Physiology of shock and volume resuscitation

Robert Jericho
Steffan Glaze

Abstract

In shock, hypoperfusion of vital organs can lead to their failure. Recognizing shock, identifying the type and treating it promptly saves lives. Monitoring of haemodynamic and cellular end points is crucial in guiding treatment and improving outcomes. This article therefore focuses on the pathophysiology of shock, volume resuscitation, haemostasis and approaches to management. The body has a number of intrinsic homeostatic mechanisms for controlling blood pressure and organ perfusion which are pushed to their limits and beyond in disease. Replacement of circulating volume with fluids or blood is often necessary, but the best strategy depends on the clinical situation and latest evidence. Coagulopathy can accompany haemorrhage, particularly in trauma, and correction should be guided by testing. In haemorrhage, the aim is to stabilize the patient until definitive control can be achieved by intervention. Drug therapy to increase blood pressure and cardiac output may be necessary to increase the time available to treat underlying pathologies.

Keywords Cardiac physiology; fluid resuscitation; haemorrhage; homeostasis; hypovolaemia; shock; transfusion

Introduction

Shock is an acute failure of circulation resulting in insufficient delivery of oxygen and nutrients to tissues. If this state persists, hypoxia results in cell death which impairs organ function and leads to their failure. However, there are a broad range of causes with potentially opposing management strategies. The typical broad classifications are hypovolaemic, cardiogenic, obstructive or distributive. Hypovolaemic shock is a common cause where there is inadequate circulating volume due to fluid loss, secondary to conditions such as haemorrhage. A true clinical definition of shock is difficult due to the variance in baseline physiology, and it may present differently due to its underlying cause. However, it can be identified by evidence of inadequate perfusion of tissues (e.g. reduced consciousness, poor urine output or cool peripheries), or by derangement of vital signs associated with compensatory mechanisms (e.g. tachycardia). Management of this clinical condition requires treatment of the underlying cause while supporting adequate perfusion with resuscitation and volume replacement. This article aims to discuss some of the key pathophysiology and management approaches.

Robert Jericho *MEng MBBS MRCP is an ACCS Anaesthetics Trainee (CT4) at the Royal Berkshire NHS Foundation Trust, Reading, UK. Conflicts of interest: none declared.*

Steffan Glaze *MA BMBCh FRCA is a Specialist Registrar in Anaesthetics and Intensive Care at the Nuffield Department of Anaesthesia, Oxford University Hospitals, UK. Conflicts of interest: none declared.*

Pathophysiology

Types of shock

Shock can be categorized into types by underlying pathophysiology, including hypovolaemic, cardiogenic, distributive and obstructive. All can lead to a globally insufficient tissue delivery or utilization of oxygen, leading to cellular and tissue hypoxia. While the investigation and management strategies discussed later principally relate to hypovolaemic shock, it is important to recognize that there are many other causes of shock.

Hypovolaemic shock is characterized by reduced circulating blood volume. Heart rate and systemic vascular resistance (SVR) typically increase to compensate for reduced cardiac output. Causes are haemorrhagic or non-haemorrhagic. Haemorrhagic causes include pathologies such as gastrointestinal bleeding (gastric ulcers, colonic lesions), trauma, vascular aetiologies (ruptured aneurysm, aorto-enteric fistulae), as well as uncontrolled intraoperative bleeding. Non-haemorrhagic causes include gastrointestinal losses (diarrhoea, vomiting), renal losses (diuretic use, diabetes insipidus), skin losses (excessive insensible losses, plasma loss in burns) and third space losses (cirrhosis, pancreatitis).[1]

Cardiogenic shock is characterized by primary cardiac pump failure. As in hypovolaemic shock, heart rate and SVR typically increase, which worsens the imbalance between myocardial oxygen supply and demand — the heart struggles to compensate for its own failure. The most common cause is acute myocardial infarction, though it can also be caused by myocarditis, prolonged brady- or tachy-arrhythmias, acute valve dysfunction, septal or ventricular rupture, or overdose of certain drugs (β-blockers, calcium channel blockers). Treating the underlying cause is the immediate priority, though it carries a very high in-hospital mortality rate.[2]

