The role of the host defence response in the progression and outcome of ARDS: pathophysiological correlations and response to glucocorticoid treatment

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ABSTRACT: The host defence response (HDR) to insults is similar regardless of the tissue involved and consists of an interactive network of simultaneously activated pathways that act in synergy to increase the host's chance of survival. Among this cascade of integrated pathways, three aspects of the HDR, inflammation, coagulation and tissue repair, are analysed separately to explain the histological and physiological changes occurring at the tissue level in unresolving acute respiratory distress syndrome (ARDS). Cellular responses in HDR are regulated by a complex interaction among cytokines, and cytokines have concentration-dependent biological effects. The degree of initial HDR may determine the progression of ARDS. On Day 1 of mechanical ventilation and over time, nonsurvivors of ARDS have significantly higher plasma and bronchoalveolar lavage inflammatory cytokines levels than survivors. In the absence of inhibitory signals, the continued production of HDR mediators prevents effective restoration of lung anatomy and function by sustaining inflammation with tissue injury, intra- and extravascular coagulation and proliferation of mesenchymal cells (fibroproliferation) with deposition of extracellular matrix resulting in fibrosis.

Glucocorticoids inhibit the HDR cascade at virtually all levels; their gradual and generalized suppressive influence protects the host from overshooting. In patients with exaggerated HDR, however, cytokine elevation may cause a concentration-dependent resistance to glucocorticoids by reducing glucocorticoid receptor binding affinity. Recent clinical and experimental studies have shown that effective containment of the HDR in unresolving ARDS may be achieved only if glucocorticoid administration is prolonged. A double-blind randomized study is in progress to evaluate the role of prolonged glucocorticoid treatment in unresolving ARDS.

Acute respiratory distress syndrome (ARDS) describes the clinical syndrome associated with the morphological lesion termed "diffuse alveolar damage" (DAD). At presentation, (early) ARDS manifests with acute and diffuse injury to the endothelial and epithelial lining of the terminal respiratory units and causes increased vascular permeability with protein-rich exudative oedema. Despite improvements in supportive care and multiple therapeutic efforts directed at modifying the course of this condition, mortality still remains above 50%. In nonsurvivors of ARDS (table 1), DAD rapidly advances through three histological phases (exudative, fibroproliferative and fibrotic) with different clinicophysiological features. The objective of this review is to describe systematically the pathophysiology of unresolving ARDS relating to mechanisms of its development, structural alterations induced in the lung and functional consequences of these morphological changes. Intentionally, I will place the host defence response (HDR) at centre stage as a critical reference point for explaining how ARDS progresses in nonsurvivors and to provide a rationale to evaluate glucocorticoid (GC) treatment and other therapeutic strategies.

Most ARDS patients (85–95%) survive the initial direct or indirect insult that precipitated acute respiratory failure and progress into the reparative stage, where outcome varies (table 2) from complete recovery (groups 2 and 3) to rapid death from accelerated pulmonary fibrosis (group 5) [11]. In patients who recover, the permeability defect and gas exchange abnormalities do improve (adaptive response) [12]. Conversely, ineffective repair is manifested by progression of fibroproliferation, inability to improve lung function (groups 4 and 5) and unfavourable outcome (maladaptive response) [10]. Most nonsurvivors invariably develop fever, systemic inflammatory response syndrome (SIRS) [13], clinical manifestations of sepsis [14–16] and multiple organ dysfunction syndrome (MODS) [5] and die after a prolonged period of ventilatory support (group 4). At autopsy, ARDS nonsurvivors are found to have extensive pulmonary fibrosis in 55% and pneumonia in 69% of cases [10]. Patients whose disease results in ineffective lung repair require...
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Continuous ventilation (unresolving ARDS) and are predisposed to develop pneumonia, extrapulmonary infections and sepsis. Sepsis has been associated with (but not proven to be causative of) death in 36–90% of ARDS nonsurvivors [15–18]. The hypothesis has been formulated on clinical criteria that, in unresolving ARDS, serious nosocomial infections, such as ventilator-associated pneumonia (VAP) amplify SIRS and lead to MODS and death [5, 6, 15, 16]. MODS develops more frequently in patients dying with sepsis than in those dying with refractory hypoxaemia [19–20]. Progression of fibroproliferation to extensive pulmonary fibrosis directly causes respiratory death in 15–40% of ARDS patients (table 2) [17, 15, 17].

Because there is no animal model to study the progression of ARDS, clinical investigation has become of primary importance for advancing understanding in this field. Our group has recently completed a series of clinical studies designed to clarify key pathogenetic aspects of ARDS progression and outcome. We have obtained serial quantitative measurements of HDR mediators in the lung and in the circulation and have correlated these measurements with pathophysiological variables over time. ARDS was studied during its natural progression and also in response to GC rescue treatment. During these investigations, a careful effort was made to accurately diagnose VAP (bronchoscopic methods) and pulmonary fibroproliferation (open-lung biopsy) following recently developed guidelines [21, 22]. In this review, I will highlight selected conceptual themes to provide a unifying pathogenetic model of ARDS, showing how an exaggerated and protracted HDR plays a key role in ARDS outcome and is accountable for the histological, laboratory, clinical and physiological findings observed during the course of unresolving ARDS.

### Table 1. – Histological changes in unresolving ARDS

| Timing | Exudative | Proliferative | Fibrotic |
|--------|-----------|---------------|----------|
| **Macroscopic** | Oedema | Organization (repair) | Fibrosis |
| Consistency | Early (<1 week) | Intermediate | Late (3 weeks) |
| Appearance | Rigid, heavy | Firm, consolidated | Spongy, cystic |
| **Microscopic** | Haemorrhagic | Pale grey | Pale |
| Vasculature | Endothelial injury (mild) | Endothelial injury | Endothelial injury |
| Congestion | Intimal fibroproliferation | Distortion | Compressed |
| Neutrophil aggregates | Medial hypertrophy | Thrombi | Proliferation |
| Minimal thrombi | Type 2 pneumocyte proliferation* | Fibrosis | Microcysts |
| Alveoli | Hyaline membranes* | Increased fibroblast invasion | Collagen deposition |
| Partial collapse | Collagen deposition | Disruption |
| Basement membrane | Denuded | Gaps with myofibroblast invasion |
| Alveolar wall | Oedema | Myofibroblast proliferation |
| Alveolar duct | Dilated | Myofibroblast proliferation |
| Interstitium | Volume↑ | Volume↑↑ |
| Pleura | Oedema | Myofibroblast proliferation |
| Pleural ischaemic changes | Subpleural necrosis |

* the endothelial cell layer is usually continuous with cell junction; endothelial gaps are rarely observed [1]; †: stem cell function for the entire epithelium; #: hyaline membranes are composed of fibrin, fibronectin and cellular debris adhering over denud-
Tissue host defence response

Tissue consists of organized groups of cells attached to an extracellular matrix (ECM) and surrounded by a network of blood vessels. The ECM occupies a significant proportion of the volume of any tissue and is indispensable for its structural integrity [23]. Tissue steady state, or homeostasis, is maintained by co-ordinating cell growth and proliferation with the production and turnover of ECM. Cells achieve a remarkable co-ordination by constantly signalling to themselves (autocrine activity) and each other (paracrine activity) by means of polypeptides called "cytokines" (also known as growth factors). Cell-cell and cell-matrix interactions, through cytokine networking, are essential not only for maintaining homeostasis, but also for providing a rapid defence (stress) response against intrinsic or extrinsic disturbing (infectious and noninfectious) forces.

