Multi-organ dysfunction in the critically ill: effects on different organs

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This article provides a short overview of the manifestations and mechanisms of dysfunction of specific organs.

Cardiovascular system

Sepsis usually generates a high cardiac output with a fall in systemic vascular resistance. None the less, reversible depression of myocardial function is well documented. Cytokines (specifically tumour necrosis factor, and interleukin-1), changes in adrenergic signal transduction and nitric oxide (NO) have been implicated. Survivors of septic shock show progressive improvement in myocardial contractility, while non-survivors have persisting dysfunction. Survivors often have acute left ventricular dilatation, maintaining a normal/raised stroke volume despite the reduced contractility. Dilatation may therefore be an adaptive response which is not seen in non-survivors, for unknown reasons.

Sepsis is classically associated with an overall loss of vascular tone, though areas of microvascular constriction coexist alongside areas of dilated microcirculation. Differences in arterial vasoconstrictor responsiveness have been shown between and within tissue beds. Intravascular microaggregates of leukocytes, platelets and fibrin deposits obstruct blood flow. Decreases in red cell deformability also parallel microvascular blood flow disruption. The systemic vasculature becomes less responsive to catecholamines, with reduced α-adrenoceptor density and activity. There are associated reductions in myocardial cAMP, myocardial performance and epinephrine responsiveness.

NO mediates a diverse array of physiological processes, including modulation of vascular tone, neurotransmission, prevention of platelet aggregation, regulation of cellular respiration and cytotoxicity. NO is produced by numerous cell types, including macrophages, endothelial cells, neurons and hepatocytes, either by the action of NO synthases (NOS) on L-arginine, or derived from endogenous NO donors. Overproduction of NO is heavily implicated in the generalised vasodilatation and (often) refractory hypotension seen in septic shock. By inhibiting NO synthesis, the circulation can often be restored and vasopressor hyporesponsiveness reversed.

Inhibition of NO can, however, be detrimental. A recent (as yet unpublished) multicentre study of non-specific NOS inhibition in septic shock patients was terminated prematurely due to an excess of deaths, particularly in patients with low cardiac outputs or who were receiving the highest dose of the drug, L-N-monomethyl arginine (L-NMMA). Interestingly, the converse was seen with lower doses of L-NMMA and in patients with higher baseline cardiac output states. (R Grover; personal communication). A specific inhibitor of the inducible NOS (iNOS) isoform may be more beneficial, though none has yet undergone clinical trials.

Other mediators involved in vascular tone include the arachidonic acid metabolites (prostaglandins (PGs), thromboxanes (TXs) and leukotrienes). These are also involved in vascular permeability, platelet aggregability and immune modulation. Cyclooxygenase inhibitors improved survival in animal models but not in septic patients.

Gastrointestinal tract

Many patients who develop MODS have no evidence of an infective source. Many authorities consider the gut to play a major role in the development of systemic inflammation and MODS through ingress (translocation) of bacteria and endotoxin from the bowel lumen into the portal, lymphatic, and hence systemic, circulations. The barrier function of the gut mucosa is compromised by redistribution of its already precarious blood supply, loss of luminal derived substrates and/or disruption of bioenergetic pathways. However, evidence in animal models has not translated to humans. It remains uncertain whether translocation is causative of sepsis or an epiphenomenon.

The upper gastrointestinal (GI) tract maintains its near-sterility by a low gastric pH, intestinal motility, immunoglobulin (Ig)A secretion, and a resistance to colonisation offered by indigenous anaerobic flora. Critical illness and its
treatments result in a rise in intragastric pH, particularly with the use of acid suppressing drugs, parenteral nutrition, reduced motility (ileus) and reduced secretory IgA production. Broad-spectrum antibiotics disrupt the normal bowel flora, so the upper GI tract becomes colonized with large numbers of enteric organisms (e.g. Pseudomonas, Enterococcus). These same organisms are also isolated in ‘intensive care unit (ICU) infections’.

