1 Shock

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Take home messages

- Human survival is absolutely dependent on oxygen for respiration, the process by which cells derive energy in the form of adenosine triphosphate (ATP).
- Mitochondrial respiration is compromised by a reduction in oxygen delivery due to circulatory failure (e.g. hypovolaemic shock) and/or an inability to appropriately utilise delivered oxygen (e.g. during sepsis).
- Circulatory failure of any cause activates a systemic immune/inflammatory response.
- Inflammatory signalling and gene expression of inflammatory mediators starts a cascade of downstream effects often culminating in organ dysfunction or failure.

1.1 Introduction

Oxygen is the most supply-limited metabolic substrate. Under normal physiological conditions oxygen (O_2) supply is closely matched to mitochondrial consumption. Shock is caused by an imbalance between the supply and demand of oxygen. Depending on the aetiology, either the delivery of oxygen and other metabolic substrate is reduced or increased metabolic requirements are unmet despite increased delivery. The inability of peripheral tissues to utilise substrate may contribute to this imbalance.

A number of different conditions can cause shock (Table 1.1). The original Hinshaw and Cox classification differentiated between four main categories [1]. More recently, endocrine shock, caused by thyroid disease or adrenal insufficiency, was recognised as another aetiological category but will not be discussed here [2].

To unravel the often complex clinical scenarios associated with shock, we find it useful to start by differentiating between low versus high cardiac output states. We therefore divide this overview of shock into three parts:

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Table 1.1 Classification of shock.

Category	Cause of shock
Hypovolaemic	Loss of circulating volume
Cardiogenic	Myocardial or endocardial disease
Obstructive	Mechanical extra-cardiac obstruction of blood flow
Distributive	Vasodilatation and altered distribution of blood flow
Endocrine	Thyroid disease, adrenal insufficiency

- low cardiac output states,
- high output states, and
- the pathway to multi-organ failure.

1.2 Low output states

Low cardiac output and systemic hypoperfusion leads to oxygen supply failure. This situation is exacerbated by anaemia in haemorrhagic shock – oxygen delivery (DO_2I) is determined by the cardiac output (CO) and blood O_2 content (C_aO_2), with the latter predominantly a function of haemoglobin concentration and arterial oxygen saturations.

$$DO_2I = CO \times C_aO_2$$
$$CO = [HR \times SV]$$
$$C_aO_2 = \text{Hb-bound } O_2 + \text{dissolved } O_2$$
$$= [1.39^{*} \times \text{Hb concentration} \times \text{arterial } O_2 \text{ saturation}] + [0.02^{\ddagger} \times p_aO_2]$$

HR: heart rate; SV: stroke volume; Hb: haemoglobin.

*Each gram of normal haemoglobin contains 1.39 of O_2 when fully saturated. A figure of 1.34 is usually used due to the presence of inactive haemoglobin derivatives.

‡The amount of dissolved O_2 is linearly related to the partial pressure of oxygen (p_aO_2).

Initially, peripheral tissues compensate for the reduced DO_2I through increased O_2 extraction, thus maintaining normal levels of O_2 consumption (VO_2) [3]. This mechanism cannot compensate for DO_2I reductions below a critical level, beyond which VO_2 declines to become 'supply-limited'. Anaerobic metabolism and hyperlactataemia follows while organ function deteriorates in the face of adenosine triphosphate (ATP) depletion and a failure of ion pumps to maintain trans-membrane gradients and cell integrity.

Cellular and tissue hypoxia form a central element in development of multiple organ failure and activate the immune system through a number of mechanisms (see below) [4, 5]. Irrespective of initial cause, continued hypoperfusion and cellular ischaemia triggers complex cascades resulting in the production of pro-inflammatory mediators and leukocyte activation

with the release of reactive oxygen species (ROS) and proteolytic enzymes. Nuclear factor kappa-β (NF-kB), hypoxia inducible factor (HIF)-1 and inducible nitric oxide synthase (iNOS) play critical roles [6–10]. As a consequence, the vascular endothelium becomes permeable and expresses cellular adhesion molecules (CAM) and other inflammatory mediators [11, 12].

Low cardiac output-associated oxygen debt is associated with multiple organ failure (MOF) and mortality in post-operative patients [13]. The degree of tissue oxygen debt is similarly related to enhanced inflammatory responses, increased risk of acute lung injury and increased mortality [14]. Clinical studies demonstrate a causal relationship between traumatic injury and/or shock and a predisposition to sepsis/MOF, probably due to an excessive inflammatory response coupled with failure of cell-mediated immunity [15–17].

Hypovolaemic shock

Hypovolaemic shock is caused by a loss of circulating volume and/or non-haemorrhagic causes [2]. The latter include absolute loss of fluid (vomiting, diarrhoea, high-output fistulas or evaporative losses: fever, surgery, burns), or third space fluid sequestration through shifts between the intravascular and extravascular space (trauma, ileus, small bowel obstruction). The resulting decrease in intravascular volume reduces venous return, stroke volume and ultimately cardiac output causing tissue hypoperfusion.

Acute volume loss leads to the activation of compensatory mechanisms involving [18, 19]:

- volume and pressure receptors,
- the sympathetic nervous system (SNS),
- the renin-angiotensin (RAAS) system, and
- anti-diuretic hormone (ADH).

