

## Sepsis: Is There Room for Vasopressin?

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**Abstract.** Cardiovascular dysfunction contributes importantly to the high mortality of septic shock, which remains in excess of 50%. Non-survivors are characterized by an inadequate response to fluid resuscitation and catecholamine infusions. A number of recent reports suggest that vasopressin, a non-catecholamine vasopressor, may contribute usefully to the cardiovascular management of septic shock and other forms of vasodilatory shock. Here we review the clinical studies to date of vasopressin use in septic shock and other vasodilatory shock. We then review the known physiology of vasopressin to help understand why vasopressin may be beneficial in this setting. In general, humans having severe vasodilatory shock demonstrate low endogenous vasopressin blood concentration. Low-dose vasopressin infusion in this setting increases blood vasopressin concentration to that observed in hypotension of other causes, results in an increase in mean arterial pressure, and reduces the need for additional  $\alpha$ -adrenergic vasopressor infusions. Current studies in low numbers of patients suggest that low-dose vasopressin may increase urine output in this setting. Vasopressin infusion increases blood pressure by V1 receptor stimulation on vascular smooth muscle. This vasoconstrictor effect is less pronounced in the cerebral, coronary, and renal circulations. Diminished vasoconstriction in some regional circulations may be contributed to by nitric oxide-mediated vasodilation resulting from oxytocin receptor stimulation by low-dose vasopressin. Thus, low-dose vasopressin infusion may be a useful adjunct to fluid resuscitation and catecholamine infusion in severe septic shock and other forms of vasodilatory shock.

**Keywords.** sepsis, shock, vasopressin, hemodynamics

### Introduction

Septic shock is the most common cause of death in intensive care units [1] and the thirteenth most common cause of all deaths in North America from 1979 to 1987 [2]. Cardiovascular dysfunction contributes importantly to the high mortality of septic shock, which remains in excess of 50% [3]. Current cardiovascular management of septic shock involves fluid administration and use of inotropes and vasopressor agents [2]. Non-survivors of septic shock are characterized by persistent vasodilation [4] and failure to increase mean arterial pressure and cardiac output in response to resuscitation [5,6]. Thus, the goals of cardiovascular management of septic shock are to maintain an ade-

quate arterial perfusing pressure, cardiac output, and oxygen delivery to vital organs.

Catecholamines are most often used to achieve these goals. Recent studies favor norepinephrine as an effective vasopressor to maintain an adequate mean arterial pressure during septic shock [7]. However, a wide array of catecholamines, including norepinephrine, epinephrine, phenylephrine, dopamine, dopexamine, dobutamine, and others are used in the cardiovascular management of septic shock. All of these catecholamines have important adverse effects. Alpha-adrenergic effects of norepinephrine and other catecholamines decrease cardiac output and oxygen delivery. Regionally, at higher doses,  $\alpha$ -agonists can significantly decrease renal and mesenteric blood flow and may contribute to renal, gut, and other organ failure in septic shock [8]. Arrhythmias may result from  $\beta$ -adrenergic effects. Over a short time, vascular and cardiac responsiveness to  $\alpha$ - and  $\beta$ -adrenergic agonists diminishes [9,10].

In view of these concerns, recent studies have examined vasopressor agents acting via alternative pathways. For example, nitric oxide synthase (NOS) inhibitors increase blood pressure in patients having septic shock. Unfortunately, non-selective NOS inhibition detrimentally reduces cardiac output and increases mortality [11]. In contrast, a number of preliminary reports of the use of vasopressin in septic shock and other forms of vasodilatory shock are encouraging. Here we review this preliminary data and, based on this, speculate that a clear role for vasopressin in the cardiovascular management of septic shock will be identified in upcoming clinical trials.

### Human Trials of Low-Dose Vasopressin

In 1991 Morrison, Doepfner, and Park commented on the possible use of vasopressin to treat septic shock in

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Support: Keith R. Walley is a BC Lung Association/St. Paul's Hospital Foundation Scientist

