State of the Art Review

Controversies regarding choice of vasopressor therapy for management of septic shock in animals

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Abstract

Objective – To review and appraise common vasopressor drugs used to treat septic shock-induced hypotension in volume replete animals.
Data Sources – Human and animal publications were searched using PubMed without time limits and the following keywords were used: "vasopressor," "septic shock," "norepinephrine," "dopamine," "epinephrine," and "vasopressin."
Human Data Synthesis – The choice of vasopressor drug is unlikely to have a marked impact on outcome, but the incidence of adverse events (eg, tachycardia) varies greatly between the various treatment options. In agreement with the 2012 Cochrane Database consensus, norepinephrine is the first-choice vasopressor to maintain a mean arterial pressure ≥65 mm Hg. If an additional agent is required, epinephrine should be administered. Low-dose vasopressin can be added to norepinephrine to either increase the arterial blood pressure to the target goal value or decrease the norepinephrine dose, but should not be used as the initial vasopressor. Dopamine is not recommended except in highly selected circumstances.
Veterinary Data Synthesis – There is insufficient evidence to make definitive conclusions regarding the treatment of naturally occurring septic shock, but clinical studies are underway to provide further data.
Conclusions – The treatment of hypotension in people or animals with septic shock is challenging and vasopressor therapy is associated with a variety of adverse effects. Further research is warranted in dogs and cats to establish evidence-based guidelines.

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Keywords: dopamine, epinephrine, hypotension, norepinephrine, vasopressin

Introduction

Sepsis is a common cause of morbidity and mortality in both veterinary and human medicine. Although the incidence of sepsis is unknown in veterinary medicine, septic shock contributes to 5% to 19% of human ICU admissions.[1,2] The mortality rate associated with septic shock has been reported to range from 20% to 68%.[3,4] Sepsis is a complex clinical syndrome resulting from the interaction between the host and the infecting organisms and is generally assumed to be maladaptive. The host's response involves the activation of both pro- and anti-inflammatory mediators as well as cellular and humoral reactions that contribute to changes in vascular tone, cardiac function, blood flow redistribution between organs, and microcirculatory flow. The presence of sepsis complicated by tissue hypoperfusion or organ dysfunction is referred to as severe sepsis; septic patients with circulatory failure despite adequate intravascular volume resuscitation suffer from septic shock.[5,6] Recently, the use of early goal-directed therapy has been popularized in an attempt to correct abnormal measurable indices of tissue perfusion and oxygenation.[4,7,8] However, the optimal treatment of hypotension in volume-replete patients remains controversial. In the Cochrane Database review titled "Vasopressors for Hypotensive Shock" performed in 2011,[9] the reviewers identified 23 randomized controlled trials involving 6 different vasopressors in more than 3,200 patients and greater than 1,600 mortality outcomes. A third reviewer was actually required to resolve the disagreements between the 2 independent reviewers, thus underscoring the controversial nature of the issue.

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Table 1: Receptor activity, cardiopressor effects, and dosages of commonly administered vasopressor drugs. (Modified with permission from Haskin SC. Catecholamines. In: Silverstein DC, Hopper K. eds. Small Animal Critical Care Medicine, 2nd ed. St. Louis: Elsevier Saunders; 2015, p. 830).

	Receptor activity			Effect on*					Dosage
	β_1	β_2	α_1 & α_2	Contractility	Heart rate	Cardiac output	Vasomotor tone	Blood pressure	
Dobutamine	++	+	+	↑↑	↑	↑↑	↓	Variable	5–20 μg/kg/min
Dopamine§	++	+	++	↑↑	↑↑	Variable	↑↑	↑↑	5–20 μg/kg/min
Epinephrine	+++	+++	+++	↑↑↑	↑↑↑	↑↑	↑↑↑	↑↑↑	0.05–1 μg/kg/min
Norepinephrine	+	0	+++	↑	Variable	Variable	↑↑↑	↑↑↑	0.1–2 μg/kg/min
Phenylephrine	0	0	+++	0	↓	↓	↑↑↑	↑↑↑	0.5–5 μg/kg/min
Vasopressin	0	0	0	0	↓	↓	↑↑	↑↑	0.5–5 mU/kg/min

*Effects are estimated for the higher dose ranges.
§Dose-dependent effects ranging from dopaminergic at low doses, β-agonist at mid doses, and α-agonist at high doses.
Activity ranges from no activity (0) to maximal activity (+++).
Possible cardiopressor effects include a decrease (↓), mild increase (↑), moderate increase (↑↑), or marked increase (↑↑↑).

