

Effects of Vasopressin in Septic Shock

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ABSTRACT

Septic shock continues to be one of the leading causes of death in the intensive care unit today. The confluence of many factors contributes to the deterioration of patients' condition in septic shock. Increased levels of nitric oxide, in part, mediate the cardiovascular effects of septic shock. Nitric oxide is major mediator of vasodilation and hypotension as well as myocardial depression. It also contributes to decreased production and release of endogenous vasopressin. Vasopressin effects are actualized by stimulation of V1, V2, and V3 receptors located in various parts of the body.

The response is dose dependent. Endogenous vasopressin and angiotensin II act synergistically to preserve and restore blood pressure levels. Decreased circulating vasopressin contributes to adrenal insufficiency via hypothalamic-pituitary-adrenal axis suppression and increased catecholamine resistance to vasopressors. Exogenous vasopressin supplementation in physiologic doses has been shown to improve blood pressure levels and decrease vasopressor needs in patients with septic shock. **Keywords:** vasopressin, septic shock, V receptors

Case Study

A 76-year-old woman with urosepsis was admitted to the intensive care unit. She was initially volume resuscitated and started on antibiotic therapy in the emergency department. She was hypotensive despite adequate fluid resuscitation with crystalloids. Her systolic blood pressure was 70 mm Hg, and a norepinephrine infusion was initiated at 10 mcg/min. She required high doses of norepinephrine (30 mcg/min) to maintain a systolic blood pressure of 90 mm Hg. Therefore, a vasopressin infusion was initiated at 0.04 units/min. Within an hour, her blood pressure stabilized and the norepinephrine was weaned to 5 mcg/min. Eight hours later her vasopressin infusion was discontinued; however, her norepinephrine requirement rebounded to a dose of 15 mcg/min to maintain an acceptable blood pressure level.

Epidemiology

Septic shock affects more than 200 000 patients annually.¹ It is one of the most common reasons for admission to the intensive

care unit and is the 10th leading cause of death in the United States.² Mortality in severe sepsis and septic shock remains about 30% to 50% despite advances in advanced life support and antimicrobial therapy.² Although mortality remains unacceptably high, it is on decline in recent years.³ *Sepsis* is defined as having 2 or more of the systemic inflammatory response syndrome criteria that include an alteration in temperature and white blood cell count and elevated respiratory and heart rates (Table 1). According to the American College of Chest Physicians and the Society of Critical Care Medicine consensus definition,⁴ *septic shock* is defined as sepsis with hypotension despite adequate fluid resuscitation, along with perfusion abnormalities manifested by, but not limited to, lactic acidosis, oliguria, and mental status changes. Some degree of organ dysfunction is present. When fluid resuscitation is not enough

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Table 1: Systemic Inflammatory Response Syndrome Criteria*

White blood cell count	<4000 or >12 000 mm ³ , or >10% bands
Respiratory rate	> 20 breaths/min
Temperature	<36°C or >38°C
Heart rate	> 90 beats/min

*Data were derived from Dellinger et al for the Surviving Sepsis Campaign Management Guidelines Committee.⁴

to maintain an adequate blood pressure level, pressor agents may be necessary. Although not a first-line drug, vasopressin is among the agents used to help maintain blood pressure levels.^{4,5} It can be used alone or in combination with other pressor agents to achieve blood pressure goals.

Pathogenesis of Hypotension in Septic Shock

One of the cardiovascular effects of septic shock is hypotension. Widespread vasodilation creates a relative hypovolemia, which produces hypotension,⁶ and a vasodilatory shock state. Hypotension also occurs as a result of vasopressor resistance.⁶ Nitric oxide (NO) is a major mediator in this vasodilation

and hypotension. It is synthesized by the action of an enzyme, nitric oxide synthase (NOS). Three isoforms of NOS are present. The 2 constitutively expressed forms of NOS (cNOS) are endothelial NOS (eNOS), which is bound to the endothelial membrane, and neuronal NOS (nNOS), which is found in high concentrations in the brain. An inducible form of NOS (iNOS) is also present. Proinflammatory cytokines released in sepsis upregulate the expression of iNOS, which results in NO production much greater than that of cNOS.⁷ Nitric oxide is synthesized in endothelial cells (Figure 1). When it is released by the endothelium, it diffuses into nearby vascular smooth muscle cells where it produces cyclic guanosine monophosphate (cGMP) from guanosine triphosphate.⁷ An increase in cGMP activates a kinase system, which then inhibits calcium from entering vascular smooth muscle cells. Vascular smooth muscle cells are dependent on extracellular calcium for contraction. Because cGMP prevents calcium from entering vascular smooth muscle cells, they cannot contract and therefore remain vasodilated.⁸ Nitric oxide also inhibits the endogenous production and release of vasopressin.^{5,9}

