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Management of vasoplegic shock

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Learning objectives

By reading this article, you should be able to:

- List the causes of vasoplegic shock.
- Explain the mechanisms of vasoplegic shock.
- Outline the goals of supportive care.
- Describe the mechanism of action of vasopressors and their adverse effects.
- Discuss the role of adjuvant therapies for vasoplegic shock.

Vasoplegic shock is common, contributing up to two-thirds of cases of shock admitted to the ICU.[1,2] For the two most common causes of vasoplegic shock—septic shock and vasoplegic shock after cardiopulmonary bypass (CPB)—mortality is 25–50%.[2–4]

There is no consensus definition of vasoplegic shock. A working definition is that of sustained hypotension caused by pathological vasodilation in combination with an increasing requirement for vasopressor drugs, and evidence of capillary leak and tissue hypoperfusion. Vasoplegia can be defined as excessive vasodilation without tissue hypoperfusion. A consensus definition of vasoplegia and vasoplegic shock would be helpful in terms of evaluating published evidence and planning future research.[4,5]

In this review we describe the mechanisms of vasoplegic shock, provide a rationale for supportive care and suggest a strategy for pharmacological management.

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Key points

- There is no consensus definition for vasoplegic shock. The diagnosis is based on clinical features.
- A multimodal approach to vasopressor therapy—targeting a number of different receptors—is probably the best way of achieving haemodynamic targets and minimising drug-specific adverse effects.
- Angiotensin II is a promising therapy for vasoplegic shock, but further research is needed to define its role.
- Hydrocortisone is a safe and useful adjunct in vasoplegic shock.

Mechanisms of vasoplegic shock

The pathophysiological mechanisms of vasoplegic shock can broadly be categorised as vasodilatory, vascular hyporesponsiveness, capillary leak and tissue hypoxia (Fig. 1). The underlying cause is systemic inflammation. Systemic inflammation arises from the interaction between the immune system and cellular material from damaged tissue, pathogens, or both.

Tissue injury releases damage-associated molecular patterns (DAMPS) whilst structural components of pathogens known as pathogen-associated molecular patterns (PAMPS) interact with pattern recognition receptors, such as the toll-like receptors on immune cells.[6] Activation of the toll-like receptors leads to the release of inflammatory cytokines, including interleukin-1, interleukin-6 and tumour necrosis factor-α. Important DAMPS and PAMPS are listed in Table 1.

Vasodilation

Inflammation leads to the increased production of endogenous vasodilators, the most important being nitric oxide. Inflammatory cytokines cause the upregulation of the enzyme inducible nitric oxide synthase (iNOS), resulting in an increased production of nitric oxide. In the cytoplasm, nitric

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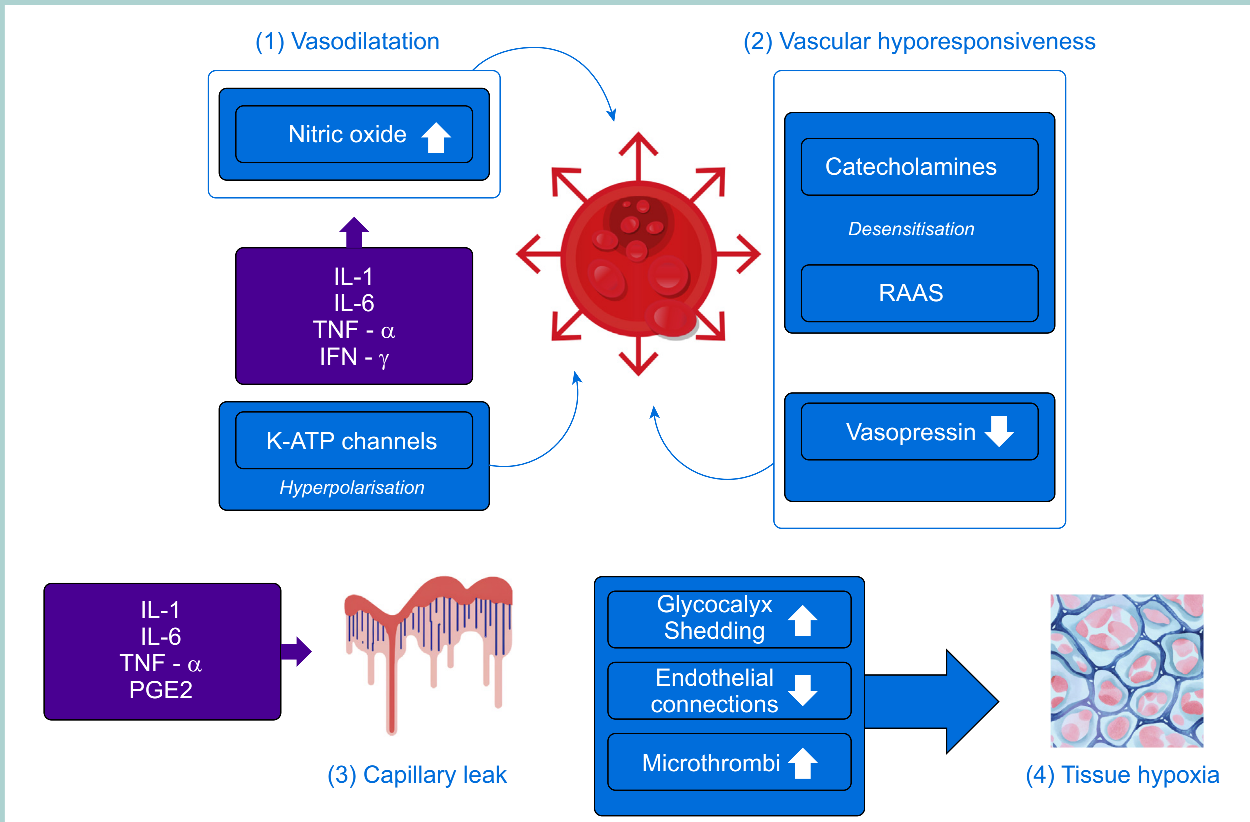