The earliest response arises from mainly atrial and pulmonary pressure receptors. The baroreceptor response and activation of the SNS produces arterial and venous vasoconstriction, and tachycardia. Venous vasoconstriction aims to restore preload and cardiac output, while arterial vasoconstriction increases mean arterial pressure (MAP). Blood flow is also diverted to vital organs (brain, heart, kidneys). Interstitium-to-intravascular space fluid shift (facilitated by reduced capillary pressures) also occurs and expands intravascular volume by as much as 1 litre in the first hour and a further 1 litre during the first 48 hours [20].

The RAAS is activated by the SNS and by a reduction in renal blood flow. Renin, released by the juxtaglomerular cells, leads to an increase in angiotensin II (AT-II). AT-II, a potent vasoconstrictor, stimulates the adrenal production of aldosterone, which in turn promotes renal sodium and water retention. ADH/vasopressin, a hormone secreted by the posterior pituitary, is a potent vasoconstrictor and increases water retention by the kidneys. These events increase circulating volume. During the later stages, erythropoietin is secreted to increase red cell volume and plasma protein synthesis is increased.

Table 1.2 Estimated fluid loss in haemorrhagic shock*.

	Class I	Class II	Class III	Class IV
Blood loss (ml)	Up to 750	750–1500	1500–2000	> 2000
Percentage blood volume	Up to 15%	15–30%	30–40%	> 40%
Pulse rate (bpm)	< 100	> 100	> 120	> 140
Systolic blood pressure	Normal	Normal	Decreased	Decreased
Diastolic blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (per min)	14–20	20–30	30–40	> 35
Urine output (ml/hour)	> 30	20–30	5–15	< 5
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

* For a 70-kg man.
Adapted from Committee on Trauma of the American College of Surgeons [23].

Healthy individuals can compensate for fluid losses of up to 30% of the circulating volume (Table 1.2). However, compensatory responses are highly variable and the ability to tolerate a reduction in cardiac output is greatly influenced by coexisting cardiovascular disease, autonomic neuropathy and medication such as beta-receptor antagonists.

Clinical features

The amount of volume loss chiefly determines the clinical picture. The presentation of hypovolaemic shock is that of a low cardiac output state. SNS activation causes vasoconstriction of cutaneous vessels and activation of sympathetic innervated sweat glands. Tachycardia, and pale, cold, clammy skin, or diaphoresis is clinically seen while capillary refill is reduced. Oliguria reflects a decreased renal perfusion pressure and insufficient compensatory mechanisms to minimise renal fluid losses. Similarly, cerebral hypoperfusion leads to agitation and later to coma. Respiratory compensation for the developing metabolic acidosis is evident as tachypnoea, often without a subjective feeling of shortness of breath.

Management

Managing a patient with shock requires a robust and organised team approach. The sequence of interventions is dictated by the presenting picture. As a general rule the aims of management are to maintain oxygenation, control bleeding and substitute circulating volume sufficiently to avoid significant cellular hypoxia, but without aiming for a normal blood pressure.

Resuscitation should be guided by clinical and laboratory makers of tissue perfusion (such as pH, lactate and base excess). Importantly, clinicians should remember that all of these markers share the disadvantage of being global indicators which show delayed normalisation during resuscitation. A trend towards improvement rather than full normalisation of these parameters is an appropriate short-term goal.

Although securing the airway and maintaining oxygenation is a priority in any critical condition, controlling the source of bleeding is the crucial first step in the management of haemorrhagic shock. This may have to be achieved by direct compression or rapid surgical intervention, occasionally prior to the restoration of circulating volume. Fluid resuscitation should, however, be commenced concurrently. Large bore intravenous access must be established rapidly and rapid infusing devices may be needed to keep up with losses. The source of bleeding may be external and obvious, but source identification may require investigations such as ultrasound scan, computed tomography (CT) or angiography.

In less severe bleeding or after the initial control of bleeding, at least partial restoration of circulating volume is the major management component. Aggressive restoration of circulating volume and mean arterial pressure before surgical treatment may worsen the outcome, possibly by promoting clot dissolution and rebleeding [21]. Clinicians must therefore find a balance between these complications and maintaining a DO_2I sufficient to avoid multiple organ failure.

Blood loss up to 20–30% of circulating volume may be replaced with balanced crystalloid or colloid solutions; beyond that, red cell transfusion is usually required. Whether crystalloids or colloids are superior for fluid resuscitation is still under debate. Crystalloids distribute in the extracellular space, with about 20% of the infused volume remaining in the circulation. This necessitates infusion of large volumes, with the potential for causing oedema and subsequent impaired oxygen and substrate diffusion into cells. Activation of neutrophils, which contribute to organ dysfunction, and dilution of plasma proteins are further disadvantages [22]. To avoid hyperchloraemic acidosis, balanced solutions such as Hartmann's should be used instead of normal saline.

