Differing effects of epinephrine, norepinephrine, and vasopressin on survival in a canine model of septic shock

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Minneci, Peter C., Katherine J. Deans, Steven M. Banks, Renee Costello, Gyorgy Csako, Peter Q. Eichacker, Robert L. Danner, Charles Natanson, and Steven B. Solomon. Differing effects of epinephrine, norepinephrine, and vasopressin on survival in a canine model of septic shock. Am J Physiol Heart Circ Physiol 287: H2545–H2554, 2004. First published August 19, 2004; doi:10.1152/ajpheart.00450.2004.—During sepsis, limited data on the survival effects of vasopressors are available to guide therapy. Therefore, we compared the effects of three vasopressors on survival in a canine septic shock model. Seventy-eight awake dogs infected with differing doses of intraperitoneal Escherichia coli to produce increasing mortality were randomized to receive epinephrine (0.2, 0.8, or 2.0 μg·kg−1·min−1), norepinephrine (0.2, 1.0, or 2.0 μg·kg−1·min−1), vasopressin (0.01 or 0.04 U/min), or placebo in addition to antibiotics and fluids. Serial hemodynamic and biochemical variables were measured. Increasing doses of bacteria caused progressively greater decreases in survival (P < 0.06), mean arterial pressure (MAP) (P < 0.05), cardiac index (CI) (P < 0.02), and ejection fraction (EF) (P = 0.02). The effects of epinephrine on survival were significantly different from those of norepinephrine and vasopressin (P = 0.03). Epinephrine had a harmful effect on survival that was significantly related to drug dose (P = 0.02) but not bacterial dose. Norepinephrine and vasopressin had beneficial effects on survival that were similar at all drug and bacteria doses. Compared with concurrent infected controls, epinephrine caused greater decreases in CI, EF, and pH, and greater increases in systemic vascular resistance and serum creatinine than norepinephrine and vasopressin. These epinephrine-induced changes were significantly related to the dose of epinephrine administered. In this study, the effects of vasopressors were independent of severity of infection but dependent on the type and dose of vasopressor used. Epinephrine adversely affected organ function, systemic perfusion, and survival compared with norepinephrine and vasopressin. In the ranges studied, norepinephrine and vasopressin have more favorable risk-benefit profiles than epinephrine during sepsis.

vasopressors and systemic perfusion; low cardiac output septic shock; vasopressors and acidosis; vasopressors and cardiac function

DESPITE CONTINUED IMPROVEMENTS in medical therapy, mortality from septic shock has remained between 30% and 60% for the past three decades (1, 2). Septic shock is a clinically descriptive term that refers to a pathophysiologic state of cardiovascular collapse associated with overwhelming infection. After adequate volume resuscitation, severe septic shock is often characterized by a hyperdynamic state with increased cardiac output (CO), hypotension, and decreased systemic vascular resistance (SVR). However, despite adequate volume resuscitation, 20–25% of adult septic patients and 50–60% of pediatric septic patients will present with low CO (3, 33, 34). The majority of septic patients will develop myocardial dysfunction and many will die as a consequence of multiple organ failure (17, 35, 44). During septic shock, tissue perfusion is compromised by hypotension, by the loss of vascular integrity with extravasation of fluid into the interstitium, and by the altered distribution of blood flow within the microcirculation (44a).

One of the primary goals in the treatment of septic shock is the maintenance of systemic arterial pressure with the restoration of adequate tissue perfusion (43, 44a). The initiation of vasopressor therapy during septic shock is often necessary to maintain adequate tissue perfusion and prevent rapid death. Whereas many studies have documented the physiological effects of various vasopressor agents in sepsis, few have compared their effects on survival. Furthermore, there are few data examining the effects of a single agent over a wide range of doses or in varying levels of severity of infection. Because of the lack of available data, the vasopressor agent selected to treat hypotension during septic shock is usually based on patient-specific characteristics, physiological parameters, and clinical experience. Over the past 20 years, epinephrine therapy has been used to treat patients with low CO septic shock (particularly children) with the rationale that these patients will benefit from its β-agonist inotropic effects (18, 44, 44a). Norepinephrine is commonly used to treat hypertensive patients with hyperdynamic septic shock because of its strong α-agonist vasoconstrictor properties (19), and recently, low-dose vasopressin is being used more frequently to treat refractory hypotension in patients with septic shock (15, 16, 20, 47). The purpose of our study was to design a model of lethal septic shock to prospectively evaluate and compare the effects of epinephrine, norepinephrine, and vasopressin in conjunction with antibiotics and intravenous fluid on 28-day survival.

