Case Series

Journal of Veterinary Emergency and Critical Care **17**(4) 2007, pp 399–408
doi: 10.1111/j.1476-4431.2007.00235.x

Vasopressin therapy in dogs with dopamine-resistant hypotension and vasodilatory shock

Deborah C. Silverstein, DVM, DACVECC, Lori S. Waddell, DVM, DACVECC, Kenneth J. Drobatz, DVM, MSCE, DACVIM, DACVECC and Lesley G. King, MVB, DACVIM, DACVECC

Abstract

Objective: To describe the therapeutic use of vasopressin in dogs with dopamine-resistant hypotension and vasodilatory shock.

Series summary: We report the effects of intravenous vasopressin therapy on mean arterial blood pressure and central venous pressure (CVP) in 5 dogs with dopamine-resistant hypotension from vasodilatory shock. All subjects had documented hypotension and vasodilation, despite adequate intravascular volume and catecholamine therapy. There was an increase in mean arterial pressure following vasopressin administration. No cardiac arrhythmias were noted, nor were there clinically significant changes in CVP.

New information provided: Mean arterial blood pressure increased following vasopressin therapy in all of the dogs. Vasopressin may prove useful in the treatment of vasodilatory shock, however further research is warranted.

(J Vet Emerg Crit Care 2007; 17(4): 399–408) doi: 10.1111/j.1476-4431.2007.00235.x

Keywords: antidiuretic hormone, canine, catecholamine-resistance, central venous pressure, heart rate, hypotension, mean arterial pressure

Introduction

In animals with normal vasomotor tone, a decrease in arterial blood pressure should trigger vasoconstriction leading to pale mucous membranes (MM).[1] During septic shock, this vasoconstrictive response often fails and inappropriate vasodilation known as vasoplegia manifests clinically as red MM and warm extremities.[2,3] In most patients, this type of vasodilatory hypotension responds clinically to the administration of intravenous fluids and catecholamines such as dopamine, dobutamine, phenylephrine, norepinephrine, or epinephrine. In severely affected animals, 'catecholamine-resistant vasodilatory shock' is characterized by refractory hypotension despite intravascular fluid resuscitation and catecholamine administration. Catecholamine-resistant vasodilation is a potentially fatal complication of septic shock, the systemic inflammatory response syndrome (SIRS) and multiple-organ dysfunction syndrome (MODS), and is a final common pathway of death in patients that sustain severe, prolonged shock states of any origin.

Catecholamine-resistant vasodilation is caused by derangements of normal vasodilatory and vasoconstrictor mechanisms, and occurs despite increased levels of norepinephrine, endothelin, and angiotensin II.[4] Elevated levels of nitric oxide and activation of the smooth muscle ATP-sensitive potassium (K_{ATP}) channels and calcium-regulated potassium channels ($K_{Ca^{2+}}$) are the primary causes of the inappropriate vasodilation, but the lack of reflex vasoconstriction is not as clearly understood.[2,5] Other potential contributors to vasoplegia include fatal injuries to the vascular endothelial cells from prolonged hypotension, inadequate oxygen extraction from the tissues, and an increase in the activity of vasodilatory prostaglandins.[6–8] An additional mechanism that may play a significant role in the pathogenesis of refractory vasodilatory shock in both small animals and humans is a deficiency of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH).[2,9] The vasoconstrictive effects of AVP are non-adrenergic and mediated by direct and indirect effects on arterial smooth muscle. In vitro, AVP is a more po-

From the Section of Critical Care, Department of Clinical Studies-Philadelphia, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA.

Address correspondence and reprint requests to:
Dr. Deborah C. Silverstein, Department of Clinical Studies-Philadelphia, School of Veterinary Medicine, University of Pennsylvania, 3900 Delancey St., Philadelphia, PA 19104-6010.
E-mail: dcsilver@vet.upenn.edu

tent vasoconstrictor than angiotensin II, norepinephrine, or phenylephrine, and it also enhances the sensitivity of the vascular endothelium to other pressor agents.[10–14]

Humans with advanced vasodilatory shock have decreased AVP secretion and an enhanced sensitivity to AVP-induced blood pressure changes.[9,11,15] The serum AVP levels are not always consistent with the hemodynamic parameters, however.[16,17] Preliminary studies have demonstrated promising results in the management of humans with refractory hypotension using intravenous infusions of AVP, and many human patients can be weaned off catecholamine support by the addition of AVP therapy.[18–21] A multicenter human clinical trial is currently underway.

Although animal models of sepsis and hemorrhage have demonstrated that there is initially a marked increase in AVP levels, a rapid decline subsequently ensues.[9,22,23] In dogs with experimentally induced septic shock, AVP therapy caused an increase in mean arterial pressure (MAP), oxygen delivery (DO_2), cardiac output (CO), renal blood flow, and survival, without any adverse effects, although high-dose therapy may not restore intestinal blood flow and can result in a hypercoagulable state in human plasma samples.[24–27] The authors are unaware of any clinical veterinary reports of AVP therapy in dopamine-resistant hypotension secondary to vasodilatory shock.

This paper describes the use of AVP to treat 5 dogs with vasodilation and dopamine-resistant hypotension at a university hospital. These cases constitute the first report of administration of AVP to clinical canine patients with persistent hypotension following failure of conventional therapy. Owners gave consent for therapy with a non-standard drug because conventional therapy was not effective. The importance of this report is that it documents an improvement in blood pressure in response to AVP in critically ill dogs with dopamine-resistant shock.