The host defence response to insults is similar regardless of the tissue involved and consists of an interactive network of simultaneously activated pathways that act in synergy to increase the host's chance of survival. Among this complex cascade of integrated pathways, five aspects of the HDR are important for understanding the clinical development and evolution of ARDS (table 3): inflammation, coagulation (intravascular clotting and extravascular fibrin deposition), modulation of the immune response, tissue repair and activation of the hypothalamic-pituitary-adrenal (HPA) axis with production of glucocorticoids. Activation of the sympathetic system to release catecholamines and increased hepatic production of acute-phase reactants are an integral part of the host defence response and are under the influence of glucocorticoids. During stress, epinephrine response parallels HPA axis stimulation [24]. Glucocorticoids and ACTH affect several key regulatory enzymes in catecholamine biosynthesis and influence the number and functional state of adrenergic receptors [24]. Catecholamine-glucocorticoid interactions play an important role in maintaining vascular tone [24]. Acute phase reactants are essential in many aspects of the host defence (fibrinogen (coagulation and tissue repair), complement C3 (opsonization), C-reactive protein (inhibitor of neutrophil chemotaxis) and protease inhibitors (limit tissue damage during inflammation)) and their production is enhanced by glucocorticoids [25, 26]. The HDR is essentially a protective response of tissues, which serves to destroy, dilute, or contain injurious agents and to repair any consequent tissue damage. Repair consists of replacing injured tissue by regenerating native parenchymal cells and filling defects with fibroblastic tissue. Three aspects of the HDR, (inflammation, coagulation and tissue repair) can be analysed separately to explain the histological and physiological changes occurring at the tissue level in unresolved ARDS.

Cytokines, glucocorticoids and catecholamines are capable of modulating gene expression, primarily by altering the rate at which a given gene is transcribed into messenger ribonucleic acid (mRNA). For this process to occur, the deoxyribonucleic acid (DNA) sequences that regulate transcription of that particular gene must be identified by the transacting moiety. This recognition process appears to be performed almost entirely by specific proteins called "transcription factors." These regulatory proteins are able with great selectivity, to bind with high affinity to the correct DNA-binding site [24]. Cytokines and glucocorticoids enhance the expression and activity of transcription factors [24]. Important transcription factors associated with the HDR and discussed in this review include the glucocorticoid receptor complex, nuclear factor interleukin-6 (NF-IL6), NF-kB, activator protein-1 (AP-1 [c-Jun and c-Fos]), and the heat-shock transcription factor (HSF) [24].

Cellular responses in HDR are regulated by a complex interaction among cytokines with final effects on the surrounding microenvironment not directly induced by the initiating insult. In this regard, cytokines have concentration-dependent biological effects [27]. At low concentration they regulate homeostasis; at progressively higher concentrations they mediate proportional stronger local and then systemic responses. Among a broad spectrum of proximal mediators, cytokines of the interleukin-1 (IL-1) and tumour necrosis factor (TNF) family appear uniquely important in initiating all key aspects of the host defence response. TNF-α and IL-1β stimulate their own and each other's secretion, and both promote the release of IL-6 (NF-IL6 is the transcription factor responsible for IL-6 gene activation after IL-1 stimulation). The cell most commonly associated with initiating the host defence response cascade is the tissue macrophage or the blood monocyte [25]. Once released, TNF-α and IL-1β act on epithelial cells, stromal cells.

Table 3. – Components of the host defence response

| Inflammation                      |
|----------------------------------|
| Vasodilatation and stasis        |
| Increased expression of adhesion molecules |
| Increased permeability of the microvasculature with exudative oedema |
| Leucocyte extravasation          |
| Release of leucocyte products potentially causing tissue damage |
| Coagulation                      |
| Activation of coagulation        |
| Inhibition of fibrinolysis       |
| Intravascular clotting           |
| Extravascular fibrin deposition  |
| Modulation of the immune response|
| Fever                            |
| Induction of heat-shock proteins |
| Release of neutrophils from the bone marrow |
| Priming of phagocytic cells      |
| T-cell proliferation             |
| Antibody production              |
| Tissue repair                    |
| Angiogenesis                     |
| Epithelial growth                |
| Fibroblast migration and prolifetration |
| Deposition of extracellular matrix and remodelling |
| Activation of the hypothalamic-pituitary-adrenal axis |
| Release of ACTH with cortisol production |
| ACTH and cortisol modulation of the sympathetic nervous system |
| Cortisol modulation of acute-phase protein production by the liver |

*: initially polymorphonuclear cells and later monocytes; †: elevated levels of circulating glucocorticoids synergize with IL-6 in inducing hepatic synthesis and secretion of "acute-phase" reactants, such as fibrinogen, protease inhibitors, complement C3, ceruloplasmin, haptoglobin, and C-reactive protein. ACTH: adrenocorticotropic hormone; IL-6: interleukin-6.
Glucocorticoids inhibit the HDR cascade at virtually all levels; their gradual and generalized suppressive influence protects the host from overshooting [30]. This influence is assumed to be sufficiently delayed in relation to the initial stress stimulus to allow the appropriate defence mechanisms to become activated [30, 31]. However, this protective mechanism is not always effective, as demonstrated by the exaggerated and autodestructive host reaction seen in nonsurvivors of sepsis or ARDS. The encouraging results of recent studies with prolonged GC administration in patients with ARDS [2, 3, 32–34] and sepsis [35–37] indicate that the HPA axis plays an important role in resolving the HDR, which could be enhanced by exogenous GC administration.

Peripherally generated TNF-α, IL-1β, and IL-6 activate the HPA axis independently at some or all of its levels, and in combination their effects are synergistic [38, 39]. The HPA axis responds in a graded manner to greater intensities of stress with increased production of ACTH and GCs. ACTH is the predominant, but not the only, regulator of GC secretion. Other factors, including angiotensin and vasopressin, also influence adrenal GC secretion [40]. Glucocorticoids are secreted directly into the circulation immediately after their synthesis. Cortisol, the major human GC, circulates bound (95%) to a corticosteroid-binding globulin (CBG) synthesized primarily at the liver, or released at sites of inflammation or tissue remodelling [41]. Glucocorticoids exert most of their effects through specific, ubiquitously distributed (3,000–100,000 per cell) intracellular GC receptors (GCR), which are found abundantly in diverse genes encoding cytokines as well as other mediators or cellular regulatory elements of the HDR. The affinity of a given glucocorticoid for its receptor is the major determinant of its biological activity.

GCR activation and translocation have been studied extensively, and the molecular mechanisms involved in these processes were recently reviewed [24, 42]. Inactivated GCRs are anchored to a heat-shock protein (HSP) heterocomplex, which is composed of HSP90, HSP70 and HSP56, that seems to facilitate the response of the GCR to GCs [43]. After steroid-binding, the HSP heterocomplex facilitates the transport of the GCR to the nucleus and dissociates from the receptor, thereby "exposing" the DNA-binding site. The hormone-activated receptor acts as a transcription factor by binding to specific DNA sequences, termed "GC response elements". Binding of the receptor to the GC response elements modulates the rate of transcription of specific mRNAs, which in turn affects the levels of encoded protein products [24]. The GC-GCR complex is subsequently dissociated from the host cell DNA and is "inactivated" by reassociation with the HSP heterocomplex.

Several cytokines produce their cellular effects by activating transcription factors (AP-1 and NF-κB), which activate or repress target genes that are regulated in an opposing manner by GCR [42]. Activated GCRs inhibit the transcription of several cytokines (IL-1, IL-2, IL-6, TNF, interferon-γ (IFN-γ) and others) by binding to transcription factors (AP-1 and NF-κB) and blocking their cellular action [42, 44]. Glucocorticoids also suppress the synthesis of phospholipase A2 (PLA2), cyclooxygenase 2 and nitric oxide synthase 1 genes, decreasing the production of prostanoids (PLA2 is the rate-limiting enzyme in eicosanoid metabolism), platelet-activating factor and nitric oxide, three key molecules in the inflammatory pathway [42, 45]. Glucocorticoids induce lipo- cortin production [45] and have an inhibitory effect on the expression of adhesion molecules [42]. Glucocorticoids also act in synergy with IL-1RA [47] and IL-4 [29] to control the HDR.

