Vasopressin is emerging as a rational therapy for the hemodynamic support of septic shock and vasodilatory shock due to systemic inflammatory response syndrome. The goal of this review is to understand the physiology of vasopressin relevant to septic shock in order to maximize its safety and efficacy in clinical trials and in subsequent therapeutic use. Vasopressin is both a vasopressor and an antidiuretic hormone. It also has hemorrhagic, GI, and thermoregulatory effects, and is an adrenocorticotropic hormone secretagogue. Vasopressin is released from the axonal terminals of magnocellular neurons in the hypothalamus. Vasopressin mediates vasoconstriction via V1-receptor activation on vascular smooth muscle and mediates its antidiuretic effect via V2-receptor activation in the renal collecting duct system. In addition, vasopressin, at low plasma concentrations, mediates vasodilation in coronary, cerebral, and pulmonary arterial circulations. Septic shock causes first a transient early increase in blood vasopressin concentrations that decrease later in septic shock to very low levels compared to other causes of hypotension. Vasopressin infusion of 0.01 to 0.04 U/min in patients with septic shock increases plasma vasopressin levels to those observed in patients with hypotension from other causes, such as cardiogenic shock. Increased vasopressin levels are associated with a lesser need for other vasopressors. Urinary output may increase, and pulmonary vascular resistance may decrease. Infusions of > 0.04 U/min may lead to adverse, likely vasoconstriction-mediated events. Because clinical studies have been relatively small, focused on physiologic end points, and because of potential adverse effects of vasopressin, clinical use of vasopressin should await a randomized controlled trial of its effects on clinical outcomes such as organ failure and mortality.

(CHEST 2001; 120:989–1002)

**Key words:** adrenergic agents; antidiuretic hormone; hypotension; septic shock; systemic inflammatory response syndrome; vasoconstrictor agents; vasodilation; vasopressins

**Abbreviations:** ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; cAMP = cyclic adenosine monophosphate; CI = cardiac index; K-ATP = K+-sensitive adenosine triphosphate; LVAD = left ventricular-assist device; NO = nitric oxide; OTR = oxytoxin receptor; SIRS = systemic inflammatory response syndrome; V1R = V1 vascular receptor; V2R = V2 renal receptor

Vasopressin, also known as antidiuretic hormone (ADH), is essential for cardiovascular homeostasis. Vasopressin is one of the first described and structurally characterized peptide hormones and, as a result, has been very extensively studied and used clinically over the past 5 decades, mainly to treat variceal hemorrhage and diabetes insipidus. Vasopressin is now emerging as a rational therapy in the management of septic shock and vasodilatory shock (systemic inflammatory response syndrome [SIRS] with hypotension) from other causes.1,2

A key lesson learned from the unsuccessful cytokine-modulating clinical trials is that greater physiologic understanding of potential new therapies of septic
shock is essential to develop successful therapeutic strategies. Thus, the goal of this review is to understand the physiology of vasopressin relevant to septic shock in order to maximize its safety and efficacy in clinical trials and in subsequent therapeutic use in patients with septic shock or SIRS and hypotension from other causes.

**History**

Vasopressin is essential for survival as attested to by its teleologic persistence. The oxytocin-vasopressin superfamily is found in both vertebrates and invertebrates with a conserved nonapeptide structure. Therefore, the ancestral gene encoding the precursor protein predates the divergence of the two groups about 700 million years ago. Oliver and Schafer in 1895 first observed the vasopressor effect of pituitary extract, attributed to the posterior lobe. More than 10 years later, the antidiuretic effect was described. Two physicians, Farini (in 1913) in Italy and von den Velden (also in 1913), in Germany successfully treated patients with diabetes insipidus by injection of neurohypophysial extracts. The extract decreased urinary output, increased the density of the urine, and reduced thirst. In the late 1920s, Krogh established that topical application of the posterior pituitary hormone to the capillaries induced vasoconstriction in the web feet of the frog and the ears of the dog. After isolation and synthesis of vasopressin by Turner et al in 1951 and du Vigneaud et al in 1954, it was proven that the same hormone in the posterior pituitary is responsible for both antidiuretic and vasopressor effects.

**Physiology**

**Structure and Synthesis**

Vasopressin is a nonapeptide with a disulfide bridge between two cysteine amino acids. Vasopressin is synthesized as a large prohormone in magnocellular neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. The hormone and neurohypophysin, an axonal carrier protein, then migrate via the supraoptic-hypophysial tract to the axonal terminals of the magnocellular neurons, located in the pars nervosa of the posterior pituitary, where vasopressin is stored in granules. Vasopressin is released from the axonal terminals of magnocellular neurons in the hypothalamus, and the rate of release increases as the frequency of action potentials stimulating these neurons increases. Only 10 to 20% of the total hormonal pool within the posterior pituitary can be readily released. Once this amount is discharged into the circulation, vasopressin continues to be secreted in response to appropriate stimuli but at a greatly reduced rate. This is likely relevant to understanding of the biphasic response of vasopressin to septic shock, with high levels early and low levels later. The entire process of vasopressin synthesis, transport, and neurohypophysial storage takes from 1 to 2 h (Fig 1).