Case 1

A 12-year-old spayed female mixed breed dog weighing 22.4 kg was presented for evaluation of polyuria and polydipsia (5-day duration), anorexia, and vomiting (both of 1-day duration). At presentation, the dog was alert but depressed with a rectal temperature of 35.8 °C (96.5 °F), and had a heart rate (HR) of 120 beats per minute (BPM), respiratory rate of 40 breaths per minute (bpm), pink, dry MM with a capillary refill time (CRT) of 2 seconds, estimated dehydration of 6–8%, a distended abdomen, and cranial organomegaly. The dog's MAP using a Dinamap[a] was 76 mmHg. Laboratory abnormalities included a neutrophilia with mild toxic changes (17,600 cells/μL; reference interval, 5300–19,800 cells/μL), a mild leukocytosis (16,500 cells/μL; reference interval, 3100–14,400 cells/μL), thrombocytosis (712,000/μL; reference interval, 177,000–398,000 cells/μL), hyperglycemia (658 mg/dL, reference interval, 65–112 mg/dL), azotemia (BUN 86 mg/dL; reference interval, 9–33 mg/dL; creatinine 2.9 mg/dL; reference interval, 0.7–1.8 mg/dL), hyperphosphatemia (9.4 mg/dL; reference interval, 2.8–6.0 mg/dL), hypernatremia (158 mmol/L; reference interval, 140–150 mmol/L), increased liver enzymes (alanine aminotranferase 258 IU/L; reference interval, 16–91 U/L; aspartate transaminase 88 IU/L; reference interval, 23–65 IU/L; alkaline phosphatase [ALKP] 2142 IU/L; reference interval, 24–174 IU/L; and γ-glutamyl transferase 267 IU/L; reference interval, 7–24 IU/L), hypercholesterolemia (664 mg/dL; reference interval, 128–371 mg/dL), and hypermagnesemia (3.3 mg/dL; reference interval, 1.6–2.5 mg/dL). Urine was obtained by cystocentesis and a urinalysis revealed a pH of 6.0 with a specific gravity of 1.017, 3+protein, trace ketone bodies, 1+hemoglobin, 2+bile pigments, 1–2 white blood cells per high-power field (HPF), 1–3 red blood cells per HPF, 8–12 epithelial cells per HPF, 0–1 fine granular and coarse granular casts per HPF, and a large number of gram-negative rod-shaped bacteria. A coagulation screen was unremarkable. The dog was diagnosed with diabetic ketoacidosis, a urinary tract infection, a hepatopathy (based on laboratory analysis) and pancreatitis (based on abdominal ultrasound findings). The dog was treated with aggressive intravenous fluid therapy, electrolyte supplementation, broad-spectrum antibiotics, antiemetic therapy, analgesics (buprenorphine,[b] 0.01 mg/kg, IV, every 4–6 hours), and regular insulin as a continuous rate infusion. An arterial catheter[c] was placed for direct pressure monitoring using a bedside monitor.[d] After 24 hours of treatment, the dog's HR had increased to 140 bpm and the MAP had decreased to 50 mmHg. A total of 2255 mL of isotonic crystalloids had been administered (approximately 94 mL/hr) and approximately 600 mL of urine and vomitus had been lost over this time period. The dog's colloid osmotic pressure was 16.4 mmHg. The MM remained pink and the CRT was 1 second. Vasodilatory shock was diagnosed, presumptively caused by the SIRS associated with pancreatitis and urosepsis. A multi-lumen catheter[e] was placed in the jugular vein, allowing measurement of the central venous pressure (CVP), which was 6 mmHg, and a urinary catheter[f] was placed for urine output (UOP) monitoring. Dopamine[g] was given intravenously at 10 μg/kg/min, but had no effect on the MAP or HR. AVP[h] was added as an intravenous infusion at 0.5 mU/kg/min. The MAP increased to 71 mmHg within 5 minutes. Forty minutes later, the MAP was 80 mmHg, CVP remained at 6 mmHg, and

the HR had decreased to 128 BPM. The AVP infusion was continued at the same dose, and dopamine was continued at 10 μg/kg/min for 1 hour and 40 minutes after starting the AVP, at which time the dog's MAP was 90 mmHg, the CVP was 7 mmHg, and the HR was 123 BPM. The dog's MM were pink with a CRT of 1 second throughout this time period. The UOP remained at 1.5 mL/kg/hr during the AVP infusion. Due to continued vomiting and concern for aspiration pneumonia, the owners elected to euthanize the dog. A necropsy examination confirmed multifocal, acute pancreatic necrosis with inflammation and moderate to severe hepatocellular fatty change.

Case 2

A 10-year-old spayed female Malamute weighing 42.8 kg presented to the referring veterinarian for evaluation of decreased appetite (1 week duration), polydipsia, and vomiting (1 day duration). The dog was diagnosed with septic peritonitis based on cytologic analysis of an abdominocentesis fluid sample and was referred for surgery. At presentation, the dog was depressed but alert, had a rectal temperature of 40.9 °C (105.6 °F), HR of 80 BPM, respiratory rate of 36 bpm, red and tacky MM with a CRT of 1.5 seconds, and a distended and painful abdomen. The dog was given a bolus of crystalloid fluids intravenously, broad-spectrum antibiotics, and exploratory surgery was performed. Septic peritonitis from a jejunal perforation secondary to foreign body was diagnosed. A jejunal resection and anastomosis was performed. The dog was stable throughout the surgery and recovered uneventfully, except for intermittent vomiting. Aggressive fluid therapy was continued using balanced electrolyte replacement solutions, natural (fresh frozen plasma), and synthetic colloids. Antibiotic therapy was initiated using ampicillin[i] (22 mg/kg, IV, q 8 h) and enrofloxacin[j] (10 mg/kg, IV, q 24 h), pain was treated with an intravenous butorphanol[k] continuous rate infusion (CRI) at 0.2 mg/kg/hr.

The MAP was stable for 4 hours postoperatively, then hypotension developed secondary to presumed septic shock. A multi-lumen catheter was placed in the jugular vein. The CVP was 4 mmHg, the MAP was 62 mmHg, and the HR was 140 BPM. A urinary catheter was placed to monitor UOP. The dog remained febrile with a rectal temperature of 40 °C (104 °F) with red MM with a CRT of 1–2 seconds. The UOP averaged 1–1.5 mL/kg/hr. A CRI of dopamine was started at 10 μg/kg/min. At first, the MAP responded to the dopamine and remained >70 mmHg for the next 12 hours, with a HR that ranged from 104–142 BPM. After 12 hours of dopamine therapy, the MAP decreased to 60 mmHg, the CVP remained at 4 mmHg, and the HR was 140 BPM. The blood pressure was not responsive to an IV bolus of 10 mL/kg of synthetic colloids administered over 30 minutes. Therefore, an AVP CRI was initiated (in addition to the dopamine) at 0.5 mU/kg/min intravenously. Within 30 minutes, the MAP increased to 67 mmHg and the HR decreased to 117 BPM. UOP remained unchanged. Within 30 minutes of increasing the AVP CRI dose to 0.6 mU/kg/min, the MAP increased further to 72 mmHg, the CVP increased to 8 mmHg, and the HR was 108 BPM. The UOP increased to 1.17–2.48 mL/kg/hr during this time. Because the MAP intermittently decreased to the mid-high 60's, the AVP CRI was gradually increased by 0.1 mU/kg/min over the next 3 hours, to a maximum dose of 1 mU/kg/min. The UOP ranged from 1.67–1.82 mL/kg/hr over this period. At this AVP dose, the MAP was improved at 77 mmHg, the CVP remained at 8 mmHg, and the HR was 130 BPM. The dog remained on AVP and dopamine infusions for the next 6 hours, at which point the MAP decreased again to 64 mmHg. The UOP over this 6 hour period was 1.5–3.85 mL/kg/hr. The dopamine was increased to 12 μg/kg/min, resulting in an increase of the MAP to 70 mmHg, with a CVP of 7 mmHg, and a HR of 145 BPM. The UOP remained at 3 mL/kg/hr. The owners elected to euthanize the dog due to continued vomiting and expense. The total duration of AVP therapy was 12 hours. A necropsy was performed and severe peritonitis secondary to multifocal chronic intestinal perforations with fibrous omental adhesions were found throughout the small intestine. The anastomosis site was leaking, and additional perforations were present that had not been appreciated at the time of surgical exploration.