METHODS

Experimental design. The experiments described below were performed as part of an approved protocol by the Institutional Animal Care and Use Committee of the Clinical Center at the National Institutes of Health. Eighty-four purpose-bred beagles (12–28 mo of age, 10–12 kg body wt) were studied. Bacterial peritonitis was...
induced by implantation of a fibrin clot containing live *Escherichia coli* 0111:B4 into the abdominal cavity. This encapsulated serum-resistant strain of *E. coli* produces persistent positive blood cultures with progressive increases in blood endotoxin levels in animals not receiving antibiotics (12, 14, 42). Clots contained one of three concentration ranges of organism: 3–4, 7.5–15, or 18 × 10^6 colony forming units (CFU)/kg of body wt (Table 1). Comprehensive evaluations were performed at baseline (7 days before clot implantation) and then at 6, 24, and 48 h after clot implantation. The indicated evaluations were performed in conscious animals and consisted of physiological measurements using arterial and pulmonary artery catheters, laboratory tests, and gated radionuclide cineangiograms of the left ventricle.

Vasopressor or saline (control) infusions were started 6 h after bacterial clot implantation and were infused for 48 h. Three vasopressors were studied at multiple doses (Table 1). Titration entailed a 50% reduction in drug dose if mean arterial pressure (MAP) was greater than normal for dogs (120 mmHg). All animals received daily antibiotics for 72 h (ceftriaxone 100 mg/kg im) beginning 6 h after clot implantation. A 5% dextrose-lactated Ringer solution was infused for a total of 42 h beginning at 6 h postclot implantation to provide fluid resuscitation to attain a pulmonary capillary wedge pressure (PCWP) between 12 and 15 mmHg (30). The infusion rate was 8 ml·kg⁻¹·h⁻¹ for 30 h and was then reduced to 4 ml·kg⁻¹·h⁻¹ for the last 12 h and discontinued (30, 31). The dogs were maintained in cages that provided an atmosphere of humidified oxygen (50% H₂O; Fio₂ = 40%) at a temperature of 37°C.

Animals were continuously observed for the first 48 h after clot implantation and then at least twice a day for the next 26 days or until death. Animals were randomly assigned to a treatment arm, and the veterinarians making euthanasia decisions were blinded. As prospectively determined, any animal euthanized before completion of the 28-day study was considered a nonsurvivor and was included in the analysis.

**Bacterial clot implantation.** Animals were premedicated (xylocaine 0.75 mg/kg and atropine 0.04 mg/kg im). Anesthesia was induced using propofol and maintained with inhalation of 1–3% isoflurane. An upper abdominal midline laparotomy was performed using aseptic technique, and bacterial peritonitis was induced by implanting a fibrin-thrombin clot with a known number of CFUs of viable *E. coli*. A 7-Fr pulmonary artery thermodilution catheter (Abbott Laboratories, North Chicago, IL) was introduced through the catheter in the external jugular vein. The animals were anesthetized in a similar fashion to the clot implantation procedure using inhalational agents for 15–20 min. The catheters were removed at the end of the 6-h baseline study. This same procedure was used for recovery studies 28 days after clot implantation.

For the sepsis studies, the catheters were placed percutaneously immediately before clot implantation using the methods described above; these catheters remained in place for 55 h before removal.

**Physiological measurements.** CO, mean pulmonary artery pressure (MPAP), PCWP, and central venous pressure (CVP) were determined via pulmonary artery thermodilution catheter. MAP was measured and heart rate (HR) was calculated via the femoral arterial pressure recording. Left ventricular ejection fraction (LVEF) was determined using cineangiography as previously described (31). The CO was standardized to the animal’s weight in kilograms [cardiac index (CI)]. These measurements were performed at baseline, 6, 24, and 48 h after bacterial clot implantation. At 6 and 48 h, the study was performed and then repeated after treatment was initiated and terminated, respectively.

