



Vasopressin and septic shock

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ABSTRACT

Septic shock continues to be one of the leading causes of death in the Intensive Care Units. When the shock state persists after adequate fluid resuscitation, vasopressor therapy is required to improve and maintain adequate tissue/organ perfusion in an attempt to improve survival and prevent the development of multiple organ dysfunction and failure. Various studies have suggested that exogenous administration of arginine vasopressin may be an effective adjunctive therapy to traditional catecholamines for the management of hypotension during septic shock. Vasopressin is both a vasopressor and an antidiuretic hormone. It also has hemostatic, gastrointestinal 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. Vasopressin infusion of 0.01 to 0.04 U/min in patients with septic shock increases plasma vasopressin levels. Current guidelines from the Surviving Sepsis Campaign recommend arginine vasopressin 0.03 unit/minute may be added to norepinephrine with the anticipation of an effect equal to higher doses of norepinephrine alone. Clinicians must be knowledgeable about the use of vasopressin in septic shock, including controversial areas where guidelines do not always provide solid recommendations.

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Introduction

Vasopressin, also known as antidiuretic hormone (ADH) is crucial for osmoregulation, cardiovascular control and homeostasis. Vasopressin has been extensively studied and used clinically over the past 5 decades to treat upper gastrointestinal bleeding, central diabetes insipidus and bleeding disorders. Emerging bodies of evidences suggest new indications for vasopressin in the management of septic shock and vasodilatory shock (Systemic Inflammatory Syndrome [SIRS] with hypotension) from other causes (1).

Sepsis is the main cause of multiple organ failure (MOF) and remains a concern because of its associated high morbidity and mortality (2). Outcome improvement requires understanding the pathophysiology, recognizing the process early and finally finding an effective therapy. There is evidence that microcirculatory and mitochondrial dysfunction plays a role in the development of sepsis-induced organ failure (3). There are some selected therapeutic agents such as Activated Protein C that have been used to improve and preserve microcirculatory function in sepsis (4). Vasopressin especially epinephrine and norepinephrine maintain perfusion pressure but impair the microcirculatory function (5). In the treatment of sepsis, vasopressin exhibit organ-specific heterogeneity in vascular responsiveness compared to norepinephrine (5)

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and could be a potential therapy instead of norepinephrine for the treatment of septic shock regarding improvement in microcirculatory function. Thus the goal of this review is to understand the physiology of vasopressin relevant to septic shock based on the latest trial.

Physiology of vasopressin

Synthesis and Release

Vasopressin is a nonopeptide synthesized as a prohormone in magnocellular neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. It is bound to a carrier protein, neurohypophysin and migrated via the supraoptic- hypophyseal tract to the axonal terminals of magnocellular neurons located in the posterior pituitary (6). Only 10% to 20% of the total hormonal pool within the posterior pituitary can be readily released, after that vasopressin continues to be secreted in response to appropriate stimuli but at a reduced rate (7). Secretion of vasopressin in septic shock is biphasic (high levels early and low levels later) that could be related to this special pattern of secretion. The whole process of synthesis, transport and storage take 1-2 hours (8).

The most important stimuli that evoke vasopressin release are increased plasma osmolality (osmotic regulation) and severe hypovolemia and hypotension (hypovolemic regulation). Pain, nausea, hypoxia, pharyngeal stimuli and endogenous and exogenous chemical mediators also increase vasopressin release (9, 10).

Hyperosmolarity is sensed by both central and peripheral osmoreceptors. Central osmoreceptors located in region of the brain excluded from the blood brain barrier and detected plasma osmolality. Peripheral osmoreceptors are found in the portal veins which allow early warning of ingested food and fluid osmolality. Signals are transmitted via the vagus to the nucleus tractus solitaries, area postrema and ventrolateral medulla and finally to the paraventricular nuclei and supraoptic nuclei where vasopressin is synthesized (10, 11).