Vasopressor resistance is refractory in shock despite adequate fluid resuscitation and high-dose conventional vasopressors.⁴

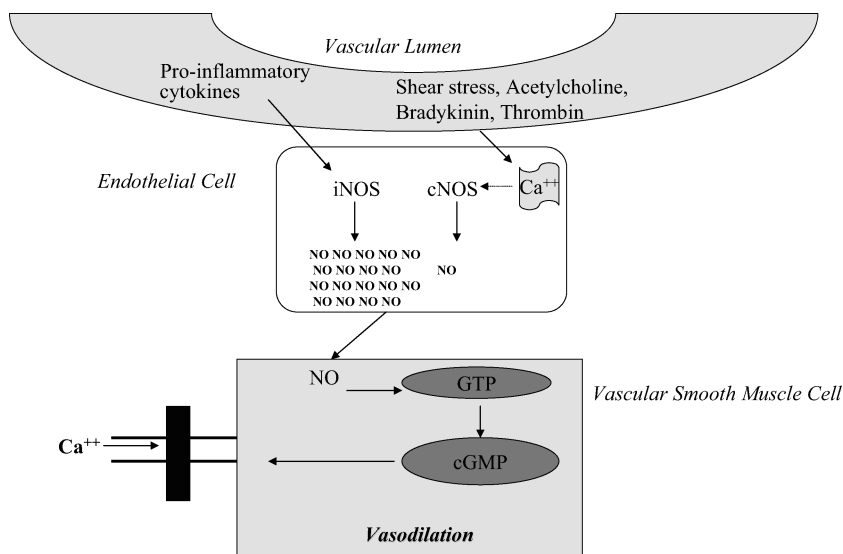


Figure 1: Depiction of vascular effects of increased nitric oxide formation from inducible nitric oxide synthase. Abbreviations: Ca⁺⁺, calcium; cNOS, constitutive nitric oxide synthase; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; iNOS, inducible nitric oxide synthase; NO, nitric oxide.

The case study demonstrates vasopressor resistance in a patient with adequate fluid resuscitation requiring 30 mcg/min of norepinephrine to maintain systolic blood pressure of 90 mm Hg. Vasopressor resistance occurs through the activation of the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels in vascular smooth muscle. This is due to decreased intracellular levels of ATP, which can occur as the result of hypoxia and/or increased intracellular levels of hydrogen ions and lactate.⁵ The activation of K_{ATP} channels causes hyperpolarization of the plasma membrane on vascular smooth muscle, which inhibits the influx of calcium (Ca^{2+}) into the cell and prevents vasoconstriction.⁵ Angiotensin II and norepinephrine also depend on open Ca^{2+} channels. Therefore, vascular resistance to these vasopressor hormones occurs in addition to decreased levels of endogenous vasopressin; all these contribute to a failure of the reflex vasoconstriction mechanism.⁶

Manifestation of decreased systemic vascular resistance leads to vasodilation associated with septic shock. However, this widespread vasodilation does not occur in a uniform fashion throughout the body. The net result is a maldistribution in blood flow and tissue hypoxia. Vasoconstriction occurs because of various inflammatory mediators. These key mediators include tumor necrosis factor α and endothelin. Endothelin, a potent vasoconstrictor, is released by the endothelium. Inadequate tissue perfusion is further exacerbated by leukocytes binding to the endothelium and occluding the microvasculature.

In addition to hypotension, septic shock is also associated with myocardial depression. Myocardial depression is a combination of both systolic and diastolic dysfunction resulting in cardiac impairment.¹⁰ Biventricular dilation, decrease in ejection fraction, and decrease in the contractile response to fluid resuscitation occur in the presence of myocardial depression. The effect begins hours after initial exposure and may persist for days.¹⁰ Myocardial depression is caused by myocardial depressant factors, not by altered perfusion of coronaries or global ischemia. It exists despite a fluid resuscitation-dependent hyperdynamic state. The pathogenesis of myocardial depression may be related to the presence of NO, cGMP, and altered signal transduction by β -receptors in myocardial cells.^{6,10}