Fig 1 Pathophysiological mechanisms of vasoplegic shock. IFN-γ, interferon gamma; IL-1, interleukin-1; IL-6 interleukin-6; K-ATP, potassium-adenosine triphosphate channel; PGE2, prostaglandin E2; RAAS, renin-angiotensin-aldosterone system; TNF-α, tumour necrosis factor alpha.

Table 1 Important damage-associated-molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPS). DAMPs and PAMPs are molecules that trigger host immune responses. DAMPs indicate cellular stress or damage and PAMPs signal the presence of pathogens. See text for details. ATP, adenosine triphosphate; HMGB-1, high mobility group box 1; S100, soluble 100 proteins.

DAMPS	PAMPS
HMGB-1	Lipopolysaccharide
S100	Peptidoglycan monomers
DNA	Teichoic acid
ATP	Porins
Histones	Flagellin

oxide activates guanylate cyclase, which in turn activates various protein kinases. Protein kinases increase the reuptake of calcium into the sarcoplasmic reticulum leading to the relaxation of vascular smooth muscle.

A further mechanism of vasodilation is nitric oxide-induced activation of adenosine triphosphate-sensitive potassium (K-ATP) channels, which causes the hyperpolarisation of cell membranes, leading to impaired contraction of vascular smooth muscle.

Vascular hyporesponsiveness

High circulating concentrations of endogenous adrenaline (epinephrine), noradrenaline (norepinephrine) and angiotensin II lead to the downregulation of the receptors for these hormones. Vasopressin is released from the posterior pituitary in response to decreased intravascular volume and low serum osmolarity. Sustained secretion of vasopressin results in depletion of stores in the posterior pituitary, leading to reduced release in response to hypovolaemia.

Metabolic acidaemia also contributes to activation of K-ATP channels and desensitisation of catecholamine receptors.[7]

Microcirculatory dysfunction

Vasoplegic shock is associated microcirculatory dysfunction, which encompasses capillary leak and stasis of blood flow. Release of inflammatory mediators leads to shedding of the vascular endothelial glycocalyx—the gel-like protective layer on the luminal surface of capillaries—and damages endothelial cell junctions, resulting in the translocation of fluid and plasma proteins from the intravascular space to the extravascular space.

Shedding of the glycocalyx also leads to increased expression of adhesion molecules on the luminal surface of blood vessels. The presence of adhesion molecules, along with inflammatory-mediated activation of platelets and coagulation proteins, leads to the formation of microthrombi with stasis of capillary blood flow. Reduced capillary blood flow leads to tissue hypoxia and risks ischaemia.

As a consequence of the mechanisms described above, there is intravascular hypovolaemia, tissue oedema and end-organ hypoperfusion.[8] In addition to effects on the systemic microcirculation, there may be involvement of the pulmonary microcirculation with disruption of the alveolar-capillary membrane leading to the development of acute respiratory distress syndrome (ARDS).