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humans [12]. It was not until 1997 that the first reports of vasopressin use in humans were published [13]. Subsequently, a number of human trials of vasopressin in the management of human septic and distributive shock have been reported. The human trials of low-dose ( $\leq 0.1$  U/min) vasopressin in vasodilatory shock are shown in Table 1. There are ten trials to date; 3 in septic shock patients [13–15], 5 in post-bypass patients [16–19] (including one in children [20]), one in organ donors with vasodilatory shock [21] and one in patients with milrinone-induced hypotension [22]. All trials were designed to look at hemodynamic endpoints only. All trials show an increase in blood pressure and decrease or discontinuance of catecholamine infusions. Increased urine output following vasopressin infusion was found in 3/5 patients in one trial [13]. Low plasma vasopressin levels were found in 3 patient subtypes in 5 trials; septic shock [13], post-bypass vasodilatory shock [16,17] and organ donors having vasodilatory shock [21]. Only 2 trials were randomized, controlled trials; one in 10 trauma patients in septic shock ( $n = 10$ ) [15], and one in 10 patients having vasodilatory shock post implantation of left-ventricular-assist-device [16]. Both of these trials used normal saline as the control intervention.

The first of these ten studies was a case series by Landry and co-workers that reported the effects of vasopressin administration to five patients having septic shock [13]. He found that vasopressin administration in very low doses (0.01–0.05 U/min) was effective in raising mean arterial pressure and, in three patients, norepinephrine could be discontinued. Interestingly, 3/5 patients had a marked increase in urine output on vasopressin infusion. In normal humans, much higher doses of vasopressin exert little or no pressor effect [23,24]. He concluded that patients with vasodilatory septic shock have an exquisite pressor sensitivity to low-dose vasopressin.

Subsequently Landry and colleagues reported in 1997 that low serum levels of vasopressin are found in patients having advanced vasodilatory septic shock [14]. Nineteen patients with septic shock were compared to 12 patients with cardiogenic shock. Patients having septic shock had baseline vasopressin levels of  $3.1 \pm 0.4$  pg/ml while patients with cardiogenic shock with comparable hypotension had vasopressin levels of  $22.7 \pm 2.2$  pg/ml. Again, contrary to normal subjects, in whom higher doses of vasopressin have little pressor effect [23,24], low-dose infusions of vasopressin at 0.04 units/min increased systolic blood pressure from 92 to 146 mmHg in the septic shock patients [14]. This was due to increased systemic vascular resistance by 79%; cardiac output decreased by 12%. He concluded that septic shock is a unique state characterized by a deficiency of endogenous vasopressin.

An important finding in Landry's study [14] was that infusion of exogenous vasopressin restored plasma vasopressin levels. Infusion of 0.01 U/min in 2 patients increased plasma concentrations to 27 and 34

pg/ml. Additionally, infusion of 0.04 U/min been previously found to yield levels of 100 pg/ml [25].

More recently Malay and co-workers randomized patients with septic shock to receive either vasopressin at 0.04 units/min ( $n = 5$ ) or normal saline as placebo ( $n = 5$ ). The study was blinded and groups were similar at the start of the study. One hour after initiation of the study drug, mean arterial pressure significantly increased in the treatment group. This increase in blood pressure was attributable to an increase in systemic vasoconstriction. Cardiac index, heart rate and pulmonary artery pressures were relatively unchanged. Two patients in the placebo group died within 24 hours of entry into the study; both died of refractory hypotension. At 24 hours, all standard vasopressor agents in the treatment arm could be withdrawn compared with only one patient in the placebo arm. Serum sodium, base deficit and serum creatinine were unchanged in the treatment group. Importantly, throughout the study there were no observed adverse cardiac events or episodes suggestive of mesenteric ischemia.

Argenziano and co-workers studied the effects of vasopressin infusion in patients with distributive shock following placement of a left ventricular assist device. Those patients having a mean arterial pressure less than 70 mm/Hg despite a norepinephrine infusion of 8  $\mu$ /min were randomized to receive vasopressin at 0.10 units/min or placebo. Vasopressin increased mean arterial pressure from 50 to 84 mmHg and allowed reduction in the norepinephrine infusion rate. Similar to septic shock, plasma vasopressin concentrations were low in these post-cardiopulmonary bypass surgical patients. In a retrospective study, this same group of investigators confirmed the observation that vasopressin plasma concentrations are decreased post-cardiac pulmonary bypass in patients with vasodilatory shock. Vasopressin administration once again increased mean arterial pressure and reduced the requirement for catecholamine pressor agents. A similar retrospective analysis by Morales and colleagues [19] in 50 patients demonstrated that vasopressin infusion increased mean arterial pressure and reduced pressor requirements.