Case 3

A 10-year-old spayed female Labrador Retriever weighing 27 kg was presented for evaluation of progressive ataxia and apparent cervical pain of 2 weeks duration. Physical examination revealed normal vital signs, a short-strided thoracic limb gait, pelvic limb ataxia with conscious proprioceptive deficits, and apparent pain when the neck was moved dorsally or to the left. All laboratory tests were unremarkable and no abnormalities were observed on thoracic radiographs. The dog was anesthetized for a lumbosacral cerebrospinal fluid (CSF) tap, survey cervical radiographs, and myelogram. The CSF was clear with a total protein of 90 mg/dL and a nucleated cell count of 3 cells/μL. A mild mononuclear pleocytosis was present. An extradural lesion at C7-T1 resulting in spinal cord compression due to intervertebral disc disease was present on the myelogram. A ventral slot was performed at the site. The dog was stable under anesthesia. The dog was treated with hydromorphone[l] (0.1 mg/kg, IM, q 4–6 h) and deracoxib[m] (3 mg/kg, PO, q 24 h) for pain after

surgery. Postoperatively, the dog had a mild Horner's syndrome on the right and was intermittently gagging, but was ambulatory and demonstrated neurological improvement. Two days after surgery, the dog became lethargic, developed a fever (39.4 °C, 103 °F), tachycardia (140 BPM), and tachypnea (40 bpm) with an increased respiratory rate and effort. Chest radiographs revealed an alveolar pattern in the right cranial, right middle, and left cranial lung fields, and a normal cardiac silhouette. A transtracheal wash was performed and suppurative inflammation with bacterial rods was present in the cytologic sample. A bacterial culture was subsequently positive for *Escherichia coli*. A complete blood count (CBC) was performed and a leukopenia (493 cells/μL; reference interval, 5300–19,800 cells/μL) with marked toxic changes noted, neutropenia (334 cells/μL; reference interval, 3100–14,400 cells/μL), lymphopenia (113 cells/μL; reference interval, 900–5500 cells/μL), and thrombocytopenia (168,000 cells/μL; reference interval, 177,000–398,000 cells/μL) were present. The dog was treated with ampicillin (22 mg/kg, IV, q 8 h), enrofloxacin (10 mg/kg, IV, q 24 h), and amikacin[n] (15 mg/kg, IV, q 24 h) for the pneumonia. Famotidine[o] (0.5 mg/kg, IV, q 12 h) and metoclopramide[p] (1 mg/kg/day CRI) were also administered for the vomiting.

An arterial blood gas and stat chemistry was analyzed and detected hypoxemia (PaO_2 60 mmHg; reference interval, 85–100 mmHg), hypocarbia ($PaCO_2$ 25.7 mmHg; reference interval, 34–40 mmHg), an elevation of the alveolar–arterial gradient (61.7; reference interval, <15), a normal pH (pH 7.37; reference interval, 7.35–7.45), metabolic acidosis (HCO_3 15 mmol/L; reference interval, 20–24 mmol/L), elevated base excess (−10 mmol/L; reference interval, −5 to 0) an increased lactate (5.0 mmol/L; reference interval, <2.0 mmol/L), hypoglycemia (40 mg/dL; reference interval, 65–112 mg/dL), and normal electrolyte (sodium, potassium, chloride, calcium, magnesium) concentrations. Oxygen was administered (2.5 L/min) through nasal prongs, and 0.25 g/kg of dextrose was administered IV. A direct blood pressure was measured and the MAP was 55 mmHg with a HR of 128 BPM. Multiple isotonic crystalloid and synthetic colloid boluses (totaling 50 and 10 mL/kg, respectively) were administered intravenously. The dog's MAP did not improve following aggressive fluid resuscitation and the lactate increased to 12.3 mmol/L over the following 4 hours. A CRI of dopamine was initiated at 10 and subsequently increased to 15 μg/kg/min IV. The dog had bright pink MM, a CRT of 1 second, and a rectal temperature of 38.4 °C (101.2 °F) 1 hour later, and was diagnosed with septic shock secondary to presumptive aspiration pneumonia. The MAP did not improve and in fact decreased to 38 mmHg, with a HR of 135 BPM. At that time the lactate had increased to 13.3 mmol/L.

AVP was administered at 0.5 mU/kg/min IV because of the drop in MAP in the face of dopamine therapy, and the MAP increased to 54 mmHg and HR decreased to 128 within 5 minutes. Fifteen minutes later, the dose of the AVP infusion was increased to 0.75 mU/kg/min and the MAP increased to 61 mmHg and the HR decreased to 118 BPM. The lactate also decreased to 12.6 mmol/L. The AVP was increased in further increments of 0.1–0.25 mU/kg/min every 15–20 minutes to a maximum rate of 1.25 mU/kg/min at which point the MAP increased to 71 mmHg, the HR decreased to 105 BPM, and lactate decreased to 11.4 mmol/L. The dog vomited several times and the dyspnea worsened. Mechanical ventilation was recommended, but the owners declined. Five hours after initiating AVP therapy, the dog's PaO_2 was 43 mmHg with an inspired oxygen concentration of approximately 60%, the $PaCO_2$ was 33 mmHg, and the lactate was 13.3 mmol/L. A respiratory arrest occurred and mechanical ventilation was initiated with permission from the owners. During the arrest, the HR decreased to 50 BPM and 0.05 mg of atropine[q] was administered IV. The hypoglycemia persisted and further dextrose boluses were necessary. The dog was placed on fentanyl[r] (1 μg/kg/min) and diazepam[s] (0.25 mg/kg/hr) IV in order to maintain endotracheal intubation and mechanical ventilation with positive end-expiratory pressure. The MAP decreased to 45 mmHg following the arrest and the AVP infusion was increased to 5 mU/kg/min. The MAP increased to 51 mmHg, at which point the owners elected to euthanize the dog due to the poor prognosis and financial constraints. A necropsy confirmed the presence of severe, multifocal to coalescing, suppurative, and necrotizing bronchopneumonia with intrabronchial foreign material (consistent with aspiration pneumonia) and multifocal, peracute myelomalacia at segments C8-T1.