**Regulation of Vasopressin Release**

The regulation of vasopressin release is complex and can be classified into osmotic and nonosmotic stimuli. As a result, vasopressin release is influenced by CNS input, by direct hypothalamic input, and by other circulating hormones and mediators. Increased plasma osmolality (osmotic regulation) and severe hypovolemia and hypotension (hypovolemic regula-
tion) are the most potent stimuli to vasopressin release. Pain, nausea, hypoxia, pharyngeal stimuli, and endogenous and exogenous chemicals also increase release of vasopressin (Table 119-21). These latter stimuli often result in relatively inappropriate release of vasopressin resulting in excess water retention and thus hyponatremia; this syndrome is better known as the syndrome of inappropriate ADH release.19

**Osmotic Regulation:** Hyperosmolality is a potent osmotic stimulus to vasopressin release. Sophisticated behavioral (appetite and thirst) and physiologic responses (vasopressin and natriuretic hormones) have developed in mammals to defend osmolality of extracellular fluid. Osmotic regulation of vasopressin production and release is controlled by osmoreceptors located peripherally and centrally. Peripheral osmoreceptors are located in the region of the hepatic portal vein, which allow early detection of the osmotic impact of ingested foods and fluids. Afferents ascend via the vagus nerve to nuclei in the brain, which project to the magnocellular neurons of the hypothalamus. Changes in systemic osmolality are also detected centrally in regions of the brain excluded from the blood brain barrier. Finally, magnocellular neurons of the hypothalamus are directly depolarized by hypertonic conditions (hence releasing more vasopressin) and are hyperpolarized by hypotonic conditions (hence releasing less vasopressin; Fig 2).18

**Hypovolemic Regulation:** Hypotension and decreased intravascular volume are potent nonosmotic stimuli that exponentially increase vasopressin levels. Interestingly, this rise in vasopressin level does not disrupt normal osmoregulation, because hypotension increases the plasma osmolality-vasopressin relationship so that higher plasma vasopressin levels are required to maintain normal osmolality.20,22,23 That is, hypovolemia shifts the osmolality-vasopressin relationship up and to the left by changing the threshold for vasopressin release without changing the sensitivity (slope) of the relationship (Fig 3).20

Volume and pressure stimuli modify vasopressin release. Nonspecifically, afferent impulses from stretch receptors in the left atrium, aortic arch, and carotid sinus carried by the vagus nerve tonically inhibit vasopressin secretion; conversely, a reduction in discharge rate increases vasopressin release.25 Whereas baroreceptors in the atrium and ventricles signal changes in blood volume, the receptors of the aortic arch and carotid sinuses signal changes in arterial BP. Unloading arterial baroreceptors, not cardiac receptors, predominantly drives increased vasopressin during hypotensive hemorrhage.26–30 In contrast, atrial stretch receptors influence control of blood volume primarily through atrial natriuretic peptide, sympathetic stimulation, and renin release. Accordingly, a fall in central venous pressure evokes an increase in norepinephrine and renin, while vasopressin does not increase until mean arterial pressure falls.31–35 Conversely, volume expansion and large increases in BP transiently inhibit vasopressin release, due more to atrial stretch receptors than to arterial baroreceptors.36

**Hormonal Regulation:** Other nonosmotic stimuli that are relevant in critical illness and septic shock include hormones and mediators that directly stimulate vasopressin release, such as acetylcholine (via nicotinic receptors), histamine, nicotine, dopamine, prostaglandins, angiotensin II, and other catecholamines.17 Of these various hormonal and mediator effects, adrenergic regulation plays a particularly important role. Of relevance to critical illness, high PaCO2 or low PaO2 stimulate carotid body chemoreceptors and thus increase vasopressin levels.16 Inhibitors of vasopressin release include opioids, γ-aminobutyric acid, and atrial natriuretic peptide. Neurohumoral inhibition of vasopressin release is mediated by nitric oxide (NO) via cyclic guanosine monophosphate,47 which may be important during sepsis.

Norepinephrine has complex effects on vasopressin release. The hypothalamic projections are predominantly noradrenergic.16 Injection of norepinephrine or phenylephrine into the cerebral ventricles or directly into the magnocellular nuclei stimulates vasopressin release,38 an effect mediated by α2-adrenergic receptors.39 Noradrenaline also inhibits vasopressin and oxytocin release via α2-adrenoceptors or possibly β-adrenoceptors. α-Adrenergic and β-adrenergic receptors may be distributed differentially on the surface of magnocellular neurons allowing different noradrenergic inputs to be excitatory or inhibitory.16

**Table 1—Stimuli of Vasopressin Release in Shock**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Kovacs and Robertson19</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Schrier et al20</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Wood and Chen21</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Schrier et al20</td>
</tr>
</tbody>
</table>

**Vasopressin Levels and Metabolism**

Plasma vasopressin levels are normally < 4 pg/mL in overnight fasted, hydrated humans.40 The osmoreceptor-vasopressin renal mechanism has exquisite
sensitivity and gain. As a result, small increases in plasma osmolality are quickly sensed, vasopressin is released, and urine osmolality increases, thereby correcting increased plasma osmolality. Water deprivation increases plasma osmolality and raises vasopressin levels to 10 pg/mL. Maximal increase in urine osmolality requires vasopressin levels ≥ 20 pg/mL. Vasopressin is rapidly metabolized by liver and kidney vasopressinases, making the hormone half-life 10 to 35 min. A 75% reduction in glomerular filtration rate reduces vasopressin clearance to 30% in dogs, and the liver and the intestines share the splanchnic clearance of vasopressin equally.