Colloids expand the intravascular space more and for longer than crystalloids. If endothelial integrity becomes compromised, however, leakage into the interstitium may occur and worsen oedema. Colloids also affect clotting and impair renal function. Gelatins are currently considered to have the least detrimental effect on the kidneys and may be the colloid of choice. In analogy to the finding with crystalloids, solutions with a balanced electrolyte composition could be advantageous. The Advanced Trauma Life Support guidelines currently recommend crystalloids as the fluid of choice in haemorrhagic shock, but since the question is not clearly settled many clinicians continue to use a combination of colloids and crystalloids [23].

Severe bleeding is associated with consumption and dilution of clotting factors and platelets. Platelets and clotting factors (fresh frozen plasma, cryoprecipitate) are therefore commonly replaced. Other pro-coagulant agents, such as recombinant factor VIIa or prothrombin complex, have been successfully used in severe haemorrhage, but their effectiveness remains unconfirmed by randomised trials. Point of care testing is increasingly used and is in the authors' experience very helpful, giving accurate results within minutes.

Clotting products and platelets should ideally be administered after obtaining appropriate laboratory results (prothrombin time, PT; activated

partial thromboplastin time, APTT; fibrinogen levels, platelet count). Fresh frozen plasma (FFP) is usually administered if clotting times are more than 1.5 times normal, particularly if bleeding is ongoing. Fibrinogen levels should be checked and cryoprecipitate given if levels are less than 1.0 mg/dl. The threshold for platelet transfusion is less clearly defined. Platelet counts of less than 50 000 μ/l with ongoing bleeding may warrant substitution. In patients on antiplatelet medication higher thresholds may be appropriate.

Cardiogenic shock

In cardiogenic shock, primary cardiac dysfunction in the presence of an adequate circulating volume causes tissue hypoperfusion and hypoxia. Haemodynamic criteria for diagnosis include hypotension (systolic blood pressure < 90 mmHg), reduced cardiac index (cardiac output related to body surface area; CI < 2.2 l/min/m^2) and elevated pulmonary capillary wedge pressure (a reflection of left ventricular end-diastolic pressure; PCWP > 15 mmHg).

Myocardial infarction is the commonest cause. Other causes include myocarditis, end-stage cardiomyopathy, myocardial contusion after chest trauma and endocardial pathology (e.g. acute endocarditis or papillary muscle rupture causing acute regurgitant valvular defects).

Myocardial perfusion is critically dependent on the perfusion window, determined by perfusion *pressure* (diastolic pressure in proximal aorta minus ventricular wall pressure) and perfusion *time* (diastolic time). Myocardial relaxation (diastolic) and contractility (systolic) dysfunction due to ischaemia reduce myocardial compliance, and hence filling. As a consequence, stroke volume, cardiac output and proximal aortic blood pressure fall. Simultaneous increases in ventricular end-diastolic pressures increase wall tension. Furthermore, tachycardia reduces perfusion time. Together, these changes cause a further decrease in coronary perfusion and further aggravate the situation.

Compensatory mechanisms (SNS, RAAS) resulting in tachycardia, higher afterload and fluid retention increase myocardial oxygen demand at a time when supply is already significantly impaired. Arrhythmias and valvular dysfunction sometimes associated with ventricular dilatation often make a bad situation worse.

The clinical features and management options are discussed in detail in Chapters 13 and 14.

Obstructive shock

Mechanical obstruction of cardiac output can be caused by impaired ventricular filling due to cardiac tamponade, tension pneumothorax, pulmonary embolus or uncommonly haemothorax and ascites.

Cardiac tamponade occurs as a complication of acute myocardial infarction with rupture of the free ventricular wall, after cardiac surgery or following chest trauma. A relatively small but rapidly expanding accumulation of blood within the pericardium (less than 200 ml) impairs ventricular filling to such a degree that cardiac output is compromised. A slowly accumulating effusion can also eventually lead to significant filling

impairment, but much higher amounts of pericardial fluid are necessary as the pericardial sack has sufficient time to stretch.

Typical clinical features of tamponade are tachycardia, jugular venous distension, muffled heart sounds and pulsus paradoxus. Hypotension, largely resistant to fluid administration, is present. The diagnosis is usually made or confirmed by echocardiography. Drainage of the accumulated pericardial blood or fluid is the definitive treatment. Following cardiac surgery, anecdotal evidence suggests that oliguria and a worsening base deficit in the context of rising central venous pressures should prompt urgent echocardiography to exclude tamponade.

Tension pneumothorax presents with a very similar picture, but absent breath sounds and hyperresonance of the affected side suggest pneumothorax. It develops when air entering the pleural space cannot escape due to a flap-valve mechanism. Intrapleural accumulation of air leads to a rise in intrathoracic pressure, collapse of the affected lung, and mediastinal shift to the opposite side, which severely reduces cardiac filling and output. Immediate release of the intrathoracic pressure by placement of a large bore needle in the second intercostal space in the mid-clavicular line on the affected side is the appropriate treatment.

Obstruction of the pulmonary vasculature by *pulmonary emboli* (thrombus or air) may cause a clinical picture similar to that described above. Large pulmonary emboli lead to a sudden increase in right ventricular afterload and right ventricular failure. It is not clear whether mechanical outflow obstruction alone causes this picture of acute pulmonary hypertension and subsequent circulatory failure; the release of vasoactive mediators has also been implicated [24]. The clinical features and management options of thromboembolic disease are discussed in detail in Chapter 21.

