Analytic Review

A Guide to the Use of Vasopressors and Inotropes for Patients in Shock

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Abstract

Shock is a life-threatening circulatory failure that results in inadequate tissue perfusion and oxygenation. Vasopressors and inotropes are vasoactive medications that are vital in increasing systemic vascular resistance and cardiac contractility, respectively, in patients presenting with shock. To be well versed in using these agents is an important skill to have in the critical care setting where patients can frequently exhibit symptoms of shock. In this review, we will discuss the pathophysiological mechanisms of shock and evaluate the current evidence behind the management of shock with an emphasis on vasopressors and inotropes.

Keywords

shock, vasopressors, inotropes, cardiogenic shock, hypovolemic shock, distributive shock, obstructive shock, septic shock, neurogenic shock

Pathophysiology of Shock

Shock can be categorized into 4 main types: distributive, cardiogenic, hypovolemic, and obstructive. While each type of shock has its own unique etiology, the pathophysiology behind each is similar. The categories of shock can be further subcategorized into 3 progressive stages beginning with compensated (nonprogressive) shock, uncompensated (progressive) shock, and ending with irreversible (refractory) shock. In compensated shock, homeostasis is maintained through compensatory mechanisms. Both cardiac output and systemic vascular resistance increase to keep blood pressure within normal limits. This stage of shock is reversible, and clinical presentation reflects the imbalance between tissue oxygen supply and demand.[1] Blood pressure will decrease due to a decrease in cardiac output (obstructive/cardiogenic/hypovolemic shock) or systemic vascular resistance (distributive shock). However, baroreceptors in the carotid and aortic bodies respond to this drop in blood pressure immediately through activation of the sympathetic nervous system. This activation of the sympathetic nervous system results in vasoconstriction through the release of epinephrine and norepinephrine (potent vasoconstrictors) from the adrenal medulla. Further, as a compensatory measure to prevent vital organ death, blood flow to organs such as the kidneys, skin, lungs, gastrointestinal (GI) tract, and liver is redirected to maintain blood flow to more vital organs such as the heart and brain. This decrease in blood flow to the kidneys activates the renin–angiotensin–aldosterone system (RAAS) resulting in the release of renin. Renin activates angiotensin to produce angiotensin I, which is converted to angiotensin II. Angiotensin II promotes vasoconstriction in the arterial and venous circulation. At this stage of shock, the body can compensate, and the patient will recover with little or no residual effects if treated. If allowed to progress, compensated shock will evolve into uncompensated shock.

Uncompensated (progressive) shock occurs when the body is no longer able to compensate for the mismatch in oxygen supply and demand. Aggressive interventions are necessary to prevent the patient from developing multiple organ dysfunction syndrome and continuing into irreversible shock. A distinguishing feature of this type of shock is the continued decrease in cellular perfusion resulting from altered capillary permeability. Altered capillary permeability allows for the leakage of fluid and protein from the vascular space into the interstitial space, decreasing circulating fluid volume and increasing interstitial edema. Fluid loss from the vascular space affects the solid organs, liver, spleen, GI tract, lungs, and peripheral tissues as it further decreases perfusion due to the resultant intravascular hypovolemia.

The final stage of shock is irreversible (refractory) shock. It is characterized by decreased perfusion from peripheral vasoconstriction and decreased cardiac output exacerbating anaerobic metabolism. Lactic acid accumulates, resulting in an increased capillary

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permeability and dilation. Increased permeability allows fluid to leave the vasculature and move into the interstitial space. Blood will pool in the capillary beds due to constriction of veins and dilation of arteries. The loss of intravascular volume results in worsening hypotension and tachycardia, decreasing blood flow to the coronary arteries. Reduction in coronary blood flow greatly diminishes cardiac output; as a result, cerebral blood flow cannot be maintained resulting in cerebral ischemia. Irreversible shock, as the name suggests, has progressed past the stage in which therapy is beneficial.

Distributive shock, also called vasodilatory shock, is caused by systemic vasodilation that leads to inadequate blood flow to the brain, heart, and kidneys damaging these vital organs.[2] This systemic vasodilation results in a decrease in systemic vascular resistance (SVR) and afterload. SVR can be calculated using Poiseuille's equation (Figure 1A). As the blood vessels dilate, the radius increases, resulting in a net lowering of resistance (blood pressure).[3] Distributive shock may also result in edema fluid loss into the surrounding tissue further lowering blood pressure due to the shift in volume distribution.[2] Important etiologies of distributive shock include sepsis, anaphylaxis, and neurogenic causes.