Distributive shock is characterized by peripheral vasodilation. Heart rate and contractility increase to maintain cardiac output, sympathetic nervous system (SNS) activation causes vasoconstriction in non-essential sites such as the skin and kidneys, and activation of the renin–angiotensin–aldosterone system (RAAS) promotes fluid retention. The most common cause of distributive shock is sepsis, but anaphylaxis and neurogenic shock are other causes. In sepsis, various vasodilatory mediators cause peripheral vasodilation and increased membrane permeability. In anaphylaxis, massive histamine release causes widespread increased membrane permeability. In neurogenic shock, a spinal cord lesion causes a disruption of sympathetic outflow below that level, leading to vagally induced vasodilation, hypotension, and bradycardia. The underlying cause must be identified and treated, while supporting organ perfusion with vasoactive drugs and resuscitation fluids.

Obstructive shock is characterized by a mechanical obstruction which prevents the heart from filling or pumping effectively. This mechanical obstruction may be within the heart (valve disease, atrial myxoma), caused by external compression on the heart (cardiac tamponade, pneumothorax) or related to the vasculature exiting the heart (pulmonary embolus, ventricular

outflow obstruction). The underlying cause must be identified and treated as a priority, while providing appropriate supportive treatment.[3]

Cellular and tissue hypoxia

The circulatory insufficiency in shock leads to tissue hypoperfusion and inadequate oxygen delivery, which can lead to the life-threatening sequelae of organ failure. An understanding of the pathophysiology clarifies the priorities of resuscitation.

Oxygen delivery (DO_2, ml/minute) is defined as the volume of oxygen delivered to tissues per unit time, and is equal to the product of cardiac output (CO, litres/minute) and the arterial oxygen content (CaO_2, ml/litre). Oxygen is carried in the blood either bound to haemoglobin or directly dissolved in the blood.

Oxygen consumption (VO_2, ml/minute) varies by end organ and metabolic state. At rest, the heart and brain consume more oxygen per unit weight (50 ml/100 g/minute and 80 ml/100 g/minute, respectively) and the skin and skeletal muscle consume less (10 ml/100 g/minute and 1–4 ml/100 g/minute, respectively). In an exercise state, the skeletal muscle can increase its oxygen consumption significantly, to 50–100 ml/100 g/minute.[4]

At rest for a 75 kg adult, DO_2 is typically around 1000 ml/minute, and VO_2 is typically around 250–500 ml/minute. This means that more oxygen is delivered than is consumed. At this point, VO_2 is considered 'supply independent'. If the DO_2 falls due to shock, this reserve can be depleted, and if DO_2 falls below VO_2, then VO_2 will fall in line with DO_2. At this point, VO_2 is considered 'supply dependent'. This point below which this occurs is known as critical DO_2 (Figure 1).

Above critical DO_2, aerobic cellular metabolism can take place. In this state, glucose is fully broken down to produce energy in the form of adenosine triphosphate (ATP), with water and carbon dioxide formed as by-products. This allows essential cellular mechanisms to take place, including membrane transport, muscle contraction, protein synthesis, and intracellular signalling.

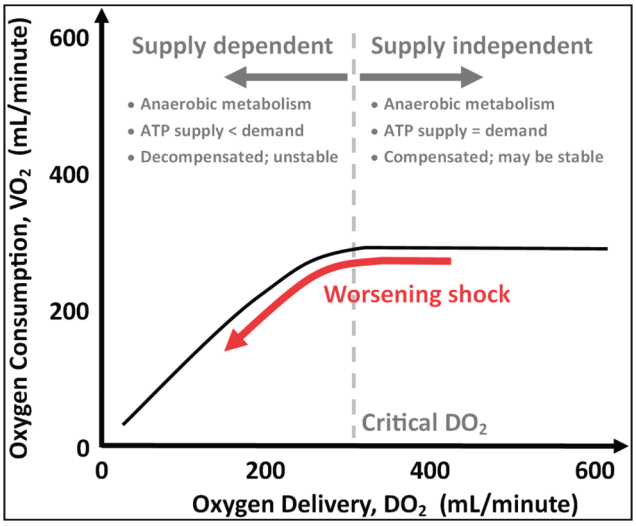

Figure 1 Relationship between oxygen delivery and oxygen consumption, showing the impact of worsening shock. Above critical DO_2, VO_2 is supply independent, and below critical DO_2, VO_2 is supply dependent.

