Reversal of Vasodilatory Shock: Current Perspectives on Conventional, Rescue, and Emerging Vasoactive Agents for the Treatment of Shock

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Understanding the different mechanisms of vasoconstrictors is crucial to their optimal application to clinically diverse shock states. We present a comprehensive review of conventional, rescue, and novel vasoactive agents including their pharmacology and evidence supporting their use in vasodilatory shock. The role of each drug in relation to the Surviving Sepsis Guidelines is discussed to provide a context of how each one fits into the algorithm for treating vasodilatory shock. Rescue agents can be utilized when conventional medications fail, although there are varying levels of evidence on their clinical effectiveness. In addition, novel agents for the treatment of vasodilatory shock have recently emerged such as ascorbic acid and angiotensin II. Ascorbic acid has been used with some success in vasoplegia and is currently undergoing a more rigorous evaluation of its utility. Angiotensin II (Ang-2) is the newest available vasopressor for the treatment of vasodilatory shock. In addition to its catecholamine-sparing properties, it has been shown to hold promising mortality benefits in certain subsets of critically ill patients. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

AC = adenylyl cyclase; **ACE** = angiotensin-converting enzyme; **ACE-I** = ACE inhibitors; **ADH** = antidiuretic hormone; **ADRENAL** = Adjunctive Glucocorticoid Therapy in Patients with Septic Shock; **AKI** = acute kidney injury; **Ang-1** = angiotensin I; **Ang-2** = angiotensin II; **APACHE** = Acute Physiology and Chronic Health Evaluation; **APROCCHSS** = Hydrocortisone Plus Fludrocortisone for Adults with Septic Shock; **ARB** = angiotensin receptor blocker; **ARDS** = acute respiratory distress syndrome; **AT_1** = angiotensin-type 1 receptor; **AT_2** = angiotensin-type 2 receptor; **ATHOS** = Angiotensin II for the Treatment of High-Output Shock; **ATP** = adenosine triphosphate; **cAMP** = cyclic adenosine monophosphate; **CBF** = coronary blood flow; **cGMP** = cyclic guanosine monophosphate; **CI** = confidence interval; **CM** = calmodulin; **CORTICUS** = Corticosteroid Therapy of Septic Shock; **CPB** = cardiopulmonary bypass; **D1** = dopamine-type 1 receptor; **DAG** = diacylglycerol; **EGDT** = early goal–directed therapy; **Epi** = epinephrine; **FDA** = Food and Drug Administration; **GC** = guanylyl cyclase; **GPCR** = G-protein–coupled receptors; **HPA** = hypothalamic–pituitary–adrenal; **HR** = hazard ratio; **ICU** = intensive care unit; **IP** = prostaglandin I_2 receptor; **IP_3** = inositol triphosphate; **IQR** = interquartile range; **IV** = intravenous; **JAK2** = Janus kinase 2; **L-DOPA** = levodopa; **LOS** = length of stay; **M3** = muscarinic acetylcholine receptor; **MAP** = mean arterial pressure; **MB** = methylene blue; **MLC** = myosin light chain; **MLCK** = myosin light-chain kinase; **MLCP** = myosin light-chain phosphatase; **N/A** = not applicable; **NE** = norepinephrine; **NEpi** = norepinephrine; **NOS** = nitric oxide synthase; **OR** = odds ratio; **PIP_2** = Phosphatidylinositol 4,5-bisphosphate; **PLC** = phospholipase C; **RAA** = renin–angiotensin–aldosterone; **RCT** = randomized control trial; **ROS** = reactive oxygen species; **RR** = relative risk; **RRT** = renal replacement therapy; **SOC** = standard of care; **SOFA** = Sequential Organ Failure Assessment; **SVR** = systemic vascular resistance; **V_{1a}** = vasopressin-type 1a receptor; **VANCS** = Vasopressin versus NE in Patients with Vasoplegic Shock after Cardiac Surgery; **VANISH** = The Effect of Early Vasopressin versus Norepinephrine on Kidney Failure in Patients with Septic Shock; **VASST** = Vasopressin Versus NE Infusion in Patients with Septic Shock; **VICTAS** = vitamin C, thiamine, and steroids in sepsis; **VS** = vasoplegic syndrome; **VV-ECMO** = veno-veno extracorporeal membrane oxygenation

There are several classes of shock that anesthesiologists and intensivists frequently encounter: distributive, cardiogenic, obstructive, and hypovolemic. Each class of shock has a unique etiology and thus a different treatment. An important distinction is that shock is a syndrome graded into 4 classes, while hypotension is a clinical sign of class III or IV shock.[1] Vasodilatory shock is the most common form and represents 68% of all shock in the intensive care unit (ICU).[2] Sepsis accounts for approximately 91% of vasodilatory shock cases.[2] Other forms of vasodilatory shock come in the form of burns, pancreatitis, anaphylaxis, and spinal cord injuries. In the operating room and labor and delivery suite, vasodilation is also frequently encountered after induction of general anesthesia and administration of neuraxial local anesthetics, and, thus, knowledge regarding this class of shock is highly relevant not just to intensivists, but also to anesthesiologists.

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Because of its prevalence, the treatment of vasodilatory shock has largely relied on the Surviving Sepsis Guidelines, which are updated biannually. After procurement of blood cultures, establishment of source control, administration of broad-spectrum antibiotics, and rapid administration of crystalloids, the treatment of vasodilatory shock relies on pharmacological interventions to maintain adequate mean arterial pressure (MAP) >65 mm Hg.[3]

Treating hypotension is critical in preventing adverse outcomes. Walsh et al[4] demonstrated that, in patients undergoing noncardiac surgery, hypotension for a period of only 60 s resulted in increased odds of postoperative acute kidney injury (AKI; odds ratio [OR] = 1.2; 95% confidence interval [CI], 1.06–1.31). Similarly, hypotension for 6–10 minutes resulted in an increase in postoperative myocardial injury (OR = 1.47), and persistent hypotension for >20 minutes resulted in an increase in postoperative cardiac complications by almost 2 times.[4] Thus, rapid control of hypotension is critical to decrease morbidity. Several pharmacological interventions are available to rapidly treat hypotension due to vasodilation, all of which have different mechanisms and distribution of target receptors.

Given the increasing number of vasoactive agents, an updated review of their pharmacological properties should help clinicians better implement a vasopressor strategy according to the underlying condition. We aim to provide a narrative review on vasopressor pharmacology and clinical evidence for the most commonly used vasoconstrictors in vasodilatory shock (Figure 1).

MECHANISM OF VASOCONSTRICTION AND VASODILATION

The mechanisms of action of major vasoconstrictors are mediated by G-protein–coupled receptors (GPCRs), also known as 7-transmembrane receptors on vascular smooth muscle cell membranes (Figure 2). G_q proteins activate smooth muscle contraction through the inositol triphosphate (IP_3) signal transduction pathway.[5,6] Vasopressin-type 1a (V_{1a}) and angiotensin-type 1 (AT_1) receptors are activated by vasopressin and angiotensin II (Ang-2), respectively. α-1 receptors are activated by vasoconstrictors such as norepinephrine (NE), Epinephrine (Epi), and phenylephrine. Receptor activation triggers a cascade of events, leading to intracellular release of Ca^{2+}, which activates myosin light-chain kinase (MLCK) and allows the contraction to begin (vasoconstriction).[5,6]

The mechanisms of vasodilation are summarized in Figure 3. G_s proteins are activated by Epi, adenosine, or prostacyclin, causing smooth muscle relaxation through the cyclic adenosine monophosphate (cAMP) signal transduction pathway

