Hypotension

Clinical problems

Update 2012

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## Hypotension
### Update 2012

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LEARNING OBJECTIVES

After studying this module on Hypotension, you should be able to:

1. Define hypotension and shock and list causes of hypotension
2. Select the appropriate monitoring and initiate treatment to restore circulation
3. Effectively manage patients with persistent hypotension
4. Outline outcomes that may result from hypotension

FACULTY DISCLOSURES

The authors of this module have not reported any disclosures.

DURATION
7 hours

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INTRODUCTION

Hypotension is a commonplace occurrence on the ward, in the emergency department, in the operating theatre and in the ICU. There are multiple causes, either acting alone or in combination, that have to be considered, diagnosed and promptly acted upon to prevent further deterioration in organ perfusion and function. Contrary to the misconception we may have learnt as medical students, hypotension is not synonymous with shock; each can exist without the other. Misunderstanding of basic physiology can thus result in missed diagnosis or misdiagnosis, inadequate or inappropriate treatment and avoidable deterioration in organ function. This module attempts to demystify and clarify, and place hypotension in a correct context.

1/ DEFINING HYPOTENSION

What is hypotension?

No specific value of blood pressure exists for the population-at-large below which hypotension can be said to be present. Blood pressure increases with age. At any given age, it will vary between individuals. Some patients are chronically hypertensive, while others are on long-term therapy e.g. β-blockade or angiotensin-converting enzyme (ACE) inhibition which results in low-pressure values that can be considered the ‘normal’ baseline for that person. It is important for the intensivist to establish, wherever possible, an individual patient’s usual blood pressure (BP), plus any relevant medication, by direct questioning of the patient, relatives or family practitioner, and/or interrogation of recent hospital records. A short-lived episode of hypotension may be completely asymptomatic. Alternatively, it may be associated with transient dizziness or syncope. Unless the patient is awake, these usually pass unrecognised.

Criteria for hypotension: A drop in systolic blood pressure more than 40–50 mmHg from baseline, a systolic value less than 90 mmHg or a mean BP below 60 mmHg are often cited as criteria for hypotension, but these should be placed in context with the comments made above. For example, an 18-year-old may have a usual reading of 85/55 mmHg but is likely to be symptomatic well before his systolic pressure has fallen to 45 mmHg. On the other hand, a chronic, untreated hypertensive 70-year-old may or may not be symptomatic if his blood pressure falls from a normal value of 190/95 to 140/70 mmHg.
Q. What techniques can measure blood pressure?  
A. Blood pressure can be measured invasively via a pressure transducer connected to an intra-arterial cannula, or non-invasively by sphygmomanometry.

Q. Are fingertip, photoplethysmographic devices useful in the critically ill?  
A. They are not sufficiently reliable or validated in the critically ill to be recommended for use.

Q. What are the advantages and pitfalls of the invasive technique?  
A. The advantages of the invasive approach are the ability to monitor blood pressure continuously; to derive additional information from the arterial pressure waveform such as systolic pressure variation which is a marker of fluid responsiveness in mechanically ventilated, non-spontaneously breathing patients; and to use the arterial cannula to draw blood samples without discomfort to the patient. Pitfalls include the risks inherent in placing an invasive device, such as infection, bleeding, thrombus and pseudoaneurysm formation. Furthermore, erroneous data may be obtained for a variety of reasons.

Q. Summarise the causes of erroneous data.  
A. Reasons include faulty calibration, under- or over-damping of the signal, or zeroing the transducer at the wrong location (it should be at the level of the left atrium). Also, a discrepancy between right and left-sided invasive assessments could occur due to presence of an arterial stenosis.

Q. Outline the causes for error and disadvantages of non-invasive sphygmomanometry.  
A. Causes include erroneous readings if the wrong cuff width relative to the patient’s arm is applied. It may have difficulty in detecting an accurate blood pressure if the pressure is very low or tachyarrhythmias are present. In patients with coagulopathy, frequent inflation of the cuff can lead to local purpura or bruising.

See the PACT module on Haemodynamic monitoring

**Note**  
Hypotension may thus be considered to be an unusually low blood pressure at which a patient is often symptomatic or manifests clinical features. These may be relatively mild and non-specific (e.g. dizziness or malaise), organ-specific (e.g. coma or chest pain), or associated with systemic features of shock.
Q. How can you distinguish between hypotension and shock?

A. With shock, the patient is usually severely ill with generalised features of impaired organ perfusion and function, metabolic acidemia ± hypotension. Hypotension in the absence of systemic shock may produce no symptoms whatsoever, or features varying from mild (e.g. dizziness on standing) to severe.

The severe manifestations of hypotension are usually more single organ-specific compared to shock and usually affect an already compromised blood supply to that organ, for example a cerebrovascular event, or cardiac ischaemia.

Q. List examples of hypotension which may not require treatment; and give reasons for your answers.

A.
- Idiopathic hypotension: blood pressure is normally distributed so a proportion of healthy individuals will have a low blood pressure.
- Drug-induced: for example, many elderly patients on ACE (angiotensin-converting enzyme) inhibitor treatment for heart failure are hypotensive and may be completely asymptomatic.
- Postural hypotension: this is often transient on changing to an erect posture and may result in giddiness, vertigo or syncope. The vast majority of affected subjects can be managed by simple advice alone.
- In the ICU, patients may be hypotensive as a result of sedatives and/or vasodilators and/or the disease process but show no signs of organ hypoperfusion. In such circumstances it is acceptable to closely monitor and only treat if the need arises.

Hypotension and shock

In clinical practice, the terms hypotension and shock are often used interchangeably. However, it is important to stress that shock may be present despite a normal blood pressure. Conversely, the blood pressure may be low without shock being present.

Hypotension does not necessarily equate to shock but, in the critically ill patient, is often associated with impaired O₂ transport (TO₂) to tissues or impaired oxygen utilisation/consumption (VO₂), therein. A fall in TO₂ can result in decreased tissue oxygenation and an inadequate supply of adenosine triphosphate (ATP) relative to cellular requirements. Dysoxia (impairment of tissue oxygenation) may also occur as a consequence of mitochondrial damage or inhibition where oxygen is available but not consumed, e.g. carbon monoxide or cyanide poisoning, and sepsis.
Causes of hypotension

The aetiology may be pathological or iatrogenic and is often multifactorial. For example, myocardial ischaemia may ensue from severe haemorrhage, resulting in further compromise of cardiac function.

Two important questions the clinician needs to ask are whether there is a low cardiac output and is this low cardiac output preload-dependent?

Causes of hypotension may be classified as follows:

- Reduced ventricular filling (hypovolaemic):
  - Haemorrhage
  - Third space fluid losses e.g. increased capillary leak in sepsis, burns
  - GI losses e.g. diarrhoea, fistulae, large gastric aspirates/vomiting
  - Transdermal losses e.g. burns, hyperpyrexia syndromes
  - Polyuria e.g. diabetes insipidus, diuretics
  - Inadequate fluid intake or administration
  - Vasodilating drugs e.g. nitrates, propofol

- Reduced ventricular filling (obstructive):
  - Flow obstruction e.g. pulmonary embolus, tension pneumothorax, cardiac tamponade, lung hyperinflation

- Reduced ventricular contractility (cardiogenic):
  - Myocardial ischaemia, infarction, stunning
  - Severe tachycardia, arrhythmia
  - Myocarditis/cardiomyopathy e.g. viral
  - Systemic inflammation e.g. sepsis, anaphylaxis, post-cardiac surgery
  - Drugs e.g. β-blockers, calcium channel blockers, anthracycline chemotherapy
  - Myocardial contusion from direct trauma

- Decrease in systemic vascular resistance due to excess arterioidilation ± vascular hyporeactivity (distributive):
  - Systemic inflammation e.g. sepsis, anaphylaxis, post-cardiac surgery
  - Drugs e.g. ACE inhibitors, nitrates, calcium antagonists, sedatives
  - Endocrine disorders e.g. absolute (Addison’s) or relative adrenocortical insufficiency, phaeochromocytoma (may present with paroxysmal hypotension)
  - Loss of peripheral sympathetic activation, e.g. epidural, spinal cord injury
Clinical features

Cardiogenic, hypovolaemic and obstructive aetiologies are generally associated with low cardiac output states and have corresponding clinical features. The circulation of a patient who is hypotensive due to a septic, anaphylactoid or neurogenic cause is usually hyperdynamic. However, profound myocardial depression, major third space fluid losses and/or extreme vasodilatation may produce a low flow state. Conversely, a high-output cardiac failure can be recognised in situations such as severe valvular regurgitation (e.g. endocarditis), wet beriberi and thyrotoxicosis.

An 18-year-old previously fit patient presented with meningococcal septicaemia. He received high volume fluid loading to correct his hypotension. Within an hour, frothy pink sputum appeared in the tracheal tube indicating pulmonary oedema. Greater care and perhaps earlier monitoring might have protected against pulmonary oedema because this patient had profound myocardial depression. Failure to respond as expected to fluid loading is reason to consider additional monitoring.

Q. Is the differentiation between hypotension due to a low or high output state straightforward clinically? Give reasons.

A. No. This can present considerable diagnostic difficulty and it is unlikely that any clinician can differentiate between high and low cardiac output states with complete certainty.

Q. Is the blood lactate level a distinguishing marker? Explain why.

A. No. It may be elevated in both types of hypotensive state.

Q. Describe clinical features that help to distinguish hypotensive patients with low or high cardiac output.

A.

i. High outpout (hypotensive) states:
In general (though not always), patients with hyperdynamic circulations have bounding pulses (carotid and radial), a pulsatile precordium, dilated peripheral vessels, increased pulse pressure and warm peripheries.

ii. Low cardiac output states manifest clinical features of vasoconstriction with cold, white peripheries, constricted hand veins, narrow pulse pressure and a thready pulse.

In the next ten hypotensive patients that you see, identify the key clinical symptoms that help to categorise the different types of hypotension: discuss the specificity of these clinical symptoms with colleagues. How many of them have single or multifactorial causes?
If cardiac output is also being measured, assess the accuracy of your clinical assessment. Re-evaluate the patient in the light of this knowledge. You may also be able to question the accuracy of the cardiac output measurement; the technique itself may be invalid in some situations (e.g. classic bolus thermodilution in severe tricuspid regurgitation) or when incorrectly set up.
2/ IMMEDIATE TREATMENT AND MONITORING – UNDERSTANDING THE PATHOPHYSIOLOGY

As seen in Task 1, hypotension results from circulatory failure. The principal aim of treatment is to restore an adequate circulation in terms of both pressure and tissue perfusion.

Due to the lack of specificity of key clinical features in categorising hypotension (see activity in Task 1), diagnosis and treatment should be considered simultaneously since a good response to treatment helps to confirm the working diagnosis.

Immediate management includes ensuring oxygen supply, fluid therapy, assessment of the need for inotrope or vasopressor therapy and consideration of specific treatments to deal with the direct cause, e.g. drainage of tension pneumothorax. These will be considered later; the interventions involved are summarised in a management algorithm below.

Summary management algorithm

The figure below shows a clinical management algorithm for instituting ‘first aid’ treatments (such as oxygen and fluid), and considering the underlying cause, should hypotension persist after perceived adequate fluid resuscitation – see also next task on persistent hypotension.
Clinical management algorithm
Physiological principles and monitoring techniques

As previously mentioned (Task 1), hypotension can result from either a low cardiac output (CO) and/or a low vascular resistance (MAP = CO × SVR).

A low cardiac output is likely to be associated with a low TO₂ (TO₂ = CO × CaO₂, where CaO₂ is arterial O₂ content).

**Note**

TO₂ (oxygen transport) is being used interchangeably here with DO₂ (oxygen delivery).

