

# Refractory Hypotension in a Patient with a History of Anabolic Steroid Abuse Taking an Angiotensin-II Receptor Blocker: A Case Report

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*The renin-angiotensin-aldosterone system (RAAS) is a key component of blood pressure regulation. Patients who take RAAS antagonists on the morning of surgery are at risk of developing hypotension under anesthesia that is refractory to treatment with fluid boluses and conventional vasopressors. This case report describes a unique case of refractory hypotension in a patient with a history of anabolic steroid abuse taking an angiotensin II receptor blocker. An understanding of the role of the RAAS in blood pressure regulation is*

*essential for managing refractory hypotension in the patient under general anesthesia. A scarcity of data on the anesthetic implications of anabolic steroid abuse exists, but an understanding of the physiologic implications of anabolic steroid abuse can help guide management for these patients.*

**Keywords:** Anabolic steroid abuse, anesthesia, angiotensin-receptor blockers, refractory hypotension.

Some degree of hypotension after the induction of anesthesia is not uncommon.<sup>1-3</sup> Patients who take renin-angiotensin-aldosterone system (RAAS) antagonists such as an angiotensin II receptor blocker (ARB) on the morning of surgery are at risk of hypotension that may not be responsive to the conventional treatment of fluid boluses, ephedrine, phenylephrine, and/or decreasing the depth of anesthesia.<sup>1</sup> This case report will describe the clinical course of a patient with an unknown history of anabolic steroid abuse who took an ARB on the morning of surgery. Following the case summary, the authors will review the incidence of intraoperative hypotension, the anesthetic implications of RAAS inhibitors and anabolic steroids, and case reports of potential treatments of RAAS-inhibitor-induced refractory hypotension.

## Case Summary

A 55-year-old, 97-kg, 189-cm man presented for a right hemithyroidectomy for treatment of squamous cell carcinoma. Three months before admission, the patient had a wide local excision of squamous cell carcinoma of the neck and lip performed at another hospital. Previous anesthetic records were not available, but the patient denied any history of anesthetic complications. The patient reported allergies to penicillin, sulfa drugs, prednisone, and "steroids," the latter causing "violent hiccups." His medical history was remarkable for hypertension, obstructive sleep apnea, renal insufficiency, hypogonadism, depression, insomnia, and back pain. His medications included hydrochlorothiazide-valsartan (320 mg/25 mg), oxycodone-acetaminophen (10 mg/325 mg), tramadol

(50 mg), trazadone (150 mg), duloxetine (60 mg), diclofenac (75 mg), aspirin (81 mg), omeprazole (20 mg), sildenafil (100 mg), and testosterone (30 mg/1.5 mL) transdermal patch. He had taken hydrochlorothiazide-valsartan and duloxetine 2 hours before arrival.

The patient's preoperative laboratory values were within normal limits except for serum creatinine level of 1.70 mg/dL, a glomerular filtration rate of 44 mL/min, and blood glucose level of 120 mg/dL. His preoperative blood pressure was 127/80 mm Hg with a heart rate of 88/min and a room air oxygen saturation of 98%. Airway assessment revealed a Mallampati class 2 airway with intact dentition and limited neck extension due to the previous wide local neck excision. His ASA physical status was 3.

In the preoperative area, an 18-gauge peripheral intravenous (IV) catheter was started in the dorsum of the left hand. The patient received 20 mg of famotidine IV and 4 mg of ondansetron IV, and a 1.5-mg scopolamine transdermal patch was placed behind his left ear for preemptive postoperative nausea and vomiting prophylaxis. He also received 500 mg of acetaminophen orally as an adjunct analgesic, and 2 mg of midazolam IV was administered directly before transportation to the operating room.