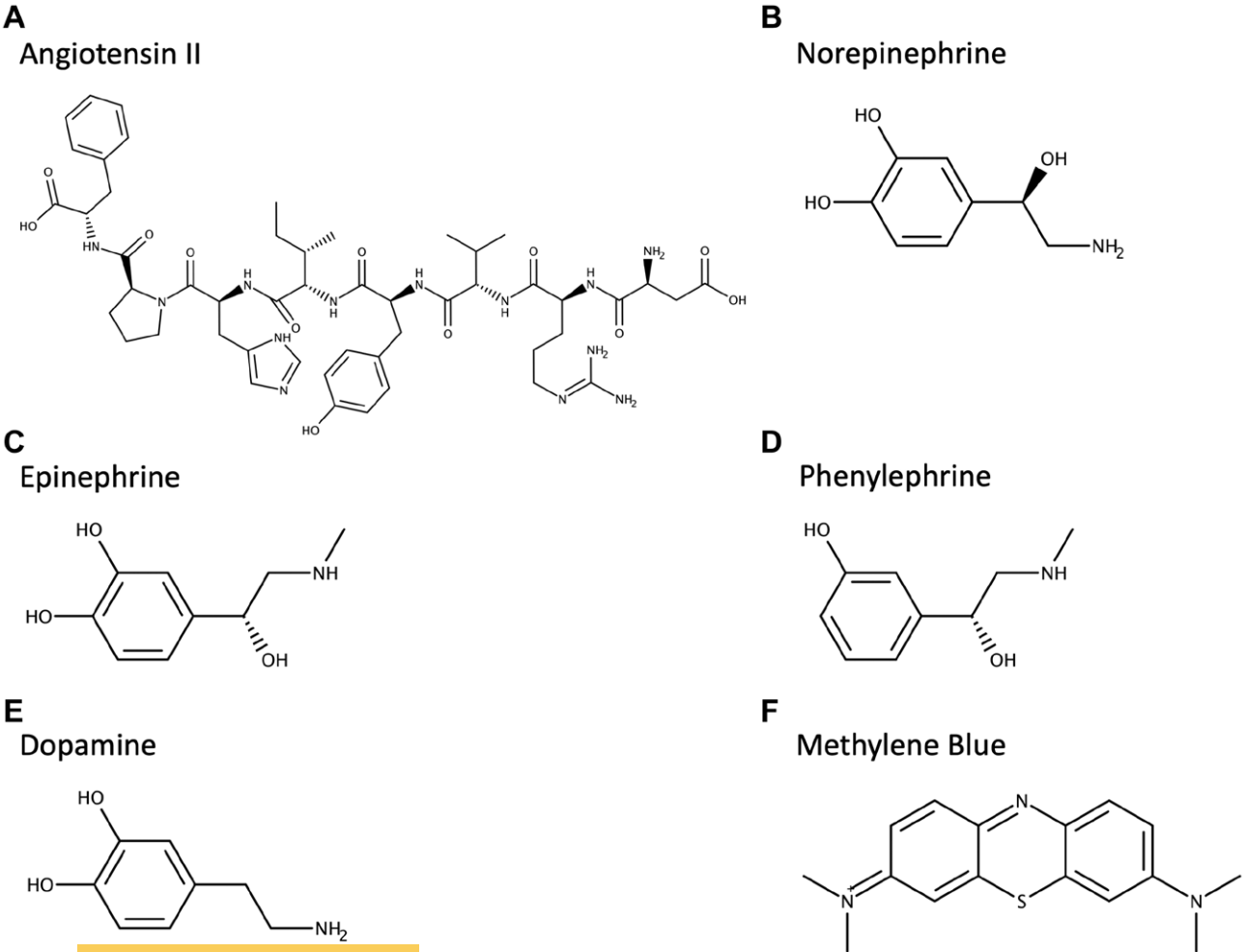

Figure 1. Chemical structure of vasoconstrictors. Structures created with MarvinSketch (ChemAxon, Ltd, Cambridge, MA).

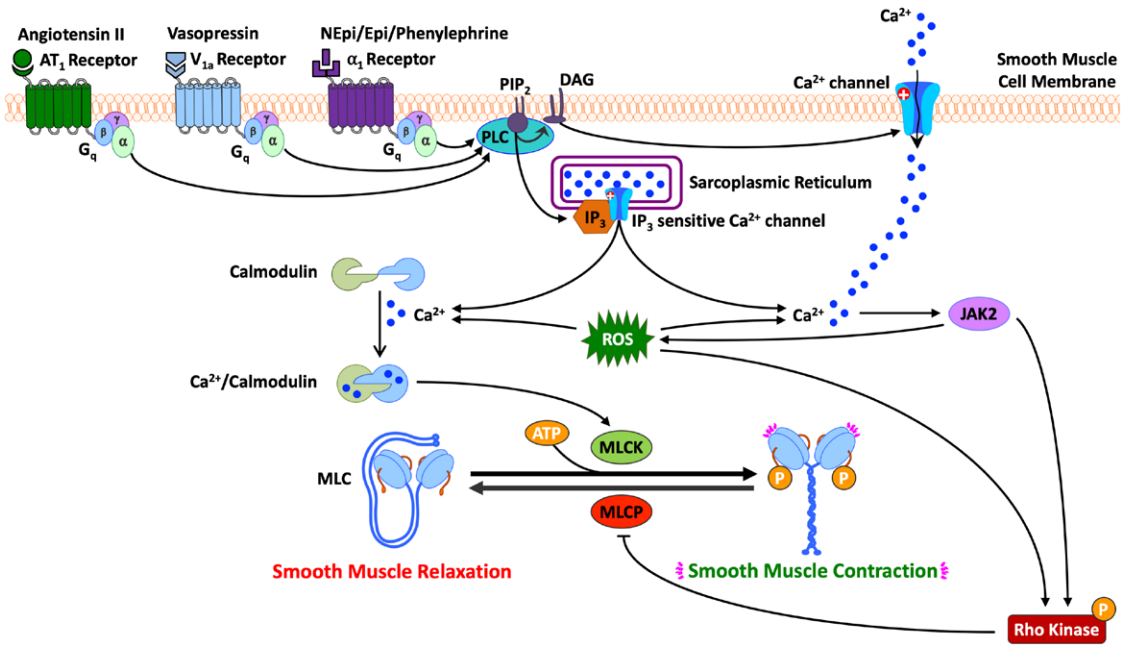

Figure 2. Vasoconstriction via the IP_3-mediated signal transduction pathway. G_q proteins activate smooth muscle contraction through the IP_3 signal transduction pathway. V_{1a} and AT_1 receptors are activated by vasopressin/terlipressin and angiotensin II, respectively, while α_1 receptors are activated by NE, Epi, and phenylephrine. Receptor activation triggers stimulation of PLC, which leads to the formation of IP_3 and DAG. DAG remains in the cell membrane and stimulates the influx of Ca^{2+} into the cell. IP_3 diffuses into the cell to act on an IP_3-sensitive Ca^{2+} channel on the surface of the endoplasmic reticulum. The release of intracellular Ca^{2+} stimulates the CM and JAK2 pathways. Ca^{2+} binds to CM and forms a Ca^{2+}-CM complex that activates MLCK. With the addition of ATP, MLCK phosphorylates MLC and causes vasoconstriction. In the JAK2 pathway, JAK2 activates Rho kinase and prevents smooth muscle relaxation from occurring. JAK2 also leads to the release of ROS, which further increases sensitivity to Ca^{2+} and leads to additional stimulation of Rho kinase. Figure created with Motifolio Toolkit (Ellicott City, MD). AT_1 indicates angiotensin-type 1 receptor; ATP, adenosine triphosphate; CM, calmodulin; DAG, diacylglycerol; Epi, epinephrine; IP_3, inositol triphosphate; JAK2, Janus kinase 2; MLCK, myosin light-chain kinase; MLC, myosin light chain; MLCP, myosin light chain phosphatase; NE, norepinephrine; PIP_2, Phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; ROS, reactive oxygen species; V_{1a}, vasopressin-type 1a receptor.

(Figure 3A). This inhibits MLCK and causes vasodilation to occur.[5,6] Counterbalancing this pathway are G_i proteins that are activated by α_2 receptors bound to NE. This inhibits cAMP and leads to further inhibition of the vasodilatory pathway.

Vascular shear forces can also lead to vasodilation, and this is accomplished in a receptor-independent pathway through the release of intracellular Ca^{2+}, which upregulates nitric oxide synthase (NOS) and NO production (Figure 3B). NO rapidly diffuses across the cell membrane into a smooth muscle cell where it inhibits MLCK, leading to vasodilation.

NOREPINEPHRINE AS AN INITIAL AGENT

Pharmacology

NE is recommended as the first-line agent for the treatment of vasodilatory shock.[3] NE is an endogenous sympathetic hormone (Figure 1), and its potent vasoconstrictor effects are mediated by agonism of α_1 receptors on vascular smooth muscle cells (Figure 2). By this same mechanism, at high doses, NE can also increase pulmonary vascular resistance, increase myocardial workload, cause cardiac ischemia, and lead to severe hypertension.[7] Systemic vasoconstriction can impair perfusion of the mesentery, resulting in organ dysfunction and metabolic acidosis at high doses.