Causes of vasoplegic shock

Systemic inflammation can present in a variety of ways, which broadly fall under the umbrella of the systemic inflammatory response syndrome (SIRS). Systemic inflammatory response syndrome is defined on the basis of fever, tachycardia, tachypnoea and leukocyte count. However, the criteria for SIRS fail to identify some patients with sepsis.[9] Nevertheless, vasoplegic shock can be considered as a manifestation of SIRS.

Table 2 lists the important causes of vasoplegia and vasoplegic shock encountered in anaesthesia and critical care practice. Depending on the underlying mechanism and pathophysiological processes, vasoplegia can progress to vasoplegic shock. Sepsis and cardiac surgery with CPB are two important causes of vasoplegic shock.

The incidence of vasoplegic shock after cardiac surgery is 5–25% although, as noted, the lack of consensus diagnostic criteria make comparisons across studies difficult.[4] While the mechanisms of vasoplegic shock in sepsis and CPB are similar, the triggers are different. With sepsis, the initial triggers for systemic inflammation are components of the pathogenic microorganism (PAMPS). After CPB, likely triggers are exposure of blood components to the extracorporeal circuit, surgical handling, tissue trauma, ischaemia-reperfusion and bacterial translocation from the gut. Use of drugs with vasodilator properties (e.g. milrinone) exacerbate arteriolar vasodilation. Risk factors for vasoplegic shock after CPB include: impaired ventricular function, prolonged CPB and the preoperative use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers.[10]

Assessment and initial management

The initial evaluation and management of patients with suspected vasoplegic shock involves identifying the primary cause of the shocked state, treating the underlying pathological process (e.g. antibiotics for sepsis), initiating supportive therapies (i.v. fluid, vasopressors, mechanical ventilation), and excluding other causes for the shocked state. The clinical presentation and information from the physical examination usually indicate the primary pathological process.

Several forms of shock can coexist in the same patient. The contribution of vasoplegia to the shocked state may evolve over time and should be re-evaluated frequently. After cardiac surgery, shock may arise from hypovolaemia (e.g. secondary to haemorrhage); left and right ventricular dysfunction (e.g. secondary to myocardial stunning, myocardial ischaemia, pre-existing cardiac dysfunction); cardiac tamponade; or left ventricular outflow tract obstruction. Patients with septic shock may also have sepsis-induced myocardial depression. If ARDS coexists with shock, there may be acute cor pulmonale resulting in impaired right ventricular function. Importantly, vasoplegic shock frequently coexists with hypovolaemia because of capillary leak.

Table 2 The causes of vasoplegia and vasoplegic shock.

Sepsis
Cardiac surgery with cardiopulmonary bypass
Major noncardiac surgery
Major trauma
Pancreatitis
Burns
Ischaemia–reperfusion injury
Anaphylaxis
Adrenal insufficiency
Liver failure
Neuraxial anaesthesia with high block
Toxicities (e.g. calcium channel blocker overdose)
High spinal cord injury

The haemodynamic state

Vasoplegia and vasoplegic shock present with hypotension, manifested by low mean arterial pressure (MAP <65 mmHg) and low diastolic blood pressure, (<40–50 mmHg). Patients typically present with warm peripheries and bounding peripheral pulses, although these signs may be absent in vasoplegic shock after cardiac surgery.

Pulmonary artery catheters (PACs) are rarely used except in cardiac surgical patients. However, if present, a PAC typically shows a high cardiac output (cardiac index >2.5 L min^{-1} m^{-2}) and low systemic vascular resistance (systemic vascular resistance index <800 dyne s cm^{-5}).[11] Mixed venous oxygen saturation may be normal, high, or low. In the presence of microcirculatory dysfunction, reduced oxygen delivery to tissues leads to reduced oxygen extraction and (counterintuitively) a normal or high venous oxygen saturation despite the presence of tissue hypoxia.

Recently, echocardiography and arterial waveform pulse contour analysis have become popular tools for assessing the haemodynamic state. Table 3 provides a comparison of haemodynamic assessment with PAC, echocardiography and pulse contour analysis. Irrespective of the approach taken to assessing the haemodynamic state, it is essential to exclude low cardiac output, as vasoplegia is the only clinically relevant cause of shock where cardiac output is high.