Vasopressin Levels in Shock

Both hemorrhagic and septic shock are associated with a biphasic response in vasopressin levels (Table 2). In early shock, appropriately high levels of vasopressin are produced to defend organ perfusion. As the shock state progresses, plasma vasopressin levels fall for reasons that are not entirely clear. Hypotensive hemorrhage in dogs and monkeys can acutely increase plasma levels to 100 to 1,000 pg/mL. However, during prolonged hemorrhagic shock in dogs, an initial increase in plasma vasopressin levels to 319 pg/mL was followed by a decrease to 29 pg/mL. Similarly, acute endotoxin-induced shock results in extremely high levels of vasopressin (> 500 pg/mL in dogs and > 300 pg/mL in baboons).

Importantly, vasopressin levels in established septic shock and vasodilatory shock are low (Table 2). The reason for this relative deficiency is uncertain, and several mechanisms have been proposed (Table 3). First, depletion of neurohypophyseal stores of vasopressin in advanced shock due to excessive baroreceptor firing has been postulated. Second, others have postulated autonomic insufficiency, citing lack of baroreflex-mediated bradycardia after vasopressin infusion as evidence. Third, low concentrations of norepinephrine excite central vasopressin-
ergic neurons, whereas elevated norepinephrine levels (endogenous or exogenous) have a central inhibitory effect on vasopressin release. Finally, increased NO production by vascular endothelium within the posterior pituitary during sepsis may inhibit vasopressin production.

Vasopressin Receptors

It is important to understand the various vasopressin receptors in septic shock to fully understand the effects of vasopressin. Vasopressin-receptor subtypes are of the G protein-coupled receptor superfamily with seven transmembrane-spanning domains. Similar to adrenoreceptors and muscarinic receptors, ligand binding to vasopressin receptors occurs in a pocket formed by the ring-like arrangement of the seven transmembrane domains. It is relevant to emphasize that the location, density, and distribution of vasopressin receptors account for many of the potentially beneficial effects of vasopressin in patients with sepsis and SIRS (Table 4).

V1 vascular receptors (V1R; formerly known as V1a receptors) are located on vascular smooth muscle and mediate vasoconstriction. Additionally, V1 receptors are found in the kidney, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, and testis. V1-receptor activation mediates vasoconstriction by receptor-coupled activation of phospholipase C and release of Ca\(^{++}\) from intracellular stores via the phosphoinositide cascade. V2 renal receptors (V2R), which cause the antidiuretic effects of vasopressin, are present in the renal collecting duct system and endothelial cells. Kidney V2 receptors interact with adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) and cause retention of water. This interaction occurs through the coupling of the receptor with the s subunit of the G protein complex. V3 pituitary receptors (formerly known as V1b) have central effects, such as

![Figure 3. Influence of hypotension on threshold and sensitivity of vasopressin release induced by osmotic stimuli. Adapted from Robertson et al 24 with permission.](image-url)

<table>
<thead>
<tr>
<th>Shock States</th>
<th>Vasopressin Levels, pg/mL</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs</td>
<td>319–991</td>
<td>Wang et al 44; Morales et al 45; Errington and Rocha e Silva 46</td>
</tr>
<tr>
<td>Monkeys</td>
<td>180</td>
<td>Arnauld et al 49</td>
</tr>
<tr>
<td>Endotoxic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>Up to 144</td>
<td>Brackett et al 47</td>
</tr>
<tr>
<td>Dogs</td>
<td>500–1,200</td>
<td>Wilson et al 48</td>
</tr>
<tr>
<td>Baboons</td>
<td>300–1,800</td>
<td>Wilson et al 48</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>Appropriate levels, 22.7 ± 2.2</td>
<td>Landry et al 1</td>
</tr>
<tr>
<td>Late shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogs</td>
<td>Decreased to 29</td>
<td>Morales et al 45; Errington and Rocha e Silva 46</td>
</tr>
<tr>
<td>Septic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans</td>
<td>3.1 ± 1.0</td>
<td>Landry et al 1</td>
</tr>
<tr>
<td>Vasodilatory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humans after LVAD insertion</td>
<td>Five of eight patients had levels &lt; 10</td>
<td>Argenziano et al 49</td>
</tr>
<tr>
<td>Humans after CPB</td>
<td>12.0 ± 6.6</td>
<td>Argenziano et al 49</td>
</tr>
<tr>
<td>Children after CPB</td>
<td>Median, 3.3</td>
<td>Rosenzweig et al 51</td>
</tr>
<tr>
<td>Human organ donors</td>
<td>2.9 ± 0.8</td>
<td>Chen et al 52</td>
</tr>
</tbody>
</table>

* CPB = cardiopulmonary bypass.
increasing adrenocorticotropic hormone (ACTH) production, activating different G proteins, and increasing intracellular cAMP.62

