

Reversal by Vasopressin of Intractable Hypotension in the Late Phase of Hemorrhagic Shock

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Background—Hypovolemic shock of marked severity and duration may progress to cardiovascular collapse unresponsive to volume replacement and drug intervention. On the basis of clinical observations, we investigated the action of vasopressin in an animal model of this condition.

Methods and Results—In 7 dogs, prolonged hemorrhagic shock (mean arterial pressure [MAP] of ≈ 40 mm Hg) was induced by exsanguination into a reservoir. After ≈ 30 minutes, progressive reinfusion was needed to maintain MAP at ≈ 40 mm Hg, and by ≈ 1 hour, despite complete restoration of blood volume, the administration of norepinephrine $\approx 3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was required to maintain this pressure. At this moment, administration of vasopressin 1 to $4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increased MAP from 39 ± 6 to 128 ± 9 mm Hg ($P < 0.001$), primarily because of peripheral vasoconstriction. In 3 dogs subjected to similar prolonged hemorrhagic shock, angiotensin II $180 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ had only a marginal effect on MAP (45 ± 12 to 49 ± 15 mm Hg). Plasma vasopressin was markedly elevated during acute hemorrhage but fell from 319 ± 66 to 29 ± 9 pg/mL before administration of vasopressin ($P < 0.01$).

Conclusions—Vasopressin is a uniquely effective pressor in the irreversible phase of hemorrhagic shock unresponsive to volume replacement and catecholamine vasopressors. Vasopressin deficiency may contribute to the pathogenesis of this condition. (*Circulation*. 1999;100:226-229.)

Key Words: vasopressin ■ shock ■ hemorrhage

Profound and prolonged hypotension due to hemorrhage may progress to shock unresponsive to volume replacement and vasoconstrictors such as norepinephrine.¹⁻⁸ We recently observed a patient with bleeding esophageal varices who developed severe hypotension unresponsive to administration of volume replacement, large doses of catecholamine pressors, and compression of the esophageal varices. To facilitate hemostasis by constriction of the mesenteric vasculature, vasopressin was administered.⁹ This was followed immediately by a marked increase in arterial pressure. A similar observation in a second patient without cirrhosis and our previous observation that vasopressin is an effective pressor in septic shock¹⁰ suggested that vasopressin might also be effective in the late, irreversible phase of hemorrhagic shock. To test this, we induced prolonged hemorrhagic shock in the dog.

Methods

Case Reports

Two patients admitted to the Medical Intensive Care Unit of Columbia-Presbyterian Medical Center for acute gastrointestinal hemorrhage were treated with vasopressin by their Attending Physicians. The reported cases are consecutive and span a period of 17

months. The study was approved by the Institutional Review Board of Columbia University.

Patient 1 was a 46-year-old woman who presented with cirrhosis, gastrointestinal bleeding, and renal failure. Her baseline systolic arterial pressure (SAP) was 130 mm Hg, but on admission, her SAP was 90 mm Hg. An emergency esophagogastroduodenoscopy revealed bleeding esophageal varices, and sclerotherapy was performed. Shortly afterward, she experienced a second, large upper gastrointestinal hemorrhage and, as shown in Figure 1, her SAP declined to 45 mm Hg. Intravenous saline and blood products were administered, and to maintain SAP at ≈ 90 mm Hg, intravenous norepinephrine was administered and the dose was increased as needed. However, as shown in the figure, the pressure again declined (SAP < 60 mm Hg), and intravenous dopamine was started. Her plasma bicarbonate fell quickly from 23 to 15 mEq/L as her arterial pH decreased from 7.46 to 7.23. A Sengstocken-Blakemore tube was inserted, and after aspiration of 500 mL of bloody gastric fluid, the hemorrhage appeared to have ceased. Despite > 4.0 L of intravenous fluids, including normal saline (2 L), fresh frozen plasma (10 U), platelets (6 U), and packed red blood cells (6 U), and despite escalating doses of catecholamine pressors (reaching a maximum of $6.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for norepinephrine and $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for dopamine), her SAP remained at ≈ 50 mm Hg for > 60 minutes. Intravenous vasopressin was then begun at $4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and as shown in Figure 1, within 10 minutes her SAP increased to 160 mm Hg, and catecholamine pressors were discontinued. Administration of volume replacement was stopped, and the dose of