Clinical Studies

Although no vasopressor has demonstrated a mortality benefit over another in septic shock,[8–10] NE is more likely to improve hypotension with fewer arrhythmias (relative risk [RR] = 0.43; 95% CI, 0.26–0.69; $P < .001$) when compared to dopamine.[11] The same study found that use of NE over dopamine was associated with a lower rate of in-hospital or 28-day mortality (RR = 0.91; 95% CI, 0.83–0.99; $P = .028$).[11] In a randomized control trial (RCT) comparing NE against Epi, there was also no difference in 28-day mortality, 90-day mortality, or the time to achieve target MAP.[10] However, those receiving Epi did develop tachycardia, lactic acidosis, and hyperglycemia at a significantly higher rate than patients who were randomly assigned to NE.[10]

NE has not only been used to treat septic shock, but it also has been used extensively to treat vasoplegic syndrome (VS) associated with liver transplantation and cardiopulmonary bypass (CPB). In cardiac surgery, the Vasopressin versus NE in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS) trial found that the rate of mortality and major complications occurred more frequently in the NE arm than in the vasopressin arm (32% vasopressin versus 49% NE, hazard ratio [HR] for vasopressin, 0.55; 95% CI, 0.38–0.80; $P = .0014$).[12] NE use was also associated with a higher rate of atrial fibrillation (82.1% NE versus 63.8% vasopressin, $P = .0014$), although there was no difference in the rates of mesenteric ischemia (1.3% NE versus 2.0% vasopressin, $P = .68$) or myocardial infarction (11.3% NE versus 7.4% vasopressin, $P = .25$).[12]

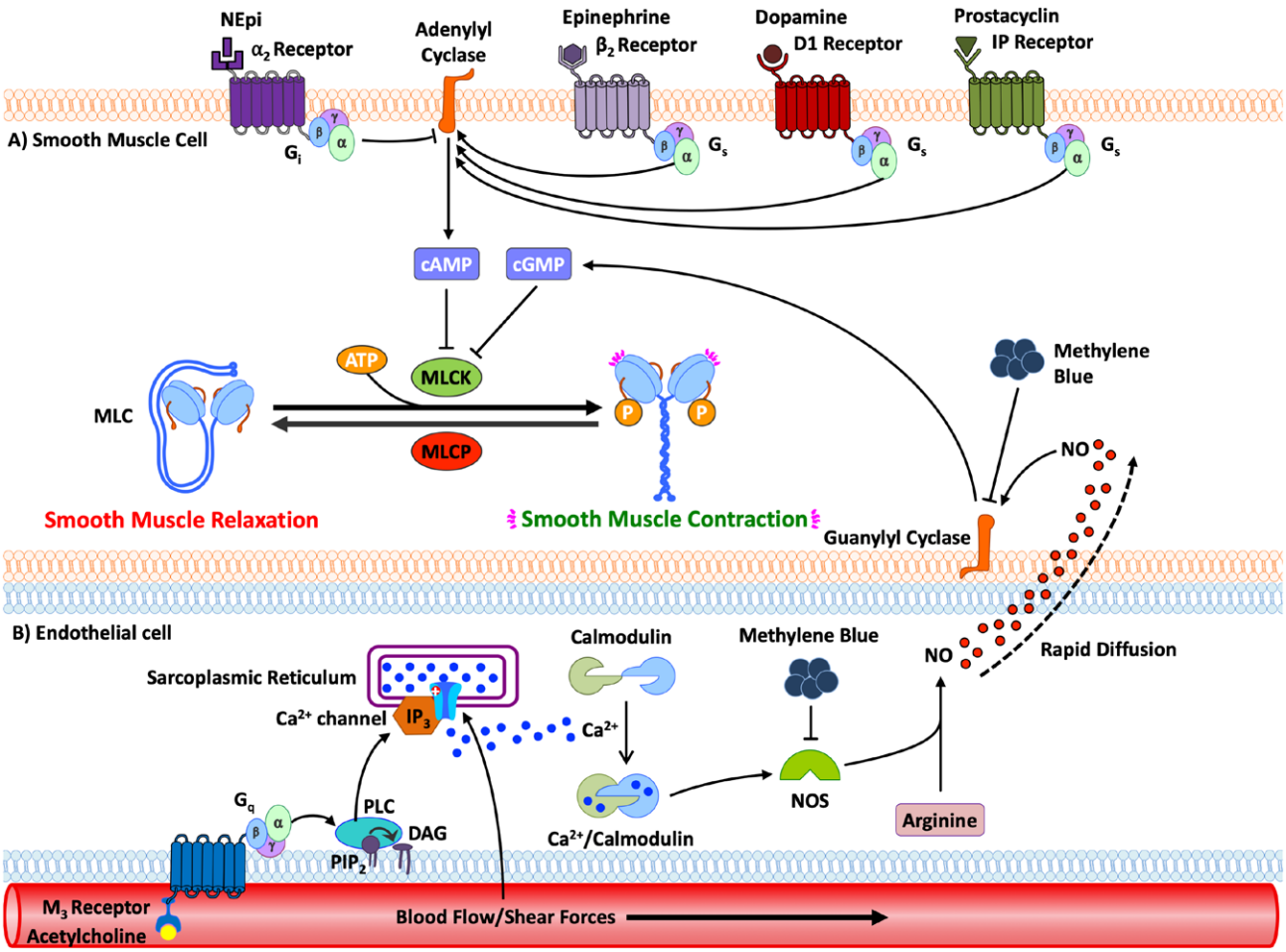

Figure 3. Vasodilation via the cAMP/cGMP signal transduction pathway. A, Smooth muscle cell. Activation of β_2, D1, and IP receptors by epinephrine, dopamine, or prostacyclin leads to stimulation of AC. Increases in AC increase the inhibitory effect of cAMP on MLCK and leads to smooth muscle relaxation. Conversely, α_2 receptors are activated by NE, which inhibits AC and decreases cAMP. This decreases the inhibition of MLCK and leads to smooth muscle contraction. B, Endothelial cell. Acetylcholine binds to M_3 receptors to trigger signaling through an IP_3 transduction pathway, which leads to the intracellular release of Ca^{2+}. Vascular shear forces also increase the release of intracellular Ca^{2+}. The resulting Ca^{2+}-CM complex activates NOS. This leads to the production of NO which rapidly diffuses across the cell membrane into a smooth muscle cell, where GC and cGMP are activated. Inhibition of MLCK causes vasodilation to occur. Methylene blue interacts at 2 points in this pathway by inhibiting NOS and GC, thus causing the prevention of vasodilation. Figure created with Motifolio Toolkit. AC indicates adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CM, calmodulin; D1, dopamine-type 1 receptor; DAG, diacylglycerol; GC, guanylyl cyclase; IP, prostaglandin I_2 receptor; IP_3, inositol triphosphate; M_3, muscarinic acetylcholine receptor; MLCK, myosin light-chain kinase; MLC, myosin light chain; MLCP, myosin light chain phosphatase; NE, norepinephrine; NEpi, norepinephrine; NOS, nitric oxide synthase; PIP_2, Phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C.

Clinical Use

The initial dose of NE ranges from 0.08 to 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and no studies have been adequately powered to detect dosing difference in the elderly population.[13] It is well established that as the dose of NE increases, receptor desensitization and tachyphylaxis occur from phosphorylation and internalization of α_1 receptors on vascular smooth muscle cells.[14] When this tachyphylaxis occurs, other vasoconstrictors with mechanisms distinct from NE must be used for maintenance of blood pressure.

VASOPRESSIN AS A SECOND-LINE AGENT

Unlike NE, which achieves vasoconstriction through agonism of α_1 receptors, vasopressin increases vascular tone through agonism of V_{1a} receptors (Figure 2). Thus, during states of rapidly escalating NE doses and refractory shock, vasopressin is able to provide a distinct mechanism of vasoconstriction.

