Vasopressin in Vasodilatory Shock

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INTRODUCTION

Vasodilatory shock is characterized by a failure of peripheral vascular vasoconstriction in the face of low systemic arterial pressure, resulting in inadequate tissue perfusion.1 Several causes have been identified that result in vasodilatory shock, the most common of these being sepsis, which is also the leading cause of mortality in hospitalized critically ill patients.2 Vasoplegia, a subset of vasodilatory shock, is a phenomenon that encompasses not only a failure of vasoconstriction but also a diminished responsiveness to vasopressor therapy. Furthermore, it is well accepted that vasodilatory shock and vasoplegia are the common consequence of all prolonged states of severe shock of any etiology.1

Treatment of vasodilatory shock includes infusion of vasopressors. The most commonly used vasopressors are catecholamines, including norepinephrine (NE), epinephrine, and phenylephrine. It is increasingly clear, however, that the addition of noncatecholamine vasopressors, such as vasopressin (VP) and angiotensin II, may be helpful. These agents engage alternate signaling pathways resulting in a different spectrum of actions that may be usefully used in certain clinical situations. This article reviews the role of VP in the management of vasodilatory shock.

KEYWORDS

• Vasopressin • Antidiuretic hormone • Vasodilatory shock • Vasoplegia • Sepsis

KEY POINTS

• Vasodilatory shock is the final common pathway for all forms of severe shock.
• Vasopressin deficiency seems to play a significant role in vasodilatory shock.
• In contrast to catecholamines, vasopressin acts through alternate signaling pathways and uniquely modulates the pathophysiology of vasodilatory shock.
MECHANISMS OF VASODILATORY SHOCK AND VASOPLEGIA

The pathophysiology underlying vasodilatory shock and vasoplegia is incompletely elucidated. Several mechanisms have been shown to be contributory, involving an interplay between nitric oxide (NO)-mediated pathways; endothelium-derived hyperpolarizing factor (EDHF) activity; ATP-sensitive potassium (K<sub>ATP</sub>) channel activation; down-regulation of vasopressor receptors, leading to vasopressor hyposensitivity; and deficiency of the neuropeptide hormone VP.1,3

Nitric Oxide–mediated Vasodilatation

Over-production of NO is a key component of the vasodilation and vasopressor refractoriness of vasodilatory shock.4 The increase in NO synthesis results from up-regulation of the inducible form of NO synthase (iNOS), a calcium (Ca<sup>2+</sup>)-independent and calmodulin-independent isofrom of NO synthase (NOS). Inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interferon-γ, and bacterial lipopolysaccharide, are inducers of iNOS in vascular smooth muscle,5,6 importantly via the inflammatory transcription factor nuclear factor (NF)-κB.5,7 Endothelial NOS (eNOS) seems to play a facilitatory role in iNOS induction.5

NO produced as a result of increased iNOS activity leads to activation of soluble guanylyl cyclase (sGC), increased intracellular cyclic guanosine monophosphate (cGMP), and vascular smooth muscle relaxation.8,9 Increased cGMP and the subsequent fall in intracellular calcium (Ca<sup>2+</sup>) cause vasodilation through a combination of K<sub>ATP</sub> channel and large-conductance Ca<sup>2+</sup>-dependent potassium (K<sub>Ca</sub>) channel activation. There is concurrent increased activity of small-conductance Ca<sup>2+</sup>-dependent K<sub>Ca</sub> channels, also causing hyperpolarization of smooth muscle cells and vasodilation.10 Typically, these channels open in response to raised Ca<sup>2+</sup>, and mitigate the effects of vasoconstrictors that raise Ca<sup>2+</sup>, such as α-adrenergic stimulation of vascular smooth muscle.1,11 Persistent activation of iNOS and sGC in this way contributes to profound vasodilation and the resultant state of shock.12

Endothelium-derived Hyperpolarizing Factors

Several EDHFs have thus far been demonstrated, including epoxyeicosatrienoic acids, K<sup>+</sup> ions, gap junctions, and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>).13 Activation of these factors results in increased K<sup>+</sup> conductance through small-conductance K<sup>+</sup> channels, hyperpolarization, and vasodilation as with the NO-mediated pathway, described previously. EDHFs are believed to provide an alternative vasodilatory pathway in the setting of impaired NO-mediated responses.14 Several studies support the finding that EDHFs have an important role in management of microvascular perfusion and have demonstrated a greater effect of EDHFs in smaller resistance vessels than in large arteries.5,15 eNOS-derived reactive oxygen species, such as H<sub>2</sub>O<sub>2</sub>, are a source of EDHFs; however, there are several contributory enzymatic pathways for the production of superoxide anions and H<sub>2</sub>O<sub>2</sub> in human and animal models.10,16