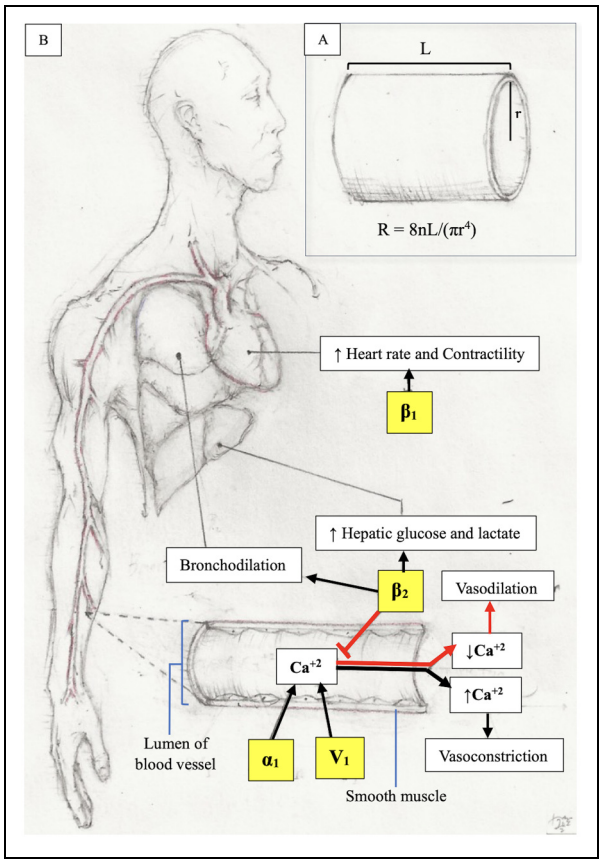

Figure 1. Panel A depicts Poiseulle's equation to calculate vessel resistance (*R*) which is directly proportional to length (*L*) and viscosity (*n*), and inversely proportional to radius (*r*) of the blood vessel. Panel B shows the vasopressor and inotrope receptor physiology. Common vasopressor and inotrope receptor targets are depicted as yellow boxes. Activation of β_1-receptor in the heart results in increased heart rate (chronotropy) and cardiac contractility (inotropy). V_1 and α_1-receptors activation in vasculature increases intracellular calcium (Ca^{2+}) concentrations leading to vasoconstriction of smooth muscle. This is counteracted by the activation of β_2-receptor in vasculature leading to vasodilation by decreasing intracellular Ca^{2+} concentrations. Also, β_2-receptor activation in the lungs and liver leads to bronchodilation, and increases glucose and lactate production, respectively. V_1 denotes vasopressin.

Cardiogenic shock is classified broadly as a cardiac disorder characterized by a decrease in ventricular function that results in end-organ hypoperfusion and tissue hypoxia. This decreased cardiac output activates the aforementioned RAAS cascade leading to water and salt retention.[4] RAAS cascade activation results in a vicious cycle that ultimately leads to the worsening of coronary ischemia and progressive volume overload with eventual circulatory collapse.[5]

Hypovolemic shock is caused by intravascular volume loss of blood or fluid resulting in circulatory failure. This fluid loss decreases preload, which in turn decreases cardiac output resulting in tissue hypoperfusion and hypoxia. SVR increases in an effort to compensate for declining cardiac output and blood pressure.[3,6]

Obstructive shock results in decreased cardiac output usually from extracardiac causes. Obstructive shock may be due to an increase in pulmonary vascular resistance or extrinsic mechanical compression of the superior and inferior vena cava carrying blood to the heart. Increased pulmonary vascular resistance is characterized by right ventricular heart failure due to the inability to overcome the high resistance of the pulmonary vasculature (eg, massive pulmonary embolism), while the latter is due to decreased preload from a reduction in venous return due to compression of the superior and inferior vena cava (eg, tension pneumothorax). Obstructive shock may also be caused by intracardiac obstruction (eg, hypertrophic cardiomyopathy or critical aortic stenosis) or external compression of the heart itself (eg, cardiac tamponade or constrictive pericarditis).[7]

Distributive Shock

Septic Shock

Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection.[8] The third international consensus definitions for sepsis and septic shock (Sepsis-3) define sepsis as a documented or suspected infection with a Sequential Organ Failure Assessment (SOFA) score ≥ 2.[8] Septic shock (the most common cause of shock) is currently defined as sepsis meeting the above criteria in patients who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg and have a serum lactate level > 2 mmol/L.[8–12] Hospital mortality for septic shock is often $> 40\%$.[8]

The Surviving Sepsis Campaign (SSC) was created in 2004 to provide international guidelines for the management of sepsis and septic shock, with updates published every 4 years. The most recent version of the SSC (2021) made 6 main recommendation changes from the 2016 iteration: (1) the recommendation of initiating a fluid bolus of 30 mL/kg was downgraded to a weak recommendation based on the low quality of evidence,

(2) normal saline is no longer recommended for fluid resuscitation; only balanced crystalloid solutions should be used, (3) for adults in septic shock, prompt initiation of vasopressors is recommended even if this means peripheral administration, (4) the SSC suggests against the use of intravenous (IV) vitamin C, (5) IV corticosteroids are suggested for adults in septic shock with ongoing vasopressor therapy needs, and (6) it is recommended that adult survivors of sepsis or septic shock be assessed for physical, cognitive, and emotional problems after hospital discharge.[13] In addition to these changes, the 2021 SSC guidelines no longer recommend the Quick Sequential Organ Failure Assessment (qSOFA) as a single screening tool for suspected sepsis due to a lack of sensitivity and specificity,[14] which could lead to missed diagnoses.[13] These guidelines did not propose new diagnostic criteria for sepsis or septic shock, but did make a weak recommendation for using lactate levels to help screen for sepsis. In patients with suspected sepsis, the presence of an elevated lactate level significantly increases the likelihood of a final diagnosis of sepsis.[13]

