Treatment of haemodynamic disturbance

Part one of this two-part series outlined the approach to assessing haemodynamic disturbance on the ward. If initial efforts to re-establish stability have failed, use of vasoactive drugs should be considered. This article uses two examples of shock (septic and cardiogenic) to illustrate the structured approach to management and the drugs commonly used. It must be emphasized that senior support should have already been mobilized and relocation of the patient considered.

Vasoactive drugs

When restoration of adequate tissue perfusion has failed with fluid resuscitation, vasoactive agents should be initiated. The choice of agent should be based on the mechanism of action and desired effects according to the goals of therapy, which will vary depending on the type of shock. Cardiac output is the primary problem in hypovolaemic, cardiogenic and obstructive shock, so inotropes are often initially used (*Table 1*). Reduced systemic vascular resistance and maldistribution of blood flow is the primary problem in distributive shock, so vasopressors are often chosen. In certain instances, a combination of the two may be necessary.

In the face of life-threatening perfusion, vasopressors are the initial drug of choice until definitive therapy is established, with noradrenaline being the commonly accepted first line. It is important that fluid status is frequently reassessed. Owing to the short half-life, these drugs are given as continuous infusions via a central venous catheter. There is a risk of skin necrosis if extravasation occurs through a peripheral line.

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Table 1. Catecholamine receptors

		Cardiac		Peripheral vasculature	
Receptor	**Location**	**Heart rate**	**Contractility**	**Vasoconstriction**	**Vasodilatation**
Alpha 1	Vascular smooth muscle – peripheral, renal and coronary			✓	
Beta 1	Heart	✓	✓		
Beta 2	Vascular smooth muscle – peripheral, pulmonary and renal				✓
Dopamine	Vascular smooth muscle and heart		✓		✓ Renal, splanchnic and coronary vascular beds

Prolonged use of vasoactive drugs is undesirable because of the risk of tachyphylaxis, increased myocardial oxygen demand and resultant myocardial damage. It is important to note that all vasoactive drugs can cause tachyarrhythmias and worsen lactic acidosis.

The most commonly used vasoactive drugs started outside the intensive care setting are those that work on catecholamine and dopamine receptors. *Tables 1* and *2* show the main actions of these receptors and the drugs.

Septic shock

Sepsis is the presence of a source of infection with a systemic inflammatory response syndrome in response to that infection. Septic shock is sepsis plus either hypotension (refractory to intravenous fluids) or hyperlactaemia ≥4 mmol/litre (Levy et al, 2003).

The haemodynamic disturbance

It is theorised that overwhelming sepsis occurs as a result of a dysregulation in the complex balance between proinflammatory mediators (systemic inflammatory response syndrome) and the compensatory anti-inflammatory response. Simply put this causes endothelial damage and impairment of the microcirculation, resulting in tissue hypoxia and ultimately leading to multiorgan failure (Perman et al, 2012; Angus et al, 2013).

The sum of these processes predominantly causes a high-output, low-resistance state, thereby creating a distributive shock. As no targeted therapies are currently recommended for the treatment of microcirculatory failure, existing treatment strategies focus on optimizing preload, perfusion pressure, oxygen delivery and source control.

Detection

The role of the junior doctor is to recognize the early signs of organ dysfunction, instigate time-critical resuscitation according to protocolized early goal-directed therapy and mobilize senior support in order to mitigate the effects of uncontrolled sepsis.

Specific laboratory investigations for septic shock include coagulopathy, thrombocytopaenia and hyperbilirubinaemia, leukocytosis, leukopaenia, and raised C-reactive protein and procalcitonin levels (Angus et al, 2013).

Intervention

In the first 3 hours, the Surviving Sepsis Campaign (Dellinger et al, 2013) suggests measuring lactate, taking blood cultures before administering antibiotics, administering antibiotics within 1 hour and delivering the initial fluid bolus 30ml/kg crystalloid (if hypotensive or lactate ≥4 mmol/litre).