Bowel permeability, as measured by sugar absorption tests, is also increased in critical illness and normalizes upon recovery. No correlation has been drawn with translocation because endotoxin and micro-organisms pass through intact enterocytes rather than between cells. Ileus and intolerance to enteral feeding are well recognised, presenting as large gastric aspirates, abdominal distension or diarrhoea. The ability of the gut to absorb amino acids and glucose is impaired, as is the ability to utilise glutamine, its principal fuel. Despite these findings, early enteral feeding appears safe, and it will decrease mucosal permeability and the severity of organ dysfunction in trauma patients⁴.

Stress ulceration

Critical illness predisposes to ‘stress’ gastric erosions and ulcers. Approximately 20% of ICU patients have endoscopic evidence of stress ulceration, though significant haemorrhage is rare (<2%). Independent risk factors include mechanical ventilation and coagulopathy. Critically ill patients have reduced gastric acid production, but are also likely to have reduced endogenous protection to which a lack of feeding contributes.

Acalculous cholecystitis

The gall bladder of the critically ill patient often has a thickened, boggy wall containing biliary sludge. Acalculous cholecystitis can develop, sometimes as a secondary infection of the gall bladder during bacteraemia. The pathogenesis remains unclear.

Pancreatitis

Though well recognised as an initiator of systemic inflammation and multi-organ dysfunction, pancreatitis can occur as a secondary complication. Autopsy studies suggest a 10% incidence, rising to 50% in shocked patients with acute renal failure. Inadequate perfusion has been proposed as an aetiological factor. Because of its ability to initiate a generalised inflammatory response, pancreatic injury during critical illness may lead to either maintenance or amplification of the systemic inflammatory response.

Hepatic dysfunction

Jaundice and abnormal liver function tests occur frequently, though fulminant hepatic failure is rare. Dysfunction is compounded by drugs, massive blood transfusion and total parenteral nutrition. Hepatic blood flow is increased in the critically ill, though unrelated to global haemodynamic indices. The synthetic capacity of the liver increases markedly in sepsis, with a switch away from albumin production towards fibrinogen and acute-phase proteins.

Like the gut, the liver has also been proposed as a possible driver of the systemic inflammatory response. Bacteria and endotoxin translocating from the bowel are filtered from the portal system by Kupffer cells; these cells become activated, releasing large amounts of pro-inflammatory mediators into the surrounding tissue and ‘spilling over’ into the systemic circulation.

Renal system

Fifteen percent of ICU patients have evidence of renal failure, either acute or acute-on-chronic, of whom 66% require renal replacement therapy⁶. Approximately 60% die, though rarely due to renal failure per se. Sepsis is responsible for 50% of cases, with haemodynamic and toxic factors accounting for most of the others. The pathology occurs at different levels, with disturbances in renal artery blood flow, glomerular filtration and tubular function.

Renal artery flow and glomerular filtration

Variable changes in renal blood flow occur, depending on the model investigated. Vasconstrictors (e.g. endothelin, TX, angiotensin, vasopressin, norepinephrine) and vasodilators (e.g. NO, PGs) affect total and intrarenal flow. NO correlates with the degree of renal dysfunction, though non-specific NOS inhibition worsened renal function in endotoxemic rats, despite restoring blood pressure, with a significantly higher level of glomerular capillary thrombosis and fibrin deposition. Of interest, specific iNOS inhibition prevented the fall in both blood pressure and glomerular filtration rate (GFR). The sepsis-induced reduction in GFR appears greater than any depression in renal blood flow. Indomethacin, normally toxic to hypoperfused kidneys, was protective. Although ibuprofen failed to improve renal function in human sepsis, it did not cause overt harm.

Tubular function

After endotoxin challenge, the tubules look microscopically normal, though peritubular capillaries demonstrate endothelial oedema and neutrophil sequestration. Blood flow is redirected from the cortex to the juxtamedullary areas, possibly causing a wash-out effect on the interstitial medullary concentration gradient, resulting in inappropriately high water and salt loss. There is an abnormal excretion of tubular proteins and increased lysozyme clearance. It should be stressed that widespread acute tubular necrosis is uncommon.