When vasopressor support is required, the most commonly used drugs include α- and β-adrenergic agonists.[a] Alpha-adrenergic agonists are commonly employed to increase vascular tone, but may decrease cardiac output and regional blood flow, especially in cutaneous, splanchnic, and renal capillary beds.[10] Beta-adrenergic agonists are also frequently used to help maintain cardiac output via positive inotropic and chronotropic effects, as well as increased splanchnic perfusion, but these drugs can also have deleterious effects such as increased cellular metabolism and immunosuppression. Other effects of vasoactive drugs, such as dopaminergic and nonadrenergic effects, will be discussed with some of the more frequently used and studied vasopressor therapies in veterinary medicine. Some of the commonly used vasopressor drugs, along with their associated receptor activity, cardiopressor effects, and dosages are listed in Table 1. It is also important to note that the choice of vasopressor therapy may influence volume expansion dynamics following isotonic crystalloid infusions, thus complicating the response to any given drug.[11,12]

Catecholamine vasopressor drugs

Catecholamine agents are the most commonly used vasopressor drugs by Diplomates of the American College of Emergency and Critical Care according to a recent survey.[a] The action of these drugs is determined by their affinity for 3 major subclasses of adrenergic receptor subtypes: α-adrenergic (α-1 and α-2), β-adrenergic (β-1 and β-2), and dopaminergic (dopamine receptors 1–5), although there may be additional receptor types within each class that play an important role.[13]

Alpha-adrenergic receptors are located within pre- and postsynaptic regions of sympathetic nerve endings on smooth muscle cells and (in lesser numbers) on myocardial cells.[14] Stimulation of α-receptors in the vascular muscle causes vasoconstriction and increases blood pressure, whereas myocardial α-receptor stimulation may have a slower onset and lead to a prolonged increase in the inotropic state of the heart.[15]

Beta-adrenergic receptors are found in the myocardium,[16] although β-2 receptors are also located in the peripheral vascular and bronchial smooth muscle. Beta-adrenergic receptor stimulation leads to positive inotropic and chronotropic effects within the myocardium and relaxation of smooth muscle in the bronchial tree and the vasculature. Stimulation of β-adrenergic receptors increases splanchnic and microcirculatory perfusion.[17–20] However, potential adverse effects of β-adrenergic agonists include arrhythmias as well as cellular modifications (eg, insulin secretion, glycogenolysis, glucagon secretion, and lipolysis)[21] that increase energy requirements, lactate production, and may cause immunosuppression.[22] The immune effects of β-adrenergic agonists include both T cell and monocyte inhibition,[23,24] as well as reduced cytokine production,[25] although there are controversial reports of their proinflammatory effects.[26]

Dopamine receptors are located in the smooth muscle of renal, coronary, splanchnic, and cerebrovascular beds.[10] Upon stimulation of dopamine receptors, there is inhibition of norepinephrine release from the sympathetic nerve terminals, leading to vasodilation of the local vessels.[27] Age- and species-related changes in dopamine physiology have been studied and cross-species studies should be interpreted with caution.[28,29] Dopaminergic stimulation is also associated with changes in the endocrine system, which may affect immunocompetency.[30] Dopamine has numerous immunomodulatory actions in septic animals and people, primarily via inhibition of inflammation-induced upregulation of cytokines, chemokines, and adhesion molecules, as well as induction of the production of anti-inflammatory mediators.[31]

In addition to the maladaptive inflammatory responses that occur during sepsis and their effects on cardiovascular tone (eg, nitric oxide),[32] as well as the proven effectiveness of catecholamine therapy in reversing these untoward effects,[33–36] there may also be diminished responsiveness to adrenergic vasoconstrictors in patients with septic shock that are exposed to prolonged use of catecholamine pressors.[37] This may be caused by prolonged use of catecholamine drugs and subsequent downregulation of α-adrenergic receptors in the arterial smooth muscle.[38,39] Both epinephrine and norepinephrine have similar vasopressor effectiveness for the treatment of septic shock, while dopamine fails to normalize blood pressure in up to 40% of people with hypotension.[40] The incidence of vasopressor failure in small animal patients is not currently known.