**The host defence response in ARDS**

ARDS is characterized by acute onset of diffuse and severe HDR of the lung parenchyma to a direct or indirect insult that disrupts the alveolocapillary membrane with loss of compartmentalization [48]. The magnitude of the initial HDR appears to be a major determinant of the progression and outcome in ARDS. Our group recently reported that on Day 1 of mechanical ventilation (MV), nonsurvivors of ARDS had significantly (p<0.0001) higher plasma (fig. 1) and bronchoalveolar lavage (BAL) TNF-α, IL-1β, IL-2, IL-4, IL-6 and IL-8 levels than survivors [49, 50]. Although cytokine levels may not reflect activity, these findings are similar to those reported by others (table 4) and agree with studies indicating that the evolution of ARDS is determined by the extent of initial pulmonary HDR in the form of alveolar denudation, basement membrane destruction, vascular permeability and quantity of intra-alveolar exudate [74–77].
In agreement with others [66, 78–81], we have found an increased BAL:plasma ratio for all measured cytokines [49, 50]. Increased BAL levels indicate increased intra-pulmonary production and not leakage into the lung from increased vascular permeability [79]. In early ARDS, alveolar macrophages have been shown to be an important source of TNF-α [82, 83], IL-1β [84] and IL-8 production [85]. Experimental work indicates that alveolar macrophages and neutrophils represent different temporal and cellular waves of cytokine expression in early lung injury [86]. We have found patients, stratified by the presence or absence of sepsis, with direct and indirect ARDS to have similar plasma and BAL inflammatory cytokines levels [87].

Of significant importance, during the progression of ARDS, we have found nonsurvivors to have persistent and marked elevation of plasma and BAL inflammatory cytokine levels over time, while survivors had a rapid reduction in inflammatory cytokine levels (fig. 1) [49, 50]. Furthermore, in nonsurvivors the BAL:plasma ratio for TNF-α, IL-1β, IL-6 and IL-8 remained unchanged throughout the course of the disease, while it rapidly decreased in survivors [50]. Other groups have also reported nonsurvivors of ARDS or sepsis to have persistent elevation of inflammatory cytokines (table 4).

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other components of the HDR (i.e., PLA₂, leukotrienes and complement) over time [51, 67, 88–90]. This finding is important to understanding why treatment modalities of limited duration may be ineffective in ARDS. It is well-accepted that during ARDS the HDR is not limited to the lung [91]. In patients with unresolving ARDS, disruption of alveolocapillary membrane [92] causes release of cytokines into the systemic circulation and contributes to the development and/or maintenance of SIRS and MODS [48, 68]. Strong correlation among TNF-α, IL-1β, IL-6 and IL-8 at the onset of ARDS and over time is consistent with a broad and integrated host defence response [49].

In patients with early ARDS, one study found soluble TNF receptor inhibitor levels to be significantly increased compared to pre-ARDS levels and to correlate (r=0.71; p<0.005) with BAL TNF-α levels [66]. Administering IL-1RA in experimental ARDS decreases vascular permeability and neutrophil influx [93]. At the onset of ARDS, we have found plasma IL-4 to be significantly (p<0.001) higher in nonsurvivors. Plasma and BAL IL-4 levels increased over time, irrespective of outcome. We have found plasma IL-10 levels to be significantly higher in the early phase of ARDS in patients who improve lung function by Day 7 of MV (personal unpublished data). Others have found increased BAL IL-10 levels to correlate with survival [94].

Overall a strong line of evidence supports the view that an overaggressive and protracted HDR, rather than the aetiological condition precipitating respiratory failure, is the major factor influencing outcome in ARDS. In agreement with this statement are the findings that ARDS patients may not improve despite appropriate treatment of the precipitating disease, while mortality may decrease when the HDR is adequately suppressed by prolonged GC administration [95]. In ARDS, continued production of HDR mediators prevents effective restoration of lung anatomy and function by sustaining ongoing injury, coagulation and fibroproliferation (the three act in synergy). New injury to previously spared endothelial and epithelial surfaces occurs in conjunction with an amplified reparative (coagulation and fibroproliferation with deposition of ECM) process over previously damaged areas. At histology, these two processes can be seen adjacent to each other [1] and have been described in detail [92]. Persistent endothelial and epithelial injury promotes vascular permeability in the lung and systemically. Intravascular coagulation decreases available pulmonary vascular bed, while intra-alveolar fibrin deposition promotes cell-matrix organization by fibroproliferation [96]. Most clinical and physiological derangements observed in unresolving ARDS are attributable to unrestrained coagulation and fibroproliferation and are discussed below.

Coagulation

During ARDS, normal intra-alveolar fibrinolytic activity (urokinase-like plasminogen activators produced by alveolar macrophages) and endothelium anticoagulant activity (heparin-like molecules, thrombomodulin) are severely compromised and lead to accelerated vascular and extravascular fibrin deposition [97–99]. Megakaryocytes are markedly increased in the lungs of ARDS patients [100]. In patients with ARDS, BAL has increased procoagulant activity due to tissue factor associated with factor VII [101] and concomitant depression of fibrinolytic activity attributable to increased levels of both plasminogen activator inhibitor-1 (PAI-1) and antithrombin [101–103]. In humans [101, 104], derangements of intra-alveolar fibrin turnover occur early (1–3 days) and persist for ≥14 days. Depressed BAL fibrinolytic activity at day 7 of ARDS correlates with poor outcome [101]. Despite a depression in fibrinolytic activity, BAL fibrinogen degradation products (FDP) are markedly increased and remain elevated over time and correlate significantly with BAL total protein concentration and number of neutrophils [104]. Patients with ARDS also have marked and prolonged systemic procoagulant activity and rapid exhaustion of the fibrinolytic system [105]. In sepsis, high levels of PAI-1 are associated with a poor prognosis [106] and correlate with TNF, IL-6 and complement 3a levels [51]. Virtually all ARDS patients have increased circulating FDP levels [107]. Disseminated intravascular coagulation (DIC) is a frequent finding in ARDS and carries a higher mortality rate. Even in patients without DIC, a reduction in circulating platelets of at least 50% of the initial values is frequently observed during the course of ARDS, and nonsurvivors have a greater degree of thrombocytopenia than survivors [108]. Thrombocytopenia does not result from decreased platelet production, but from decreased platelet survival (one third of normal), a result of increased pulmonary sequestration [109].

Patients with early ARDS, as well as patients with late unresolving ARDS, show diffuse pulmonary sequestration of intravenously administered radio labelled fibrinogen [110]. Pathways for increased fibrinogen uptake include: 1) increased microvascular permeability with exudation of fibrinogen into pulmonary interstitial and intra-alveolar oedema; 2) intravascular and extravascular fibrin formation; and 3) fibrinogen binding to injured endothelial cells [110]. Recovery from lung injury is associated with normalization of radio labelled fibrinogen uptake [110]. As a result of downregulation of thrombomodulin and the expression of tissue factor, cytokines TNF-α, IL-1β, and IL-6 alter the surface of the endothelium from an anticoagulant into a procoagulant moiety and are able to enhance the synthesis of PAI-1 [106, 111].

