Applied physiology: Understanding shock

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Summary
The primary function of the cardiovascular system is to maintain an adequate delivery of oxygen to the tissues to ensure the continued production of ATP via oxidative phosphorylation. Oxygen delivery is primarily dependent on cardiac function and is therefore sensitive to changes in myocardial contractility, preload and afterload. However, matching oxygen delivery to metabolic activity requires circulatory adjustments and normal transfer kinetics. This article will discuss the regulation and defence of cardiac output and oxygen delivery in health and in shock.

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Practice points

- Blood pressure is regulated to ensure tissue perfusion; it is not an end in itself
- The patient does not have to decompensate to be in shock
- Therapy should be aggressive and concentrate on improving cardiac output
- Once organ injury occurs, shock cannot always be corrected by treating the aetiology

Normal cardiac physiology

‘Arterial oxygen content, arterial pressures, velocity of bloodstream, mode of cardiac work, mode of respiration, … all combine their actions only in the service to the cells’ (Pfluger, 1872).

Prior to discussing shock states, it is useful to review normal cardiac physiology and the dynamics of oxygen supply, albeit in a relatively selective and superficial way, since this will permit clarity later.

Metabolic function of oxygen

The functions of the body require the continuous production of ATP. In the absence of oxygen to act as an electron acceptor within the mitochondria, oxidative phosphorylation cannot occur. The level of mitochondrial oxygen required to ensure the continued generation of ATP via the tricarboxylic acid cycle is 0.1–0.3 kPa, and the oxygen concentration required in the capillary blood to ensure this level of intramitochondrial oxygen is 1–3 kPa. The remit of the cardiovascular system is to ensure the maintenance of this gradient for oxygen transport to the mitochondria.

Cardiac output and oxygen delivery

The heart generates the motive force required to propel blood into the arterial system. The volume of blood expelled from each ventricle during systole (stroke volume) is...
determined by the degree of ventricular filling during diastole (preload), the contractility of the myocardium and the resistance against which the ventricle pumps (afterload). The total volume of blood ejected per minute is termed the ‘cardiac output’ (stroke volume heart rate). Sympathetic activity can increase cardiac performance by increasing venous return, and hence preload, cardiac contractility and heart rate. It may also, by increasing the afterload through peripheral vasoconstriction, impede cardiac output. The systemic cardiac output arises from the left ventricle and carries oxygenated haemoglobin. The cardiac output therefore provides convective oxygen transport to the individual organs. In the tissues, an extensive capillary network with a large combined surface area ensures that the capillary blood flow is slow and lies in close proximity to the cells. These factors ensure that the diffusion of oxygen from the blood to the cells is facilitated. The oxygen made available to the body (or organ) is the oxygen delivery and is the product of the arterial concentration of oxygen and the flow to the body (or organ) per minute:

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\text{Oxygen delivery} = \text{cardiac output} \times \text{arterial oxygen concentration.}
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As blood traverses the capillary beds, oxygen is extracted by the tissues and used to drive metabolism. The oxygen so used represents the oxygen consumption. This concept can be applied to the whole body or to an individual organ. In health, whole-body oxygen delivery exceeds consumption by a factor of approximately 4, so it is evident that there is a ‘safety margin’ before a reduction in oxygen delivery will adversely affect tissue function through hypoxia. It should be borne in mind, however, that individual organs have different oxygen delivery/consumption relationships. The kidney has a very high blood flow and extracts relatively little oxygen, whereas the heart extracts over 50% of the oxygen delivered to it. The cardiovascular system will initially compensate for an increase in oxygen consumption by increasing oxygen supply, largely by increasing cardiac output, in order to maintain an extraction ratio of 4. When increasing oxygen demand can no longer be met by raising the oxygen delivery, the amount of oxygen extracted per unit of blood flow will increase.

Blood flow to the individual organs is dependent upon their metabolic activity and therefore their demand for oxygen. The products of local cellular metabolism act upon the vascular supply to produce vasodilatation. This response is sufficient to counteract the vasoconstriction induced by sympathetic discharge, and ensures the matching of oxygen delivery and consumption. At the level of the microvasculature, reduced oxygen delivery may result in a relaxation of the precapillary arterioles, resulting in the recruitment of capillary vessels and increasing the density of perfused capillaries within the tissue. Capillary recruitment reduces the diffusion distance between the blood and the cells, and further increases capillary transit time so that oxygen extraction is maximized.

