Multiple organ dysfunction syndrome in patients with severe sepsis: more than just inflammation

ROBERT A BALK1 AND RICHERT E GOYETTE2

1RUSH MEDICAL COLLEGE, RUSH-PRESBYTERIAN-ST LUKE'S MEDICAL CENTER, CHICAGO, ILLINOIS, USA
2CONSULTANT IN HEMATOLOGY, KNOXVILLE, TENNESSEE, USA

Multiple organ system dysfunction syndrome in critically ill patients was first described in 1973 by Tilney et al(1). The authors reported that massive blood loss associated with the rupture of abdominal aortic aneurysms led to progressive failure of previously intact organs. Shortly thereafter, Eiseman et al described 'multiple organ failure' as a syndrome occurring in patients kept alive solely by mechanical and pharmacologic support(2). In addition to emphasizing the economic significance of the disorder, this report stressed the association between sepsis and dysfunction of one or more organ systems. The syndrome was more fully characterized in 1980, when Fry et al stressed the role of infection in its pathogenesis and noted that the temporal sequence of organ failure often progresses from the lung to the liver, gastric mucosa and kidney(3).

Multiple organ dysfunction syndrome (MODS) was brought to the attention of the general medical community through the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference definitions and terminology(4). In this model, MODS characterized an entity that produced progressive physiologic failure of several organ systems in acutely ill patients, such that homeostasis could not be maintained without intervention(4). In addition, MODS could be either primary or secondary. Primary MODS resulted from direct organ-system injury (eg pulmonary contusion) or the accompanying haemodynamic alterations (eg hypotension), whereas secondary MODS characterized an exaggerated host response to the inciting insult, usually becoming manifest after a latent period(4,5).
As anticipated by the ACCP/SCCM committee, knowledge of the pathophysiology of sepsis and MODS has evolved over the ensuing years. Within the past decade, it has become clear that sepsis complicated by acute organ dysfunction and MODS is more than a set of isolated inflammatory changes. The haemostatic system plays an integral role in the development of and recovery from the septic process\(^6\)\(^-\)\(^{11}\). This paper discusses advances in knowledge of the tightly linked haemostatic and inflammatory mechanisms that are active in patients with severe sepsis and MODS.

Multiple organ dysfunction occurs not only in patients with sepsis, but also may be associated with other clinical conditions, including severe burns, acute necrotizing pancreatitis, severe trauma or haemorrhagic shock\(^{12}\). Although MODS may result from diverse mechanisms, the host response is probably more important in the genesis of the process than is the specific bacterium, virus or traumatic insult. Despite improvements in fluid resuscitation, availability of more potent antibiotics and greater sophistication in support and monitoring strategies, there are no reliable or specific treatments for MODS. Unfortunately, MODS remains one of the most common causes of death in noncoronary intensive care units (ICUs), with little change in outcome over the past two decades\(^{5,13}\).

**Clinical markers of organ dysfunction**

The prognosis of patients with severe sepsis is related to the severity of organ dysfunction at the time of ICU admission (Figure 1). Mortality rate was lowest in patients with no organ dysfunction at the time of ICU admission. As the number of organ failures increased, the mortality rate also increased. The Sequential Organ Failure Assessment (SOFA) score, which measures organ dysfunction, is a useful tool for predicting outcome in patients with severe sepsis. Patients with a SOFA score of 0 to 1 have a low risk of mortality, while patients with a SOFA score of 3 to 4 have a high risk of mortality. This information can be used to guide treatment decisions and improve patient outcomes.
failure (9%) and increased progressively in patients with failure in one (22%), two (38%), three (69%) and four or more (83%) organs \((p<0.0001)\)\(^{(13)}\). Other studies have shown that mortality in severe sepsis is a function of the number of failing organ systems and the severity of dysfunction within the system\(^{(14-16)}\). The risk of mortality may also be influenced by the duration of organ dysfunction\(^{(17,18)}\).

In the past, it often was not important for clinicians to classify patients specifically with sepsis and acute organ dysfunction (ie severe sepsis). This was because the treatment of septic patients consisted of standard care, with additional interventions, such as institution of mechanical ventilation or use of vasopressor therapy, employed as needed\(^{4,19}\). However, as specific interventions become available for the treatment of patients with sepsis and acute organ dysfunction, searching for signs of acute organ dysfunction will become increasingly important in order to facilitate timely administration of specific antisepsis therapies.