Pulmonary thromboemboli are a frequent histological finding in patients with unresolving ARDS subjected to open-lung biopsy [92] and are found on postmortem exam in 95% of ARDS nonsurvivors [112, 113]. Macrothrombi (in arteries greater than 1 mm diameter) are found by postmortem angiography in 86% of patients and are more prevalent in patients who died in the early phase of ARDS [113]. Microthrombi are as prevalent as macrothrombi but tend to be distributed throughout all phases of ARDS. Filling defects at angiography correlate with the severity of ARDS, the degree of pulmonary hypertension and the presence of DIC [112]. Unfortunately, anticoagulant treatment does not improve outcome in ARDS [112] and this has applied to any treatment directed at one single facet of the complex host response. Ischaemic or avascular necrosis, particularly in the sub-pleural regions, is a common feature of unresolving ARDS [92, 112].
Fibrin deposition also influences the course of tissue injury and repair. Thrombin, fibrin and fibrin degradation products (FDPs) play an important role in amplifying inflammation by promoting neutrophil chemotaxis, adhesiveness and by directly causing increased endothelial permeability [99, 114, 115]. Experimental infusion of thrombin or FDP causes acute lung injury, mediated by neutrophil activation via complement and arachidonic acid metabolites [99]. Thrombin is also a potent inducer of platelet degranulation with additional release of host defence response mediators. Coagulation and fibrinolysis also interact with the kallikrein-kinin system with release of bradykinin. Bradykinin increases vascular permeability and stimulates collagen production by fibroblasts [116].

Animal studies have demonstrated that intra-alveolar fibrin deposition is typical of DAD, even when injury resolves without fibrosis, indicating that fibrin deposition of limited duration is essential for effective lung repair [117]. In the presence of a protracted host defence response, however, persistent intra-alveolar fibrin deposition contributes to airspace organization and fibrosis [97, 117, 118]. In vitro data demonstrate that fibrin forms a matrix on which fibroblasts may aggregate and secrete collagen [119]. In addition, thrombin binds to thrombin receptors on fibroblasts and promotes their proliferation [120].

Fibroproliferation

Fibroproliferation is a stereotypical reparative response to injury. In ARDS, pulmonary fibroproliferation manifests with the accumulation of myofibroblasts and their connective tissue products in the airspaces, interstitium, respiratory bronchioles and walls of the intra-acinar microvessels [113, 121]. Pulmonary fibroproliferation is a diffuse process, as indicated by the findings of chest computed tomography [92], gross inspection at surgery, microscopic analysis of biopsies from different lobes [122] and bilateral BAL findings [50]. At microscopy, however, regional heterogeneity exists, and focal areas of normal parenchyma are occasionally found [1, 123]. Unhalted fibroproliferation results in extensive fibrotic remodelling of the lung parenchyma. Macroscopically, the lung shows irregular zones of diffuse scarring with formation of numerous microcystic reorganized airspaces measuring 1–2 mm, most prominent in the subpleural zones [92].

Pulmonary fibroproliferation in ARDS shares a common pathogenetic mechanism with other fibroproliferative diseases, where degree and duration of the host defence response dictate the ultimate reparative outcome [28]. In this "linear" concept of tissue response to injury, mediators of the host defence response sustain the fibrotic process [124]. Fibrosis ensues when the host defence response is intense and prolonged, leading to released profibrotic moieties and trophic factors for mesenchymal cells. Experimental work indicates that severity of acute lung injury determines the intensity of chronic inflammation and fibrosis [125]. In agreement, we have found that patients with higher plasma IL-6 on days 1–3 of ARDS are more likely to develop accelerated fibroproliferation unresponsive to GC rescue treatment (fig. 2) [95].

Morphometric analysis of lung tissue in late ARDS has shown that intra-alveolar fibroproliferation predominates over interstitial fibroproliferation [121]. The histological sequence leading to intra-alveolar fibroproliferation has been clearly characterized [121]. Epithelial injury provides focal discontinuities (gaps) in the alveolar basement membrane (BM) resulting in direct communication of interstitial cells and matrix elements with the alveolar airspaces [92, 126]. Activated myofibroblasts from the interstitium migrate into the alveoli in response to chemotactic signals and attach to the luminal surface of the damaged BM [121, 126]. Myofibroblasts, once they have migrated into the alveoli, proliferate and actively produce collagen [126], transforming the initially fibrinous intra-alveolar exudate into myxoid connective tissue matrix and eventually into dense acellular fibrous tissue. TNF-α and IL-1β, among other HDRI mediators, stimulate chemotaxis and are important modulators of fibroblast proliferation and collagen deposition [127].

Morphometric studies in nonsurvivors of ARDS have shown intra-alveolar (and, to a lesser degree, interstitial) fibroproliferation to occur within 7 days of the onset of ARDS and to have a rapid increase in the second and third week of respiratory failure [121]. The rate of progression varies [1, 3, 8]. Newly produced matrix stains intensely for cell-associated fibronectin and type 3 procollagen [126]. Type III collagen (newly formed, flexible, and more susceptible to digestion by collagenase) predominates in the intermediate proliferative phase, while type I collagen (composed of thick fibrils, more resistant to digestion) is the major collagen present in the late fibrotic phase. In nonsurvivors, the collagen content of the lung is increased two- to threefold after 2 weeks of ARDS and parallels the development of fibrosis [7]. Patients with ARDS dying after 7 days of respiratory failure have, in contrast to survivors, persistent elevation of extracellular matrix components (procollagen III) in the BAL and serum, indicating ongoing fibrogenesis [77, 128–130]. Patients with a procollagen III level greater than 1.75 U·mL⁻¹ in BAL on day 7 had a 72% mortality rate compared with a 20% mortality rate in patients with a procollagen III level less than 1.75 U·mL⁻¹ [131]. BAL procollagen III levels correlate with histological evidence of intra-alveolar fibrosis [132]. Finding fibrosis at open-lung biopsy or transbronchial biopsy is a poor prognostic factor [4, 133].

The patterns of fibrous reorganization of the lung in ARDS have been described [74]. Intra-alveolar fibroblastic aggregation is continuous with a similar process in the terminal bronchioles, respiratory bronchioles, alveolar ducts, and the interstitium [8]. The bronchiolar intraluminal (bud-like) fibrosis found in patients with fibroproliferation [3] is similar to the one described in interstitial lung disorders. The coexistence of unaffected bronchioles surrounded by parenchymal interstitial and alveolar space fibrosis indicates lung injury-induced patchy bronchial epithelial and basement membrane damage. Intraluminal fibrosis as a model of inflammatory lung disease has been extensively reviewed [96]. In our experience, intraluminal fibrosis at open-lung biopsy in patients with unresolving ARDS predicts reversibility of fibroproliferation with GC rescue treatment [3], similar to the response observed in patients with bronchiolitis obliterans organizing pneumonia [96].
The pulmonary vascular changes occurring during the progression of ARDS are shown in table 5. Of significance, we and others have described microscopic and ultrastructural evidence of ongoing epithelial and endothelial injury in patients with advanced fibroproliferation [1, 3, 92, 113]. Despite the high turnover rate and ability of endothelial cells to repair themselves, acute endothelial injury is more pronounced in the proliferative phase than in the exudative phase of ARDS [1, 113], consistent with a continuous injury process. Fibrocellular intimal proliferation, the sequela of endothelial injury, involves predominantly the small arteries, but also the veins and lymphatics. Absence of arteriolar subintimal fibroproliferation at open-lung biopsy in patients with unresolving ARDS predicts reversibility of fibroproliferation with GC rescue treatment [3].

The pulmonary vascular changes occurring during the progression of ARDS are shown in table 5. Of significance, we and others have described microscopic and ultrastructural evidence of ongoing epithelial and endothelial injury in patients with advanced fibroproliferation [1, 3, 92, 113]. Despite the high turnover rate and ability of endothelial cells to repair themselves, acute endothelial injury is more pronounced in the proliferative phase than in the exudative phase of ARDS [1, 113], consistent with a continuous injury process. Fibrocellular intimal proliferation, the sequela of endothelial injury, involves predominantly the small arteries, but also the veins and lymphatics. Absence of arteriolar subintimal fibroproliferation at open-lung biopsy in patients with unresolving ARDS predicts reversibility of fibroproliferation with GC rescue treatment [3].