Plasma volume and arterial pressure also modify vasopressin release. A 20-30% reduction in Mean Arterial Pressure (MAP) is needed to induce a response through stimulation of receptors in aortic arch and carotid sinuses. An 8-10% reduction in plasma volume detected by baroreceptors in the atrium and ventricles is required to induce an exponential increase in vasopressin release (12). Reduction in MAP increases plasma vasopressin concentration while norepinephrine and renin increase following a reduction in plasma volume (13).

Acetylcholine, histamine, nicotine, dopamine, prostaglandins, angiotensin II and other catecholamines directly stimulate vasopressin release (11). Of relevance to critical illness, high PaCO₂ or low PaO₂ stimulate carotid body

chemoreceptors and thus increase vasopressin levels. Inhibitors of vasopressin release include opioids, β -aminobutyric acid, and arterial natriuretic peptide. Neurohormonal inhibition of vasopressin release is mediated by Nitric Oxide (NO) via cyclic guanosine monophosphate (14) which may be important during sepsis.

Norepinephrine inhibits vasopressin release via both α_1 and α_2 adrenoreceptors in magnocellular nuclei (15).

Vasopressin metabolism

Vasopressin is rapidly metabolized by liver and kidney vasopressinases and has a half life of 10-35 minutes. Normal vasopressin levels are 0.5-5 pg/ml in overnight fasted, hydrated humans (16). Water deprivation increase plasma osmolality and raises vasopressin to 10 pg/ml (17). Maximal increase in urine osmolality requires vasopressin levels \geq 20 pg/ml.

Vasopressin and septic shock

A biphasic response to vasopressin concentration is observed in septic shock with high concentration ($>$ 500 pg/ml) in the early phase to maintain organ perfusion, but as the shock state progress, plasma vasopressin fall for reasons that are not entirely clear (18, 19). A relative vasopressin deficiency was more likely to occur after 36 hours from the onset of shock in approximately one-third of late septic shock patients (20).

Importantly, vasopressin levels in established septic shock and vasodilatory shock are low (21, 22). Possible reasons include exhaustion of stores, autonomic nervous system dysfunction and elevated norepinephrine levels which have a central inhibitory effect on vasopressin release (21, 22). Finally increased NO production by vascular endothelium within the posterior pituitary sepsis may inhibit vasopressin production (23).

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Vasopressin receptors

It is important to understand the various vasopressin receptors in septic shock to fully understand the effects of vasopressin. V1 vascular receptors mediate vasoconstriction and are located on vascular smooth muscle. V1 receptors are found in the kidney, myometrium, bladder, adipocytes, platelets, spleen and testis. These G-protein coupled receptors activate phospholipase-C via Gq G-protein which ultimately leads to an increase in intracellular calcium (24).

V2 receptors are predominantly located in the distal tubule and collecting ducts of the kidney. These receptors activate adenyl cyclase to increase cyclic adenosine monophosphate. This mobilizes aquaporin channels, which are inserted into the apical membrane of the renal collecting duct cells and endothelial cells. V2 receptors are responsible for antidiuretic effects of vasopressin. V3 pituitary receptors have central effects, such as increasing

adrenocorticotrophic hormone (ACTH) production (25). Vasopressin has equal affinity for oxytocin receptors (OTRs) as oxytocin. Activation of these receptors raises intracellular calcium via the phospholipase C and phosphoinositide pathway. They are found predominantly on myometrium and vascular smooth muscle. OTRs also mediate a calcium-dependent vasodilatory response via stimulation of the NO pathway on endothelial cells which is important in septic shock (25, 26).

Effects of vasopressin

Vasopressin has multiple physiologic effects. Vasopressin has a direct vasoconstrictor effect on systemic vascular smooth muscle via V1 receptors and osmoregulation and maintenance of normovolemia mediated by V2 receptors in the kidney. At certain concentrations vasopressin provokes vasodilation in some vascular regions via OTRs. Vasopressin also acts as an ACTH secretagogue, functions in maintaining homeostasis, has GI effects, and plays a role in temperature regulation, memory and sleep cycles.