Although there are no universally accepted parameters for assessment of abnormal organ function in patients with suspected MODS, a number of scoring systems have been developed objectively to describe and quantify the level of organ dysfunction in critically ill patients. Examples include the Multiple Organ Dysfunction Score, Sequential Organ Failure Assessment (SOFA), Logistic Organ Dysfunction System (LODS) and Brussels score\(^{13,14,20,21}\). Most organ dysfunction scores have been designed for repeated assessment to describe evolving morbidity\(^{(22,23)}\). These tools can help evaluate the need for and limitations of therapy and they have been used primarily in evaluations of various investigational agents. With most of these tools, evaluation of disease severity involves the use of clinical criteria and laboratory markers to assess the major organ systems: respiratory, renal, hepatic, gastrointestinal, haematologic and central nervous (Table 1)\(^{(5)}\). The variation in specific criteria for organ function assessment may reflect efforts to describe different populations, but it has contributed to the confusion surrounding the terminology used to describe MODS and may have hindered comparison of clinical study results.

Mediators and methods of organ dysfunction

MODS is a systemic process involving both coagulation and inflammatory pathways with potential mediators including a complex variety of humoral substances, cellular effectors and bacterial products\(^{(5,12,24-30)}\). Important humoral mediators include the proinflammatory cytokines tumour necrosis factor-(TNF)-\(\alpha\) and interleukin (IL)-1, as well as IL-6, which has both proinflammatory and anti-inflammatory properties\(^{(27,26)}\). Other potential mediators include soluble TNF-\(\alpha\) receptors I and II (sTNFR-I, II), interferon (IFN)-\(\gamma\) and various growth factors, such as granulocyte colony-stimulating factor (G-CSF) and transforming
growth factor (TGF)-β. This list also includes various adhesion molecules, products of arachidonic acid metabolism (e.g. prostaglandins, prostacyclin [PGI₂], thromboxane A₂ and leukotrienes), components of the complement system, bradykinin and other kinins, procoagulants, coagulation factors and their degradation products, platelet activating factor (PAF), nitric oxide (NO) and other reactive oxygen species, vasoactive polypeptides and amines, endorphins, histamine and serotonin, neuroendocrine factors and myocardial depressant factor.
MULTIPLE ORGAN DYSFUNCTION SYNDROME IN PATIENTS WITH SEVERE SEPSIS

Cellular effectors associated with the events characterizing MODS include: immune cells, such as monocytes, macrophages, leukocytes, polymorphonuclear neutrophil leukocytes (PMNs), mast cells and platelets; vascular and lymphatic endothelial cells; as well as lung epithelial cells. Bacterial products implicated as mediators include endotoxin (lipopolysaccharide [LPS]), other toxins and surface molecules from Gram-negative bacteria, as well as exotoxins, enterotoxins, lipoteichoic acid and various cell-wall components of Gram-positive organisms.

The postulated roles of the various endogenous and exogenous mediators have been reviewed in a number of recent publications. Acting in concert, these humoral, cellular and bacterial mediators produce the endothelial injury that leads to the clinical manifestations of MODS (Table 2).

Critical factors in the development of MODS

A number of factors appear to play a role in the development of MODS. However, organ failure is a secondary event and it is probable that more than one hit is required before the full manifestations of MODS develop. In patients with severe sepsis, MODS appears to result from a cascade of bacterial factors, inflammatory mediators, endothelial injury, disturbed haemostasis and microcirculatory failure.

Host factors

Organ dysfunction is a reflection of the host response and various patient-specific factors may contribute to this process. Age, an important risk factor for MODS, may compound the
effects of pre-existing illness on organ dysfunction\textsuperscript{(23,34,35)}. Data suggest a strong genetic determination in the production of TNF-\(\alpha\) and IL-10 and polymorphisms of these cytokines probably contribute to increased morbidity and mortality in severe sepsis\textsuperscript{(36−39)}. Also implicated are genetic determinants for other cytokine mediators (eg IL-1 and IL-1ra) and toll-like receptor 4 (TLR4) that have an important role in the LPS response, as well as genetic variants for superoxide dismutase (SOD), including manganese and extracellular SOD and alveolar surfactant proteins (SP-A and SP-B)\textsuperscript{(40)}. Gender, perhaps through differences in sex hormones that influence immune and organ responses, has been implicated in the susceptibility to and outcome of septic conditions\textsuperscript{(41,42)}. However, data are inconsistent in terms of outcome, which may reflect other factors, such as differences in risk factor distribution or access to care\textsuperscript{(41,44)}.