It is important to realize that α-adrenergic effects lead to an increase in left ventricular afterload and may subsequently decrease cardiac output if used alone, therefore decreasing regional blood flow.[10] It is for this reason that most vasopressor agents commonly used to treat hypotension have some degree of β-adrenergic activity (and dopaminergic activity if using dopamine) that leads to differences in hemodynamic and metabolic effects, and specific catecholamine therapy can be titrated to the needs of the patient.[41–43] Dopamine and norepinephrine, which have similarly proportional α- and β-adrenergic properties, increase cardiac output and arterial blood pressure. Norepinephrine primarily stimulates α-adrenergic receptors to increase arterial blood pressure with only a mild increase (or at least preserved) cardiac output, while phenylephrine, a pure α-adrenergic agonist, increases arterial blood pressure only and subsequently there is a slight decrease in cardiac output.[10] These types of differences in receptor stimulation may also cause differences in perfusion of regional capillary beds.

Dopamine versus norepinephrine

Dopamine and norepinephrine are 2 of the most commonly used vasopressors in small animal veterinary emergency and critical care medicine,[a] although there is a dearth of literature comparing the 2 drugs in dogs and cats. Although some human trials have found that dopamine improved myocardial contractility more than norepinephrine,[44,45] others have found no difference.[17,46] The effects on splanchnic blood flow and gastric PCO_2 as markers of splanchnic perfusion, are also controversial.[17,47] The incidence of tachyarrhythmias is higher in people receiving dopamine compared to norepinephrine.[46,48,49]

There are observational data and 1 meta-analysis suggesting that the use of dopamine is associated with a worse outcome in people; however, dopamine may still be beneficial in certain patients.[49–52] The largest of these trials included over 1,000 shock patients and found that those treated with dopamine had a higher ICU (42.9% vs. 35.7%, P = 0.02), in-hospital (49.9% vs. 41.7%, P = 0.01), and 30-day mortality (44.5% vs. 36.9%, P = 0.013) compared to other patients in shock.[51] A large multicenter trial was performed to compare the effects of dopamine and norepinephrine as first-line vasopressor therapy for the treatment of 1,679 people with shock, 63% of whom suffered from septic shock.[46] The patients were randomly allocated to receive dopamine up to 20 μg/kg/min or norepinephrine up to 0.19 μg/kg/min. If additional vasopressor therapy was needed, an open-label infusion of norepinephrine or epinephrine was added without a dose limitation. The 28-day mortality was 52.5% in the dopamine group and 48.5% in the norepinephrine group (odds ratio 1.17 [0.97–1.42], P = 0.07). A similar randomized, single-center trial investigating 252 people with septic shock found a 28-day mortality rate of 50% in the dopamine group compared with 43% in the norepinephrine group (P = 0.282).[48] However, there was a significant increase in the incidence of tachyarrhythmias in the dopamine group. A meta-analysis that included 2,043 shock patients discovered that the combined risk of death was lower for those receiving norepinephrine compared to dopamine (relative risk 0.91 [0.83–0.99], P = 0.028).[53] Another meta-analysis of 1,408 patients with septic shock found that the aggregated risk of death was higher in the group that received dopamine compared to norepinephrine (relative risk 1.10 [1.01–1.20], P = 0.035).[49] Overall, these studies suggest that norepinephrine might be preferable over dopamine, although dogs and cats may differ from people in their response and adverse effects. Prospective research is currently underway comparing the effectiveness and adverse events of dopamine and norepinephrine in dogs and cats.