The microcirculation

As vasoplegia evolves into vasoplegic shock, patients may develop features of microcirculatory failure with cool, mottled peripheries and prolonged capillary refill time (>3 s). Increased serum lactate is common and is a useful marker of tissue oxidative stress. However, increased lactate can also indicate accelerated aerobic metabolism and is therefore not specific for tissue hypoxia.[12] The causes of high lactate concentrations are listed in Box 1. In one multicentre randomised trial, clinical assessment of the peripheral perfusion was comparable to the serum lactate as a guide to fluid resuscitation.[13]

Other clinical features

In addition to the features of circulatory failure discussed above, patients with vasoplegic shock may have fever, acute

Table 3 Haemodynamic monitoring in patients with vasoplegic shock. CI, cardiac index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT VTI, left ventricular outflow tract velocity time integral; PVV, pulse pressure variation; Svo_2, mixed venous oxygen saturation; SVRI, systemic vascular resistance index; SVV, stroke volume variation; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography. *Findings may be influenced by coexisting conditions, (e.g. hypovolaemia, left ventricular dysfunction, etc).

Method	Measurement (normal values)	Vasoplegic shock*	Comment
Pulmonary artery catheter	CI (2.5–3.5 L min^{-1} m^{-2}) Svo_2 (60–75%) SVRI (1200–2400 dynes s cm^{-5} m^{-2})	High May be normal, high or low (normal or high Svo_2 may be a result of regional hypoperfusion, leading to reduced oxygen extraction) Low	• Invasive • Rarely used except for cardiac surgery • Risks of arrhythmia, pulmonary artery injury • CI and SVRI measurements do not account for regional variation in vascular tone • Svo_2 measurement does not account for regional variation in oxygen delivery and consumption
Echocardiography (TTE, TOE)	LVEF (50–70%) LVOT VTI (17–22 cm)	May be high because of low LV afterload High	• Require training and experience to use • Potential for poor acoustic windows (TTE) • Difficulty aligning Doppler beam across LVOT, causing inaccuracy in the LVOT VTI measurement (TOE) • Semi-invasive (TOE)
Pulse contour analysis	CI (2.5–3.5 L min^{-1} m^{-2}) SVRI (1200–2400 dynes s cm^{-5} m^{-2}) SVV (<10%) PPV (<10%)	High Low High (>10%) if volume responsive, otherwise normal High (>10%) if volume responsive, otherwise normal	• Not well validated in critically ill patients • Analysis is performed using proprietary algorithms • Not valid when arterial waveform is under- or overdamped; not valid in the presence of arrhythmias • May require femoral arterial catheter • CI and SVRI measurements do not account for regional variation in vascular tone • SVV and PPV analysis only appropriate for patients receiving mechanical ventilation

Box 1

Causes of an increased serum lactate.

Microvascular failure with tissue hypoxia (e.g. vasoplegic shock)
Low cardiac output (e.g. cardiogenic shock)
Accelerated aerobic metabolism (e.g. adrenaline infusion, salbutamol infusion)
Reduced lactate clearance (e.g. hepatic failure)
Mitochondrial dysfunction (e.g. metformin)

kidney injury, metabolic disturbance (metabolic acidosis, increased lactate), respiratory failure, altered sensorium and—for patients with sepsis—signs and symptoms related the underlying infection (e.g. pneumonia).

Arterial blood pressure targets

The optimal arterial pressure in patients with vasoplegic shock is unknown but an MAP target ≥65 mmHg is reasonable. In patients with sepsis, a higher MAP target (75–85 mmHg) has not been shown to improve mortality, even in older patients.[14]

The site of intra-arterial pressure monitoring is important, as a femoral-to-radial artery pressure gradient, (femoral MAP > radial MAP) is common in patients with vasoplegic shock, especially after cardiac surgery. Resolution of vasoplegic shock is associated with equalisation of radial and femoral blood pressure.[15] Again, monitoring of cardiac output is helpful, as achieving an MAP target with vasopressors at the expense of cardiac output is likely to lead to a worse clinical outcome.

Fluids

Intravenous fluid therapy is the first-line management of vasoplegic shock. The choice of fluid has not been shown to influence mortality in patients with sepsis.[16] For sepsis, guidelines recommend at least 30 ml kg^{-1} of initial fluid for resuscitation.[9] Meta-analysis of randomised trials of early goal-directed therapy involving titration to fixed endpoints for central venous pressure or central venous oxygen saturation have not demonstrated improved outcomes compared with usual care.[17] Inadequate fluid resuscitation risks exacerbating tissue hypoperfusion whilst over-resuscitation increases fluid redistribution to the tissues and may increase mortality.[18]

It is important to recognise that in patients with vasoplegic shock, restoring circulating volume will not correct hypotension on its own. Identifying patients who are fluid responsive is not straightforward. Pulse pressure variation using pulse contour analysis devices and echocardiography-guided measurement of changes in the velocity-time integral across the left ventricular outflow tract with passive leg raises and fluid challenges are potentially useful in patients undergoing mechanical ventilation (Table 3).[19]

Vasopressor drugs

Along with i.v. fluids, vasopressors are the mainstay of supportive care for vasoplegic shock. Individuals vary in their response to different vasopressors and no specific agent has been shown to be clearly superior.[3] As noted above, the response to catecholamines is reduced in patients with vasoplegic shock and a multimodal approach, targeting different receptors, is likely to be the optimal strategy. Figure 2 provides an approach to titrating vasopressor therapy.