Case 4

An 8-year-old castrated male Jack Russell Terrier weighing 14.3 kg was presented for evaluation of progressive respiratory distress of 5 weeks duration and anorexia of 2 days duration. The dog was depressed, but responsive at presentation. The rectal temperature was 39.2 °C (102.6 °F), the HR was 132 BPM with weak, synchronous femoral pulses, and the respiratory rate was 52 bpm with an increase in inspiratory effort and stridor. A bilateral clear nasal discharge from thickened, hyperpigmented nares was present. The MM were red with a CRT of 1 second. The oxygen saturation measured by pulse oximetry was 92% on room air and an indirect MAP was 55 mmHg. Initial laboratory analyses revealed a nonregenerative anemia (hematocrit 33.4%; reference interval, 40.3–60.3%; absolute ret-

iculocyte count 8000 cells/μL; reference interval for regeneration, >80,000 cells/μL) and a lymphopenia (479 cells/μL; reference interval, 900–5500 cells/μL). Although the total white blood cell count was normal, there were 3200 band neutrophils/μL with marked toxic change. The BUN and phosphorous were mildly elevated (36 mg/dL; reference interval, 9–33 mg/dL and 7.3 mg/dL; reference interval, 2.8–6.1 mg/dL, respectively) and the ALKP was also increased (683 IU/L; reference interval, 24–174 IU/L). Urinalysis was unremarkable. Rickettsial disease and *Aspergillus sp*. titers were negative. Thoracic radiographs were unremarkable and hepatomegaly was evident on abdominal radiographs. An abdominal ultrasound was performed and revealed multiple nodules within the liver and bilateral adrenomegaly. A fine needle aspirate of the liver nodules revealed a mild vacuolar hepatopathy with evidence of extramedullary hematopoiesis. The dyspnea appeared to be secondary to an upper airway obstruction based on the inspiratory stridor. The hemodynamic status was consistent with distributive shock, although a source of sepsis or systemic inflammation was not immediately evident.

Isotonic crystalloids and synthetic colloid boluses were administered and the MAP increased to 74 mmHg. Broad spectrum antibiotic therapy was initiated. Intermittent hypoglycemia was treated with dextrose supplementation. Approximately 24 hours after presentation, the MAP decreased to 50 mmHg and was unresponsive to additional fluid therapy. Dopamine was administered at 5 μg/kg/min IV. The dose was gradually increased to 20 μg/kg/min over 4 hours and the MAP increased to 70 mmHg with a HR of 120 BPM. A multi-lumen jugular catheter was placed and the CVP was 5 mmHg. Six hours later, the MAP fell again to 50 mmHg. The CVP was 7 mmHg, the HR was 100 BPM, and the MM were pink with a CRT of 1 second. AVP therapy was added to the dopamine therapy at a dose of 0.5 mU/kg/min and the MAP increased to 80 mmHg. The dopamine infusion was gradually decreased to 10 μ/kg/min and the MAP was 82 mmHg, the CVP was 8 mmHg, and the HR was 82 BPM. The dog remained on the AVP and dopamine for 9 hours with stable hemodynamic indices. Thereafter, the MAP decreased again to 57 mmHg, the HR increased to 104 BPM and the CVP increased to 9 mmHg. The AVP infusion was increased to 0.6 mU/kg/min and the MAP increased to 71 mmHg, the CVP decreased to 8 mmHg, and the HR decreased to 83 BPM. Fourteen hours after increasing the dose to 0.6 mU/kg/min (and 23 hours after starting AVP therapy), the dog was anesthetized for nasal computerized tomography (CT). An aggressive osteolytic lesion was present, originating from the caudal aspect of the left nasal passage and invading the brain through the cribiform plate. Twenty-six hours after starting AVP therapy, the owner elected to euthanize the dog based on the poor long-term prognosis. At the time of euthanasia, the MAP was 88 mmHg, the CVP was 15 mmHg, and the HR was 100 BPM. A necropsy examination was performed and a nasal adenocarcinoma with erosion of the cribiform plate and the left frontal bone was confirmed. Additionally, acute multifocal hepatitis and nephritis with multiple renal interstitial abscesses were present. Severe myeloid hyperplasia was found in the bone marrow.

Case 5

An 11-year-old spayed female Golden Retriever weighing 35 kg was presented for evaluation of anorexia, lethargy, and regurgitation of phlegm for 4 days. The dog was alert and responsive at presentation. A physical examination revealed a rectal temperature of 38.9 °C (102 °F), a HR of 160 BPM, and panting with a mild to moderate increase in respiratory effort. A CBC, biochemical profile, and urinalysis were unremarkable. A large cranial mediastinal mass that displaced the heart caudally and a megaesophagus were observed on thoracic radiographs. An abdominal ultrasonographic examination was unremarkable and a thoracic ultrasonographic examination revealed a cystic, septated cranial mediastinal mass. An acetylcholine receptor antibody test was submitted. A positive result for myasthenia gravis was reported following death of the patient. The dog was anesthetized and a thoracic CT was performed. The mediastinal mass appeared to compress the esophagus on the CT. A median sternotomy was performed and the mass was resected (final histopathological diagnosis was mediastinal adenocarcinoma). A partial lobectomy of the left cranial lung lobe and a left phrenic nerve transection were performed to facilitate removal of the tumor. During anesthesia, the dog received multiple fluid boluses, dopamine (7 μg/kg/min, IV) and phenylephrine[t] (0.2–0.3 μg/kg/min, IV) for hypotension, and atropine (0.02 mg/kg, IV) for bradycardia. Surgical blood loss was minimal.

Following surgery, the dog was hypotensive with a MAP of 43 mmHg and a CVP of 10 mmHg while on 7 μg/kg/min of dopamine. The dopamine was increased to 10 μg/kg/min and the MAP improved to 78 mmHg. The dog was also hypoventilating, with an increased abdominal effort and minimal chest wall movement. The $PaCO_2$ was 77 mmHg and the PaO_2 was 195 mmHg while breathing 100% oxygen. The dog was mechanically ventilated, and fentanyl and diazepam CRIs were initiated for sedation. Over the next 4 hours, the dopamine was weaned off and the dog re-

mained normotensive but continued to require mechanical ventilation. Every 12 hours an attempt was made to wean the dog from mechanical ventilation, but the dog continued to hypoventilate and weaning attempts were unsuccessful. Therefore, the dog remained anesthetized and intubated on a ventilator. Twenty-nine hours after discontinuing the dopamine, the dog became hypotensive again with a MAP of 53 mmHg, a CVP of 11 mmHg, and a HR of 95 BPM. Vasodilatory shock secondary to ventilator-acquired or aspiration pneumonia was suspected.