**Primary cellular injury and inadequate tissue/organ perfusion**

Primary cellular injury may result directly from the underlying disease process (eg severe tissue injury or a nidus of infection) or the toxic effects of various mediators\textsuperscript{(8,31,45,46)}. Excess levels of proinflammatory cytokines and other systemic mediators can induce endothelial damage and increase vascular permeability, shunt flow and vasospasm\textsuperscript{(8)}. Given these and other sepsis-induced changes, maldistribution of blood flow can impair the delivery of oxygen, nutrients and other substrates that are essential for organ function and preservation\textsuperscript{(5,47)}. Low systemic perfusion pressure frequently accompanies severe sepsis and there also may be selective alterations in the perfusion of an organ system. Sustained vasodilation of small arterioles in skeletal muscle beds may be accompanied by hypoperfusion in the mesenteric circulation, perhaps reflecting higher oxygen requirements of the gut\textsuperscript{(31,47)}.

**Ischaemia/reperfusion**

Microaggregates composed of neutrophils, platelets, red blood cells (RBCs) and fibrin can impair microcirculatory flow, producing tissue ischaemia that may persist despite restoration of blood flow (the no-reflow phenomenon)\textsuperscript{(48,49)}. RBC deformability is important to allow its passage through a capillary with a smaller diameter and loss of this property may impair perfusion\textsuperscript{(5,47)}. Clinical and experimental data indicate that RBC deformability is decreased in sepsis, producing stagnation or enhancing microaggregation with plugging of the microcirculation and arteriovenous shunting of blood\textsuperscript{(50,51)}. Distant septic foci may have an occluding effect on microanastomosis and, in some cases, opening of arteriovenous shunts may deprive capillary beds of blood flow\textsuperscript{(31,52,53)}. Reperfusion injury may involve toxic oxygen metabolites (eg superoxide) that induce apoptosis through changes related to oxidative stress, C\textsubscript{5b-9} membrane attack complexes and disturbances in calcium homeostasis\textsuperscript{(27,48)}. Together, these factors
may compound the endothelial damage and permeability abnormalities induced by bacterial products, cytokines and other mediators.

**Diffuse endothelial cell injury**

Diffuse injury causes endothelial cell dysfunction and plays an important role in the development of MODS. Vasomotor tone may be directly altered by local mediators, some of which (e.g., endothelin, vasopressin) act as vasoconstrictors, whereas others (e.g., NO, bradykinin, histamine, PGI2) produce vasodilatation, which may lead to low perfusion pressures or hypotension. Along with these changes, diffuse endothelial cell reperfusion injury can cause oedema related to capillary leakage of protein-rich fluid and continued tissue damage. Although often first observed as pulmonary oedema, such leakage and cellular infiltration may also occur in the liver, kidneys, heart, skin, muscle and brain of patients with severe sepsis or trauma.

**Humoral factors and immune/inflammatory mediators**

Even if blood flow to various tissue beds is adequate, the ability of cells to extract or utilize oxygen and substrate may be complicated by mitochondrial dysfunction or other factors related to the metabolic disturbances in sepsis. Endotoxin has complex effects on cellular energy metabolism and can reduce maximal oxygen consumption independent of any hypoxic insult. Oxidants produced during endotoxin-induced shock can trigger the activation of the nuclear enzyme poly(ADP-ribose) synthetase (PARS), leading to intracellular energetic failure. Experimentally, PARS activation mediates pulmonary microvascular and intestinal mucosal dysfunction. Apart from the disease entity itself, sepsis induces a metabolic state characterized by an increase in resting calorie consumption, extensive protein and fat catabolism, negative nitrogen balance, hyperglycaemia and an increase in hepatic gluconeogenesis. This hypermetabolic state affects virtually all tissues, causing reduced gut function, skeletal and respiratory muscle wasting, loss of body cell mass, impaired wound healing, alterations in protein synthesis and impairment of the host response to infection. Along with ischaemia/reperfusion injury and other causes of cellular damage, these metabolic disturbances suggest a mechanism for alterations in gut intestinal barrier function. At least in theory, increased intestinal permeability permits the translocation of bacteria, bacterial products and/or proinflammatory cytokines into the mesenteric lymph, the portal and/or systemic circulation, representing a potential stimulus for the development of MODS. In animal models of severe sepsis, reductions in mesenteric perfusion and oxygen delivery have been associated with gut mucosal and microvascular injury, barrier dysfunction and bacterial translocation, and these changes appeared to vary with the septic stage.
In severe sepsis and other overwhelming insults, the systemic inflammatory response is characterized by excess levels of proinflammatory cytokines and the concomitant activation of the endothelium and circulating immune effector cells (e.g., PMNs). In this setting, IL-6 is an important marker of systemic inflammation and sustained elevations of TNF-α and IL-6 are associated with the development of MODS and death [24,45]. Endothelial cell activation involves the increased expression of potentially injurious molecules, including the inducible form of nitric oxide synthase (iNOS) which generates excess NO, and intercellular adhesion molecules (ICAM-1, ICAM-2) that promote neutrophil chemotaxis and endothelial cell interactions [6]. Simultaneously, PMN activation, characterized by loss of L-selectin and increased α2-integrin (CD11b/CD18) expression, further enhances endothelial-cell interactions with the release of NO and lysosomal enzymes that induce microvascular injury [26,49,61]. In septic patients, upregulation of circulating PMN CD11b expression parallels the mean serum IL-6 levels and predicts the severity of organ injury [62]. Counterbalancing the systemic inflammatory response, anti-inflammatory processes are reflected by increased levels of circulating anti-inflammatory cytokines (e.g., IL-4, IL-13), increased expression of receptor antagonists (e.g., IL-1ra) and shedding of soluble receptors such as TNF-α receptor I (sTNFR-1) [27,28]. In addition directly to blocking the binding of proinflammatory stimuli to their cell-surface receptors, these mediators induce an anti-inflammatory state on TGF-α and IL-10, thus further dampening the inflammatory response [26,61,64]. At the cellular level, the anti-inflammatory state involves a decrease in monocyte antigen processing ability related to decreased HLA-DR expression, as well as impairment of PMN upregulation and eventual apoptosis in response to proinflammatory stimuli [26]. Persistence of this hyporesponsive state has been associated with an increased risk of nosocomial infection and death [31,65].