Pharmacology

Arginine vasopressin is an endogenous peptide hormone synthesized in the hypothalamus and released from the posterior pituitary. Initially used in the management of diabetes insipidus and variceal hemorrhage, vasopressin was approved as a vasoconstrictor for vasodilatory shock almost half a century ago.[15] Vasopressin receptors belong to the GPCR superfamily, and V_{1a} receptor agonism leads to increased vascular tone, which is especially pronounced in physiologic states of hypovolemia and low autonomic tone.[16–18] Agonism of V_1 receptors causes vascular and mesenteric vasoconstriction, while agonism of V_2 receptors in the kidney leads to retention of free water and release of von Willebrand factor, factor VIII, and tissue plasminogen activator from endothelial cells.[9,19,20] Selective agonism of V_2 receptors by desmopressin causes vasodilation via cAMP-mediated endothelial NOS activation.[20]

Stimulation of V_3 receptors located in the pituitary causes increased adrenocorticotropic hormone production.[17,21] Vasopressin can have vasodilatory effects in certain vascular beds, including the pulmonary arterial system, possibly through activation of oxytocin receptors.[22]

Synthetic Vasopressin Analogues

Terlipressin and selepressin are synthetic analogues of lysine vasopressin with a chemical structure preferentially selective for the V_1 receptor.[23] In contrast to vasopressin, which has a V_1 to V_2 binding ratio of 1, terlipressin has a ratio of 2.2, indicating that its action is more selective for vascular and mesenteric vasoconstriction than for retention of free water.[23] Selepressin has been shown to have 100% sensitivity for V_1 receptor agonism and does not exhibit any V_2 activity.[24] While the prodrug terlipressin is a partial V_1 agonist, its active metabolite lysine vasopressin is a full V_1 agonist, which explains its relatively longer half-life of 4–6 hours when compared to arginine vasopressin.[25] Therefore, in contrast to vasopressin, it can be given either as an intermittent bolus of 0.25–1 mg every 6–8 hours or as a continuous infusion.[23]

Clinical Studies

Vasopressin has been studied extensively in septic shock, and, in 2008, the Vasopressin Versus NE Infusion in Patients with Septic Shock (VASST) trial found no significant mortality difference between vasopressin and NE at 28 days (35.4% vasopressin versus 30.3% NE, $P = .26$) or 90 days (43.9% vasopressin versus 49.6% NE, $P = .11$).[9] There were also no significant differences in the rate of serious adverse events (10.3% vasopressin versus 10.5% NE, $P = 1.00$). These data suggest that vasopressin can be a potentially safe and noninferior alternative to NE in the treatment of septic shock.[9]

The Effect of Early Vasopressin versus Norepinephrine on Kidney Failure in Patients with Septic Shock (VANISH) trial examined the rate of renal failure in septic shock and found no significant difference in the number of kidney failure–free days (57.0% vasopressin versus 59.2% NE; 95% CI, −13.0% to 8.5%). Although the vasopressin group was found to have improved creatinine, enhanced urine output, and decreased rate of renal replacement therapy (RRT), there was no difference in 28-day mortality (30.9% vasopressin versus 27.5% NE; absolute difference, 3.4%; 95% CI, −5.4% to 12.3%).[26]

In contrast, there has been a scarce number of RCTs investigating the use of terlipressin in septic shock. Terlipressin has been shown to be superior to vasopressin in reducing catecholamine requirements at 48 hours and was associated with less rebound hypotension when discontinued.[27] However, bolus administration of terlipressin was associated with decreased oxygen delivery, coronary vasoconstriction, excessive splanchnic vasoconstriction, and portal hypertension, which may limit its ability to be given as a bolus medication during vasodilatory shock.[28]

Thresholds for Initiation of Vasopressin

When vasopressin is administered for vasodilatory shock, it is recommended to be infused at a rate of 0.03 units·min^{-1}.[29] Doses higher than 0.03–0.04 units·min^{-1} have been associated with cardiac and mesenteric ischemia.[30] There have not been adequate studies examining modification of this dosage in the elderly population, and precise NE thresholds for the initiation of vasopressin have not yet been established.[31] NE doses higher than 0.5 μg·kg^{-1}·min^{-1} have been associated with adverse events, and 1 study demonstrated that NE ≥0.5 μg·kg^{-1}·min^{-1} was independently associated with a 5-fold increase in mortality (OR = 5.1; 95% CI, 2.0–12.9; $P = .001$).[32] In an a priori defined subgroup analysis of the VASST trial, patients randomly assigned to vasopressin when the NE dose was <15 μg·min^{-1} had improved 28- and 90-day survival compared with those randomly assigned to vasopressin when NE dose exceeded 15 μg·min^{-1}.[9]

For these reasons, to take advantage of vasopressin's catecholamine-sparing properties while avoiding the adverse effects of toxic NE doses, we recommend starting vasopressin early in the course of shock, when NE dose exceeds 0.15 μg·kg^{-1}·min^{-1}. However, there is a paucity of high-quality evidence for this threshold, which is why such wide variability exists among institutions.

EPI AS A THIRD-LINE AGENT

Frequently, NE and vasopressin may not be adequate in managing the hemodynamics of vasodilatory shock. Epi, as a potent α_1 agonist, can be used as an additional adjunct to maintain acceptable blood pressures. It is a derivative of tyrosine and an endogenous sympathomimetic catecholamine produced in the adrenal gland (Figure 1).[33] Its vasoconstrictor effect is mediated through stimulation of α_1 receptors on vascular smooth muscle cells, which are also coupled to the G_q protein (Figure 2).[5,6]

Dose-Dependent Effects of Epi

Vascular smooth muscle possesses a high density of α_1 receptors relative to β_2 receptors, but Epi has a higher affinity for β_2 receptors than α_1 receptors. Consequently, Epi effect on systemic vascular resistance (SVR) is dose dependent. At low-to-moderate doses (2–10 μg·min^{-1}), Epi predominately stimulates β_2 receptors, resulting in an increase in inotropy and a decrease in SVR (Figure 3). Conversely, at higher doses (>10 μg·min^{-1}), Epi predominately stimulates α_1 receptors (Figure 2). Because of a higher density of α_1 receptors in the systemic vasculature, SVR and MAP increase.[34,35]

Clinical Studies

The 2018 guidelines of the Surviving Sepsis Campaign recommend adding Epi as a secondary or tertiary vasopressor when escalating doses of NE and vasopressin are unable to achieve normotension.[3] Although a trial between NE and Epi found no difference in mortality or time to resolution of hypotension, there was a significantly higher incidence of tachycardia, lactate acidosis, and hyperglycemia in patients receiving Epi, which is why it is only recommended as a third-line agent.[10] However, Epi is still favored over dopamine in septic shock because of previous trials that have attributed dopamine with in-hospital mortality and 28-day mortality.[11,36]

Epi mechanism of vasoconstriction targets the same α_1 receptors as NE. When NE is already at a high dose, as

would be the case when utilizing a third-line agent, there may be limited utility in administering a drug that targets receptors that are likely already saturated, downregulated, and tachyphylactic.[14] For this reason, unless myocardial dysfunction is present, Epi may not be an optimal drug for the treatment of septic shock.

In other subsets of vasodilatory shock such as anaphylactic shock, Epi is the medication of choice because it reverses the pathophysiologic derangements of anaphylaxis. Its vasoconstrictor effect not only restores SVR and MAP but also improves airway edema from the massive vasodilation of capillary beds.[37] Through its effect on β_2 receptors in pulmonary endothelium, it is a potent bronchodilator that improves bronchospasm (Figure 2A).[37] On β_2 receptors of mast cells, Epi prevents mast cell degranulation, which suppresses the release of histamine and prostaglandins. This may also explain the efficacy of Epi in treating hypotension associated with systemic mastocytosis.[38]

PHENYLEPHRINE

Phenylephrine is not recommended for the routine management of septic shock. However, it still plays an important role in the management of other forms of vasodilatory shock, such as anesthetic-induced hypotension from induction agents, volatile anesthetics, and neuraxial medications. Unlike the previously described medications, phenylephrine can be administered peripherally, which makes it a useful medication to rapidly control hypotension when a central venous catheter is not present.

Pharmacology

Structurally, phenylephrine is closely related to Epi and is an exogenous selective α_1 agonist. It lacks the hydroxyl group in position 4 (Figure 1) and is also missing the typical catechol (benzene-1,2-diol) structure and is therefore not considered a catecholamine.[39] It is renally excreted with a half-life of 2.1–3.4 hours.

Three different subtypes of α_1 receptors exist (α_{1a}, α_{1b}, α_{1d}), and the difference in their distribution accounts for the variable effect phenylephrine has on the vasculature, heart, eyes, and bladder.[40] The smooth muscle cells of the vasculature contain α_1 and β_2 adrenergic receptors, while myocardial cells predominantly contain β_1 and β_2 adrenergic receptors. Therefore, phenylephrine increases venous return and can cause reflex bradycardia secondary to systemic vasoconstriction.

