

# Shock

Kenwyn James

Max Jonas

## Abstract

Shock is a frequently misused and misunderstood term. When used to describe the process of tissue hypoperfusion, leading to cellular hypoxia and organ failure, it describes a medical emergency with a high mortality. Early recognition of the condition and prompt, appropriate management is essential to increase survival. This includes timely use of appropriate monitoring including clinical signs, biochemical tests, and invasive pressure and flow monitoring. In carefully selected patients, measurement and manipulation of oxygen delivery has been shown to improve outcome. Rapid identification of the underlying cause and definitive treatment are needed to reduce morbidity and mortality. In the clinical scenario of septic shock, early antibiotics are vital. Every hour's delay in the administration of appropriate antibiotics is associated with approximately an 8% decrease in survival.

**Keywords** antibiotics; hypoperfusion; hypovolaemia; oxygen delivery; septic shock; shock

## Definition

Shock is a clinical state that occurs when a mismatch arises between oxygen supply and metabolic demand, resulting in cellular hypoxia. If not recognized, and treated appropriately, shock will ultimately progress to organ failure. In health, the perfusion of individual tissues is closely matched to their metabolic demands. This is regulated by local and systemic factors.

The aetiology of shock is diverse but the causes can be broadly divided into those resulting in a decreased cardiac output and those causing a drop in systemic vascular resistance (Table 1). There is often overlap between the different types of shock and more than one type can coexist.

## Pathophysiology

In most cases of shock, cellular hypoxia and impaired cellular metabolism occurs as a result of either inadequate oxygen delivery or an inability, at tissue level, to use what oxygen is

**Kenwyn James FRCA MRCP BA (Hons)** is a Specialist Registrar in Anaesthesia and Critical Care at Southampton General Hospital, Southampton, Hampshire, UK. Competing interests: none declared.

**Max Jonas FRCA** is a Consultant and Honorary Senior Lecturer in Critical Care at Southampton General Hospital, Southampton, Hampshire, UK. Competing interests: none declared.

## Aetiology of shock

### Reduced cardiac output

#### Hypovolaemic shock

Reduction in circulating volume causing a reduction in venous return and consequential reduction in cardiac output

- haemorrhage
- dehydration

#### Obstructive shock

Mechanical obstruction to normal venous return or cardiac output

- massive pulmonary embolism
- tension pneumothorax
- cardiac tamponade

#### Cardiogenic shock

Cardiac pump failure

- post-myocardial infarction
- cardiomyopathy
- myocarditis (including septic)
- drugs, e.g.  $\beta$ -blockers/calcium channel blockers

### Low peripheral resistance

#### Distributive shock

Peripheral vasodilatation – may be associated with inadequate increase in cardiac output

- septic shock
- anaphylaxis
- neurogenic

#### Endocrine shock

- Addisonian crisis
- hyper/hypothyroid crisis

**Table 1**

delivered. By definition oxygen delivery ( $DO_2$ ) is the product of cardiac output (CO) and arterial oxygen content ( $CaO_2$ ),

$$DO_2 = CO \times CaO_2$$

and CO is the product of heart rate (HR) and stroke volume (SV).  $CaO_2$  approximates to the haemoglobin concentration times the arterial oxygen saturation ( $SaO_2$ )  $\times 1.34$  (the number ml of oxygen carried by 1 g of fully saturated haemoglobin *in vivo*).

$$CO = HR \times SV$$

$$CaO_2 = [Hb] \times SaO_2 \times 1.34$$

In the early stages of shock due to hypoperfusion, tissues compensate for the decrease in oxygen delivery by extracting a greater proportion of oxygen. Once oxygen delivery drops below a critical point, this compensation is inadequate and oxygen extraction decreases. Anaerobic cellular metabolism occurs with depletion of adenosine triphosphate and increased production of lactic acid.