Dopamine was reinstituted at 5 μg/kg/min and gradually increased to 14 μg/kg/min over the ensuing 12 hours. Despite the dopamine therapy, the MAP remained at 60 mmHg with a CVP of 8 mmHg and a HR of 150 BPM. The dog continued to require anesthesia for mechanical ventilation and the MM were pink with a CRT of 1 second and the rectal temperature was 37.3 °C (99.2 °F). Arterial blood gases remained within the normal range with mechanical ventilation and an FiO_2 of 0.3–0.4. AVP therapy was added at 0.5 mU/kg/min and the MAP increased to 69 mmHg within 15 minutes and increased further up to 80–85 mmHg for the next 3 hours, the CVP increased to 10 mmHg, and the HR decreased to 118–148 BPM. The MAP then decreased to 66 mmHg, therefore the AVP CRI was increased to 0.6 mU/kg/min. The MAP increased to 103 mmHg within 30 minutes and the dopamine dose was decreased to 10 μg/kg/min from 14 μg/kg/min. The MAP decreased to 70 mmHg after this change. The owner elected to euthanize the dog at that time due to the histopathologic diagnosis of adenocarcinoma (possibly originating from thyroglossal duct remnants). The dog received AVP for a total of 4 hours. A necropsy examination was performed and severe, multifocal, fibrinohemorrhagic pleuritis and necrosis was present, as well as severe, multifocal, peripancreatic fat necrosis with saponification. The lungs had moderate congestion with mild, multifocal, alveolar histiocytosis and mild, focal fibrinous pleuritis. The left cranial lung lobe had severe, focally extensive pleural hemorrhage with compression and alveolar histiocytosis. Bacterial pneumonia was not identified, and vasodilatory shock is presumed to have been caused by pancreatitis and pleuritis.

Discussion

To the authors' knowledge this is the first report of the clinical use of AVP infusions for the treatment of hypotension in 5 critically ill dogs with dopamine-resistant hypotension and vasodilatory shock. The dogs in this study all had refractory vasodilatory shock and all were unresponsive to standard medical management including aggressive fluid resuscitation and dopamine CRIs at doses ≥ 10 μg/kg/min. Our intent in presenting these cases is to provide examples of doses and responses to therapeutic AVP administration to dogs with persistent hypotension despite conventional therapy, rather than to discuss specific case management before the use of AVP.

SIRS can be initiated by sepsis, by severe sterile inflammatory processes such as pancreatitis, or by neoplasia, all of which can cause vasodilation and hypotension. Three of the dogs in this report had a known septic process: septic peritonitis (Dog 2), bacterial pneumonia (Dog 3), and probable urosepsis (in addition to neoplasia)(Dog 4). Dog 1 had a hepatopathy, pancreatitis, and possible urosepsis and Dog 5 had severe pleuritis, pancreatitis, and neoplasia. All of the 5 dogs had evidence of vasodilation based on physical examination (pink or red MM and normal to increased rectal temperature), despite severe hypotension (MAP <60 mmHg). Before initiation of AVP therapy, volume expansion and cardiovascular resuscitation was attempted with IV fluids. In 4 of the dogs the CVP was documented to be greater than 4 mmHg. CVP was not measured in one dog because it did not have a central venous catheter, but Dog 3 had received aggressive crystalloid and synthetic colloid boluses (totaling 50 and 10 mL/kg, respectively) with no improvement in blood pressure. All of the dogs were hypotensive (MAP <60 mmHg) despite dopamine therapy at 10–20 μg/kg/min. Thus, these dogs were all suffering from SIRS, with dopamine-resistant hypotension and vasodilatory shock. Typically, patients failing this type of standard resuscitation are considered to be in an extremely morbid (even terminal) condition, and a high mortality rate is predicted.

In retrospect, some additional management strategies might have proven useful in this group of dogs. For all of the dogs, evaluation of the cardiovascular system using a pulmonary artery catheter might have enabled a more accurate assessment of their intravascular volume status by measurement of pulmonary artery wedge pressure. In addition, the CO and systemic vascular resistance before and during vasopressin therapy could have been monitored and any deleterious effects on CO recognized. More frequent monitoring of UOP, lactate measurements, and central venous oxygen saturation would have been useful in these patients. Ideally, recurrence of septic peritonitis might have been diagnosed more rapidly in Dog 2 if a drain had been in place postoperatively. The hemodynamic status of Dog 3 might have been accurately assessed with either a central venous or pulmonary artery catheter, but jugular catheter placement was not possible due to the surgical incision in the neck. In Dog 4, a CT scan was

initially postponed because the animal was not deemed stable for general anesthesia, but in fact, earlier diagnosis of the osteolytic lesion would have assisted in decision-making for that dog. In Dog 5, the administration of pyridostigmine might have facilitated weaning from mechanical ventilation, but the result of the acetycholine receptor antibody titer was not yet available, and hypoventilation was tentatively attributed to surgical resection of the phrenic nerve. Myasthenia gravis in this case was documented to be a paraneoplastic syndrome associated with a cranial medistinal adenocarcinoma rather than the more common cause of thymoma.

AVP is a potent vasoconstrictor peptide, synthesized in the hypothalamus and stored in the posterior pituitary.[28] Normally, it is released into the circulation in response to an increase in the serum osmolality (sensed in the brain) or a reduction in plasma volume (sensed by baroreceptors in the left atrium, aortic arch, and carotid sinus).[13,29] In addition, plasma AVP levels commonly increase in response to pain, nausea, hypoxia, hypercarbia, hypoxemia, drugs or chemicals (i.e., acetylcholine, dopamine, angiotensin II, prostaglandins), certain malignant tumors, and mechanical ventilation.[30–33]

The cellular effects of AVP are mediated by interactions of the hormone with 2 principal types of receptors: V_1 and V_2.[30,34,35] V_1 receptors, previously known as V_{1a} receptors, are predominantly located in the gastrointestinal tract and vascular smooth muscle, and these receptors primarily mediate the vasoconstrictive response to the hormone. In addition, when present in high concentrations, AVP causes the HR-arterial pressure baroreflex curve to shift leftwards by interacting with V_1 receptors in the brain.[10,36,37] In contrast, V_2 receptors are primarily found in the principal cells of the renal cortical and medullary collecting ducts, and these receptors primarily mediate the antidiuretic effects of the hormone.[38] AVP also blunts the accelerated synthesis of nitric oxide following LPS and IL-1β stimulation in sepsis, and also reduces the vasodilatory effects of nitric oxide, thereby preventing the nitric oxide-mediated vasodilation that occurs in sepsis.[39,40]

After initiation of the continuous infusion of AVP in the dogs in this report, an increase in MAP was observed in all 5 dogs within the first 15 minutes of therapy. This case series therefore suggests that exogenous AVP can act as a potent vasoconstrictor in dogs with refractory vasodilatory shock. The starting dose (0.5 mU/kg/min) of AVP was extrapolated from a low-dose AVP protocol used in human medicine (0.04 U/min or 0.57 mU/kg/min for a 70 kg human).[19] Only Dog 1 responded adequately to the initial dose of 0.5 mU/kg/min and remained normotensive on this dose for 140 minutes. Dogs 4 and 5 required 0.6 mU/kg/min, one after 9 hours and the other after 3 hours of starting the drug at 0.5 mU/kg/min. Dog 4 remained on the 0.6 mU/kg/min dose for the remaining 14 hours of life. The remaining 2 dogs required higher doses of AVP, although the reasons for these dose requirements are uncertain. Their doses were titrated up to maximum doses of 1 and 5 mU/kg/min, however the dog that was given 5 mU/kg/min of AVP had shown an a positive response to 1.25 mU/kg/min until an acute episode of vomiting and aspiration occurred, after which the dog experienced respiratory arrest and needed the higher dose. In one human study comparing the effects of high-dose (mean 0.36 U/min [5.1 mU/kg/min in a 70 kg human], range 0.1–0.9 U/min) versus low-dose (mean 0.057 U/min [0.81 mU/kg/min in a 70 kg human], range 0.03–0.08 U/min) AVP infusions in patients with septic shock, no difference in MAP was seen at 6 hours, although the dose of norepinephrine (a concurrently administered vasopressor) was significantly lower in the high-dose group.[u] The potential adverse effects of high-dose vasoconstrictor therapy were considered when choosing the dose for the dogs reported in this study, and efforts were made to minimize the dose as much as possible while maintaining the improvement in MAP. Species differences may exist, however, as we found that our patients required higher doses of AVP than most humans in order to see a satisfactory improvement in MAP. In human patients, catecholamine requirements often decrease upon initiating AVP therapy, possibly because of sensitization at the catecholamine receptors.[41] The dopamine dose was decreased in 2 of the dogs after starting AVP, but the dose remained the same in the other 3 dogs receiving the AVP infusion.