Pneumonia is responsible for about half of all cases of sepsis.[12] Other common causes of sepsis include intra-abdominal and urinary tract infections. Hypotension, reduced red-cell deformability, and microvascular thrombosis are potential mechanisms that contribute to reduced oxygen delivery to tissues in septic shock.[15] In 40% of patients with sepsis, hypotension is the presenting abnormality.[16]

Once septic shock is suspected, initial management is important. The initial measures include the use of IV fluid resuscitation (30 mL/kg in the first 3 hours), IV antibiotics within 1 hour,[13] oxygen therapy, and mechanical ventilation if clinically indicated.[15,17] These recommendations are concordant with the 2021 SSC guidelines. After the initial fluid bolus of 30 mL/kg, monitoring for dynamic blood pressure response (eg, an increase in cardiac output occurring within 60 seconds of passive leg raising to a 45° incline) helps identify patients who may respond to additional fluids.[18] It is also advised to use lactate to assess tissue perfusion (lactate clearance) and to maintain a urine output goal of ≥0.5 mL/kg/h.[14] These measures help to safely guide fluid resuscitation while minimizing fluid overload. Of note, variation in cardiac output after passive leg raising may be more accurate than pulse pressure variation with respiration or using static tests such as central venous pressure in predicting fluid responsiveness in hemodynamically unstable patients.[18]

If the patient remains hypotensive despite fluid resuscitation, vasopressor therapy is indicated.[12,19] However, the notion of starting a vasopressor only after the patient is not fluid-responsive has been challenged.[20] Early administration of vasopressors could reduce fluid overload from excessive fluid use,[21,22] potentially improve tissue oxygenation, and recruit microvessels leading to better microcirculation.[23,24] However, a recent unblinded randomized control trial (The CLOVERS trial) involving 1563 patients with sepsis-induced hypotension refractory to initial treatment with 1 to 3 L of IV fluid, found that a restrictive fluid strategy (with earlier vasopressor use) did not result in significantly lower or higher mortality before discharge by day 90 than a more liberal fluid administration strategy (with later vasopressor use).[25] Thus, it remains unclear if early vasopressor use in septic shock affects outcomes.

The first-line vasopressor recommended for septic shock is norepinephrine (Table 1 and Figure 1B).[26–28] Norepinephrine is usually started at a dose between 0.01 and 0.05 μg/kg/min, which may be titrated up at increments of 0.02 to 0.04 μg/kg/min every 5 to 15 minutes until the MAP goal of 65 mm Hg or greater is reached.[29,30] Vasopressin or antidiuretic hormone (ADH) is produced in the supraoptic and paraventricular nuclei in the hypothalamus and then stored in the posterior pituitary gland. The vasoconstrictive property of vasopressin is through the stimulation of V1 receptors in vasculature smooth muscle.[31] Low-dose vasopressin (0.03 units/min) may be added as a second-line agent if the MAP goal ≥ 65 mm Hg is not met with high doses of norepinephrine (> 0.2 μg/kg/min).[32–34] Retrospective studies have shown an associated improvement in mortality in patients with septic shock when prehospital norepinephrine was administered,[30] and when vasopressin was added to low-dose norepinephrine (< 0.25 μg/kg/min), but not high-dose norepinephrine (> 0.25 μg/kg/min).[35] However, the high-dose norepinephrine group might have had more severe disease resulting in worse outcomes. It appears that vasopressin has a synergistic effect when combined with norepinephrine, which may allow for a dose reduction of norepinephrine.[36] In addition, vasopressin may still produce vasoconstriction during acidotic states (eg, septic shock) when α_1-agonists (eg, norepinephrine) become less effective.[37]

Epinephrine is another second-line vasopressor that may be used, especially if the heart rate or cardiac output is inadequate (as this affect has both inotropic and chronotropic actions).[29] Alternatively, epinephrine may be added as part of a three-drug combination if a prompt response to the second vasopressor is not seen, especially in patients with concomitant myocardial dysfunction.[33,46] It is important to note that epinephrine has a higher risk of inducing tachyarrhythmias when compared to norepinephrine.[36] Further, the 2021 SSC guidelines proposed using hydrocortisone 200 mg/day (either as a bolus of 50 mg every 6 hours or as a continuous infusion) in septic shock patients with ongoing requirements for vasopressors despite adequate fluid resuscitation.[13]

Ideally, vasopressor therapy is given through a central venous catheter (CVC) due to concerns for vasopressor-induced local tissue injury (tissue necrosis) when a peripheral venous catheter (PVC) is used. However, the risk of tissue necrosis with the use of a PVC is limited, especially for short-term use (<6 hours) in a PVC placed proximal to the antecubital fossa.[47–50] Therefore, peripheral administration of vasopressors may be given temporarily until a CVC is placed,[49] even in children.[51]