When TO₂ decreases, VO₂ is maintained (at least, initially) by an increase in EO₂ (oxygen extraction). When TO₂ decreases beyond a certain threshold it induces a decrease in VO₂. This point is known as the critical TO₂ (TO₂crit), below which there is a state of O₂ uptake-to-supply dependency (shock; see figure, below). Below the TO₂crit a decrease in consumption (VO₂) is associated with an increase in lactic acid production.

**O₂ uptake (VO₂) to O₂ supply (TO₂) relationship**

On the other hand, a low vascular resistance is often associated with impaired O₂ extraction (EO₂) by the tissues due to a mitochondrial pathology.
Q. What are the determinants of \( \text{CaO}_2 \)?

A. Haemoglobin (g/dL) \times 10 \times \text{arterial saturation} \times 1.34 \text{ (mL O}_2 \text{ carried by 1 g of Hb)}. The amount of oxygen dissolved in plasma can be ignored in non-hyperbaric conditions.

Q. What is the most effective way of increasing \( \text{CaO}_2 \)? Explain why.

A. As arterial saturation is usually >95% unless the patient is very hypoxaemic, the most effective means of increasing \( \text{CaO}_2 \) is to increase the Hb concentration. A rise from 8 to 10 g/dL will increase content by 25%.

Q. Can it be assumed that the transfused blood is immediately able to carry oxygen effectively? Give reasons.

A. No. Decreased 2,3-DPG and other factors may reduce oxygen carrying ability though this cannot be routinely measured \textit{in vivo}.

Central or mixed venous \( O_2 \) saturation

In the clinical setting, the mixed venous \( O_2 \) saturation (\( S\overline{v}O_2 \)) can be used to assess the whole body \( \text{VO}_2\text{–TO}_2 \) relationship. In the absence of a pulmonary artery catheter, the central venous \( O_2 \) saturation (Scv\( O_2 \)) is being increasingly used as a reasonably accurate surrogate.

According to the Fick equation, tissue \( \text{VO}_2 \) is proportional to \( \text{CO} \), as \( \text{VO}_2 = \text{CO} \times (\text{CaO}_2 – \overline{\text{CvO}}_2) \) where \( \overline{\text{CvO}}_2 \) is the mixed venous blood \( O_2 \) content. As the dissolved content of \( O_2 \) in plasma is very low in a non-hyperbaric environment, this component can be ignored. Thus: \( \text{VO}_2 \) (mL/min) = \( \text{CO} \times (\text{SaO}_2 – \overline{\text{SvO}}_2) \times \text{Hb} \times 1.34 \times 10 \).

The four determinants responsible, alone or in combination, for a decrease in \( \overline{\text{SvO}}_2 \) are:

- Hypoxaemia (decrease in \( \text{SaO}_2 \))
- An increase in \( \text{VO}_2 \) without an increase in \( \text{TO}_2 \)
- A fall in \( \text{CO} \) (for example due to hypovolaemia, cardiac failure, obstructive shock)
- A decrease in \( \text{Hb} \)

The normal range for \( \overline{\text{SvO}}_2 \) is 68 to 77%. An increase in \( \text{VO}_2 \) without an increase in \( \text{CO} \) or \( \text{TO}_2 \), or a decrease in \( \text{TO}_2 \) and no change in \( O_2 \) requirements, will result in an increase in extraction (EO\( _2 \)) and a fall in \( \overline{\text{SvO}}_2 \). \( EO_2 \) and \( \overline{\text{SvO}}_2 \) are linked by a simple equation: \( EO_2 = 1 – \overline{\text{SvO}}_2 \), assuming \( \text{SaO}_2 = 1 \).

Due to the shape of the oxyhaemoglobin dissociation curve (figure, below), a small imbalance in the \( O_2 \) supply–demand relationship will result in a big decrease in \( \overline{\text{SvO}}_2 \).
Tissue hypoxia is usually present when $S_vO_2$ falls below 40–50%, however this may also occur at higher levels of $S_vO_2$. Other markers of cellular $O_2$ inadequacy (e.g. hyperlactataemia, markers of organ dysfunction) should be assessed in conjunction with $S_vO_2$. It is important to remember that high $S_vO_2$ (and $ScvO_2$) can also be an indicator of impaired tissue oxygenation.


**Venous $O_2$ saturation ($S_vO_2$) to cardiac index (CI) relationship**

According to the modified Fick equation, the relationship $S_vO_2$/CI is curvilinear. Subsequently, when $O_2$ uptake ($VO_2$) is constant, CI variations lead to large variations in $S_vO_2$ when the initial CI value is low.

If initial therapy to treat the hypotension ($O_2$, fluid resuscitation and/or low dose inotropes and/or red blood cell transfusion) does not restore $S_vO_2$ to at least 65% (the Surviving Sepsis guidelines – see below), then Hb, $SaO_2$, and CO should be individually measured and further treatment titrated accordingly.

Research has emphasised the potential utility of central venous oxygen saturation ($ScvO_2$) for ready detection of a global oxygenation impairment. Experimental studies show that changes in $S_vO_2$ and $ScvO_2$ closely reflect circulatory disturbances during periods of hypoxaemia, haemorrhage and subsequent resuscitation. Although absolute values differed, the change in these two variables correlated closely.
Q. Provide a rationale to explain why \( \text{ScvO}_2 \) is usually higher than mixed \( \text{SvO}_2 \) in shock?

A. The level of oxygen extraction by upper body organs that drain their venous blood into the superior vena cava is usually lower than that extracted by lower body organs draining into the inferior vena cava during shock. Thus central venous saturations are usually higher than mixed venous values in shock states.

**Note** Remember: in the initial resuscitation of circulatory shock, insertion of a central venous catheter is a routine technique. This is a more rapid and simpler procedure than pulmonary artery catheterisation which is generally not a resuscitation procedure – but does provide the gold-standard \( \text{SvO}_2 \) measurement.

**Important results**: in the well-known study by Rivers et al, patients admitted to the emergency department with severe sepsis and septic shock were randomised to standard therapy (aiming for a central venous pressure (CVP) of 8–12 mmHg, MAP >65 mmHg, and urine output >0.5 ml/kg⁻¹/h⁻¹) or to early goal-directed therapy (EGDT) where, in addition, an \( \text{ScvO}_2 \) of >70% was targeted by optimising fluid administration, keeping haematocrit >30%, and/or giving dobutamine to a maximum of 20 µg/kg⁻¹/min⁻¹.

The initial \( \text{ScvO}_2 \) in both groups was low (49 ± 12%), reminding us that severe sepsis is often a hypodynamic condition before fluid resuscitation is started.

It is important to note that other studies have not reported such low \( \text{ScvO}_2 \) values and mortality rates in the control group were quite high and therefore the results of this single centre study must be interpreted cautiously when applied to different settings. However, hospital mortality fell significantly in the EGDT group. Importantly, 99.2% of patients receiving EGDT achieved their haemodynamic goals within the first six hours compared with 86% in the standard group. It remains unclear which aspect of the package of EGDT might improve outcome but this was the first study demonstrating that early identification of patients with sepsis **plus** timely initiation of therapy to achieve an adequate level of tissue oxygenation significantly improves mortality. Other groups have since suggested that using lactate clearance might be an alternative target to guide management in EGDT. Ongoing trials in the US, UK and Australia will hopefully provide further information to better inform how early sepsis resuscitation can be provided.

**References**


Assessing global flow

Global flow (CO) is dependent on preload, myocardial contractility, afterload, and heart rate. Regional flow distribution is not homogeneous but is dependent on central and local vascular tone.

Vascular resistance

Measurement of regional resistance is not routinely accessible in clinical practice; the composite whole body systemic vascular resistance (SVR) is taken as a surrogate. As a simplification, mean arterial pressure (MAP) = CO × SVR. When CO decreases, MAP remains stable if SVR increases to ‘compensate’; this corresponds to increased sympathetic tone with vasoconstriction. In organs with a low EO₂ reserve (heart, brain), flow is preserved. By contrast, flow is reduced in organs with a high reserve. Overall, EO₂ increases and S\(\bar{\text{v}}\)O₂ decreases.

The flow-pressure relationship

Minimal data exist to guide selection of the optimal threshold for blood pressure maintenance. Arbitrary values of a systolic blood pressure (SBP) of 90 mmHg or a MAP of 60–65 mmHg have traditionally been chosen. However, these should be placed in context with the patient’s age and normal blood pressure. Such values are normal for a young adult but may be insufficient for a patient with chronic hypertension.

In the next two septic and two non-septic oliguric patients you see with a MAP ≤55 mmHg after adequate fluid resuscitation, observe at what level of MAP the urine output recovers (or not). What do you conclude?

Evidence suggestive of inadequate tissue perfusion (e.g. hyperlactataemia, metabolic acidosis, S\(\bar{\text{v}}\)O₂ <40%, decreased urinary flow) and its persistence despite initial therapy (fluid, low dose inotropes, red cell transfusion) should prompt optimisation of stroke volume according to the Frank–Starling curve. This can be assessed by a number of invasive or non/minimally invasive techniques (see below).

Refer to the PACT modules on Haemodynamic monitoring and Oliguria and anuria (Acute Kidney Injury Part I).

Q. What x-axis and y-axis variables can be used to construct the Frank–Starling relationship in a given patient?

A. Assuming blood pressure does not change, stroke volume can be plotted on the y-axis. For the x-axis, the ideal variable should be left ventricular end-diastolic volume.
However, as this is not routinely measured, pulmonary artery wedge pressure or central venous pressure can be used instead, recognising the problem that filling pressures correlate poorly with filling volume.

**Select the appropriate monitoring for the situation**

> In life-threatening situations empiric treatment should not be delayed while monitoring devices are being inserted.

PACT module on Haemodynamic monitoring

**Basic cardiorespiratory monitoring**

Basic cardiorespiratory monitoring comprises heart rate, blood pressure and pulse oximetry. Arterial blood pressure should be recorded at a minimum of five minute intervals but, ideally, this should be monitored continuously (and invasively) in the unstable patient.

**Central venous catheter**

A central venous catheter placed in an internal jugular or subclavian vein allows measurement of central venous pressure (CVP). A static measurement of CVP is not particularly useful in deciding the need for fluid administration, though it is generally indicative when the pressure is $\leq 5$ mmHg. The dynamic response of CVP to a fluid bolus is more useful (fluid challenge – see below). The central venous catheter also allows continuous monitoring of ScvO$_2$, if an oximetric catheter is inserted, or sampling of blood for intermittent measurement of ScvO$_2$. Other benefit is that central venous catheters are simpler to insert, and generally safer and less costly than pulmonary artery (Swan-Ganz) catheters.

Refer to the PACT module on Haemodynamic monitoring for further information about inserting and using a CVC. For more information about interpreting CVP correctly a good reference is:


**Echocardiography**

Echocardiography should ideally be performed promptly, in the context of congestive heart failure and/or myocardial ischaemia and/or sudden collapse, to diagnose any potentially reversible ventricular, valvular or obstructive pathology. It may provide a rapid insight into the differential diagnosis, particularly when the true problem is unclear. It provides information on both left and right ventricular function and can provide an initial assessment of preload and the presence of any regional wall motion abnormalities. Echocardiography should not be placed simply within the context of cardiac output assessment but within
the context of global cardiac performance. An audit of use and two review articles (see below) address its role in Intensive Care and the Round Table considers that the basics of echocardiography and non-invasive haemodynamics are mandatory in the curriculum for an intensivist.


**Cardiac output monitoring**

A pulmonary artery catheter (which may be equipped with continuous CO and $\text{SvO}_2$ monitoring modalities) and/or any less invasive flow assessment technique (e.g. transoesophageal echo, oesophageal Doppler, peripheral transpulmonary dilution) is recommended when hypotension persists or precise CO optimisation is required (e.g. for repeated fluid loading). Fluid challenges should be repeated until the top of the Frank–Starling curve is reached, i.e. stroke volume does not increase $\text{SV} > 10\%$ following a $200–400 \text{ mL}$ fluid challenge. At this point the ventricle becomes preload-independent.