Oxytocin receptors (OTRs) have been found in the uterus and mammary gland and, more recently, in endothelial cells of human umbilical vein, aorta, and pulmonary artery.63 OTRs activate phospholipase C and induce an increase in cytosolic calcium (responsible for the strong contractions of the uterus at term13). One important action when considering the beneficial effects of vasopressin infusion in septic patients is that OTRs also mediate a calcium-dependent vasodilatory response via stimulation of the NO pathway on endothelial cells.63

Table 3—Proposed Mechanisms of Vasopressin Deficiency in Shock

<table>
<thead>
<tr>
<th>Proposed Mechanism</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depletion of neurohypophyseal stores due to excessive stimulation/baroreceptor firing</td>
<td>Hypoxia, acidosis, and hypotension are powerful stimuli of vasopressin release (Table 2)</td>
</tr>
<tr>
<td>Decreased stimulation of vasopressin release due to:</td>
<td>Only 10 to 20% of the total neurohypophyseal pool of vasopressin can be readily released17</td>
</tr>
<tr>
<td>Impaired autonomic reflexes</td>
<td>The autonomic nervous system is impaired in sepsis96,57</td>
</tr>
<tr>
<td>Tonic inhibition by atrial stretch receptor (volume loading, mechanical ventilation)</td>
<td>Atrial stretch receptors tonically inhibit vasopressin16</td>
</tr>
<tr>
<td>Inhibition of vasopressin release due to:</td>
<td>NO inhibits vasopressin release37</td>
</tr>
<tr>
<td>NO release in sepsis</td>
<td>High levels of norepinephrine inhibit vasopressin release38</td>
</tr>
<tr>
<td>High circulating norepinephrine levels</td>
<td></td>
</tr>
</tbody>
</table>

Vasopressin has multiple physiologic effects. Its most well-known effects are suggested by its two names. Vasopressin is a direct vasoconstrictor of the systemic vasculature mediated by V1 receptors. Also known as ADH, one of the primary functions of vasopressin is osmoregulation and maintenance of normovolemia mediated by V2 receptors in the kidney. However, vasopressin has many other physiologic functions. Importantly, vasopressin also vasodilates some vascular beds at certain concentrations, probably by stimulation of OTR. Vasopressin also acts as an ACTH secretagogue, functions in maintaining hemostasis, has GI effects, and plays a role in temperature regulation, memory, and sleep cycles.

**Vasoconstrictor Effects**

Vasopressin has little effect on BP under normal conditions and at normal concentrations.64,65 Supraphysiologic plasma vasopressin levels of about 50 pg/mL must be attained before a significant increase in mean arterial BP is achieved in normal dogs and humans.30,66 However during hypovolemia, vasopressin helps maintain arterial BP. V1-receptor antagonists administered to animals subjected to hemorrhage cause hypotension,10,67 and vasopressin levels rise during hypotension22,68; therefore, vasopressin is an important hormone in preserving perfusion pressure during hemorrhage. The vasoconstrictive effect of high-dose vasopressin treatment has been utilized with some success in cardiac arrest states.69

Vasopressin differs from catecholamines in several respects. Vasopressin is a weak vasoconstrictor in animals with an intact autonomic nervous system because it causes leftward shift of the heart rate-arterial pressure baroreflex curve by acting on V1 receptors in the brain.70–72 As a result, the hypertensive effects of vasopressin are diminished because vasopressin causes a reduction in heart rate greater than that observed with other vasoconstrictors, thus decreasing BP. This is one of several unique differences of vasopressin compared to vasopressors used in sepsis, such as norepinephrine, epinephrine, and dopamine.

Vasopressin is a potent vasoconstrictor in skin, skeletal muscle, fat, pancreas, and thyroid gland.10 In contrast, vasopressin causes less vasoconstriction in mesenteric, coronary, and cerebral circulations.73 Less vasoconstriction in coronary and cerebral circulations may be due to the additional NO-mediated vasodilating effect of vasopressin on these circulations.74,75 The effects of vasopressin on the heart (reduced cardiac output and heart rate) are mainly due to increased vagal tone and decreased sympathetic tone as well as a decrease in coronary blood flow at high circulating levels of vasopressin.10

Of relevance to septic shock, vasopressin enhances the sensitivity of the vasculature to other pressor agents.76 Vasopressin potentiates the contractile effect of norepinephrine, electrical stimulation, and KCl in rat and human arteries.77,78 This augmentation effect can be inhibited by cortisol and lithium, suggesting that it is prostaglandin mediated.
Vasopressin blocks K\(^+\)-sensitive adenosine triphosphate (K-ATP) channels in a dose-dependent manner, an effect that may restore vascular tone in patients with septic shock. The membrane potential of arterial smooth-muscle cells, which is regulated by K\(^+\) channels, is an important regulator of arterial tone. The opening of K\(^+\) channels closes voltage-dependent Ca\(^{2+}\) channels, decreasing Ca\(^{2+}\) entry, which leads to dilatation. Endotoxic shock is associated with excessive activation of K-ATP channels. Vasopressin could cause mesenteric vasoconstriction, which could be an adverse effect in septic shock. Vasopressin vasoconstricts the mesenteric circulation in physiologic concentrations (as low as 10 pg/mL). This mesenteric vasoconstrictor effect is mediated via the V1R and has been demonstrated in vitro and in vivo in several animal models, and it is dose dependent. These mesenteric vascular effects of vasopressin are, of course, utilized in the treatment of variceal bleeding secondary to portal hypertension.