In the operating room, standard monitors were applied, and the patient was preoxygenated with 100% oxygen for 2 minutes. Induction of anesthesia was accomplished with 150 µg of fentanyl, 80 mg of lidocaine, 5 mg of rocuronium, 140 mg of succinylcholine, and 200 mg of propofol. The eyes were taped shut, and the patient was mask ventilated with oxygen and sevoflurane

(2% inspired concentration) for 1 minute. Laryngoscopy was performed with a video laryngoscope (GlideScope Advanced Video Laryngoscope, Verathon) within approximately 15 seconds. A 7.0-mm nerve integrity monitor endotracheal (ET) tube was passed through the vocal cords, at which point the patient began to cough vigorously. An additional 50 mg of propofol was administered. The ET tube was secured, and desflurane and oxygen were administered to achieve an end-tidal concentration of 6.0% to 6.5%. A shoulder roll was placed, and the video laryngoscope was used a second time to confirm correct placement of the nerve integrity monitor ET tube with the surgeon. A second 20-gauge peripheral IV catheter was started in the dorsum of the right hand, and an infusion of Ringer's lactate solution was started. The patient then received 25 mg of diphenhydramine, 100 µg of fentanyl, and 1 mg of hydromorphone IV. Two infusions were subsequently started: 900 mg of clindamycin in one IV line and propofol at a rate of 50 µg/kg/min in the second line. The bispectral index monitor reading was 39. The nurse inserted a Foley catheter while the surgeons stepped out of the room to scrub.

The hemodynamic parameters and subsequent treatment are listed in the Table. Blood pressure measurements were taken every 2 minutes but recorded on the anesthesia record only in 5-minute intervals. The patient's first low blood pressure occurred 20 minutes after induction of anesthesia. By that point, the patient had received approximately 500 mL of lactated Ringer's solution. After that point, fluids were opened wide through both peripheral IV catheters. Repeated doses of phenylephrine and ephedrine failed to increase the mean arterial pressure (MAP) above 55 mm Hg. The depth of anesthesia was decreased, calcium was administered, and a phenylephrine infusion was started. These measures subsequently proved unsuccessful, so a transition was made to vasopressin, administered in repeated boluses of 2 U. The MAP improved to greater than 60 mm Hg but remained labile.

The deteriorating clinical situation was discussed with the surgeon, who remembered that the patient had a history of anabolic steroid use. His last known use was 6 months ago. The patient did not reveal this history to the anesthesia team during the preoperative interview. Despite the documented history of allergy to steroids, the decision was made to give 100 mg of hydrocortisone IV over 10 minutes. The blood pressure stabilized, and the procedure was able to proceed as planned without further incident. The patient had an uneventful emergence and recovery, and he was discharged from the hospital within 24 hours without major changes in renal function, measured by a serum creatinine level of 1.47 mg/dL.

## Discussion

Hypotension after induction of anesthesia is common.<sup>1-3</sup>

Anesthetized patients have decreased sympathetic activity compared to nonanesthetized patients.<sup>4</sup> As reported by Goldmann et al,<sup>4</sup> after induction with thiopental plasma norepinephrine levels fell by more than 50% and did not increase until after surgical incision. A landmark study of 25,000 patients found that approximately 15% of patients had a systolic blood pressure less than 90 mm Hg after induction of anesthesia with propofol.<sup>2</sup> A study by Reich et al<sup>3</sup> found that 12.6% of ASA classes 3 and 4 patients and 7.7% of ASA classes 1 and 2 patients were severely hypotensive within the 10 minutes immediately following induction of general anesthesia. Risk factors for severe postinduction hypotension included ASA physical status 3 through 5, baseline MAP below 70 mm Hg, age 50 years or older, use of propofol for induction, and increasing induction dosage of fentanyl. Our patient had several of these risk factors, including ASA physical status 3, age greater than 50 years, and the use of propofol (2.1 mg/kg) and fentanyl (1.5 µg/kg) for induction.

