differentiate into type I cells.[23] Fibroblasts become apparent in the interstitial space and later in the alveolar lumen.[24] These processes result in extreme narrowing or even obliteration of the airspaces. Fibrin and cell debris are progressively replaced by collagen fibrils. The main site of fibrosis is the intra-alveolar space, but it also occurs within the interstitium.

Fibrotic phase

This can begin from day 10 after initiating injury. Macroscopically, the lungs have a cobblestoned character due to scarring.[2–5] The vasculature is grossly deranged with vessels narrowed by myointimal thickening and mural fibrosis. The microscopic events occurring in the repair phase are not well documented, mainly because of a paucity of histological data as patients recover. Some insights have been obtained from bronchoalveolar lavage (BAL), radiology, and from animal models.[25] BAL confirms a marked decline in neutrophils and a relative accumulation of lymphocytes and macrophages. The most dramatic, although unpredictable, changes are those of lung collagen.[26] Total lung collagen content may double within the first 2 weeks,[27] but this burden can be eliminated and many, albeit small, studies show that survivors can return to relatively normal lung function.[28] Interestingly, although the severity of pathological changes in the first few weeks (hyaline membrane, airspace organisation, or cellularity) do not seem to correlate with late functional recovery, the degree of fibrosis is a key predictor of outcome.[29 30] High levels of procollagen peptides detected early in ARDS have been repeatedly shown to predict a poor outcome.[31 32] Moreover, established fibrosis reduces lung compliance thereby increasing the work of breathing, decreasing the tidal volume, and resulting in CO_2 retention. Also, because of the alveolar obliteration and interstitial thickening, gas exchange is reduced which contributes to hypoxia and ventilator dependence. Although late deaths from ARDS have been ascribed mainly to sepsis rather than progressive hypoxia, sepsis is a common complication in these patients. It is usually the consequence of ventilator associated pneumonia or other nosocomial infections related to their ventilator dependence.[33 34]

Recent evidence suggests that there is a much greater overlap of the inflammatory and fibroproliferative phases than previously thought,[7] and many mediators are common to both processes.[25] The fibroproliferative response begins remarkably early with N-terminal procollagen III peptide levels, a marker for collagen turnover, being raised in BAL fluid within 24 hours of ventilation for ARDS.[31] Myofibroblast cells also show an early increase in the alveolar walls, and BAL fluid from ARDS patients within 48 hours of diagnosis is intensely mitogenic for fibroblasts.[32] This all suggests that the fibrosis characteristic of ARDS may not be a late event but is switched on at a very early stage. This is particularly important as the inflammatory and fibrotic processes, although closely overlapping, appear to be separately regulated, thus offering the possibility for early directed treatments against fibrosis independent of the effects on inflammation.[35]

PATHOGENESIS

Lung injury is initiated by a specific insult but can be exacerbated by inappropriate mechanical ventilatory strategies (reviewed by Whitehead and Slutsky later in this series). Briefly, alveolar overdistension can generate a proinflammatory response which is exacerbated by repetitive opening and closing of alveoli as occurs through the use of inappropriately low levels of positive end expiratory pressure (PEEP).[8] Indeed,

overdistension or recurrent opening/closing of alveoli can also induce structural damage to the lung.[36] [37] The effect of high inspired concentrations of oxygen on the disease process is uncertain, particularly in humans. However, prolonged exposure to 100% oxygen is fatal in most animal models, producing neutrophil influx and alveolar oedema that can be blocked in rodents using anti-inflammatory strategies such as inhaled low dose carbon monoxide.[38] [39]

The main players in the inflammatory process are neutrophils and multiple mediator cascades.[40–42] The fibroblast is key in the fibroproliferative response and is the target of regulators of matrix deposition.[43] A complex interplay of regulatory cytokines counteracts the inflammatory mediators; similarly, matrix deposition is balanced by the actions of the metalloproteases. There is no uniform response to injury: some patients develop ARDS, some ALI, and some do not develop pulmonary symptoms at all. The reasons for this are not clear but may be partly genetic. There is evidence for a genetic susceptibility to sepsis and, recently, to ARDS itself.[44–46]