**Laboratory data.** Blood samples were obtained at baseline and at 8, 24, and 48 h after bacterial clot implantation. Arterial and mixed venous blood gases were measured (ABL 500; Radiometer, Copenhagen, Denmark). Complete blood counts were performed using an automatic analyzer (model STK-S; Coulter Electronics, Hialeah, FL). Quantitative blood cultures (isolator tubes) and routine serum chemistry were also performed. Routine chemistry was performed with automated chemistry analyzers.

**Pain management.** To relieve pain caused by peritonitis, all animals had epidural catheters placed while under general anesthesia immediately before clot implantation. Previous experiments utilizing sterile clots in this model have demonstrated that the epidural anesthesia does not significantly change LVEF, MAP, and survival (42). The epidural also does not cause qualitative changes in the hemodynamic alterations that occur during sepsis other than making them more pronounced (42). To control nausea and vomiting induced by peritonitis, all animals received intravenous ondansetron (1.0 mg/kg) every 4 h for 48 h beginning immediately after clot implantation.

**Epidural procedure.** All animals were placed in the sternal recumbency position with the rear limbs drawn forward (24, 48). After sterile preparation, a 19-g Touhy needle was inserted into the posterior lumbosacral epidural space inferior to the seventh lumbar vertebrae (L7) by loss of resistance. An epidural catheter was placed and the tip positioned at the L2–3 vertebral fluoroscopically. The catheter was then secured, injected with a loading dose of morphine sulfate (0.1 mg/kg) and bupivicaine (1.25 mg/kg), and attached to a constant-infusion pump. The morphine-bupivicaine epidural was administered as a 50:50 mix of 0.10% morphine with 0.125% bupivicaine. A 55-h continuous epidural infusion was initiated (0.3 mg·kg⁻¹·day⁻¹ morphine in combination with bupivicaine) immediately after clot placement (42).

**Animal care.** This experimental protocol was approved by the Animal Care and Use Committee of the Clinical Center of the National Institutes of Health. Throughout the studies, all efforts were taken to minimize animal pain and suffering. A pain score was performed each hour for the first 48 h following clot implantation and then every 4 h until 72 h. The pain scoring was then continued twice a day until 7 days. The evaluators were blinded to the treatment groups and to the dose of bacteria. The criteria for euthanasia included a predetermined pain score, respiratory rate of <5 breaths/min, seizure activity, or uncontrolled hemorrhage for >2 min. In addition, at any time during the study, animals were euthanized if they were noted to be in pain or distress that could not be relieved by the facility veterinarian or designee.

**Statistical methods.** Cox Proportional Hazards survival models were used to assess significant differences in survival data (6). Hemodynamic analyses of control animals were performed using a
three-way analysis of variance (ANOVA), with main effects for bacterial dose, animal variability nested within bacterial dose and time, and a two-way interaction between dose and time (38). All interactions including animal variability nested within bacterial dose were pooled to form the error term. The normal range identified on the graph (31).

The hemodynamic and laboratory analyses of vasopressors during sepsis were performed by first computing the change from start of infusion to follow-up time points for each individual animal. These changes were then analyzed using ANOVA to estimate dose effects.

RESULTS

Effects of increasing bacterial dose on survival rates and hemodynamics independent of vasopressor therapy. In control animals, increasing doses of implanted E. coli resulted in dose-dependent decreases in survival rates that approached statistical significance [3–4 × 10⁹ (n = 6) ≤ 7.5–15 × 10⁹ (n = 6) ≤ 18 × 10⁹ (n = 14) CFUs of E. coli] (P < 0.06) (Fig. 1A). By 6 h after clot implantation, increasing bacterial doses caused dose-dependent decreases in MAP, mean CI, and LVEF (P < 0.05, P = 0.016, and P = 0.02 respectively) (Fig. 1, B–D). In contrast, changes in CVP and PCWP were not related to bacterial dose (all P = not significant). During the administration of fluid therapy from 6 to 48 h after clot implantation, the mean CVP and PCWP in control animals increased from 5 to 10 mmHg and from 8 to 13 mmHg, respectively (both P < 0.05).