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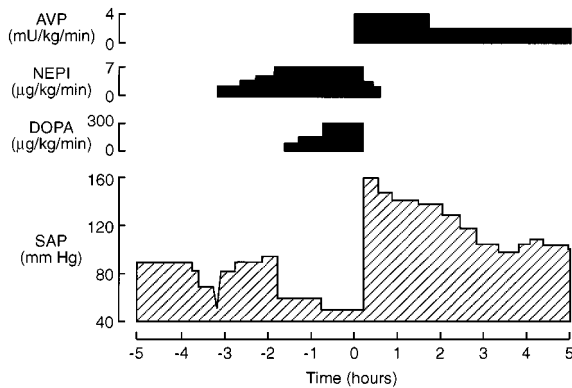


Figure 1. Patient 1. SAP during 5 hours before and 5 hours during administration of arginine vasopressin (AVP). NEPI indicates norepinephrine; DOPA, dopamine.

vasopressin was decreased to $2 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, with SAP remaining at $\approx 105 \text{ mm Hg}$. Vasopressin was discontinued uneventfully after 26 hours of administration.

The patient underwent placement of a transvenous intrahepatic portosystemic shunt and was discharged from the hospital 2 weeks thereafter.

Patient 2 was a 26-year-old woman with end-stage renal disease and hypertension who was admitted for a cadaveric renal transplant. During her second postoperative week, with her antihypertensive medications discontinued and SAP $\approx 150 \text{ mm Hg}$, she had an upper gastrointestinal hemorrhage with sustained hypotension (SAP 70 mm Hg). Intravenous administration of normal saline (2 L) and packed red blood cells (5 U) failed to restore her blood pressure, despite a central venous pressure (CVP) of 17 mm Hg . Intravenous norepinephrine was then administered and progressively increased up to $2.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ because of minor pressor response. During this period, her plasma bicarbonate fell quickly from 16 to 8 mEq/L and arterial blood pH from 7.39 to 7.00. Intravenous administration of vasopressin was begun at $1 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and within 10 minutes, SAP rose to 130 mm Hg and norepinephrine was decreased to $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, with SAP maintained at $>110 \text{ mm Hg}$. A plasma sample drawn just before administration of vasopressin showed a vasopressin concentration¹⁰ of 5.1 pg/mL , inappropriately low for the degree of hypotension (SAP 80 mm Hg).^{11,12} A subtotal gastrectomy was performed immediately, and with the patient remaining hemodynamically stable, vasopressin was discontinued uneventfully after 2 hours of administration.

One week later, the patient sustained a pulmonary embolism and died after an asystolic arrest.

Experimental Hemorrhagic Shock

Mongrel dogs ($27.4 \pm 0.6 \text{ kg}$, mean \pm SEM) were anesthetized with pentobarbital, endotracheally intubated, and ventilated with room air. A thoracotomy was performed, and an aortic flow probe (Transonic Systems Inc) was placed at the aortic arch for cardiac output determinations. Arterial pressure and CVP were transduced from catheters in the femoral artery and internal jugular vein, respectively. The irreversible phase of hemorrhagic shock was induced by a variant of the method of Bond et al.^{4,6} By this method, prolonged hypotension was induced by allowing the animal's blood to fill a reservoir in open communication with a femoral artery and adjusting the height of the reservoir to maintain mean arterial pressure (MAP) at $\approx 40 \text{ mm Hg}$. As illustrated in Figure 2, after a variable period of hypovolemic hypotension, systemic vasodilation was evidenced by the onset of passive transfer of blood from the reservoir into the animal. Passive reuptake of the blood was extended beyond the method of Bond et al.^{4,6} and until $\approx 50\%$ of the blood in the reservoir had returned to the animal. At this time, the remaining blood could be actively reintroduced in increments without arterial pressure being restored, and, in fact, to maintain MAP at $\approx 40 \text{ mm Hg}$, norepinephrine