Adenosine Triphosphate-Sensitive Potassium Channel Activation and Vascular Smooth Muscle Hyperpolarization

Activation of K<sub>ATP</sub> channels causes an efflux of intracellular K<sup>+</sup> ions, leading to hyperpolarization of the cell membrane, inactivation of voltage-gated Ca<sup>2+</sup> channels, vasodilation, and improved regional blood flow.17,18 K<sub>ATP</sub> channels are activated by increases in intracellular lactate and hydrogen ions and decreases in cellular ATP, thereby coupling their function to cellular respiration. Excessive activation of K<sub>ATP</sub> channels in vasodilatory shock is believed in part responsible for vascular smooth
muscle vasopressor hyporeactivity. Additional activators of $K_{\text{ATP}}$ channels include atrial natriuretic peptide, calcitonin gene-related peptide, and adenosine, which have all been identified in significantly elevated plasma levels in septic shock.\textsuperscript{19–21} Despite promising animal studies,\textsuperscript{22–24} the therapeutic use of $K_{\text{ATP}}$ antagonists, such as the sulfonylurea glibenclamide, in humans with septic vasodilatory shock thus far has proved unsuccessful, improving neither arterial blood pressure nor vasopressor sensitivity.\textsuperscript{2,25–27}

Vasoconstrictor Receptor Down-regulation and Hyposensitivity

With prolongation of the vasodilatory shocked state, vascular smooth muscle exhibits progressively impaired responses to circulating vasoconstrictors.\textsuperscript{28} This is believed due to decreased vasoconstrictor receptor activity either through receptor down-regulation, uncoupling from intracellular second messengers, or both, in response to circulating inflammatory mediators.\textsuperscript{28,29} As highlighted in a recent review by Burgdorff and colleagues,\textsuperscript{3} down-regulation or decreased activity of several vasoconstrictor receptors has been demonstrated in vivo and in vitro in several human and animal models of vasodilatory shock due to sepsis. Decreased expression and/or function of angiotensin receptor type 1 and angiotensin receptor type 2, $\alpha_1$-adrenergic receptors, and the V1 VP receptor subtype (V1R) have all been demonstrated in response to the activity of several cytokines, including IL-1$\beta$, TNF-$\alpha$ and INF-$\gamma$.\textsuperscript{3,30–36} Despite good evidence supporting V1R down-regulation due to cytokine activity, there seems to be an exaggerated pressor effect of exogenously administered VP.\textsuperscript{1,37,38} Furthermore, this occurs in the setting of relative deficiency of circulating endogenous VP in the established stages of vasodilatory shock, a major contributor to the pathologic vasodilation of this state.\textsuperscript{39,40} The exact mechanism underlying this phenomenon is not clear; however, these findings have led to a focus on VP as a key element not only in the pathophysiology of vasodilatory shock but also potentially in its management.\textsuperscript{40,41}

VASOPRESSIN

VP is a cyclic nonapeptide hormone also known as antidiuretic hormone. It plays an important role in the homeostatic mechanisms of the cardiovascular system, exhibiting multiple hormonal and osmoregulatory effects beyond its pressor activity.\textsuperscript{40} Its significance in vasodilatory shock has been extensively investigated, and it has been identified as a primary protagonist in the acute vasoconstrictor response to both hemorrhagic and vasodilatory shock.\textsuperscript{37–39,42–44} Equally important is the fall in VP levels identified in late-stage shock, which has raised the possibility of VP deficiency as a key factor in persistent vasodilatory shock as well as a possible target for therapeutic intervention.\textsuperscript{37–39,44} VP is synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. It subsequently migrates as a prohormone bound to the axonal carrier protein, neurohypophysin, to the pars nervosa of the posterior pituitary via the supraoptic-hypophyseal tract. VP-containing storage granules in the posterior pituitary release VP from hypothalamic magnocellular neuron axonal terminals in response to depolarization.\textsuperscript{40,45} Only 10% to 20% of the stored hormone can be rapidly released from the posterior pituitary, with the rate of release falling significantly thereafter, despite appropriate stimulation. This offers an explanation for the biphasic response observed in septic shock, with a late drop trough in VP levels.\textsuperscript{46} VP activity classically occurs through binding to the $G_{\alpha/11}$ family of G-protein-coupled transmembrane receptors; however, $G_\text{s}$ subtype binding has also been
described. Three receptor subtypes are responsible for the physiologic effects of VP: V1 (previously V1a), V2, and V3 (previously V1b). These are widely distributed through numerous tissues and organ systems (Fig. 1), resulting in widespread and varied effects when activated.