Established vasopressors

Noradrenaline

Noradrenaline is a direct α_1-adrenoreceptor agonist with some activity at β_1-receptors and minimal activity at β_2-receptors. Noradrenaline helps restore arteriolar tone, increasing MAP and diastolic blood pressure. Noradrenaline also increases vascular tone in venous capacitance vessels and helps maintain preload.

Guidelines recommend using noradrenaline as the first line agent in septic shock.[9] The starting dose is as an i.v. infusion at 0.05–0.1 μg kg^{-1} min^{-1}. The maximum beneficial dose is uncertain. Contemporary data show an associated mortality of 40% with high-dose noradrenaline (>1 μg kg^{-1} min^{-1}).[20] Variability in the salt formulation (i.e. hydrochloride, bitrate, tartrate), which are not yet standardised globally, can affect the dose of noradrenaline provided at a given infusion rate.[21]

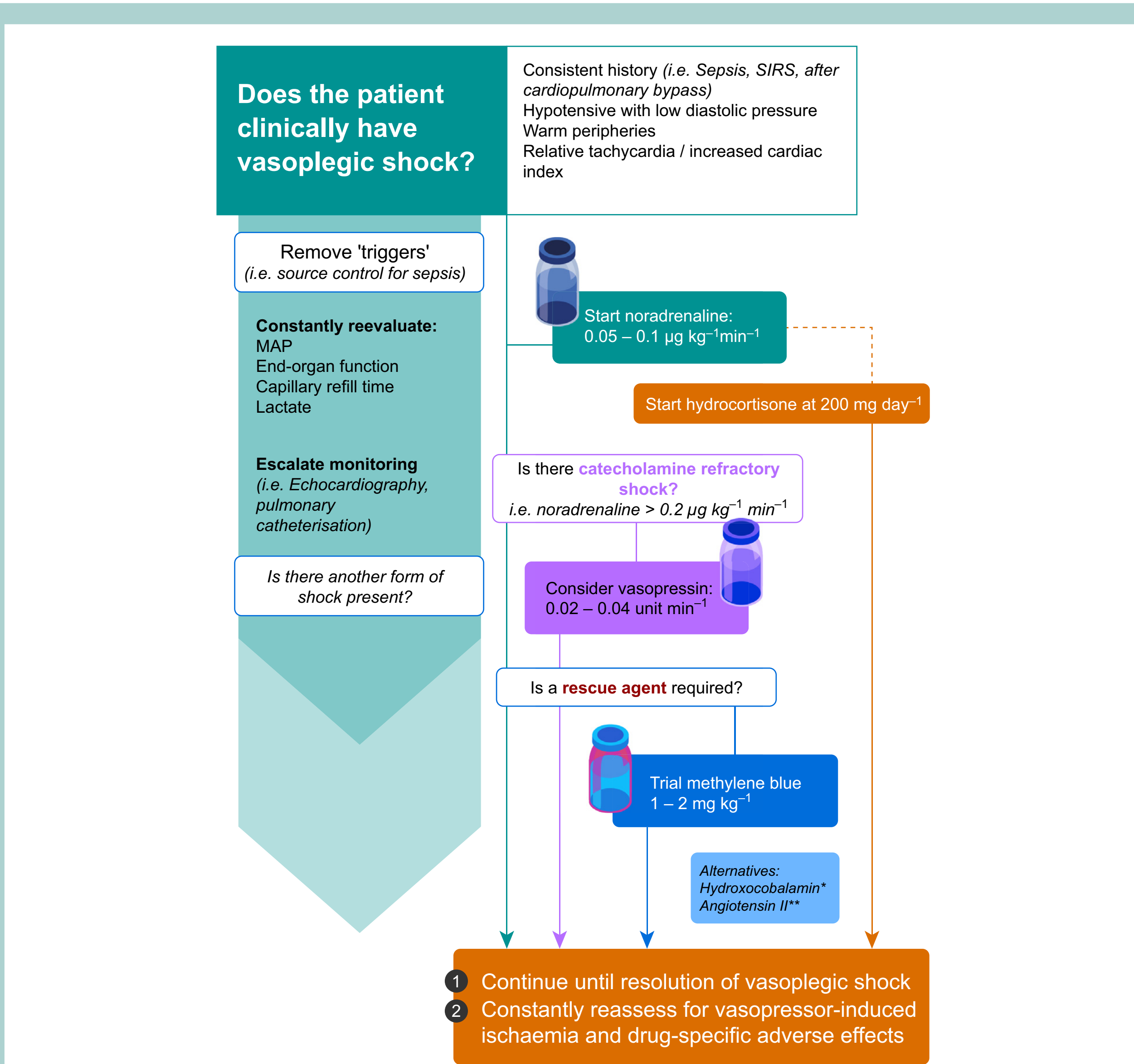

Fig 2 An approach to titrating vasopressor therapy in vasoplegic shock. MAP, mean arterial blood pressure; SIRS, systemic inflammatory response syndrome. *Weak evidence for benefit. **Not yet widely available.

In one study of patients with septic shock, serious adverse effects (including arrhythmias, myocardial ischaemia, stroke and digital ischaemia) with noradrenaline shock occurred in 10% of patients.[22] When compared with vasopressin, noradrenaline is associated with an increased risk of tachyarrhythmias, particularly atrial fibrillation.[23] Cardiac surgery-associated acute kidney injury has been weakly associated with high doses of noradrenaline.[24]

There is uncertainty as to the optimal time to initiate noradrenaline in vasoplegic shock. Though guidelines recommend commencing noradrenaline after an initial i.v. fluid resuscitation of 30 ml kg^{-1}, we advocate commencing noradrenaline earlier in patients who are no longer preload responsive.[9] The ARISE FLUIDS trial is investigating whether early commencement of noradrenaline with a restrictive fluid strategy (>1000 ml) compared with the usual improves 90-day mortality (trial registration NCT04569942).

Adrenaline

Adrenaline is a direct α- and β-adrenoreceptor agonist. Compared with noradrenaline, adrenaline has increased β_1 activity and also has activity at α_2-adrenoreceptors. β-Receptor activity predominates at lower doses (0.01–0.1 μg kg^{-1} min^{-1}) and mediates vasodilation and metabolic effects (β_2-adrenoreceptors) and chronotropy and inotropy (β_1-adrenoreceptors). α_1 Activity (vasoconstriction of systemic arterioles and venous capacitance vessels) predominates at higher doses (>0.1 μg kg^{-1} min^{-1}).