Table 2. Commonly used vasoactive drugs

Drug	Type	Receptor	Overall action	Use	Dose (mcg/kg/min)	Main adverse effects
Noradrenaline	Vasopressor	A1>B1 (contractility > heart rate) >B2	↑ Systemic vascular resistance ↑ Cardiac output	Distributive shock	0.01–2 Onset: immediate Half-life: 1–2 minutes	Limb ischaemia
Metaraminol	Vasopressor	Alpha 1	↑ Systemic vascular resistance	Distributive shock	0.5–1 mg bolus Onset: 1–2 minutes Half-life: 20–60 minutes	Bradycardia
Adrenaline	Both	B1> A1 B2 (at low doses)	↑ Systemic vascular resistance ↑ Cardiac output Bronchodilatation	Refractory shock, anaphylaxis	0.01–0.1 Onset: immediate Half-life: 1 hour	Lactic acidosis, decreased splanchnic blood flow
Dobutamine	Inotrope	B1 (contractility > heart rate) >B2	↑ Cardiac output ↓ Systemic vascular resistance	Cardiogenic shock	2–20 Onset: 1–10 minutes Half-life: 2 minutes	Hypotension
Dopamine	Both	Low doses (1–3): dopamine Medium doses (3–10): B1 High doses (>10): A1	↓ Systemic vascular resistance > ↑ cardiac output ↑ Cardiac output ↑ Systemic vascular resistance and mean arterial pressure	Cardiogenic and distributive	2–20 Onset: 5 minutes Half-life: 2 minutes	Tachyarrhythmias – often restricts use more than other agents

Table 3. Early goal-directed therapy for the resuscitation of septic shock

Aims		Intervention	Tips
Optimizing preload	Central venous pressure 8–12 mmHg*	1. Further fluid boluses if haemodynamic improvement noted† 2. Consider albumin when substantial amounts of crystalloid required 3. Avoid hetastarch preparations	Ensure no technical factors spuriously affecting measurement, e.g. transducer height
Maintaining perfusion pressure	Mean arterial pressure ≥65 mmHg	1. Fluid administration as above 2. Add vasopressors if unresponsive to fluids 3. If ongoing haemodynamic instability, add hydrocortisone 200 mg/day	
	Urine output ≥0.5 ml/kg/hr	Fluid administration as above	Flush catheter if sudden decrease in urine output
Matching oxygen supply and demand	Central venous oxygen saturation ~70%	1. Fluid administration and/or inotropes to increase cardiac output 2. Increase fractional inspired oxygen 3. Target haemoglobin of 7–9 g/dl‡	Change one parameter at a time and recheck central venous oxygen saturation – this can be raised in severe sepsis as a result of reduced tissue extraction
	Lactate clearance	Combination of the above	Maintain consistency in type of sample used (arterial or venous) May not be elevated in shock

** Judicious serial assessment of jugular venous pressure can be used initially. † Reduction in tachycardia, increased mean arterial pressure and central venous pressure response. ‡ If no extenuating circumstances, e.g. cardiac ischaemia*

Table 3 outlines the aims of early goal-directed therapy for the first 6 hours of resuscitation, if there is persistent hypotension or if the initial lactate level is ≥4 mmol/litre.

Vasoactive drugs of choice

Once fluid status is assessed and optimized, one can think about manipulating cardiac output and systemic vascular resistance using vasoactive drugs.

Vasopressors

The first choice single agent is noradrenaline, but adrenaline can be added. Vasopressin (0.03 unit/min) can also be added to noradrenaline to achieve a targeted mean arterial pressure or wean off noradrenaline.

Avoid use of dopamine except in certain patients, e.g. those with a low risk of arrhythmia, marked left ventricular systolic dysfunction or low heart rate.

Inotropes

If the patient has myocardial dysfunction or ongoing signs of hypoperfusion despite adequate volume and mean arterial pressure resuscitation, consider a trial of dobutamine infusion with vasopressor therapy (if in use).

Cardiogenic shock

Cardiogenic shock can be defined as inadequate tissue perfusion and oxygenation as a result of cardiac dysfunction in the presence of adequate intravascular volume. It can be precipitated by a wide array of insults and can occur as the result of an acute or acute-on-chronic event. In the context of acute myocardial infarction, the SHOCK trial reports that left ventricular failure is the most common cause (Hochman et al, 2000).