Endogenous Vasopressin

Endogenous vasopressin acts as a compensatory mechanism to support blood pressure levels during septic shock. Vasopressin, a peptide hormone, is produced within the supraoptic and paraventricular nuclei of the hypothalamus⁵ and stored in the posterior pituitary gland. It is released into circulation in response to both increased plasma osmolality, as detected by osmoreceptors located in the periphery and specialized cells within the hypothalamus, and decreased blood pressure levels, as detected by baroreceptors in aortic arch and carotid sinus.⁵ Although vasopressin is endogenously produced, levels quickly rise in septic shock and then fall to subphysiologic levels, resulting in a relative vasopressin deficiency.¹¹

The renin-angiotensin-aldosterone system acts synergistically with vasopressin to augment blood pressure levels. Decreased renal perfusion is detected by special receptors in the renal artery. These receptors stimulate the juxtaglomerular cells in the kidneys to secrete renin. Renin circulates to the liver where it converts angiotensinogen to angiotensin I. Circulating angiotensin I encounters angiotensin-converting enzyme, which is mainly located on the luminal surface of endothelial cells, and converts angiotensin I to angiotensin II. Angiotensin II is released into the circulation and is a potent vasoconstrictor. It also acts on the central nervous system (CNS) to stimulate the posterior pituitary gland to secrete vasopressin. In summary, angiotensin II acts on blood vessels to cause vasoconstriction; on the CNS to cause thirst and stimulation of the posterior pituitary gland to increase vasopressin secretion, which, in turn, causes water retention by the kidneys; and on the adrenal cortex to cause aldosterone secretion, which acts on the kidneys to cause sodium retention.¹²

During stress states, such as septic shock, the hypothalamic-pituitary-adrenal (HPA) axis is stimulated¹³ and causes the release of norepinephrine, epinephrine, antidiuretic hormone, aldosterone, and cortisol. Corticotropin (ACTH)-releasing hormone stimulates the sympathetic nervous system to release epinephrine and norepinephrine, which results in vascular smooth muscle vasoconstriction and enhanced myocardial inotropic response. The posterior pituitary gland is stimulated to release antidiuretic hormone, also known as arginine vasopressin (AVP), to promote intravascular fluid retention. The anterior pituitary

releases ACTH, which then stimulates the adrenal cortex to release aldosterone, a mineralocorticoid, to promote intravascular fluid retention. The adrenal cortex also releases the glucocorticoid cortisol, which increases the availability of substrates for metabolism and modulates the immune/inflammatory response. Cortisol also increases transcription and expression of receptors for catecholamines and angiotensin II, which maintain vascular tone.¹³ The integrity and responsiveness of the HPA axis are major determinants of the host's response in sepsis. Failure of the HPA axis may result in a relative adrenal insufficiency and adrenergic hyporesponsiveness. Inflammatory cytokines released during septic shock promote corticosteroid resistance and may suppress normal adrenal responses.¹³

Exogenous vasopressin is a direct vasoconstrictor without direct inotropic and chronotropic properties; however, in larger doses and through compensatory mechanisms, vasopressin may exhibit these properties.¹⁴ Arginine vasopressin can potentially decrease stroke volume and may result in decreased cardiac output and hepatosplanchnic flow.² It may actually have negative inotropic effects by decreasing cardiac output secondary to an increased systemic vascular resistance. Arginine vasopressin may have secondary negative chronotropic effects manifested by a decreased heart rate due to the baroreceptor response from vasoconstriction.¹⁵ Doses greater than 0.04 unit/min have been associated with myocardial ischemia, significant decrease in cardiac output, and even cardiac arrest.^{4,14,16} Holmes et al¹⁶ showed no increase in benefit in doses greater than 0.04 unit/min. All of the patients in the study who had cardiac arrest were on doses greater than 0.03 unit/min (up to 0.06).

During early septic shock, vasopressin concentrations are elevated (approximately 20% of stores are released in the initial surge) and plasma concentrations increase 20 to 200 times of normal serum concentrations.¹⁷ However, with continued shock, concentrations decrease well below the normal, which results in a relative vasopressin deficiency.¹⁷ Because vasopressin has also been shown to increase serum cortisol levels via stimulation of ACTH release, a relative vasopressin deficiency can predispose a relative adrenal insufficiency and increase mortality.⁹ Evidence exists that survival is improved with the supplementation of physio-