1.3 High output states

Sepsis

Sepsis is an overwhelming response to infection characterised by systemic inflammation and widespread tissue injury [25, 26]. Clinical diagnosis requires evidence of infection plus, traditionally, at least two signs of systemic inflammatory response syndrome (SIRS). However, expanded diagnostic criteria for SIRS in response to infection were recently proposed (Table 1.3) [27]. Severe sepsis is defined as sepsis with new onset organ failure. Septic shock represents a state of persistent arterial hypotension despite adequate volume resuscitation, and which is unexplained by other causes.

Epidemiology

Sepsis occurs in approximately 25% of ICU patients, and bacteraemic sepsis in 10% [28]. Furthermore, approximately 27% of patients admitted to ICU in the United Kingdom meet the criteria for severe sepsis within 24 hours following ICU admission [29]. Mortality rates range between 19 and 96%

Table 1.3 Diagnostic criteria for sepsis and severe sepsis.

Infection	
Documented or suspected *and* some of the signs of systemic inflammation	
Signs of systemic inflammation	
General parameters	Fever or hypothermia; heart rate; tachypnoea; altered mental state; significant oedema or positive fluid balance; hyperglycaemia
Inflammatory parameters	Leukocytosis or leukopaenia; increase in immature white cell bands; elevated CRP or procalcitonin
Haemodynamic parameters	Arterial hypotension; elevated mixed venous oxygen saturation or cardiac index; arterial hypoxaemia; acute oliguria; increased creatinine; coagulation abnormalities; ileus; thrombocytopenia; hyperbilirubinaemia
Tissue perfusion parameters	Hyperlactataemia; decreased capillary refill or mottling
Organ dysfunction and failure	
Organ failure can be diagnosed by using the MODS or SOFA score [63, 64].	
Septic shock	
A state characterised by persistent arterial hypotension despite adequate volume resuscitation, and unexplained by other causes.	
Hypotension is defined by	systolic arterial pressure below 90 mmHg, or mean arterial pressure lower than 60 mmHg, or reduction in systolic blood pressure of more than 40 mmHg from baseline

Adapted from Levy et al. [27].
MODS, multiple organ dysfunction score; SOFA, sequential organ failure assessment.

[28]. Note, patients still categorised as having severe sepsis at the end of the 30-day follow-up period had a 96% mortality rate [30]. In the same study, progression to severe sepsis and septic shock in patients with infection/sepsis occurred in 10.9 and 13.1%, respectively.

Pathophysiology

The receptors of the innate immune system recognise pathogen-associated molecular patterns. Pattern recognition receptors (PRRs) (Table 1.4) have a number of functions, including opsonisation, activation of complement, activation of the coagulation cascades, phagocytosis, activation of proinflammatory signal pathways, and the induction of apoptosis. Cells bearing PRRs – macrophages, dendritic cells, mast cells, neutrophils, eosinophils, natural killer (NK) cells – are activated by inflammation and rapidly differentiate into short-lived effector cells to eradicate the infection.

Toll-like receptors (TLRs) are cell surface-based PRRs. TLRs are potent initiators of the host response to infection and have been termed the 'light and the fire' of septic shock [31]. TLRs have a wide range of specificity, being activated by bacterial, fungal and yeast proteins. For example, host cell activation following exposure to lipopolysaccharide (LPS), originating from Gram-negative bacteria, is dependent on LPS-binding protein (LBP)

Table 1.4 Pattern recognition receptors (PRR).

PRRs in the extracellular compartment
- Mannan-binding lection (MBL)
- C-reactive protein (CRP)
- Serum amyloid protein (SAP)

PRRs based on cell surfaces
- Toll-like receptors (TLRs)
- Peptidoglycan-recognition proteins (PGRPs)
- Triggering receptor expressed on myeloid cells (TREM-1)
- Myeloid DAP12-associating lectin (MDL-1)
- Macrophage mannose receptor (MMR)
- Macrophage scavenging receptor (MSR)

PRRs in the intracellular compartment
- Protein kinase (PKR)
- Nucleotide-binding oligomerisation domain (NOD-1, NOD-2)
- 2′–5′-oligoadenylate synthase (OAS)/ RNaseL pathway (OAS/RNaseL)

and the opsonic receptor CD14. The LPS/LBP-CD14 complex binds TLR4, leading to the activation of inflammatory signalling.

Clinical picture

Patients with septic shock by definition have an infection, show signs of systemic inflammation, and will be hypotensive with concomitant symptoms and signs of inadequate tissue perfusion. Patients may have fever or be hypothermic. Heart and respiratory rates are elevated. Further signs of SIRS, such as leukocytosis or leukopaenia, hyperglycaemia and peripheral oedema, are often present. CRP and procalcitonin levels are usually increased. Unless the patient is also hypovolaemic, the typical picture is one of a high cardiac output and reduced systemic vascular resistance.

Systolic blood pressures below 90 mmHg or mean arterial pressures below 70 mmHg in the absence of vasopressors are commonly seen. Signs of inadequate tissue perfusion, such as hyperlactataemia and decreased capillary refill time or mottled skin, are also often present. Mixed or central venous oxygen saturation is often elevated due to reduced peripheral extraction. However, low saturations imply an inadequate cardiac output for the existing metabolic demand. This finding is especially important when associated with a raised lactate level since it highlights potentially correctable cellular hypoxia.

