Catecholamine-Resistant Hypotension Following Induction for Spinal Exploration

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Systemic blood pressure is regulated by 3 mechanisms: the sympathetic nervous system, the renin-angiotensin system, and the arginine-vasopressin system. The use of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors has become prevalent in the medical treatment of hypertension. These classes of medications inhibit the renin-angiotensin-aldosterone system, specifically the action of angiotensin II, a potent vasoconstrictor. This article describes the case of a 67-year-old man undergoing surgery for a spinal exploration who had hypotension following induction that was refractory to fluid administration and agents with mixed α-β agonistic activity but responded to a vasopressin and phenylephrine infusion. Following the case study is a discussion of the impact that angiotensin II inhibitors may have on a patient undergoing general anesthesia and the role of vasopressin in reversing catecholamine-resistant hypotension.

Keywords: Blood pressure regulation, catecholamine-resistant hypotension, complications, drug interactions, general anesthesia.

Hypotension following induction of general anesthesia is a common occurrence. Many of the medications used for anesthetic induction produce a mild to moderate decrease in the systemic vascular resistance (SVR) with a subsequent decrease in arterial blood pressure. The cardiovascular effects of these medications are widely known, and their judicious use can safely restore arterial blood pressure. Profound, sustained hypotension, however, can have a global impact, resulting in a failure to adequately perfuse systemic capillary networks.[1,2] If decreased coronary circulation occurs, myocardial infarction and stroke may be precipitated.[1,2] Hypotension is more likely in patients with clinically significant comorbidities, and there is an observed deleterious effect on blood pressure by certain classes of prescribed medications, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs).[3,4]

The following case study describes a patient who experienced profound hypotension following the induction of anesthesia. The patient was unresponsive to fluid resuscitation and catecholamine administration. This case study underscores the potential for profound hypotension in patients receiving ACEIs or ARBs. The use of vasopressin to treat refractory hypotension is also discussed.

Case Summary

The patient was a 67-year-old morbidly obese man who weighed 129 kg and was 185 cm tall, with a resultant body mass index of 38.9 kg/m^2. He had no known drug allergies. His complex medical history included controlled hypertension, hyperlipidemia, gastroesophageal reflux disease, chronic obstructive pulmonary disease, confirmed obstructive sleep apnea that was treated with continuous positive airway pressure during sleep, type 2 diabetes mellitus, and Parkinson disease. The patient had no known symptoms of autonomic dysfunction or symptoms of orthostatic hypotension. He was admitted to the operating room for a planned spinal exploration for symptoms of back pain and bilateral lower extremity paresthesias. The patient's surgical history included an L3-S1 laminectomy and decompression 18 months earlier. A second back surgery was performed 2 months earlier that consisted of an L2-L4 laminectomy with diskectomy and screwed fixation from T11 to S1. The patient had also received a single corticosteroid injection to the affected region 1 week before the presently scheduled surgery. There were no known anesthetic complications from the previous surgeries.

The patient had an extensive list of medications that included atenolol (selective β_1-adrenergic receptor antagonist), irbesartan (angiotensin II receptor antagonist), furosemide (loop diuretic), doxazosin (selective α_1-adrenergic receptor antagonist), spironolactone (aldosterone receptor antagonist), omeprazole (proton pump inhibitor), carbidopa-levodopa (inhibitor of peripheral levodopa decarboxylation to dopamine), 70/30 insulin (protein hormone), atorvastatin (cholesterol biosynthesis inhibitor), and an albuterol inhaler (selective β_2-adrenergic receptor agonist). Assessment of the patient resulted in a physical status class of III. On the morning of surgery, the patient received atenolol, irbesartan, omeprazole, and carbidopa-levodopa. The albuterol inhaler was administered on arrival in the operating room.