Vasoconstrictor effects

Under physiological conditions, vasopressin has only a minor effect on arterial pressure (27). This moderate effect can be explained by the indirect bradycardic effect resulting from vasopressin's action on baroreflexes. This effect on baroreflex is mediated by the central V1 receptors (28). Plasma vasopressin levels of 50 pg/ml must be attained before any significant increase in MAP (29).

Sepsis causes a down regulation of V1 receptors, an effect mediated through pro-inflammatory cytokines (30). Endotoxines, through cytokines, initiate a vasodilatory effect on the vessels, which is NO mediated. The norepinephrine response to endotoxine attenuates quickly, but the vasopressin vasoconstricting effect lasts several hours longer than norepinephrine and has a positive effect on the contracting abilities of norepinephrine (31). 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 (32). Endotoxic shock is associated with excessive activation of K-ATP channels.

The hemodynamic responses on administered vasopressin in patients with advanced vasodilatory shock are independent of baseline vasopressin concentrations (33), suggesting that vasopressin has a direct pharmacologic effect, rather than the effect of only the replacement of the vasopressin deficiency.

In situation like sepsis where the baroreflex receptor system is impaired, vasopressin effect is clearer. The normally occurring leftward shift of heart rate-arterial baroreflex curve through V1 receptor is absent and the

vasopressin causes an increase in blood pressure, without increasing heart rate (34).

Vasopressin is a potent vasoconstrictor in skin, skeletal muscle, fat, pancreas and thyroid gland. In contrast vasopressin causes less vasoconstriction in mesenteric, coronary and cerebral circulation (35, 36). Less vasoconstriction in coronary and cerebral circulations may be due to the additional NO-mediated vasodilating effect of vasopressin on these circulations (37). The effect of vasopressin on the 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 (27).

Vasodilatory effect

The vasodilatory effect of certain vascular regions is another difference between vasopressin and catecholamines in septic shock such as production of NO at the level of the endothelial cells (14). The vasodilation effect occur at low concentrations. Vascular regions response differently to vasopressin. For example arteries of the circle of Willis are more sensitive to the vasodilatory effect of vasopressin than other intracranial and extracranial arteries (38).

V2 and OTR receptors might be involved in vasodilatory effect of vasopressin, however all of the studies suggest that vasopressin include vasodilation is mediated through NO release (26). Vasopressin may provoke vasodilation of the pulmonary artery both under physiological and hypoxic condition; this effect is mediated by V1 receptors that cause release of endothelium-derived NO (39).

Renal effect

The renal effect of vasopressin is different from other catecholamines. In response to blood hyperosmolarity it reduces urine output through its action on the V2 receptors, which induce re-absorption of water. Vasopressin contributes to further concentration of urine by increasing medullary concentration gradient by activating a distinct urea transporter (40). Paradoxically, vasopressin has diuretic properties in case of hepatorenal syndrome, congestive heart failure (41) and septic shock (42). The mechanisms are poorly understood. Possible mechanisms include down regulation of the V2 receptors, NO-mediated afferent arteriolar vasodilation, selective efferent arteriolar vasoconstriction and OTR-activated natriuresis (43).

Some studies recently reported a significant improvement in diuresis and creatinine clearance in patients with septic shock under vasopressin treatment as compared with patients treated with norepinephrine (5, 44). All of the investigators who found a beneficial effect following treatment with vasopressin for septic

shock used minimal doses, however high levels of vasopressin (pressor doses), cause a dose-dependent fall in renal blood flow, glomerular filtration rate and sodium extraction (45).

Other organ system effects

Vasopressin increase cortisol, which could be relevant in patients with septic shock. Vasopressin acts on the corticotrophic axis by potentiating the effect of the corticotrophin-releasing hormone on the hypophyseal production of adrenocorticotrophic hormone (46). Low levels of vasopressin may play a role in the adrenal insufficiency of the critically ill patients.