Adrenaline is cheap and widely available and is as effective as noradrenaline in achieving a target MAP.[25] The main advantage of adrenaline over noradrenaline is that it is a more potent inotropic drug, which may be beneficial in patients with impaired ventricular function. The main disadvantages of adrenaline are adverse metabolic effects and an increased potential for tachyarrhythmias. β_1-Adrenoreceptor-mediated tachyarrhythmias are most pronounced in the first 4–24 h.[25] Echocardiography is useful to evaluate ventricular function and, in rare circumstances, exclude adrenaline-induced left ventricular outflow tract obstruction.

β_2-Adrenoreceptor-mediated metabolic complications are common. Adrenaline antagonises the effects of insulin via gluconeogenic, glycogenolytic and lipolytic effects, causing hyperglycaemia and insulin resistance. Accelerated aerobic metabolism can cause or exacerbate hyperlactataemia. Increased lactate can make it difficult to evaluate the patient's response to supportive treatments and is most pronounced in the first 4–24 h.[25] β_2-Adrenoreceptor-mediated cellular uptake of potassium can lead to hypokalaemia, which in turn can exacerbate tachyarrhythmias.

Whilst short-term infusion of noradrenaline and adrenaline via a peripheral i.v. cannula might be reasonable, central venous access should be obtained as soon as possible to minimise the risk of tissue necrosis in the event of extravasation.[26]

Dopamine

Dopamine is a mixed, direct and indirect catecholamine precursor and has dose-dependent activity at dopamine-1 and β_1- and α_1-adrenoreceptors. Dopamine is not recommended for treating vasoplegic shock because of the risk of tachyarrhythmias compared with noradrenaline.[27] Dopamine has been associated with increased mortality in patients with septic shock.[27]

Vasopressin

Vasopressin is a non-catecholaminergic nonapeptide with activity on vasopressin V_1 (vascular smooth muscle contraction) and V_2 (antidiuretic effects) receptors. Vasoconstrictor effects are seen at higher plasma concentrations (10–200 pg $millilitre^{-1}$). Vasopressin leads to inactivation of K-ATP channels, potentiates the effects of catecholamines and reduces iNOS production.[28]