The airway assessment revealed an obese man with a Mallampati class III airway, a thyromental distance

greater than 3 finger widths, and maintenance of adequate and full extension of his neck without pain. Auscultation of the thorax revealed clear lung sounds and heart tones that were regular without murmur. A 12-lead electrocardiogram was performed before surgery and confirmed a normal sinus rhythm. No edema was noted in the extremities. The patient had verbalized severe back pain accompanied by numbness, tingling, and paresthesias in both legs. The pain worsened with movement that severely limited his ability to walk. The patient was able to lie flat without increased pain.

A review of preoperative laboratory data revealed a hemoglobin level of 12.3 g/dL, a hematocrit value of 38%, a platelet count of $332 \times 10^3/\mu L$, and a white blood cell count of 8,800/μL. Blood chemistry values were as follows: sodium, 138 mmol/L; potassium, 4.3 mmol/L; chloride, 96 mmol/L; bicarbonate, 28 mmol/L; blood urea nitrogen, 35 mmol/L; creatinine, 1.1 mg/dL; and serum glucose, 181 mg/dL. The patient's preoperative vital signs were as follows: blood pressure, 110/65 mm Hg; pulse, 69 beats/min; and oxygen saturation, 92% while breathing room air.

For the elective spinal exploration, the patient had a 16-gauge intravenous (IV) catheter in place with lactated Ringer's infusing. Standard monitors applied while the patient was positioned supine on the bed and preoxygenated for about 5 minutes before induction. Induction was initiated with the administration of midazolam, 1 mg, and fentanyl, 50 μg, in succession, followed 5 minutes later with repeated dosing. Following a period of 5 minutes to facilitate central distribution of the previously administered agents, cricoid pressure was applied, and 100 mg of IV lidocaine was administered followed by IV propofol, 200 mg (1.5 mg/kg), and IV succinylcholine, 100 mg. Direct laryngoscopy was performed using a Macintosh blade, size 3, immediately following the cessation of fasciculations. The vocal cords were easily visualized, and the placement of an 8.0 mm oral endotracheal tube proceeded without complication. Successful intubation was verified through bilateral breath sounds that were noted with auscultation and an end-tidal carbon dioxide tracing on the capnogram. Cricoid pressure was discontinued. The oral endotracheal tube was taped securely, and the patient was given a fraction of inspired oxygen of 100%. Ventilation was facilitated with the volume control mode with desflurane dialed in for an end-tidal concentration of 6%.

Within the 15-minute period following induction, the patient's blood pressure dropped to 50/20 mm Hg accompanied by a mild decrease in heart rate (HR) from a preinduction rate of 69 beats/min to the upper 50s. Initially, fluid boluses totaling 1,000 mL were administered. Because the fluid boluses failed to increase the blood pressure, phenylephrine, 200 μg, was administered during 1-minute intervals. The blood pressure did not respond to 4 boluses of phenylephrine. The blood pressure, now 50/25 mm Hg, and an HR of 58 beats/min did not respond to 3 bolus doses of ephedrine (10, 20, and 20 mg). Next, IV epinephrine, 25 μg, was given, which resulted in an HR increase to 90 beats/min and a blood pressure of 103/52 mm Hg. Colloid volume expansion was not considered because of the lack of response from the crystalloid boluses. An arterial line was inserted, and additional IV access was established. Vasopressin was chosen because of its potent vasoconstrictive properties and administered in a single 2-unit dose, after which the blood pressure increased to 153/62 mm Hg and the HR was 65 beats/min. Within 10 minutes following the first dose of vasopressin, the blood pressure fell to 108/51 mm Hg and the HR remained at 65 beats/min. A vasopressin infusion was initiated at 0.04 U/min to maintain the systolic blood pressure within the range of 100 to 110 mm Hg and a mean arterial pressure (MAP) of more than 65 mm Hg. A bedside transesophageal echocardiogram was performed, revealing adequate contractility and filling pressures without evidence of wall motion abnormalities or filling defects. There were no ischemic changes noted on the electrocardiogram. A blood sample for a critical care panel and blood gas measurement was obtained; the hemoglobin level was 11.9 g/dL; hematocrit value, 37%; sodium level, 137 mmol/L; potassium level, 4.5 mmol/L; chloride level, 104 mmol/L; serum glucose level, 194 mg/dL; pH, 7.38; PCO_2, 44 torr; PO_2, 125 torr; base excess, 0 mEq/L; and bicarbonate, 25 mEq/L. After discussion with the surgical team, the decision was made to proceed with the case.