Epinephrine versus norepinephrine

Although epinephrine and norepinephrine have a similar mechanism of action as vasopressor agents, only high doses of epinephrine (0.12 μg/kg/min, range 0.05–0.04 μg/kg/min) are correlated with a higher cardiac index (and heart rate) compared with equivalent doses of norepinephrine (0.18 μg/kg/min, range 0.02–0.35 μg/kg/min) in a study titrating these drugs to maintain an MAP>65 mm Hg in people with septic shock.[17] Epinephrine is also associated with elevations in heart rate and serum lactate and a decrease in splanchnic perfusion that can persist for up to 48 hours in people with septic shock or circulatory failure from other causes.[54–56] The β-adrenergic stimulation

caused by epinephrine is also more likely to cause tachyarrhythmias compared to norepinephrine.[54,56]

Epinephrine and norepinephrine were compared in 2 randomized trials that comprised 610 shock patients.[55,56] The first looked at 330 people with septic shock and found no difference in adverse events or 28-day mortality rates between patients receiving epinephrine and norepinephrine (40% vs. 34%, respectively, $P > 0.05$).[55] It is important to note that this particular study was powered to detect a 20% absolute reduction in mortality, and was therefore underpowered to evaluate the observed 6% absolute (15% relative) reduction in mortality at day 28 in the patients that were treated with norepinephrine. The second randomized trial was also underpowered and used hemodynamic success (MAP $\geq$ 70 mm Hg) as the primary outcome in 280 critically ill people. There was no difference in 28-day mortality (26% vs. 23%, $P = 0.48$), but several patients were excluded due to tachycardia (seen in 13% of patients treated with epinephrine vs. 3% with norepinephrine).[56] Therefore, this limits the overall conclusions of the study; it appears that the controversy between epinephrine and norepinephrine continues and further research is warranted, especially in veterinary medicine.

Vasopressin

Vasopressin is a nonadrenergic vasopressor that also potentiates the effects of α-adrenergic agonist drugs. It is synthesized in the hypothalamus and subsequently transported to the pituitary gland for storage. It is released in response to a decrease in blood pressure, decreased intravascular volume, and increased osmolality.[57] Although shock states cause a 20- to 200-fold increase in vasopressin concentrations,[58–62] prolonged hypotension may lead to depletion of vasopressin stores.[63–66] Vasopressin causes constriction of vascular smooth muscle by directly activating the V1 receptors,[67] which leads to an increase in intracellular calcium via the phosphatidylinositol-bisphosphonate cascade.[68] In addition, vasopressin inhibits Interleukin (IL)-β-induced production of nitric oxide and cyclic guanosine monophosphate, as well as inducible nitric oxide synthase mRNA expression via the V1 receptor.[67,69] It also blocks the K^+-sensitive ATP channels in the vascular endothelium, which are activated with endotoxemia, decreasing the amount of K^+ flux and subsequently opening the voltage-dependent calcium channels, which further increases the intracellular calcium concentrations and promotes vasoconstriction.[70] In vitro studies of human gastroepiploic arterial rings have shown that vasopressin produces concentration-dependent, endothelium-independent contractions and potentiates the contraction stimulated by norepinephrine in

the presence or absence of endothelium.[71] Although afterload does increase in response to the increase in systemic vascular resistance from vasopressin therapy in people with vasodilatory shock,[72] a decrease in cardiac output was not observed with vasopressin administration in a large prospective study comparing the effects of vasopressin to norepinephrine in 241 people with septic shock, possibly due to increased coronary blood flow.[73]

It is not clear how the various vasopressor drugs compare in their effects on inflammatory cytokines or leukocytes. However, vasopressin has been shown to decrease cytokine levels more than norepinephrine in the first 24 hours of therapy in people with septic shock, and the decrease in cytokine levels has been linked to survival.[74]

There have been numerous small noncontrolled trials using vasopressin for the treatment of hypotension in septic patients since the first report of its success by Landry et al.[72] An example of 1 such trial examined 24 human patients with septic shock that were given a low dose of vasopressin (median 0.06 U/min) and found that their dose of norepinephrine could be decreased while the mean arterial blood pressure and cardiac index were maintained.[75] This finding has also been seen in an experimental, randomized porcine peritonitis septic shock model.[76] The administration of vasopressin was associated with a lower total norepinephrine and fluid requirement in order to maintain mean arterial pressure and pulmonary capillary wedge pressure in the target range. In addition, there was a statistically significant improvement in renal function (based on urine output, renal blood flow, and decreased serum creatinine) in the vasopressin group compared to the norepinephrine group ($P < 0.05$).