**Vasodilator Effects**

Another difference between vasopressin and catecholamines in septic shock is that vasopressin may cause vasodilation in selected organs. Vasopressin-induced vasodilation is likely mediated ultimately by NO. Although the main effect of vasopressin in mammals is vasoconstriction, studies using selective V1R-antagonists unmask a vasodilatory effect of vasopressin. The vasoconstriction produced by vasopressin is mediated by V1 receptors that cause release of endothelium-derived NO, a finding confirmed by others. The receptor subtype responsible for vasodilation is uncertain. The V2 receptor agonist 1-desamino-8-D-arginine vasopressin causes a decrease in BP and facial flushing in humans and peripheral vasodilation in dogs. V2R-antagonist administration also inhibits the vasodilatory response of the renal afferent arteriole to vasopressin. Thibonnier and co-workers have identified endothelial OTRs that mediate vasopressin-induced vasodilation through reverse transcriptase-polymerase chain reaction techniques. Stimulation of endothelial cells by oxytocin produced mobilization of intracellular calcium and the release of NO. Thus, despite implicating different receptors, all of these studies suggest that vasopressin-induced vasodilation is mediated ultimately through NO release.

**Pulmonary Vascular Effects**

Vasopressin may cause pulmonary vasodilation, which is of relevance to septic shock because pulmonary vascular tone and resistance are usually increased in patients with septic shock. Vasopressin decreases pulmonary artery pressure when infused in normal or hypoxic conditions. Pulmonary vascular resistance does not increase until very high levels of plasma vasopressin are achieved (300 to 500 \(\mu\)g/mL). Pulmonary vasodilation by vasopressin is mediated by V1 receptors that cause release of endothelium-derived NO, a finding confirmed by others.

**Renal Effects of Vasopressin**

The renal effects of vasopressin also differ from the effects of catecholamines and have potentially great relevance in septic shock. However, the renal effects of vasopressin are complex and require understanding of the interplay of osmoregulatory and renovascular balance for interpretation of effects of vasopressin on renal function and urine output in

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**Table 4—Vasopressin Receptors**

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Tissues</th>
<th>Principal Effects</th>
<th>Intracellular Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1R</td>
<td>Vascular smooth muscle</td>
<td>Direct and indirect vasodilation</td>
<td>Phosphoinositide pathway (activate phospholipase C)</td>
</tr>
<tr>
<td></td>
<td>Kidney (bladder, adipocytes, platelets, spleen, testis)</td>
<td></td>
<td>Increased intracellular Ca(^{2+})</td>
</tr>
<tr>
<td>V2R</td>
<td>Renal collecting duct</td>
<td>Increased permeability to water</td>
<td>Increased cAMP</td>
</tr>
<tr>
<td>V3R</td>
<td>Endothelium</td>
<td>Vasodilation</td>
<td>NO mediated</td>
</tr>
<tr>
<td>OTR</td>
<td>Pituitary</td>
<td>Neurotransmitter release</td>
<td>Increased cAMP</td>
</tr>
<tr>
<td></td>
<td>Kidney (bladder, adipocytes, platelets, spleen, testis)</td>
<td>Vasodilation</td>
<td>Phospholipase C</td>
</tr>
<tr>
<td></td>
<td>Platelet</td>
<td>Vasoconstriction</td>
<td>NO mediated</td>
</tr>
</tbody>
</table>

* V3R = V3 pituitary receptors.
septic shock (Table 5). Vasopressin regulates urine osmolality by increasing cortical and medullary collecting duct luminal membrane permeability to water by activation of V2 receptors. V2 receptors are located on the basolateral membrane of the principal cells of the tubular epithelium. This adenylate cyclase-dependent process increases intracellular cAMP, which, through protein kinase activation, results in water channels (aquaporins) containing vesicles to fuse with the luminal membrane (an effect inhibited by V1 receptor-mediated production of prostaglandin E₂). The increased intracellular water then osmotically equilibrates with the interstitial fluid, and the urine becomes more concentrated. Vasopressin contributes to further concentration of urine by increasing the medullary concentration gradient by activating a distinct urea transporter. Vasopressin also induces a selective decrease in inner medullary blood flow without altering cortical blood flow, which also contributes to the maximum concentrating ability of the kidney.

Paradoxically, low-dose vasopressin induces diuresis in humans with hepatorenal syndrome and congestive heart failure, in patients with septic shock, and in patients with milrinone-induced hypotension. The mechanisms of the diuretic effect of vasopressin have not been fully explained. Possible mechanisms include downregulation of the V2R, NO-mediated afferent arteriolar vasodilation, selective efferent arteriolar vasoconstriction, and OTR-activated natriuresis. Higher levels of vasopressin (pressor doses), however, cause a dose-dependent fall in renal blood flow (afferent arteriole and medulla most sensitive), glomerular filtration rate, and sodium excretion. A V1R antagonist can block the vasoconstrictor action of vasopressin on the afferent arteriole. Interestingly, even norepinephrine-induced vasoconstriction of the afferent arteriole can be abolished by treatment with vasopressin if the V1R is blocked.