Below critical DO_2, however, inadequate oxygen delivery leads to anaerobic cellular metabolism. In this state, only very limited glucose breakdown and ATP production is possible, causing failure of essential cellular mechanisms and leading to irreversible cell damage. Lactic acid is created as a by-product, contributing to acidaemia which has further detrimental effects on cellular function.

Compensatory physiological mechanisms in shock

Shock leads to a cascade of physiological responses that can be divided into immediate (seconds to minutes), intermediate (minutes to hours) and delayed (hours to days). Immediate responses are based on sympathetic stimulation in response to shock. Intermediate responses include fluid redistribution and rapid hormonal mechanisms. Delayed responses are driven by ongoing hormonal mechanisms. These will be described in order to understand how shock can impact them.

Cardiac physiology: cardiac output (CO, litres/minute) is defined as the amount of blood that the heart pumps in 1 minute. It is equal to stroke volume (SV, ml) multiplied by the heart rate (HR, beats/minute). Stroke volume is the difference between end diastolic volume (EDV, ml) and end systolic volume (ESV, ml). EDV and ESV are impacted by preload, afterload, and contractility (Figure 2). As such, the four determinants of cardiac output are heart rate, preload, afterload, and contractility. Each of these has a number of physiological determinants, discussed below. Furthermore, they are all interdependent, each having an impact on each other.

Heart rate is impacted by sympathetic and parasympathetic stimulation, as well as by numerous medications. Agents which increase and decrease heart rate are known as positive and negative chronotropes, respectively. Preload is the stretch of the ventricles before they start to contract. Greater stretch causes greater contraction (analogous to the recoil of a rubber band), but only up to a point. This is demonstrated by the Frank–Starling curve (Figure 3). Preload is impacted by central venous pressure (reduced in hypovolaemia), ventricular compliance (reduced in left ventricular hypertrophy), atrial contraction, ventricular filling (reduced in tachycardia) and valve

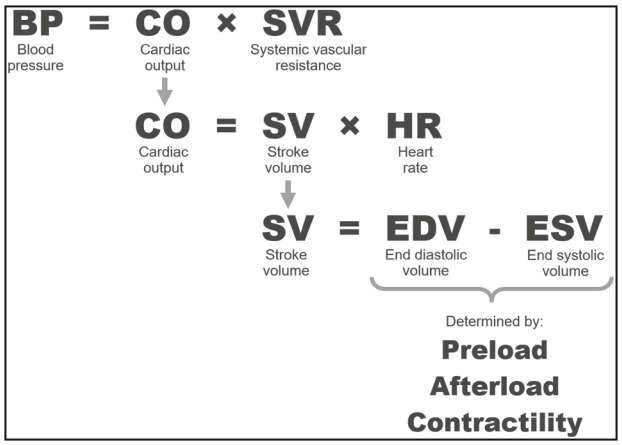

Figure 2 Relationship between blood pressure, cardiac output, stroke volume and heart rate. This shows the four determinants of cardiac output, which are heart rate, preload, afterload, and contractility.

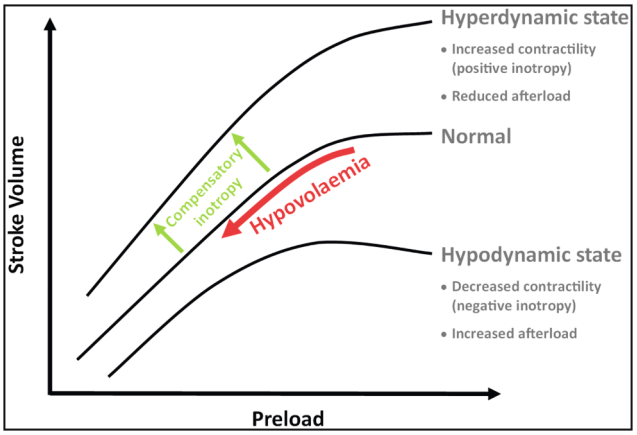

Figure 3 Frank–Starling curves showing relationship between preload and stroke volume, the impact of increased or decreased contractility and afterload, and the impact of hypovolaemia and compensatory inotropy.