The paradoxical coexistence of proinflammatory and anti-inflammatory substances and their conflicting signals may cause immune dysregulation, which is primarily observed at the transcriptional level [26–28]. After early inflammatory changes induce its activation through oxidative stress, nuclear factor kappa-β (NFκβ) migrates into the nucleus and promotes signal translation for many proinflammatory cytokines, iNOS, adhesion molecules and acute-phase proteins. Downregulation of the inflammatory response is related to inhibition of NFκβ activation by various factors, including IL-10, antioxidants, glucocorticoids and several feedback mechanisms. The cellular stress response involves a transient downregulation of most cell products but upregulation of heat shock proteins. At least in part by inhibiting NFκβ activation, these proteins protect against oxidative stress, attenuate the cellular response to proinflammatory stimuli and minimize subcellular injury [27].

Along with their previously highlighted effects, various inflammatory and humoral mediators appear to play a role in sepsis-related myocardial dysfunction, which is characterized by
decreased myocardial contractility, reduction in ejection fraction and consequent dilata-
tion(25). Bacterial products and both TNF-α and IL-1, perhaps by increasing NO formation
through iNOS, have been implicated as potential myocardial depressants(25,31,66). A number of
experimental and clinical studies have reported circulating humoral factors, termed myocar-
dial depressant factor(s), with negative inotropic effects on the heart in severe sepsis and sep-
tic shock(67,68). Other factors with negative inotropic properties include ?-atrial natriuretic
peptide, activated complement, arachidonic acid metabolites and neutrophil products, such as
oxygen free radicals(69).

Directed treatment/medication

Treatment itself may be associated with organ dysfunction. Blood transfusions have been
associated with immune suppression and increased risk for infection, and have been identified
as an independent risk factor for the development of MODS(34,70). Other commonly impli-
cated treatments include nephrotoxic antimicrobial agents (eg aminoglycosides, amphotericin
B) and invasive devices. Although it does not appear to rapidly disrupt the Protein C/Protein
S system, haemodialysis may involve systemic anticoagulation or activation of PMNs on pas-
sage over the membranes, with damage to microvasculature in the lungs or other organs(71,72).

In the host response, the systematic activation of the immune response invariably is accom-
panied by excessive intravascular activation of coagulation associated with a relative insuffi-
ciency of fibrinolysis(73,74). This imbalance may result in the generation and deposition of
fibrin, leading to the formation of microvascular thrombi that can compromise blood supply
to various organs(11,32,75,76). This condition, termed disseminated intravascular coagulation
(DIC), is most commonly found in patients with severe sepsis and serves as a strong predictor
of a poor prognosis(77,78). As discussed, recent studies in severe sepsis have underscored the
crucial role of the coagulation system and microvascular thrombosis, which may be a primary
factor driving organ dysfunction and death(6-9,32,77).