There was no position change of the patient until he was placed prone, with careful padding and positioning of the head, face, and extremities. Anesthesia was then maintained with a 50% fraction of inspired oxygen, end-tidal concentrations of desflurane of 5.6% to 5.8%, intermittent 50-μg boluses of fentanyl, a vasopressin infusion at 0.04 U/min, and a phenylephrine infusion titrated to maintain a MAP of more than 65 mm Hg. With these infusions, blood pressure was controlled for the remainder of the case at 100 to 120 mm Hg systolic and 50 to 60 mm Hg diastolic, with an HR in the range of 55 to 70 beats/min. The heart rhythm was normal sinus with occasional premature atrial contractions.

The remainder of the case was uneventful. The surgical procedure consisted of an L4-L5 laminotomy and removal of T11 and T12 pedicle screws. During the case, a cyst was found on 1 nerve root in the surgical field. The cyst was excised and sent for culture. The wound was irrigated and closed, and the patient was returned to the supine position. Blood loss for the entire case was approximately 250 mL. Intraoperative blood samples were obtained 2 hours into the case and revealed a stable hemoglobin level of 10.6 g/dL and a hematocrit value of 33%; the blood glucose level was 222 mg/dL. After

Drug	Primary receptors	Action	Hemodynamic effect
Catecholamines			
Epinephrine	α1, β1	↑ SVR, ↑ HR	↑ MAP, ↑ CO
Norepinephrine	α1	↑ SVR	↑ MAP, ↓ CO
Dopamine	α1, β1, D1, D2	↑ SVR, ↑ HR	↑ MAP, ↑ CO
Noncatecholamines			
Phenylephrine	α1	↑ SVR	↑ MAP, ↓ CO
Ephedrine	α1, β1	↑ SVR, ↑ HR	↑ MAP, ↑ CO
Other			
Vasopressin	V1, V2	↑ SVR	↑ MAP, ↑ CO[a]
Calcium	NA	↑ SVR	↑ MAP, ↑ CO[b]

Table 1. Commonly Used Vasopressors for the Treatment of Intraoperative Hypotension

[a] The increase in CO is due to the increase in stroke volume from increased extracellular fluid volume.
[b] The increase in CO is due to increased cardiac contractility.
Abbreviations: SVR, systemic vascular resistance; HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; NA, not applicable; ↑, increased; ↓, decreased.

6 hours into the case, the hemoglobin level was 10.4 g/dL and the hematocrit value was 32%; the blood glucose level was 216 mg/dL. The total case duration was 8 hours, crystalloid infusions totaled 3,800 mL, and the total urine output was 900 mL.

The case lasted approximately 8 hours, and the patient remained in the prone position for 8 hours that resulted in significant facial swelling. Because of the effects of the duration of the prone position and the history of chronic obstructive pulmonary disease, sleep apnea, and blood pressure instability noted at beginning of the operation, the patient remained intubated and sedated and was admitted to the intensive care unit. The phenylephrine infusion continued overnight, and the vasopressin infusion was discontinued on arrival in the intensive care unit. On postoperative day 1, the patient was extubated and the phenylephrine infusion was discontinued. At this time, a neurological examination was performed by the neurosurgeons and was determined to be at baseline. The patient was transferred from the intensive care unit on postoperative day 2. No further episodes of hypotension were noted during the remainder of the patient's hospital stay. Analysis of the cystic fluid revealed an infectious cyst, cultured as the gram-positive cocci, *Propionibacterium acnes*. Consequently, the patient was prescribed a 6-week course of vancomycin therapy via a peripherally inserted central catheter. The patient was discharged to home on postoperative day 6 with adequate pain control and plans for continuation of antibiotic therapy at a local hospital.