Septic shock is often associated with increased  $DO_2$  and increased oxygen extraction, although inadequate for the tissue's metabolic needs. The resulting lactic acidosis is due to anaerobic metabolism and is caused by an inability of the mitochondria to use oxygen delivered normally, with additional problems in red cell oxygen transfer in the microcirculation.

### Cardiac output

CO represents the volume of blood ejected into the aorta by the left ventricle per minute, i.e. the stroke volume multiplied by the heart rate per minute. Stroke volume itself is determined by the relationship between preload, contractility and afterload. The overall cardiac performance is also reliant on cardiac valve function and the structural integrity of the heart.

Estimation of CO without formal measurement is virtually impossible and can lead to inappropriate treatment. Frequently blood pressure is incorrectly used as a surrogate for cardiac output. It should be stressed that the relationship between mean arterial pressure (MAP) and cardiac output is indirect and dependent on the systemic vascular resistance (SVR), which is deceptively difficult to estimate clinically.

$$\text{MAP} = \text{CO} \times \text{SVR}$$

Without knowing the SVR, the patient's cardiac output and tissue perfusion cannot be assessed from knowledge of their blood pressure. A patient with a low MAP could be in cardiogenic shock, with a low CO and high SVR, or in septic shock, with vasodilatation and a very high CO. Recent studies have clearly shown that clinical estimates of cardiac output result in therapies that are changed 50% of the time when the CO is subsequently measured.

### Reduced venous return

Reduced venous return usually follows two clinical scenarios. The simplest cause of a reduction in venous return is a reduction in circulating blood volume, which represents hypovolaemic shock. The second type results from impairment of cardiovascular performance because of mechanical impairment to blood flow, e.g. major pulmonary embolism, pericardial effusion with tamponade.

The body's normal response to hypovolaemia is complex, and initial compensation mechanisms include an increase in heart rate and systemic vascular resistance. Ultimately, if these acute physiological mechanisms fail, falling intravascular volume will result in hypotension.

Venous return can also be mechanically compromised, as in a patient with a massive pulmonary embolism. Significantly sized thrombi cause obstruction to pulmonary blood flow and reduce left-sided filling of the heart, which results in a falling CO.

### Myocardial performance

Cardiogenic shock is due to an inability of the heart to perform as an efficient pump despite an adequate preload. This is commonly seen following myocardial infarction and is generally associated with a loss of more than 40% of the left ventricular myocardium. Other causes of cardiogenic shock include acute structural damage (e.g. to valves, valvular support, free wall or ventricular septum), myocarditis and sustained dysrhythmias. Sepsis and drugs, for example  $\beta$ -blockers, can also cause myocardial depression.

### Low peripheral resistance states

#### Distributive shock

The physiology associated with distributive shock is varied and unpredictable. Anaphylactic shock is an immune-mediated

profound vasodilatation through the release of histamine and other vasoactive mediators from mast cells and basophils. This produces a relative hypovolaemia because of increased venous capacitance, with the same blood volume now occupying a greater vascular space. In addition, vascular permeability changes cause capillary leakage with plasma loss through extravasation, causing additional reductions in circulating volume and also leading to an absolute hypovolaemia. Paradoxically, a frequently missed cause of anaphylaxis are the colloid solutions, used in resuscitation of the circulatory compromise!

Spinal, or neurogenic, shock is uncommon and results from damage to the spinal cord at a cervical or high thoracic level. Damage to the sympathetic outflow tracts causes loss of peripheral vasoconstriction, resulting in vasodilatation. Compensatory cardiac responses are obtunded as they, too, are sympathetically mediated.

### Septic shock

Septic shock is the extreme end of the spectrum of a disease process associated with infection (Table 2). There may be a genetic predisposition to the development of septic shock and current evidence suggests that at least three mechanisms contribute to the vasodilatation and a resistance to the effects of vasoactive drugs:

- vasopressin deficiency
- activation of ATP-sensitive potassium channels (KATP)
- activation of the inducible form of nitric oxide synthase enzyme.