**V1 Receptor**

The V1R is responsible for most of the hemodynamic effects of VP. The gene encoding for V1R is found on the 12q14-15 region of chromosome 12. This subtype is predominantly found in smooth muscle cells of the vasculature and in cardiac myocytes, although its distribution extends beyond this to multiple tissues and organ systems. Stimulation of vascular V1R causes receptor-coupled activation of intracellular phospholipase C (PLC) via Gq/11 binding, which in turn causes an increase in Ca^{2+} via the phosphatidylinositol pathway, resulting in vasoconstriction. Gs binding couples to the

![Fig. 1](image-url)  
*Fig. 1. Distribution of V1, V2, and V3 vasopressin receptor subtypes throughout the body.*
cyclic AMP (cAMP) intracellular signaling cascade, activating multiple intracellular pathways.\textsuperscript{48} In addition to activation of multiple second messenger signaling pathways, VP exhibits direct ion channel effects (Fig. 2), with dose-dependent blockade of K\textsuperscript{+}\textsubscript{ATP} channels responsible for systemic vasodilation.\textsuperscript{49} As described previously, these channels play a significant role in the regulation of arterial vascular tone. The inhibitory action of VP at this site may be an important aspect of the restoration of vascular tone—and therefore systemic blood pressure—in patients with vasodilatory shock, particularly due to endotoxemic sepsis.\textsuperscript{22}

Renal expression of V1R can be seen in medullary interstitial cells and in the vasa recta. Medullary vascular V1R activation selectively decreases inner medullary blood flow without altering cortical blood flow, an effect that plays an important role in the kidney’s ability to maximally concentrate urine in states of water deprivation.\textsuperscript{50} The efferent glomerular artery and epithelial cells of the collecting duct also demonstrate V1R expression. Efferent arteriolar contraction in response to V1R stimulation produces an increase in glomerular filtration rate due to the lack of concurrent afferent arteriolar constriction, in contrast to catecholaminergic vasopressors.\textsuperscript{48} This action likely accounts for the paradoxic increase in urine output seen with VP administration in vasodilatory shock, despite its typically antidiuretic effects.\textsuperscript{51}

Platelet expression of V1R and the role of VP in platelet aggregation and hemostasis is an area of ongoing investigation. Stimulation of platelet V1R is known to result in increased Ca\textsuperscript{2+}, thereby facilitating thrombosis, although this may be an undesired

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**Fig. 2.** Cellular actions of vasopressin. (A) Direct inhibition of K\textsubscript{ATP} channels. (B) Indirect actions through vasopressin receptor-binding and activation of G-protein–coupled second messenger signaling pathways. AC, adenylyl cyclase; AQP-2, aquaporin-2 channel; CDKs, Ca\textsuperscript{2+}-dependent kinases; CML, calmodulin; DAG, diacylglycerol; ER, endoplasmic reticulum; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IP\textsubscript{3}, inositol 1,4,5-triphosphate; PIP\textsubscript{2}, phosphatidylinositol 4.5-biphosphate; PKA, protein kinase A; PKC, protein kinase C; VR, VP receptor; α, G-protein alpha subunit; β, G-protein beta subunit; γ, G-protein gamma subunit.
effect in the setting of vasodilatory shock with microvascular dysfunction and the potential for microthrombus formation and worsened end organ perfusion.\textsuperscript{52,53} There is, however, great variability in the aggregation response to VP of normal human platelets, and platelet V1R polymorphism has been proposed as a possible explanation for this observation.\textsuperscript{48} It is, therefore, currently unknown whether V1R platelet activity is of any significance in the vasodilatory shock state. V1R has also been identified in the myometrium, bladder, spleen, testes, and on adipocytes and hepatocytes.\textsuperscript{48} The exact action of V1R in all these regions remains to be characterized.