Discussion

The MAP is maintained through the interplay of cardiac output (CO) and SVR, explained by the equation, CO × SVR = MAP. The CO is determined by the HR and stroke volume (SV), shown by the equation, HR × SV = CO. Such as the situation in this case study, prescribed medications and anesthesia affect the mechanisms by which the body controls the MAP and requires the use of inotropic agents or vasopressors to combat hypotension (Table 1). The 3 neurohumoral pathways that are activated in response to hypotension and involved in the maintenance of blood pressure during anesthesia are the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and the arginine-vasopressin system.[5,6] Each system induces vasoconstriction in vascular smooth muscle, and the systems work synergistically to improve arterial blood pressure, while also acting to compensate when another system is depressed.[7,8] When 1 or 2 of these systems become blocked, hypotension can be reversed by stimulating the unblocked systems.[6] The Figure shows the relationship among the 3 systems in response to hypotension.[9-11]

Patients receiving ACEIs or ARBs preoperatively have a higher and more profound risk of hypotension with a decreased responsiveness to α-adrenergic agonists.[12,13] The action of the SNS is diminished in patients following the induction of anesthesia, and the decreased SVR is attenuated by administering IV fluid or an $α_1$ agonist.[12,14] The RAAS has a vital role in the homeostatic control of blood pressure, and blunting this system may lead to more profound episodes of hypotension.[8,12] The lack of sympathetic outflow during anesthesia emphasizes the importance of the RAAS and arginine-vasopressin system on blood pressure control.[5]

Activation of the RAAS is primarily dependent on intravascular fluid volumes and is known to increase in states of hypovolemia, hemorrhage, sodium depletion, and anesthesia-induced abrupt reduction of sympathetic tone.[5,8] This system involves a hormonal cascade of several chemical reactions that produces angiotensin II, the primary active component of the RAAS.[3,8] It has
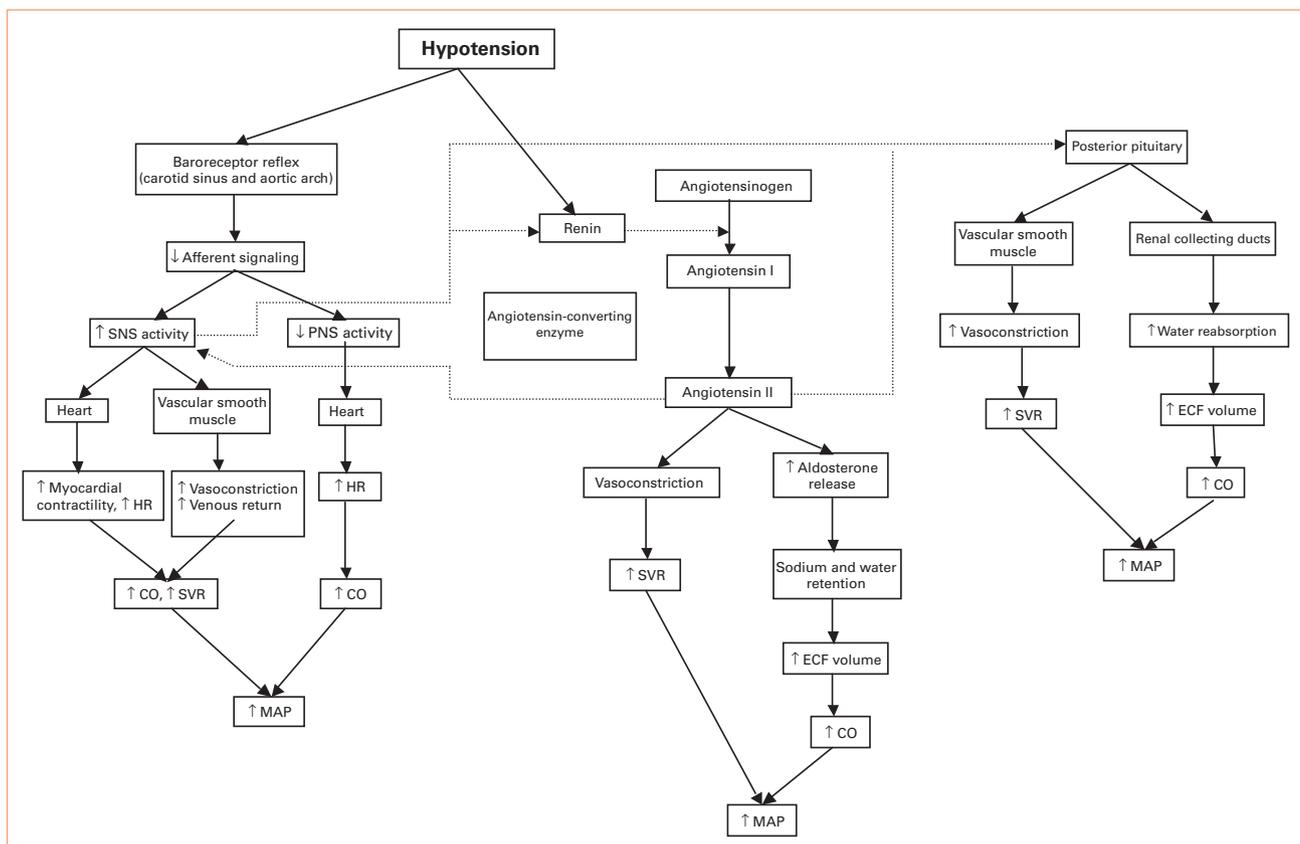
Figure. Interaction Among the Sympathetic Nervous System (SNS), the Renin-Angiotensin-Aldosterone System, and the Arginine-Vasopressin System During Hypotension[9-11]