Due to the combination of a dysregulated circulation (at systemic and microcirculatory level) and the inflammatory response, the function of other organs is often disturbed and arterial hypoxaemia, acute oliguria and an increased creatinine, hyperbilirubinaemia, and alterations in mental state or coma are frequently encountered.

Management

Critical care and infectious disease experts representing 11 international organisations recently developed management guidelines for severe sepsis

and septic shock [32]. These guidelines, presented in the form of a Resuscitation Bundle and a Management Bundle, integrate evidence-based interventions with process-of-care measures (Table 1.4). The haemodynamic management of septic shock is referred to here but is discussed in detail in Chapter 12.

Other high output shock states

Neurogenic shock resulting from spinal cord damage at or above the upper thoracic level is commonly seen after trauma. The central nervous system injury causes autonomic dysfunction. Disruption of the sympathetic innervation leads to vasodilatation and bradycardia. It is characterised by severe hypotension, slow or normal heart rate and warm skin, indicating the inability to respond to the reduced systemic vascular resistance, with vasoconstriction and an increased heart rate. The relative hypovolaemia is treated with cautious fluid resuscitation, taking into account that coexisting injuries with blood loss may aggravate the picture and warrant a more aggressive approach. Vasoconstrictors are indicated when hypotension persists despite euvolaemia. Bradycardia is treated with anticholinergic agents.

Anaphylactic shock occurs when a sensitised individual with pre-existing IgE antibodies is exposed to an antigen. The binding of the antigen to its corresponding IgE antibody on the surface of mast cells causes a type I immune response with mast cell degranulation and release of vasoactive substances such as histamine.

The clinical picture reflects the resulting vasodilatation, increased vascular permeability, bronchospasm and in severe cases myocardial depression: urticaria or generalised erythema, breathing difficulties and hypotension or cardiovascular collapse characterise the condition. Treatment consists of stopping exposure to the antigen, ensuring oxygenation and use of adrenaline as primary therapy, followed by fluid resuscitation. Corticosteroids and antihistamine agents are also administered [33].

1.4 The pathway to organ failure

Shock and resuscitation produce inflammation. Irrespective of the initiating trigger, similar inflammatory pathways are activated which leads to similar downstream effects on organ function (Figure 1.1).

Intracellular signal pathways and inflammatory gene expression

Signals from the extracellular space are transmitted through the cell membrane and subsequently propagated via a number of serial or parallel proteins serving as transducers or regulators. The main pathways are the protein kinase system activating the transcription factor nuclear factor-κB (NF-κB), and three mitogen-activated protein kinase (MAPK) cascades which lead to the activation of other transcription factors including the activator protein-1 (AP-1) family [34].

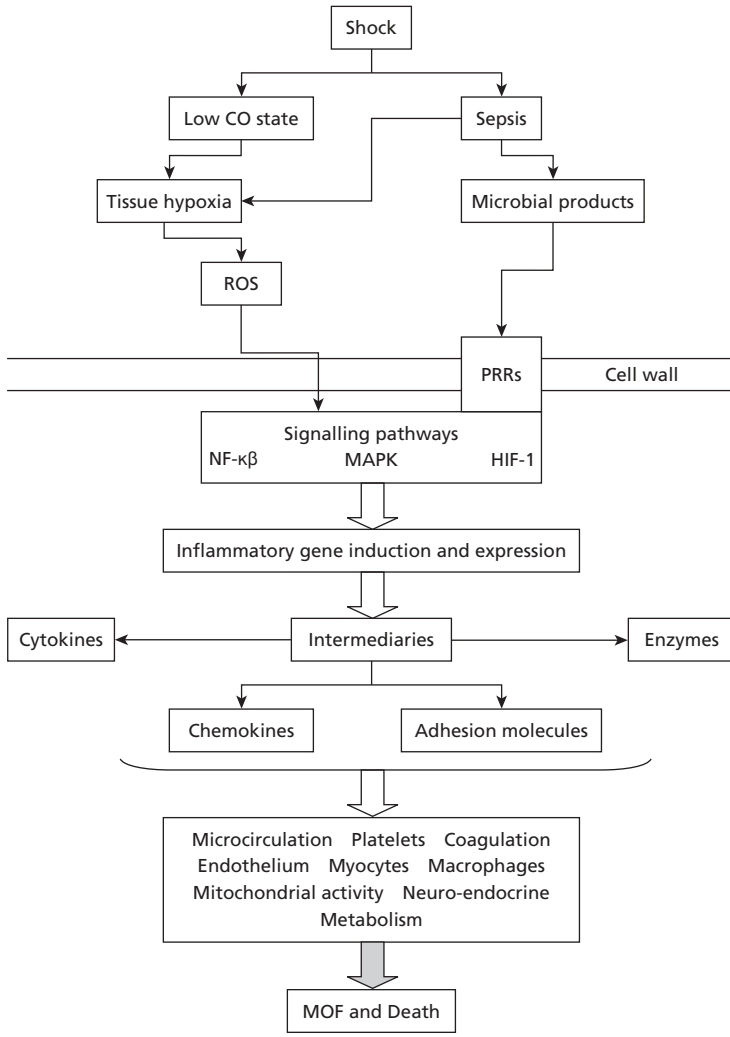

Figure 1.1 The pathways from shock to organ failure and death.