Neurogenic Shock

Neurogenic shock is an important cause of distributive shock when the spinal cord is damaged. The hypoperfusion seen in

Table 1. Commonly Used Inotropes and Vasopressors in Shock.[29,33,36,38–45]

Medication	Dosing	Receptor binding	Adverse effects	Comments
Norepinephrine (NE)	• Initial dose: 0.01-0.05 μg/kg/min • Dose range: 0.01-1 μg/kg/min	$\alpha_1 > \beta_1 > \beta_2$	Tachyarrhythmias, increased pulmonary vascular resistance, peripheral (digital) ischemia	First-line vasopressor in septic and cardiogenic shock
Epinephrine (EPI)	• Initial dose: 0.01-0.05 μg/kg/min • Dose range: 0.01-0.3 μg/kg/min	$\alpha_1 = \beta_1 > \beta_2$	• Tachyarrhythmias, cardiac ischemia • Splanchnic vasoconstriction leading to abdominal organ ischemia • Hyperlactemia and hyperglycemia	• First-line vasopressor in anaphylactic shock and cardiac arrest • Hyperlactemia makes lactate a less reliable measure of end-organ perfusion
Dopamine (DOPA)	• Initial dose: 2-10 μg/kg/min • Dose range: 2-20 μg/kg/min[a]	$DA_1 > \beta_1 > \alpha_1$	Tachyarrhythmias, cardiac ischemia	• Second-line inotrope in adults • Used in select patients with low risk of tachyarrhythmias and bradycardia
Phenylephrine (PHEN)	• Initial dose: 0.1-0.3 μg/kg/min • Dose range: 0.1-1 μg/kg/min	α_1	• Reflex bradycardia • Severe peripheral ischemia	Useful for tachyarrhythmias, or in patients with adequate cardiac output and persistently low blood pressure
Vasopressin (VASO)	• Initial dose: 0.01-0.04 units/min • Dose range: 0.01-0.06 units/min	V_1	• Possible gastrointestinal hypoperfusion due to splanchnic vasoconstriction	• Usually used as an adjunct to norepinephrine in septic shock • Does not increase pulmonary vascular resistance
Dobutamine (DOB)	• Initial dose: 2-5 μg/kg/min • Dose range: 2-10 μg/kg/min	$\beta_1 > \beta_2 > \alpha_1$	• Hypotension, tachyarrhythmias, tachyphylaxis (infusions greater than 72 hours)	• First-line inotrope for most forms of shock • Quick onset of action
Milrinone (MIL)	• Initial dose: 0.1-0.25 μg/kg/min • Dose range: 0.1-0.5 μg/kg/min	Phosphodiesterase-3 inhibitor	• Hypotension (causes greater vasodilation than DOB), tachyarrhythmias, Torsades de pointes	• Useful inotrope in patients with significant pulmonary vascular resistance

Abbreviations: V_1, Vasopressin receptor; DA_1, dopaminergic receptor.
Tachyarrhythmia risk: DOPA, DOB, EPI > MIL, NE > VASO, PHEN.
[a]Vasoconstriction in most vascular beds (vasopressor effect) is seen with dopamine doses ≥10 μg/kg/min.

neurogenic shock is due to loss of sympathetic control of vascular tone that is often seen in upper spinal cord injuries, especially above the T6 level since the sympathetic neurons that innervate the heart reside from T1 to T4.[52,53] Early surgical intervention (< 24 hours) to decompress and stabilize the vertebral column is key.[52,54] It is also important to correct hypotension (systolic blood pressure < 90 mm Hg) to prevent secondary damage of the spinal cord from ischemia resulting in worsening of neurological outcomes.[55]

A vasopressor with both α and β activities such as dopamine or norepinephrine is commonly used to manage neurogenic shock when fluid resuscitation is insufficient. A small

prospective cross-over interventional study of 11 patients showed that norepinephrine was able to maintain MAP with a lower intrathecal pressure and a higher spinal cord perfusion pressure (~2 mm Hg) compared to dopamine.[56] One review showed that vasopressor complications were greater for dopamine (especially tachyarrhythmias) when compared to phenylephrine in patients with acute spinal cord injuries.[53] A more recent systematic review proposed that in acute traumatic spinal cord injuries, norepinephrine may be the vasopressor of choice.[57] Nevertheless, due to lack of high-quality evidence there remains no consensus on the optimal therapy for neurogenic shock. Another commonly used agent, phenylephrine, may induce reflex bradycardia (Table 1) which could be dangerous in patients with spinal injuries above T6, who are already prone to bradycardia due to sympathetic dysfunction. Therefore, it is recommended to use pure vasoconstrictors such as phenylephrine for lower spinal cord injuries (ie, below T6).[58,59] Conversely, norepinephrine or dopamine are used for upper spinal cord injuries (ie, at or above T6).[59] However, these agents may cause excessive inotropy in the context of increased peripheral vascular resistance if they are used for lower spinal cord injuries.[53]

The most current guidelines released in 2013 recommend maintaining a MAP within 85-90 mm Hg for 7 days in patients after acute spinal cord injuries.[60] However, there is only limited evidence to support this recommendation. Moreover, it is a challenge to maintain such MAP goals in general practice.[61] A recent retrospective study has shown higher rates of neurologic recovery in patients who maintained a MAP > 85 mm Hg consistently over a shorter period of time of 5 days after spinal cord injury.[62] Indeed, another retrospective study showed that higher average MAP values correlated best with improved recovery in the first 2 to 3 days after spinal cord injury, with this correlation becoming weaker in subsequent days.[63] This experience suggests that using vasopressors for less than the recommended 7 days may not negatively affect neurological outcomes. Therefore, maintaining the MAP goal of >85 mm Hg for 5 days after acute spinal injury is reasonable.