Clinical Studies

Phenylephrine has been studied under a wide variety of conditions, including during general anesthesia, but there is limited evidence supporting its use in sepsis.[29] In a small human study of 32 patients with septic shock, patients were randomly assigned to either phenylephrine or NE to maintain MAP >65 mm Hg.[41] There was no difference between the groups with respect to CO, acidemia, gastric tonometry, and creatinine. Another study of only 15 patients examined the short-term effects of an 8-hour temporary switch from NE to phenylephrine during septic shock and found that this switch was associated with a significant increase in lactate and a decrease in renal clearance and hepatosplanchnic blood flow.[42] Large-scale RCT data are lacking, and, for this reason, phenylephrine's effects in septic shock are not known.

Phenylephrine is, however, routinely used in the perioperative setting for the short-term treatment of hypotension associated with administration of anesthesia. Tachyphylaxis has been observed with prolonged infusion due to downregulation of α_1 receptors.[43] Dosing ranges from 10 to 200 μg as a bolus, while infusion dosing ranges from 0.05 to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. There is evidence that age has an effect on the dose response to phenylephrine. In a study evaluating hemodynamic changes during phenylephrine infusion in 27 healthy volunteers, those in the older group (mean, 69 years old) were found to have a higher increase in systolic blood pressure and a smaller heart rate decrease than those in the younger group (mean, 26 years old).[44] Age-related vascular stiffness is thus an important consideration in titrating phenylephrine.

DOPAMINE AS AN ALTERNATIVE IN HIGHLY SELECTED POPULATIONS

There is no role for the routine use of dopamine when NE, vasopressin, or Epi has failed to control shock. Dopamine should only be used as an agent for vasodilatory shock in highly selected populations with relative bradycardia and low risk of developing tachyarrhythmias. Through agonism of D1-type receptors, dopamine increases cardiac output through its inotropic and chronotropic effects on stroke volume and heart rate, respectively.[45]

Pharmacology

Dopamine is an endogenous catecholamine that is derived from the amino acid tyrosine (Figure 1) and synthesized in multiple sites throughout the body. Dopamine production is particularly important in the substantia nigra of midbrain, and its loss causes Parkinson disease.[46,47]

Dopamine has numerous physiologic effects on the heart, vasculature, and kidney, all of which can influence systemic blood pressure (Table 1). Five dopamine receptors (D1, D2, D3, D4, and D5) have been described, all of which are GPCRs. Dopamine receptors are classified into 2 groups: D1-type receptors (D1 and D5) and D2-type receptors (D2, D3, and D4).[45] Stimulation of D1-type receptors leads to direct arterial vasodilation by activation of adenylate cyclase (Figure 3). Conversely, stimulation of D2-type receptors inhibits adenylate cyclase and causes an increase in smooth vascular tone by decreasing cAMP.[48,49] At low doses (0.5–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine primarily acts on D1-type receptors, while at intermediate doses (2–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), it predominately acts on β_1 receptors to cause enhanced chronotropy, inotropy, and lusitropy. At high doses (>10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine's main effect is on α receptors, which causes vasoconstriction through an adenylate cyclase–mediated pathway (Figure 3).

Clinical Studies

Low-dose dopamine has been shown to increase renal blood flow by as much as 30%–40%, and there appears to be no additional increase in renal blood flow with doses above 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[50,51] Dopamine leads to enhanced natriuresis with approximately a 2-fold increase in the 1–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ range.[50] Multiple mechanisms account for enhanced natriuresis, including increased renal blood flow and D1 receptor–mediated inhibition of the Na^+H^+ antiport in proximal tubular cells and the Na^+K^+-ATPase in both

Table 1. Receptor Distribution and Pharmacologic Effects on Heart, Vasculature, and Kidneys

Action	Receptor	Drug
Heart		
Chronotropy	β_1- and D1-type receptors	Epinephrine, dopamine
Inotropy and lusitropy	β_1- and D1-type receptors	Epinephrine, dopamine
Coronary blood flow	D1-type receptors and increased CBF related to increased inotropy	Dopamine
Peripheral arteries		
Vasodilation	β_2-, AT_2-, D1-type receptors	Epi (low dose), dopamine (low dose)
Vasoconstriction	α_1-, α_2-, V_1-, AT_1-, D2-type receptors	NE, phenylephrine, vasopressin, terlipressin, Ang-2, Epi (high dose), dopamine (high dose)
Kidneys		
Increased renal blood flow, naturesis, diuresis	D1-type receptors	Dopamine
Reduced aldosterone secretion	D2-type receptors in adrenal gland	Dopamine
Increased aldosterone secretion	AT_1 receptors	Ang-2
Free water retention	V_2, AT_1 receptors	Vasopressin, terlipressin, Ang-2

Lusitropy refers to the rate of myocardial relaxation.
Abbreviations: Ang-2, angiotensin 2; AT_1, angiotensin-type 1 receptor; AT_2, angiotensin-type 2 receptor; CBF, coronary blood flow; D1, dopamine-type 1 receptor; Epi, epinephrine; NE, norepinephrine; V_1, vasopressin-type 1 receptor; V_2, vasopressin-type 2 receptor.

proximal tubular cells and the loop of Henle.[50] Despite this, there is strong evidence against the use of low-dose dopamine for renal protection in vasodilatory shock.[29]

Dopamine was compared as a first-line vasopressor against NE in over 1600 patients with septic shock.[2] There was no difference in 28-day mortality between patients in the 2 groups; however, patients receiving dopamine had a higher incidence of atrial fibrillation. Furthermore, in subgroup analysis, patients with cardiogenic shock who received dopamine had increased mortality. A contemporary meta-analysis that included 6 RCTs and 5 observational studies suggested that dopamine was associated with an increased risk of death compared to NE when used in patients with septic shock (RR of NE, 0.89; 95% CI, 0.81–0.98).[52] In septic shock, dopamine has been relegated as a tertiary drug and is not used for the routine management of vasodilatory shock. Because of its inotropic properties, dopamine may be useful in the subset of patients with impaired systolic heart function, but caution must be used due to its chronotropy and its tendency to increase mortality in cardiogenic shock.[2]

DOBUTAMINE FOR CONCOMITANT VASODILATORY SHOCK AND CARDIAC DYSFUNCTION

Cardiac dysfunction is found in over 50% of patients with septic shock and in up to 90% of patients with culture-proven septic shock.[53] Dobutamine has been used for cardiogenic shock for decades, and, not surprisingly, there has been much interest in the use of dobutamine to augment cardiac output when vasodilatory shock is complicated by underlying cardiac dysfunction. Because it can cause hypotension and increase myocardial oxygen demand, dobutamine is another agent that should not be used indiscriminately in vasodilatory shock.

Pharmacology

Dobutamine is a synthetic catecholamine that is typically used as an inotrope for heart failure.[54] It is most commonly found as a racemic mixture, and the enantiomers have different adrenergic effects. The negative enantiomer (–) predominantly acts as an α_1 receptor agonist with weak β_1 and β_2 receptor interaction. Conversely, the positive enantiomer (+) predominately acts as β_1 and β_2 receptor agonists and an α_1 receptor antagonist.[55] In the cardiovascular system, racemic dobutamine targets myocardial α_1 and β_1 receptor activation to cause increased contractility.[55,56] In other organ systems, dobutamine decreases vascular smooth muscle resistance and causes increased organ perfusion through α_1 receptor inhibition and β_2 receptor activation.

Clinical Studies

There are variations in the response to dobutamine in patients with septic shock. Some studies have shown improved oxygen delivery, mesenteric perfusion, and microcirculation perfusion due to the β_2 effects of the drug.[55] For this reason, dobutamine was frequently used in early goal–directed therapy (EGDT) protocols to maximize oxygen delivery and cardiac output.[57–59] These RCTs did not detect any significant mortality differences between the EGDT and standard-of-care groups. Another large-scale RCT of dobutamine for augmenting cardiac output in septic shock found that, although dobutamine did successfully increase cardiac output from baseline, it did not result in any significant improvement in mortality.[60] Furthermore, when comparing the use of NE plus dobutamine versus Epi alone in septic shock, there was also no difference in 28-day mortality (RR, 0.86; 95% CI, 0.65–1.14; $P = .31$), time to successful hemodynamic resuscitation (log-rank $P = .67$), and time to vasopressor withdrawal (log rank $P = .09$) between the 2 groups.[61]

One retrospective study propensity matched 526 patients receiving inotropes during septic shock and found that the use of dobutamine, Epi, or multiple inotropes was associated with an increase in 90-day mortality.[62] However, this was a retrospective study, and the conclusions must be critically evaluated as there were significant differences in the baseline dose of NE between the groups, as well as large differences in baseline Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores.