**Clinical and physiological manifestations of the host defence response in unresolving ARDS**

Morphological changes at epithelial and endothelial levels caused by recurrent injury, ongoing coagulation, and amplified fibroproliferation can explain the physiological and laboratory findings seen in patients with unresolving ARDS.

**Gas exchange and lung mechanics**

Gaps in the alveolar BM in unresolving ARDS [92] allow communication between the alveoli and the interstitium for entrance of vascular and interstitial components into the airspaces (fig. 3). Myofibroblasts migrate, proliferate, and produce collagen. Progressive fibroproliferation leads to obliteration of the respiratory units, changing their mechanical properties (loss of inflection point in the pressure-volume (P-V) curve and lack of recruitability by positive end-expiratory pressure (PEEP)), increasing dead space ventilation (VD/VT) and further compromising of gas exchange [135–137]. A concomitant reduction in capillary volume and thickening of the alveolar septa additionally contributes to reducing gas transfer and increasing VD/VT [1]. In several studies, the arterial oxygen tension (PaO₂): inspiratory oxygen fraction (FiO₂) ratio, although similar at the onset of
ARDS, by day 3–7 clearly separated survivors (increased) from nonsurvivors (decreased or no change) [50, 108, 138–145]. In one report, mortality rate in patients with and without improvement in lung function by day 7 of ARDS was 43 and 97%, respectively [141].

Pulmonary vascular permeability

Endothelial injury [92] in unresolving ARDS favours the passage of vascular products in the alveoli (fig. 4).

Among the many cells and substances that are exuded in the airspaces, the following have been the subject of clinical investigations: albumin, proteins, neutrophils and $^{67}$Ga.

BAL albumin and total protein are markers of pulmonary endothelial permeability in ARDS [146]. At the onset of ARDS, we have found BAL albumin and total protein levels to be similar in survivors and nonsurvivors. In agreement with others [144, 147], we noted survivors to have a progressive decline in BAL albumin and total protein levels over time (not seen in nonsurvivors),

Table 5. – Pulmonary vascular changes in unresolving ARDS

|                      | Early     | Intermediate | Late                  |
|----------------------|-----------|--------------|-----------------------|
| Mean PAP             | 36±7.3    | 42±9.4       | 42.4±3.8              |
| Vasoconstrictor component | ++(a)       | -            | -                     |
| Acinar*              |           |              |                       |
| Acute endothelial injury | +         | ++          | ++                    |
| PMN aggregates in capillaries | +++(b)   | -           | -                     |
| Hyaline microthrombi† | +++        | -           | -                     |
| Organizing microthrombi † | + (c)     | ++          | ++                    |
| Increased medial wall thickness | +       | ++          | ++                    |
| Compression by oedema | +         | -           | -                     |
| Compression by fibrosis | -       | ++          | +++                   |
| Capillary proliferation | -       | ++          | +++                   |
| Architecture          | Normal    | Up to 50% reduction (c) More than 50% reduction(c) |
| Macrothrombi          | +++       | ++          | +                     |
| Infarction (subpleural)| -        | ++          | +                     |
| Intimal fibroproliferation | -        | ++          | +++                   |
| Increased medial wall thickness | +     | ++          | +                     |
| Decreased external diameter | +    | ++          | +++                   |
| Decreased arterial filling | + (d)   | ++          | +++                   |
| Remodelling with tortuosity | -    | ++          | +++                   |
| Lymphatics obstruction | +        | ++          | ++                    |

(a): from reference [134]; (b): more prominent in ARDS induced by septicaemia; (c): from reference [1]; (d): narrowing by interstitial oedema; *: intra-acinar landmarks: terminal and respiratory bronchioles, alveolar ducts; †: hyaline thrombi, consisting of platelets and fibrin; ‡: organizing microthrombi, formed of red and white blood cells with layered fibrin, *: present; ++: marked; +++: very marked. Reproduced with permission from reference [10]. Above data are modified from reference [113].
suggested effective repair of the alveolar-endothelial surface [50]. We have also identified a consistent correlation between BAL albumin and total protein levels and BAL TNF-α, IL-1β, IL-6 and IL-8 levels [50].

BAL neutrophilia (≥70%) is invariably found in early ARDS [147, 148]. The percentage of BAL neutrophils parallels BAL protein [75, 144] and albumin [50] concentration and correlates with the severity in gas exchange [147]. We and others have identified a positive correlation between total neutrophil count and BAL TNF-α, IL-1β and IL-8 levels [50, 69, 149]. Persistent elevation of neutrophils in the BAL by days 7 and 14 of ARDS is associated with poor outcome [150, 151]. Resolution of ARDS, on the contrary, is associated with a dramatic fall in neutrophils and an increased number of macrophages [150].

The origin of neutrophils recovered by BAL in unresolving ARDS requires a clarification. In patients with unresolving ARDS subjected both to bronchoscopy and open-lung biopsy, at an average of 14 days into respiratory failure, we have found a significant discrepancy between marked BAL neutrophilia (60% of recovered cells) and an almost complete absence of neutrophils in the airways, alveoli, and interstitium at histology [3]. It has been recognized that the alveolocapillary membrane is permeable to fluids and that in normal patients 39% of the aspirated BAL fluid originates from the circulation [152]. In conditions associated with disruption of vascular and epithelial integrity, such as unresolving ARDS, the circulatory component of BAL effluent becomes more significant, and cells such as neutrophils and erythrocytes are aspirated into the alveoli when negative pressure is applied during suction [152]. Therefore, BAL neutrophilia in unresolving ARDS is a marker of endothelial permeability [3, 75, 144], not a reflection of "neutrophilic alveolitis," and it is unlikely that neutrophils play a major role in the progression of unresolving ARDS.

$^{67}$Ga uptake in the lung is an additional marker of endothelial permeability [153]. In the lung, $^{67}$Ga concentration is normally low. Diffuse $^{67}$Ga uptake has been used as a sensitive but nonspecific test to identify patients with active pulmonary inflammation who may respond to GC treatment. Five reports (total of 44 patients) have described marked and diffuse uptake of $^{67}$Ga in the lung of patients with unresolving ARDS and who subsequently responded to GC rescue treatment [3, 32–24, 154]. Diffuse and marked pulmonary uptake of $^{67}$Ga in unresolving ARDS correlates with BAL neutrophilia [153]. The diagnostic role of $^{67}$Ga scintigraphy in ARDS was reported [153].

**Pulmonary hypertension**

While in early ARDS the pulmonary vasculature is available for dilation and/or recruitment, vascular changes (table 5) in unresolving ARDS are less responsive to vasodilator treatment [134]. In these patients, vascular obstruction from thrombosis, subintimal fibroproliferation of the small arteries and compression from alveolar and interstitial expansion significantly reduces the capacity of the pulmonary microcirculation [1] and subjects the patent vascular bed to abnormally high flow, stimulating medial hypertrophy of the muscular and partially muscular arteries [155]. These changes are similar to those seen in pulmonary hypertension of thromboembolic origin [155], and they worsen with progression of fibroproliferation [108, 140, 143]. In early ARDS, there is a marked elevation in circulating levels of endothelin-1, a mediator of vascular remodelling and pulmonary hypertension [52]. With the progression of ARDS, endothelin-1 levels drop to normal values in patients improving lung function but remain elevated in patients who worsen [52]. Persistent elevation or worsening pulmonary artery pressure is a poor prognostic sign [108, 140, 143]. In the final stages of ARDS, the mean pulmonary artery pressure can exceed 40 mmHg as a result of a fourfold elevation of vascular resistance [134].