Neurological system

Encephalopathy

Septic encephalopathy, characterised by agitation, confusion and altered levels of consciousness, is a reversible derangement in central nervous system
(CNS) function affecting up to 70% of septic patients. Electroencephalography demonstrates diffuse abnormalities. The severity of the encephalopathy correlates well with mortality and with the degree of renal and hepatic dysfunction. However, no good evidence exists for direct CNS invasion by bacteria or endotoxin. The aetiology is probably multifactorial, including altered catecholamine levels, metabolites and amino acid metabolism and a decrease in forebrain \( \beta \)-receptor density.

The adequacy of cerebral perfusion during sepsis has also been questioned. Animal models have shown variable effects on cerebral blood flow. A decrease in cerebral blood flow was demonstrated in septic patients\(^6\). Abnormalities in autoregulation remain speculative.

**Peripheral nervous system**

MODS is often associated with a peripheral ‘critical illness neuropathy’, complicating about 70% of cases with sepsis\(^9\). It is an important cause of failure to wean from mechanical ventilation. Both motor and sensory fibres are affected, with electrophysiological changes characteristic of axonal damage. Although muscle strength is reduced in these patients as a result of denervation, a primary myopathy is also recognised, with evidence of scattered necrotic muscle fibres.

Generalised muscle weakness is frequently seen in both critical illness neuropathy and myopathy. It may be so profound as to render the patient immobile; recovery usually occurs, but sometimes takes several months. Like other organ failures, the cause is unknown but may be related to disrupted microvasculature. A hotly debated area is the role of nutritional deficiencies, and concurrently administered aminoglycosides, neuromuscular blocking agents and steroids.

**Respiratory system**

Lung involvement presents as a spectrum of dysfunction with ‘acute lung injury’ and the acute respiratory distress syndrome (ARDS) defining progressively severe manifestations (Table 1\(^1\)). Mortality differs, depending upon aetiology: 60% in septic patients, 43% in non-septic patients, and 10–22% if trauma-related. Direct lung injury, age and cirrhosis are associated with worse outcome\(^12\). With advances in support technology, few patients now die from intractable hypoxaemia or hypercapnia; the majority die from their underlying illness, new-onset nosocomial infection and/or irreversible multi-organ failure.

An important pathogenic mechanism of lung destruction is the recruitment and degranulation of neutrophils. The number of neutrophils obtained from bronchoalveolar lavage directly correlates with the degree of impairment of gas exchange and the permeability of the lung epithelium. High levels of neutrophil-derived enzymes and free radicals can impair surfactant function\(^13\). Therapeutic use of high inspired concentrations of oxygen and NO may also compound the oxidant/radical problem, while mechanical ventilation may add a barotrauma component, in particular the use of high tidal volumes (‘volutrauma’).

Although the typical radiographic appearance of ARDS shows diffuse shadowing, computed tomography (CT) reveals marked heterogeneity, with patchy areas of consolidation, pneumothoraces and bullae interspersed with relatively normal areas.
(Fig 1). Patients with ARDS of non-pulmonary origin demonstrate a more symmetrical ground-glass pattern with increased densities in dependent regions. These regions alter rapidly when the patient changes position.

ARDS can be divided into a primary chest aetiology (eg pneumonia) or secondary to distant processes such as abdominal sepsis. Interstitial oedema, collapse, fibrosis and vascular alterations are associated with a decrease in lung compliance, lung volumes and the transfer coefficient. However, lung compliance is greater, and recruitment of collapsed alveoli easier, in non-pulmonary causes of ARDS. Coupled with the above CT observations, this has prompted investigators to consider redefining ARDS.

Haematological system

Haemoglobin fails in multi-organ failure, due in part to the quantity of blood sampling, to haemodilution with non-blood products, and as a direct consequence of the disease process. Erythropoietin levels are depressed in sepsis, leading to a degree of marrow failure.

Neutrophil and platelet counts are frequently depressed, due both to marrow failure and to increased adherence in various organs, including lung, liver and gut. Activation of platelets and coagulation pathways occur, with high levels of tissue factor, fibrinogen, thrombin and markers of platelet activation. Consumption of clotting factors and endogenous anti-coagulants such as antithrombin III and activated protein C is also well recognised. Impaired hepatic synthesis or destruction by proteases may further contribute to the subnormal levels. Although low level coagulopathy is commonplace, frank disseminated intravascular coagulation is rare except in specific conditions such as meningococcal septicaemia.

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