An inotrope and/or mechanical support should be considered if an inadequate MAP persists with signs suggestive of organ hypoperfusion, e.g. oliguria, altered conscious state, low $\text{SvO}_2$, elevated lactate concentration or arterial base deficit, chest pain, ECG changes.

**Q. In which situations does the left ventricle remain underfilled (i.e. preload-dependent) yet stroke volume fails to increase following a fluid challenge?**

**A.**

- Massive fluid loss where the rate of loss equals or exceeds the rate of fluid input.
- Conditions of right heart failure or obstruction preventing entry of sufficient blood into the left ventricle. Examples include massive pulmonary embolus, cardiac tamponade, severe mitral stenosis, right heart failure.
**Systolic and pulse pressure variation (SPV and deltaPP)**

In the sedated, intubated and ventilated patient, recordings of systolic pressure variation (SPV) and/or pulse pressure variation (deltaPP) can be helpful in the absence of more invasive flow monitoring technology; the left ventricle remains preload-dependent until the SPV is <10 mmHg (stroke volume variation threshold of 10%) and/or deltaPP <13%. Arrhythmias or spontaneous breathing unfortunately preclude this type of evaluation.

**THINK** Arterial cannulation allows regular sampling plus continuous pressure monitoring. The blood gas analysis facilitates the more complete evaluation of global tissue oxygenation and acid-base status.

For further information on monitoring, see the PACT module on Haemodynamic monitoring

**Role of echocardiography**

When available, echocardiography may be utilised in the evaluation of Systolic pressure variation (SPV), delta Pulse Pressure (deltaPP) and Stroke volume variation (SVV). As assessment is dependent on ventricular function, preliminary echocardiographic evaluation of the function of the left ventricle (LV), right ventricle (RV) and pericardium and knowledge of ventilator settings is required. See note for details:

**Note** The following limitations and cautions apply in relation to these assessments:
1. Left ventricular status: a compromised LV produces an effect known as the dUp effect (reversed pulsus paradoxus) which is falsely positive for fluid loading in the presence of a high left ventricular end-diastolic pressure (LVEDP)
2. Right ventricular status: a compromised RV produces a dDown effect, which again is falsely positive for fluid loading in a dilated RV
3. Pericardium: pulsus paradoxus, SPV, deltaPP are signs of tamponade or constrictive pericarditis, again resulting in a false positivity for fluid loading
4. Ventilator setting: Vt of 6–8 mL/kg is acceptable. Higher Vt will likely create the impression of hypovolaemia but passive leg raising may help in minimising the effect of a high Vt on systolic pressure variation (SPV).

**Management**

**Oxygen supply**

**Note** All patients with hypotension and signs of impaired tissue perfusion should receive supplemental oxygen (O₂) to restore/maintain an adequate arterial oxygen saturation. An appropriate target value is ≥94% (i.e. avoid hyperoxia), though a lower saturation (e.g. 90–94%) may be acceptable in patients with chronic type II respiratory failure. Continued acute hypoxaemia, below a patient’s normal values, will compromise oxygen delivery (TO₂) and likely cause fatigue (especially their respiratory muscles), leading to hypercapnia.
**Fluid therapy**

With the possible exception of severe heart failure, the vast majority of hypotensive patients require fluid as first-line therapy because hypovolaemia is nearly always present. The response to initial treatment dictates further management. In situations such as trauma, where volume loss is likely, immediate fluid resuscitation should be started before further investigations are carried out.

Fluid therapy maintains a preload level necessary to support cardiac output and systemic $\text{TO}_2$. Crystalloids and/or colloids and/or packed red cells are used for this purpose. Although it has been considered, on physiological grounds, that the necessary volume of fluid to achieve a given level of intravascular expansion should be three-fold greater for crystalloid than for colloid therapy, recent studies of fluid therapy (SAFE and CRYSTMAS) have cast doubt on the validity of this 3:1 relationship in clinical, critical care practice.


Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. Crit Care 2012; 16(3): R94. PMID 22624531

Though experts argue over the merits and demerits of particular colloid or crystalloid solutions, there is complete consensus on the need to give enough fluid to restore an adequate circulation, but not an excessive amount.

For further information, see the following references.


Hypovolaemia can be absolute or relative. Absolute hypovolaemia is observed with loss of intravascular fluid externally (haemorrhage, gastrointestinal or renal losses) or into extravascular compartments (e.g. sepsis, burns). Relative hypovolaemia is observed when vascular tone is decreased (sepsis, anaphylaxis) resulting in an increase in the total intravascular compartment.

**THINK** A combination of absolute and relative hypovolaemia can exist in specific conditions such as sepsis. Think about the reasons.

**Q. What diagnostic techniques can be used to assess preload dependency in both conscious and unconscious hypotensive patients?**

**A.**
- Haemodynamic challenges such as changes in posture (e.g. straight leg raising or putting the patient’s bed/trolley into a ‘head-down’ position). For information about straight leg raise see Boulain reference, below.
- Change in CVP, stroke volume or blood pressure following a fluid challenge.
- Systolic, stroke volume or pulse pressure variation with the respiratory cycle in mechanically ventilated, non-spontaneously breathing patients.
- Echocardiography (e.g. looking at inferior vena cava, hepatic vein or ventricular end-diastolic volume).


**Q. The following arterial pressure waveform (figure below) was obtained in a 70-year-old patient who was sedated and mechanically ventilated. The patient was oliguric and the mean arterial pressure was 70 mmHg. Would you consider giving a fluid challenge to this patient? Justify your answer.**
A. Yes, as the patient was showing features of poor organ perfusion (i.e. oliguria) and the presence of a large respiratory swing in blood pressure is suggestive of marked underfilling of the left ventricle, of which hypovolaemia is the commonest cause. Failure to improve following fluid challenges should prompt a search for haemorrhage or investigation of possible flow obstruction, e.g. tamponade, pulmonary embolus.

In the next ten patients in whom an arterial line, central venous catheter and a cardiac output monitor are in place, assess fluid responsiveness by the change in pulse pressure variation, central venous pressure and stroke volume before and after a fluid challenge. Establish a correlation between these measures (refer to the following reference).


**Initial management of hypovolaemia**

- Establish large venous access sites
- Intravenous fluids with colloids and/or crystalloids
- Draw blood:
  - Full blood count and coagulation screen
  - Biochemistry (including lactate)
  - Arterial blood gases (including acid-base status e.g. using base deficit)
  - Cross-match (if indicated)
- Maintain SaO₂ at ≥ 94%
- Consider blood component therapy if massive bleeding:
  - Red blood cells
  - Fresh frozen plasma
  - Platelets
  - Other blood products as indicated

For information on blood component therapy see PACT module on Bleeding and thrombosis.
For acid-base analysis, see PACT module on Electrolytes and Homeostasis.

**Note** The decision to transfuse can be delayed except in acute life-threatening haemorrhage, very severe anaemia and/or in those patients with severe cardiac disorders where the reduction in CaO₂ cannot be compensated by an increase in CO. This may include in ICU such specialised fixed flow (cardiac output) situations as left ventricular assist device (LVAD) and extra-corporeal membrane oxygenation (ECMO) patients. ScvO₂ can be a useful guide to trigger transfusion. When blood is transfused, the patient should be re-assessed after each unit given.
Q. Consider a septic patient. At what haemoglobin concentration or haematocrit level would you start your transfusion? Justify your answer.

A. The optimal level is still unknown. The evidence (see below) suggests that a reasonable aim is a Hb level of ~10 g/dL in the very early phases of resuscitation in septic shock but, later on when the clinical status is more stable, an Hb level of 7–9 g/dL may be adequate or superior.

Q. If the patient has concurrent, suspected coronary disease, would you modify your approach?

A. If evidence of myocardial ischaemia persists (e.g. chest pain, electrocardiographic ST segment or T-wave changes), transfusion to increase the Hb level ≥10 g/dL may be considered.

The basis for this approach is the evidence of the landmark Canadian study (reference below) which found that a transfusion trigger of 7 g/dL is superior in terms of clinical outcomes compared to a higher threshold (10 g/dL) in euvoalaemic patients with the possible exception of patients with an acute coronary syndrome (e.g. myocardial infarction or unstable angina). In contrast, Rivers et al used a transfusion trigger of a 30% haematocrit (approximates to Hb ≥10 g/dL) as part of their early goal-directed therapy approach which also resulted in improved survival.

The optimal transfusion trigger is now being revisited in a multicentre European study as leukodepleted blood may affect immune function in a different manner to non-leukodepleted blood. Three multicentre studies in the US, UK and Australasia are currently investigating whether the benefit achieved by Rivers and colleagues is generalisable.


You will find additional information about resuscitation from circulatory shock in the following reference.

3/ MANAGING THE PATIENT WITH PERSISTENT HYPOTENSION

Problem-solving

Failure to promptly reverse hypotension following initial resuscitative measures should stimulate various thought processes, chief among which are:

- ‘Have I made the right diagnosis?’
- ‘Have I adequately fluid-resuscitated the patient?’
- ‘Are the therapies I am using producing an unpredictable or unexpected response?’

Have I made the right diagnosis?

The key questions are:

Is my initial diagnosis still likely to be correct?

Re-evaluate the evidence; consider whether this still holds true in light of the previous response to therapy, any new test results, etc. Re-examine the patient for any new or previously missed signs, e.g. a distending abdomen.

Is co-existing pathology present?

For example, the patient may have suffered a myocardial infarction as a consequence of haemorrhage-induced hypotension.

Do I need to perform further investigations or initiate more sophisticated monitoring? See Task 2

Q. List clinical scenarios which explain why a patient might remain hypotensive despite treatment for haemorrhagic shock.

A. The obvious problem to exclude is inadequate resuscitation or continued bleeding. Examples of co-existing pathology that may contribute to persisting hypotension include myocardial ischaemia secondary to haemorrhage/hypovolaemia; ischaemia-reperfusion injury following resuscitation; sepsis and stress ulcer-related haemorrhage; pulmonary embolus and anticoagulation-related haemorrhage, neurogenic shock and haemorrhage following spinal cord injury.

Q. List iatrogenic causes which might explain why a patient remains hypotensive despite treatment for shock.

A. Iatrogenic causes include excess drug-induced vasodilatation (e.g. with propofol), or excess intra-thoracic pressure e.g. due to air-trapping in a ventilated patient or to a tension pneumothorax following central line placement.
A middle-aged female was admitted from the ward with sudden onset of collapse and hypotension requiring urgent intubation, mechanical ventilation and fluid loading. She had been started on heparin with a presumptive diagnosis of massive pulmonary embolus but this had been discontinued after an experienced cardiologist decided that the echocardiogram performed was normal. On arrival in the ICU she was hypotensive (85/55 mmHg), tachycardic (125 bpm) and the central venous pressure (CVP) was measured as 15 mmHg. Cardiac output was promptly measured using an oesophageal Doppler technique and revealed a stroke volume of just 20 mL but reasonable ventricular contractility. A 200 mL colloid challenge failed to improve stroke volume but increased CVP to 19 mmHg. This suggested flow obstruction and so the heparin was recommenced while waiting for an urgent spiral CT scan. This revealed large emboli at the pulmonary bifurcation and in major segmental pulmonary arteries. She received thrombolytic therapy, subsequently improved and was discharged home in good health.

Have I given adequate fluid resuscitation?

Is the intravascular compartment replete?

Re-assess the adequacy of filling of the intravascular compartment.

Do I need to instigate more sophisticated monitoring?
See Task 2 and PACT module on Haemodynamic monitoring.