**Barotrauma**

In unresolving ARDS, vascular obstruction with subpleural tissue necrosis and endoluminal fibrosis with intraparenchymal pseudocyst formation contribute to alveolar rupture. Barotrauma may manifest as intraparenchymal and subpleural pneumatocele, large compliant air collections or bullae, pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, subcutaneous emphysema and, rarely, pneumoperitoneum [156]. Barotrauma in ARDS is related to the severity of lung dysfunction and is associated with a higher mortality [157–159]. An increase in the alveolar-arterial pressure gradient, from either hyperinflation and/or reduced blood flow, causes disruption at the common border between the alveolar base and the vascular sheath [155, 160]. Partial obliteration (endoluminal fibrosis) of terminal airways leads to cyst formation by valvular mechanism and by compensatory dilatation of neighbouring bronchioles [159]. Tissue necrosis distal to pulmonary artery thrombi [112] is prominent in the subpleural regions where insufficient collateral blood flow makes lung tissue particularly susceptible to ischaemia [161]. At angiography, a "picket-fence" appearance is seen, caused by dilated subpleural arteries bridging regions of oligaemia and necrosis distal to the thrombotic arterial occlusion [161]. With
progressive fibroproliferation, preferential ventilation to these hypoperfused peripheral areas may occur, contributing to the development of barotrauma [161].

**Fever of infectious and noninfectious origin**

Fever is caused by the systemic release of endogenous pyrogens; TNF-α, IL-1β and IL-6. Upon reaching the hypothalamic thermoregulatory centre, these cytokines induce an abrupt release of prostaglandins that increase the thermostatic set point and produce heat [162]. Fever induces production of heat-shock proteins (see later) that have an important role in cell survival under stress (cytoprotection) [163]. Fever and SIRS invariably develop during the course of unresolving ARDS, even in the absence of infections [14, 34, 164]. Clinical studies have attributed the frequent occurrence of fever and SIRS in late ARDS to VAP [15], and the assumption has been made that in these patients, nosocomial infections (mainly VAP) amplify SIRS and lead to MODS and death [5, 6, 15, 16].

Recognizing that clinical criteria are sensitive but nonspecific in diagnosing VAP or other nosocomial infections has promoted clinical investigations following recently developed guidelines [21]. Three important findings have resulted: 1) during the course of ARDS, VAP is less frequent than clinically suspected [165, 166]; 2) pulmonary host defense response itself is a frequent source of fever, clinically indistinguishable from VAP or other sources of sepsis [2, 14, 34]; and 3) during the course of ARDS, VAP or other nosocomial infections do not amplify SIRS [164]. In a prospective epidemiological study using strict diagnostic criteria, VAP was identified with protected bronchoscopic techniques in only 20% of patients with ARDS on MV for more than 48 hr (the study excluded patients with pneumonia-causing ARDS) [165]. The pathogenesis of VAP in ARDS has been reviewed [167, 168]. In a prospective study designed to identify by strict criteria all potential infectious and noninfectious sources of fever (single episode) in 20 patients with late ARDS (>48 h), we identified pneumonia in seven (35%) and noninfectious pulmonary HDR alone in five (25%) [169]. The latter diagnosis was established by open-lung biopsy in febrile patients without infection detected by an extensive and systematic evaluation [169]. Lung histology showed advanced fibroproliferation, acute epithelial and endothelial injury, vascular thrombosis, but no pneumonia.

While at autopsy histological pneumonia is most often disseminated to both lungs [170], during the course of ARDS pneumonia is frequently detectable by bronchoscopy in one lung only [171]. Among 23 patients with late ARDS and fever who were undergoing bilateral BAL, we found pneumonia to be unilateral in 47% [171]. These findings were confirmed in a larger series involving more than 100 patients (personal unpublished data). Moreover, we found that pneumonia with a low concentration of bacteria (≤105 colony forming units (CFU)·mL⁻¹) was usually unilateral, whereas pneumonia with a high bacterial load (≥106 CFU·mL⁻¹) was frequently bilateral (p=0.002) and associated with a worse short-term outcome (10 day mortality was 50%) [171]. Histological pneumonia at autopsy, therefore, may be more representative of a severe pneumonia that led to the patient’s demise or of premortem dissemination of the infection in the terminal stage of the disease [21]. In agreement with prior work [172], we have found radiographic findings for pneumonia to be nonspecific in ARDS [173].

**Correlation between nosocomial infections and cytokine response**

In a study involving serial measurements of plasma and BAL inflammatory cytokines and careful search and diagnosis of infections, we found that nosocomial infections (including seven cases of pneumonia) developing in 34 patients with ARDS, who had been on MV for >72 h caused neither a transient nor a sustained increase in plasma and BAL inflammatory cytokines levels (TNF-α, IL-1β, IL-6 and IL-8) or SIRS score [164]. These findings are similar to those reported by others [174] and question the prior hypothesis, based on clinical criteria, that in unresolving ARDS, nosocomial infections amplify SIRS leading to MODS and death [5, 6, 15, 16]. Furthermore, two recent studies indicate that the development of MODS and outcome in surgical critical illness are related to the magnitude of SIRS and are independent of the presence of infection [175, 176].

In agreement with our findings, several recent experimental and clinical studies have shown that production of inflammatory cytokines in response to a bacterial challenge can be suppressed by prior activation of the HDR. Although, this phenomenon serves to protect the host (cytoprotection) from overwhelming cytotoxicity, an almost complete inhibition of inflammatory cytokine release may potentially cause immunodeficiency [177]. Two processes with a potentially common mechanism have been investigated: downregulation and induction of stress tolerance [178]. In agreement with experimental work [179, 180], the monocytes of patients with sepsis and ARDS show downregulation of inflammatory cytokine release in response to lipopolysaccharide (LPS) [177, 181]. Furthermore, stimulated monocytes from non-surviving septic patients showed a significant reduction in IL-1 production when compared to survivors [182]. Pot-ential mediators of inflammatory cytokine down-regulation include prostaglandin E₂, glucocorticoids, IL-4, IL-10, TGF-β [177] and induction of HSPs [178].

In experimental models of lung injury and sepsis, induction of HSPs prior to an otherwise lethal stress, protected animals (stress tolerance) during the time course of HSP elevation with reduced organ damage and improved survival [165, 178]. Cytokines, TNF, IL-1, IL-2, and IL-6 can induce the synthesis of HSPs in a dose-dependent manner [183]. In a negative feedback, HSPs can downregulate LPS-induced monocyte production of TNF and IL-1 [184, 185], while other macrophage functions (i.e. phagocytosis) remain intact [185]. Although the precise mechanism of action is not known, ample evidence indicates that many HSPs act as chaperones and assist in the process of protein folding and translocation across membranes [186]. Furthermore, HSPs are directly responsible for binding TNF intracellularly and preventing its release from the macrophage [187]. The importance of HSPs in the host defence response and their intimate association with activation of the HPA axis and sympathetic nervous system have recently been appreciated [24],...
Expression of HSPs is regulated primarily through the activity of transcription factor HSFs [24]. Experimental work has shown that HSP70 levels are increased in the adrenal gland and in the vasculature of stressed animals [24]. Adrenal expression is mediated via ACTH, while vasculature response is subject to $\alpha_1$-adrenergic control [188]. Long-term glucocorticoid treatment significantly decreases adrenal HSP70 expression [189]. Of interest, experimental work indicates that GC may reinstate cell responsiveness and offset downregulation of inflammatory cytokine production [190, 191].

**Systemic effects of the host defence response**

Figure 5 displays the local and systemic effects of a prolonged HDR in ARDS. Systemic release of HDR mediators causes: 1) SIRS; 2) development and progression of MODS (by a mechanism similar to the one causing progression of ARDS); and 3) increased systemic endothelial permeability. Fever is a common clinical denominator to noninfectious SIRS and nosocomial infections.