logic doses of steroids and vasopressin.^{14,18} The adjunctive use of vasopressin in septic shock, however, remains controversial. The Vasopressin in Septic Shock Trial analyzed patients in septic shock requiring vasopressors for at least 6 hours and showed no increased survival at day 28 between randomized group that received vasopressin (AVP) and randomized group that received norepinephrine (35.4% vs 39.3%, $P = .27$). However, when the groups were stratified into those with more severe hypotension using greater than 15 mcg/min of norepinephrine and those with less severe hypotension using less than 15 mcg/min of norepinephrine, the patients with lower dose of norepinephrine had increased survival with AVP at both 28 days (26.5% vs 35.7%, $P = .05$) and 90 days (35.8% vs 46.1%, $P = .04$).¹⁹ This trial is the largest randomized controlled trial powered for mortality that compares low-dose vasopressin with norepinephrine infusion in patients with septic shock.²⁰

Vasopressin Receptors

Three types of vasopressin receptors are located throughout the body (Table 2). Vasopressin V1 receptors are located in vascular smooth muscle in the systemic, splanchnic, renal, and coronary circulations.⁸ V1 receptors are also found in the kidneys, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, and testis.¹⁴ Stimulation of these receptors causes vasoconstriction through several mechanisms. Vasoconstriction is mediated by activating Ca^{2+} channels to allow influx of extracellular Ca^{2+} to maintain balance. The

Table 2: Vasopressin Receptors^a

Vasopressin Receptors	Location
V1	Vascular smooth muscle in the systemic, splanchnic, renal, and coronary circulations Kidneys, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, and testis
V2	Distal convoluted tubules and medullary collecting ducts in the kidneys Endothelium
V3	Pituitary

^aData were derived from Holmes et al.¹⁴

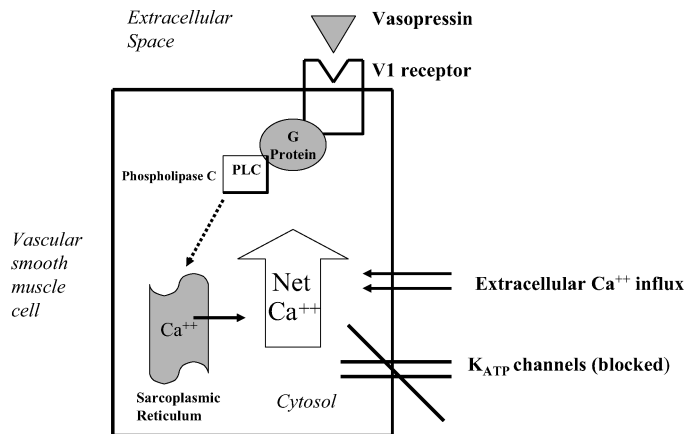


Figure 2: Depiction of movement of intracellular contents with vasopressin activation. Abbreviations: K_{ATP}, adenosine triphosphate-activated potassium channels; Ca²⁺, calcium; PLC, phospholipase C.

membrane or arterial smooth muscle, which is regulated by potassium channels, is an important regulator of arterial tone. The opening of potassium channels closes voltage-dependent Ca²⁺ channels, thereby decreasing Ca²⁺ entry, which leads to dilation. Septic shock is associated with the excessive activation of K_{ATP} channels.¹⁴ K_{ATP} channels are blocked by vasopressin in a dose-dependent manner.¹⁴

Stimulation of V1 receptors enhances the vasoconstrictor action of catecholamines by enhancing the sensitivity of vascular smooth muscle to sympathetic stimulation in a dose-dependent manner, an effect that may restore vascular tone in patients with septic shock. It mediates vasoconstriction by G(q) receptor-coupled activation of phospholipase C and release of Ca²⁺ from intracellular stores⁸ (Figure 2). G proteins are cell membrane proteins that function as intermediaries between hormone receptors and effector enzymes and enable the cell to regulate its metabolism in response to hormonal changes. The sarcoplasmic reticulum, which holds the Ca²⁺ stores, transiently increases the cytoplasmic levels of Ca²⁺. Sustained increases in Ca²⁺ levels are achieved through the extracellular influx of Ca²⁺.⁸ This increase in Ca²⁺ contributes directly to contraction of the vascular smooth muscle cell, resulting in vasoconstriction. The administration of exogenous vasopressin results in heart rate reduction, which may be due to baroreflex greater than that observed with other vasoconstrictors such as norepinephrine and dopamine.¹⁴ This reflex, which decreases

heart rate when blood pressure increases, is mediated through increased vagal tone. Vasopressin causes a leftward shift of the heart rate-arterial pressure barocurve by acting on the V1 receptors in the brain, thereby rendering systemic hypertensive effects less than those obtained with other vasoconstrictors through heart rate reduction.^{14,15} Vasoconstriction effects of vasopressin are potent in the skin, skeletal muscle, fat, pancreas, and thyroid gland. Impaired vasoconstriction is observed in the coronary and cerebral circulations, which may be due to additional NO-mediated vasodilating effect of vasopressin on these circulations.¹⁴ Reductions in heart rate and cardiac output are due to increased vagal tone, decreased sympathetic tone, and decreased coronary blood flow at high circulating levels.¹⁴