Elderly patients (≥ 65 years of age) might be particularly prone to complications with vasopressor use. Recent studies have shown that elderly patients with spinal cord injuries are particularly susceptible to cardiovascular complications[64] from vasopressors, especially with dopamine.[53,65,66] Clinical judgment is needed to determine the risk–benefit balance for vasopressor administration (especially dopamine) in the elderly who are often already burdened by chronic cardiovascular comorbidities. Downward adjustment of MAP goals is advisable, especially if there is no neurological improvement after the first 3 days after spinal cord injury.[52] It is important to note that blood pressure augmentation to MAP goals > 85 mm Hg in patients with concurrent hemorrhagic shock, aortic dissection, or intracranial hemorrhage could worsen these conditions, which are not uncommon in trauma.[52] More prospective studies are needed not only to determine the optimal vasopressor agent, but also to determine if MAP goals < 85 mm Hg can maintain adequate spinal cord perfusion pressure to minimize the use of vasopressors.

In patients who can tolerate oral medications, Midodrine (an α-1 agonist) may be given as 10 mg orally 3 times daily for prophylaxis or treatment of orthostatic hypotension often seen with spinal cord injuries.[67] Interestingly, oral midodrine may reduce IV vasopressor requirements for patients needing prolonged support after cervical spinal cord injury.[68] Droxidopa (a synthetic precursor of norepinephrine) is another oral agent that may be used to wean patients off IV vasopressors if patients are intolerant to midodrine.[69] Other medications to consider include atropine to treat bradycardia, which most commonly presents as sinus bradycardia.[53]

Anaphylactic Shock

Anaphylaxis is a serious allergic reaction that commonly presents with a rash (ie, urticaria), itch, and dyspnea (shortness of breath).[70] A diagnostic criteria for anaphylaxis was developed by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) symposium in 2006 (Table 2).[71]

Table 2. Diagnostic Criteria for Anaphylaxis.[71,72]

Anaphylaxis is highly likely when one of the following 3 criteria are met:

1. Acute onset of an illness with involvement of the mucosal tissue, skin, or both (eg, pruritus, flushing, generalized hives, edema of the lips-tongue-uvula) AND one of the following: A) Respiratory compromise (eg, bronchospasm, wheezing, dyspnea, stridor, reduced peak expiratory flow, and hypoxemia) B) Symptoms of end-organ dysfunction (eg, hypotonia, syncope, and incontinence), or systolic blood pressure (SBP) < 90 mm Hg
2. Exposure to a likely allergen for that patient AND 2 or more of the following occurring rapidly: A) Involvement of the skin-mucosal tissue (eg, edema of the lips-tongue-uvula, hives, pruritus, and flushing) B) SBP < 90 mm Hg or associated symptoms (eg, hypotonia, syncope, and incontinence) C) Respiratory compromise (eg, dyspnea, wheezing, bronchospasm, stridor, hypoxemia, and reduced peak expiratory flow) D) Persistent gastrointestinal symptoms (eg, nausea/vomiting and abdominal pain)
3. Hypotension occurring rapidly after exposure to known allergen for that patient: A) Adults: >30% decrease from that person's SBP baseline or SBP < 90 mm Hg B) Infants and children: >30% decrease in SBP or low SBP by age*

*Low SBP definition by age:
- 1 month to 1 year: <70 mm Hg
- 1-10 years: less than (70 mm Hg + [2 × age])
- 11-17 years: <90 mm Hg

Between 30% and 50% of patients with anaphylaxis develop shock.[73,74] Distributive shock from anaphylaxis is due to IgE- and non-IgE mediated release of vasoactive mediators (eg, histamine) from basophils and mast cells resulting in hypotension.[72] Vasodilation, bronchoconstriction, and cardiac depression seen in anaphylactic shock are all counteracted by the administration of epinephrine.[75] Therefore, epinephrine is the vasopressor of choice in anaphylactic shock. Intramuscular (IM) epinephrine [0.3-0.5 mg, 1:1000 (1 mg/mL)] should be given immediately into the middle anterolateral thigh musculature while intravenous access is being obtained.[72] An IV infusion of epinephrine should be started at 1 to 10 μg/min and titrated up by half of the starting dose every 2 to 3 minutes to achieve a MAP > 65 mm Hg.[76]