Q. What are the limitations of clinical examination and static haemodynamic e.g. JVP/CVP measurements?

A. A raised jugular venous pressure is not diagnostic of adequate filling; it may be related to decreased right ventricular and/or venous compliance, one cause of which is actually hypovolaemia, particularly in patients with strongly preserved vasoconstrictor reflex responses.

Q. Outline other symptoms and signs suggestive (but not indicative) of intravascular volume inadequacy?

A. Thirst, tachycardia, oliguria, and an increased core-toe temperature difference. Postural changes in blood pressure, a big swing in central venous pressure during spontaneous breathing, or an increased systolic, stroke volume or pulse pressure variation in ventilated, non-spontaneously breathing patients may be helpful.

Q. How can dynamic changes to haemodynamics be used to assess intravascular volume adequacy?

A. The ‘stress’ response to a change in posture or bolus injection of a drug with vasodilator properties (e.g. nitrate) will give a much better physiological indication of intravascular volume adequacy; for example, a rise in blood pressure and fall in heart rate in response to a straight leg raise suggests further fluid repletion would be beneficial. Similarly, a dynamic response in stroke volume, central venous pressure or pulmonary artery wedge pressure to a circulatory challenge (fluid, PEEP, posture) is also superior to assessment of a ‘static’ baseline value.
**Is current e.g. drug infusion therapy contributing to the persisting hypotension?**

An idiosyncratic or exaggerated response to a particular therapy should be considered. For example, dobutamine may have a large $\beta_2$-adrenergic effect in some individuals, resulting in excessive vasodilatation.

**Q. Give other examples of unpredictable responses to vasoactive therapies.**

A. Though occurring less frequently than dobutamine, epinephrine can occasionally cause excessive vasodilatation and hypotension at lower doses. A significant fall in blood pressure in response to low doses of a nitrate (or other vasodilator – including propofol) suggests unrecognised hypovolaemia, or a circulatory obstruction such as cardiac tamponade, massive pulmonary embolus or major right ventricle compromise, e.g. in pulmonary hypertension on positive pressure ventilation. A compromised right ventricle is sensitive to changes in preload caused by nitrates.

**Q. Give examples of sedation-related and heart–lung interactive causes for unpredictable circulatory responses?**

A. Large doses of sedatives or analgesics can have significant vasodilating and/or cardiodepressant effects (N.B. these agents and/or active metabolites may accumulate in hepatic or renal failure so relatively low doses may cause haemodynamic compromise). An increase in PEEP may result in hypotension related to left ventricular underfilling and increase of right ventricle afterload.

**Causes of persisting hypotension**

Failure to respond to initial fluid resuscitation should lead to consideration of the following:

**THINK** List the major causes of hypotension that were identified initially. Have you considered all of them? If not, go back to Task 1.

**Q. Summarise the major causes of hypotension which are non-responsive to perceived adequate fluid loading which you would consider in an ICU patient who is sedated, intubated and ventilated?**

A. Persisting hypovolaemia (e.g. continuing haemorrhage), cardiogenic shock, arrhythmia, vasodilatory shock (e.g. sepsis, post-cardiopulmonary bypass surgery or other causes of severe systemic inflammation), anaphylactoid reaction, flow obstruction (e.g. tamponade, massive pulmonary embolus) and neurogenic causes. Drug-related effects such as excess vasodilatation and myocardial depression should also be considered, particularly if self-poisoning or iatrogenic overdose may have occurred.

**Q. Assuming clinical examination has not revealed the cause, outline the supplementary testing and initial investigations to be considered in confirming or refuting the above diagnoses?**

A. Initial investigations to consider include:
1. Persisting hypovolaemia: positive response to fluid challenge, low mixed (central) venous saturation, ultrasound (Focused Assessment with Sonography [FAST] in trauma) or CT scan, falling haematocrit (N.B. this may be a dilutional effect).
2. Pump failure: ECG, echocardiogram, biochemical markers of myocardial injury or failure (e.g. troponin, cardiac enzymes and BNP).
3. Septic shock (or other causes of severe systemic inflammation): blood and other appropriate samples to microbiology, blood markers of inflammation (e.g. CRP, procalcitonin), amylase, ultrasound, CT scan.
4. Major anaphylactic/anaphylactoid reaction: keep sample of implicated drug or transfusion fluid, plasma histamine, tryptase and IgE levels.
5. Flow obstruction: chest X-ray, echo, CT scan.
6. Neurogenic (e.g. spinal cord injury): CT scan.
7. Drug-related: consider possibility of (self-)poisoning – Take patient’s history again, arterial and central venous blood gas analysis possibly including co-oximetry to exclude pathologic haemoglobins, check osmolality, calculate osmolar gap and think of organotoxic poisons (cardiac medications, paracetamol, methaemoglobin and carboxyhaemoglobin causing agents, cyanide etc ...). Repeat toxicology screen in urine. Check correct dosage and dilution of drugs being administered.


PACT module on Major intoxication

Pathophysiology of sepsis-induced persistent hypotension

Sepsis is defined as the systemic inflammatory response to infection (see the PACT module on Sepsis and MODS). A similar clinical manifestation can follow non-infectious insults, e.g. burns, pancreatitis, post-reperfusion injury. Excessive activation of cells (e.g. macrophages, neutrophils, endothelium) and over-production of proinflammatory mediators (e.g. prostanoids, nitric oxide, kinins) and pyrogens lead to vasodilatation, vascular hyporeactivity (i.e. decreased responsiveness to catecholamines) and capillary leak with third space losses. This is compounded by variable degrees of endocrine dysfunction (notably adrenocortical) and myocardial depression (from excess nitric oxide production and release of myocardial depressant factors), plus additional fluid and electrolyte depletion from a variety of sources, e.g. sweat, vomitus, diarrhoea.

Patients in septic shock may thus present with a high or low cardiac output, and a variable amount of intravascular volume depletion.

Q. What are the pathophysiological and clinical features of cardiogenic persistent hypotension?

A. Cardiogenic hypotension is usually due to pump failure related to ischaemic heart disease, or to other causes such as arrhythmias, valvular dysfunction, and cardiomyopathy/myocarditis. The cardiac output is usually low and the patient manifests evidence of decreased tissue perfusion and vasoconstriction.
Q. Outline the features of sepsis-related persistent hypotension?

A. The hypotension related to sepsis may also have a significant component of myocardial depression but is more commonly due to excessive peripheral vasodilatation and vascular hyporeactivity. The circulation is more frequently hyperdynamic with warm peripheries, bounding pulses, dilated vessels and sweating.

Q. As above, the aetiology of sepsis-related hypotension may be mixed. Is hypovolaemia a recognised factor? Give reasons.

A. Yes, hypovolaemia is often co-associated due to increased capillary leak and other fluid losses from the intravascular compartment e.g. sweating, ileus, ascites. Cardiac output may be low, however, with signs of poor organ perfusion, especially prior to fluid resuscitation.

Q. Is pulmonary oedema a feature of both categories of persistent hypotension?

A. Yes, the signs, symptoms and radiological appearance of pulmonary oedema may be present in both conditions, being related to pulmonary venous (hydrostatic) congestion in cardiogenic shock, and to ARDS and sepsis-related capillary dysfunction ('leaky capillaries') in sepsis.

See PACT module on Clinical examination – the chest X-ray.

Q. To what extent do these similarities affect your treatment?

A. In both septic and cardiogenic low output states causing hypotension and organ dysfunction, a therapeutic elevation in both flow and pressure is necessary to restore adequate organ perfusion. Though the patient who has heart failure may have excessive total body fluid, they are frequently intravascularly hypovolaemic and may benefit from judicious fluid loading. This is often tracked clinically but may be best followed with either of a number of supplementary monitoring systems such as repeated echocardiographic examination, continuous cardiac output and pulmonary artery occlusion pressure (PAOP) measurement or, perhaps serial lung water measurement.

See PACT module on Haemodynamic monitoring.

Care should be taken in both conditions not to give too much fluid as gas exchange may worsen considerably. Inotropic support may be then necessary in both categories of persistent hypotension

Q. To what extent do the differences affect your treatment?

A. In high-output sepsis, fluid is the appropriate first-line therapy though, again, excessive fluid loading should be avoided and vasopressor (or ino-constrictor e.g. epinephrine or norepinephrine) therapy may need to be commenced to achieve an adequate perfusion pressure in the presence of the usual high flow state.

In cardiogenic persistent hypotension, inodilator infusion therapy e.g. dobutamine or mechanical support e.g. an intra-aortic balloon pump are more likely to be appropriate for the low-flow state – see below.
If doubt exists as to the true nature of the circulation, or the patient fails to respond, then further investigation and flow monitoring needs to be promptly instituted.

**Administration of inotropes: inodilators and/or inoconstrictors**

As you saw in Task 1, hypotension results from decreases in systemic vascular resistance, ventricular filling and/or ventricular contractility. Besides hypovolaemia, the causes of hypotension can be categorised as vasodilatory, cardiogenic, or obstructive.

Q. Outline a classification of shock states based on alterations in cellular oxygenation i.e. caused by abnormalities in 1. cardiac output, 2. oxygen saturation, 3. haemoglobin and 4. cellular oxygen extraction. Give clinical examples of each.

A.  
1. **Circulatory hypoxia** – a problem with CO – e.g. heart failure, severe hypovolaemia, tamponade.
2. **Hypoxic hypoxia** – a problem with SaO₂ – e.g. ARDS, pneumonia, carbon monoxide poisoning.
3. **Anaemic hypoxia** – a problem with Hb – e.g. haemorrhage, bone marrow depression.
4. **Histotoxic or cytopathic dysoxia** – a problem with cellular O₂ utilisation – e.g. sepsis, carbon monoxide poisoning, cyanide poisoning.

**Note**

After adequately restoring intravascular fluid volume, persistent hypotension requires the use of drugs that either improve myocardial contractility (to increase CO) and/or increase vascular tone (to increase SVR).

Due to their short half-life (minutes) and familiarity with their use, catecholamines are usually the preferred first-line agents (see Table below). Taking into account their effects on cardiac contractility (inotropy) and vascular tone (constrictor or dilator effects), they can be separated into two major classes: **inodilator** (inotrope + vasodilator) or **inoconstrictor** (inotrope + vasoconstrictor). See inodilator/inoconstrictor table below.

- **Inodilators**: low dose dopamine, dobutamine, milrinone or dopexamine.
- **Inoconstrictors**: high dose dopamine, any dose of norepinephrine and moderate-to-high doses of epinephrine.

Inodilators increase flow though may have excessive vasodilating effects; inoconstrictors increase perfusion pressure with variable effects on flow. Due to a highly variable individual sensitivity to these different catecholamine agents, dose titration is strongly recommended, ideally against measurement of CO as well as blood pressure and other relevant variables such as base deficit, urine output, and $\text{SvO}_2$ or $\text{ScvO}_2$. 

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A recent Cochrane review concluded that there is insufficient evidence to recommend a particular vasopressor over others. However, in a large multicentre trial comparing norepinephrine to dopamine in the management of shock, serious tachyarrhythmias were twice as common in the dopamine-treated patients. Epinephrine can induce a lactic acidosis through acceleration of glycolytic metabolism. Though the clinical relevance is unclear, this effect prevents the use of lactate levels to guide therapy in shock states. For these reasons norepinephrine is currently the most commonly used vasopressor.

**Note** It is important to emphasise that a rise in blood pressure may not be a surrogate of clinical benefit. Indeed, in a large placebo-controlled clinical trial (see reference below), administration of the non-selective nitric oxide inhibitor NG-methyl-L-arginine in septic shock produced both significant increases in blood pressure and mortality.

**Note** The aim is to improve tissue perfusion and not simply to increase blood pressure.


Because increasing blood pressure through vasoconstriction is often associated with a decrease in CO, a trade-off is necessary between raising blood pressure and decreasing CO. This balance of effects will dictate the choice and dosage of vasopressor and/or vasoconstrictor as no pure inotropic agent exists.