**Vasopressin** is a posterior pituitary hormone released in response to increased plasma osmolality or decreased intravascular volume.

### Systemic inflammatory response syndrome (SIRS)

**A clinical response arising from a non-specific insult consisting of two or more of the following:**

- temperature  $>38^\circ\text{C}$  or  $<36^\circ\text{C}$
- heart rate  $>90$  beats/min
- respiratory rate  $>20$  breaths/min or  $\text{PaCO}_2 <4.3$  kPa
- white cell count  $>12 \times 10^9/\text{litre}$ ,  $<4 \times 10^9/\text{litre}$  or  $>10\%$  immature forms on peripheral blood film

#### Sepsis

- SIRS plus an infection

#### Severe sepsis

- sepsis plus evidence of organ dysfunction, hypoperfusion or hypotension

#### Septic shock

- sepsis with persistent hypotension despite adequate fluid resuscitation

#### Hypotension

- systolic blood pressure  $<90$  mmHg or a reduction of  $>40$  mmHg from baseline in the absence of other causes of shock, i.e. cardiogenic

**Table 2**

It increases renal reabsorption of water, and under normal conditions has a minor role in the maintenance of blood pressure. High plasma concentrations occur in hypotension, probably through a baroreceptor reflex, and physiologically are considered pivotal in the maintenance of blood pressure in the initial phase of shock. Plasma vasopressin levels subsequently decline, secondary to depletion of the pituitary neurohypophyseal stores.

**ATP-sensitive potassium channels** are implicated in the vasodilatory response of vascular smooth muscle to metabolically produced substances such as histamine and autotoxins. KATP channel opening allows an efflux of potassium ions and results in membrane hyperpolarization and reduced calcium ion movement into the cell. Under resting conditions, the KATP channels are closed but altered tissue metabolism or hypoxia leads to channels activation, causing vasodilatation and increased local blood flow. KATP channels are known to be activated in sepsis, augmenting the generalized vasodilatation frequently found.

**Nitric oxide** is a vasodilator produced in vascular endothelium. Its production is controlled by a group of enzymes called nitric oxide synthases. In sepsis, there is an increased expression of the inducible form of nitric oxide synthase (NOS) due to circulating cytokines. Increased NOS activity results in increased levels of nitric oxide, causing vascular smooth muscle relaxation and vasodilatation.

It is also recognized that in sepsis there is depression of myocardial function, which is thought to be due to circulating factors which impair the ability of the heart to compensate for the associated vasodilatation.

## Management of shock

### Diagnosis

It is important to identify the presence of shock early to allow prompt resuscitation and definitive treatment of the precipitating cause(s) (Table 1).

**Clinical history:** a clear history from the patient or any other available source can be essential for identifying the cause of shock. In some cases the cause is clear; in others it may be more difficult to establish. For instance, following trauma a hypotensive patient may be shocked because of massive blood loss (hypovolaemic), tension pneumothorax or cardiac tamponade (obstructive), spinal cord injury (neurogenic) or a drug reaction (anaphylactic).

**Clinical examination:** examination of the patient in conjunction with the history should help to clarify the cause of shock. Clinical examination is also invaluable in assessing the severity of shock and the effects on end organs. The shocked patient is often tachycardic, tachypnoeic, confused and oliguric. Blood pressure may be normal. Peripheries may be cold or warm depending on whether the cardiac output is increased or not. A systematic approach is useful to avoid missing relevant signs.

**Laboratory tests:** the most useful blood test for identifying shock is a blood gas, preferably arterial. The results on a standard blood gas machine, including pH, base excess and lactate, give considerable information about the metabolic status of the patient. A full set of blood tests, including full blood count, electrolytes,

glucose, renal function, liver function tests, clotting screen, group and save/crossmatch, inflammatory markers (e.g. C-reactive protein, procalcitonin, interleukin 6) and blood cultures should be obtained. These can provide indicators of the possible cause of shock and the presence of any organ dysfunction.