### Other Organ System Effects

Vasopressin increases cortisol, which could be very relevant in patients with septic shock, because cortisol levels may not be adequate. Pharmacologic doses of vasopressin in animals and man induce a prompt rise in plasma cortisol levels. In man, adrenocortical activation occurs directly via vasopressin stimulation of ACTH release. This effect is likely mediated through NO and cyclic guanosine monophosphate via the V3 receptor. Subsets of patients in septic shock have “relative adrenal insufficiency” that independently predicts mortality. This raises the interesting speculation that low blood levels of vasopressin in humans may play a role in the adrenal insufficiency of the critically ill.

Vasopressin causes aggregation of human blood platelets, a potential adverse effect in septic shock. The V2-selective agonist 1-desamino-8-D-arginine vasopressin causes release of factor VIIIc and von Willebrand factor, and has been used extensively in treating bleeding due to dysfunctional platelets. However, low doses of vasopressin are less likely to stimulate platelet aggregation in most individuals.

The brain has a rich innervation by vasopressin-containing fibers. Vasopressin appears to act as a

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### Table 5—Renal Effects of Vasopressin

<table>
<thead>
<tr>
<th>Effects</th>
<th>Receptors</th>
<th>Mechanisms</th>
<th>Models</th>
<th>Vasopressin Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiuresis</td>
<td>V2R</td>
<td>Increased collecting duct permeability (inhibited by V1 via prostaglandin)</td>
<td>Animal and human</td>
<td>10–20 pg/mL (higher levels downregulate V2R&lt;sub&gt;102&lt;/sub&gt;) 1–1,000 pg/mL</td>
</tr>
<tr>
<td>Diuresis</td>
<td>V1R</td>
<td>Efferent arteriolar vasoconstriction&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Isolated rabbit cortical arteries</td>
<td>Subpressor doses (0.06–3.5 U/min equivalent in 70-kg man)</td>
</tr>
<tr>
<td>Diuresis/natriuresis</td>
<td>??</td>
<td>Inhibits Na reabsorption distal to the proximal tubule&lt;sup&gt;104&lt;/sup&gt;</td>
<td>Bicarbonate and glucose-loaded dogs</td>
<td>Subpressor doses (up to 0.04 U/min equivalent in 70-kg man)</td>
</tr>
<tr>
<td>Diuresis</td>
<td>OTR</td>
<td>Natriuresis&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Anesthetized rat</td>
<td></td>
</tr>
<tr>
<td>Increased renal blood flow</td>
<td>NO med (blocked by L-NAME)</td>
<td>Decreased renovascular resistance&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Anesthetized rat</td>
<td>Subpressor doses (up to 0.04 U/min equivalent in 70-kg man)</td>
</tr>
<tr>
<td>Decreased renal blood flow</td>
<td>V1R</td>
<td>Vasoconstriction&lt;sup&gt;107&lt;/sup&gt;</td>
<td>Rat (inulin/para-amillo hippurate method)</td>
<td>Doses &gt; 0.5 U/min equivalent in 70-kg man</td>
</tr>
</tbody>
</table>

<sup>*L-NAME = nitro-L-arginine methyl ester.</sup>
neurotransmitter involved in the central control of circadian rhythmicity,120,121 water intake, cardiovascular regulation, thermoregulation,122 regulation of ACTH release, and nociception.123 Thus, vasopressin acts centrally, coordinating autonomic and endocrine responses to homeostatic perturbations.

VASOPRESSIN IN SEPTIC SHOCK AND SIRS

We have reviewed the human trials of low-dose vasopressin in septic shock and other forms of vasodilatory shock (Table 6). There is evidence for both a deficiency and an exquisite sensitivity to vasopressin, which has mechanistic and therapeutic implications.

Most forms of hypotension are associated with appropriately high levels of vasopressin.29,54,125,126 Landry et al observed that some patients with advanced vasodilatory septic shock had inappropriately low plasma levels of vasopressin. Plasma levels of vasopressin were 3.1 ± 0.4 pg/mL in the septic shock patients (n = 19) and 22.7 ± 2.2 pg/mL in cardiogenic shock patients (n = 12). Exogenous infusion of 0.01 U/min of vasopressin in two patients increased vasopressin levels to 27 pg/mL and 34 pg/mL, respectively, indicating that the low vasopressin levels in patients with septic shock were due to impaired vasopressin secretion, not increased vasopressin metabolism or clearance. These results implicated a relative deficiency of vasopressin in patients with late septic shock.

Additionally, septic shock patients are exquisitely sensitive to low-dose vasopressin.1,2 Ten patients received vasopressin at 0.04 U/min, which increased plasma concentrations to 100 pg/mL, increased systolic BP from 92 to 146 mm Hg (p < 0.001), increased systemic vascular resistance by 79% (p < 0.001), and decreased cardiac output by 12% (p < 0.01). Reduction of the infusion to 0.01 U/min resulted in plasma levels of 30 pg/mL. Six patients were able to receive vasopressin as their sole pressor agent. Discontinuation of vasopressin treatment in these patients resulted in a sudden decrease in arterial pressure.