At a supraphysiological dose, vasopressin acts as a platelet-aggregating agent (47). The coagulation problems in septic shock make this effect undesirable. However, the low doses used are less likely to stimulate platelet aggregation in most individuals.

Vasopressin and treatment of septic shock

Despite antimicrobials and aggressive fluid resuscitation, patients with septic shock frequently require vasoactive drugs for hemodynamic support. The 2008 surviving sepsis campaign guidelines recommend norepinephrine as the first-line vasopressor when blood pressure does not respond to fluid administration (48). Additional options besides catecholamines for hemodynamic support include corticosteroid and low dose vasopressin (0.03 units/min). Although, particularly norepinephrine is a potent and highly effective vasopressor agent, it cannot stabilize cardiovascular function in some patients with severe hemodynamic failure and sepsis-mediated vascular hyposensitivity to endogenous and exogenous catecholamines (49). By further increasing norepinephrine dosage (> 0.5 - 1 mcg/kg/min) to guarantee adequate perfusion pressure at these stages of shock, often significant side effects occur that further deteriorate shock and contribute to an adverse outcome (tachyarrhythmia, myocardial ischemia, decreased cardiac output, increased tissue oxygen consumption, pulmonary hypertension, etc) (50). In cases of catecholamine-resistant septic shock mortality approaches 80-100%. Landry et al., first reported the successful stabilization of catecholamine-resistant septic shock by infusion of vasopressin (51). This study showed that 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 27pg/ml and 34pg/ml respectively suggesting a secretion defect. Additionally, septic shock patients are sensitive to low dose of vasopressin.

Six prospective randomized comparator trials that used arginine vasopressin in septic shock and one prospective randomized study that compared two different doses of vasopressin (Table 1).

Compared with control, vasopressin was demonstrated to improve blood pressure, reduce open-label catecholamine doses and improve renal function. A randomized placebo-controlled study was conducted in 10 patients (5 placebos, 5 vasopressin) with resistant septic shock (53). The patients who received low-dose vasopressin (0.04 unit/min) had a significant increase in systolic arterial pressure (from 98 to 125mmHg; $P<0.05$) and were able to have treatment with all other catecholamines withdrawn. All patients in the treatment group survived the 24 hour study period. The control subjects had no statistically significant change in BP, none were able to have vasopressor therapy withdrawn and two died of refractory hypotension within 24h. The cardiac index did not differ between the two groups.

Patel and coworkers in a double-blind randomized study compared the effects of norepinephrine with vasopressin in septic shock (54). Patients were receiving norepinephrine before the study. They were randomized to receive, in a double-blind method, either norepinephrine or vasopressin. The main objective of the study was to keep MAP constant. In the vasopressin group norepinephrine doses were significantly reduced at hour 4 (from 25 to 5mcg/min; $P<0.001$). Vasopressin doses varied between 0.01 and 0.08 unit/min. In the norepinephrine group, doses of norepinephrine were not significantly modified. MAP and cardiac index were not modified. Diuresis and creatinine clearance were significantly increased in the vasopressin group. The gastric carbon dioxide gradient and the ECG ST segment were unchanged in both groups. The authors concluded that administration of vasopressin made it possible to spare other vasopressor agents and significantly improve renal function in those patients with septic shock.

Dunser and coworkers (22) conducted a prospective randomized controlled study in 48 patients with advanced vasodilatory shock. Patients were treated with a combined infusion of vasopressin (0.067units/min) and norepinephrine or norepinephrine alone. Vasopressin increased MAP from 63 ± 7 to 82 ± 10 mmHg at 1 hour ($P<0.050$ and also significantly lower heart rate. Norepinephrine dosage decreased from 25 to 5.3mcg/min at 4 hours ($P<0.001$). Total bilirubin concentrations increased significantly in patients' receiving vasopressin. The possible mechanisms may be an AVP-mediated reduction in hepatic blood flow or a direct impairment in hepatocellular function. The authors concluded that AVP plus norepinephrine was superior to norepinephrine alone in treating cardio circulatory failure in vasodilatory shock.