However, there were also multiple reports of vasopressin-induced splanchnic ischemia, primarily seen when high doses of the drug were used.[77–79] Low-dose vasopressin therapy (0.01–0.03 U/min) was then studied in a randomized trial of 778 people with septic shock. There was no difference in the incidence of adverse effects or mortality at 28 days in the vasopressin group versus those that received norepinephrine (35% vs. 39%, respectively, $P = 0.26$).[80] There was, however, a decrease in mortality in the predefined subgroup of patients with less severe septic shock that were treated with vasopressin compared to norepinephrine (26.5% vs. 35.7%, $P = 0.05$).

A recent retrospective study attempted to determine whether norepinephrine or vasopressin was a more effective vasopressor monotherapy in the first 6 hours of goal-directed therapy in 130 people with septic shock.[81] There was no difference in the proportion of patients that achieved the goal arterial blood pressure in the vasopressin versus norepinephrine groups (63% vs. 67.7%, 95% CI). However, there was a potential survival benefit

in a separate Vasopressin and Septic Shock Trial (VASST) that prospectively defined a stratum of patients with less severe septic shock (those receiving 5–15 μg/min norepinephrine at the time of randomization); vasopressin might have decreased mortality when compared to norepinephrine (26.5% vs. 35.7%, respectively, $P = 0.05$ within stratum).[80] In addition, low-dose vasopressin plus corticosteroid therapy significantly improved 28-day mortality compared to norepinephrine plus corticosteroid therapy (44.7% vs. 35.9%, respectively, $P = 0.03$; $P = 0.008$ interaction statistic) in a post hoc analysis of the VASST study.[82] The role of critical illness-related corticosteroid insufficiency (also known as CIRCI) may be of importance as it related to vasopressor refractory states, as seen in this study, but further discussion is beyond the scope of this review and the reader is referred elsewhere.[83,84]

The use of vasopressin for the treatment of septic shock in small animals has not been extensively researched. One case series did report its success in raising blood pressure in dogs with catecholamine-refractory hypotension, but 4/5 dogs were euthanized due to a grave prognosis and 1 animal died of respiratory arrest secondary to severe pulmonary disease.[85] There were no definitive adverse events, but these might have been difficult to discern in the severely ill population of dogs. Further research is currently underway.

Conclusions

As the 2011 Cochrane Database review[9] so accurately stated, "There is not sufficient evidence of any difference between any of the 6 vasopressors examined. Probably the choice of vasopressors in patients with shock does not influence the outcome, rather than any vasoactive effect per se. There is not sufficient evidence that any one of the investigated vasopressors is clearly superior over others." Despite the conflicting evidence and controversy surrounding the various vasopressor choices, the 2012 Surviving Sepsis Guidelines[86] recommends the following treatment approach in people with hypotension despite fluid resuscitation: norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure ≥65 mm Hg (1B evidence); epinephrine administration when an additional agent is required (2B evidence); vasopressin (0.03 U/min) can be added to norepinephrine to either raise the arterial blood pressure to the goal value or decrease the norepinephrine dose, but should not be used as the initial vasopressor; dopamine is not recommended except in highly selected circumstances (2C evidence).

The past is history and the present seems uncertain. Perhaps in 10 years, the recommendations will be for low-dose cholecytokinin,[87] dexmedetomidine,[88] 25% albumin,[89] methylene blue,[90] and intravenous enalaprilat?[91] In the meantime, perhaps it is opportune for the veterinary community to establish their own evidence-based vasopressor guidelines, but first we must create the evidence.

Footnote

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