Rosenweig and colleagues administered vasopressin to 11 critically ill children with refractory vasodilatory shock post-cardiac surgery [20]. Similar to the above reported studies, these investigators found low plasma levels of vasopressin (4.4 pg/ml), an increase in blood pressure following initiation of vasopressin infusion, and a reduced need for other pressor agents. Two smaller studies reported by Chen and colleagues [21] and Gold and colleagues [22] demonstrated similar results upon initiation of vasopressin infusion in organ donors with vasodilatory shock and in milrinone-induced hypotension.

We conducted a prospective randomized controlled trial of norepinephrine versus vasopressin in 8 patients having septic shock [26]. A four-hour infusion of vaso-

**Table 1.** *Trials of low-dose vasopressin in human vasodilatory shock*

First author	Ref.	Date	Trial	N	Patients	Endpoint	Findings	Mortality
Landry DW	[13]	1997	Case Series	5	Septic Shock	Hemodynamic	A, B, C	3/5
Landry DW	[14]	1997	Matched Cohort	19	Septic Shock	Hemodynamic	A, B, D in Septic Group	Not stated
Malay MB	[15]	1999	RCT	12	Cardiogenic Shock			
Argenziano M	[17]	1999	Placebo: N/S	10	Septic Shock—Trauma	Hemodynamic	A B in Treatment Arm	0/5 in VP 2/5 in placebo
Argenziano M	[16]	1998	Retrospective	40	Post-bypass	Hemodynamic	A, B, D	
Argenziano M	[18]	1997	Case Series	10	Vasodilatory Shock	Hemodynamic	A, B in Treatment Arm	Not stated
Argenziano M	[18]	1999	RCT	10	Vasodilatory Shock	Hemodynamic	A, B in all	
Rosenzweig EB	[15]	1999	Placebo: N/S	20	post LVAD Implant	Hemodynamic	A, B	
Morales DL	[19]	1999	Case Series	11	Vasodilatory Shock	Hemodynamic	A, B, D	2/11: low CO
Chen JM	[21]	2000	Case Series	50	Post Cardiac Transplant	Hemodynamic	A, B, D	
Gold J	[22]	2000	Case Series	7	Pediatric—Vasodilatory Shock Post Bypass	Hemodynamic	A, B, C	
					Post LVAD Implantation	Hemodynamic	A, B	Not stated
					Organ Donors with Vasodilatory Shock	Hemodynamic	A, D	Not stated
					Mirinone-hypotension	Hemodynamic	A, B, C	Not stated

RCT: randomized, controlled trial, LVAD: left ventricular assist device, N/S: normal saline, VP: vasopressin, CO: cardiac output

FINDINGS: A: Increase in blood pressure, B: Decrease or discontinuance of catecholamines, C: Increase in urine output, D: Low plasma vasopressin levels in subjects.

pressin produced a significant increase in mean arterial pressure and decreased pressor requirements. Urine output did not change from baseline to 4 hours in the norepinephrine group but more than doubled from baseline to 4 hours in the vasopressin group. Pulmonary vascular resistance decreased significantly in the vasopressin group but did not change in the norepinephrine group. Vasopressin did not appear to have deleterious effects on other organ perfusion and function. Specifically, gastric-arterial  $\text{PCO}_2$  gradient did not change in either group. There was no evidence of coronary hypoperfusion (no change in ST segments, no arrhythmias and no change in cardiac index). Thus, the principal findings of this preliminary study are that, compared to a hemodynamically equivalent dose of norepinephrine, vasopressin infusion in patients with severe septic shock significantly increased urine output, decreased pulmonary vascular resistance, and had no measurable adverse impact on perfusion of the heart or gut while maintaining mean arterial pressure and cardiac output.

We have recently conducted a retrospective review of all patients in our institution who received vasopressin infusion for septic shock [27]. We identified 45 critically ill patients who received vasopressin for more than 2 hours for septic shock. Generally these patients had severe refractory septic shock where vasopressin was used as rescue therapy on a compassionate basis. The average age was  $60 \pm 14$  years, the average APACHE II score was  $28 \pm 6$ . The average dose of vasopressin used was 0.05 units/min (range 0.01 to 0.6 units/min) and hospital mortality was 85%. Mean arterial pressure on infusion of vasopressin increased significantly by 18% at 4 hours and remained at that level 24 and 48 hours later ( $p < 0.01$ ). Systolic pulmonary artery pressure remained unchanged on infusion at 45 mmHg. Mean cardiac index decreased by 11% at 4 hours and did not change past that time point. Urine output compared to baseline (excluding anuric patients) increased 79% at 4 hours ( $p = 0.01$ ), 37% at 24 hours and 77% at 48 hours for patients still alive and on vasopressin. Mean dosage of catecholamine vasopressors decreased by 33% at 4 hours ( $p = 0.01$ ), decreased by 53% at 24 hours ( $p < 0.01$ ), and decreased by 48% at 48 hours compared to baseline. We concluded that vasopressin use in this unselected group of patients in late septic shock had a beneficial effect on hemodynamic indices and urine output and spared conventional pressor agents.