Effect of vasopressors on MAP during sepsis. During sepsis, epinephrine and norepinephrine significantly increased MAP compared with controls (P = 0.0002 and 0.0097), whereas vasopressin did not (P = not significant). After clot implantation, only the higher doses of epinephrine (0.8 and 2.0 µg·kg⁻¹·min⁻¹) and norepinephrine (1.0 and 2.0 µg·kg⁻¹·min⁻¹) increased MAP into the normal or near normal range (Fig. 2).

Effect of vasopressors on survival during sepsis. Overall, the effect of epinephrine on survival was significantly different from norepinephrine and vasopressin (P = 0.03). Compared with concurrent controls, epinephrine therapy caused a decrease in survival, whereas norepinephrine and vasopressin therapy improved survival (Fig. 3). The survival effects of these agents were consistent over all doses of E. coli studied but not over all doses of drug studied (Fig. 4). With epinephrine therapy, the decreases in the odds ratio of survival were significantly related to drug dose with the higher drug doses being the most harmful (2.0 ± 0.8 ± 0.2 µg·kg⁻¹·min⁻¹ of epinephrine) (P = 0.02) (Fig. 4).

Effects of vasopressors on hemodynamic measurements during sepsis (from 6 to 48 h). Upon examination of the differences between treated animals and concurrent control animals.
during sepsis, there was a significantly greater decrease in mean CI and LVEF and a significantly greater increase in SVR index (SVRI) with epinephrine therapy compared with norepinephrine and vasopressin therapy \((P < 0.0155, P < 0.0448,\) and \(P < 0.003,\) respectively) (Fig. 5). These changes in CI, LVEF, and SVRI caused by epinephrine treatment were dose dependent \((2.0 \pm 0.8 \pm 0.2 \mu g \cdot kg^{-1} \cdot min^{-1})\). Changes in CVP and PCWP in the vasopressor treatment groups were similar to controls \((P = 0.007,\) and \(P = 0.0001,\) respectively).

With the examination of the differences between treated animals and concurrent control animals during sepsis (from 6 to 48 h). Upon examination of the differences between treated animals and concurrent control animals during sepsis, there was a greater increase in creatinine, blood urea nitrogen (BUN), and phosphate \((P < 0.0004, P = 0.0005,\) and \(P = 0.0003,\) respectively) and a greater decrease in arterial pH, bicarbonate, and base excess \((P = 0.07, P = 0.02,\) and \(P = 0.02,\) respectively) with epinephrine therapy compared with norepinephrine and vasopressin therapy (Figs. 6 and 7). The changes in these laboratory parameters caused by epinephrine treatment were dose dependent \((2.0 \pm 0.8 \pm 0.2 \mu g \cdot kg^{-1} \cdot min^{-1})\) (parameter: \(P = 0.02,\) and \(P = 0.0002\) ) (Figs. 6 and 7).

**DISCUSSION**

Our canine sepsis model demonstrated a bacterial dose-dependent effect on survival with higher control mortality with more severe infections. This effect was due to bacterial dose-dependent decreases in MAP, CI, and LVEF. Epinephrine therapy was associated with a significantly different effect on outcome than norepinephrine and vasopressin. Compared with concurrent controls, which received only antibiotics and intravenous fluids, the addition of an epinephrine infusion had a harmful effect on survival. In contrast, the addition of vasopressin or norepinephrine resulted in improved survival compared with concurrent controls. Further examination of the effect of each vasopressor on survival demonstrated that their effects were independent of severity of infection. However, the...
Fig. 4. Left: effect of each vasopressor on survival at the various bacterial challenge levels is shown averaged over all drug dose levels. Right: effect of each vasopressor on survival at the different drug dose levels is shown averaged over all bacterial challenge levels. The effects of each vasopressor agent were not dependent on bacterial challenge level; each agent demonstrated similar effects across all bacterial doses studied. Epinephrine demonstrated a significant drug dose-dependent harmful effect on survival characterized by increasing harm with increasing drug doses. Norepinephrine and vasopressin demonstrated similar beneficial effects across all drug doses administered.
harmful effects of epinephrine on survival were demonstrated to be drug dose dependent with increasing harm occurring at increasing doses of epinephrine.