Because of the difficulties in obtaining histological samples in humans, studies have been undertaken in animals and have provided a valuable understanding of the mechanisms driving lung injury.[47] It is important to be aware of the limitations of these models as animals differ in their sensitivity to the initiating insult (especially endotoxin) and in their pulmonary responses. The timing and severity of the insults and, especially, the degree of subsequent resuscitation also do not mirror the clinical condition. Models include direct challenge to the lung such as bleomycin, endotoxin or acid aspiration, surfactant washout and oxygen toxicity, or intravenous challenges including endotoxin, complement or microemboli: all have features in common with the human counterpart including inflammatory cell influx and endothelial damage.[39] [48] [49] Animals challenged with endotoxin develop endothelial and epithelial barrier dysfunction although the endothelium appears to be more sensitive than the epithelium, whereas in humans it is the epithelium that shows greater damage.[50] Animal models have also been used to examine the later stages of ARDS. The best are studies in primates exposed to high concentrations of oxygen which showed enlarged airspaces, thickened alveolar walls and interstitial fibrosis, and in the survivors there was decreased alveolarisation and bronchopulmonary dysplasia.[39]

INFLAMMATION

With initiation of inflammation there is increased leucocyte production and rapid recruitment to the inflamed site. There is also activation of mediator cascades including the production of cytokines, chemokines, acute phase proteins, free radicals, complement, coagulation pathway components, and focal upregulation of adhesion molecule expression. The "anti-inflammatory" response includes the glucocorticoids, cytokines (interleukin (IL)-4, IL-10 and IL-1 receptor antagonist (IL-1ra)) and other mechanisms such as shedding of adhesion molecules.[40–42]

The neutrophil

This is the dominant leucocyte found both in BAL fluid and in histological specimens from patients with ARDS.[21] In many animal models the degree of lung injury is reduced dramatically if neutrophil influx is ablated, although this is not a universal finding.[51] [52] However, ARDS can develop in neutropenic patients, hence neutrophils are believed to be an important but not essential component of the injurious response.[53] Neutrophils cause cell damage though the production of free radicals, inflammatory mediators, and proteases. Excessive quantities of neutrophil products including elastase, collagenase, reactive oxygen species, and cytokines such as tumour necrosis factor α (TNF-α) have been found in patients with ARDS.[21] [42] [54–57] Recent studies with mice deficient in neutrophil elastase suggest that this enzyme may be an important mediator of damage to the alveolar epithelium and the progression to fibrosis.[58]

Adhesion molecules, notably β_2 integrins, mediate neutrophil binding to the pulmonary endothelium. This process is believed to promote leucocyte induced lung injury although some investigators suggest that adhesion molecules have a diminished role in the pulmonary compared with the systemic circulation.[59] [60] Adhesion molecules also modulate activation and mediator release by neutrophils. In a landmark study Folkesson and Matthay induced pulmonary injury in the presence of β_2 integrin blocking antibodies and demonstrated that, while neutrophil migration still occurred, a number of indices of inflammation were reduced.[61] Neutrophil activation leads to cytoskeletal changes that reduce cell deformability and slow their transit time through the lung capillary bed, providing an integrin independent mechanism whereby neutrophil contact with the pulmonary endothelium is increased.[62] Other inflammatory cells including macrophages and, later, lymphocytes are involved, while platelets may exacerbate the vascular injury and endothelial cells themselves are capable of producing many damaging mediators of inflammation.

Inflammatory mediators

The inflammatory process is driven in part by cytokines including TNF-α and IL-1β, IL-6, and IL-8. All have been found in BAL fluid and plasma of patients with ARDS.[57] [63] [64] TNF-α and IL-1β can both produce an ARDS-like condition when administered to rodents. They are produced by inflammatory cells and can promote neutrophil-endothelial adhesion, microvascular leakage, and amplify other proinflammatory responses. Despite their profile in the septic response, the importance of these cytokines in the pathogenesis of ARDS is unclear. Levels of TNF-α are not uniformly increased in patients with lung injury and anti-TNF-α and IL-1 therapies have been disappointing. The increase in TNF-α levels occurs very early in the clinical course and may be missed by the time of presentation, although anti-TNF-α therapies can still be of benefit in some cases of sepsis.[65] The huge redundancy in the proinflammatory mediator systems suggests that the search for a "common pathway" susceptible to inhibition may be too simplistic.[40] Many proinflammatory mediators including endotoxin, proinflammatory cytokines, vascular endothelial growth factor (VEGF), high mobility group-1 protein, and thrombin are implicated in the increased vascular permeability that contributes to oedema in lung injury.[66] The balance of "anti-inflammatory" cytokines and mediators must also be considered. There is now good experimental evidence that mediators such as IL-1ra, soluble TNF receptors (sTNF-R), IL-4, IL-10, and even other molecules such as carbon monoxide at very low concentrations are powerful downregulators of the inflammatory response.[38] [65]

The intense neutrophilic infiltrate has led to a search for the chemotactic factors responsible. Early studies implicated complement; however, more recently, the focus has been on chemokines. IL-8 levels are raised in the BAL fluid of patients at risk who ultimately develop ARDS.[64] It is a powerful neutrophil chemoattractant derived from alveolar macrophages and other cells that is regulated by hypoxia/hyperoxia.[67] Another neutrophil chemoattractant, ENA-78, may account for IL-8 independent neutrophil adhesion in ARDS. MIF, a neuropeptide, is increased in ARDS but its role is unclear.