The haemodynamic disturbance

Cardiogenic shock is the final result of a cascade of derangements in the circulatory system. An insult significantly reduces cardiac

KEY POINTS

- Up to 50% of patients with shock are not volume responsive, requiring use of vasoactive drugs.
- In life-threatening hypotension, even when hypovolaemia has not been resolved, early vasopressor use may be required – this may worsen organ perfusion and tachycardia.
- Choose the vasoactive drug according to the desired effect: inotropes increase cardiac output and vasopressors increase systemic vascular resistance.

output, causing myocardial systolic and/or diastolic dysfunction. This leads to systemic hypotension, as well as reduced coronary filling and subsequent cardiac ischaemia. As a result of this downward spiralling circulatory failure, the neurohumoural compensatory responses (activation of the renin–angiotensin–aldosterone and sympathetic systems) result in vasoconstriction, fluid retention, positive chronotropy and inotropy. This eventually causes an increase in myocardial oxygen demand, which is clearly detrimental in an already failing heart.

There is also a well-documented systemic inflammatory response in some patients with cardiogenic shock. The production of inflammatory cytokines has a negative inotropic effect, which worsens vasodilatation and hypotension. The ischaemic cascade leads to worsening left ventricular diastolic dysfunction resulting in pulmonary congestion, hypoxia and a further reduction in coronary reserve (Cooper and Panza, 2013).

Detection

Formal diagnostic criteria for cardiogenic shock often rely on invasive haemodynamic monitoring, although thorough clinical examination will often differentiate cardiogenic shock from other types.

Assessment of hypoperfusion and tissue hypoxia is as described in part one. Those in cardiogenic shock will likely have cool, cyanotic peripheries in contrast to the vasodilatory, 'warm' shock of sepsis. This will initially manifest as a relative rise or preservation of diastolic blood pressure (narrow pulse pressure). Further examination findings can help to determine the possible underlying aetiology and predominant failure, i.e. right or left ventricular failure, which is important in initial management

Table 4. Signs of right *vs* left ventricular failure

Right ventricular failure	Raised jugular venous pressure with clear lung fields, peripheral oedema, palpable liver
	Kussmaul's sign
Left ventricular failure	Pulmonary congestion (highest mortality if present with peripheral vasoconstriction; Nohria et al, 2003)
	Precordial exam: S3 +/- S4, displaced apex

(*Table 4*). This should be complemented with an electrocardiogram, chest X-ray and urgent echocardiogram if possible.

Intervention

Optimizing preload

Consider a fluid challenge in those without pulmonary congestion or signs of volume overload. Patients with isolated right ventricular failure are preload sensitive and require several fluid boluses.

Maintaining perfusion pressure

Consider prompt cardioversion for arrhythmias and management of bradycardia. Early use of vasoactive drugs is recommended.

Matching oxygen supply and demand

Treatment of pulmonary congestion is essential and can be problematic with concurrent hypotension – use vasoactive drugs to facilitate diuresis. Assess patients for early non-invasive ventilation or intubation to improve the work of breathing and treat pulmonary oedema.

Vasoactive drugs of choice

Vasoactive drugs are often required early in cardiogenic shock and will unfortunately increase myocardial oxygen demand and aggravate ischaemia as well as having their own toxic effects. Use the lowest doses possible to avoid the higher mortality associated with high dose regimens (Klein and Ramani, 2012).

There are no specific guidelines on which regimen to use but the general consensus seems to advocate the use of dobutamine in moderately severe cardiogenic shock. In those with life-threatening hypotension, it would be reasonable to commence noradrenaline first and add in dobutamine if required. Vasopressin could be considered in addition to noradrenaline in order to reduce the noradrenaline requirements. In low doses, vasopressors have the added benefit of increasing coronary perfusion pressure and reducing myocardial ischaemia. Higher doses can increase afterload, thus decreasing stroke volume and cardiac output as well as worsening myocardial dysfunction and ischaemia with coronary vasoconstriction.

Dopamine is generally avoided, as it increases mortality as a first-line agent in cardiogenic shock (De Backer et al, 2010).

Conclusions

Via worked examples, this article has shown how to apply the approach set out in part one. There are many instances where cardiovascular support using vasoactive drugs is required. Knowledge of the underlying pathophysiology and the pharmacodynamics of these drugs is crucial in choosing the appropriate agent to aid resuscitation. These articles provide the junior doctor with a clear way to view and deal with haemodynamic disturbance. **BJHM**

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