Haemostatic abnormalities in severe sepsis and MODS

Coagulation abnormalities

The close association between the coagulation system and the inflammatory response is a
phylogenetically ancient, adaptative response that has been preserved from the early stages of
eukaryotic evolution(79). Although lacking formed elements of blood, most invertebrate
species possess a common cellular and humoral pathway of inflammation and clotting that is
activated after trauma or infection. A similar linkage occurs in vertebrates, with proinflam-
matory stimuli activating both the coagulation cascade and immune effector cells.
Haemostatic activation appears to be almost universal in patients with severe sepsis. Evidence of this response has been reported by experimental studies in humans and primates, and confirmed by recent clinical studies in severe sepsis which have employed sensitive and specific markers of coagulation activation\^{75,78,80-83}. For example, elevated levels of D-dimer, indicating activation of both coagulation and fibrinolysis, and depressed concentrations of Protein C, indicating a relative lack of physiologic anticoagulation, were identified in almost 100% of patients in the Ibuprofen in Sepsis trial\^{83,84}. In contrast, the combination of clinical and laboratory abnormalities traditionally required for a diagnosis of DIC are uncommon. In a large prospective survey, the incidence of DIC in patients with severe sepsis was only 18\%\^{14}. In the Ibuprofen in Sepsis trial, fewer than 10% of the study population developed thrombocytopenia, prolongation of the PT and APTT, increased fibrin split products and decreased fibrinogen levels, the classical laboratory markers of DIC\^{84}. Supporting the value of the newer assays, recent investigations suggest a continuum of coagulopathy in sepsis, with coagulation abnormalities developing before the onset of clinical parameters of severe sepsis or septic shock\^{7,73-75,85}.

During infection or after experimental stimulation with endotoxin or certain proinflammatory cytokines (eg TNF-\(\alpha\), IL-1, IL-6), the expression of tissue factor (TF) is rapidly upregulated on monocytes and perhaps a subset of endothelial cells\^{6,86}. This is immediately followed by a decrease in levels of the extrinsic clotting system components, factor VII and factor VIIa. Activation of the final common pathway is reflected by increases in markers for the generation of thrombin, such as prothrombin fragment F1.2 and thrombin–antithrombin (TAT) complexes\^{73,81}. As indicated by these haemostatic changes, TF expression in sepsis activates the extrinsic system of coagulation, with the conversion of prothrombin to thrombin\^{11}.

The intrinsic system may be less important in generating the initial haemostatic response to sepsis or tissue injury, but appears to play a more critical role in amplifying the response via activation of the fibrinolytic system\^{11,75,87}. Activation of this system involves a combination of cross-talk and feedback mechanisms. Factor VIIa of the extrinsic system activates factor IX of the intrinsic system to factor IXa (cross-talk). Thrombin, generated by the actions of both the extrinsic and intrinsic systems, amplifies the initial prothrombotic response by activating the intrinsic system through conversion of factor XI to Xla and factor VIII to VIIIa (feedback).

**Fibrinolysis abnormalities**

Fibrinolysis is normally tightly linked to coagulation. By removing thrombi and preserving the fluidity of the blood, fibrinolysis is an essential component of microcirculatory homeostasis\^{9}. Endothelial cells are the principal sources of tissue-type plasminogen activator (t-PA),
MULTIPLE ORGAN DYSFUNCTION SYNDROME IN PATIENTS WITH SEVERE SEPSIS

the primary enzyme responsible for activation of fibrinolysis through the conversion of plasminogen to plasmin\(^{8,80}\). In turn, plasminogen activator inhibitor type-1 (PAI-1), a product of platelets and endothelium, is the primary inhibitor of both t-PA and urokinase-type plasminogen activator (u-PA)\(^ {8,89}\). Additional inhibition of fibrinolysis occurs through the actions of \(\alpha_2\)-antiplasmin and thrombin-activatable-fibrinolytic inhibitor (TAFI).

Experimentally, the infusion of TNF or IL-1 can activate fibrinolysis, reflected by the appearance of plasmin-\(\alpha_2\)-antiplasmin (PAP) complexes that have no proteolytic activity but serve as a sensitive indicator of plasmin generation\(^ {7,9}\). Approximately 1–2 hours after infusion of proinflammatory cytokines or endotoxin, inhibition of the early burst of fibrinolytic activity is shown by a progressive increase in the synthesis of PAI-1, a decrease in PAP complex levels and the appearance of t-PA–PAI-1 complexes. This appears to be secondary to a cytokine-induced increase in PAI-1 synthesis in several organs, which may contribute to the imbalance between coagulation and fibrinolysis and result in disruption of the microcirculation\(^ {7,75,76,81,89,90}\). Levels of PAI-1 may remain within the normal range in patients with uncomplicated sepsis, but are usually markedly elevated in patients with septic shock and correlate with an unfavourable outcome\(^ {8,85,91,92}\).