**Relationship between exaggerated host defence response and endogenous glucocorticoid function**

The pathophysiology of septic shock is similar to that of ARDS, and reference to this literature is frequently necessary to explain the complex relationship between exaggerated HDR and glucocorticoid function in unresolved ARDS. Although glucocorticoids are the most important modulator of the HDR, nonsurvivors of septic shock have an exaggerated and prolonged release of inflammatory cytokines (table 4) despite a marked elevation in baseline plasma ACTH and cortisol levels [192]. Furthermore, the degree of cortisolaemia frequently correlates with severity of illness and mortality rate [193, 194] and is associated with an altered response of the HPA axis to suppression by dexamethasone and stimulation by corticotrophin-releasing hormone (CRH) and ACTH [194]. Cortisol elevation is achieved by several mechanisms including: 1) activation of the HPA axis; 2) GC resistance resulting from alterations in GCR binding; 3) failure of pituitary and hypothalamus glucocorticoid negative feedback; 4) decreased binding to CBG [195–197]; and 5) decreased cortisol extraction from the blood [192, 193]. In critically ill patients, dexamethasone infusion, at a dose that easily suppresses ACTH and cortisol secretions in normal subjects, is minimally effective [194, 195], with pre- and postinfusion cortisol and ACTH levels remaining significantly higher in nonsurvivors [194]. In addition, the negative feedback of endogenous glucocorticoid is clearly altered, and stimulation with CRH causes a significant increase (7–450%) in ACTH response, in spite of cortisol levels sufficient to abolish a CRH-induced ACTH surge in normal subjects [194]. Following CRH stimulation, nonsurvivors have a smaller increase in cortisol levels, despite a percentage increase in ACTH production similar to survivors [194]. Other studies have also found a lower cortisol response to ACTH in nonsurvivors of septic shock [36, 198, 199]. Although several potential mechanisms have been described [40], glucocorticoid resistance from altered GCR function may be partially responsible for the changes in the HPA axis of critically ill patients and could result in an augmented ACTH response to CRH [194]. It is now recognized that cytokines can cause a concentration-dependent resistance to glucocorticoids by reducing GCR binding affinity [200, 201]. Many cytokines produce their cellular effects by activating transcription factors, AP-1 and NF-κB [42]. For example, TNF-α activates both AP-1 and NF-κB in human lung [202]. These activated transcription factors may then form complexes with activated GCR, preventing GCR interaction with DNA [42]. When T-cells are incubated with either the combination of IL-2 and IL-4 [201], or IL-1, IL-6 and IFN-γ [200], GC resistance is induced in a concentration-dependent fashion. Resistance results from a marked reduction in GCR binding affinity that is reversed by removal of cytokines [201]. In our patients with
ARDS, we have found significantly higher (p<0.001) plasma levels of IL-2 and IL-4 (fig. 2) as well as plasma (fig. 1) and BAL IL-1β, IL-6 and TNF-α (p<0.0001) in nonsurvivors than in survivors [49]. This line of evidence is reinforced by the results of recent experimental studies [131, 203, 204]. In a sheep model of sepsis-induced ARDS, maximal binding capacity of GCR decreased continuously after endotoxin infusion, despite marked elevation in cortisol levels [203]. Furthermore, reduced GCR binding correlated negatively (r=-0.87; p<0.01) with PLAS activity. In a rat model of septic shock, GCR blockade exacerbated the pathological changes induced by endotoxaemia, especially in the lung and small intestine [204]. PLAS activity in rats with 80% GCR blockade was more marked than in those with 50% GCR blockade [204]. Monocytes of patients with sepsis have decreased GCR affinity [131]. TNF-α and IFN-γ also block, in a concentration-dependent manner, the stimulatory effects of CRH and ACTH on the pituitary and adrenal cortex, respectively [205, 206]. Any reduction in GC responsiveness, therefore, would be greater as the intensity of the HDR increases. The ACTH and cortisol profile observed over time in critically ill patients [40] can be reproduced in cancer patients by daily administration of recombinant IL-6 [207]. Syndromes of glucocorticoid resistance respond to treatment with exogenous glucocorticoids [44].

Additional factors contributing to hypercortisolaemia include decreased binding to CBG [195–197] and decreased cortisol extraction from the blood [192, 193]. Septic patients have a rapid depletion in CBG with increased free (nonbound) cortisol [195–197]. The mechanism for the high rate of degradation or removal (protein leak?) of cortisol is unknown, but it parallels an increase in C-reactive protein levels [197]. In survivors, in contrast to nonsurvivors, CBG and cortisol levels return to normal during recovery [197] and correlate positively with a reduction in PLAS levels (r=0.833; p<0.0001) [88]. Furthermore, nonsurvivors of sepsis, in contrast to survivors, also have impaired removal of injected cortisol from the plasma [193].

Response to glucocorticoid therapy in unresolving ARDS

At present, there is no established treatment to halt the progression of ARDS [208]. In theory, however, a treatment aimed at arresting an exaggerated and sustained HDR should promote epithelial and endothelial cell repair, halt fibroproliferation, and decrease extracellular matrix deposition while stimulating its net resorption. Glucocorticoids can potentially fulfil these requirements through a broad range of inhibitory effects on the HDR, including modulation of macrophage and fibroblast activity (previously reviewed in [34]). Although, large randomized clinical trials have clearly shown no benefit when a short course (≤48 h) of high-dose intravenous GC is administered in early sepsis and ARDS [209, 210], no randomized study has yet evaluated prolonged GC treatment in this patient population.

Three groups of investigators have reported a significant improvement in lung function during prolonged GC administration in patients with unresolving ARDS (rescue treatment) [2, 3, 32–34]. We have investigated the effects of i.v. methylprednisolone sodium succinate (2–3 mg·kg⁻¹ daily on days 1–14, 1 mg·kg⁻¹ daily on days 15–28, 0.5 mg·kg⁻¹ daily on days 28–35, followed by tapering over 7 days for a total treatment duration of 6 weeks) administered after 15±7 days of MV in 25 patients with unresolving ARDS and without active pulmonary or extrapulmonary nosocomial infection (confirmed in 13 patients by open-lung biopsy) [3]. Most patients had fever (56%), leukocytosis (88%), significant BAL neutrophilia (86%), diffuse alveolar densities on chest radiograph (83%) and diffuse marked uptake of ⁶⁷Ga in both lung fields (100%). A significant physiological improvement, defined as a reduction in lung injury score (LIS) [211] of more than one point or an improvement in Pao₂/FiO₂ ratio of >100, was seen within 7 days of therapy in 15 patients (rapid responders) and 14 days in 7 (delayed responders) and was not seen in 3 (nonresponders) [3]. In rapid responders, the mean LIS decreased from 2.97±0.13 (day treatment was started) to 2.22±0.14 (day 3) (p=0.0002) and 1.55±0.13 (day 7) (p=0.0001); the Pao₂/FiO₂ increased from 170±17 to 237±18 (day 3) (p=0.008) and 280±18 (day 7) (p=0.0001); the mean pulmonary artery pressure decreased from 34±3.1 to 24±4 (day 5) (p=0.04) and 14.5±9 (day 14) [3]. Treatment was also associated with resolution of fever, clearing of densities on chest radiograph, normalization of ⁶⁷Ga pulmonary uptake, reduction in BAL neutrophilia (from 60±6 to 29±12% in 14 days) and albumin and restoration of normal alveolar architecture (documented by follow-up histology in two patients) [3, 95]. The three patients failing to improve LIS died of respiratory disease, while mortality was only 14% in the 22 responders, indicating that reversal of fibroproliferation improves outcome. Surveillance bilateral BAL with quantitative bacterial cultures for early recognition and treatment of VAP was an integral part of our protocol and may have contributed to improved outcome [3]. Earlier extubation decreased the incidence of nosocomial infections [3]. Normalization of surfactant production with corticosteroid treatment of late adult ARDS has been described [212].