Patients on β-blockers may have an inadequate response to epinephrine infusions due to the blunted cardiovascular effect resulting from β-blockade. Glucagon in this scenario might prove useful because it increases inotropy and chronotropy without activating the β-receptors.[76,77] Indeed, glucagon should be given to any patient who is not responding to epinephrine regardless if they are taking a β-blocker or not.[78] For adults, glucagon 1 to 5 mg (pediatrics: 20-30 μg/kg) IV should be given over 5 minutes, followed by an infusion of 5 to 15 μg/min.[76] A second vasopressor (eg, norepinephrine and vasopressin) may be added as a second-line agent if epinephrine is inadequate.[76]

Cardiogenic Shock

Cardiogenic shock is due to cardiac dysfunction that leads to inadequate tissue perfusion. Acute myocardial infarction is the most common cause of cardiogenic shock.[5] Patients are also at risk of developing cardiogenic shock after an out-of-hospital cardiac arrest (OHCA). It is not necessarily the resuscitation that results in cardiac dysfunction (although damage to the heart from resuscitation may contribute) but more likely the coronary malperfusion resulting from the subsequent cardiac arrest. A cardiac ischemic event may result in an OHCA and subsequent cardiogenic shock. Signs of hypoperfusion seen in shock include tachycardia, altered mental status, elevated lactate, and oliguria (<400 mL/day). A low mixed venous oxygen saturation (SvO_2), a high central venous pressure, a reduced cardiac index (≤ 2.2 L/min/m^2), and typical echocardiographic features (eg, reduced ejection fraction and enlarged ventricles) are features that help differentiate cardiogenic shock from other etiologies of shock.[5,9]

Though meta-analyses have shown epinephrine to increase survival to hospital admission from OHCA, most of these studies evaluated prehospital epinephrine administration in the context of cardiac arrest and associated return of spontaneous circulation (ROSC), rather than cardiogenic shock specifically.[79–81] Norepinephrine is the recommended first-line vasopressor in cardiogenic shock.[17,39] The duration and severity of hypotension following resuscitation from OHCA have been associated with worse outcomes.[82] Observational studies have shown that post-OHCA patients with shock who received norepinephrine were less prone to recurrent cardiac arrest and had lower all-cause mortality when compared to patients who received epinephrine.[83,84] Norepinephrine increases the MAP without a significant effect on heart rate.[26] In cardiogenic shock, the minimal β-adrenergic effect seen with norepinephrine is less likely to lead to arrhythmias or significant myocardial oxygen consumption.[85] Unlike norepinephrine, epinephrine efficiently increases the MAP at a higher cost in terms of cardiac energy expenditure leading to more severe side effects (eg, cardiac ischemia).[39] Moreover, norepinephrine does not elevate lactate like epinephrine, allowing lactate to be used as a surrogate marker to monitor for developing organ ischemia.[43] The hyperlactemia and hyperglycemia seen with epinephrine is thought to be due to its strong β_2-stimulation (Figure 1B). Sustained infusions of epinephrine to maintain blood pressure in patients with cardiogenic shock should be avoided,[38,86] especially in patients with acute myocardial infarction.[87] Dopamine is not recommended for cardiogenic shock because of its greater chronotropic effects, and norepinephrine has been shown to be superior in the reduction of mortality.[26,88] Phenylephrine should be avoided in most scenarios as it may decrease cardiac output, further worsening cardiogenic shock.[45]

Inotropic agents need to be considered when cardiac pump impairment is contributing to organ ischemia. Dobutamine acts primarily as a β_1 agonist resulting in increased inotropy with limited effect on blood pressure (Table 1).[85] Dobutamine is a commonly used inotrope in cardiogenic shock, especially in combination with norepinephrine in patients requiring both inotropic and vasopressor support.[39] Milrinone is another inotrope that improves cardiac contractility through the inhibition of phosphodiesterase type-3. This mechanism of action of milrinone may allow it to maintain effectiveness during β-blockade (ie, patients on β-blockers).[89] Dobutamine has a faster onset of action with a stronger inotropic effect compared with milrinone.[33,90] In a recent trial, 192 patients with cardiogenic shock were randomized to receive either dobutamine or milrinone and showed no difference in outcomes (eg, in-hospital death from any cause, stroke, or cardiovascular or renal events).[91] However, milrinone should be used with caution in patients with renal dysfunction due to the increased risk of drug accumulation leading to prolonged hypotension.[29] Due to the unpredictable effects of inotropes on blood pressure, MAP should not be used to guide the titration of inotropes. Instead, titration should be guided by achieving adequate end-organ perfusion such as urine output >0.5 mL/kg/h with normalized or decreasing lactate level.[29] Titrating an inotrope to improve SvO_2 or central venous oxygen saturation ($ScvO_2$) values may also be useful since they reflect the balance between oxygen demand and supply.[9,29]

Patients with cardiogenic shock from left ventricular dysfunction may still benefit from fluids and appropriate assessment for fluid responsiveness (eg, cardiac output changes after passive leg raise) is advised.[9] However, in elderly patients with extensive left ventricular infarction, aggressive fluid resuscitation should be avoided.[38] The SHOCK trial has shown that

urgent revascularization is ultimately the definitive therapeutic option in cardiogenic shock following an acute myocardial infarction.[92]