Abbreviations: PNS, parasympathetic nervous system; HR, heart rate; SVR, systemic vascular resistance; CO, cardiac output; MAP, mean arterial pressure; ECF, extracellular fluid.

direct effects on arterial blood pressure by inducing vasoconstriction and improves fluid balance by stimulating the action of aldosterone.[9] Aldosterone accounts for the reabsorption of sodium and water in the exchange for potassium in the distal tubules and collecting ducts of the kidney.[9] Although the regulation of fluid volume may take hours to days, the vasoconstrictive response to hypovolemia is activated quickly.[8] Under conditions in which the SNS is blocked, the RAAS and arginine-vasopressin system undertake more substantial roles in maintaining arterial blood pressure.[15]

Vasopressin is a peptide hormone synthesized by the hypothalamus and stored in vesicles in the posterior pituitary gland.[16] The primary role of vasopressin is to regulate serum osmolarity and to assist in maintaining cardiovascular homeostasis.[16] Its release into the bloodstream results from high serum osmolarity, arterial hypotension, and hypovolemia.[16] Vasopressin or its synthetic analogs, such as terlipressin, stimulate the V1 receptor that is found on vascular smooth muscle resulting in vasoconstriction.[5,12] It has been demonstrated that the administration of vasopressin to healthy subjects does not affect arterial pressure but elicits a substantial vasoconstrictor response in patients with dangerously low arterial pressures.[5]

Vasopressin has been implicated in the treatment of circulatory arrest and septic shock.[16] Several studies have also demonstrated its effectiveness at restoring arterial blood pressure when the SNS and RAAS have been blocked. Boccara et al[16] randomized patients undergoing elective carotid endarterectomy who had been receiving ACEIs or ARBs to receive boluses of terlipressin or an infusion of norepinephrine to resolve hypotension unresponsive to three 6-mg ephedrine boluses. Terlipressin was infused in 1-mg IV boluses, up to 3 mg if needed. The norepinephrine infusion began at an initial rate of 500 μg/h and was titrated up at a rate of 100 μg/h if needed. The terlipressin group experienced a shorter duration of hypotension (< 90 mm Hg) and 0 of 10 of the patients were considered to be unresponsive to treatment. Of the patients treated with norepinephrine, 8 of 10 were unresponsive to treatment, with 1 reported postoperative myocardial infarction. Eyraud et al[17] found 10 of 51 vascular surgery patients treated with ACEIs or ARBs to be refractory to a 6-mg bolus of ephedrine or a 100-μg bolus of phenylephrine. These boluses were repeated twice if the systolic blood pressure did not remain above 100 mm Hg for 1 minute. For patients who were considered to have refractory hypotension, a 1-mg bolus