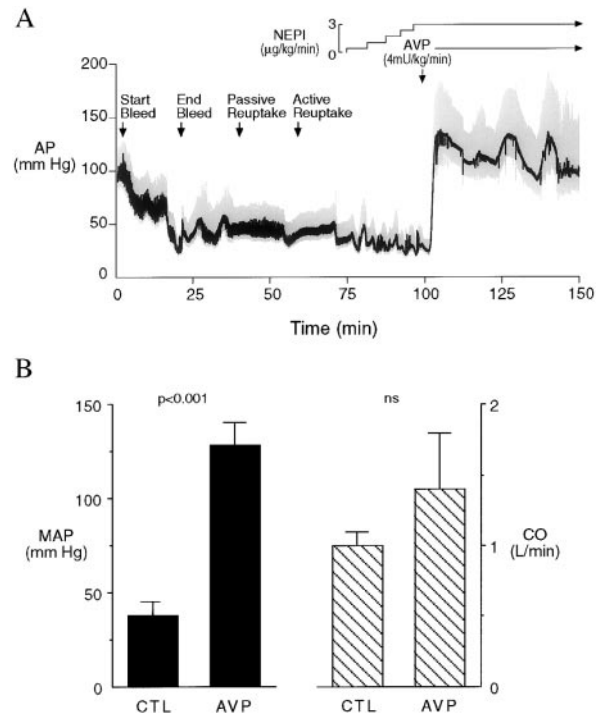


Figure 2. A, Arterial pressure (AP) tracing in experimental hemorrhagic shock in a dog. Other abbreviations as in Figure 1. Black tracing indicates MAP; gray, systolic-diastolic range. B, MAP and cardiac output (CO) during control period (CTL) and during administration of AVP in dogs ($n=7$). Continuous measurements were averaged during 5-minute interval immediately before and after peak response to vasopressin 1 to $4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; all dogs received norepinephrine (see text).

rine was soon required. Normal saline was administered as needed to maintain CVP at $>5 \text{ mm Hg}$. The dose of norepinephrine was progressively increased as needed up to $\approx 3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (the average dose administered to our patients), at which time vasopressin was administered. Blood samples were obtained after acute hemorrhage and immediately before vasopressin infusion for determination of the plasma vasopressin concentration, as described.¹⁰ All results are expressed as mean \pm SEM. Data were analyzed with the paired Student's *t* test, and differences were taken as significant if the *t* value exceeded the critical value for the 5% level.

Results

The arterial pressure response to vasopressin during the late irreversible phase of hemorrhagic shock is illustrated in the experiment shown in Figure 2A. After volume replacement, the infusion of norepinephrine at $3.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ maintained a MAP of only $\approx 40 \text{ mm Hg}$. Within 5 minutes of vasopressin infusion ($4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), MAP increased to 140 mm Hg and despite fluctuations remained $>90 \text{ mm Hg}$ for the next 50 minutes of observation.

Figure 2B shows mean values for MAP and cardiac output in 7 dogs in the late phase of hemorrhagic shock just before and immediately after vasopressin administration. Despite restoration of blood volume and administration of large doses of norepinephrine ($3.4 \pm 1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), MAP averaged $39 \pm 6 \text{ mm Hg}$ during the control period. Vasopressin was administered at $4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (the dose given to patient 1) in 4 dogs, and the other 3 received $1 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (the

dose given to patient 2); both doses increased MAP significantly and to a similar degree, and the data were pooled. As shown, vasopressin increased MAP from 39 ± 6 to 128 ± 9 mm Hg ($P < 0.001$) without significantly changing cardiac output. The pressor effect of vasopressin was sustained during the period of observation (≈ 1 hour), and in all cases the experiment was terminated by design.