To our knowledge, there has been only one small randomized controlled trial of vasopressin in patients with septic shock. Malay and colleagues127 studied 10 patients admitted to the trauma ICU with vasodilatory septic shock (need for pressor agents to maintain mean arterial pressure > 70 mm Hg, cardiac index [CI] > 2.5 L/min/m2, and pulmonary wedge pressure > 12 mm Hg), who were randomized to receive either vasopressin at 0.04 U/min (n = 5) or placebo (n = 5). Patients receiving vasopressin had an increase in systolic BP from 98 to 125 mm Hg (p < 0.05) and were able to have treatment with all other catecholamines withdrawn. All patients in the treatment group survived the 24-h study period. The control patients had no statistically significant change in BP, none were able to have vasopressor therapy withdrawn, and two died of refractory hypotension within 24 h. Vasopressin administration had no effect on heart rate, CI, and/or pulmonary artery pressure. The results of this small study further highlight the increased pressor sensitivity to vasopressin in patients with vasodilatory shock.

Table 6—Trials of Low-Dose Vasopressin in Human Septic and Vasodilatory Shock*

<table>
<thead>
<tr>
<th>Source</th>
<th>Date</th>
<th>Trial</th>
<th>Patients, No./Conditions</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landry et al2</td>
<td>1997</td>
<td>Case series</td>
<td>5/septic shock</td>
<td>A, B, C</td>
</tr>
<tr>
<td>Landry et al1</td>
<td>1997</td>
<td>Matched cohort</td>
<td>19/septic shock</td>
<td>A, B, D in septic group</td>
</tr>
<tr>
<td>Malay et al127</td>
<td>1999</td>
<td>RCT</td>
<td>12/cardiogenic shock</td>
<td>A, B, C</td>
</tr>
<tr>
<td>Argenziano et al50</td>
<td>1998</td>
<td>Retrospective case series</td>
<td>40/after bypass vasodilatory shock</td>
<td>A, B, D</td>
</tr>
<tr>
<td>Argenziano et al49</td>
<td>1997</td>
<td>RCT</td>
<td>12/vasodilatory shock after LVAD implant</td>
<td>A, B, D in treatment arm</td>
</tr>
<tr>
<td>Argenziano et al124</td>
<td>1999</td>
<td>Case series</td>
<td>20/vasodilatory shock after cardiac transplant</td>
<td>A, B</td>
</tr>
<tr>
<td>Rosenzweig et al34</td>
<td>1999</td>
<td>Case series</td>
<td>11/Pediatric, vasodilatory shock after bypass</td>
<td>A, B, D</td>
</tr>
<tr>
<td>Morales et al128</td>
<td>2000</td>
<td>Retrospective case series</td>
<td>50/vasodilatory shock after LVAD implantation</td>
<td>A, B</td>
</tr>
<tr>
<td>Chen et al52</td>
<td>1999</td>
<td>Case series</td>
<td>10/organ donors with vasodilatory shock</td>
<td>A, D</td>
</tr>
<tr>
<td>Gold et al111</td>
<td>2000</td>
<td>Case series</td>
<td>7/milrinone, hypotension</td>
<td>A, B, C</td>
</tr>
</tbody>
</table>

*A = increase in BP; B = decrease or discontinuance of catecholamines; C = increase in urine output; D = low plasma vasopressin levels in subjects; RCT = randomized controlled trial; NS = not significant.
shock and again raises speculation as to how this may occur. The authors noted lack of baroreflex-mediated decrease in heart rate in these patients, supporting the theory of autonomic insufficiency in septic shock.

Subsequently, Argenziano and colleagues\(^49\) investigated the role of vasopressin in other forms of vasodilatory shock (SIRS of noninfectious origin) following placement of a left ventricular-assist device (LVAD) for end-stage heart failure. On weaning from cardiopulmonary bypass, selected subjects had mean arterial pressure < 70 mm Hg despite norepinephrine infusion of 8 \(\mu g/min\) and LVAD-assisted CI > 2.5 L/min/m\(^2\). Consecutive eligible subjects were blindly randomized 5 min after bypass to receive vasopressin at 0.10 U/min or placebo. Ten of 23 LVAD recipients met inclusion criteria. Vasopressin infusion rapidly and significantly increased mean arterial pressure (57 to 84 mm Hg), and norepinephrine infusion rate was decreased by > 50% and then was gradually discontinued. Baseline plasma vasopressin levels were inappropriately low for patients in shock; 7 of 10 patients had levels < 20 pg/mL. The dose of 0.10 U/min produced plasma levels of 150 pg/mL. Argenziano and colleagues\(^49\) concluded that vasopressin is an effective pressor for LVAD recipients with vasodilatory shock after cardiopulmonary bypass, significantly increasing mean arterial pressure while rapidly reducing catecholamine requirements.

Argenziano and coworkers\(^50\) prospectively studied 145 patients undergoing cardiopulmonary bypass for elective cardiac surgery and retrospectively analyzed 40 patients who had postbypass vasodilatory shock and who received vasopressin. In the prospective study,\(^50\) they found that vasodilatory shock after cardiopulmonary bypass is associated with vasopressin deficiency and that this syndrome is more common among patients with low ejection fraction and those receiving angiotensin-converting enzyme inhibitors. In the retrospective group, they observed that in patients undergoing LVAD implantation, administration of vasopressin significantly increased mean arterial pressure while reducing the requirements for catecholamine pressor agents. These investigators\(^50\) were able to rapidly taper the initial infusion of 0.10 U/min to 0.01 U/min. Morales and coworkers\(^127\) also reported a retrospective series of 50 patients who received vasopressin after LVAD implantation, again showing an increase in mean arterial pressure and a reduction in pressor requirements.