Animal model work suggests that free radicals are fundamental to the tissue damage resulting from proinflammatory stimuli and that antioxidants, including glutathione and superoxide dismutase, are important protective mechanisms. Similarly, in humans oxidant stress is increased and

plasma antioxidant levels are reduced in patients with ARDS.[56 68] Nitric oxide may play a role in septic lung injury as nitrotyrosine, a product derived from peroxynitrite, is found in increased amounts in patients with ARDS.[69] The lipid mediator platelet activating factor (PAF) can activate both neutrophils and platelets and administration can mimic many features of lung injury. Other mechanisms for the generation of barrier dysfunction during the inflammatory phase include pathological changes in the regulation of apoptosis. In this regard soluble Fas ligand (sFasL) has been shown to drive alveolar epithelial cell apoptosis in vitro, and to cause lung injury with increased airway cell apoptosis in vivo, to be released in the airspaces of and be localised to the lung epithelial cells in patients with ARDS.[70] In addition to excess apoptosis in the parenchymal cells, delayed apoptosis in the infiltrating neutrophils may contribute to the proinflammatory load.[71]

Mediators of pulmonary hypertension

Mild pulmonary arterial hypertension is frequently seen in patients with ARDS, and loss of normal control over pulmonary vasomotor tone is an important mechanism underlying refractory hypoxaemia. Hypoxic pulmonary vasoconstriction is lost in sepsis induced lung injury as inhalation of 100% oxygen before and during endotoxin challenge does not prevent pulmonary hypertension and hypoxic vasoconstriction is inhibited for several hours after endotoxin challenge.[72] Studies with knockout mice have demonstrated a central role for nitric oxide (NO) in the normal modulation of pulmonary vascular tone. The mechanisms whereby this regulation is lost in lung injury are not clear, but it is known that endotoxin induces COX-2 and inducible nitric oxide synthase (iNOS) expression in the pulmonary vasculature.[73] The situation is complicated, however, as endotoxin contributes to an early marked pulmonary hypertension despite the induction of iNOS and irrespective of the pulmonary artery occlusion pressure or cardiac output.[74] Increased expression of the powerful vasoconstrictor endothelin-1 is associated with pulmonary hypertension in sepsis and ARDS.[75] Thromboxane B_2, another pulmonary vasoconstrictor, may also be an important mediator of pulmonary hypertension in ARDS as COX inhibitors reduce the early pulmonary hypertension induced by endotoxin. Other pulmonary vasoconstrictors may also be released in ARDS and other mechanisms of pulmonary hypertension such as microthromboembolism probably contribute. Inflammation leads to a procoagulant state and disseminated intravascular coagulation which is well recognised in ARDS and sepsis. Thrombin can also potentiate inflammation and lead to endothelial barrier dysfunction, in addition to its profibrotic effects (see below).

Surfactant dysfunction

Inflammation leads to surfactant dysfunction in ARDS.[76] Surfactant is secreted mainly by alveolar type II cells and consists of phospholipids (predominantly phosphatidylcholine) and surfactant specific proteins, SP-A, SP-B, SP-C and SP-D.[77] The ability of surfactant to lower surface tension is critically dependent on both the phospholipid and the protein components, especially the hydrophobic proteins SP-B and SP-C. The phospholipids are stored in the lamellar bodies of type II cells and interact with surfactant proteins upon release from the cells, forming large aggregates called tubular myelin. During the normal cycle of breathing these functional large surfactant aggregates become dissipated, reducing to smaller aggregates which do not have the same surface tension lowering properties. Type II cells take up these small aggregates and recycle them into new surfactant. The hydrophilic surfactant protein SP-A, quantitatively the major surfactant protein, plays a key role in this process. The other hydrophilic surfactant protein is SP-D, which may also have a function in

phospholipid recycling. SP-A and SP-D are members of the collectin family and form part of the innate immune system in the lung; interestingly, both have significant antibacterial activity and inhibit neutrophil apoptosis.[78]

Surfactant levels are dramatically decreased in the infant respiratory distress syndrome due to immaturity of the type II cells. By contrast, in ARDS surfactant deficiency is not a primary causal event; rather, the inflammatory processes lead to surfactant dysfunction as a secondary factor. Damage and loss of type II cells leads to decreased synthesis and recirculation of surfactant. This defect in turnover can lead to accumulation of small aggregates, while overall surfactant performance follows a reduction in the functional large surfactant aggregates and damage to surfactant proteins.[79] In addition, the protein rich oedema in ARDS "contaminates" surfactant, further reducing its functional capacity. Furthermore, in lung injury the ratio of minor phospholipids to phosphatidylcholine increases, possibly indicating damage and release of cell membrane lipids. The degree to which surfactant dysfunction contributes to the pathogenesis of ARDS is currently not clear.