Effects of gene induction and the role of intermediaries

Gene induction and expression generate a variety of inflammatory mediators, which include cytokines, chemokines, adhesion molecules and enzymes.

Cytokines

Numerous cytokines are produced with pro- and anti-inflammatory actions (Table 1.5). The primary proinflammatory cytokines are interleukin (IL)-1 and tissue necrosis factor (TNF)-α. Both further activate inflammatory signalling pathways, leading to an amplification of the response. TNF-α additionally activates apoptosis via a 'death' pathway.

Table 1.5 Main actions and effects of inflammatory cytokines [50, 62, 65–67].

Pro-inflammatory cytokines	Anti-inflammatory cytokines
TNF-α ● regulates cell proliferation and apoptosis ● recruits and activate neutrophils, macrophages and lymphocytes **IL-1β** ● similar biological effects to TNF-α but produces less severe response ● causes hypotension, increased cardiac output, leuko- and thrombocytopenia, pulmonary oedema and lactic acidosis **IL-6** ● stimulates release of acute-phase proteins (e.g. CRP, SAA) by hepatocytes **IL-12** ● hepato- and splenomegaly, leukopaenia, anaemia, myelodepression, pulmonary oedema ● interstitial macrophage infiltration **IFN-γ** ● tachycardia, myalgia, malaise and leukopaenia ● enhances mortality and levels of circulating TNF-α induced by LPS **LIF/OSM** ● LIF: activates other cytokines ● OSM: enhances expression of chemokines **MIF** ● enhances lethality of LPS ● counter-regulates the inhibitory effects of glucocorticoids on cytokine production ● activates lymphocytes and stimulates antibody production ● causes the release of IL-2 and IFN-γ ● increases the production of pro-inflammatory cytokines and chemokines by macrophages **HMGB1** ● phagocytic cell activation ● evokes intracellular signalling with increased expression of RAGE, adhesion molecules, TNF-α, chemokines, PAI-1 and tPA ● increases activity of iNOS in enterocytes **G-CSF** ● proliferation, differentiation and activation of lymphocytes	**IL-4** ● reduces LPS-induced cytokine production by monocytes and macrophages **IL-10** ● inhibits release of TNF-α, IL-1 and IL-6 by endotoxin-stimulated macrophages **IL-13** ● downregulates monocyte and macrophage function **IL-6** ● inhibits release of IL-1 and TNF-α **TGF-β** ● deactivates monocytes and macrophages ● decreases expression of MHC class II ● inhibits synthesis of TNF-α and IL-1 **IL-1ra** ● competitive inhibitor of IL-1 receptor **Soluble receptors** ● TNFR: binds TNF-α to prevent ligand–receptor interaction ● IL-6R: prolongs half-life of IL-6

TNF-α, tissue necrosis factor; IL, interleukin; CRP, C-reactive protein; SAA, serum amyloid A; IFN, interferon; LIF, leukaemia inhibitory factor; OSM, oncostatin M; MIF, macrophage migration factor; LPS, lipopolysaccharide; HMGB1, high mobility group B1; PAI, platelet activator inhibitor; tPA, tissue plasminogen activator; G-CSF, granulocyte-colony stimulating factor; TGF, transforming growth factor; TNF-α/IL-ra, interleukin receptor antagonist; RAGE, receptor of advanced glycation end-products.

Chemokines

Chemokines affect leukocyte function and trafficking. IL-8, a major neutrophil chemotactic factor, is expressed under the influence of TNF-α and IL-1. Its actions include the proliferation, differentiation and activation of leukocytes. RANTES (regulated upon activation, normal T-cells

expressed and secreted) are mainly produced by activated T-cells and are stimulated by IL-1 and TNF-α. RANTES recruits and activates monocytes, lymphocytes and eosinophils. Lastly, monocyte-chemoattractant protein (MCP)-1 contributes to the recruitment of inflammatory macrophages.

Adhesion molecules

Activated endothelial and epithelial cells express adhesion receptors which control leukocyte adhesion and trafficking at the site of inflammation. Selectins (P-, E- and L-selectin) mediate leukocyte rolling along the vessel wall, simultaneously sensing the presence of activating factors on endothelial cell surface (EC) surface. Stimulated neutrophils express beta-2 integrins, which mediate firm adhesion to ECs by binding to intercellular adhesion molecules (ICAM-1, 2) and vascular cell adhesion molecule (VCAM-1). These firm associations with neutrophils precede their transmigration through the EC layer into inflammed tissues. Soluble forms of various adhesion molecules, such as the selectins, are released into plasma during an inflammatory response and therefore have been used as markers of endothelial activation.

Enzymes

The two main enzyme systems activated as part of the inflammatory process involve eiconasoids and nitric oxide synthase [35–37].