**V2 Receptor**

The V2 receptor subtype (V2R) is responsible for the antidiuretic and osmoregulatory effects of VP. Originally believed found exclusively in the collecting ducts and endothelial cells of the kidney, there is growing evidence to support the existence of extra-renal V2Rs in vascular and other tissues and with it an expansion in the significance of V2R beyond osmoregulation.\textsuperscript{38,48,54} The chromosome Xq28 region carries the V2R gene, and V2R is structurally similar to V1R, differing only in the number of N-linked glycosylation sites. The 2 subtypes are, however, functionally distinct.\textsuperscript{48}

The primary action of V2R in the kidney is to increase collecting duct permeability to water. This is achieved by interaction of VP-activated V2R with adenylyl cyclase, causing increased production of cAMP and activation of the protein kinase A enzymatic pathway (see Fig. 2). Aquaporin-2–containing vesicles subsequently fuse with the luminal membrane of the collecting duct, thereby increasing water permeability. Water is drawn down a concentration gradient from the collecting duct cells into the hyperosmolar renal interstitium, leaving behind more concentrated urine.\textsuperscript{48,50} V2Rs also exist in the thick ascending limb of the loop of Henle, where they influence NaCl transport and the countercurrent multiplication mechanism.\textsuperscript{54} V2R activation of a distinct urea transporter, further contributes to maintenance of the medullary concentrating gradient.\textsuperscript{55,56}

Afferent arteriolar vasodilation is known to occur in response to V2R stimulation, although the underlying mechanism continues to be debated.\textsuperscript{57} Vasodilation in response to VP activity has been demonstrated in several extrarenal vascular beds—including heart, lung, and skeletal muscle—and there is evidence to support V2 as the receptor subtype responsible in both human and animal models.\textsuperscript{58} Endothelial V2R activation seems to increase cAMP, causing a decrease in Ca\textsuperscript{2+} and activation of NO-mediated mediated pathways (see Fig. 2), leading to vasodilation.\textsuperscript{38,58} V2R expression has also been identified in splenic tissue and on human T cells, raising the possibility of an immunomodulatory role of VP via V2R. Moreover, pulmonary epithelial V2R activation has been found to cause a reduction in lipopolysaccharide-induced inflammation seen in a mouse model, as measured by a fall in IL-6 levels. V2R modulation of NF-κB signaling is believed the likely mechanism.\textsuperscript{59} The significance of these findings, in particular their relevance in the widespread inflammatory response seen in vasodilatory shock, is unclear. It is possible that a combination of activation of NO-mediated pulmonary microvascular vasodilation and modulation of the inflammatory response may be of benefit in vasodilatory shock, although this remains unproved in large clinical trials.\textsuperscript{60} Endothelial V2Rs also have an important role in hemostasis through stimulation of von Willebrand factor secretion in response to cAMP-mediated signaling.\textsuperscript{51}

**V3 Receptor**

The V3 receptor subtype (V3R) is a distinct G-protein–coupled pituitary receptor that stimulates corticotropin secretion from the anterior pituitary in a dose-dependent
manner when activated by VP. A variety of signaling pathways may be activated by V3R depending on its degree of expression, and over-expression is seen in corticotropin-hypersecretory tumors.62 The gene encoding V3R is found on chromosome 1q32.48

**Oxytocin Receptor**

The oxytocin receptor (OTR) is present in myometrial and mammary myoepithelial smooth muscle cells, eliciting smooth muscle contraction through Gq/11-binding, activation of PLC signaling pathways, and increased Ca2+;38 It exhibits equal affinity for VP and oxytocin binding, and circulating VP, therefore, elicits full receptor activation. In addition to myometrial and mammary tissue, OTRs are also abundantly found in vascular endothelial cells where activation and increased Ca2+ stimulates increased eNOS activity and NO-mediated vasodilation. Furthermore, OTRs can be found in the heart, where they stimulate release of atrial natriuretic peptide, a hormone whose actions influence natriuresis, blood pressure control, and cardiomyocyte differentiation.38,48 It is clear that there are conflicting actions of OTRs and the various VP receptor subtypes; however, the precise implications of these variable effects is at present unknown.