**Other investigations:** an ECG and echocardiogram are mandatory, especially if a cardiogenic cause for shock is considered or tamponade is suspected. In massive pulmonary embolism, echocardiography will reveal signs of acute right heart failure and rarely visual confirmation of thrombi. Radiological investigations depend on the history and examination. Plain radiographs alone may sometimes suffice, although CT scanning is an essential investigation in the assessment of chest and abdominal trauma, and can confirm intra-abdominal pathology such as bowel perforation. Ultrasound scanning may be useful to image the abdominal cavity, for instance in ruptured abdominal aortic aneurysm with associated hypovolaemic haemorrhagic shock.

### Monitoring of shock

A patient with suspected shock will need careful monitoring of vital signs (heart rate, respiratory rate and MAP) and indices of organ perfusion (conscious level, urine output and biochemical markers). These are often incorporated in physiological scoring systems such as the Early Warning Scoring System (EWS) or Modified Early Warning Scoring Systems (MEWS).

The level and invasiveness of monitoring will depend on the severity of the shock and the response to early treatment. A minimum level of monitoring should include continuous pulse oximetry and ECG monitoring, and intermittent non-invasive blood pressure monitoring. It should be also noted that automated non-invasive blood pressure machines are inaccurate in shock, and manual cuffs and brachial auscultation should be used. In severe illness, patients who fail to respond to initial treatment or who are unstable should have more invasive monitoring, such as arterial/central venous pressure and cardiac output monitoring. These should be considered essential if the patient receives significant vasopressor or inotropic support.

A lactate level of greater than 4 mmol/litre is usually suggestive of organ hypoperfusion and tissue hypoxia, even in the absence of hypotension. Hypoperfusion, even without a raised lactate, is likely to be associated with a demonstrable base deficit. Central venous saturations (ScvO<sub>2</sub>) can be viewed under some circumstances as a non-specific, surrogate marker of organ perfusion. A value of less than 70% suggests inadequate organ perfusion or oxygen delivery, but it is the trends rather than the absolute values which are clinically useful (see below). Serial measurements of these clinical and biochemical markers can be used to guide and assess the physiological response to resuscitation.

### Central venous access

Central venous cannulation is indicated in shocked patients for the ongoing assessment of fluid status using fluid challenges as well as for the administration of vasoactive drugs, if required to support the circulation. It should be noted that the standard CVP cannulae are not designed for the rapid infusion of fluids, as the resistance to flow is far greater than through shorter peripheral cannulae of equal diameter (Poiseuille's law).

The CVP measurement gives an indication of venous return to the right side of the heart and ventricular preload. The normal CVP in the supine spontaneously breathing patient is 0–5 cmH<sub>2</sub>O. The relationship between volume status and CVP is inconsistent between patients, so absolute target values should not be set. The CVP, therefore, should be used only as a guide to volume status, by assessing dynamic changes rather than watching absolute values. For example, following a fluid challenge of 200–300 ml, continued hypotension with a non-sustained rise in CVP indicates the need for more volume. A persistent rise in CVP is more suggestive, although not diagnostic, of adequate filling. Finally, central venous access can also be used to obtain blood samples for assessment of ScvO<sub>2</sub>, which, it should be noted, is not the same as mixed venous oxygen SvO<sub>2</sub>. SvO<sub>2</sub> is a physiological variable related to oxygen delivery consumption and cardiac output. It is measured in the pulmonary artery and represents the mixing of inferior and superior vena-caval blood in the right ventricle. The ScvO<sub>2</sub> is a measurement that is dependent on whether it is assessed in the venous return from the body, or head and neck, prior to mixing in the ventricle. Manipulation of the circulation to maintain ScvO<sub>2</sub> greater than 70% in the first 6 hours of septic shock has been associated with improved outcome.