The CVP was 4–8 mmHg before starting the AVP infusion in the 4 dogs in which it could be measured. The CVP increased following AVP therapy in the 4 dogs with a central catheter; by 1–2 mmHg in Dogs 1 and 5, by 3–4 mmHg in Dog 2, and by 8 mmHg in Dog 4. There were no major changes in fluid therapy or measured alterations in UOP that might have affected the CVP value during AVP therapy in Dog 4. Therefore, we speculate that this increase may have occurred secondary to central pooling of the blood volume and a decrease in CO due to the increase in afterload, although this finding was not reproduced in an experimental canine study.[24] During the AVP infusion, we did not observe any brady- or tachyarrhythmias in the dogs.

The global hemodynamic effects of AVP are interesting. Concerns exist that AVP may increase afterload secondary to vasoconstriction, thereby decreasing CO. In human clinical cases, there was an 11% decrease in cardiac index, an 18% increase in MAP, and no signifi-

cant change in pulmonary vascular resistance during AVP treatment.[42] There is evidence that V_1 receptors are present on cardiac myocytes and that stimulation of these receptors leads to an increase in intracellular calcium concentrations and positive inotropic effects, which might contribute to an increase in CO and blood pressure.[24,43–45] There is evidence in dogs that stimulation of the V_2 receptor can cause peripheral vasodilation, and this may account for the initial decrease in systemic vascular resistance (SVR) seen in some experimental studies.[46,47] This decrease in SVR in conjunction with an increase in cardiac index was also reported by Minecci et al. in a study of septic dogs.[24]

Experimental canine studies have also shown decreases in pulmonary, coronary, and vertebrobasilar arterial resistance following AVP administration.[43,48–54] This vasodilation may be secondary to activation of endothelial oxytocin receptors (OTRs) that trigger activation of endothelial isoforms of nitric oxide synthetase. Although these local changes in blood flow would not significantly affect the systemic blood pressure, they are theoretically desirable in order to prevent vasoconstriction to these vital organs. There is one canine study, however, that showed coronary artery vasoconstriction and ischemia in response to AVP administration.[55] In rats, AVP has been shown to increase renal blood flow by inducing renal vasodilation, and to stimulate the release of prostacyclin in cardiac myocytes.[56] The use of AVP did not alter sublingual microcirculatory (MC) perfusion measurements, but did increase MAP, in a man with refractory shock following cardiac bypass, although terlipressin worsened sublingual MC in another patient.[57,58] Using intravital microscopy, a non-septic hamster model demonstrated selective vasoconstriction of large arterioles, but not small vessels, during an AVP infusion.[59] In summary, it appears that AVP causes vasoconstriction as well as vasodilation, depending on the species, vascular bed studied, the receptor density of V_1 receptors versus OTRs, the dose of AVP used, and the duration of exposure to the hormone.[60] As none of our clinical patients had a pulmonary artery catheter in place, the cardiac index, SVR, and pulmonary vascular index were not measured. Further studies, with standardized treatments such as fluid therapy and other vasopressors, are needed to accurately understand the effects of AVP therapy on cardiac index and blood flow to vital organs in clinical canine patients.

Human studies have shown a 79% increase in UOP during AVP therapy.[42] Neonates with hypotension and acute renal injury also showed a positive response to AVP treatment.[61] This seems paradoxical as ADH's action on V_2 receptors in the kidney leads to an increase in free water resorption and decrease in UOP. Possible mechanisms for the increase in UOP following AVP therapy include an increase in MAP and subsequent renal perfusion, downregulation of the V_2 receptor, nitric-oxide mediated afferent arteriolar vasodilation, selective efferent arteriolar vasoconstriction, and OTR-activated natriuresis.[62–64] Although no conclusions can be made about the UOP in Dogs 1 and 2, it evident that the urine production was maintained, if not increased, following AVP therapy. UOP was not assessed in the other dogs of this report, as the short timeline precluded its accurate analysis during AVP administration. Further studies in dogs are warranted to elucidate the effects of AVP infusions on UOP.

At the time of euthanasia, 4 of the dogs were normotensive with MAP ≥ 70 mmHg. Dog 3 had just been resuscitated from a respiratory arrest and was moribund. We documented no obvious side effects from the AVP treatment, but it might have been difficult to appreciate mild changes due to the drug, and it is difficult to determine whether any end-organ damage might have resulted from the AVP therapy. We recognize that blood pressure by itself does relate directly to outcome or perfusion and organ blood flow, but it is one measure of perfusion that is readily available in the clinical setting. Although the dogs in this report were all euthanized, the outcome if therapy was continued is unknown. For all dogs, the decision to euthanize was made based on the severity of the clinical condition in spite of aggressive treatment, poor long-term prognosis, and expense.

There are several potential limitations to this case series. First, the number of animals reported is small. Second, pulmonary artery catheter monitoring in the dogs would have been ideal, as pulmonary capillary wedge pressure would have given a more accurate estimate of the adequacy of intravascular volume loading than CVP; other hemodynamic parameters could have been monitored. Finally, the medical therapy of the dogs was not controlled and we did not standardize or regulate the administration of fluid boluses, blood products, analgesics, or anesthetics that might contribute to changes in MAP, HR, and CVP independent of the AVP infusion. Despite these limitations, this is the first report of the use of AVP infusions to successfully treat dopamine-resistant hypotension in clinical canine patients. Based on these cases, dogs with hypotension despite fluid resuscitation and conventional vasopressor therapy may benefit from treatment with an AVP infusion.