disorders. Afterload is the force against which ventricles must contract in order to circulate blood. Higher afterload reduces the heart's ability to circulate blood. Afterload is primarily impacted by SVR (controlled by endogenous and exogenous vasoconstrictors and vasodilators, and increased by atherosclerosis), though can also be impacted by ventricular outflow obstruction (e.g., aortic stenosis). Finally, contractility is how hard the myocardium contracts for a given preload. Like heart rate, it is impacted by sympathetic and parasympathetic stimulation, as well as many medications, and availability of intracellular calcium in myocytes. Agents which increase and decrease contractility are known as positive and negative inotropes, respectively.[5]

Autonomic nervous system: The autonomic nervous system has a number of mechanisms to regulate blood pressure in health, which are also crucial to responses in loss of circulating volume. Changes in blood pressure from the loss of volume are detected by baroreceptors. These are either high pressure, found in the aortic arch and carotid sinus; or low pressure, found in the atria, pulmonary arteries, cardiac veins and ventricles. High-pressure baroreceptors are continuously firing and increase their rate of activation as blood pressure increases. They are sensitive to changes in pulse pressure as well as overall pressure. In contrast, low-pressure baroreceptors fire more as the pressure drops. They are found in larger capacitance vessels, their role is also to detect overall blood volume by their stretch. Afferents from these receptors integrate in the medullary cardiovascular centres, where systemic effects are elicited by changes to the output of sympathetic and parasympathetic nervous systems. Adrenergic receptors respond to direct neural stimulation and increases in systemic adrenaline. The effect depends on the location and type of receptor, for example α-1 and α-2 receptors trigger vasoconstriction, while β-1 receptors increase cardiac contractility and rate. When considering the immediate responses to loss of circulating volume, there is an increase in arterial tone which increases vascular resistance and thus maintains mean arterial pressure. In the heart, vagal activity which usually slows heart rate is impaired and sympathetic effects result in tachycardia and increased contractility. The sympathetic response to increased heart rate is blunted in patients taking β-blockers (e.g. bisoprolol), which impair their ability to compensate for hypovolaemia with tachycardia. Chemoreceptors located in the carotid bodies which usually sense changes in arterial oxygen content can contribute to neural responses at particularly low mean arterial pressures, where their function is impaired by inadequate blood flow. All of these mechanisms are attenuated in patients with chronic hypertension, where their circulation is dependent on a persistently raised blood pressure.

Fluid redistribution: After hours of sustained hypovolaemia, intermediate responses engage. There is a reduction in capillary pressure, causing fluid shift from the interstitium into the vasculature then protein shift to plasma, drawing in fluid to restore intravascular loss. Up to 2 litres of fluid can shift in the first 24–48 hours to maintain the intravascular compartment.

Hormonal changes: A variety of hormones mediate delayed responses over hours to days. Renal retention of fluid is increased by renin, angiotensin, aldosterone and antidiuretic hormone secretion which helps maintain circulating volume. These mechanisms that compensate for chronic hypovolaemia are also frequently used as targets for drug therapy for hypertension.

Recognizing hypovolaemic shock

Signs, symptoms and basic monitoring

Hypovolaemic shock causes well-known clinical signs and symptoms. These are the sequelae of the haemodynamic and cellular changes described above. Heart rate increases to compensate for reduced cardiac output. Blood pressure falls with cardiac output, as venous return falls and hence ventricular filling and stroke volume are depleted. Urine output is reduced due to decreased renal blood flow, constriction of the renal arterioles due to sympathetic stimulation, and fluid retention via the RAAS. Pallor is caused by peripheral vasoconstriction, which also prolongs capillary refill time. Dyspnoea is a compensatory mechanism for reduced oxygen delivery to tissues, and for metabolic acidosis caused by lactic acid accumulation. Changes in mental status are caused by release of stress hormones and later by cerebral hypoperfusion. Diaphoresis occurs with increased sympathetic stimulation.

Assessment of the shocked patient should include basic monitoring of heart rate, blood pressure, urine output and respiratory rate. Clinical examination should note capillary refill time, temperature of peripheries, pallor, and mental status. Monitoring should be performed at regular intervals to identify deterioration in unwell patients, and continuously in those who are most unwell.

Determining severity and stages of shock

Severity can be determined in a number of ways. In many contexts, an estimate of the circulating volume lost gives an initial indication of severity. In haemorrhagic causes, blood loss may be estimated visually or measured in suction reservoirs or by weighing surgical swabs and gauze. Concealed blood should also be considered, and may be difficult to quantify. In non-haemorrhagic causes, gastrointestinal or renal losses (vomit, stool output, or urine output) may be directly measurable,

however third-space losses (such as in pancreatitis or cirrhosis) may not.