Table 1. Prospective randomized trials of Arginine vasopressin for the treatment of vasodilatory shock.

Type of Shock	Study Design	AVP Dosing Method	Blood Pressure Effects	Open-Label Catecholamine Effects *	Other Outcomes	Comments and Additional Results
Septic shock requiring catecholamines (norepinephrine ≥ 5 $\mu\text{g}/\text{min}$) (52)	AVP (n=5) Placebo (n=5)	Fixed, 0.08 unit/min	AVP: SBP increased from 95 ± 8.3 to 117 ± 15.4 mm Hg at 1 hr (p=0.0001)	AVP: decreased norepinephrine after 1 hr (p<0.006) Placebo: no significant effect	Not reported	Published as abstract only AVP increased SVR, but decreased cardiac output
Septic shock requiring Catecholamines (53)	AVP (n= 5) Placebo (n=5)	Fixed, 0.04 unit/min	AVP: MAP increased from 65.0 ± 6.0 to 80.0 ± 8.0 mm Hg at 1 hr (p<0.05) Placebo: no change in MAP at 1 hr	AVP: catecholamines discontinued at 24 hrs in all patients (except dopamine 3 $\mu\text{g}/\text{kg}/\text{min}$) Placebo: not reported	Placebo: two patients died of refractory shock within 24 hrs AVP: no patients died within 24 hrs	AVP primarily increased blood pressure by increasing SVR Cardiac index did not change significantly in AVP group
Septic shock requiring catecholamines (norepinephrine > 5 $\mu\text{g}/\text{min}$) (54)	AVP (n=13) Norepinephrine (n=11)	Titrated, 0.01–0.08 unit/min Median dose 0.06 unit/min	No change in MAP in either group (by study design)	AVP: norepinephrine decreased from 25.0 to 5.3 $\mu\text{g}/\text{min}$ at 4 hrs (p<0.001) Norepinephrine: no significant change in total norepinephrine dose	AVP increased urine output at 4 hrs No change in urine output in norepinephrine group	No change in gastric mucosal pCO ₂ gradient or ST segment on ECG in either group
Vasodilatory shock from sepsis or cardiovascular surgery , requiring catecholamines (norepinephrine >0.5 $\mu\text{g}/\text{min}$) (22)	AVP (n=24) Norepinephrine (n=24)	Fixed, 0.067 unit/min	AVP: MAP increased from 63 ± 7 to 82 ± 10 mm Hg at 1 hr (p<0.05) Norepinephrine: no change in MAP at 1 hr	AVP: norepinephrine decreased from 0.84 ± 0.55 to 0.59 ± 0.54 $\mu\text{g}/\text{kg}/\text{min}$ at 24 hrs (p<0.05) Norepinephrine: total norepinephrine increased from 0.84 ± 0.41 to 1.36 ± 1.86 $\mu\text{g}/\text{kg}/\text{min}$ at 24 hrs (p<0.05) Norepinephrine dose significantly lower in AVP group than in norepinephrine group over time (p<0.001)	ICU mortality rate: 70.8% in each group	Platelet count significantly decreased and bilirubin level significantly increased in AVP group New-onset atrial fibrillation less frequent in AVP group (8.3% vs 54.3%, p<0.001)