Another risk factor for hypotension may be the failure to discontinue RAAS inhibitors on the morning of surgery. The RAAS acts to increase blood pressure in response to hypotension, sodium depletion, or sympathetic nervous system stimulation.<sup>5</sup> The first step in this process is the release of renin by the juxtaglomerular cells of the kidney. Renin interacts with angiotensinogen, a glycoprotein produced in the liver, to form angiotensin I. In the lungs, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II then binds to the angiotensin (AT) receptor, which has 4 subtypes.<sup>6</sup> The AT<sub>1</sub> subtype is responsible for direct vascular smooth-muscle contraction, stimulation of aldosterone production and secretion, sodium retention, and ultimately increased blood pressure. AT<sub>1</sub> receptor blockade causes a relative sympatholysis and may also cause decreased responsiveness to exogenous catecholamines.<sup>1</sup>

Our patient took hydrochlorothiazide-valsartan on the morning of surgery. Valsartan is an angiotensin II receptor blocker (ARB) that has a peak effect at 2 to 4 hours after administration and an average half-life of 6 hours.<sup>7</sup> Because ARBs bind to the AT<sub>1</sub> receptor and prevent angiotensin II from binding to it, they prevent its physiologic effects of raising blood pressure during states of relative hypovolemia. Several case studies report refractory hypotension in patients taking a RAAS inhibitor such as an ACE inhibitor and/or ARB on the morning of surgery.<sup>8-10</sup> In addition, several prospective studies have found an increased incidence of moderate to severe hypotension after induction in these patients. One study found that patients who take an ACE inhibitor or ARB within 10 hours of the start of surgery have a higher incidence of moderate hypotension during the postinduction period compared with patients who stop their ACE inhibitor and/or ARB regimen more than 10 hours before surgery.<sup>11</sup> Another study found that vascu-

Time after intubation (min)	BP (mm Hg)	Heart rate (/min)	Treatment (IV)	Comments
-5	127/80	88		
0	120/75	92		
5	107/64	98		
10	114/68	94		
15	109/66	102		
20	77/42	90	Phenylephrine 100 µg × 2, fluid bolus initiated	BP cuff size verified, moved from right upper arm to left upper arm
25	73/37	80	Phenylephrine boluses 200 µg × 3 and ephedrine 10 mg × 2; propofol infusion stopped	Desflurane inspired concentration decreased to 3%-3.5%
30	80/37	79	1,000 mg calcium chloride, phenylephrine infusion at 1 µg/kg/min, 40 mg ketamine, vasopressin 2 U	60% nitrous oxide started
35	93/56	75	Vasopressin 2 U	
40	99/45	74	Vasopressin 2 U	
45	83/48	72	Vasopressin 4 U	
50	84/34	67	Vasopressin 4 U	
55	91/50	67	Vasopressin 4 U	
60	80/54	70	Vasopressin 4 U, 100 mg hydrocortisone infusion started	
65	107/46	70		
70	123/79	67		
75	102/70	68		Total LR infused = 2,500 mL; urine output = 75 mL
80	115/64	66		

**Table.** Intraoperative Hemodynamic Parameters and Treatment

Abbreviations: BP, blood pressure; IV, intravenous; LR, lactated Ringer's solution; ×, times.

lar surgical patients who took an ARB before induction of anesthesia had a higher incidence of hypotension after induction of anesthesia and had an increased need for vasoactive drugs.<sup>12</sup> However, there are no definitive guidelines regarding the discontinuation of RAAS inhibitors before surgery, and many patients continue to take their RAAS inhibitors through the day of surgery.<sup>13</sup> Our patient took his morning dose of valsartan 2 hours before arriving in the preoperative area. The combination of the expected decrease in sympathetic activity caused by general anesthesia and the additional sympatholysis caused by an ARB may explain our patient's postinduction hypotension.

An interesting feature of our patient's hypotension is that initially it was not responsive to the conventional treatment of fluid boluses, ephedrine, and phenylephrine. In one study of patients undergoing vascular surgery, those who received ARBs required increased doses of ephedrine compared with patients taking ACE inhibitors or β-blockers, and had a higher incidence of hypotension refractory to phenylephrine or ephedrine.<sup>14</sup> These patients were successfully treated with terlipressin, an analog of vasopressin that is not available in the United States. Another study found that in patients