**Arterial peripheral circulation**

The action of carotid and aortic baroreceptors determines the arterial resistance and, together with the cardiac output, produces a blood pressure (blood pressure = cardiac output x peripheral resistance). In the arterial system, a high blood pressure is maintained by the presence of a high vascular tone (low vascular capacitance). In health, arterial blood pressure is controlled within tight limits. Blood pressure is maintained to supply the flow demands of all the organ beds despite variations in the regional demand for organ blood flow. The vascular beds of the individual organs vary in their response to sympathetic vasoconstrictor activity. In the brain and heart, local factors control blood flow through the vascular beds, and these mechanisms are capable of over-riding sympathetically driven vasoconstriction. In these organs, it is metabolic activity that determines the flow through the vascular bed. In organs with a blood flow in excess of their metabolic needs, as seen in the thermoregulatory function of the skin or the excretory function of the kidney, the action of sympathetic vasoconstriction is more pronounced.

Changes in arterial pressure produced via the action of carotid and aortic baroreceptors, and therefore the pressor vasomotor centre of the medulla, are intended to counteract the fluctuations in arterial blood pressure caused by the variation in regional demands. Alone, these mechanisms are unable to maintain a normal blood pressure if cardiac output is not maintained. The response range of the baroreceptors is narrow so, in adults, maximal sympathetic outflow is induced via the arterial baroreceptors by a mean arterial pressure of 70mmHg. However, the aortic and carotid bodies can continue to stimulate sympathetic activity via the action of chemoreceptors responsive to a reduced oxygen delivery as cardiac output falls.

**Venous peripheral circulation**

Seventy-five percent of the total blood volume is contained within the venous system. Despite this large volume of blood, the intravascular pressure is low as a result of the high vascular capacitance. Venous blood flow to the heart is dependent upon a pressure gradient between the peripheral and central veins, and an alteration in the volume of blood within the venous system or the capacitance of the venous vessels will vary the pressure gradient and therefore the venous return to the heart. Sympathetic activity reduces the compliance of venous vessels so that, for any given blood volume, the venous pressure will increase and the gradient for venous return to the right atrium will be augmented. Venous resistance may unfortunately also be increased, and this will tend to impede venous return. The cardiac filling pressure is monitored by stretch receptors in the central veins, right atrium and pulmonary artery. Any reduction in cardiac filling will result in an enhanced sympathetic action on both the arterial and the venous vessels, increasing blood flow to the heart. The heart responds to this increased venous return by increasing the cardiac output. It is obvious that the two must match over any significant period of time.

**Summary and conclusion**

In response to acute cardiovascular compromise, the body defends the cardiac output and therefore oxygen delivery by
augmenting cardiac function, increasing venous return and redirecting the arterial blood flow from non-nutritive functions by the action of the sympathetic system. Individual organs regulate their blood flow in proportion to their metabolic demands. Arterial blood pressure cannot be maintained through the action of sympathetic activity alone and ultimately requires an adequate cardiac output.

**Physiology of shock**

‘Shock is the manifestation of the rude unhinging of the machinery of life’ (Samuel V. Gross, 1872).

**Classification of shock**

Shock is an inadequate delivery of oxygen and nutritive substrates to the tissues, and has usually been classified on the basis of its aetiology. This is, however, unhelpful in understanding the basic physiological disruptions present in the shock patient. Guyton proposed that shock states could essentially be classified into decreased cardiac output arising from factors related to either the peripheral circulation or primary cardiac dysfunction. In Guyton’s scheme, the gradient driving the venous return to the heart could be altered by changes in the capacitance of the circulation and the blood volume. A low capacitance and normal or increased blood volume will result in an increased venous return. High capacitance will reduce venous return, as will a decreased blood volume. Under this paradigm, shock occurs because of an increase in vascular capacitance (anaphylaxis, spinal shock) or a reduction in blood volume (haemorrhage, burns, dehydration). A resistance to venous return will impair cardiac filling and hence cardiac output (tension pneumothorax).

Although an oversimplification (and reflecting Guyton’s bias that the peripheral circulation is the key to understanding cardiovascular physiology), this approach provides a physiological basis for understanding shock. Shoemaker et al. also pointed out the limitations of the traditional classification, and directed his attention towards identifying patterns of oxygen transport in shock patients. Shock is often now discussed in terms of the interaction between cardiac output and vascular resistance, thus conveying better the clinical state of the patient. The majority of paediatric patients presenting in shock will have one of three aetiologies: hypovolaemia, cardiac failure or sepsis. In considering these entities, it will become apparent that there are similarities in both the physiological disruption they cause and the compensatory mechanisms they invoke.