Type of Shock	Study Design	AVP Dosing Method	Blood Pressure Effects	Open-Label Catecholamine Effects ^a	Other Outcomes	Comments and Additional Results
Septic shock requiring Catecholamines (55)	AVP (n=13) Norepinephrine (n=10)	Titration, 0.04–0.2 unit/min Mean ± SD dose 0.09 ± 0.08 unit/hr at 24 hrs	AVP: MAP increased from 72 ± 7 to 81 ± 11 mm Hg at 24 hrs (p<0.05) Norepinephrine: No change in MAP at 24 hrs	AVP: 11/13 patients (85%) receiving norepinephrine at baseline with median dose of 0.16 µg/kg/min; at 24 hrs, 3/11 (27%) were receiving norepinephrine at median dose of 0.0 µg/kg/min (p<0.05) Norepinephrine: no significant difference in proportion of patients receiving norepinephrine or dose of norepinephrine at 24 hrs	Modified SOFA score decreased in AVP group from 8.5 ± 1.3 to 6.2 ± 2.8 at 48 hrs (p=0.04), was not significantly changed in norepinephrine group, and was significantly lower in AVP group (p<0.05) Three patients in each group died during their ICU stay	First randomized trial of AVP for early (< 12 hrs after onset) septic shock AVP decreased cardiac index due to decreased heart rate (no effect on SVI) Indexed oxygen delivery significantly lower over time in AVP group, but not significantly different from norepinephrine group Creatinine clearance and daily urine output significantly improved in AVP group but unchanged in norepinephrine group
Septic shock requiring catecholamines (norepinephrine ≥ 5 µg/min) (56)	AVP (n=396) Norepinephrine (n=382)	Titration, 0.01–0.03 unit/min	No change in MAP in either group (by study design)	Rate of total norepinephrine infusion significantly lower in AVP group than in norepinephrine group over first 4 days (p<0.001)	28-day mortality rates: 35.4% vs 39.3%, AVP vs norepinephrine (p=0.26) No significant difference in rate of adverse events between groups	
Vasodilatory shock from sepsis or cardiovascular surgery, requiring catecholamines (norepinephrine > 0.6 µg/kg/min) (57)	AVP (n=50)	Fixed, randomized to either 0.033 (n=25) or 0.067 (n=25) unit/min	MAP increased significantly over time in both dose groups (0.033 unit/min, p=0.02; 0.067 unit/min, p<0.001), but difference was not significant between groups (p=0.66)	Norepinephrine dose lower in 0.067-unit/min group than in 0.033-unit/min group (p=0.006 over time between groups)	ICU mortality rate 52% in each dose group	

AVP = Arginine vasopressin; SBP = Systolic Blood Pressure; SVR = Systemic Vascular Resistance; MAP = Mean Arterial Pressure; pCO₂ = Partial pressure of carbon dioxide; ECG = Electrocardiogram; ICU = Intensive Care Unit; SOFA = Sequential Organ Failure Assessment; SVI = Stroke Volume Index.

^aOpen-label catecholamines were titrated to maintain a target MAP or SBP.

Only one multicenter, randomized, controlled trial (RCT) on administration of AVP in patients with septic shock has been published (56). The vasopressin and septic shock trial (VAAST) included 778 adult patients with septic shock who received a norepinephrine dose of at least 5mcg/min. Patients were randomly assigned to treatment with either AVP (0.01-0.03 units/min) or NE (5-15mcg/min) in addition to open-label vasopressors. Depending on the vasopressor dose at the time of randomization, patients stratified into a less severe (<15mcg/min NE) and more severe septic shock (>15mcg/min NE). The primary study hypothesis was the administration of AVP would decrease 28 day mortality. The secondary hypothesis was that AVP would prove more effective in patients with more severe septic shock. However, no significant overall differences were found in 28-day (35.4 vs. 39.3%, P: 0.26) and 90-day mortality (43.9 vs. 49.6%, P: 0.11) between the AVP and NE groups. The results of this multicenter RCT suggest that low-dose AVP plus NE infusion in septic shock patients was as safe and efficacious as treatment with NE alone.

Despite its favorable effects on global hemodynamic and renal function (table 1) little is known about possible adverse effects of AVP on organ function; in particular, gastrointestinal hypoperfusion- a common complication of septic shock- may be aggravated by this drugs but conflicting conclusions have been reported in human studies (58, 59). AVP also had mixed effects on hepatosplenic hemodynamic. Hepatosplenic blood flow was preserved, but a dramatic increase in gastric PCO₂ gap suggested that gut blood flow could have been redistributed to the detriment of the mucosa (60). In endotoxaemic pigs, vasopressin decreased superior mesenteric artery and portal vein blood flow, whereas NE did not (61).