A commonly used classification of severity is described in Advanced Trauma Life Support,[6] which defines four stages of shock (Table 1). Stage 1 is characterized by minimal blood loss, with no changes in the main clinical parameters. Stage 2 describes 15–30% blood loss, at which point the main signs of tachycardia, hypotension and oliguria are observed. At this point, VO_2 remains 'supply independent', that is, supply of oxygen and ATP still meets demand. Stage 3 describes 30–40% blood loss, which crosses the critical DO_2 threshold. Demand now outstrips supply, with subsequent clinical signs of inadequate perfusion such as confusion and significant oliguria. Stage 4 describes greater than 40% blood loss, which is described as immediately life-threatening.

Other commonly used scoring systems include the National Early Warning Score (NEWS) 2,[7] a widely implemented tool for tracking the progressive deterioration of acutely unwell patients in hospital. It includes many (but not all) of the physiological parameters described above, and also indicates the required frequency of clinical monitoring, with those scoring higher requiring more frequent monitoring. The Sequential Organ Failure Assessment (SOFA)[8] score can be used in intensive care patients to quantify the degree of failure of the central nervous, respiratory and cardiovascular systems; coagulation status; and liver and renal function. It is based on measured parameters, laboratory blood results and degree of organ support.

Point-of-care testing

Common point-of-care analysers are capable of rapid measurement of many parameters useful for the assessment of shock, as well as the effectiveness of management. These include blood gases (pH, pO_2, pCO_2, base excess), metabolites (including lactate), electrolytes and oximetry (including total haemoglobin). Lactate elevation gives an indication of severity, as does the resulting metabolic acidosis (reduced pH and base excess), with or without respiratory compensation (reduced pCO_2). Serial blood gas and lactate measurements are important markers for satisfactory management of shock. Serial haemoglobin measurements can provide indicators of ongoing bleeding, however in acute haemorrhage dilution of the haemoglobin can be delayed and as such normal results are falsely reassuring in this context.

Advanced haemodynamic monitoring

Invasive arterial blood pressure monitoring (using an arterial cannula) not only allows continuous monitoring of systolic, diastolic and mean blood pressure, but also quantifies other physiological parameters. For example, pulse pressure variation (PPV) is the difference between the maximum and minimum pulse pressure over a respiratory cycle, and is an indicator of fluid responsiveness in mechanically ventilated patients. Left ventricular contractility and systemic vascular resistance can be estimated from the gradient of the upstroke in systole, and the position of the dicrotic notch, respectively. Finally, pulse contour analysis can determine stroke volume and cardiac output. This helps the clinician differentiate between the need for fluids, inotropes and vasopressors. A 2020 systematic review published by the UK National Institute for Health and Care Excellence (NICE) showed a reduced rate of complications in surgical patients for whom cardiac output monitoring was used intraoperatively, compared to conventional clinical care.[9]

Other forms of cardiac output monitoring may be considered. Invasive methods include thermodilution and dye dilution techniques, requiring central venous or pulmonary artery catheterization. Oesophageal Doppler uses an ultrasound probe inserted into the oesophagus at the level of the descending aorta, to measure blood velocity. Non-invasive methods include transcutaneous Doppler (similar in principle to oesophageal Doppler) or transthoracic echo, measuring velocity at the left ventricular outflow tract.[10]

Volume resuscitation

Aims of volume resuscitation

The main goal of resuscitation is to sufficiently replace circulating volume to restore tissue perfusion and oxygenation. Volume, rate and type of fluid or blood product to achieve this depends on the underlying aetiology and status of the patient. In cases of haemorrhage, prompt control of the source of bleeding is essential to reduce the need for further volume replacement.