**Hypovolaemic (haemorrhagic) shock**

Examination reveals a child with cold, clammy skin, reduced peripheral perfusion, tachycardia with thready pulses (indicating a narrow pulse pressure), oliguria and tachypnoea. The blood pressure is often normal or only slightly reduced. As the blood pressure falls, the child becomes increasingly unresponsive. A blood gas examination will show a metabolic acidosis with evidence of compensatory hypocapnia (a mixed respiratory and metabolic acidosis in this situation indicating an imminent collapse). A raised serum lactate level suggests anaerobic metabolism and a failure of adequate tissue oxygen delivery.

With the loss of volume, venous pressure and, therefore, cardiac preload are reduced and cardiac output falls. Stretch receptors in the great vessels and atria detect the reduced preload, and stimulate sympathetic outflow from the pressor area of the medulla. Sympathetic vasoconstriction reduces the capacitance of the peripheral circulation, resulting in an increased venous return. Arterial vasoconstriction initially preserves the blood pressure through an increase in resistance alone, but as blood loss continues, perfusion is diverted from non-essential areas such as the skin and kidneys, with the result that the skin becomes cool, the capillary refill time lengthens and oliguria develops. Blood is also diverted from the splanchnic circulation. This is not the diversion of luxury perfusion, and it may thus threaten the integrity of the gastrointestinal tissue.

The mobilization of sequestered venous blood volume and vasoconstriction initially maintains the blood pressure (so-called ‘compensated shock’) but, as volume loss continues, hypotension supervenes. Blood flow, and hence oxygen, is directed towards those organs whose autoregulatory mechanisms counteract the generalized vasoconstriction. Sympathetic stimulation increases myocardial contractility and heart rate in an attempt to maintain cardiac output and oxygen delivery.

With a continued volume loss, myocardial work increases to the point at which the circulation cannot meet the demands of the heart itself, and cardiac failure ensues. Oxygen consumption eventually falls as oxygen delivery becomes inadequate, resulting in organ injury. Tissue hypoxia results in acidosis that drives a respiratory compensation. Sympathetic activity will be augmented by the action of chemoreceptors and centrally as cerebral perfusion is impaired. As the system is unable to meet the demands of the ventilatory pump (the intercostal muscles and diaphragm), respiratory failure ensues. The degree of hypovolaemia associated with these changes has been investigated in acute haemorrhage. An acute loss of circulating blood volume of 10–20% induces the onset of tachycardia, hypotension and vasoconstriction, whereas a volume loss >40% induces complete circulatory collapse.

As the severity of oxygen delivery impairment increases, alterations arise in the microcirculation, and cytokines are released from injured tissue. These changes are not reversed by volume resuscitation. A point is reached at which the hypovolaemic shock is not reversible by a mere correction of the initial aetiology. In hamsters experiencing acute haemorrhage to a mean arterial pressure of 40 mmHg (from a normal level of 80 mmHg) that was maintained for 4 h, reduced tissue capillary density and tissue hypoxia persisted in approximately 70% of animals despite replacement of the blood volume. In a rat model of haemorrhagic shock, 1 h of hypovolaemia was associated with reduced cardiac function and a raised level of tumour necrosis factor-alpha (TNF-α). That TNF-α was responsible for the altered cardiac function was supported by a 50% improvement in cardiac function following immunoneutralization of the TNF-α.
Cardiogenic shock

In all forms of shock, progression to cardiovascular collapse will occur unless appropriate and timely therapy is offered. To this extent, cardiogenic shock can complicate all shock states. Cardiogenic shock traditionally implies a primary cardiac disease as the cause of the shock state; in the paediatric population, it is often encountered in the setting of congenital heart disease, especially in the post-operative population. These patients are particularly at risk as they have experienced ischaemic and reperfusion injuries to a myocardium that was preoperatively dysfunctional.

The equation above illustrates that, in the face of an acute reduction in CO₂, oxygen delivery cannot be sustained. The circulation employs the array of compensatory mechanisms discussed in the previous section, although their effectiveness depends on preservation of cardiac function. In the setting of cardiac failure, it is likely that they will serve only to cause further cardiac decompensation. As myocardial function deteriorates and stroke volume is compromised, cardiac output is maximized by increasing heart rate. Tachycardia results, however, in increased cardiac work, and vasoconstriction results in increased afterload. An increase in venous return augments the ventricular end-diastolic volume. The myocardium is stretched by this volume and, as in Starling’s isolated heart tissue model, will respond by a greater force of contraction. The resulting cardiac dilatation may initially help to preserve the stroke volume, but eventually results in increasing cardiac dysfunction. Salt and water retention is encouraged by the action of the renin-angiotensin system increasing cardiac dysfunction. Salt and water retention is preserved to maintain stroke volume despite a reduced ejection fraction. Systolic and diastolic dysfunction may both be seen, frequent finding of a normal or even increased cardiac output. Despite this, oliguria is frequently present, and a compensated metabolic acidosis or raised serum lactate level indicates that the cardiovascular system is under strain.