Drug	Bolus	Repeated dose	Infusion rate
Vasopressin	0.4-2 U	0.4-2 U	0.04-0.06 U/min; 2.4-3.6 U/h
Terlipressin	1 mg	1 mg × 2	NA

Table 2. Summary of Vasopressin and Terlipressin Administration
Abbreviation: NA, not applicable.

of IV terlipressin was administered and repeated once or twice if the systolic blood pressure did not remain above 100 mm Hg within 3 minutes following injection. In 8 patients, only 1 dose of terlipressin was required, and the other 2 patients required 3 doses. Wheeler et al[12] described the administration of vasopressin to correct hypotension unresponsive to ephedrine, phenylephrine, and epinephrine. Following induction of anesthesia for a 56-year-old patient taking an ARB who was undergoing a cochlear implant, several boluses of phenylephrine and ephedrine were administered without improvement in hemodynamics; epinephrine was given that resulted in transient increases in pressure. A vasopressin bolus of 0.4 U was administered with mild improvement and was repeated. Following 2 boluses of 2 U, an infusion was started at 0.04 U/min and titrated to 0.06 U/min. In circumstances when hypotension does not respond appropriately to common vasopressor and fluid administration, vasopressin or terlipressin becomes an effective alternative.[12,16,17] Table 2 summarizes the use of vasopressin and terlipressin to treat intraoperative hypotension refractory to vasopressor administration. Given the potential for excessive vasoconstriction, terlipressin and vasopressin should be titrated to an acceptable hemodynamic level.[12]

When patients do not respond to catecholamine administration, vasopressin or terlipressin become viable alternatives to restore hemodynamics.[12,16,17] Although both medications offer a vasoconstrictive effect, their uses and half-lives are distinct. Vasopressin has an elimination half-life of 6 minutes and can be administered as a bolus or an infusion.[18] Terlipressin, on the other hand, has an elimination half-life of 50 minutes and is given only as intermittent boluses.[18] Therefore, a vasopressin infusion is titratable, offering more control over a patient's hemodynamics, and is less likely to cause rebound hypertension when anesthesia is discontinued at the end of the case.[12] A notable adverse effect of these medications is the vasoconstriction and possible hypoperfusion of the splanchnic, skeletal muscle, and skin circulations.[19]

Several causes predisposed our patient to primary hypertension. Obese patients may have increased involvement of the RAAS leading to angiotensin II–mediated vasoconstriction and water and sodium reabsorption

from overactivity of aldosterone.[20] Obese patients also have increased SNS activity that causes peripheral vasoconstriction and increased renal sodium reabsorption.[20] Sleep apnea contributes to hypertension by increasing the activity of the SNS and angiotensin II sensitivity.[21] Therefore, hypertension results from insufficient sodium excretion, water retention, and SNS- and RAAS-mediated vasoconstriction.

Conclusion

In this case study, a patient who received preoperative ARBs experienced profound hypotension shortly after induction that proved resistant to conventional treatments with fluid boluses, phenylephrine, and ephedrine. Such refractory hypotension is uncommon in the general patient population. A solid understanding of the physiologic mechanisms of blood pressure control and the effects of various medications on these mechanisms is essential for anesthesia providers. When faced with refractory hypotension, alternative methods to achieve hemodynamic stability may be required. The use of small doses of vasopressin was successful in normalizing the patient's blood pressure during this case. With the administration of a vasopressin infusion, the patient remained in hemodynamically stable condition throughout the remainder of the surgery and had no ill effects from the episode of refractory hypotension that occurred after induction. Vasopressin may prove to be a useful medication in the treatment of persistent hypotension in a patient taking ACEI or ARB medications who is undergoing surgery.

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