THE FIBROPROLIFERATIVE RESPONSE

Fibroproliferation is a stereotypical part of the normal repair process which, if not closely regulated, can have serious consequences. The fibrotic response is fuelled by mediators that stimulate local fibroblasts to migrate, replicate, and produce excessive connective tissue.[7 25 43] Animal models have suggested a number of potential profibrotic factors. For example, the expression of TNF-α in the lung, using an SP-C promoter for tissue specificity, led to the development of a T lymphocyte predominant alveolitis which progressed steadily to a histological picture resembling idiopathic pulmonary fibrosis.[80] These data suggest that TNF-α and other proinflammatory mediators, including IL-1β, play important roles in the development of pulmonary fibrosis. Similarly, expression of transforming growth factor α (TGF-α) in the distal pulmonary epithelium induced pulmonary fibrosis, the extent of which is related to the level of gene expression.[47] The Th2 cytokines have been implicated in fibroproliferative disorders and both IL-4 and IL-13 are increased in a bleomycin model of fibrosis; interestingly, inhibition of IL-13 significantly abrogated this fibrotic response.[81] Although many mediators regulate collagen metabolism in pulmonary fibrosis, studies of these in ARDS are very limited. There is evidence that the levels of TGF-α and a platelet derived growth factor (PDGF)-like factor are increased in BAL fluid from patients with ARDS.[82 83] A number of products of the coagulation cascade—particularly fibrin, thrombin, and factor Xa—are important mediators of the pulmonary profibrotic response and are increased in patients with ARDS.[25]

The archetypal profibrotic cytokine is TGF-β, of which there are three closely related isoforms (TGF-β1, 2 and 3) that exert nearly identical effects as modulators of inflammation, inhibitors of growth and differentiation, and regulators of extracellular matrix production.[84] Studies in animals and in humans strongly suggest that TGF-β is important in the pathogenesis of pulmonary fibrosis.[85] It has been shown be mitogenic and chemotactic for fibroblasts, to increase the synthesis of extracellular matrix proteins, and to inhibit the production of matrix degrading enzymes.[25] TGF-β1 should not be simply viewed as a profibrotic cytokine, however, as it has multiple other actions—it is anti-inflammatory, decreases epithelial proliferation, and can be pro-apoptotic for many cell types. It is also a powerful chemotactic agent for monocytes and macrophages, essential cells in the process of wound healing. In the normal repair process the secretion of TGF-β1 is thus a powerful effector for resolution and it is only when its expression is persistent or excessive that it leads to pathological fibrosis. TGF-β1 is produced as a latent precursor that is converted into the mature bioactive form after cleavage of the

N-terminal portion, termed the latency associated peptide (LAP). In animal models the transfection of active (but not latent) TGF-β1 results in severe fibrosis.[86] More recently it has been shown that the integrin αvβ6, an adhesion molecule that binds matrix and anchors cells, can bind LAP and activate TGF-β1.[87] The expression of this integrin is very low or absent on most normal adult epithelial cells but is upregulated dramatically after injury.[47] Failure to express this adhesion molecule confers almost complete protection against bleomycin induced lung injury and fibrosis in mice. This highlights the role of the alveolar epithelium, integrins, and TGF-β1 in the regulation of the inflammatory and repair processes.

RESOLUTION OF ARDS
Liquid is gradually cleared from airspaces by ion pumps that transport sodium with osmotically driven water movement across the alveolar epithelium via membrane water channels.[88] Catecholamines may increase this while propranolol or amiloride inhibit sodium transport and impede clearance of alveolar fluid. Repair of the injured lung requires an intact epithelial basal lamina which facilitates restoration of the epithelial barrier and may thus further promote clearance of oedema.[89] Lung lymph flow, a much ignored subject, may also contribute to the clearance of pulmonary oedema.