In summary, there is only one published randomized controlled trial of vasopressin in septic shock [15] and it was a small trial designed to examine hemodynamic endpoints. The results of hemodynamic studies and retrospective case series suggest that vasopressin can restore vasomotor tone in septic shock and may preserve end-organ perfusion. Whether this will translate to improved morbidity (less organ failure) and improved mortality has not been shown. A review of the physiology of vasopressin suggests a number of poten-

tial mechanisms of vasopressin's effects during septic/distributive shock

### Summary of Vasopressin Physiology

Vasopressin is synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus [28], then migrates to the axonal terminals of these cells located in the posterior pituitary, and is stored in granules. Vasopressin synthesis, transport and neuro-hypophysial storage takes between 1 and 2 hours [29]. Vasopressin release is regulated largely in response to hypotension and hyperosmolality although central nervous system input and other circulating hormones and mediators influence synthesis and release.

Hypotension is the most important non-osmotic stimulus to vasopressin release. A decrease in blood pressure, sensed by aortic arch and carotid sinus arterial baroreceptors, reduces the normal tonic inhibitory discharge of these receptors thus leading to increased vasopressin release [30–35]. Stretch receptors in the left atrium and ventricles more closely reflect changes in blood volume, have a lesser impact on vasopressin release, and act primarily via atrial natriuretic peptide, sympathetic stimulation and renin release [36–40]. Interestingly, increased vasopressin levels due to hypotension do not disrupt osmoregulation because hypotension shifts the plasma osmolality-vasopressin relationship so that higher plasma vasopressin levels are required to maintain normal osmolality [41–43].

V1 vascular receptors (V1R, formerly known as V1a receptors) on vascular smooth muscle mediate vasoconstriction. V2 renal receptors (V2R) on renal collecting duct and endothelial cells mediate the antidiuretic effects of vasopressin [44]. Vasopressin can also stimulate oxytocin receptors (OTR) and mediate a vasodilatory response via stimulation of the nitric oxide pathway on endothelial cells in some vascular beds [45].

Serum vasopressin levels in humans are normally less than 4 pg/ml [46]. Increased serum osmolality due to water deprivation increases vasopressin levels to 10 pg/ml [47]. Hypotensive hemorrhage increases serum levels to 100–1000 pg/ml [34,48,49]. Under normal conditions vasopressin has little effect on vascular smooth muscle [50,51]. Vasopressin is a weak pressor when the autonomic system is intact because vasopressin reduces heart rate to a greater extent than observed with other vasoconstrictors [52–54]. Plasma vasopressin levels in excess of 50 pg/ml increase in mean arterial blood pressure in humans and in animals [25,48]. Thus, vasopressin normally has little impact on blood pressure but during hypotension and hypovolemia, vasopressin helps maintain arterial blood pressure [41,43,55–57].

Cerebral, coronary, and renal vasculature is particularly resistant to the vasoconstrictor effects of vasopressin [58–60]. In the kidney the efferent arteriole is

more vasopressin sensitive than the afferent arteriole [61], an effect that could help explain the increase in urine output after vasopressin administration in some disease state [62]. Low dose vasopressin in humans with hepatorenal syndrome and congestive heart failure, may induce diuresis with variable effects on creatinine clearance [62].

### **Potential Mechanisms of Vasopressin's Beneficial Effects**

Sepsis and shock induce a marked increase in vasopressin levels very early in many species [63,64], yet paradoxically, late septic shock is associated with a relative deficiency of vasopressin. Wilson and coworkers demonstrated an early peak and plateau in plasma levels of vasopressin during shock induced by *E. Coli* in the baboon (>300 pg/ml) and by endotoxin in the anesthetized dog (>500 pg/ml) [63] within 15 minutes of infusion of *E. Coli* or endotoxin. However, later in shock vasopressin levels decrease substantially [64]. Landry has subsequently described a relative deficiency of vasopressin in 19 patients having septic shock [14]. Other forms of vasodilatory shock have also been associated with inappropriately low plasma vasopressin levels [16,20,21] yet patients in cardiogenic shock had appropriately elevated levels of vasopressin [14].