V2 receptors are located in distal convoluted tubules and medullary collecting ducts in the kidneys. Stimulation of these receptors produces the antidiuretic effect of vasopressin and contributes to urine concentration by increasing the medullary concentration gradient.⁵ It induces selective decrease in inner medullary blood flow along the loops of Henle and collecting tubule without altering the cortical blood flow along the glomeruli and proximal and distal convoluted tubules. This allows for increased urine concentration and decreased urine output. However, in the setting of shock, vasopressin may actually increase urine output by maintaining glomerular perfusion pressure.²¹ Glomerular perfusion pressure depends on the pressure gradient created by dilating and

constricting the afferent and efferent arterioles, respectively. One study compared the microvascular effects of vasopressin and norepinephrine and concluded that norepinephrine decreased the lumen size of both the afferent and efferent arterioles to nearly 100% whereas only the efferent lumen was vasoconstricted in the vasopressin population.²² This preserves the pressure gradient and permits maintenance or glomerular perfusion pressure. Patel et al²³ found that AVP infusion increased urine output and creatinine clearance in severe septic shock in comparison with norepinephrine alone. Vasopressin could prove to be advantageous in preserving renal blood flow and controlling hypotension in comparison with other adrenergic agonists.¹⁵

The V2 receptor pathway occurs when V2 receptors interact with adenylyl cyclase and couple with the G(s) protein-receptor complex. This increases intracellular second messenger cyclic adenosine monophosphate, which facilitates the insertion of aquaporin-2 water channels into the luminal surface of the renal collecting duct cells. This regulates the permeability of the kidneys to water and maintains homeostasis. V2 receptors are also located on the endothelium. Vasorelaxation occurs in selected organs and appears to be NO mediated.⁸ In the cerebral, coronary, and pulmonary artery circulations,⁵ an increase in intracellular calcium activates constitutive eNOS to release NO, thus resulting in vasodilation.

V3 receptors are located in the anterior pituitary gland. Stimulation of the V3 receptors increases ACTH release.⁸ It also stimulates the activation of different G proteins and increases intracellular cyclic adenosine monophosphate.

Summary

Increased NO levels inhibit the release of vasopressin and may contribute to the relative vasopressin deficiency in septic shock. A vasopressin deficiency can lead to an adrenal insufficiency via inhibition of the HPA axis. This may contribute to vasopressor resistance due to downregulation of catecholamine receptors and decrease transcription and expression of genes for catecholamines. Low levels of angiotensin II and dopamine stimulate the release of vasopressin; however, stores may be depleted in the ongoing circulatory failure. Exogenous administration in the setting of septic shock has been shown to increase blood pressure, whereas it does not increase blood pressure in a healthy individual.⁸

Case Study Application

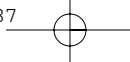
As seen in our case study, supplementation of exogenous vasopressin leads to less dependence on vasopressors, potentially due to a relative vasopressin deficiency. The volume-resuscitated patient required 30 mcg/min of norepinephrine to maintain systolic blood pressure of 90 mm Hg. When vasopressin was added to the therapeutic regimen, vasopressor resistance decreased and acceptable blood pressure level was maintained. The cessation of physiologic doses of vasopressin quickly led to an escalation in norepinephrine doses and subsequent restarting of the drug. Although the impact of vasopressin on overall survival is debatable, there may be some potentially beneficial physiologic effects in using low-dose vasopressin. It is a catecholamine-sparing adjunct to therapy that may increase creatinine clearance and urine output. The 2008 Surviving Sepsis Campaign international guidelines for management of severe sepsis and septic shock recommends the use of norepinephrine or dopamine as a first-choice drug for hypotension.²⁴ Low-dose vasopressin, as an adjunct to norepinephrine, may be beneficial in raising blood pressure levels for patients in septic shock refractory to conventional vasopressor agents. It is recommended that vasopressin may be added to norepinephrine at a dose of 0.03 units/min.

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