**Think** When considering titrating vasopressors versus fluid loading, think how $S\bar{V}_O_2$ and/or $Sc\bar{V}_O_2$ could determine the success of the initial therapy (see the paragraph on central or mixed venous $O_2$ saturation, above).

Non-catecholamine vasopressors such as vasopressin, a balanced vasoconstrictor with V2 receptor activity, is an alternative vasopressor that can be used in vasodilatory shock states but is not available in all (including European) countries. A relative vasopressin insufficiency, yet increased sensitivity to exogeneous vasopressin, has been demonstrated in human septic shock. Vasopressin has been used successfully and safely to treat arterial hypotension associated with hyperdynamic, catecholamine-resistant, vasoplegic states. However, to date, there is no clear evidence to demonstrate superiority. The
VASST study (reference below) found that vasopressin may improve outcomes in less severe shock, however these findings require further validation. If there is a benefit in using vasopressin, it would seem appropriate to use it in less severe shock rather than as a late rescue therapy for severe refractory shock.

Its synthetic analogue, terlipressin (with selective V1 and V3 action) has also been used in the treatment of septic shock but its particular indications are:

- Low SVR and liver failure
- Portal hypertension and variceal bleeding and
- Reversing oliguria in incipient hepatorenal syndrome.

Levosimendan is a novel agent (not yet available in the USA and parts of Europe) that increases cardiac output through increased cardiomyocyte sensitivity to calcium and by peripheral vasodilatation through an ATP-sensitive potassium channel opening effect. Its advantage over catecholamine inotropes is that it does not increase cardiac work which is a beneficial attribute in the failing heart. It has been used successfully in heart failure states. Caution should be exercised as it may exacerbate hypotension through excessive vasodilatation. This can be at least partially avoided by not giving a bolus loading dose in an unstable ICU patient.

**Inodilators and Inoconstrictors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>α-agonist</th>
<th>β1-agonist</th>
<th>β2-agonist</th>
<th>Dopaminergic effect</th>
<th>Clinical use</th>
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<tbody>
<tr>
<td><strong>Inodilators</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Dopamine &lt;5 µg/kg/min</td>
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<td>-/+</td>
<td>-</td>
<td>++</td>
<td>All forms of hypotension</td>
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<tr>
<td>Dopexamine</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>Low output states, e.g. cardiac failure, obstructive shock</td>
</tr>
<tr>
<td>Milrinone, Enoximone</td>
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<td></td>
<td></td>
<td>Cardiac failure</td>
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<tr>
<td>Levosimendan</td>
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<td></td>
<td></td>
<td>Cardiac failure</td>
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<tr>
<td><strong>Inoconstrictors</strong></td>
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<tr>
<td>Dopamine &gt;5 µg/kg/min</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Distributive shock</td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>Cardiac arrest Anaphylactic shock Cardiogenic shock Distributive shock</td>
</tr>
<tr>
<td>Norepinephrine (noradrenaline)</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Distributive shock Refractory hypotension</td>
</tr>
</tbody>
</table>

**Steroids in refractory shock**

In septic shock, stress-dose (‘low dose’) steroid therapy (hydrocortisone 200 mg/day) reduced catecholamine requirements and shortened the duration of shock in the CORTICUS trial. However, there was no improvement in survival rates and an increased rate of superinfection was reported. This contrasts with an
earlier study by Annane and colleagues. Current (Surviving Sepsis) guidelines suggest that steroid therapy (less than 300 mg/day) should only be started in refractory shock that is poorly responsive to fluids and vasopressor therapy. A corticotrophin (ACTH) stimulation test is not recommended as the results are laboratory and kit specific, difficult to interpret in an ICU setting, and not predictive of response. The duration of therapy should be kept as short as possible and tapered off once the shock has resolved. See the following references and the PACT module on Electrolytes and Homeostasis


4/ Outcomes arising from hypotension

Outcomes arising from hypotension depend on the severity of the hypotension, its duration, concurrent falls in regional blood flow and/or arterial oxygen saturation, and any chronic conditions that may compromise organ function still further, e.g. coronary artery disease.

Q. Provide some examples of avoidable/iatrogenic, short-lived hypotension occurring in the ICU.

A. Allowing infusion of inotrope/pressor to run out; excessive bolus of sedative or vasodilator; rapid postural movement of patient; ultrafiltration in a hypovolaemic patient; a large increase in PEEP.

Organ-specific outcomes

The brain is the most obviously sensitive organ to changes in blood pressure. However, the brain is the organ most difficult to assess in the critically ill, particularly as sedation is usually being administered. More severe, longer-lasting hypotension is usually associated with changes in level of consciousness which can vary from confusion and agitation to drowsiness, seizures or coma.

The ability of the brain to recover normal function after cardiac arrest/prolonged hypotension is inferior to that of all other organs. Classical opinion states that three minutes without a cerebral circulation is sufficient to cause irreversible brain injury. This may lead to severe consequences such as brain death, vegetative states, status epilepticus and focal neurological defects (e.g. hemiplegia, blindness).

How often, after an out-of-hospital cardiorespiratory arrest with return of spontaneous circulation and subsequent admission to the ICU, do you see either complete functional restoration of all organs, isolated brain injury, or multiple organ dysfunction? In the case of multiple organ dysfunction, how often is the brain not involved?

Other organs are affected to a greater or lesser extent depending on their resistance/sensitivity to hypotension and/or hypoperfusion. This is usually determined by co-morbid conditions; for example, coronary artery disease may result in cardiac ischaemia whereas bowel ischaemia may be manifest if mesenteric atheroma is present. The lung is rarely involved directly, especially in terms of focal damage, unless ARDS (mild, moderate or severe) develops as part of the subsequent inflammatory response. Remember, it may not be the hypotension per se that causes organ damage but the injury following on from systemic inflammation or reperfusion/reoxygenation.

Ischaemia-reperfusion (hypoxia-reoxygenation) injury may contribute considerably to the organ dysfunction following hypotension.
Q. List some other organ-specific presentations of complications of prolonged hypotension/prolonged hypoperfusion.

A. Organ-specific presentations of complications include:

- Brain: focal pathology (e.g. hemiplegia, ‘watershed’ infarct), epilepsy, hypoxic-ischaemic encephalopathy, blindness
- Heart: angina, arrhythmias, ischaemic changes on ECG
- GI: abdominal pain, bowel ischaemia, haematemesis, melaena, signs of bowel perforation
- Liver: rise in plasma liver enzyme levels, jaundice
- Kidney: oligo-anuria, azotaemia, acute kidney injury
- Skin: digital ischaemia, pressure sores
- Muscle: pain, rhabdomyolysis


Rank in order of frequency the complications you see in the next ten patients you treat for hypotension. Now rank them again in order of the severity of complication. How do you compare the severity of complication between different organs? This can be achieved using scoring systems such as SOFA (sequential organ failure assessment), MODS (multi-organ dysfunction score) or LOD (logistic organ dysfunction), some of which have been weighted in terms of eventual outcome. See the PACT module on Clinical outcome.

**CONCLUSION**

This module has highlighted how hypotension, a common occurrence in the critically ill, has multiple causes (alone or in combination) for which a pathophysiological explanation is usually forthcoming. Hypotension should be taken in the context of the patient as a whole as an asymptomatic, adequately perfused patient may require no treatment, whereas a chronic hypertensive may be compromised by a relatively small drop from their normal, pre-morbid blood pressure level. This module uses a physiology-based approach to the diagnosis and management of hypotension. Indeed, we strongly commend this over a didactic, numbers-driven strategy. Understanding the altered physiology allows targeted treatment of the underlying condition rather than an empiric correction of abnormal numbers which may prove detrimental rather than beneficial. The aetiology may not be immediately apparent and this should prompt an early diagnostic search as potentially life-saving interventions may be necessary, e.g. pericardiocentesis.

The patient who does not rapidly respond to first-line oxygen and fluid therapy warrants further haemodynamic monitoring to aid diagnosis and better titration of treatment. However, critical care is a rapidly evolving speciality and today’s guidelines and recommendations may be revised in the future by compelling new data, especially as the quality of evidence underpinning our current practice is not particularly strong. Nevertheless, even though treatments may change, the principles upon which this module is based are sound and will hopefully stand the test of time.
SELF-ASSESSMENT

EDIC-style Type K

1. Frequently used criteria for hypotension include:
   A. A fall in systolic blood pressure of 40–50 mmHg below baseline value
   B. A systolic blood pressure value below 100 mmHg
   C. A diastolic blood pressure below 60 mmHg
   D. A mean arterial blood pressure below 60 mmHg

2. The terms hypotension and shock are often used interchangeably. What is/are correct statement(s) when these two terms are compared?
   A. They are identical and describe exactly the same pathophysiology
   B. Shock is always present together with hypotension but not vice versa
   C. A normal blood-pressure does not exclude shock
   D. Shock may be present in the presence of normotension

3. A 72-year-old female patient with pneumonia is intubated because of severe hypoxic respiratory failure and exhaustion. Immediately after sedation/intubation her blood pressure drops from supranormal values to MAP of 45 mmHg. Which of the following reasons is/are most likely to cause this hypotension?
   A. Intravenous propofol given for sedation
   B. Inflow obstruction to the right side of the heart
   C. Acute myocardial infarction
   D. Sudden loss of adrenergic stimulation

4. Oxygen delivery is directly dependent on:
   A. Central venous oxygen content
   B. Haemoglobin concentration
   C. Systemic vascular resistance
   D. Oxygen extraction rate

5. The mixed venous O₂ saturation is measured in the:
   A. Right atrium
   B. Vena cava superior
   C. Right ventricle
   D. Pulmonary artery

6. The mixed venous oxygen saturation/content is dependent on:
   A. Haemoglobin concentration
   B. Cardiac output
   C. Metabolic demand
   D. Mean arterial pressure (MAP)
7. Systemic vascular resistance (SVR):
   A. Can only directly be measured using a pulmonary artery catheter
   B. Is equal to CO/MAP
   C. Is equal to pulmonary vascular resistance
   D. SVR always falls when CO decreases

8. A 21-year-old motor cyclist was admitted after a severe injury. He was bleeding from external wounds as well as from fracture haematomas. He is admitted to the ICU intubated and ventilated after emergency surgery. Presuming that analgesia has been satisfactorily achieved, what clinical signs are useful for assessing his volume status?
   A. Tachycardia
   B. Raised jugular venous pressure (>12 cmH₂O)
   C. Low jugular venous pressure (<3 cmH₂O)
   D. A decrease in the pulse-pressure variation

9. How would you assess fluid responsiveness in the patient above (Q8)?
   A. Blood-pressure response to a straight leg raising test
   B. Blood-pressure response to 1000 mL saline i.v. over 2 hours
   C. Blood-pressure response to 2 fresh-frozen plasma over 1 hour
   D. Blood-pressure response to 250 mL saline over 10 minutes

10. If the same patient is fluid responsive necessitating aggressive fluid therapy, what is/are the most likely cause(s) of his hypovolaemia?
    A. Continuing haemorrhage due to trauma
    B. Vasodilation in association with an observed rise in his body temperature
    C. Acute pulmonary embolism
    D. Positive pressure ventilation

11. Norepinephrine (NE) is often suggested as the ‘drug of choice’ when using a vasopressor. This is because:
    A. NE can be given in a peripheral vein not using a central venous catheter
    B. Randomised controlled trials (RCTs) show superiority of NE relative to other vasopressors
    C. NE does not augment glycolytic metabolism and hence induce increased lactic acid levels
    D. NE is less arrhythmogenic than vasopressors which are relatively more β-adrenergic in their effects