Histologically, the resolution phase of ARDS has been the least clearly documented. Apoptosis is essential to the clearance of neutrophils and has been clearly demonstrated in the lung in patients with ARDS.[71 90] Apoptosis is also responsible for removing surplus alveolar type II cells while survivors differentiate into a type I phenotype. BAL fluid recovered from patients with ALI during the repair phase can induce fibroblast and endothelial cell death. This provides a mechanism to clear excess cells while retaining underlying normal lung structure. Resolution of ARDS requires more than the clearance of leucocytes; for successful healing the fibroproliferative response must be terminated and excess mesenchymal cells cleared. As the inflammatory and fibroproliferative processes are intimately linked and many mediators such as thrombin and IL-1 are central to both, it is likely that the resolution of inflammation makes a major contribution to the resolution of fibroproliferation.[35] Other mediators will be produced that promote resolution—for example, interferon (IFN)γ produced by activated T cells downregulates the transcription of the TGF-β1 gene. The generation of pulmonary fibrosis involves a complex interplay between collagen deposition and degradation, with the early balance shifted dramatically towards deposition. In ARDS type III collagen is initially deposited which is more flexible and susceptible to breakdown; later this is remodelled to the thicker and more resistant type I collagen.[27] The mechanisms involved in the clearance of the fibrotic matrix are not well established but are likely to involve matrix metalloproteases (MMPs) and gelatinases that digest collagens. At least two of these—MMP-2 and MMP-9—are increased in the lungs of patients with ARDS.[91] The MMPs are further regulated by tissue inhibitors of metalloproteases (TIMPs), although the relative balance of these systems during ARDS is unknown.

The pulmonary fibrosis in ARDS does not necessarily completely resolve and can lead to persisting pulmonary problems both during weaning and after patients leave the intensive care unit. Recovery of lung function can be slow, with some patients taking up to 12 months to return to baseline while others have persisting abnormalities. In the majority, however, lung mechanics fully recover suggesting that the pulmonary fibrosis in ARDS is reversible.[2 28]

PATHOPHYSIOLOGY RELATED TO PATHOLOGY
Refractory hypoxaemia may be multifactorial, but intrapulmonary shunting with ventilation-perfusion mismatching is

- There is much greater overlap of the inflammatory and fibroproliferative phases of ARDS than previously imagined, with the fibroproliferative response beginning within 24 hours and its severity being directly related to the outcome.
- An exaggerated inflammatory response underlies the pathogenesis of ARDS. The neutrophil is the dominant leucocyte, while many proinflammatory agents including endotoxin, proinflammatory and chemotactic cytokines, vascular endothelial growth factor, high mobility group-1 protein and thrombin, together with oxidant stress, are all implicated in vascular leakage and lung damage.
- Surfactant deficiency is not a primary causal event in ARDS; rather, the inflammatory processes lead to surfactant dysfunction as a secondary factor.
- Alveolar type II cell proliferation and enhanced fibroproliferation are key steps in attempts at repair in the lung; both offer potential targets for future therapies.

believed to be the primary cause. Studies on patients with ARDS have shown that the degree of intrapulmonary shunting is sufficient to account for the entire alveolar-arterial oxygen gradient, suggesting that a decrease in transfer factor may be of secondary importance.[2] Microscopic studies have shown that the alveolar airspaces are filled with oedema, debris, hyaline membranes, and matrix or lost through alveolar collapse, creating a huge physiological deadspace. The effects of this on gas exchange are maximised by loss of hypoxic pulmonary vasoconstriction and by the widespread patchy vascular defects so common in ARDS. Pulmonary oedema will also lead to a significant diffusion block. The causes of pulmonary oedema are multiple and include mediator induced vascular permeability, increased pulmonary pressures, and alterations to the oncotic pressure as suggested in the seminal studies by Guyton in 1959.[92]

Lung compliance is markedly decreased in ARDS. This will be related initially to flooding of the alveoli and the interstitial spaces with fluid inflammatory cells and debris. Progressively, this inflammatory response is organised and replaced by matrix that further reduces compliance. The effects of this on the pressure-volume curve and on mechanical ventilation will be reviewed in greater detail by Cordingley and Keogh in a later article in this series.

CONCLUSIONS
Understanding the pathogenesis of ARDS is essential both to choosing effective management strategies and to looking for novel treatments. We have seen that mechanical ventilation can induce inflammation if applied inappropriately or reduce mortality if correctly used, and that this has a clear pathophysiological rationale. Similar concepts have led to ongoing studies of prone ventilation and to the investigation of other ventilatory strategies such as high frequency ventilation and lung rest with extracorporeal membrane oxygenation.

This review has outlined the key mediators involved in both the inflammatory and fibroproliferative responses and highlighted some of the important mechanisms through which these responses are regulated. Many of these mediators will be examined in more detail in later articles in this series dealing with treatment options.

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