### Cardiac output monitors

Monitoring of CO is often carried out in shocked patients, where it can aid diagnosis and guide therapy. There is some evidence to support the early measurement and manipulation of oxygen delivery in shocked patients and this requires the measurement of cardiac output.

There are a number of CO monitors in current clinical use. They all produce an estimate of CO and a calculated peripheral resistance. Some of these monitors use a calibration (thermal dilution, lithium dilution) and others use iterative ‘approximations’ and statistical algorithms. The measurements available, how they are obtained, the degree of invasiveness and the accuracy of the measurements vary between different monitors.

A pulmonary artery flotation catheter (PAC) is passed via a central vein through the right side of the heart to rest with the tip in a proximal branch of the pulmonary artery. Cardiac output is measured using a thermodilution technique. The use of PAC has decreased in recent years, owing to complications and perceptions associated with their use. This has resulted in a decline of confidence, especially following equivocal studies potentially suggesting harm, or no benefit, from their use and now with the availability of less invasive methods of monitoring cardiac output. A multicentre randomized controlled trial done in the UK (PAC-man trial), however, demonstrated that the use of PAC was not associated with any effect (either harmful or beneficial) on patient outcome.<sup>1</sup> However, it should be remembered that the recent studies had no protocol for the clinical use of PAC data, which may explain the neutral conclusions. Published positive trials using CO monitoring have used targeted protocols.

### Less invasive CO methods

**Pulse Contour analysis** (e.g. PICCO monitor) and **Pulse Power analysis** (e.g. LiDCO monitor) measure cardiac output by using calculations based on the displayed arterial pressure waveform. They have the advantage of being less invasive than the pulmonary artery flotation catheter, and unlike the Doppler technique

are continuous beat-by-beat monitors of CO and SVR. The ability to check the values produced by a monitor with an independent calibration technique, such as thermal (PICCO) or lithium dilution (LiDCO), adds not only a validation of the output but also boosts clinical confidence. This is important if the result is to be used to dictate management.

### Treatment of the shocked patient

Circulatory shock is a medical emergency. Management can be divided into general measures applicable to all patients, aimed at maximizing oxygen delivery to the tissues, and definitive treatment of the underlying cause, where possible (Table 3). Protocols for early identification and resuscitation of the shocked patient, such as those available for sepsis, will ultimately produce best medical practice.

### Initial approach

The initial approach should be focused on rapid assessment and simultaneous resuscitation of the patient. Airway, breathing and

### Definitive management – correcting the cause

#### *Hypovolaemic*

##### Haemorrhage

- stop bleeding
- correct coagulopathy
- surgical intervention

#### *Obstructive*

##### Pulmonary embolus

- thrombolysis
- embolectomy

##### Tension pneumothorax

- needle thoracocentesis

##### Cardiac tamponade

- drain pericardial blood

#### *Cardiogenic*

##### Myocardial infarction

- thrombolysis
- revascularization

##### Cardiac dysrhythmia

- cardioversion
- antidysrhythmics
- pacing

##### Structural abnormality

- surgical correction, e.g. valve replacement

#### *Distributive*

##### Anaphylaxis

- remove putative causative agent
- adrenaline

##### Sepsis

- early antibiotics (within 1 hour)
- drain collections

##### Addisonian crisis

- steroid replacement

Table 3

circulation should be addressed in a systematic and stepwise manner.

All patients should be given a high-inspired oxygen concentration through a patent airway, to improve arterial oxygen saturation and oxygen delivery. Intubation and mechanical ventilation may be necessary but should be performed only by someone familiar with this procedure in shocked patients. Induction of anaesthesia to allow intubation can result in significant cardiovascular collapse.