Microcirculatory thrombosis

Although a number of interactive factors appear to promote the development of MODS, cytokine-induced prothrombotic abnormalities within the microcirculation play a major role in the process. The thrombotic diathesis results when proinflammatory cytokines upregulate TF, downregulate the Protein C/Protein S system and impair the body’s natural ability to dissolve clots by stimulating the production and release of PAI-1\(^ {9}\). Within hours of the onset of sepsis, these haemostatic alterations produce a dramatic imbalance favouring thrombosis in the microvasculature and sometimes the macrovasculature.

Microvascular thrombosis can be observed in both experimental models of sepsis and in septic patients. Experimentally, rats with *Pseudomonas aeruginosa* septic abscesses develop sterile microthrombi in distant, surgically-created microvascular anastomoses\(^ {52}\). Skin biopsies from patients with infectious purpura fulminans show dermal vascular thromboses and haemorrhagic necrosis\(^ {93,94}\). Microcirculatory abnormalities also play a role in the genesis of the acute respiratory distress syndrome (ARDS), a frequent organ system dysfunction in patients with severe sepsis and other disorders. As previously mentioned, MODS probably results as a consequence of a number of insults rather than a single event, with a majority of the action occurring in the microvasculature. For the purpose of this discussion, the following section concentrates on haemostatic and microvascular issues.
Acute respiratory distress syndrome as a model of MODS

Although a number of infectious and inflammatory disorders are associated with the development of ARDS, the highest incidence occurs in patients with severe sepsis. The respiratory system is often the first organ system to fail clinically and the pathophysiology of the process illustrates many important elements of MODS, including endothelial activation, inflammatory and haemostatic changes and vascular alterations.

Endothelial activation

Endothelial cell activation and injury are considered by many to be the principal mechanisms underlying the pathophysiologic manifestations of ARDS. Activation of pulmonary vascular endothelial cells, defined by a change in phenotype or function, can be induced by various stimuli including thrombin, systemic cytokines (eg TNF-α, IL1) and bacterial products (eg LPS). The endothelial cells can then shift to a prothrombotic state, with increased expression of surface receptors for thrombin, von Willebrand factor (vWF) and adhesion molecules (eg ICAM-1). Suggesting an activation-dependent mechanism, the sepsis-induced upregulation of selectins and integrins can lead to sequestration of inflammatory cells within the pulmonary vasculature, which is one of the earliest changes in ARDS. The complexity of endothelial cell activation, including gene clustering and the expression of adhesion and signaling molecules that mediate neutrophil interactions, has been demonstrated by *in vitro* systems. Alternatively, concentrations of soluble forms of these molecules may serve as surrogate markers of endothelial cell activation and injury. Recent studies have detected elevated plasma levels of these markers in patients with ARDS and acute lung injury (ALI), with degrees of elevation suggesting differences in endothelial cell activity among high-risk subgroups.

Thrombin regulates endothelial cell function by binding to either the thrombin receptor (TR) or thrombomodulin (TM). Binding to the TR shifts the balance of the endothelial cell to a prothrombotic phenotype, characterized by the release of PAI-1, downregulation of TM expression and other changes involving NFκβ transcription. In tissue culture, thrombin produces endothelial cell injury, manifested by increased microvascular permeability, altered endothelial cell shape and disassembly of actin myofilaments. Microscopically, thrombin increases endothelial cell permeability and produces gaps between adjacent endothelial cells. Deposition of fibrin in the microvasculature is histologically associated with endothelial cell injury and may contribute to the development of ARDS in septic patients.
Inflammatory and haemostatic activation

Of the proinflammatory cytokines associated with increased activity within the lungs of ARDS patients, TNF-α appears to play a pivotal role in initiating the coagulation response (64,96). Increased levels of TNF have been found in the pulmonary microcirculation or bronchopulmonary secretions of ARDS patients compared with patients with sepsis alone, failure of other organ systems or other types of lung disease (46,103,104). Studies comparing bronchoalveolar lavage and plasma levels of TNF in patients with ARDS indicate that the cytokine is lung derived, probably of alveolar macrophage origin and suppressed by IL-10 (64,105). A functionally active membrane-associated TNF on these cells may contribute to lung injury through the increased expression of its surface receptor.