Crystalloids and colloids

Restoration of circulating volume and haemodynamic status with isotonic crystalloid fluid has been the dogma of resuscitation strategies for decades, but controversy over the ideal solution remains. Crystalloid and colloid solutions have been investigated

The four stages of shock, characterized by the cardiovascular, respiratory, renal and central nervous system responses to blood loss, and the mismatch between supply and demand of adenosine triphosphate (ATP) at each stage

	Stage 1	Stage 2	Stage 3	Stage 4
Blood loss (ml)	<750	750–1500	1500–2000	>2000
	<15%	15%–30%	30%–40%	>40%
Heart rate (beats/minute)	<100	>100	>120	>140
Blood pressure	Normal	Reduced	Reduced	Reduced
Respiratory rate (breaths/minute)	14–20	20–30	30–40	>35
Urine output (ml/hour)	Normal	Oliguria	Oliguria	Anuria
	>30	20–30	5–15	
Neurological status	Normal	Agitated	Confused	Lethargic
ATP status	Supply = demand	Supply = demand	Supply < demand	Supply << demand

Table 1

and compared extensively. Crystalloids can be matched to plasma in terms of their tonicity, but they still redistribute readily to tissues. Colloids feature large molecules which aim to hold fluid intravascularly by osmotic pressure and maintain the volume expansion for longer than crystalloids. Clinical and experimental evidence do not point to a particular favoured crystalloid fluid for resuscitation.[11] Balanced solutions (e.g. Hartmann's) are preferred by some over normal saline due to reports of increased physiologic derangements with the latter, including hyperchloraemic acidosis, but evidence does not point to a specific benefit and normal saline (0.9%) is marginally cheaper. Colloidal solutions include hetastarch, albumin and gelatin. They are significantly more expensive than crystalloids. Synthetic colloids vary in their size and composition, and some have been removed from clinical practice due to their adverse effects, notably a risk of anaphylaxis. Furthermore, their ability to remain in the circulation is less than originally believed, particularly in disease states where the integrity of the capillary bed is altered. Given their risk of harm, but no strong evidence demonstrating benefit, colloids have generally fallen out of use. However, trials are ongoing and albumin may have a role in certain critical care scenarios but is associated with harm in patients with traumatic brain injury. In fluid resuscitation by the non-specialist, current NICE guidance recommends use of crystalloid solutions with sodium at 130–154 mmol/litre, which includes 0.9% sodium chloride and Hartmann's.[12]

Considering the volume to administer, clinical practice varies. Boluses of between 250 ml and 1000 ml are used, with further fluid guided by clinical assessment after each dose. In terms of guiding therapy, various protocols have been investigated. Although the aim is to promptly replace circulating volume to improve perfusion, it is important to consider the patient's comorbidities, possible deficit and risk of complication from excess when prescribing fluids. Fluid administration can result in complications from dilutional coagulopathy; electrolyte derangement such as hyperchloraemic metabolic acidosis; and tissue oedema from redistribution that can notably result in respiratory impairment in patients with heart failure.

Transfusion strategies

When using crystalloids in the treatment of haemorrhagic shock, a 'three to one' rule is considered: 3 ml of crystalloid may be needed for every 1 ml of blood loss to account for losses into the interstitium and tissues. Infusion of these large volumes of fluid to restore circulating volume can therefore result in coagulopathy, electrolyte derangement and impair oxygen delivery. In cases of active haemorrhage, replacement with crystalloid may cause harm and low-volume or hypotensive resuscitation is likely to be beneficial instead. This concept aims to reduce dilutional coagulopathy and prevent normal or high blood pressures disrupting newly formed clots. In haemorrhage, it is difficult to determine the thresholds for initiating transfusion. Most professional bodies set a blood transfusion threshold haemoglobin concentration of 70 g/litre, and 80 g/litre for patients with acute coronary syndrome. Up to a third of patients admitted to a critical care setting undergo transfusion, therefore restrictive (haemoglobin kept at 70–90 g/litre) versus liberal (haemoglobin kept at 100–120 g/litre) strategies in this group of patients has been examined by a large, multi-centre, randomized controlled trial.[13] Mortality was equivalent in the two groups, indicating a restrictive transfusion threshold is as safe as liberal but reduces the risk of harm associated with transfusion.

In patients with ongoing bleeding, point of care or laboratory measures of haemoglobin are likely to remain normal as it has not yet been diluted by fluid resuscitation or physiological redistribution, which limits use of this threshold. Triggers for transfusion could instead include estimation of the volume of blood loss (e.g. greater than 30%), or failure to respond to 2 litres of intravenous fluid. A study of pre-hospital administration of blood and crystalloids to treat haemorrhagic shock[14] indicated an increase in mortality if fluids were given first, and as such it is more appropriate to replace acute blood loss by transfusion.