The contrasting survival effects of these vasopressors may be explained by the significantly different effects of epinephrine, compared with vasopressin and norepinephrine, on cardiac function, SVR, and renal and systemic perfusion. Despite adequate intravenous fluid resuscitation, epinephrine treatment caused dose-dependent decreases in CI and LVEF and dose-dependent increases in SVR. Furthermore, epinephrine treatment caused harmful dose-dependent changes in renal and systemic perfusion with significantly higher creatinine, BUN, and phosphate levels and significantly lower pH, bicarbonate, and base excess levels. There were no other measured variables, including MAP, PCWP, CVP, or HR, that demonstrated different effects among epinephrine, norepinephrine, and vasopressin or that were related to the dose of epinephrine. The increased mortality associated with epinephrine therapy may be secondary to the metabolic, vascular, and myocardial effects of α- and β-adrenergic stimulation. Epinephrine-mediated adrenergic stimulation can lead to a hypermetabolic state with increased glycolysis, gluconeogenesis, and lipolysis with sub-
sequent hyperglycemia, lactic acidosis, and ketoacidosis (22, 37, 50). In our study, these metabolic derangements may account for the dose-dependent worsening of acid-base status with epinephrine therapy. In addition, the demonstrated lactic acidosis and renal dysfunction that occurred may be secondary to dose-dependent, α-adrenergic-mediated vasoconstriction with increases in SVR and decreases in hepatosplanchnic and renal blood flow (7, 22, 23). Furthermore, the dose-dependent cardiac dysfunction in our model may be due to α-adrenergic-mediated increases in afterload, catecholamine-induced β-receptor downregulation, catecholamine-induced cardiomyopathy related to prolonged exposure to high-dose epinephrine, or a combination of these three adverse effects (4, 10, 11, 23, 36, 37, 45).

Consistent with our results, increasing doses of epinephrine have been reported to have harmful effects in sepsis. In a previous canine endotoxic shock experiment, epinephrine and norepinephrine increased MAP and CI and decreased gastric mucosal pH, but only a high dose of epinephrine (1.6 μg·kg⁻¹·min⁻¹) significantly increased systemic lactic acidosis (13). Similar findings of increased lactate levels with epinephrine infusions have also been reported in patients with septic shock (22). Furthermore, in a study comparing dopamine, norepinephrine, and epinephrine titrated to maintain similar MAP values in patients with severe septic shock, high-dose epinephrine (mean 0.62, range 0.25–1.89 μg·kg⁻¹·min⁻¹) increased CI but decreased splanchnic perfusion and gastric mucosal pH compared with norepinephrine (7). In another study comparing epinephrine
to norepinephrine plus dobutamine, epinephrine (mean 0.5, range 0.13–1.00 μg·kg⁻¹·min⁻¹) produced decreases in splanchnic blood flow and oxygen uptake with lower mucosal pH (29). In contrast to high-dose epinephrine therapy, low-dose epinephrine (mean dose ≤0.3 μg·kg⁻¹·min⁻¹) has demonstrated beneficial effects in the treatment of septic shock, including improvements in MAP, CI, SVR, oxygen delivery, and gastric mucosal blood flow without detrimental effects on oxygen consumption or lactate levels (40, 50). The above studies suggest that there are dose-dependent harmful effects of epinephrine on organ perfusion in humans consistent with the dose-dependent impairment of systemic perfusion and end-organ injury seen in our canine study.

The harmful effects of epinephrine in our model raise concerns about its commonly accepted use in patients with low CO septic shock. In these patients, epinephrine is used because it is thought that its β-agonist properties should improve CO and subsequently improve systemic perfusion. However, despite adequate fluid resuscitation, epinephrine impaired cardiac function in our model of low CO septic shock. In addition, epinephrine decreased systemic perfusion, worsened acidosis, and impaired organ function in our model. Therefore, in contrast to the clinical rationale to use epinephrine for its β-agonist effects in low CO sepsis, it appears that epinephrine may have harmful effects on the myocardium and its clinical use should be carefully monitored.
The use of norepinephrine to treat septic shock is becoming standard therapy. In addition to studies demonstrating increases in MAP, CO, and improved renal and intestinal blood flow (8, 26, 27, 46), norepinephrine administration has been associated with improved outcome in septic shock patients. In a single observational study, patients receiving norepinephrine had significantly lower hospital mortality than patients receiving either high-dose dopamine or epinephrine (28). This improvement in survival is consistent with the effects of norepinephrine therapy in our study. The beneficial effects of norepinephrine are most likely the result of α-adrenergic-mediated vasoconstriction with subsequent improvements in systemic arterial blood pressure and organ perfusion. However, it remains possible that norepinephrine therapy may have harmful effects when administered at doses higher than those used in our study. Similar to high-dose epinephrine therapy, higher dose norepinephrine may lead to excessive α-adrenergic-mediated vasoconstriction with increases in SVR and decreases in organ perfusion and may potentially cause organ failure and acidosis.