Cardiac dysfunction in septic shock

The majority of patients in the early stages of sepsis present with hyperdynamic cardiovascular function, characterized by an increased cardiac output and a low peripheral resistance. The blood pressure is often only slightly lower than normal (warm shock). Patients are tachycardic and often tachypnoeic, with apparently good peripheral perfusion. Despite this, oliguria is frequently present, and a compensated metabolic acidosis or raised serum lactate level indicates that the cardiovascular system is under strain.

Vasodilatation occurs early and is initially caused by the action of constitutive nitric oxide. Later, under the action of endotoxin, constitutive nitric oxide synthetase is down-regulated, and nitric oxide production becomes a function of inducible nitric oxide synthetase. The vasodilatation is profound and hyporesponsive to sympathetic vasoconstrictor activity (vasoplegic), either endogenous or exogenous. Cardiac function is depressed early in sepsis despite the frequent finding of a normal or even increased cardiac output. Systolic and diastolic dysfunction may both be seen, with a reduction in myocardial contractility and diastolic compliance, respectively. The resulting reduction in cardiac output is compensated by tachycardia, volume loading to maintain stroke volume despite a reduced ejection fraction (the fraction of ventricular end-diastolic volume ejected during systole), and a reduced afterload associated with the intense vasodilatation. Echocardiographic evidence of ‘good ventricular function’ needs to be evaluated in light of these considerations.

This septic cardiomyopathy is attributed to the actions of cytokines, particularly TNF-α and IL-1. TNF-α may have a direct cardiotoxic effect, but it appears that TNF-α and IL-1 exert their effect by the induction of inducible nitric oxide synthetase in the myocardium. The nitric oxide produced, acting via guanylyl cyclase, increases the level of cellular cyclic guanosine monophosphate, resulting in the inhibition of calcium entry into the myocardium and therefore impaired contraction. A synergistic action of the cytokines...
TNF-α, IL-1 and IL-6 has also been proposed as a mechanism for myocardial injury, based on their action of reducing contractility in muscle strips.

**Vasculature in septic shock**

The microcirculation also exhibits injury and dysfunction. Sepsis is associated with increased vascular permeability caused by the action of complement C3a and C5a. The result is increased interstitial oedema and reduced diffusive oxygen transport to the tissues. In addition, a reduced tissue capillary density is seen. Microcirculatory compromise may be exacerbated by vascular obstruction with microthrombi formed in response to a TNF-α-induced procoagulant state. This has been attributed in part to decreased protein C and protein S activity. A recent study investigating the response of septic adult patients to activated protein C indicated improved patient survival, and a paediatric study is currently being undertaken.

The normal compensatory mechanisms, discussed above, are often overwhelmed, and the response to therapy may be poor. Improved venous return can initially help to offset impaired cardiac function, but with vasoplegia and 'capillary leak', the patient often requires large volumes of fluid for resuscitation. As mentioned above, sympathetic activity may have little effect on the peripheral vasculature, and the concern has been that sepsis represents a situation of mismatch between oxygen delivery and oxygen requirement. Microvascular abnormalities merely compound the problem of oxygen delivery to the tissues. Work in animal models and human patients with septic shock suggests that tissue oxygen delivery may, even when adequate, be associated with reduced cellular energy production. The mechanism appears to be impaired mitochondrial function, i.e. the mitochondria cannot use the available oxygen.

Different mechanisms have been proposed, but nitric oxide or its reactive product peroxynitrite appear to be involved. With progression of the disease process, a tissue oxygen debt accumulates, and cardiovascular collapse and multiple organ failure (cold shock) ensue.

**Conclusions**

This article has concentrated on the cardiovascular consequences of, and response to, shock and has not considered metabolic dysfunction or non-cardiovascular compensatory mechanisms; the interested reader will find the reference list a useful guide to locating this information. Shock is a complicated, dynamic process. Successful therapy requires an understanding of the disease process and aggressive management. An article of this length cannot convey the full complexity of the shock state; in attempting to simplify, I can only hope that I have not confused.

**References**


**Further reading**