Changes in inflammatory cytokines in patients with early ARDS are associated with histologic alterations that can be divided into exudative, proliferative and fibrotic stages (97). In the early phases of sepsis-induced ARDS, intracapillary neutrophil aggregates are focally prominent and associated with widening of the alveolar septa by interstitial oedema, fibrin deposits and extravasated erythrocytes (97). Platelet sequestration also occurs (106). This phase is marked by a prothrombotic diathesis, which primarily results from activation of the extrinsic system and may be local or become generalized (96). Levels of TF, which have a critical role in initiating the extrinsic pathway, are increased in the bronchoalveolar fluid of ARDS patients (107). Fibrinolytic activity is depressed as shown by increased concentrations of PAI-1 on bronchoalveolar lavage in the acute stage of lung injury (108). The combination of endothelial cell damage, sequestration of inflammatory cells, increased coagulation and depressed fibrinolysis promote the deposition of fibrin and the development of hyaline membranes with subsequent alveolar fibrosis.

Vascular alterations

Pulmonary vascular lesions correlate with the duration of respiratory failure. In postmortem lung specimens, thrombotic and thromboembolic lesions are detected in 95% of patients with ARDS (97). In the microcirculation, these lesions consist of hyaline platelet–fibrin thrombi in capillaries and arterioles, and laminated fibrin clots in small arteries and arterioles. Larger thrombi are found in arteries with a diameter >1 mm. Although it is difficult to determine if these thrombi are formed in situ or are of embolic origin, the combination of histologic and haemostatic changes suggests that local microvascular thrombosis plays a major role. Over time, fibrocellular intimal proliferation develops and contributes significantly to elevations in pulmonary vascular pressure. In the later stages, pulmonary vascular remodelling produces dramatic changes evident on angiography, as arterioles become more tortuous and blunted,
and pulmonary capillaries undergo progressive dilatation. Increased arterial muscularization in ARDS may result from hypoxia, pulmonary hypertension or oxygen toxicity. Experimental data suggest that such structural remodelling is irreversible.

**Vascular bed-specific determinants in MODS**

With the preponderance of evidence supporting microvascular thrombosis, it might seem surprising that extrapulmonary thrombi are difficult to demonstrate in the septic population. However, coagulation abnormalities are clearly related to the development of organ dysfunction and death, and changes in sensitive laboratory tests support the direct relationship. The thrombotic diathesis of sepsis is reflected by an elevation in the TAT/PAP ratio, which is significantly higher in patients with severe sepsis than in postsurgical controls. This prothrombotic state appears to contribute directly to mortality as TAT/PAP ratios are higher in nonsurvivors of sepsis than in survivors.

Failure to demonstrate widespread thrombosis appears to be secondary to several factors. For example, the effects of cytokines appear to be vascular-bed specific. Levels of TNF in bronchopulmonary secretions are elevated in ARDS patients compared with those having serious infections or other types of lung disease. Studies comparing bronchoalveolar lavage and plasma levels of TNF in ARDS patients indicate that the cytokine is lung derived and probably of alveolar macrophage origin. Moreover, sepsis is a dynamic process that evolves through stages marked by differential levels of proinflammatory and anti-inflammatory cytokines. The cytokine mix can vary enormously over the course of the disease; thus, the inappropriate timing of administration of investigational anti-inflammatory therapies has been postulated as one possible mechanism for clinical trial failures. Concentrations of cytokines may be lower in areas that are remote from the primary process and may vary with regional blood flow and tissue perfusion. Finally, reperfusion may fragment and sweep microthrombi from tissue beds, with subsequent clearance by the reticuloendothelial system.

**Natural inhibitors of coagulation**

The body has a number of natural inhibitors of the haemostatic system that localize coagulation and maintain homeostasis. These endogenous inhibitors include antithrombin (AT III), tissue factor pathway inhibitor (TFPI) and Protein C (PC). Because almost all patients with severe sepsis have a coagulopathy, the potential role of natural antithrombotic proteins in this disorder is discussed.
Multifunctional properties of AT III also include its anti-inflammatory effects. When bound to the endothelial cell via glycosaminoglycans (GAG), AT may release prostaglandin I2 (prostacyclin, PG12), a vasodilator and inhibitor of platelet aggregation. Antithrombin is also implicated in endotoxin resistance and the reduced release of oxygen radicals and TNF-α from monocytes stimulated by LPS(73). In severe sepsis, the dramatic decline of AT results from its acute consumption by thrombin, with the formation of TAT complexes, its extravasation due to increased permeability and its degradation by neutrophil elastase and other proteases(8,30). In animal studies, high levels of AT III (>150%) produced favourable results in DIC and MODS. Similarly, high doses of AT III generally were required to overcome the problem of antithrombin consumption in clinical studies. In a randomized, placebo-controlled study of 35 patients with septic shock, high-dose AT III significantly shortened the duration of DIC and reduced mortality, although the difference was not statistically significant(112). Subsequently, a 14-day, prospective study of 29 surgical patients reported that AT III attenuated the SIRS response, improved lung function and prevented both liver and kidney dysfunction(113). In a double-blind, randomized, placebo-controlled trial of 120 patients, AT III reduced mortality only in a subset of septic shock patients(114). Despite these promising preclinical and clinical findings, a meta-analysis of separate, large multicentre, double-blind, placebo-controlled trials failed to demonstrate a significant reduction in 28-day mortality in patients with severe sepsis treated with AT III(115). There was evidence of a significant decrease in organ system dysfunction. A subsequent large, multicentre, prospective, randomized, double-blind, placebo-controlled trial also failed to demonstrate improved survival associated with AT replacement therapy in severe sepsis and septic shock(116).