Hypovolemic Shock

Hypovolemic shock leads to inadequate oxygen delivery to tissues due to loss of effective circulating blood volume. Loss of circulating blood volume could be due to nonhemorrhagic (eg, gastrointestinal losses from severe vomiting or diarrhea) or hemorrhagic causes. The most common cause of hemorrhagic hypovolemic shock is traumatic injury.[3]

Volume resuscitation is crucial in patients with nonhemorrhagic hypovolemic shock. Extrapolating from the Sepsis guidelines, a crystalloid bolus solution of 30 mL/kg infused over 3 hours with additional fluid given based on surrogate markers for end-organ ischemia (eg, urine output and lactate clearance) is reasonable for patients presenting with nonhemorrhagic hypovolemic shock.[3,13] More caution is needed with fluid administration in hemorrhagic hypovolemic shock (or hemorrhagic shock) due to the risk of diluting clotting factor concentrations, and exacerbating hypothermia and acidemia.[93,94] Acidemia and hypothermia can further impair the function of clotting factors leading to greater blood loss.[95,96] Studies have shown that patients with penetrating injuries have better outcomes when they receive restrictive[97] or delayed[98] fluid resuscitation. One caveat is that these findings might only apply to patients with penetrating torso injuries.[98] Nevertheless, prehospital care for hemorrhagic shock involves giving limited fluid resuscitation (enough to maintain palpable radial pulse), minimizing further blood loss (eg, applying direct pressure or hemostatic dressings to bleeding sites), avoiding hypothermia, and rapid transport to a medical facility for definite treatment.[99] Rapid transport cannot be overemphasized as the median time to death in a cohort of 809 patients in hypovolemic shock was only 2 hours.[100] It is important to note that significant blood loss may occur with minimal effects on vital signs such as blood pressure, especially in pediatric patients (Table 3).[101]

A retrospective cohort study showed a significant survival benefit in combat patients who received prehospital blood product transfusions.[102] Such studies sparked the question if civilians would benefit from such a protocol. One of these studies includes the multicenter PAMPer trial in 2018, which showed that prehospital administration of thawed plasma was safe and resulted in lower 30-day mortality in injured civilians at risk for hemorrhagic shock compared to standard resuscitation.[103] Moreover, secondary analysis of this trial showed the greatest mortality benefit was seen in patients who received both prehospital packed red blood cells (PRBCs) and plasma. Patients who received crystalloids had the worst survival.[104] This is in contrast to the RePHILL trial, which did not show that prehospital PRBC and lyophilized plasma resuscitation were superior to 0.9% sodium chloride for adult patients with traumatic hemorrhagic shock.[105]

Table 3. Hemorrhagic Shock Classification.[93,101]

	Pulse rate (beats/minute)	Blood pressure	Capillary refill[a]	Respiratory rate (breaths/min)	Blood loss (% total blood volume)
Class I	< 100	Normal	Normal	14-20	≤ 15
Class 2	100-120	Normal	Delayed	20-30	15-30
Class 3	120-140	Decreased	Delayed	30-40	30-40
Class 4	>140	Decreased	Delayed	>35	>40

[a]Normal capillary refill time is 3 seconds or less.

Once the patient with hemorrhagic shock arrives at the hospital, early massive-transfusion-protocol activation allows the mobilization of blood products and hemostatic agents such as tranexamic acid to the patient's bedside. Tranexamic acid (administered as a loading dose of 1 g IV over 10 minutes, followed by 1 g IV infusion over 8 hours) is recommended as the hemostatic adjunct of choice in hemorrhagic shock. The PROMMTT study showed that higher plasma and platelet ratios used in resuscitation in patients with hemorrhagic shock due to trauma reduced short-term mortality.[106] These findings were later confirmed in the PROPPR randomized clinical trial, which showed that patients who received plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio resulted in improved hemostasis and fewer deaths due to exsanguination by 24 hours.[107] The CRASH-2 and MATTERs studies have shown that early administration of tranexamic acid improved survival in bleeding trauma patients.[108,109] A recent international randomized trial (The PATCH-Trauma trial) had a total of 1310 adults with major trauma assessed as being high risk for trauma-induced coagulopathy randomized to receive either tranexamic acid (administered intravenously as a bolus dose of 1 g before hospital admission, followed by a 1-g infusion over a period of 8 hours after arrival at the hospital) or placebo in advanced trauma systems.[110] Similar to the CRASH-2 trial, secondary outcomes of this trial showed that tranexamic improved survival at 24 hours and 28 days postinjury when compared to placebo. However, as for the primary outcome, administration of tranexamic acid did not result in more patients surviving with a favorable functional outcome at 6 months versus placebo. This is probably explained by the fact that tranexamic acid saved more critically ill patients with greater disability compared to placebo.

Using whole blood for hemorrhagic shock has the advantage of having all the components of blood in one bag. Using blood component therapy for massive transfusion requires multiple bags to create ratios that mimic whole blood. Moreover, the need to track such product ratios during massive transfusions adds management complexity and increases the risk of error.[111] Another randomized trial did show that administering whole blood in patients with hemorrhagic shock reduced transfusion volumes when compared to blood component therapy.[112] More recent prospective observational studies have shown that whole blood transfusions not only decrease blood product use,[113] but improve mortality[113,114] when compared to component therapy.