In our study, no physiological variables recorded at day 1 of ARDS or at the time of GC administration could predict the type of physiological response or final outcome. Outcome could be predicted only by: 1) open-lung biopsy histological findings; 2) the presence of liver failure; and 3) the type of physiological response. At histology, the presence of preserved alveolar architecture (p=0.045), myxoid cellular type fibrosis (p=0.045), coexistent endoluminal bronchiolar fibrosis (p=0.0045), and lack of arteriolar subintimal fibroproliferation (p=0.045) separated survivors from nonsurvivors. These histological findings indicate that GC treatment can halt progression of fibroproliferation if given before end-stage fibrosis develops. In models of tissue repair, GC treatment is more effective during the rapid phase of wound healing (approximately 21 days), when collagen biosynthesis and degradation are accelerated [213].

Host defence response with supplemental glucocorticoid administration

We provided further evidence of the important relationship between HDR and ARDS outcome by measuring
plasma and BAL inflammatory cytokine levels during GC treatment in nine patients with unresolving ARDS (day 15±9 of MV) [95] and having physiological parameters and (plasma and BAL) inflammatory cytokine levels identical to the previously reported group of ARDS nonsurvivors [49, 50]. During GC treatment, effective reduction in inflammatory cytokine levels separated survivors from nonsurvivors [95]. Significant reductions in plasma inflammatory cytokine levels were seen by day 5 (almost no change was observed in the first 2 days) of treatment in responders, while no reduction in inflammatory cytokine levels was detected in the two nonresponders (respiratory death). Moreover, improvements in pulmonary vascular permeability (BAL albumin) paralleled the reductions in both plasma and BAL TNF-α, IL-1β, IL-6 and IL-8 levels. When treatment was ineffective in lowering plasma and BAL inflammatory cytokine levels, lung function did not improve and patients died from refractory respiratory failure [95]. The striking parallelism between improvements in lung function and reduction in cytokine levels during GC treatment supported the link between HDR and progression of ARDS. Of importance is that, when effective, GC treatment suppressed production of all measured inflammatory cytokines. A similar degree of anti-inflammatory action may not be achieved by specific (expensive) antimediator therapy (i.e. monoclonal antibody directed at TNF or antagonist directed at IL-1 receptors).

We also found that intensity and duration of the host defence response prior to initiating GC treatment may have been an important factor in determining response to therapy. At initiation of treatment, rapid responders had significantly lower inflammatory cytokine values than delayed responders or nonresponders. The only observed difference between the two groups of patients was a significantly higher plasma IL-6 level in nonresponders in the early phase of ARDS (fig. 3). Nonresponders also had physiological evidence of accelerated fibroproliferation. It has been shown that IL-6 is a potent inducer of de novo synthesis of tissue inhibitor of metalloproteinases (TIMP), which inhibits collagenase [214]. It is interesting to speculate that elevated IL-6 levels in nonresponders could play a significant role in developing pulmonary fibrosis by upregulating TIMP, which would inhibit the normal remodelling and removal of newly formed collagen by collagenase. Because cytokine levels at initiation of treatment were similar between delayed and nonresponders, it is also possible that a more advanced form of fibroproliferation may have prevented adequate GC tissue penetration in the latter group. In these patients, GC administration earlier in the course of ARDS or in higher doses could have been more effective.

Our findings suggest that GC treatment should be prolonged to achieve and sustain suppression of the HDR necessary to reverse progression of ARDS. This is supported by prior animal [215–217] and clinical studies [2, 32]. In experimental acute lung injury, GC treatment is effective in decreasing lung collagen and oedema formation as long as treatment is prolonged, but withdrawal rapidly negates the positive effects of therapy [216–218]. Limiting GC treatment to the first 6 days after acute lung injury enhances accumulation of collagen after discontinuing therapy, whereas GC given later, on days 7 until 12, have an alleviating effect [217]. Furthermore, a short-course GC treatment may negatively affect the host response by significantly enhancing cytokine response to LPS for up to 6 days [219]. Two clinical studies have shown that premature discontinuation of GC administration in late ARDS was associated with deterioration in lung function that resolved with the reinstitution of treatment [2, 32].

Results similar to those reported by our group [50] were also obtained in patients with sepsis and early ARDS [35]. In 12 patients with septic shock (eight with ARDS), a 5-day continuous low-dose hydrocortisone infusion (10 mg·h⁻¹) was associated with a statistically significant (p<0.01) reduction (in comparison to 45 control patients with similar condition) in SIRS score and circulatory levels of C-reactive protein and PLAL by day 3 of treatment [35]. Upon withdrawing treatment, however, PLAL and C-reactive protein levels increased and the SIRS amplified. Amplification of SIRS was associated with a second bout of hypotension in four patients that resolved upon reinitiating GC therapy [35]. During GC treatment, suppression of the HDR was associated with a much lower mortality than in the control group (8 vs 40%). Measurement of cortisol levels during this study provided additional evidence of the central role of the HPA axis in controlling the host defence response. During hydrocortisone infusion, plasma cortisol concentration and SIRS score decreased, but returned toward baseline values after discontinuing therapy.

Conclusion

The host defence response to insults is similar regardless of the tissue involved and results from an interactive network of specialized and interconnected pathways. An exaggerated and protracted host defence response plays a key role in ARDS outcome and is accountable for the histological, laboratory, clinical, and physiological findings seen during the course of unresolving ARDS. Continued elevated production of host defence response mediators, such as TNF-α, IL-1β, and IL-6, prevents effective restoration of lung anatomy and function by sustaining inflammation, coagulation and fibroproliferation. The degree of initial host defence response may determine the progress of ARDS. Elevated levels of inflammatory cytokines cause glucocorticoid resistance, offsetting the modulatory activity of the HPA axis. Predictors of poor outcome in ARDS as reported in the literature are, in actuality, manifestations of a persistent and exaggerated host defence response. During ARDS, downregulation of the host defence response is responsible for the lack of laboratory and clinical amplification of SIRS with nosocomial infections. These findings dispute the hypothesis, based on clinical criteria, that in unresolving ARDS, nosocomial infections amplify SIRS and lead to MODS and death. Spontaneous or treatment-induced suppression of the exaggerated and autonomous pulmonary host defence response is associated with improvement in lung function and outcome. Glucocorticoid resistance in ARDS and severe sepsis may respond to exogenous glucocorticoid administration. Clinical and experimental studies monitoring laboratory and clinical markers of the host defence response have shown that
effective containment of the host defence response in ARDS and sepsis may be achieved only if glucocorticoid administration is prolonged. In ARDS, glucocorticoid treatment may be highly effective when given in noninfected patients before end-stage fibrosis develops. Glucocorticoid treatment of unresolving ARDS cannot be recommended unless proven effective in a double-blind randomized study (in progress).

Recent appreciation of the complex relationship between the HPA axis and modulation of the host defence response in critical illness, and the lack of randomized studies evaluating prolonged glucocorticoid administration in this patient population, necessitate a reappraisal of the role of exogenous glucocorticoid treatment in ARDS and sepsis. Lack of financial incentive for the pharmaceutical industry, the blind acceptance that prior randomized studies have conclusively proven the lack of efficacy for glucocorticoids and the hope of finding a “magic bullet” among the many sites of possible interaction on the host defence response web, has discouraged this type of clinical investigation. It is my hope that the information provided here will encourage a critical re-evaluation of this inexpensive form of immunomodulation, and stimulate additional research.

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