Prospective randomized studies have not found any significant differences in the frequency of adverse effects when comparing NE with AVP (55) or pharmacologic doses with physiologic doses of AVP.

The surviving sepsis campaign recommends AVP 0.03 units/min as an adjunct to first-line catecholamines for hemodynamic management of septic shock (48), however this dosing strategy questioned by others. Numerous studies have evaluated different dosing regimens for AVP in patients with vasodilatory shock, ranging from 0.01-1.8 units/min, with doses up to 0.04 units/min (being termed physiologic) and doses above that termed pharmacologic (62, 63). Both doses of AVP routinely yield plasma levels that exceed what is traditionally seen as physiologic replacement levels (30 pg/ml).

Torgerson et al., (57) report that in patients with very severe septic shock a higher dose of AVP result in more effective restoration of cardiovascular function. The authors test the null hypothesis that AVP 0.067 unit/min is no different from AVP 0.03unit/min on

hemodynamic function in 50 patients who had severe vasodilatory shock requiring NE >0.6 mg/kg/min. The number of patients randomized into the study (25 each in the lower and higher dose of AVP group) is sufficient to provide useful additional hemodynamic information, though not sufficient to test for differences in survival outcome. They find that 0.067 unit/min infusion results in lower NE infusion rates. Importantly, the incidence of adverse events in the two groups was comparable. A number of supplementary observations further support the idea that the higher dose of AVP may be beneficial including less of an increase in troponin T over 48 hour and a trend towards greater improvement in creatinine, but higher doses of AVP was associated with a greater decrease in mixed venous oxygen saturation and slightly reduced improvement in base excess.

An interesting interaction of AVP with corticosteroids is observed in the study of Torgersen et al., (64), Bauer et al., (65) and also by Russel et al., (66). Torgersen et al., found that concomitant use of steroids increase vasopressin concentration in plasma in both the low dose and high dose AVP group. Russel et al., found the same effect on plasma vasopressin levels and Bauer et al., found that AVP- corticosteroids interaction to be associated with improved survival.

Conclusion

Vasopressin deficiency may contribute to the refractory hypotension in septic shock patients. Infusion of vasopressin increases plasma levels to values found during comparable degrees of hypotension from other causes, such as cardiogenic shock. Vasopressin is an important adjunctive therapy for the hemodynamic management of septic shock but it has not been demonstrated to lead to a mortality benefit in all patients with septic shock, but may have a role for selected patients. For patients with less severe shock or risk of renal failure, vasopressin may improve survival. Vasopressin should be started early in the course of sepsis when the NE dose is around 10mcg/min (~0.15 mcg/kg/min).

There are complex interaction between the corticosteroids and AVP. Corticosteroids should be considered in all patients as soon as AVP is started and certainly added if patients are poorly responsive to fluid and vasopressors.

Doses as low as 0.01 units/min have demonstrated adequate replacement levels of vasopressin with corresponding hemodynamic response. Doses beyond 0.04 units/min have demonstrated improved blood pressure and diminished catecholamine requirements. A reasonable approach to AVP therapy may be a starting dose of 0.01unit/min with titration to the lowest dose that restores cardiovascular function (up to an AVP dose of 0.03-0.04 units/min). For patients with high

catecholamine requirements (NE > 40 mcg/min or 0.6 mcg/kg/min), further titration of the AVP dose to 0.067 units/min may be a reasonable approach to improving hemodynamic but has not been demonstrated to improve mortality.

In the treatment of sepsis AVP exhibits organ-specific heterogeneity in vascular responsiveness, compared to NE and shows promise for the treatment of septic shock, randomized controlled trials need to test this effect.

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