12. Levosimendan increases cardiac output through:
    A. Augmented β-stimulation in the myocytes
    B. Its peripheral vasodilatory action effected via angiotensin-converting enzyme (ACE) inhibition
    C. Increased sensitivity of the cardiomyocyte to calcium
    D. Effect on potassium channels in the cardiomyocyte
13. The following profile on various vasoactive receptors is typical for dobutamine: (DA=dopaminergic receptors)

A. $\alpha_+\,,\,\beta_1\,++\,,\,\beta_2\,\,\,+,\,DA\,++$
B. $\alpha_+\,,\,\beta_1\,\,\,+\,,\,\beta_2\,\,\,+,\,DA\,+$
C. $\alpha_\,-\,,\,\beta_1\,\,\,++\,,\,\beta_2\,\,\,++,\,DA\,+$
D. $\alpha\,\,-\,,\,\beta_1\,\,\,++,\,\beta_2\,\,\,++,\,DA\,+$
E. $\alpha\,++\,,\,\beta_1\,\,\,+\,,\,\beta_2\,\,\,\,+\,,\,DA\,++$

14. The advantage of invasive blood pressure monitoring includes all of the following EXCEPT:

A. Continuous display of blood pressure waveform
B. Accurate estimate of mean arterial blood pressure
C. Measurement of Diastolic pressure variation as an estimate of fluid responsiveness, in non-spontaneously breathing patients
D. More accurate recording of very low blood-pressure
E. Easy access to arterial blood samples

15. A 57-year-old patient with an exacerbation of COPD is intubated after being given the anaesthesia drugs of propofol, fentanyl and a muscle relaxant. In order to keep him calm, a low dose of both propofol and fentanyl is continued and, on this, he is sedated but easy to arouse. Two hours after intubation, and after 2000 mL of crystalloids, he is still hypotensive with MAP varying between 55–60 mmHg (normal BP found to be 120/85 in previous hospital records). He is waking up, passing urine and there have not been any ECG changes seen on the monitor. What would you consider to be the most appropriate action?

A. Give a small dose of norepinephrine to keep MAP $>70$ mmHg
B. Give dopamine $2.5–5\,\mu g/kg/min$
C. Give more fluids as colloids
D. Treat the underlying pathology but do not start any new measure for blood pressure
E. Put in a pulmonary artery catheter

16. Which of the following reasons is rarely a cause of hypotension?

A. Third space loss of fluid
B. Enterocutaneous fistula from the duodenum
C. Vaginal fistula
D. Diabetes insipidus
E. Tension pneumothorax
17. The major difference between cardiogenic (CS) and septic shock (SS) is:

A. CS patients are more tachycardic
B. SS patients have more often severe lactic acidosis
C. Diastolic pressure is very low in patients with CS
D. SS patients are usually more vasodilated
E. Hypothermia is diagnostic of SS

Self-assessment answers

1. TFTT
2. FFTT
3. TTFT
4. FTFF
5. FFFT
6. TTF
7. FFFFF
8. TFTT
9. TFTT
10. TTFF
11. FFTT
12. FFTT
13. Correct: C
14. Correct: C
15. Correct: D
16. Correct: C
17. Correct: D
PATIENT CHALLENGES

A 65-year-old previously healthy male underwent an elective hip replacement without complication. He was commenced on ibuprofen for pain relief, given subcutaneous low molecular weight heparin as prophylaxis against deep vein thrombosis, and encouraged to mobilise. Three days postoperatively he collapsed while walking to the toilet. He was carried back to his bed where he was found to be sweaty, peripherally vasoconstricted, drowsy, tachycardic (120 bpm) and hypotensive (65/45 mmHg). The jugular vein was visible but not particularly prominent in a supine posture. No focal signs were found on examination. His normal blood pressure was 150/80 mmHg. You see him within five minutes.

Learning Issues

What is hypotension?

Q. What does your initial resuscitative management consist of?

A. Airway, Breathing and Circulation problems are immediately attended to.

Learning Issues

ABCs

Link to PACT module on Airway management

You administer high flow, high concentration oxygen via a face-mask and assess the need for intubation and mechanical ventilation. You request pulse oximetry and ECG monitoring and a 12-lead ECG. You promptly obtain good quality venous access, start IV fluid resuscitation and undertake a clinical examination to evaluate for myocardial infarction and pulmonary embolism and exclude tension pneumothorax, ruptured abdominal aortic aneurysm and GI haemorrhage. You examine the surgical wound site and drain, and consider a rectal examination to see whether melaena is present. You check for continuing epidural analgesia (via an epidural catheter) and exclude postural hypotension.

Learning Issues

Basic cardiorespiratory monitoring

Clinical examination

Link to PACT module on Clinical examination
Q. Would you intubate and ventilate him immediately? Give reasons.

A. This is obviously needed if his airway is unprotected or gas exchange is still inadequate despite supplemental oxygen. However, the shock state may be further exacerbated by any use of anaesthetic agents (via vasodilation, myocardial depression and blunting of intrinsic sympathetic responses) and the institution of positive pressure ventilation. Unless immediately mandated, intubation should be delayed until an adequate circulation is restored, as there is a high likelihood of precipitating cardiovascular collapse. The patient may recover sufficiently following circulatory resuscitation such that ventilatory support is not needed.

Learning Issues

Hypotension versus shock

Q. What is the most probable diagnosis of this hypotension? Why?

A. The sudden onset suggests an acute event; standing to go to the toilet may have precipitated the incident through the gravitational fall in venous return. The likely causes of this sudden collapse are cardiogenic, hypovolaemic or obstructive e.g. pulmonary embolus, myocardial infarction or pneumothorax.

Q. Could it have been a vasovagal attack or an arrhythmia?

A. Both a vasovagal attack and a self-terminating high rate tachyarrhythmia would be unlikely to produce persisting hypotension and tachycardia after returning the patient to bed.

Q. Is a cerebrovascular accident (CVA) or an episode of hypoglycaemia a possibility? What might make these less likely?

A. Certainly, both are possible but hypotension would be unusual with a CVA and a hypoglycaemic attack would be rare in a non-diabetic in whom there has been no reported problem with eating.

Q. Could the problem be sepsis or anaphylaxis?

A. Sepsis is unlikely in view of the lack of preceding symptoms, anaphylaxis unlikely as it appears that no new drugs or fluids were recently given.
Q. Would you admit the patient to the ICU immediately?

A. Clearly, this patient is unwell and likely to need intensive care. However, the diagnosis is still unclear and it may become soon apparent that radiology, endoscopy, surgery or the cardiac catheter laboratory is urgently indicated. It is prudent to advise the ICU of the patient and the likelihood of urgent admission so they can prepare for his arrival either before or after any potential procedure.

Q. If the ICU is full, can the critical care doctor provide any useful immediate assistance?

A. The ICU doctor or outreach team may be able to assist with initial treatment on the ward. In the meantime, you should continue to resuscitate the patient (likely to be with fluids primarily – see below) and consider likely causation. It may be possible to insert an arterial catheter on the ward for continuous blood pressure monitoring and intermittent blood gas sampling prior to transfer.

While you request appropriate investigations to aid diagnosis (see below), you attempt to regain an adequate circulation and institute invasive monitoring. If blood loss is considered a high likelihood, blood for transfusion should be requested.

**Learning issues**

Appropriate monitoring

Q. Do you consider blood loss likely? Explain your answer.

A. The patient has several risk factors including recent surgery, prophylactic heparin, and is taking a non-steroidal anti-inflammatory agent (ibuprofen). Absence of malaena does not completely exclude gastrointestinal blood loss, especially if collapse occurs suddenly following an acute severe bleed. You should ask to see recent blood results to determine whether he has become progressively anaemic, or if a coagulopathy is present.

You organise an urgent blood gas analysis to provide a rapid indicator of his current Hb. It is prudent to confirm whether any cross-matched blood is currently available for him, and thus whether more needs to be requested. You send another blood sample to the laboratory to enable a new cross-match to be performed promptly, if subsequently needed.
Q. What treatment do you administer to raise the blood pressure and why?

A. The choice lies between fluid loading +/- inotropic or inoconstrictor support. This decision can be difficult on clinical grounds alone but therapy needs to be initiated early in view of the severity of illness. The clinical features suggest a low output state. Fluid loading is usually the first manoeuvre that is attempted but caution should be applied as the patient with acute myocardial dysfunction may become readily overloaded.

A 12 lead ECG has been carried out and interpreted with initial resuscitative efforts. The exclusion of myocardial ischaemia, arrhythmias and right heart strain is important because it may direct the patient management in terms of acute admission to the ICU or to the cardiac ‘cath’ lab.

Learning Issues

Fluid therapy
Administration of inotropes
Administration of inoconstrictors

Q. How can you rapidly assess volaemic status clinically without giving fluid?

A. Elevating both legs produces a rapid, transient increase in venous return. A resulting increase in blood pressure suggests that hypovolaemia (or flow obstruction) is implicated in the hypotension, indicating the need for volume replacement. The legs should be elevated in a supine patient (no trunk elevation) to at least 40° for about 3–4 minutes to see the eventual effect.

Q. How would you use CVP to help guide your fluid resuscitation?

A. A single static CVP reading only provides limited information. The CVP response to a rapid fluid bolus provides more useful information. If there is a sustained 3 mmHg rise in CVP, then the patient is probably fluid replete, whereas if there is little change in CVP the patient may still be fluid depleted.

Learning Issues

Initial management of hypovolaemia

You elevate both legs. In this particular patient the BP rose to 85/60 mmHg upon straight leg raising so you administer a rapid fluid infusion to replete intravascular volume.
Q. In this case the patient responded to fluids but what would you do if the patient does not respond?

A. No beneficial effect suggests either that the intravascular volume is replete, indicating the need for an inotrope such as epinephrine, or the amount of fluid loss (e.g. haemorrhage) is so large that the straight leg raise was unable to elicit a response.

Q. As well as the arterial blood gas analysis, what priority blood tests would you instigate?

A. As well as the arterial blood gas analysis, full blood count, coagulopathy screen, urea and electrolytes, blood sugar and bedside glucose testing. Cardiac enzymes or troponin should be taken after several hours if myocardial infarction is suspected.

See the PACT module on Acute myocardial ischaemia

Q. What diagnoses will the ECG help with?

A. An ECG may detect signs of myocardial ischaemia/infarction; right heart strain suggestive of a pulmonary embolus; or low amplitude complexes ± generalised ST elevation suggestive of a cardiac tamponade.

If myocardial ischaemia (acute coronary syndrome) is evident, this will require immediate measures – see PACT module on Acute myocardial ischaemia.

If any of the others are considered likely, an urgent echocardiogram (to evaluate for tamponade) and/or a chest CT scan with contrast injection to image the pulmonary vasculature should be requested.

Unless clinical signs indicate the need for an urgent chest X-ray, this may be delayed temporarily until after an urgent central venous catheter has been inserted.

As clinical examination and a positive response to straight leg raising suggests hypovolaemia is present, it is also worth focusing on possible causes. Rapid bleeding into the GI tract, peritoneum, retroperitoneum, pleural cavity or around the hip prosthesis should be considered if no external blood loss is apparent. A nasogastric tube is inserted and endoscopy requested if indicated. An ultrasound examination may be useful at the bedside for detecting aortic aneurysmal formation or intra-cavity/soft tissue collections of blood. If possible FAST (Focused Assessment with Sonography in Trauma) technique could be carried out examining pericardial sac, both pleural spaces, peritoneal cavity in all quadrants plus retropubic and retrovesical space for fluid collection.

Echocardiography
See the PACT module on Haemodynamic monitoring (echocardiography)

He has so far received 500 mL fluid resuscitation with some improvement in blood pressure (90/50 mmHg). The ECG shows sinus tachycardia only. Arterial blood gas analysis reveals normal gas exchange but the arterial base deficit is 8 mEq/l and the Hb is 9.6 g/dL. As he remains obtunded, he is intubated and mechanically ventilated without problem. However, large quantities of fresh blood were obtained on insertion of a nasogastric tube.