If blood transfusion is commenced, various protocols have been developed and tested to guide the administration of the correct ratio of blood products including packed red blood cells, fresh frozen plasma (FFP), platelets and cryoprecipitate (Table 2).[15,16] While red blood cells are required to increase tissue oxygen delivery, FFP and platelets are required to support coagulation. Studies, in both civilian and military settings, have compared different ratios of red cells and plasma and current practice is typically a 1:1 ratio. These issues are considered further in NICE guidelines[17] and those from the Task Force for Advanced Bleeding Care in Trauma.[18]

Haemostasis and coagulation

While resuscitation is essential to maintain perfusion, the most effective strategy to reduce the need for transfusion is to stop the source of bleeding. Haemostasis is achieved most simply in trauma by external compression of open wounds, limb tourniquets and immobilization of long-bone fractures. Where indicated, prompt transfer to the operating theatre for surgical management should occur while resuscitation is ongoing whether in trauma or other causes of haemorrhage amenable to operative control. This also relies on effective coagulation.

A basic understanding of the pathways involved in clotting is essential to manage patients with haemorrhage. Classical models of clotting have focused on the coagulation cascade, where an intrinsic and extrinsic pathway joins to generate fibrin. A 'cell-based' model has more recently been devised, which considers three stages to the formation of clot: initiation, amplification and propagation. Considered simply, injury exposes tissue factor on cells which initiates the generation of the prothrombinase complex via factor Xa. This then generates thrombin, which propagates formation of fibrin-based clots, and activates platelets. As platelets are activated, the process is amplified to generate further clot and fibrin deposition. All of the reactions in the traditional coagulation cascade occur within this pathway, but the cell-based model highlights the involvement of platelets and cells with tissue factor in the process.

As haemorrhage progresses and transfusion is used to correct hypovolaemia, coagulopathy may ensue. This can be exacerbated by anti-coagulant and anti-platelet medications and strategies must be utilized to reverse their effects or overcome inhibition in order to control bleeding. In shock and trauma, the coagulopathy seen can be worsened by consumption of coagulation factors, dilution by fluid replacement, acidosis, inflammation and hypothermia. Prompt management, temperature control and appropriate resuscitation can reduce this and the harms associated.

Blood products for transfusion in haemorrhagic shock, showing indications for use and transfusion strategies, along with typical unit volumes and practical storage considerations

Product	Indications (relating to haemorrhagic shock)	Transfusion strategies or dose	Typical volume	Storage considerations
Red blood cells (RBCs)	Acute blood loss with haemodynamic instability	As guided by haemodynamic response	220–340 ml/unit (average 280 ml)	Refrigerated at 2–6°C (return unused within 30 minutes)
Fresh frozen plasma (FFP)	Acute blood loss with haemodynamic instability Clinically significant bleeding with PT ratio >1.5	1:1 with red cells in major haemorrhage To be guided by coagulation studies (TEG, PT/APTT)	200–250 ml/unit	Frozen at −30°C (refrigerate if unused within 30 minutes and use within 24 hours)
Platelets (Plts)	Plts <30 with clinically significant bleeding Plts <50 with major haemorrhage Plts <100 with critical site bleeding (e.g. CNS)	Determined by clinical situation, patient size, previous increments, and target threshold	200 ml/unit	Stored at 20–24°C Stored with continuous agitation Use within 8 hours
Cryoprecipititate	Fibrinogen <1.5 g/L with clinically significant bleeding Fibrinogen <2.0 g/L with clinically significant obstetric bleeding	Two pooled units (10 individual units) will increase fibrinogen by ~1 g/L in an average adult	80–115 ml/unit (pooled unit)	Frozen at −30°C Use within 4 hours
Prothrombin complex concentrate (PCC)	Emergency reversal of warfarin Emergency reversal of DOACs, under specialist direction	Typically 25–50 units/kg Determined by INR and clinical situation Given alongside vitamin K	50 units/ml (reconstituted)	Stored at 0–25°C Requires reconstitution

APTT, activated partial thromboplastin time; CNS, central nervous system; DOAC, direct oral anticoagulant; INR, international normalized ratio; L, litre; PT, prothrombin; TEG, thromboelastography.