Conclusion

The development of adrenergic hyposensitivity in critically ill animals poses a clinical challenge. AVP ap-

pears to be a novel adjunct to conventional vasopressor therapy for dopamine-resistant hypotension due to vaso-dilatory shock in dogs and this therapy warrants continued investigation. Fortunately, AVP is not patented and is therefore affordable for clinical and research use. Future studies might investigate the use of AVP in a larger number of dogs with refractory hypotension, in comparison with catecholamines, using a randomized, controlled, blinded study design. In addition, it would be beneficial to measure the serum AVP or copeptin (a precursor of AVP) levels before, during, and after AVP administration.[65] If possible, necropsies should be performed on all dogs in future studies. Additional variables that should be investigated include effects on UOP, the hypothalamic-pituitary-axis, coagulation, CO, and systemic vascular resistance. This additional information will help to better understand the potential uses and side effects of this drug in veterinary patients.

Acknowledgements

The authors would like to acknowledge the critical care residents and intensive care unit nurses who assisted with data collection.

Footnotes

[a] Dinamap, Model 1846 SX, Critikon Inc., Tampa, FL.
[b] Buprenorphine hydrochloride, Hospira Inc., Lake Forest, IL.
[c] Insyte 22 gauge catheter, Becton Dickinson, Franklin Lakes, NJ.
[d] Escort II+, Medical Data Electronics, Arleta, CA.
[e] Triple lumen venous catheter, Arrow International Inc., Reading, PA.
[f] Bardex Foley Catheter, C.R. Bard Inc., Covington, GA.
[g] Dopamine hydrochloride, American Regent Inc., Shirley, NY.
[h] Vasopressin Injection, USP, American Regent Inc.
[i] Ampicillin, Sandoz Inc., Broomfield, CO.
[j] Enrofloxacin, Bayer, Shawnee, KS.
[k] Butorphanol tartrate, Fort Dodge Animal Health, Fort Dodge, IA.
[l] Hydromorphone hydrochloride, Baxter Healthcare Corp., Deerfield, IL.
[m] Deracoxib, Novartis Animal Health Inc., Greensboro, NC.
[n] Amikacin sulfate, The Butler Co., Columbus, OH.
[o] Famotidine, Baxter Healthcare Corp., Deerfield, IL.
[p] Metoclopramide, Baxter Healthcare Corp.
[q] Atropine sulfate, Butler Animal Health Supply, Dublin, OH.
[r] Fentanyl, Hospira Inc.
[s] Diazepam, Hospira Inc.
[t] Phenylephrine hydrochloride, American Regent Inc., Shirley, NY.
[u] Browning L, Piekos K, Bander J, et al. Conventional versus high-dose titratable vasopressin infusions in the treatment of vasopressor dependent septic shock. Crit Care Med 2002; 30:A106 (abstract).

References

1. Guyton AC, Hall JH. Textbook of medical physiology, In: Guyton AC, Hall JE. eds. Nervous Regulation of the Circulation, and Rapid Control of Arterial Pressure, 11th edn. Philadelphia: Elsevier Saunders; 2005, pp. 184–194.
2. Landry DW, Oliver JA. Mechanism of disease: the pathogenesis of vasodilatory shock. N Engl J Med 2001; 345(8):588–595.
3. Young JD. The heart and circulation in severe sepsis. Br J Anaesth 2004; 93(1):114–120.
4. Chernow B, Roth BL. Pharmacologic manipulation of the peripheral vasculature in shock: clinical and experimental approaches. Circ Shock 1986; 18(2):141–155.
5. Robin JK, Oliver JA, Landry DW. Vasopressin deficiency in the syndrome of irreversible shock. J Trauma 2003; 54(5 Suppl):S149–S154.
6. Byrne JJ. Shock. N Engl J Med 1966; 275(10):543–546.
7. Parrillo JE. Pathogenetic mechanisms of septic shock. N Engl J Med 1993; 328(20):1471–1477.
8. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The ibuprofen in sepsis study group. N Engl J Med 1997; 336(13):912–918.
9. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997; 95(5):1122–1125.
10. Undesser KP, Hasser EM, Haywood JR, et al. Interactions of vasopressin with the area postrema in arterial baroreflex function in conscious rabbits. Circ Res 1985; 56(3):410–417.
11. Karmazyn M, Manku MS, Horrobin DF. Changes of vascular reactivity induced by low vasopressin concentrations: interactions with cortisol and lithium and possible involvement of prostaglandins. Endocrinology 1978; 102(4):1230–1236.
12. Bartelstone HJ, Nasmyth PA. Vasopressin potentiation of catecholamine actions in dog, rat, cat, and rat aortic strip. Am J Physiol 1965; 208:754–762.
13. Mohring J, Glanzer K, Maciel, JA Jr., et al. Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension. J Cardiovasc Pharmacol 1980; 2(4):367–376.
14. Schwartz J, Keil LC, Maselli J, et al. Role of vasopressin in blood pressure regulation during adrenal insufficiency. Endocrinology 1983; 112(1):234–238.
15. Sharshar T, Blanchard A, Paillard M, et al. Circulating vasopressin levels in septic shock. Crit Care Med 2003; 31(6):1752–1758.
16. Jochberger S, Mayr VD, Luckner G, et al. Serum vasopressin concentrations in critically ill patients. Crit Care Med 2006; 34(2):293–299.
17. Lodha R, Vivekanandhan S, Sarthi M, et al. Serial circulating vasopressin levels in children with septic shock. Pediatr Crit Care Med 2006; 7(3):220–224.
18. Argenziano M, Choudhri AF, Oz MC, et al. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997; 96(9 Suppl II):286–290.
19. Malay MB, Ashton RC Jr., Landry DW, et al. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999; 47(4):699–703.
20. Dunser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation 2003; 107(18):2313–2319.
21. Patel BM, Chittock DR, Russell JA, et al. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002; 96(3):576–582.
22. Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation 1999; 100(3):226–229.
23. Errington ML, Rocha e Silva M Jr. The secretion and clearance of vasopressin during the development of irreversible haemorrhagic shock. J Physiol 1971; 217(1):43P–45P.
24. Minneci PC, Deans KJ, Banks SM, et al. Differing effects of epinephrine, norepinephrine, and vasopressin on survival in a canine model of septic shock. Am J Physiol Heart Circ Physiol 2004; 287(6):H2545–H2554.
25. Schrauwen E, Houvenaghel A. Vascular effects of vasopressin an oxytocin in the pig mesenteric bed. Pflugers Arch 1982; 392(3):301–303.
26. Filep J, Rosenkranz B. Mechanism of vasopressin-induced platelet aggregation. Thromb Res 1987; 45(1):7–15.
27. Guzman JA, Rosado AE, Kruse JA. Vasopressin vs norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. J Appl Physiol 2003; 95(2): 803–809.