Unclear Role in Vasodilatory Shock

Dobutamine's role in septic shock remains unclear. The Surviving Sepsis Guidelines stipulate that dobutamine only be used in patients with low cardiac output and adequate

blood pressure reserve.[29] Although dobutamine can augment cardiac output and splanchnic blood flow, it also increases myocardial oxygen demand and can cause hypotension.[63,64] Both increase the risk of developing cardiac ischemia and dysrhythmias and are reasons for caution when administering this drug during vasodilatory shock.

RESCUE AGENTS

Corticosteroids

Few classes of drugs have been as controversial and highly scrutinized as corticosteroids in septic shock. Recent studies have provided evidence for their use, and they are frequently utilized as first-line rescue agents when vasodilatory shock is refractory to fluid resuscitation and conventional vasopressors.[65,66]

Cortisol is the primary corticosteroid released by the hypothalamic–pituitary–adrenal (HPA) axis. Corticotropin-releasing hormone is released by the hypothalamus and stimulates the pituitary to release corticotropin.[67] This stimulates the adrenal cortex to release cortisol, which has critical roles in glucose metabolism and modulation of cytokines.[68] In vasodilatory shock, corticosteroids play an important role in the mediation of vasoconstriction through regulation of vascular smooth muscle sensitivity to Ang-2, NE, and Epi. Conversely, they also mediate vasodilation by decreasing production of NO, which is a potent endogenous vasodilator.[68]

Clinical Studies. In 2002, Annane et al[69] studied the effect of hydrocortisone and fludrocortisone in septic shock in a large RCT of patients with adrenal insufficiency. They found that patients receiving hydrocortisone 50 mg every 6 hours and fludrocortisone 50 µg every day for 7 days had a significant reduction in 28-day mortality (53% corticosteroid group versus 63% placebo; HR = 0.67; 95% CI, 0.47–0.95; P = .02) and a significant reduction in vasopressor use at day 28 (57% corticosteroid group versus 40% placebo; HR = 1.91; 95% CI, 1.29–2.84; P = .001).[69] The Corticosteroid Therapy of Septic Shock (CORTICUS) trial, which utilized hydrocortisone only, was not able to replicate this mortality benefit (28-day mortality 34.3% hydrocortisone versus 31.5% placebo, P = .51), although it found that hydrocortisone reversed shock more rapidly than placebo.[66] The follow-up Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial also only utilized hydrocortisone and found faster resolution of shock (median duration of hydrocortisone 3 days [interquartile range {IQR}, 2–5] versus placebo 4 days [IQR, 2–9]; HR, 1.32; 95% CI, 1.23–1.41; P < .001), albeit with no significant 28- or 90-day mortality benefit.[70]

The most recent RCT, the Hydrocortisone Plus Fludrocortisone for Adults with Septic Shock (APROCCHSS) trial, utilized both hydrocortisone and fludrocortisone for 7 days and found that this intervention improved the number of organ failure–free days (14 days intervention group versus 12 days placebo, P = .003) and vasopressor-free days at day 28 (17 days intervention group versus 15 days placebo, P < .001).[65] Furthermore, the relative risk of death was improved with this intervention (RR = 0.88; 95% CI, 0.78–0.99), and there was also significantly decreased mortality at ICU discharge, hospital discharge, and day 180, although this effect was not statistically significant at day 28 (33.7% vs 38.9%, P = .06).[65] Some key differences between APROCCHSS and ADRENAL which may explain the different reported mortality benefits include quicker randomization from the onset of shock (<24 hours APROCCHSS versus 20 ± 90 hours ADRENAL), faster administration of steroids (bolus dose versus continuous infusion without loading dose, respectively), and higher degree of shock at enrollment (mean, 0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ NE versus 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ NE, respectively).[65,70]

Taken together, the data from APROCCHSS indicate that the use of steroids in vasodilatory shock is safe.[65] Although they do increase the rate of hyperglycemia, steroids do not result in an increased rate of serious adverse events, gastroduodenal bleeding, or superinfections.[65] Because of the relatively wide margin of safety, many centers routinely use 7 days of hydrocortisone and fludrocortisone as first-line rescue therapy for vasodilatory shock refractory to conventional vasopressors.

Methylene Blue

Methylene blue (MB) inhibits NO-mediated stimulation of cGMP by inhibiting NOS and guanylyl cyclase (Figure 3).[71,72] Instead of raising blood pressure by causing smooth muscle contraction, it raises blood pressure by preventing vasodilation. Because it utilizes a mechanism that is distinct from conventional vasopressors, it has generated interest as a rescue medication for refractory vasoplegia.[73]

Pharmacology. The first medical use of MB was for a histochemical stain, and it is also commonly used as an indicator dye, reducing agent for methemoglobinemia, and vasoactive agent.[71,72,74,75] The mechanism of action of MB is different from the GPCR effector vasoconstrictors. It inhibits NO-mediated stimulation of cGMP by inhibiting NOS and guanylyl cyclase (Figure 3).[71,72] Thus, MB mitigates vasodilation instead of directly stimulating smooth muscle contraction.[73]

MB is typically administered intravenously and given at a dose of 1–2 mg kg^{-1} over 15 minutes and may be followed by an infusion of 0.5 mg/kg over 6 hours.[72,76,77] Toxicity in humans can include hemolytic anemia and development of methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency.[78–80] Due to its ability to inhibit monoamine oxidase, MB carries the potential for serotonin syndrome (confusion, hyperthermia, hypertonia, clonus, etc) in patients taking serotonin reuptake inhibitors.[81–83]

Clinical Data. MB's unique mechanism of action and relative safety have likely contributed to its rapid adoption into clinical practice for the treatment of shock. In 1992, the use of MB to treat 2 patients with septic shock refractory to NE was reported.[84] MB increased MAP and SVR without affecting the HR and only slightly affected the cardiac index.[84] MB was also reported to have a positive effect on SVR for VS during liver transplantation, although follow-up studies in this population have not been able to replicate these results.[85,86]

While appropriate doubt exists about its use as a first-line vasopressor, there is moderate-quality evidence supporting the use of MB for shock refractory to high-dose vasopressors.[87–90] One RCT of 638 patients with VS following CPB found MB to significantly decrease mortality (10.7% MB

versus 3.6% placebo, $P = .02$), although this mortality benefit has not been consistently replicated.[76,91] A single-center retrospective analysis found higher rates of morbidity, renal failure, and a trend toward increased in-hospital mortality, while another study found that those receiving MB had higher rates of postoperative complications (46.6% MB versus 14.8% non-MB, $P < .0001$).[91,92] However, the MB-treated group did have a higher rate of preoperative comorbidities, so at baseline, it was more likely to experience major complications, regardless of MB exposure. This same study found that when MB was administered early in the operating room, these patients did experience a significant morbidity (35.4% early versus 52.0% late, $P = .062$) and mortality benefit (10.4% early versus 28.6% late, $P = .018$), suggesting that timing and early intervention may play a critical role in ensuring maximal benefit of MB.[92]

MB appears to be a promising adjunct to noradrenergic vasopressors and vasopressin in profound vasodilatory states. While not completely without adverse effects, it does have a relatively large margin of safety in most patients making it a reasonable choice for rescue in vasodilatory shock.

Thiamine

Thiamine is another medication that can be used to rescue patients with vasodilatory shock refractory to conventional vasopressors. Also referred to as vitamin B_1, it is a water-soluble nutrient that is an essential cofactor in the Krebs cycle.[93] Deficiency of this cofactor interrupts the oxidative energy pathway, leading to an increase in anaerobic metabolism and eventual increase in lactic acid production.[94] Due to the central role of thiamine in aerobic cellular respiration and the increasing recognition of mitochondrial dysfunction as a contributor to multiorgan dysfunction, there has been an increased interest in the use of thiamine for metabolic resuscitation and clearance of lactate.[95,96]

Clinical Data. In 1988, Cruickshank et al[97] published a retrospective analysis of 158 patients admitted to the ICU who required parenteral nutrition support. They found that surviving patients had significantly higher thiamine levels than nonsurvivors. Among patients with evidence of thiamine deficiency, mortality was significantly higher than those who were not thiamine deficient (72% mortality versus 50%, respectively, $P < .05$).[97] This was one of the first studies to demonstrate the role for thiamine supplementation in the treatment of critically ill patients.