1. *Eiconasoids*: IL-1 and TNF-α stimulate membrane lipid metabolism by phospholipase A to form arachidonic acid and lyso-platelet activating factor (PAF). Arachidonic acid is subsequently metabolised via the cyclo-oxygenase and lipoxygenase pathways to form prostaglandins and leukotrienes, respectively, while lyso-PAF is transformed by acetyltransferase to platelet activating factor (PAF). The effects of eiconasoid induction are multiple (Table 1.6).
2. *Nitric oxide synthase*: Nitric oxide (NO) is physiologically produced by the constitutive enzyme endothelial NO synthase (eNOS) in response to local blood flow. NO regulates vasomotor tone and microvascular blood flow, and inhibits leukocyte and platelet adhesion.

   During inflammation, expression of an inducible form of NOS (iNOS) is increased predominantly in vascular smooth muscle. NO production by iNOS is unregulated and an order of magnitude greater than that of eNOS. The subsequent overproduction of NO is associated with a decrease in blood pressure, impaired vascular reactivity, abnormal RBC deformability and reduced oxygen consumption. Although inhibiting NO during sepsis increases blood pressure, it also reduces microvascular blood flow and exacerbates abnormal oxygen transport.

Effects of activation of the pro-inflammatory system

The expression of cytokines, chemokines, enzymes and adhesion molecules sets the scene for the development of organ failure by affecting the microcirculation, endothelium, coagulation system, mitochondrial respiration, white blood cells, neuro-endocrine system, hepatocytes and the complement system.

Table 1.6 Clinical effects of eiconasoids [35, 67].

Prostaglandins
- Smooth muscle contraction
- Mucosal oedema
- Increased vascular permeability
- Cellular infiltration
- Mucus secretion

Prostaglandin E2
- Inhibits TNF-α secretion
- Enhances IL-6 secretion

Thomboxane A2
- Stimulates TNF-α and IL-1 secretion

Leukotrienes
- Increased vascular permeability
- Vasodilation
- Smooth muscle contraction

Platelet activating factor
- Activates and aggregates platelets
- Stimulates release of vasoactive mediators

Microcirculation

Inflammation induces changes in microvascular geometry, haemodynamics and oxygen transport [36]. Increased microvascular stopped-flow (the stopping of flow through capillaries seen during sepsis) results in a maldistribution of blood flow within the microcirculation and a consequent loss of matching between local oxygen demand and delivery. Increased oxygen flow heterogeneity possibly further impairs oxygen extraction.

Endothelium

The pro-inflammatory response causes endothelial cell (EC) injury, activation and dysfunction [37]. The physical disruption associated with *endothelial injury* allows inflammatory fluid and cells to shift from the blood into the interstitial space [38]. ECs also interfere directly with the initiation and regulation of fibrin formation and removal during severe infection, and may also play a prominent role in all three major pathogenic pathways associated with coagulopathy in sepsis (see below).

Endothelial dysfunction refers to decreased endothelial-dependent vascular relaxation and decreased expression or activity of eNOS. In healthy volunteers, even brief exposure to endotoxin or certain cytokines impairs endothelium-dependent relaxation for many days [39, 40]. This effect has been termed 'endothelial stunning'. Furthermore, failure of an EC's ability to sense changes in its environment may further contribute to a failure in matching oxygen supply to demand [41].

Platelets and the coagulation system

Nearly all patients with shock have coagulation abnormalities ranging from a small decrease in the platelet count and a subclinical prolongation of

global clotting times, to fulminant disseminated intravascular coagulation (DIC) [42]. Under normal circumstances, haemostasis is a balance between opposing systems. The prothrombotic system attempts to form thrombin and a fibrin clot. Tissue factor (TF) is the main activator of coagulation. On the other hand, thrombin generation is limited by antithrombin (AT), the protein C system and tissue factor pathway inhibitor (TFPI), while ECs express various membrane-associated components with anticoagulant properties.

Pro-inflammatory mediators induce TF expression on the surface of activated mononuclear cells and vascular ECs, while the antithrombotic and fibrinolytic regulatory systems become defective due to endothelial dysfunction. This activation of coagulation and impaired fibrinolysis is associated with fibrin deposition and tissue ischaemia and necrosis, and in critically ill patients with an increased risk for death [43]. Conversely, inhibition of coagulation is associated with prevention of organ dysfunction [44].

Monocytes/macrophages

Macrophages are possibly the most important source of cytokines and are responsible for the primary response to microorganisms in most tissues [45]. Macrophages remove endotoxin and bacteria from the lymph and blood circulation. Macrophage activation also induces the production of intracellular O_2 radicals, hydrogen peroxide, NO and other microbicidal products, thus killing phagocytosed organisms. However, these products can cause extensive tissue damage.

Neutrophils

Neutrophil activation by opsonins and soluble stimuli (cytokines and chemokines) is crucial for host defence against bacterial or fungal infection. They are the principal phagocytes delivered to inflammatory sites. The neutrophil's destructive capacity leads to host injury in numerous disease states [46, 47].

Neutrophil-mediated tissue injury is dependent upon a balance of competing protective and destructive pathways. Host protection is normally achieved through a number of mechanisms. Antioxidants and powerful protease inhibitors within the extracellular matrix inactivate destructive enzymes and oxidants. These anti-proteases are in return inactivated by hypochlorous acid produced by neutrophil myeloperoxidase. Secondly, neutrophils contain antioxidants to protect themselves and surrounding tissue. Lastly, neutrophils are cleared without releasing their toxic contents as they would after necrotic cell death, through the process of apoptosis and removal by tissue macrophages. While TNF-α increases neutrophil apoptosis rates in healthy human controls, numerous inflammatory agents inhibit neutrophil apoptosis in disease states [48, 49].