**Problem-solving**

Covert sources of bleeding should be considered in a persistently hypotensive patient, particularly when there are known risk factors such as trauma, recent instrumentation, coagulopathy.

**Learning issues**

**Q.** How does this affect your management?

**A.** A traumatic insertion should be considered. However, as the cause of this large-scale bleeding, this would be an unusual occurrence. The principal differential diagnosis (for upper GI bleeding) therefore rests primarily between peptic ulcer, stress ulcer or variceal haemorrhage.

**Q.** If chronic liver disease/cirrhosis is likely, what immediate measure might control the bleeding, other than medical blood product therapy, while waiting for the endoscopist to arrive to make a formal diagnosis?

**A.** A Sengstaken-type tube may be passed to see if bleeding ceases on variceal compression.

The presence of such an acute major bleed suggests erosion into a blood vessel, rather than mucosal erosions alone. Other, much rarer, possibilities include leiomyoma, other tumours and aorto-enteric fistula but the basic management principles outlined above still apply. The severity of collapse should prompt the urgent attendance of an endoscopist, a GI surgeon and possibly an interventional radiologist, plus possible additional laboratory requests for urgent blood and blood products (e.g. fresh frozen plasma, if indicated) transfusion.

Link to PACT module on Acute hepatic failure

The patient has been moved to the endoscopy suite. Heavy bleeding has continued despite two litres of fluid infusion (including blood, fresh frozen plasma and colloid)
over the preceding hour. Blood pressure is now 100/60 mmHg and heart rate 120 bpm. Endoscopy reveals a large pre-pyloric gastric ulcer with a visible artery at its base from which blood is pumping out. Attempts to stop the bleeding by local injection of adrenaline (epinephrine) and heater probe application prove futile.

Q. What would you now consider?

A. Blood products such as platelets and cryoprecipitate are indicated if heavy bleeding continues or if a coagulopathy is known to exist. With continued large-scale bleeding and failure of endoscopic procedures, the patient should be considered for either an urgent laparotomy or radiographic embolisation (if appropriate/available).

Q. How do you know your resuscitation is adequate?

A. This can be done on clinical grounds (e.g. BP, urine output, improvement of acidosis and CVP) and augmented by surrogate biochemical markers such as central venous oxygen saturation, arterial base deficit and lactate. The latter tests will help to verify the accuracy of clinical assessment. Measurement of cardiac output and a flow-guided assessment of response to treatment can be made rapidly using devices such as the oesophageal Doppler (though this is relatively contraindicated with variceal bleeding), or a peripheral dye dilution/pulse contour technique.

The patient underwent successful angiographic embolisation and stabilised thereafter, with a good blood pressure and cardiac output. Though he had biochemical evidence of renal dysfunction for four days, he did not require renal replacement therapy. He was discharged from intensive care after four days on diet and proton pump inhibitor (PPI) and from hospital one week later – to be reviewed at surgical outpatients department.

Link to PACT module on Acute renal failure (Acute Kidney Injury Part II)

Link to PACT module on Oliguria and anuria (Acute Kidney Injury Part I)

Link to PACT module on Bleeding and thrombosis
**Patient 2**

**An emergency paramedic team was called to attend a 55-year-old lady found unconscious by her neighbours.** She lived alone in a small, poorly ventilated apartment heated by an old gas fire. Empty boxes for benzodiazepines and propranolol were found close to her body. She was known to be a heavy alcohol drinker. The paramedics found her in cardiac arrest and she had obviously vomited and aspirated. Cardiopulmonary resuscitation was commenced and the rhythm just prior to DC shock was witnessed to be ventricular fibrillation. After one shock, sinus rhythm was restored. An epinephrine (adrenaline) infusion was initiated to maintain her systolic arterial pressure above 90 mmHg. She was intubated and ventilated and transferred to your hospital’s emergency department where you are called to see her. Her initial circulatory readings are HR 80 bpm sinus rhythm, and BP of 100/65 mmHg.

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**Q. What would your initial management decisions be on her arrival in the emergency department?**

**A.** You would:

- Check the position of the tracheal tube (both hemithoraces moving equally and with good air entry bilaterally, ensure CO$_2$ detection trace).
- Titrate inspired O$_2$ to ensure SaO$_2$ ≥ 94%.
- Check mechanical ventilation to ensure adequate tidal volumes (for ventilation) and PEEP to recruit collapsed alveoli and achieve adequate oxygenation.
- Measure core temperature.
- Insert a central venous catheter (ideally with three or more lumens) and a bladder catheter.
- Ensure infusion of the correct dose of epinephrine (adrenaline), having ensured proper insertion of the central line.
- Examine the patient carefully and perform appropriate investigations.

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Link to PACT modules on Airway Management and Mechanical ventilation

Link to PACT module on Clinical examination

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**Q. What are your differential diagnoses and what urgent tests would you request?**

**A.**

1. Benzodiazepine overdose – check blood for alcohol level and urine toxicology (screening); gastric content may also be sent to toxicology.
2. Propranolol overdose: may cause bradycardia and cardiogenic shock perhaps compounded by hypothermia and post-arrest state. Check core temperature, drug levels, ECG, cardiac output measurement. A propranolol overdose is consistent with the apparently inappropriately low heart rate for a shocked state but its effects may be reversed by the concurrent epinephrine infusion. If epinephrine is not sufficient consider milrinone which acts independently of beta receptor blockade.
3. Hypo- or hyper-glycaemia: check rapid glucose test. Hypoglycaemia is more likely in those with alcoholism and possible liver failure.

4. Carbon monoxide poisoning (old heater) – N.B. arterial blood gas analysis needs to be performed on a CO-oximeter to obtain the carboxyhaemoglobin (COHb) proportion and not a spuriously elevated SaO₂ which may be the case with a standard blood gas analyser or pulse oximeter.

5. Haemorrhagic shock (possible variceal or peptic ulcer bleeding, possible liver failure resulting in coagulopathy): check full blood count, clotting screen, urea and electrolytes and liver function tests. Place a nasogastric tube.

Link to PACT module on Environmental hazards

Link to PACT module on Acute myocardial ischaemia

Link to PACT module on Heart failure

How would you manage the following possible complications:

Q. Inhalation of gastric contents and severe hypoxaemia?

A. Check arterial blood gas analysis, chest X-ray and bronchoscopy. Consider bronchoscopy in most patients who are found unconscious and after vomiting due to high likelihood of aspiration of gastric content which is often not visible on X-ray and clinical examination. There is evidence suggesting a reduction of aspiration related infections and of less need for antibiotic administration. Also, tracheal tube might be replaced early after patient’s stabilisation to eliminate gastric content from between the tracheal tube and laryngeal/tracheal wall.

Q. Rhabdomyolysis (found lying immobile)?

A. Check plasma potassium, creatine kinase, urinary myoglobin. Look for compartment syndrome in arms, legs and buttocks, and measure compartment pressures if concerned.

Q. Acute brain injury (cardiac arrest, hypoxaemia, possible prolonged hypotension, possible primary cerebrovascular event or brain trauma)?

A. Unless focal neurology is present or there is external evidence of a head injury, CT scanning need not be performed urgently. This can be done, if needed, once the patient has been stabilised. Likewise, an EEG can be performed subsequently if epileptic fits are witnessed or there are concerns about subclinical seizures.
Q. Massive pulmonary embolus?

A. Should be considered in any patient found collapsed, though less likely in this case. Check ECG, chest X-ray, blood gases. A CT pulmonary angiography is performed if indicated.

Learning issues

Link to PACT module on Coma and altered consciousness

Link to PACT module on Electrolytes and Homeostasis

Link to PACT module on Oliguria and anuria (Acute Kidney Injury Part I)

Link to PACT module on Acute renal failure (Acute Kidney Injury Part II)

On arrival, the patient had been mechanically ventilated with settings of FiO₂ 1.0, tidal volume 500 mL, rate 15 breaths/min and PEEP 7.5 cmH₂O. Central venous, arterial and bladder catheters were promptly inserted. Her blood pressure decreased to 75 mmHg systolic. Her core temperature was found to be 34.7 °C. Her Glasgow Coma Scale was scored at 4 without sedation. Rapid toxicology testing was positive for benzodiazepines.

Learning issues

Selecting appropriate monitoring – link to Task 2 in the PACT module on Haemodynamic monitoring

Q. How can her drop in blood pressure after mechanical ventilation be explained? And how would you manage this?

A. Placing her on positive pressure ventilation will decrease ventricular filling. If the baseline level of filling is already reduced, this further reduction may be sufficient to reduce her cardiac output, enough to compromise her blood pressure. Fluid challenge should be performed, e.g. with 200–400 mL fluid over five minutes, followed by further challenges depending on the response in blood pressure/CVP.

Another possibility to consider is the presence of a pneumo or haemo-thorax or cardiac tamponade. She had received cardiac compressions and manual ventilation from the paramedics, and has had a central venous catheter recently inserted. The patient should be examined in the light of these possibilities and appropriate tests performed as indicated.

Learning issues

Causes of hypotension after commencement of mechanical ventilation

Fluid therapy
Immediate fluid loading with 400 mL fluid had no effect on blood pressure or CVP. A further 200 mL was given, also without effect. The blood pressure remained at 75 mmHg systolic. Pneumothorax, haemothorax and pericardial effusion were excluded clinically.

Q. How would you now respond?

A. As no response was seen in either blood pressure or central venous pressure, it suggests that there is a likely need for more fluid loading until a sustained 3 mmHg rise in CVP is obtained. Other manoeuvres that may be considered include lowering the level of PEEP and/or the tidal volume. However, her poor gas exchange may be potentially compromised further by reducing the degree of PEEP or of ventilatory support.

A chest X-ray and ECG were performed urgently and no evidence of pneumo or haemo- thorax or tamponade was detected. Aspiration via the nasogastric tube and a rectal examination revealed no evidence of bleeding. There were stigmata of chronic liver disease with hepatomegaly and spider naevi. The ECG showed sinus tachycardia and poor R-wave progression, and the chest X-ray revealed right middle lobe shadowing with some segmental collapse.

Q. If blood pressure fails to improve with fluid loading and increasing the epinephrine infusion rate what would you do next?

A. Cardiac output measurement would be useful to better determine haemodynamic status and guide treatment. This may be performed in the emergency department with some rapid techniques such as oesophageal Doppler or pulse contour analysis ± dye/thermal dilution, or soon after admission to the ICU.

Link to PACT module on Clinical imaging

Link to PACT module on Acute hepatic failure

After 1000 mL of fluid, her blood pressure improves to 100/60 mmHg. She is transferred to the ICU and, on arrival, her initial blood tests have been reported:

- Hb 8.2 g/dL; platelets 45 000 /mm³; leukocytes = 20000 /mm³
- MCV 105
- Clotting screen normal
- Arterial blood gases (on FiO₂ 1.0): pH = 7.25; PaCO₂ = 5.3 kPa (40 mmHg)
- PaO₂ 10.6 kPa (80 mmHg); SaO₂ = 98%
- Bicarbonate 13 mmol/L; base deficit –10.5 mmol/L
- Carboxyhaemoglobin level 2.1%
- Central venous saturation: SvO₂ 35%
- Na = 135 mmol/L; Cl = 90 mmol/L; K = 6.4 mmol/L
- Lactate 6.2 mmol/L
- Blood glucose 8.5 mmol/L (153 mg/dL); urea 5.6 mmol/L (15.7 mg/dL); creatinine 280 µmol/l (3.2 mg/dL)
- SGOT 540 IU/I (9.2 µkat/l); SGPT 362 IU/I (6.2 µkat/l); bilirubin 18 µmol/l, amylase 450 IU/l (7.7 µkat/l)
- CPK = 8500 IU/l (144.5 µkat/l); CPK MB 120 IU/l (2.0 µkat/l)
- Troponin 0.02 IU/l
- Alcohol concentration = 0.20 g/l; benzodiazepine +
- Urine output minimal; urinalysis: blood +++, protein +

Q. How do you interpret the arterial blood gas data?

A. She has a metabolic acidosis (with associated hyperlactataemia) which is insufficiently compensated by ventilation. She has hyperkalaemia (acidosis, rhabdomyolysis). There is a major shunt (FiO₂ 1.0 and PaO₂ 10.6 kPa [80 mmHg]). The SvO₂ is low with a normal SaO₂, and presumably low O₂ uptake (hypothermia, unconsciousness): this is likely related to the decreased Hb and cardiac output. She does not have a high level of COHb.