An adequate circulating volume is essential in shocked patients and they will often need large volumes of fluid to be administered intravenously to achieve this. Fluids containing chloride concentrations greater than that in plasma, such as 0.9% (normal) saline and colloids suspended in saline, can produce a hyperchloraemic acidosis even though tissue perfusion may be improved. This can sometimes confuse biochemical assessment of response to therapy. Current thoughts are that balanced crystalloids such as Hartmann's or colloids suspended in balanced solutions may offer advantages. Fluid management is, therefore, best guided by dynamic measurement of filling pressures (CVP or pulmonary artery occlusion pressure) or cardiac output monitors (PICCO, LiDCO, PAC). Patients with cardiogenic shock may also benefit from judicious volume replacement using haemodynamic monitoring.

#### Ongoing circulatory support

**Inotropes/vasopressors:** following adequate fluid resuscitation, as determined by pressure or output monitoring, many shocked patients will remain hypotensive. The next step is to start a vasopressor or inotrope. The choice of drug will depend on the cause of the circulatory shock. Vasopressors are generally used for distributive shock and inotropes for cardiogenic shock, where the additional vasodilatation some provide can also be beneficial.

Commonly used vasopressors act via  $\alpha_1$ -receptors (e.g. norepinephrine, epinephrine) or via vasopressin receptors. Commonly used inotropes exert their action through  $\beta_1$ -receptors (e.g. dobutamine, epinephrine). Many of the drugs used have both inotropic and vasopressor actions. The use of these drugs should be guided by CO monitoring and SVR calculation, especially as the pharmacodynamics of vasoactive drugs can be unpredictable and vary between patients. It is important not to sacrifice blood flow for a blood pressure reading, as this would be neither physiologically appropriate nor benefit the patient. If considerable fluid and drug support is necessary, full haemodynamic monitoring (including CO) is essential to make sense of further treatment.

#### Endocrine support

**Corticosteroids:** in a proportion of critically ill patients there is a deficiency of circulating corticosteroids. The most obvious of these is in the event of an Addisonian crisis. Relative adrenal insufficiency has been noted in other critically ill patients. In these patients infusion of inotropes or vasopressors may have little effect. Studies have shown that administration of a physiological dose of corticosteroids improves the response to inotropes and vasopressors, although the same clinical trials have not confirmed a reduction in mortality.

**Insulin:** some groups of critically ill patients have an improved survival with normoglycaemia, which usually requires insulin therapy and tight regulation. This is especially true in patients on steroids and/or infusions of catecholamines for haemodynamic

support, both of which antagonize the actions of normal levels of circulating insulin. There is some dispute as to whether tight glucose control should be initiated for all patients from the time of admission to the critical care unit following evidence that, in some subgroups, outcome may be worse.

#### Septic shock

The Surviving Sepsis Guidelines for the management of severe sepsis and septic shock<sup>2</sup> are an internationally agreed set of evidence-based guidelines aimed at improving the management, and survival, of patients with these conditions. In septic shock, aggressive fluid resuscitation, haemodynamic targeting (and perhaps ventilation) in the first 6 hours, to achieve a  $SvO_2 > 70\%$ , has a significant survival benefit. It is unclear which of these manoeuvres had the impact. It should be noted that the trial data used to support this observation was related to an extremely sick group of patients all of whom had severe sepsis and were treated on admission to the accident and emergency department. Of importance is the early recognition of sepsis and early antibiotic administration, which has a major impact on outcome in patients with septic shock.<sup>3</sup> The published data suggest that in the first 6 hours following documented hypotension, survival decreases by an average of 7.6% for each hour delay in administering appropriate antibiotics. Those receiving antibiotics 5–6 hours after onset of hypotension have a survival rate of only 42%.

#### Support of other organ systems

Persistent or resistant shock leads to end-organ dysfunction and ultimately, multiple organ failure. Patients in established and ongoing shock often need support of organ systems other than just the cardiovascular system, e.g. respiratory, gastrointestinal or renal.

The mortality of circulatory shock is dependent on the aetiology and response to early treatment. Prompt and appropriate treatment is essential in reducing mortality. However, depressingly for some types of shock, even with aggressive therapy the mortality remains very high and new treatments await understanding of the molecular mechanisms at a cellular level. ◆

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