Vasopressin is typically used as a noradrenaline-sparing agent when the dose of noradrenaline exceeds 0.2 μ kg^{-1} min^{-1}. The usual dose of vasopressin is 0.02–0.04 units min^{-1}. Trial data have confirmed the safety of vasopressin in septic shock when used in combination with noradrenaline at doses <0.06 unit min^{-1}.[29,30]

Compared with catecholamines, vasopressin tends to cause less increase in pulmonary vascular resistance (PVR) and reduced rates of atrial fibrillation.[23] In a single-centre study in cardiac surgical patients, vasopressin was associated with a lower rate of the composite adverse outcome compared with noradrenaline, a difference largely resulting from lower rates of atrial fibrillation and renal failure.[31] However, vasopressin is associated with a higher risk of digital ischaemia than adrenaline and noradrenaline and should be used with caution in patients with peripheral vascular disease.[32] When used in the dose range of <0.06 unit min^{-1}, the incidence of mesenteric ischaemia is comparable to noradrenaline.[33]

Novel agents

Methylene blue

Methylene blue is a direct inhibitor of nitric oxide synthetase, with selectivity for iNOS. Methylene blue also binds to the haem moiety of guanylate cyclase, thereby inhibiting the activation of protein kinases (see above).[34]

Vasoconstriction with methylene blue occurs in the presence of vasoplegia and is largely absent in patients with normal vascular tone. In responsive individuals, methylene blue leads to an increase in MAP, systemic vascular resistance and PVR. Cardiac output seems to be preserved.[35] The dose is 1–2 mg kg^{-1} as an i.v. bolus over 15–30 min or an infusion over ≥1 h.

There are only limited data supporting the use of methylene blue in patients with vasoplegic shock. In one study of patients with septic shock, methylene blue was associated with reduced dose requirements and earlier cessation of conventional vasopressors.[34] The MAGIC trial will assess whether an infusion of methylene blue in cardiac surgical patients promotes earlier liberation from conventional vasopressors and improves mortality (trial registration ANZCTR ACTRN12621000730808).

Methylene blue causes green discoloration of the urine (Fig. 3), caused by drug eliminated renally mixing with yellow urobilin compounds in the urine. Discoloration of blood can interfere with peripheral pulse oximetry readings, resulting in a misleading reduction in oxygen saturation within 30 s of giving a dose, which dissipates within a few minutes.[36]

Methylene blue is used as a treatment for methaemoglobinaemia.[37] Conversely, in patients with glucose-6-phosphate dehydrogenase deficiency and other haemoglobinopathies, methylene blue induces oxidative stress and can *cause* methaemoglobinaemia and haemolytic anaemia and should be avoided.[4] Methylene blue can also contribute to serotonin syndrome. Doses >7 mg kg^{-1} are associated with

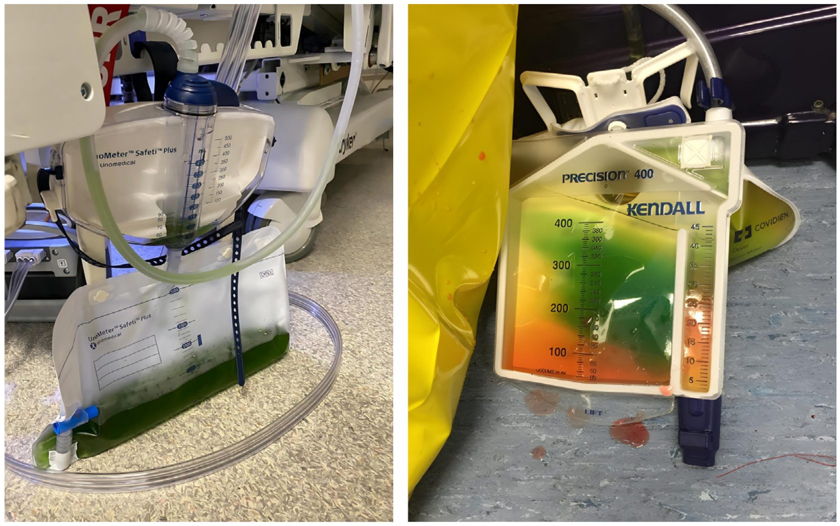

Fig 3 Altered urine colour with methylene blue and hydroxocobalamin. The left panel shows blue-green discolouration after methylene blue. The right panel shows orange-red discolouration from hydroxocobalamin. The patient in the right panel also received methylene blue, which explains the green discolouration.