**VASOPRESSIN AND VASODILATORY SHOCK**

Under normal physiologic conditions, the effect of exogenous VP on arteriolar tone and systolic blood pressure is negligible.40 In contrast, a key feature of vasodilatory shock states is marked hypersensitivity to exogenously administered VP in conjunction with the previously highlighted deficiency in plasma VP levels.38,39

Hypersensitivity to physiologic doses of VP has been demonstrated in multiple animal models of vasodilatory shock due to sepsis and in several small human studies.38 The mechanisms behind this observation are thought to relate to effects of VP on the key pathophysiologic pathways of vasodilatory shock already described. Inhibition of iNOS by VP has been demonstrated both in vitro and in vivo; however, this has not been correlated with a change in serum nitrate/nitrite levels in patients with septic shock receiving exogenous VP.63–65 In addition, there are several studies supporting the notion that excessive activation of KATP channels may be mitigated by VP activity. This may be through direct closure of the channel or through activation of calcineurin, a Ca2+-dependent phosphatase important in regulating gene transcription that has been shown to inhibit KATP channel activity.49,66,67 Furthermore, in the setting of adrenoceptor desensitization and adrenergic vasoconstrictor hyposensitivity, VP has been shown to exhibit exaggerated pressor effects as well as significant synergy with concurrently initiated adrenergic pressors, despite evidence of V1R desensitization.3,29,33,37 Possible mechanisms proposed for this observation, in addition to those already discussed, include utilization of an alternate pathway for increasing Ca2+; sensitization of the endothelial smooth muscle contractile apparatus to Ca2+ through inhibition of myosin light chain phosphatase; stimulation of production of the vasoconstrictor endothelin-1; and cross-regulation of adrenergic receptor cycling by nonreciprocal inhibition of β-adrenoceptor internalization through intracellular trafficking of β-arrestins.38

Several studies have characterized an early peak in VP levels in response to septic or hemorrhagic shock, with levels typically reaching 10-fold to 20-fold those seen in response to increased plasma osmolality. These subsequently fall away to basal levels as shock becomes established, which is believed to worsen vasoplegia due to inadequate VP levels for efficacy of the described pathways.40 Proposed mechanisms underlying this biphasic response include a combination of depletion of
neurohypophyseal stores, decreased stimulation of VP release due to impaired autonomic reflexes or tonic inhibition of atrial stretch receptors, and inhibition of release due to increased endothelial and pituitary NO or high circulating levels of NE acting centrally.

Deficiency of VP in this setting may have repercussions that go beyond impaired vascular reactivity. There has been much interest in the actions of VP outside of the well-established systemic arterial vasoconstrictor effects, particularly in the setting of septic shock. Of particular significance, several studies have demonstrated favorable pulmonary effects in septic shock with a decrease in pulmonary artery pressure under normoxic or hypoxic conditions and a possible decrease in the pulmonary inflammatory response. Pulmonary vasodilation seems to be a V1R effect and is NO-mediated. The immunomodulatory effects of VP are complex and as yet incompletely elucidated. VP expression has been demonstrated in multiple immune cells, including peripheral T cells, B cells, and monocyte/macrophage cells. It has also been found in human thymic epithelial cells and splenic B cells. Release of VP occurs in response to acute and chronic inflammatory stimuli, and its deficiency has been shown to increase natural killer cell activity in a rat model. Furthermore, VP seems to potentiate corticotropin release from peripheral monocytes, and it plays a role in T-cell activation and modulation of primary antibody production. The immunomodulatory effects of VP are complex and as yet incompletely elucidated. VP expression has been demonstrated in multiple immune cells, including peripheral T cells, B cells, and monocyte/macrophage cells. It has also been found in human thymic epithelial cells and splenic B cells. Release of VP occurs in response to acute and chronic inflammatory stimuli, and its deficiency has been shown to increase natural killer cell activity in a rat model. Furthermore, VP seems to potentiate corticotropin release from peripheral monocytes, and it plays a role in T-cell activation and modulation of primary antibody production. The latter effect was associated with a decrease in downstream cytokine production; however, this also resulted in decreased bacterial clearance from the lower urinary tract, bringing into question the net benefit of the decreased inflammatory response.

The widespread inflammatory response seen in vasodilatory shock inevitably results in increased endothelial permeability and capillary leak syndrome, a phenomenon that renders fluid resuscitation and maintenance of intravascular volume repletion problematic. Pulmonary edema inevitably ensues, exacerbating lung injury and worsening acute respiratory distress syndrome. Such edema is not confined solely to the lung, and numerous organs suffer from the resultant impaired oxygen extraction and delayed recovery of function.