Table 2

Point of care testing alongside laboratory measurement of the prothrombin time (international normalized ratio), activated partial thromboplastin time (APTT) and fibrinogen, detects abnormalities of clotting and guides clinicians on targeted replacement of factors. An example of point of care testing is thromboelastography (TEG), which is a rapid turn-around test which gives a global assessment of blood coagulability by measuring the viscoelastic properties of a blood sample during clotting. Of note, the effects of anti-platelet medications such as clopidogrel might not be revealed by usual laboratory testing that counts platelet number rather than measuring function. Furthermore, as fibrinogen is depleted in clot formation this may need to be specifically replaced in greater amounts than it is found in FFP, and as such cryoprecipitate may be indicated outside of the previously discussed blood product ratios. After the initial phase of resuscitation, it is important to use these tests to guide further blood product administration to effectively prevent or treat coagulopathy.

Tranexamic acid is an anti-fibrinolytic agent, which works by preventing the conversion of plasminogen to plasmin, and hence the breakdown of fibrin into fibrin degradation products, and therefore stabilizes blood clots once formed. The 2010 CRASH-2 trial showed a significant reduction in mortality in trauma patients at risk of major haemorrhage when given tranexamic acid within 8 hours of injury, and also showed no evidence of harm.[19] As such, intravenous tranexamic acid has been adopted as a common adjunct in management of haemorrhagic shock.

Calcium is vital for the activation of platelets and clotting factors. Citrate, an anticoagulant added to blood products, chelates calcium, and as such, patients requiring major transfusions are at risk of hypocalcaemia. This can significantly impair coagulation, as well as cause neuromuscular excitability, seizures or cardiac arrhythmias. To avoid this, intravenous calcium replacement should be given as an adjunct to major transfusions.

Vasopressors and inotropes

The early stages of resuscitation in hypovolaemic or haemorrhagic shock may require vasopressors or inotropes alongside fluids to maintain blood pressure. Patients who fail to respond to appropriate initial fluid replacement are likely to need specialist input from critical care services. However, if shock persists despite adequate volume replacement then a diagnosis other

than pure hypovolaemia should be considered, such as ongoing haemorrhage or sepsis. Drugs such as metaraminol or noradrenaline act to increase vascular tone or cardiac output in order to restore mean arterial pressure to maintain tissue perfusion. The shock state may increase the need for this due to paralysis of the vasculature and impaired cardiac contractility caused by acidosis, hypoxia and ATP depletion. Tissue perfusion is regulated by arteriolar tone, and regional changes act to maintain perfusion to critical organs during hypovolaemia resulting in the signs of peripheral hypoperfusion such as cool limbs and mottling. However in advanced shock, demand from other organs cannot be met leading to a vicious cycle of organ failure. Regardless of the cause of hypovolaemia, vasopressors should only be used temporarily while other treatment restores the circulating volume. ◆

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Practice points

- Shock is an acute failure of circulation with a wide range of aetiologies and a common set of consequences, namely globally insufficient oxygen delivery and subsequent cellular and tissue hypoxia
- The four determinants of cardiac output are heart rate, contractility, preload and afterload, and in the shocked patient these are modulated by various neuronal and hormonal compensatory mechanisms in order to maintain perfusion of vital organs
- The recognition of hypovolaemic shock relies on comprehensive clinical examination, regular monitoring of vital observations, point of care testing, and advanced haemodynamic monitoring
- Continuous cardiac output monitoring helps the clinician distinguish between the needs for fluids, inotropes and vasopressors, and reduces complications in surgical patients when used intraoperatively
- Crystalloids solutions such as 0.9% sodium chloride and Hartmann's are recommended for fluid resuscitation, and colloids are no longer used
- Hypotensive resuscitation describes keeping a patient's blood pressure lower than normal, allowing vital organ perfusion but avoiding dilutional coagulopathy and the disruption of newly formed blood clots
- Blood transfusion should be balanced, with packed red blood cells and fresh frozen plasma given in a 1:1 ratio, and platelets, cryoprecipitate and prothrombin complex concentrate if indicated by point of care testing and the clinical situation
- Tranexamic acid should be given in acute haemorrhage, calcium should be replaced in massive transfusion, and vasopressors and inotropes may be used temporarily while other treatment restores the circulating volume