Traditionally, vasopressor use in hypovolemic shock is discouraged due to concerns for worsening tissue perfusion.[109,115] Two recent retrospective studies have shown that early administration of norepinephrine did not adversely affect mortality in trauma patients with hemorrhagic shock.[116,117] Moreover, hemorrhagic shock is often associated with arginine vasopressin deficiency.[118] Supplementing such patients with vasopressin might be helpful. To help answer this question, 2 randomized controlled trials showed that trauma patients with shock who received vasopressin compared to placebo required significantly less total volume of fluid resuscitation[119] and blood products,[120] but mortality was similar between study cohorts in both trials. This is in contrast to most previous retrospective cohort studies, which showed that the administration of vasopressors (including vasopressin)[121] increased mortality in trauma patients with hemorrhagic shock.[122–124] Overall, vasopressors should have a limited role in hypovolemic shock because they do not correct the underlying problem of fluid loss. If patients with life-threatening hypotension do not respond to other measures (eg, fluids, bleeding control, and blood transfusions), vasopressors may be administered with permissive hypotension (MAP goal of 50-60 mm Hg).[125] Vasopressin given first as a bolus of 4 units and then as an intravenous infusion of $\leq$ 0.04 units/min may help achieve such resuscitative goals with less fluid and/or blood product requirements.[119,120] Additional research is needed to determine if early vasopressor (especially vasopressin) administration in patients with hemorrhagic shock improves mortality.

Obstructive Shock

Obstructive shock is considerably less common than other forms of shock. In Denmark, a 12-year cohort population study of circulatory shock had only 0.9% of subjects who presented to the Emergency Department with obstructive shock.[126] However, it is important to know when obstructive shock may occur as this may impact treatment. Overall, the main goal of treatment for obstructive shock is to clear the obstruction and restore cardiac output. However, fluid therapy and vasopressors can be used to manage obstructive shock until more definitive treatment can be managed.[127]

The use of IV crystalloids for fluid resuscitation is indicated for obstructive shock if the underlying cause of the obstruction cannot be treated.[128] However, if the cause of the obstructive shock is pulmonary embolism there is the caveat that overloading with fluids may worsen the shock as giving IV fluids can cause the right ventricular distension leading to decreasing blood pressure.[129] Generally 500 to 1000 mL of normal saline can be given with caution in cases of pulmonary embolism.[130]

Vasopressors are indicated if fluid resuscitation for obstructive shock proves to be ineffective. Norepinephrine is considered the first choice for treatment with the option to add vasopressin.[129] Another consideration with vasopressor use to support the patient with pulmonary embolism or tension pneumothorax is to prevent increased pulmonary vascular resistance.[128] Vasopressin does not increase pulmonary vascular resistance like α_1 agonists (eg, norepinephrine), which makes it useful in patients with predominant right heart failure.[85,131] Another option that may be considered if vasopressin is ineffective is phenylephrine.[130]

Depending on the cause of obstructive shock, management may be significantly different. For example, patients with obstructive shock due to left ventricular outflow obstruction (eg, hypertrophic cardiomyopathy) might benefit from pure vasoconstrictors such as phenylephrine or vasopressin since increasing cardiac contractility by giving norepinephrine might further worsen symptoms of outflow obstruction.[39,132] However, the most important treatment in such patients is fluids to support preload leading to increased left ventricular size to reduce outflow obstruction by annular dilation. Unlike cardiogenic shock, inotropes are not as beneficial in managing obstructive shock as the underlying cause is due to blockage, not cardiac dysfunction. Inotropes may be used with IV fluids in the hopes of increasing cardiac output temporarily.[128] Dopamine and dobutamine are favorable inotropes in obstructive shock due to pulmonary embolism because they increase pulmonary artery pressure to a lesser extent than cardiac output.[130]

Other Newer Vasopressors and Inotropes

Levosimendan

Levosimendan (not currently available in the United States) binds to cardiac troponin C to increase myocyte sensitivity to calcium leading to improved inotropy.[39] Levosimendan also causes vasodilation by opening ATP-dependent potassium channels in the peripheral vascular smooth muscle cells.[85] This agent may be useful in reducing cardiac filling pressures in cardiogenic shock, particularly in patients on β-blockers.[133]

Angiotensin II

Angiotensin II or Giapreza is a synthetic human peptide hormone that binds to angiotensin-1 and -2 receptors inducing vasoconstriction, vasopressin release, and aldosterone synthesis.[17] Like vasopressin, angiotensin II induces vasoconstriction without significant inotropic effects. This agent might be useful in patients with refractory distributive shock and adequate cardiac output.[33,133] Angiotensin II is given initially at 20 ng/kg/min as a continuous IV infusion that may titrated up every 5 minutes to a maximum dose of 80 ng/kg/min in the first 3 hours. Thereafter, the maintenance dose of 1.25 up to 40 ng/kg/min may be used for up to 7 days.[134,135]

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