In an ovine model of septic shock the use of terlipressin, a VP analog with relative V1R selectivity, demonstrated a decrease in positive fluid balance within 12 hours of onset of shock compared with VP treatment. This finding may point toward the role of V1R activation in limiting edema formation, potentially through decreased endothelial permeability.

A major compounding factor contributing to the organ dysfunction seen in vasodilatory shock, particularly of septic etiology, is microcirculatory failure. Hemodynamic optimization is currently limited to guidance by macrocirculatory indices, such as mean arterial pressure, or surrogate markers of tissue perfusion, such as blood lactate levels. Optimization, however, of the macrocirculation is not necessarily accompanied by improved microcirculatory function. As a potent vasoconstrictor, the potential for VP to exacerbate microcirculatory compromise, thereby leading to worsened outcomes, has been of particular concern. In numerous experimental studies, the use of VP in the setting of insufficient volume resuscitation, or when administered in high dose or by bolus dosing, was found to cause significant microcirculatory compromise in splanchic, renal and cutaneous circulations. This was somewhat ameliorated by the use a V1R-selective agent, despite the loss of vasodilatory effects of V2R activation, described previously. The use of the highly V1R-selective agent, selepressin, was found superior to either VP or NE in restoring microcirculatory function, although this was assessed by the surrogate measure of blood lactate levels.
Clinical studies have emphasized the complexity of the interplay between the macrocirculation, microvascular function, and vasopressor use. Numerous studies have provided significantly variable results.\textsuperscript{76} It seems that microcirculatory failure and the reversal thereof are perhaps determined more by factors other than the use of a specific vasopressor agent, such as adequacy of volume resuscitation, timing of therapy, and disease progression.\textsuperscript{78} In comparison to adrenergic vasopressors, VP and its analogs demonstrated no increased risk of adverse outcomes.\textsuperscript{79}

Despite the evidence demonstrating the potential benefits of VP receptor agonism in improving vascular tone, minimizing edemagenesis, and decreasing pulmonary inflammation and hypertension, clinical trials have thus far failed to deliver the expected improvements in outcomes.

**Important Clinical Trials**

The largest randomized controlled trial of VP use in septic shock to date is the multi-center Vasopressin and Septic Shock Trial (VASST) that compared the use of NE alone with that of NE and low-dose VP (0.01–0.03 U/min) in 778 patients with septic shock. The primary endpoint assessed was all-cause mortality at 28 days from the commencement of study infusion and was powered to detect a 10% absolute difference in mortality with an assumed 60% mortality rate in the NE group. No significant difference in the primary endpoint was found between the 2 groups, although analysis of an a priori defined subgroup of patients with less severe septic shock showed decreased mortality with VP treatment.\textsuperscript{60} The observed mortality rates in both groups were significantly lower than predicted (39.3% and 35.4% in the NE and VP groups, respectively), likely having an impact on the power. Although not reaching statistical significance, a relative reduction in mortality of 10% was seen in the VP group. Stratified group analysis of patients receiving early VP (≤12 h), demonstrated a trend toward higher mortality in the NE group (40.5% vs 33.2%; \( P = .12 \)) that was not seen with later VP initiation (37.5% vs 37.7%; \( P = .97 \)), suggesting the timing of VP initiation may be important. Furthermore, post hoc analysis of trial data indicated a trend toward both improved renal function with VP and a survival benefit when corticosteroids were coadministered.\textsuperscript{80,81} Decreased serum creatinine, renal failure, use of renal replacement therapy (RRT), and mortality was found associated with VP use.\textsuperscript{80} A multivariate logistic regression analysis of patients in the risk category of the risk, injury, failure, loss of function, and end-stage kidney disease (RIFLE) criteria for acute kidney failure showed a slight increase in mortality with increasing NE dose (odds ratio [OR] 1.03; 99% CI, 1.00–1.06; \( P = .02 \)). The use of VP seemed protective (OR 0.33; 99% CI, 0.1–1.09; \( P = .02 \)).