splanchnic hypoperfusion.[37] Methylene blue should be used with caution in patients with increased PVR, although, doses <2 mg kg^{-1} are probably safe.[37]

Angiotensin II

Angiotensin II is a potent vasoconstrictor that acts via angiotensin II receptors in the peripheral vasculature. Like vasopressin, angiotensin II has no inotropic properties. Angiotensin II has a very short half-life and is given by a continuous infusion. The usual dose range is 20–40 ng kg^{-1} min^{-1}, which may be titrated to a maximum dose of around 200 ng kg^{-1} min^{-1}.[11,38]

The role of angiotensin II in treating vasodilatory shock was investigated in the ATHOS-3 multicentre randomised trial.[38] The study demonstrated that in patients receiving noradrenaline >0.2 μg kg^{-1} min^{-1}, angiotensin II was more effective than noradrenaline alone in increasing arterial pressure.[38] At 48 h, SOFA (Sequential Organ Failure Assessment) scores were lower in patients who received angiotensin II. There was no difference in major adverse effects between the groups and the study was not powered to detect a difference in mortality. A *post hoc* analysis found an improvement in recovery in renal function in patients with acute kidney injury and those needing renal replacement therapy.[39]

Angiotensin II is not yet widely available and there are unanswered questions regarding its impact on patient outcome and its safety in the setting of impaired ventricular function.

Hydroxocobalamin

Hydroxocobalamin is an established treatment for cyanide toxicity. The observation of hypertension as an adverse effect has led to its off-label use as a vasopressor. However, data supporting its role as a vasopressor are limited to case series, mostly in cardiac surgical patients.[40]

The possible mechanisms of action of hydroxocobalamin include inhibition of iNOS and enhancing the elimination of hydrogen sulphide, an endogenous vasodilator that hyperpolarises cell membranes by acting on K-ATP channels.[41] For vasoplegia, a dose of 5 g, given as an i.v. infusion over 10–15 min, may be used. If effective, a decrease in requirements for conventional vasopressors is observed within 15 min.

Dark orange-red urine can be seen after an infusion of hydroxocobalamin, which may persist for up to 6 weeks (Fig. 3). The 'blood leak alarm' in some renal replacement machines can be activated, caused by a false concern about rupture of the dialyser membrane. Hypokalaemia has been described in patients with vitamin B12 deficiency. Use of hydroxocobalamin can lead to errors in blood testing, including of creatinine, glucose, liver function tests and coagulation tests.[41]

Given the limited data supporting its use in vasoplegic shock, hydroxocobalamin should be considered a vasopressor of last resort.

Adjuvant therapies

Renal replacement therapy

Metabolic acidaemia is common in patients with vasoplegic shock and often associated with an increased lactate. Early initiation of renal replacement therapy is sensible for controlling acidaemia and managing acute kidney injury.

Corticosteroids

Corticosteroids have been studied in two large, multicentre trials in patients with septic shock. One study found a reduced mortality at 90 days in patients treated with hydrocortisone (200 mg day^{-1} i.v. for 7 days) plus fludrocortisone (50 μg day^{-1} via a nasogastric tube for 7 days) compared with placebo.[42] By contrast, another—larger study—found no difference in 90-day mortality in patients treated with hydrocortisone (200 mg i.v. daily for a maximum of 7 days).[43] Both studies found a shorter time to resolution of shock in patients assigned to glucocorticoids. In both trials, the rate of serious adverse events was similar between the groups. On balance, use of hydrocortisone is reasonable in patients with vasoplegic shock.

Vitamin C and thiamine

In a multicentre trial, high-dose vitamin C was associated with increased adverse events in patients with sepsis.[44] Consequently, high-dose vitamin C should not be used in patients with vasoplegic shock.

Thiamine (vitamin B1) is cofactor for several metabolic processes. In a *post hoc* analysis of two randomised trials, thiamine supplementation in patients with septic shock who were confirmed to be thiamine deficient was associated with a reduced rate of a composite outcome of mortality and freedom from renal replacement therapy.[45] These findings require further confirmatory trial data before thiamine can be recommended in vasoplegic shock.

Conclusions

Vasoplegic shock is common and is associated with high mortality. When vasoplegic shock is suspected, the primary cause needs to be sought, and other contributing forms of shock evaluated and treated. A multimodal approach, targeting a number of different receptors, is probably the optimal approach to vasopressor therapy. Further research is needed to define the safety profile and efficacy of newer agents. A consensus definition of vasoplegic shock would be helpful for comparing evidence across studies.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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Declaration of interests

The authors declare that they have no conflicts of interest.

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