Mitochondrial activity

Although mitochondrial respiration increases during the early phase of acute critical illness, it invariably falls after 12–16 hours [50]. This decrease

appears to be an acquired intrinsic defect in cellular respiration, a phenomenon termed 'cytopathic hypoxia' [51].

Although the exact mechanism for these changes remains unclear, inhibition of cytochrome *a, a3* and one or more mitochondrial respiratory complexes may play a role. Furthermore, recent data have highlighted the importance of nicotinamide adenine dinucleotide (NAD+/NADH) depletion through the activation of the enzyme poly(ADP-ribose) polymerase-1 (PARP) [52]. PARP is a nuclear enzyme activated in response to DNA injury. Through a number of mechanisms, PARP causes acute cell dysfunction and necrotic cell death. In addition, PARP activation plays an important role in the up-regulation of inflammatory cascades through interaction with several transcription factors.

Metabolism

Profound metabolic alterations, including hypermetabolism, enhanced energy expenditure and insulin resistance, occur during shock and critical illness [53]. Alterations in carbohydrate metabolism and muscle tissue protein catabolism follow. These changes are exacerbated by cytokine release. During sepsis, glycaemic control is further disturbed due to insulin resistance and the loss of feedback control [54]. Although low cardiac output states are associated with hyperlactataemia due to tissue hypoxia, the elevated lactate levels seen in stable septic patients appear to be mainly a result of impaired clearance [55].

Neuro-endocrine system

The acute-phase response is associated with the release of stress hormones, including catecholamines, vasopressin, adrenocorticotropic hormone (and cortisol), glucagons and growth hormone. In this way an effective circulation is maintained and energy substrate levels are increased.

A number of endocrine changes are seen during critical illness and shock [56]. These include insulin resistance, reductions in vasopressin concentration, the sick euthyroid syndrome, reduced adrenal responsiveness and inhibition of anabolism. The underlying mechanisms for these changes are unclear, but increased secretions of stress hormones, cytokines and NO have been implicated [54, 57, 58]. Importantly, the magnitude of these changes has prognostic implications [59, 60].

Hormones, reactive nitrogen and oxygen species also affect mitochondrial function. Since mitochondria have receptors for glucocorticoids and thyroid hormones, increased thyroid hormone levels increase the maximum rate of ATP synthesis while reducing production efficiency [61]. All these changes combine to reduce energy production. The fall in ATP supply exerts a further negative effect on metabolic pathways.

Complement system

The complement system supports both innate and humoral immunity by depositing complement components on immune targets, and by

promoting inflammation.[62] Activation of this enzyme cascade results in a rapid amplification of the system, causing enhanced production of inflammatory mediators, increased recruitment of leukocytes to sites of infection, enhanced neutrophil–EC interaction, and increased local blood flow and capillary permeability.

1.5 Conclusion

Cell stress, in the form of inadequate tissue perfusion during low output states or direct contact with microorganisms, activates signalling pathways leading to induction and expression of inflammatory mediators. Endothelial abnormalities and associated dysregulated coagulation, coupled with the local toxic effects of immune cell activation contribute to failure of oxygen delivery and consumption at the level of the microcirculation. Meanwhile, mitochondrial dysfunction results in cellular hypoxia and decreased oxygen consumption. The end result is catastrophic destabilisation of organ function, often leading to death.

Case study

A 67-year-old female smoker presented to the emergency department with community-acquired pneumonia. She was clammy, confused and oliguric. Arterial blood gases, taken while receiving oxygen at high flow via a face mask, showed severe hypoxia (p_aO_2 6.8 kPa, p_aCO_2 4.5 kPa) and lactic acidosis (pH 7.12, lactate 7.5 mmol/l). Her mean arterial blood pressure (MAP) was 45 mmHg, white cell count 28×10^9/l and C-reactive protein level 452 mg/l.

Appropriate antibiotic therapy was administered, invasive ventilation initiated, and a central venous catheter inserted. The cardiac index and central venous oxygen saturations ($S_{cv}O_2$) at this stage were 1.8 l/min/m^2 and 52%, respectively. Rapid volume resuscitation increased her cardiac index to 2.5 l/min/m^2 and $S_{cv}O_2$ to 71%. The serum lactate decreased to 2.2 mmol/l. Despite these improvements her MAP remained low and vasopressor therapy (noradrenaline) was started, causing her MAP to increase to 65–70 mmHg.

Over the next 24 hours she was mechanically ventilated using a protective ventilatory strategy, her blood glucose level was normalised, and a low-dose hydrocortisone infusion was started pending the results of an adrenocorticotrophic hormone (ACTH) test. Continuous renal replacement therapy was also started.

Over the next 2 weeks she gradually improved. A percutaneous tracheostomy was performed on day 4 and antibiotic coverage was stopped on day 5. Her oxygenation improved and renal function recovered. On day 11 she was liberated from mechanical ventilation and was finally discharged from the ICU after 15 days.

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