These findings led to the recent VANISH (Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock) randomized clinical trial of 409 patients with septic shock. The use of early (≤6 h of hypotension) VP versus NE, either with or without hydrocortisone, was assessed for any impact on the incidence of acute kidney injury, RRT, survival, or adverse events in the 28-day period postrandomization.\textsuperscript{82} The number of kidney-failure free days was the primary outcome, measured as 2 summary measures: (1) the proportion of patients who never developed kidney failure and (2) the median number of days alive and free of kidney failure in those who died, experienced kidney failure, or both. Secondary outcome measures included rates of RRT, mortality, and serious adverse events. There was less use of RRT in the VP-treated group compared with the NE-treated group (24.5% vs 35.3%; difference −9.9%, 95% CI, −19.3 to −0.6%); however, there was no difference in the number of kidney-failure free days for those who died or experienced kidney failure (median 9 [interquartile range 1 to −24] days vs 13 [interquartile range 1 to −25] days; difference
−4 days; 95% CI, −11–5). There was once again no difference seen in either mortality or in the rate of serious adverse events, despite the early use of VP (median 3.5 hours after onset of shock) in significantly higher doses (up to 0.06 U/min) than those used in VASST. Both VASST and VANISH demonstrated a catecholamine-sparing effect of VP use, and, although no mortality benefit was seen in either study, it has been suggested that the early use of VP may help reduce the adrenergic burden associated with traditional vasoactive agents. This may be important given the previously identified association of higher doses of catecholamines with increased mortality in septic patients, and the lack of a significant effect in these studies may have been a question, certainly in VASST at least, of study power.

The relationship between VP and cortisol secretion is well established. As previously described, VP is known to stimulate corticotropin release through V3R binding. Furthermore, in septic shock, patients with low plasma cortisol levels or impaired responses to corticotropin were consistently found to have an increased VP level, at least in the early stages of shock. These findings have led to the suggestion that there may be regulatory interdependence between VP and cortisol secretion, with VP release increasing to stimulate increased corticotropin production in the setting of relative adrenal insufficiency. Moreover, post hoc analysis of the VASST cohort found that VP levels in patients who received hydrocortisone were significantly higher than those who did not at both 6 hours and 24 hours. The combination of low-dose VP and hydrocortisone administration was also associated with decreased mortality and organ dysfunction. Study design of the VANISH trial incorporated assessment of the possible interaction of corticosteroids with VP in a 2 × 2 factorial design that included a group who received hydrocortisone in combination with early VP. No impact was found from the use of corticosteroids; however, fewer than half of all patients received the second study drug (hydrocortisone/placebo) and the investigators, therefore, acknowledge that the power might be lacking to draw any significant conclusions. The interaction of corticosteroids and VP in the physiologic response to, and management of, vasodilatory shock remains controversial, and more evidence is required before any definitive conclusions can be made.

Selective VP receptor agonism may well be the key to delivering improved outcomes in the clinical setting. Terlipressin, a synthetic analog with relative V1:V2R selectivity of approximately 2:1, was shown to reduce catecholamine requirements more effectively than VP in the TERLIVAP (Continuous Terlipressin Versus Vasopressin Infusion in Septic Shock) pilot study. Subsequent studies reported, however, several concerning adverse events related to microvascular ischemia and decreased cardiac output. It is likely that the adverse events observed may relate to the differing pharmacokinetic properties of VP and terlipressin, with the latter having a much longer half-life (24 minutes vs 6 hours, respectively) and, therefore, less titratability. Furthermore, it seems that bolus dosing of terlipressin also contributed to the development of adverse events. Selepressin, a short-acting VP analog with even greater V1R selectivity, is showing promise in experimental and early clinical trials as a potential option for efficacious management of vasoplegia in vasodilatory shock, while avoiding some undesirable V2R-mediated effects previously outlined, such as fluid retention, selective vasodilation, and potentially increased platelet aggregation. The recently completed phase Ib/II SEPSIS-ACT (Selepressin Evaluation Programme for Sepsis-Induced Shock - Adaptive Clinical Trial) randomized, placebo-controlled, clinical trial (NCT02508649) will provide an increased understanding of the efficacy and safety of selepressin in this setting once final results are released.
SUMMARY

The vasoplegia seen in vasodilatory shock is the final common pathway for all advanced states of shock. A multitude of interrelated mechanisms clearly contribute to the pathophysiology of this state; however, these remain incompletely understood. As such, the availability of successful interventions to mitigate the disease burden of this ubiquitous condition continues to prove elusive. The myriad multisystem effects of VP through its receptor subtypes provide several promising opportunities for pharmacotherapeutic targeting. Finding the right balance of receptor subtype agonism/antagonism to simultaneously achieve optimal outcomes while avoiding harm will, however, require still more investigation. Selective V1R agonists may prove to be at least 1 piece of this puzzle, although this remains to be seen.

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