Link to PACT module on Electrolytes and Homeostasis

Learning Issues

Reasons for decrease in mixed venous O₂ saturation

Q. What value of O₂ extraction do you anticipate in this patient?

A. An SvO₂ of 35% corresponds to an approximate EO₂ of 65%, which is close to the critical EO₂. There is thus a high likelihood of O₂ supply dependency and tissue hypoxia.

Q. What are the acute diagnoses you have now made from your clinical examination and tests performed to date? List five diagnoses and summarise the supporting evidence.

A.
1. Benzodiazepine overdose and coma (positive urine test).
2. Cardiogenic shock (hypotension not responding to fluid and requiring epinephrine plus a low SvO₂).
3. Likely aspiration pneumonitis (right middle lobe collapse/consolidation).
4. Rhabdomyolysis (high CPK with normal cardiac isoform, high creatinine relative to urea, hyperkalaemia, oligoanuria, positive urine test for blood).
5. Hypothermia.
Q. Suggest two relevant background co-morbidities and the supportive evidence?

A.  
1. Chronic macrocytic anaemia (low Hb, high MCV).  
2. Chronic liver disease (clinical findings, anaemia, thrombocytopenia, abnormal liver function tests).

Q. There is no evidence of a recent myocardial infarction (clinical, ECG or biomarker evidence). Enumerate some possible diagnostic explanations for the cardiogenic shock?

A. Possible aetiologies include:  
1. Cardiomyopathy from chronic alcoholism  
2. Propranolol overdose  
3. Myocardial stunning ± hibernation following cardiac arrest plus  
4. Continuing hypoxaemia and hypoperfusion  
5. Myocardial depression from sepsis secondary to an aspiration pneumonia.

Learning Issues

Cardiac causes of hypotension

Sepsis-related versus cardiogenic persistent hypotension

Q. Outline your haemodynamic approach to therapy for the patient's hypotension and cardiogenic shock.

A. Insert arterial line and a monitor of cardiac output for better titration of fluids (including Hb), inotropes and other vasoactive drugs to improve tissue oxygenation and perfusion. An echocardiogram is warranted to exclude any structural abnormality that may be contributory to the cardiogenic shock state.

Q. How will you manage the probable pneumonia and likely septic component to the shock?

A. Conduct a septic work-up and start antibiotics once samples are (expeditiously) taken. Consider bronchoscopy to remove vomitus to gain BAL sample for microbiology sampling, plus hopefully expand collapsed right middle lobe and improve gas exchange. Consider recruitment, ‘bagging’ of lungs or ventilator manipulation to recruit collapsed alveoli and improve gas exchange.
Q. Outline your management of the hyperkalaemia and the evidence of rhabdomyolysis?

A. Exclude compartment syndrome and decompress if indicated. Consider fluid therapy and urinary alkalinisation and possible early haemodiafiltration (rather than CVVH) in view of persisting hyperkalaemia and oligoanuria, and likelihood that kidney recovery will not be imminent.

Q. Outline other important metabolic/nutritional care?

A. Intravenous folate, vitamin B12 and vitamins (including thiamine) in view of her macrocytic anaemia and likelihood of chronic deficiency.

Q. Will you commence rapid re-warming?

A. No. Do not rewarm and leave for 24 h at 32–34 °C, in view of cardiac arrest.

Q. Outline other relevant general supportive critical care management and reasons why?

A. Commence DVT prophylaxis (in view of her immobility) and start stress ulcer prophylaxis (history of alcoholism, thrombocytopenia, and likelihood of needing prolonged mechanical ventilation).

Learning Issues

Selecting appropriate monitoring – PACT module on Haemodynamic monitoring

Q. If you opt not to insert a cardiac output monitoring device, please provide reasons? (the answer here has four reasons)

A.
1. Lack of outcome benefit data in multicentre ICU studies.
2. May be an unnecessary additional intervention if patient continues to show signs of stabilisation/improvement using current therapy and monitoring.
3. Non-availability of technology.
4. Contraindications to using what is available.
Q. If you opt to insert a cardiac output measuring device, please justify by providing three arguments for monitoring cardiac output.

A.
1. Easier to optimise fluid status and stroke volume in terms of constructing a Frank–Starling curve, especially with concurrent use of epinephrine and poorly compliant lungs requiring high ventilator pressures and high PEEP. This may enable earlier reduction/discontinuation of inotrope.
2. She has a critically low tissue TO2 and supply–demand dependency and thus has a limited reserve to cope with further deterioration. Cardiac output monitoring will facilitate the correct choice of treatment (including blood and inotropes) and avoidance/early recognition of inappropriate and/or harmful therapies (and doses).
3. An overall lack of outcome benefit may not necessarily apply to an individual case, especially one so severe.

Q. If you opt for a pulmonary artery catheter, outline your reasons for this choice?

A. The pulmonary artery catheter will allow an assessment of preload dependency, cardiac output, and pulmonary pressures in a patient with severe lung injury. Continuous (or intermittent) monitoring of $S\bar{v}O_2$ can be used to titrate therapy to improve her oxygen supply–demand balance, e.g. aiming for a mixed $S\bar{v}O_2$ value >65%.

Q. Give a reason for caution in the assessment of $S\bar{v}O_2$ as an index of heart failure in this patient?

A. The $S\bar{v}O_2$ should be interpreted cautiously in severely altered liver function because of falsely elevated $S\bar{v}O_2$ due to limited oxygen extraction in the liver.

Echocardiography, if available, will have been used from the outset to evaluate cardiovascular function and may be useful when serially repeated. If inadequate or not available, other options include oesophageal Doppler, pulse contour analysis and/or peripheral dye dilution or thermodilution cardiac output measurement techniques. Central venous SO2 (ScvO2) monitoring (intermittent or continuous) can be used as a surrogate for mixed venous SO2 ($S\bar{v}O_2$).

Link to PACT module on Haemodynamic monitoring

The choice of monitoring technique depends on familiarity, availability, presence of exclusion criteria (e.g. classic bolus dilution techniques are inaccurate with moderate-to-severe tricuspid regurgitation), and potential risks (e.g. bleeding from line insertion if patient has concurrent coagulopathy).

**Note**

$TO_2$ (oxygen transport) is synonymous with $DO_2$ (oxygen delivery).
Techniques for measuring cardiac output

Echocardiography in the assessment of hypotension

A transthoracic echocardiogram was quickly performed, confirming neither pericardial effusion nor valvular abnormality, but an empty left ventricle. Review of the arterial waveform showed a systolic pressure averaging 105 mmHg but with a marked variation: see figure below.

Q. Why would you interpret this trace as showing preload dependency?

A. The observed systolic pressure variation is roughly equal to 13 mmHg and highly suggestive of preload dependency, particularly as she is making no spontaneous breathing efforts. Other indices which can be calculated are delta Down or pulse pressure variation (deltaPP).

Systolic and pulse pressure variation (SPV and deltaPP)

Link to PACT module on Haemodynamic monitoring

Despite the severity of her lung injury, a further four 250 mL fluid challenges were given over the next 60 min. The systolic pressure variation has fallen (see figure below), suggesting that preload independency has been reached.
Fluid therapy

After this fluid loading and continuation of epinephrine at 0.3 mcg/kg/min, cardiac output was found to be 3 L/min (1.8 L/min/m²) with a central venous ScvO₂ of 55%. Stroke volume was 33 mL and did not improve further with a fluid challenge. Blood pressure was 130/70 mmHg. Urine output was minimal. Arterial blood gases showed a worsening metabolic acidosis (pH 7.18, lactate 8.4 mmol/L), Hb of 6.8 g/dL and SaO₂ = 99%.

Q. What is your analysis of her circulatory (haemodynamic) status?

A. The oxygen transport (TO₂ = 3 × 0.99 × 6.8 × 1.39 × 10 = 280 mL/min) and oxygen consumption (VO₂ =156 mL/min) are still very low suggesting persisting tissue hypoperfusion (shock), despite the improving SvO₂. The lactic acidosis is likely a representation of the severity of the shock but may also be caused by increased washout of lactic acid related to an improvement in cardiac output from a critically low state, and/or related to the use of epinephrine (accelerated aerobic glycolysis). Her catabolic state plus renal failure may be further exacerbating the metabolic acidosis.

TO₂ and VO₂ in the analysis of hypotension and shock

Shock due to circulatory and anaemic hypoxia

Analysis of metabolic acidosis

For assessment of acidosis see PACT module on Electrolytes and Homeostasis.

Q. What further steps would you institute in her management?

A. Options include:

- Blood transfusion (preferably with fresh rather than aged donor blood) to elevate TO₂.
- Reduction of the epinephrine dose as the blood pressure is now probably higher than needed and the associated increased afterload may now be causing further strain on her poorly functioning heart.
- Consider replacing epinephrine with another inotrope, e.g. an inodilator such as dobutamine or milrinone.
- Repeating blood gases in 30–60 minutes to see if acidosis is improving.

Q. If there is refractory low cardiac output/index in this situation where propranolol toxicity may be important, what other measures might be considered?

A. Mechanical measures such as pacing or intra-aortic balloon pumping (IABP) may be considered. Also, inotropic measures not dependent on beta-receptor activation for their effect.
Atrial pacing, after testing AV conduction, at rates above 100/min was considered but the patient had a heart rate around 90/min and pacing was deemed not necessary as her cardiac output was improving.

Glucagon was also considered for the potential propranolol overdose but as her circulatory status was improving and there was no bradycardia or persisting hypotension, it was not considered necessary.

**Learning issues**

Inodilators in the treatment of cardiogenic hypotension and shock

Three hours later, she is more stable. She is now being haemodiafiltered and her K⁺ level is 5.6 mmol/L. Bronchoscopy revealed vomitus occluding the right middle lobe, removal of which (plus lung recruitment on the ventilator) resulted in marked improvement in gas exchange. No compartment syndrome was found. She had received two units of blood and the adrenaline dose had reduced by 80%. Arterial pH had improved (7.3), cardiac output is now 4.5 L/min, BP 100/60 mmHg, ScvO₂ 68%.

She made a slow recovery thereafter. She woke slowly over the next five days and came off renal replacement therapy after three weeks. Weaning was problematic as she had marked delirium related to the benzodiazepines and alcohol withdrawal, and this was punctuated by an episode of ventilator-associated pneumonia after one week. She was eventually discharged from the ICU after one month with psychiatric follow-up organised.

**Learning issues**

Nosocomial infection – pneumonia. See PACT module on Severe infection
Link to PACT module on Acute renal failure (Acute Kidney Injury Part II)

Link to PACT module on Clinical outcome

**On reflection**, these patients demonstrate how the underlying aetiology of the hypotension is not always readily apparent, and that it may be multifactorial. A rational, organised approach to diagnosis and management is mandatory alongside immediate resuscitation (see Clinical management algorithm in Task 2 above). Frequent reassessment of circulatory status and related diagnostic issues is also necessary. Application of the oxygen delivery equation is useful in considering which deficits need to be corrected.