As expected, at the beginning of the hypotensive hemorrhage, plasma vasopressin concentration was markedly elevated (319 ± 66 pg/mL), but before the administration of vasopressin, it fell to 29 ± 9 pg/mL ($P < 0.01$). Immediately before they received vasopressin, the arterial blood pH of these animals averaged 7.0 ± 0.1 and the lactate concentration averaged 15 ± 2 mg/dL, highlighting the severity of the shock state.

To examine whether the observed pressor effect of vasopressin was shared by other vasoconstrictors, angiotensin II was infused at $180 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($\approx 5 \text{ } \mu\text{g/min}$), a dose that markedly increases pressure under normal conditions.¹³ However, in 3 dogs in the late phase of hemorrhagic shock (MAP 45 ± 12 mm Hg and arterial blood pH 7.1 ± 0.1) receiving norepinephrine $3.9 \pm 0.6 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, administration of angiotensin II had only a marginal effect on MAP (49 ± 15 mm Hg), confirming previous observations.¹⁴

Discussion

The 2 patients described had severe bleeding with prolonged and severe hypotension that could not be reversed despite volume replacement and massive doses of catecholamine pressors. Similarly, in the animal model, hypotension persisted despite restoration of the blood volume and administration of large doses of norepinephrine. Inasmuch as the late phase of hemorrhagic shock, which is unresponsive to volume replacement and catecholamine pressors, is believed to be irreversible,¹⁻⁶ the observation that vasopressin is an extremely effective pressor is of considerable clinical interest.

Under normal conditions, the doses of vasopressin used have little or no pressor action,^{15,16} and significant elevation of plasma vasopressin due to unregulated release of hormone (ie, the syndrome of inappropriate secretion of antidiuretic hormone) does not cause hypertension.¹⁷ What, then, are the reasons for the observed pressor effect of vasopressin? Two possibilities are likely. First, in vascular smooth muscle, vasopressin can inhibit both ATP-sensitive potassium (K_{ATP}) channels¹⁸ and NO-induced accumulation of cGMP.¹⁹ We and others have shown that activation of the K_{ATP} channels contributes to the hypotension of several types²⁰ of shock, including hemorrhagic shock.²¹ Furthermore, activation of NO synthesis also contributes to the hypotension of this condition.⁸ Thus, vasopressin inhibits vasodilator mechanisms that contribute to both hypotension and vascular hyporeactivity in the late phase of hemorrhagic shock.

A second factor likely to contribute to the particular pressor effectiveness of exogenous vasopressin in the late phase of hemorrhagic shock is inappropriately low plasma

levels of the hormone, perhaps due to depletion of its secretory stores in the neurohypophysis. Such depletion has been described after powerful stimuli for release of vasopressin,²² and low plasma levels of the hormone have been reported during severe hypernatremia²³ and during severe hypotension due to septic shock¹⁰ and advanced hemorrhagic shock.²⁴ Indeed, the plasma vasopressin concentration in patient 2 was inappropriately low for the degree of hypotension,^{11,12} and in the experimental model, vasopressin in plasma declined as shock advanced.

The irreversible phase of hemorrhagic shock is thought to be a rare clinical entity, because management of acute hemorrhage, if effective, minimizes the severity and duration of hypotension and, if not, often results in death before restoration of circulating volume. However, all forms of shock, when advanced, can become poorly responsive to catecholamine pressors, perhaps as a result of the same pathogenetic mechanisms as those activated in the irreversible phase of hemorrhagic shock. Hence, an investigation of the effectiveness of vasopressin in their management seems warranted.

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