A single-center retrospective study of patients in septic shock propensity matched 123 patients who received thiamine supplementation within 24 hours of admission and 246 patients who did not.[98] The most common dose was 500 mg of intravenous (IV) thiamine, and it was administered for a median of 3 days. Treatment with thiamine was associated with improved lactate clearance (HR = 1.3; 95% CI, 1.002–1.704) and improved 28-day mortality (HR = 0.666; 95% CI, 0.490–0.905).[98] An RCT examining thiamine supplementation in septic shock found that 200 mg of twice daily thiamine for 7 days resulted in significantly improved 24-hour lactate (median, 2.1 mmol/L thiamine group versus 3.1 placebo, $P = .03$) and 30-day mortality (13% thiamine group versus 46% placebo, $P = .047$) in the subgroup of patients with thiamine deficiency.[99] In the general population, however, there was no difference in the time to shock resolution, ICU length of stay (LOS), hospital LOS, or mortality rate.

Current findings suggest that the benefit of thiamine is unlikely to be universal. However, its wide safety margin, benefits in those with thiamine deficiency, and the high prevalence of this deficiency in septic shock make thiamine an attractive adjunct in the management of shock refractory to conventional vasopressors.[99]

EMERGING AGENTS TO TREAT VASODILATORY SHOCK

Ascorbic Acid

Ascorbic acid, also referred to as vitamin C, is an emerging therapeutic option for the treatment of septic shock. Like thiamine, ascorbic acid is an essential cofactor in biochemical pathways and is involved in 2 reactions essential for the synthesis of catecholamines.[100] Patients with critical illness have been found to have decreased plasma ascorbic acid levels by up to 70%, which can lead to impaired catecholamine synthesis.[101,102] This forms the rationale for the use of ascorbic acid supplementation in vasodilatory shock.

Pharmacology. Synthesis of NE and Epi is a stepwise process that involves the conversion of L-tyrosine to levodopa (L-DOPA) by tyrosine hydroxylase.[100] O_2 and tetrahydrobiopterin are required for this reaction to occur, and ascorbic acid is an essential cofactor in the generation of these 2 molecules. After L-DOPA is generated, it is converted to dopamine, which is then converted to NE by dopamine β-hydroxylase. This reaction again requires O_2 and ascorbic acid for the synthesis of NE and Epi to occur.[100] In addition to being an essential cofactor, ascorbic acid also scavenges free radicals, downregulates proinflammatory mediators, and enhances vasopressor receptor sensitivity.[103–105]

Clinical Studies. A phase I RCT of patients with severe sepsis found that high-dose ascorbic acid was safe and significantly increased the rate of SOFA score improvement (slope of regression −0.044 ascorbic acid versus 0.003 placebo, $P < .01$), while also significantly reducing the plasma concentrations of the proinflammatory markers C-reactive protein and procalcitonin.[102] Another small RCT of septic shock patients found that ascorbic acid decreased the mean dose (7.4 vs 13.8 μg/min, $P = .004$) and duration of NE (49.6 vs 71.6 hours, $P = .007$), while also improving 28-day mortality (14.3% vs 62.3%, $P = .009$) when compared to placebo.[106] The largest study to date was a retrospective before–after, propensity-matched study of 94 consecutive patients in septic shock.[100] Marik et al[100] built on the previous reported benefits of corticosteroids and thiamine and intervened by creating a protocol that consisted of a combination of ascorbic acid (1.5 g every 6 hours for 4 days), hydrocortisone (50 mg every 6 hours for 7 days), and thiamine (200 mg every 12 hours for 4 days). They reported a significant improvement in 72-hour SOFA score (−4.8 treatment versus −0.9 control, $P < .001$), duration of vasopressor use (18.3 vs 54.9 hours, $P < .001$), procalcitonin clearance (86.4% vs 33.9%, $P < .001$), need for RRT (10% vs 33%, $P = .02$), and hospital mortality (8.5% vs 40.4%, $P < .001$).[100]

The retrospective, single-center nature of the study, the use of nonconcurrent controls in the before–after design, and the potential selection bias in the intervention arm all limit the generalizability of the results.[100] However, Marik et al's[100] study set the stage for a large North American RCT, the vitamin C, thiamine, and steroids in sepsis (VICTAS) Trial, which is currently ongoing.[107] This multicenter, double-blind, placebo-controlled RCT will provide the evidence that we need to critically evaluate ascorbic acid's role in the treatment of vasodilatory shock.

Angiotensin II

Ang-2 is considered to be a novel treatment for vasodilatory shock, but it has been described as early as the 1930s, and its use has been reported in patients with circulatory shock, distributive shock, and angiotensin-converting enzyme inhibitor (ACE-I) overdose.[108–110] Its Food and Drug Administration (FDA) approval in 2018 has reinvigorated interest in the drug, particularly because it utilizes a pathway distinct from traditional vasoconstrictive agents.[111]

Pharmacology. Ang-2 is a naturally occurring hormone in the renin–angiotensin–aldosterone (RAA) system. Angiotensinogen is produced by the liver and is converted to angiotensin I (Ang-1) after stimulation by renin during conditions of low renal perfusion pressure (Figure 4). Ang-2 is then derived from the hydrolysis of Ang-1 via ACE in the lung and renal endothelium. Ang-2 has a short half-life of only 30 s and directly interacts with other catecholamines and vasopressin.[112–114] It exerts its action on AT_1 and angiotensin-type 2 (AT_2) receptors.[115] The majority of Ang-2 action is through activation of AT_1 receptors on smooth muscle cell membrane (Figure 1). It causes smooth muscle contraction and stimulates release of antidiuretic hormone (ADH) and aldosterone in the adrenal cortex, which increases reabsorption of water.[108]

Clinical Data. In 1961, Del Greco and Johnson[116] examined Ang-2 use in 21 patients with shock. This case series reported a return to normotension in 15 of 21 patients without any adverse side effects from its administration. The Angiotensin II for the Treatment of High-Output Shock (ATHOS) trial was the first modern-day clinical trial of Ang-2 and found that it was efficacious as a vasopressor and a catecholamine-sparing agent (Table 2).[112]

In the phase III follow-up RCT, ATHOS-3, 344 patients in vasodilatory shock were randomly assigned to either standard vasopressors (eg, NE, vasopressin, Epi, phenylephrine) plus placebo or standard vasopressors plus Ang-2.[117] Those in the Ang-2 group achieved the target MAP at a significantly higher rate than those in the control group (69.9% Ang-2 versus 23.4% control; OR = 7.95; 95% CI, 4.76–13.3; $P < .001$; Table 2). Furthermore, those patients randomly assigned to Ang-2 had a greater change in background NE-equivalent dose than those receiving placebo plus standard vasopressors (−0.03 ng kg^{-1} min^{-1} Ang-2 versus 0.03 control, $P < .001$). The study was not powered to detect a mortality benefit, and no association was found in improving all-cause mortality at 28 days (46% mortality Ang-2 versus 54% control; HR = 0.78; 95% CI, 0.57–1.07; $P = .12$).