In another small trial in septic shock, Rosenzveig and coworkers\(^51\) evaluated vasopressin administration in 11 profoundly ill infants and children with hypotension refractory to treatment with multiple pressor agents after cardiac surgery. The mean baseline plasma vasopressin level was 4.4 pg/mL. Vasopressin administration increased mean arterial pressure in all patients and decreased pressor agents in five of eight patients. All nine children with vasodilatory shock survived their ICU stay, and two patients who received vasopressin in the setting of poor cardiac function died despite transient improvement in their BP.

Chen et al\(^52\) evaluated vasopressin in hypotension in 10 hemodynamically unstable solid-organ donors. Again, baseline vasopressin levels were inappropriately low (2.9 ± 0.8 pg/mL) for the degree of hypotension. Mean arterial pressure increased allowing discontinuation of catecholamine therapy in four subjects and reduction in requirements in four subjects.

These authors\(^111\) have also reported the use of low-dose vasopressin as an effective vasopressor for seven patients with milrinone-induced hypotension and found that vasopressin infusion at 0.03 to 0.07 U/min increased systolic arterial pressure from 90 to 127 mm Hg (\(p < 0.01\)). This pressor response allowed a decrease in the dose and incidence of administration of norepinephrine. Vasopressin did not change pulmonary artery diastolic pressure. Urinary output averaged 42 ± 10 mL/h at baseline, 44 ± 19 mL/h with milrinone (not significant), and 81 ± 20 mL/h (\(p < 0.05\)) after the addition of vasopressin. There was no decrease in CI with vasopressin administration.

**Mechanisms of Vasopressin Deficiency in Septic Shock and SIRS**

The mechanisms of vasopressin deficiency in patients with vasodilatory shock are not known. Landry and coworkers\(^1\) showed that increased metabolism or clearance of vasopressin is not a mechanism of the low vasopressin levels in patients with septic shock. The potential mechanisms of vasopressin deficiency include (1) depletion of pituitary stores of vasopressin after exhaustive release of vasopressin in early septic shock, (2) autonomic dysfunction in patients with septic shock,\(^36,57\) and (3) increased vascular endothelial dysfunction in patients with septic shock,\(^36,57\) which may downregulate vasopressin production (Table 3).\(^37\)

The mechanisms of the exquisite sensitivity of vasodilatory shock patients to vasopressin may also be multifactorial. Autonomic insufficiency in vasodilatory shock may "unmask" the pressor effects of vasopressin. Pressor sensitivity to physiologic doses of vasopressin is greatly enhanced following baroreceptor denervation in dogs.\(^72\) Threshold sensitivity was increased 11-fold, and sensitivity at higher doses...
was increased 60-fold to 100-fold. Humans with idiopathic orthostatic hypotension also exhibit a pressor response (1,000-fold sensitivity) to physiologic doses of vasopressin.\textsuperscript{64} Synergy of action with adrenergic agents at the G protein-coupled receptors may occur. Low-dose norepinephrine infusion increased sensitivity to vasopressin at physiologic doses by nearly 8,000-fold.\textsuperscript{72} Finally, blockade of K-ATP channels may be a mechanism of restoration of vascular tone by vasopressin in patients with septic shock.

CONCLUSIONS AND RECOMMENDATIONS

Vasopressin deficiency may contribute to the refractory hypotension of late, refractory septic shock. Infusion of vasopressin increases plasma levels to values found during comparable degrees of hypotension from other causes, such as cardiogenic shock. Vasopressin infusion causes a pressor response and a sparing of conventional exogenous catecholamines.

In “physiologic” doses (ie, 0.01 to 0.04 U/min yielding plasma levels of 20 to 30 pg/mL), vasopressin is synergistic with exogenous catecholamines yielding a pressor response without evidence of organ hypoperfusion, and low-dose vasopressin may vasodilate some vital vascular beds. In “pharmacologic” doses (ie, > 0.04 U/min, giving plasma levels of > 100 pg/mL), the pressor effect of vasopressin is associated with potentially deleterious vasoconstriction of renal, mesenteric, pulmonary, and coronary vasculature.

Clinical use of vasopressin should await a randomized controlled trial of the effect of vasopressin on clinical outcomes such as organ failure and mortality because it is not yet known whether vasopressin improves organ dysfunction or increases survival. A reasonable rationale for using vasopressin in a randomized controlled trial in patients with established septic shock (refractory to conventional catecholamines) would be to use vasopressin in a low dose, as an additional therapy, with the goal of restoring vasopressin levels to an “appropriate” level, ie, 20 to 30 pg/mL. Use of low-dose vasopressin in patients with severe septic shock potentially avoids renal, mesenteric, pulmonary, and coronary ischemia, as well as the hypercoagulable effects of high-dose vasopressin. The potential benefits of low-dose vasopressin include restoration of vasomotor tone and preservation of renal blood flow and urine output. Whether this will translate to improved long-term outcomes is not known.

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