Tissue factor pathway inhibitor

Tissue factor pathway inhibitor (TFPI) is found in plasma, associated with apolipoprotein II, and on the endothelium of small capillaries. TFPI is a potent but slow inhibitor of the TF-factor VIIa complex. During sepsis, TFPI levels remain stable or increase, presumably due to release from endothelial cells. A preclinical trial of TFPI in a porcine model of septic shock demonstrated improved cardiac output and attenuation of cytokine responses to sepsis, reducing peak TNF-α and IL-8 levels (p <0.05 vs control)(117). The study concluded that TFPI treatment attenuated important mediator components within the inflammatory response, but did not provide significant survival benefit(117). A phase III clinical trial of recombinant TFPI in patients with severe sepsis is ongoing.
Activated Protein C

In its natural state, Protein C is an inactive serine protease. Activated Protein C, in the presence of its cofactor Protein S, has antithrombotic, anti-inflammatory and profibrinolytic properties. The conversion of Protein C to activated Protein C requires the action of thrombin complexed with the endothelial cell glycoprotein, thrombomodulin (TM)(10). This results from a TM-induced alteration in the substrate specificity of thrombin from fibrinogen to Protein C. Thus, generation of activated Protein C occurs in rough proportion to thrombin formation. The binding of activated Protein C to Protein S facilitates cleavage of factors VIIIa and Va, thereby modulating coagulation through suppression of further thrombin production(9,118). Levels of Protein C decline early in sepsis, predominantly due to consumption and depletion(78,85,118). Activated Protein C activity also decreases in this setting as a result of consumption and endothelial cell injury, with the loss of Protein C receptors and TM expression on endothelial cells(90). Concomitantly, levels of both free Protein S and the inactive Protein S–C4b-binding protein complex remain within normal limits, which supports the role of Protein C as the determinant of sepsis severity. Consistent with its pharmacologic effects, reduced levels of Protein C correlate with morbidity and mortality in sepsis.

In addition to its anticoagulant effect, activated Protein C enhances fibrinolysis by neutralizing PAI-1 and accelerating t-PA-dependent clot lysis in a TAFI-dependent manner(9,119,120). In addition to its indirect effect on inflammation through inhibition of thrombin formation, activated Protein C has direct anti-inflammatory effects. In preclinical models, activated Protein C inhibited LPS-induced TNF-α production and translocation of NFκB in monocytes; suppressed proinflammatory cytokine release from monocytes; inhibited selectin-mediated cell adhesion; and protected baboons from lethal doses of Escherichia coli endotoxin(80,121-124). As indicated by transcriptional profiling, activated Protein C may directly affect endothelial cell function through suppression of NFκB binding and functional activity, including inhibition of TNF-α-induced upregulation of surface adhesion molecules (eg ICAM-1, E-selectin), and through modulation of gene expression to prevent apoptosis and a switch to cell survival mechanisms(125). In patients with severe meningococcaemia, activated Protein C appeared to improve the host response and reduce cytokine-mediated organ dysfunction(126,127). The effects of recombinant human activated Protein C [drotrecogin alfa (activated)] have been recently published(125) and are discussed by Bernard later in this monograph.

Conclusion

Severe sepsis is sepsis with acute organ dysfunction and is frequently accompanied by a sepsis-induced coagulopathy. Organ dysfunction in this population may be an early manifestation of
MODS, a progressive physiologic dysfunction of several organ systems such that homeostasis cannot be maintained without intervention. The presence of MODS marks a population at high risk for mortality. The pathophysiology of MODS is a complex relationships between inflammation, thrombosis and impaired fibrinolysis. Only by recognizing and addressing all of these components can there be hope of decreasing the mortality of patients with sepsis and acute organ dysfunction.

References


MULTIPLE ORGAN DYSFUNCTION SYNDROME IN PATIENTS WITH SEVERE SEPSIS


MULTIPLE ORGAN DYSFUNCTION SYNDROME IN PATIENTS WITH SEVERE SEPSIS