There have been several prespecified post hoc analyses of the ATHOS-3 data.[118–120] The first found that critically ill patients with APACHE II scores over 30 who received Ang-2 had significantly improved 28-day mortality compared to patients receiving standard vasopressors alone (51.8% Ang-2 versus 70.8% control; HR = 0.62; 95% CI, 0.39–0.98; $P = .037$; Table 2).[119] The second found that the subset of patients with AKI requiring RRT not only had improved survival with Ang-2 (53% Ang-2 versus 30% control; HR = 0.52; 95% CI, 0.30–0.87; $P = .012$) but also had improved rates of liberation from RRT by day 7 (38% Ang-2 versus 15% control; adjusted HR = 2.90; 95% CI, 1.29–6.52; $P = .007$).[120] These findings are clinically important because, with the exception of NE over

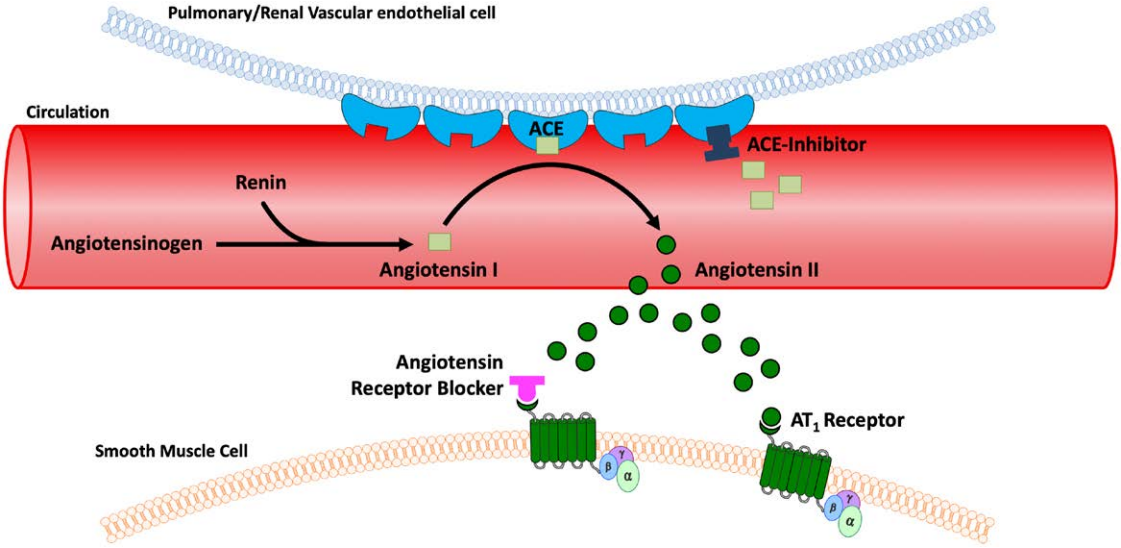

Figure 4. Renin–angiotensin–aldosterone system. Renin stimulates the conversion of angiotensinogen to Ang-1 during conditions of low renal perfusion. Via ACE, Ang-1 is converted to Ang-2 primarily in the pulmonary endothelium. Ang-2 then acts on AT_1 receptors on smooth muscle cells to cause vasoconstriction. ACE-I inhibits the action of ACE, while ARBs inhibit the binding of Ang-2 to AT_1. ACE indicates angiotensin-converting enzyme; ACE-I, ACE inhibitors; Ang-1, angiotensin I; Ang-2, angiotensin II; ARB, angiotensin receptor blocker; AT_1, angiotensin-type 1 receptor.

Table 2. Summary of Key Studies Investigating Angiotensin II

Reference	Design	Population	Dose Range	Outcome	*P* Value
Del Greco et al[116]	Case Series (n = 21)	Distributive, cardiogenic shock	0.23–100 μg min^{-1}	Return to normotension in 15/21 patients	N/A
Chawla et al[112]	RCT (n = 20)	Distributive shock	15–20 ng kg^{-1} min^{-1}	No difference in mean hour 1 NE dose. (7.4 ± 12.4 μg min^{-1} Ang-2 versus 27.6 ± 29.3 μg min^{-1} control)	.06
				No difference in mean hour 2 NE dose (7.3 ± 11.9 μg min^{-1} Ang-2 versus 28.6 ± 30.2 μg min^{-1} control)	.06
Khanna et al[117]	RCT (n = 344)	Distributive shock	20–40 ng kg^{-1} min^{-1}	Achieved target MAP by hour 1 (69.9% Ang-2 versus 23.4% SOC; OR = 7.95; 95% CI, 4.76–13.3)	<.001
				Decreased background NE-equivalent dose (−0.03 Ang-2 versus 0.03 SOC)	<.001
				No difference in 28-day all-cause mortality (46% versus 54%; HR = 0.78; 95% CI, 0.57–1.07)	.12
Wunderink et al[118]	Post hoc analysis (n = 141)	Distributive shock	Not reported	Increased 28-day mortality with Ang-2 depletion (HR = 1.78; 95% CI, 1.25–2.53)	.002
				Increased 28-day mortality with Ang-2 depletion and treatment with SOC vasopressors (HR = 1.77; 95% CI, 1.10–2.85)	.019
				Attenuation in mortality with Ang-2 depletion and treatment with Ang-2 (HR = 0.64; 95% CI, 0.41–1.00)	.047
Szerlip et al[119]	Post hoc analysis (n = 225)	Distributive shock, subset with APACHE-II score >30	Not reported	Decreased 28-day mortality in subset with APACHE-II score >30 (51.8% Ang-2 versus 70.8% SOC; HR = 0.62; 95% CI, 0.39–0.98)	.037
Tumlin et al[120]	Post hoc analysis (n = 105)	Distributive shock, subset with AKI requiring RRT	15–20 ng kg^{-1} min^{-1}	Improved 28-day survival in subset with AKI requiring RRT (53% Ang-2 versus 30% SOC; HR = 0.52; 95% CI, 0.30–0.87)	.012
				Increased rate of liberation from RRT by day 7 (38% Ang-2 versus 15% SOC; adjusted HR = 2.90; 95% CI, 1.29–6.52)	.007

Abbreviations: AKI, acute kidney injury; Ang-2, angiotensin II; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; HR, hazard ratio; MAP, mean arterial pressure; N/A, not applicable; NE, norepinephrine; OR, odds ratio; RCT, randomized control trial; RRT, renal replacement therapy; SOC, standard of care.

dopamine, no single vasopressor has been found to have mortality benefit over another in septic shock.[9,11,26,121]

Finally, patients who were Ang-2 deficient, as measured by higher Ang-1:Ang-2 ratios, were found to have higher mortality than those who were not (Table 2).[118] This higher ratio of Ang-1:Ang-2 suggests an ACE deficiency as the cause of Ang-2 depletion. Those with high ratios and randomly assigned to standard vasopressors also had higher mortality than those randomly assigned to the Ang-2 arm. Administration of Ang-2 appeared to modulate this outcome, because there was a significant treatment effect of Ang-2 on mortality among Ang-2–deficient patients. These data indicate that Ang-1:Ang-2 ratios are not only predictive of mortality, but also that Ang-2 supplementation is capable of decreasing mortality during states of Ang-2 deficiency. ACE, the enzyme that hydrolyzes Ang-1 to Ang-2, is predominantly found in pulmonary vascular endothelial cells (Figure 4).[118] Patients with pulmonary pathology, such as those with influenza, multilobar pneumonia, acute respiratory distress syndrome (ARDS), or those with mechanical bypass of ACE in the pulmonary circulation, as in the case with veno-veno extracorporeal membrane oxygenation (VV-ECMO), may suffer the most from ACE dysfunction and Ang-2 depletion. Whether they may also benefit from Ang-2 administration remains to be seen.

Use of Ang-2 as an early third-line vasopressor, as was done in the ATHOS-3 trial, is intuitive, because α_1 receptors are desensitized and internalized with repetitive exposure to NE, Epi, and phenylephrine.[14] This tachyphylaxis is well established at the toxic doses of vasopressors that are commonly used in distributive shock, and a multimodal form of therapy targeting several different receptors may be the most beneficial method to maintain MAP in vasodilatory shock.

CONCLUSIONS

Anesthesiologists and intensivists have a broad array of vasoconstrictors to utilize when treating patients in vasodilatory shock. These medications target distinct receptors in the RAA system (Ang-2), sympathetic nervous system (NE, Epi, dopamine, dobutamine, and phenylephrine), and vasopressin system (vasopressin, terlipressin, and selepressin). MB targets the NOS and guanylate cyclase pathway, while thiamine and ascorbic acid target potential deficiencies in critically important biochemical pathways.

The vasoconstrictive response can be affected by the underlying vasodilatory stimuli, and combination therapy can be important. Currently, we do not have overwhelming clinical data on either the optimal combination of drugs for vasodilatory shock or the optimal timing for initiation of secondary agents. Ang-2 and ascorbic acid represent the newest additions to our armamentarium for treating vasodilatory shock. They are promising new additions to the lineup of therapies that we have in our toolkit, and more studies are necessary to elucidate exactly which populations may benefit the most from these drugs. While promising, additional high-quality studies are needed to properly evaluate their role in the treatment algorithm for vasodilatory shock.

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