The use of vasopressin in septic shock is becoming increasingly popular secondary to the recent description of septic shock as a state of relative vasopressin deficiency. Studies have shown that vasopressin levels are elevated early in septic shock and decrease as sepsis progresses, with approximately one-third of late septic shock patients developing a vasopressin deficiency (20, 41). Low-dose vasopressin (0.02–0.08 U/min) has recently been used in small trials to treat patients with refractory septic shock. These studies have shown decreased norepinephrine requirements, increased MAP and SVR, and increased urine output without changes in gastric perfusion, creatinine, lactate, and pH (9, 16, 25, 47). There have also been reports of autonomic-mediated decreases in CI and HR with vasopressin infusions (15, 16). Although the effects of vasopressin therapy on CI in these studies were small, caution is warranted because any decrease in CI may be detrimental during sepsis, especially in those patients who have developed low CO septic shock. In all of these studies, vasopressin was administered in conjunction with another vasopressor, typically norepinephrine. Vasopressin administration may improve hemodynamic parameters in septic patients with low circulating vasopressin levels by potentiating the effects of norepinephrine and by blocking potassium-sensitive ATP channels that may be excessively activated in septic shock (21, 32, 39, 49). Our data suggest that low-dose vasopressin has a minimal pressor effect and does not decrease CI or HR. The absence of these physiological changes in our study may be secondary to sepsis-induced autonomic insufficiency or to the fact that we did not investigate the effects of vasopressin in conjunction with other vasopressor agents. However, despite not leading to increases in systemic arterial pressure and SVR, vasopressin therapy improved survival. This beneficial effect may be secondary to vasopressin causing an enhanced sensitivity to endogenous catecholamines with subsequent improvement in cardiac function. This would allow for the maintenance of organ perfusion without the potentially detrimental effects of excessive vasoconstriction from α-adrenergic stimulation with high-dose catecholamine therapy.

The limitations of our study include the general issues surrounding the extrapolation of results from an animal model to the clinical setting. In addition, the effects of epinephrine, norepinephrine, and vasopressin may be different in hyperdynamic models of septic shock and may be different when administered in doses outside of the studied ranges. Furthermore, our study did not have the power to demonstrate a significant improvement in survival with either vasopressin or norepinephrine therapy alone. Our study only showed that the effects of these two agents are better than the effects of epinephrine therapy. Future studies are needed to compare the effects of vasopressin and norepinephrine alone to a combination of norepinephrine and vasopressin on survival.

In conclusion, the use of vasopressors is often necessary to successfully treat septic shock; however, limited data are available on the effects of the different vasopressor agents on outcome. Each agent has a different risk-benefit profile, which needs to be fully characterized. Independent of the severity of infection, epinephrine demonstrated a dose-dependent harmful effect on cardiac function, organ perfusion, and survival in our canine model of low CO septic shock. High doses of epinephrine decreased EF and CI, and increased SVR leading to impaired organ perfusion with increased BUN and creatinine, decreased pH and bicarbonate, and increased mortality. These harmful effects would not have been detected without monitoring of cardiac function because other variables, including HR and MAP, did not reflect these toxic effects. Within the dose range used in our study, norepinephrine and vasopressin did not demonstrate these effects. It is possible that with further increases in dose, norepinephrine and vasopressin may produce harmful physiological effects that may increase mortality. From our study, epinephrine has a risk-benefit profile characterized by harmful dose-dependent effects, whereas norepinephrine and vasopressin demonstrate more favorable risk-benefit profiles over the dose ranges administered in our study. Norepinephrine and vasopressin should be investigated further, both independently and in combination with each other, to further characterize their effects over a wide range of doses in high- and low-output models of septic shock.

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