28. Rose BD, Post TW. Clinical physiology of acid-base and electrolyte disorders, In: Rose BD, Post TW. eds. Effects of Hormones on Renal Function, 4th edn. New York: McGraw-Hill Inc; 2001, pp. 163–238.
29. Reid IA. Role of vasopressin deficiency in the vasodilation of septic shock. Circulation 1997; 95(5):1108–1110.
30. Holmes CL, Patel BM, Russell JA, et al. Physiology of vasopressin relevant to management of septic shock. Chest 2001; 120(3):989–1002.
31. Leng G, Brown CH, Russell JA. Physiological pathways regulating the activity of magnocellular neurosecretory cells. Prog Neurobiol 1999; 57(6):625–655.
32. Leng G, Dyball RE, Luckman SM. Mechanisms of vasopressin secretion. Horm Res 1992; 37(1–2):33–38.
33. Day TA, Sibbald JR. Noxious somatic stimuli excite neurosecretory vasopressin cells via A1 cell group. Am J Physiol 1990; 258(6 Part 2):R1516–R1520.
34. Holmes CL, Landry DW, Granton JT. Science review: vasopressin and the cardiovascular system part 1 – receptor physiology. Crit Care 2003; 7(6):427–434.
35. Phillips PA, Abrahams JM, Kelly JM, et al. Localization of vasopressin binding sites in rat tissues using specific V1 and V2 selective ligands. Endocrinology 1990; 126(3):1478–1484.
36. Luk J, Ajaelo I, Wong V, et al. Role of V1 receptors in the action of vasopressin on the baroreflex control of heart rate. Am J Physiol 1993; 265(3 Part 2):R524–R529.
37. Cowley AW Jr., Switzer SJ, Guinn MM. Evidence and quantification of the vasopressin arterial pressure control system in the dog. Circ Res 1980; 46(1):58–67.
38. Thibonnier M. Signal transduction of V1-vascular vasopressin receptors. Regul Pet 1992; 38:1–11.
39. Kusano E, Tian S, Umino T, et al. Arginine vasopressin inhibits interleukin-1 beta-stimulated nitric oxide and cyclic guanosine monophosphate production via the V1 receptor in cultured rat vascular smooth muscle cells. J Hypertens 1997; 15(6):627–632.
40. Umino T, Kusano E, Muto S, et al. AVP inhibits LPS- and IL-1beta-stimulated NO and cGMP via V1 receptor in cultured rat mesangial cells. Am J Physiol 1999; 276(3 Part 2):F433–F441.
41. Luckner G, Dunser MW, Jochberger S, et al. Arginine vasopressin in 316 patients with advanced vasodilatory shock. Crit Care Med 2005; 33(11):2659–2666.
42. Holmes CL, Walley KR, Chittock DR, et al. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. Intensive Care Med 2001; 27(8):1416–1421.
43. Vanhoutte PM, Katusic ZS, Shepherd JT. Vasopressin induces endothelium-dependent relaxations of cerebral and coronary, but not of systemic arteries. J Hypertens Suppl 1984; 2(3):S421–S422.
44. Cheng CP, Igarashi Y, Klopfenstein HS, et al. Effect of vasopressin on left ventricular performance. Am J Physiol 1993; 264(1 Part 2):H53–H60.
45. Liu P, Hopfner RL, Xu YJ, et al. Vasopressin-evoked [Ca2+]i responses in neonatal rat cardiomyocytes. J Cardiovasc Pharmacol 1999; 34(4):540–546.
46. Liard JF. Peripheral vasodilatation induced by a vasopressin analogue with selective V2-agonism in dogs. Am J Physiol 1989; 256(6 Part 2):H1621–H1626.
47. Liard JF. cAMP and extrarenal vasopressin V2 receptors in dogs. Am J Physiol 1992; 263(6 Part 2):H1888–H1891.
48. Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. Chest 1993; 103(4):1241–1245.
49. Sai Y, Okamura T, Amakata Y, et al. Comparison of responses of canine pulmonary artery and vein to angiotensin II, bradykinin and vasopressin. Eur J Pharmacol 1995; 282(1–3):235–241.
50. Suzuki Y, Satoh S, Oyama H, et al. Regional differences in the vasodilator response to vasopressin in canine cerebral arteries in vivo. Stroke 1993; 24(7):1049–1053.
51. Suzuki Y, Satoh S, Kimura M, et al. Effects of vasopressin and oxytocin on canine cerebral circulation in vivo. J Neurosurg 1992; 77(3):424–431.
52. Wallace AW, Tunin CM, Shoukas AA. Effects of vasopressin on pulmonary and systemic vascular mechanics. Am J Physiol 1989; 257(4 Part 2):H1228–H1234.
53. Cosentino F, Sill JC, Katusic ZS. Endothelial L-arginine pathway and relaxations to vasopressin in canine basilar artery. Am J Physiol 1993; 264(2 Part 2):H413–H418.
54. Katusic ZS, Shepherd JT, Vanhoutte PM. Vasopressin causes endothelium-dependent relaxations of the canine basilar artery. Circ Res 1984; 55(5):575–579.
55. Maturi MF, Martin SE, Markle D, et al. Coronary vasoconstriction induced by vasopressin. Production of myocardial ischemia in dogs by constriction of nondiseased small vessels. Circulation 1991; 83(6):2111–2121.
56. Rudichenko VM, Beierwaltes WH. Arginine vasopressin-induced renal vasodilation mediated by nitric oxide. J Vasc Res 1995; 32(2):100–105.
57. Dubois MJ, De Backer D, Creteur J, et al. Effect of vasopressin on sublingual microcirculation in a patient with distributive shock. Intensive Care Med 2003; 29(6):1020–1023.
58. Boerma EC, van der Voort PH, Ince C. Sublingual microcirculatory flow is impaired by the vasopressin-analogue terlipressin in a patient with catecholamine-resistant septic shock. Acta Anaesthesiol Scand 2005; 49(9):1387–1390.
59. Friesenecker B, Tsai A, Martini J, et al. Arteriolar vasoconstrictive response: comparing the effects of arginine vasopressin and norepinephrine. Critical Care 2006; 10(3):R75.
60. Garcia-Villalon AL, Garcia JL, Fernandez N, et al. Regional differences in the arterial response to vasopressin: role of endothelial nitric oxide. Br J Pharmacol 1996; 118(7):1848–1854.
61. Meyer S, Gottschling S, Baghai A, et al. Arginine-vasopressin in catecholamine-refractory septic versus non-septic shock in extremely low birth weight infants with acute renal injury. Critical Care 2006; 10(3):R71.
62. Edwards RM, Trizna W, Kinter LB. Renal microvascular effects of vasopressin and vasopressin antagonists. Am J Physiol 1989; 256(2 Part 2):F274–F278.
63. Aiyar N, Nambi P, Crooke ST. Desensitization of vasopressin sensitive adenylate cyclase by vasopressin and phorbol esters. Cell Signal 1990; 2(2):153–160.
64. Van dB V, Church DJ, Vallotton MB, et al. [Ca2+]i and protein kinase C in vasopressin-induced prostacyclin and ANP release in rat cardiomyocytes. Am J Physiol 1994; 266(2 Part 2):H597–H605.
65. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides 2005; 26(12):2500–2504.