The mechanisms of vasopressin deficiency in septic shock (relative to cardiogenic shock) are not known. Increased peripheral degradation of vasopressin is unlikely because exogenous infusion restores serum vasopressin levels [14,25]. Potential mechanisms of decreased vasopressin production include 1) depletion of vasopressin stores by excessive baroreceptor firing, 2) autonomic insufficiency, and 3) inhibition of vasopressin release by exogenous norepinephrine administration or by endogenous NO released by vascular endothelium during sepsis. First, only 10–20% of total vasopressin stores within the posterior pituitary can be readily released. Once excessive baroreceptor firing has resulted in this degree of release, vasopressin secretion is greatly diminished in response to stimuli [29]. Second, sympathetically mediated heart rate variability is decreased during sepsis in proportion to disease severity [65] indicating impaired autonomic function. Furthermore, baroreflex-mediated bradycardia is absent during vasopressin infusion, implicating autonomic insufficiency in these patients [14]. Autonomic insufficiency may also explain the increased sensitivity of septic shock patients to exogenous vasopressin because when compensatory mechanisms are impaired there is unmasking of the vasoconstrictor activity of vasopressin, increasing blood pressure [25,66]. Third, norepinephrine has been reported to inhibit vasopressin and oxytocin release via  $\alpha_2$ - or possibly  $\beta$ -adrenoreceptors. However, norepinephrine may also stimulate vasopressin release [67] via  $\alpha_1$ -adrenoreceptors [68] so that the effect of  $\alpha$ -agonist administration depends on a bal-

ance of factors. Finally, increased NO production by vascular endothelium in the supraoptic and paraventricular nuclei during sepsis may down-regulate vasopressin production [69] since administration of L-arginine and NO donors *in vitro* and *in vivo* inhibit vasopressin secretion [70].

During hypotension vasopressin normally helps maintain arterial blood pressure by acting as a potent vasoconstrictor acting on the V1 receptor of vascular smooth muscle via the same phosphatidylinositol second messenger system as catecholamines [71]. Thus, vasopressin can act synergistically with, or as an alternative agent to adrenergic agents [72]. An additional mechanism of vascular collapse during septic shock may be due to excessive activation of ATP-sensitive  $K^+$  channels [73]. Opening of  $K_{ATP}$  channels causes membrane hyperpolarization and closing of voltage-dependent  $Ca^{2+}$  channels decreases calcium entry and leads to vasodilation of vascular smooth muscle [74]. Vasopressin modulates smooth muscle tone by blocking the  $K_{ATP}$  channel [75].

There is, therefore, a physiologic rationale for restoring endogenous vasopressin levels during septic shock and identified reasons why vasopressin may be a particularly useful agent in increase arterial blood pressure during septic shock.

### **Summary and Recommendations**

Vasopressin deficiency may contribute to the refractory hypotension of late, unresolving septic shock. Infusion of exogenous vasopressin can restore plasma levels to values found during comparable degrees of hypotension from other causes. Vasopressin infusion increases mean arterial pressure and reduces the need for conventional exogenous catecholamine infusion. It is not yet known whether infusion of vasopressin in severe septic shock or SIRS increases survival or decreases “multiple system organ failure”.

In “pharmacologic” doses, (i.e., > 0.1 U/min, giving plasma levels of >100 pg/ml) vasopressin's pressor effect is associated with potentially deleterious vasoconstriction of renal, mesenteric, pulmonary, and coronary vasculature. In lower, more “physiologic” doses (i.e., 0.01–0.04 U/min yielding plasma levels of 20–100 pg/ml), vasopressin restores vascular tone by activating V1 receptors, by blockade of  $K_{ATP}$  channels, and by synergistic effects with exogenous catecholamines. Low-dose vasopressin may be vasodilating in some vital vascular beds. A reasonable rationale for using vasopressin in septic shock would be to restore vasopressin levels to normal, i.e., 20–30 pg/ml, without renal, mesenteric or coronary ischemia, or other effects. We emphasize that clinical use of vasopressin should await a randomized controlled trial of vasopressin's effect on clinical outcomes such as organ failure and mortality.

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