treated long term with RAAS inhibitors, terlipressin corrected ephedrine-resistant hypotension in patients under general anesthesia better than norepinephrine did.<sup>15</sup> General anesthesia inhibits the sympathetic nervous system, and ARBs inhibit the RAAS, so the only compensatory response to hypotension that is not inhibited in these patients is the vasopressin system.<sup>1</sup> Vasopressin is an endogenous hormone released from the posterior pituitary gland that acts on vasopressin (V1) receptors to cause systemic arterial vasoconstriction.<sup>1</sup> In one case report, refractory hypotension in a patient taking an ARB was successfully treated with bolus doses of vasopressin followed by a continuous infusion.<sup>10</sup> Ten minutes after our patient's first low blood pressure, we administered 2 U of vasopressin IV. The blood pressure responded transiently to frequent repeated vasopressin boluses for a total of 22 U over 30 minutes. In the absence of vasopressin, however, the blood pressure remained low. There is one case report of a patient who discontinued valsartan-hydrochlorothiazide 24 hours before surgery yet experienced refractory hypotension unresponsive to fluid boluses, phenylephrine, and vasopressin boluses after induction of anesthesia.<sup>16</sup> The case was canceled, and the ARB was held postoperatively. Five days later the

patient was able to undergo the operation with the same anesthetic regimen without refractory hypotension.

One unique feature of our case is the patient's history of anabolic steroid use. "Anabolic steroids" is the name given to a large class of drugs that are synthetic derivatives of testosterone. They may be taken orally, intramuscularly, or transdermally, and are commonly taken with other supplemental drugs such as diuretics, tamoxifen, thyroxine, human growth hormone, ephedrine, and insulin to improve sports performance, bodybuilding, and/or cosmetic appearance.<sup>17</sup> The use of anabolic steroids remains illicit and stigmatized, and therefore accurately estimating the prevalence of anabolic steroid use remains a challenge.<sup>18</sup> However, anabolic steroid use may be more widespread than previously thought, and use is likely underreported to anesthesia providers. A meta-analysis published in 2014 concluded that the overall lifetime prevalence of anabolic steroid use is 6.4% among males and 1.1% among females.<sup>19</sup> A population-based cohort study conducted over an 8-year period in Sweden found that 20% of male participants tested positive for anabolic steroids, and that age-adjusted anabolic steroid exposure doubled the risk of a cardiovascular event.<sup>20</sup> A 2007 study by Cohen and colleagues<sup>18</sup> found that anabolic steroid users tended to be well educated (74.1% with postsecondary degrees), employed full time (77.7%), and financially comfortable with a median household income between \$60,000 and \$79,999 per year. To our knowledge, the only other case report of a surgical patient with a history of anabolic steroid abuse underwent an aortic valve replacement and experienced multiple postoperative complications, which ultimately resulted in respiratory failure and cardiac arrest in the hospital on postoperative day 39.<sup>21</sup>

In our case, the patient's history of anabolic steroid abuse is unclear at best; knowledge of the patient's dosing schedule, length of use, last use, and the exact agents he used would have greatly improved our understanding of his physiologic derangements and how they may have affected the anesthetic. In retrospect, the patient exhibited many classic side effects of long-term anabolic steroid abuse, including a muscular appearance, thick neck, hypertension, and hypogonadism.<sup>17</sup> Patients who take anabolic steroids appear to have an increased volume of distribution and upregulation of nicotinic acetylcholine receptors, which may explain why our patient was able to cough during intubation despite a seemingly adequate anesthetic depth and generous dose of succinylcholine.<sup>22</sup> Anabolic steroids are associated with both acute and chronic pathologic changes of the cardiovascular system; "hypertension, ventricular remodeling, myocardial ischemia, and sudden cardiac death have been temporally and causally associated with anabolic steroid use in humans. These effects persist long after their use has been discontinued and have significant impact on sub-

sequent morbidity and mortality."<sup>23(p281)</sup> In their 2009 study, Hassan and colleagues<sup>23</sup> found that body builders actively using anabolic steroids had concentric left ventricular hypertrophy and impaired diastolic function evident on echocardiography. These findings amplify those from an earlier study that found that 6 months after cessation of anabolic steroid use, 44% of users had an elevated cardiac risk, compared with 24% in the control group.<sup>24</sup> Our patient did not have a preoperative cardiac evaluation, but it is likely that he had some degree of left ventricular impairment that may have been exacerbated by the induction of general anesthesia.

Although anabolic steroids act directly to suppress the endogenous hypothalamic-pituitary-gonadal axis, their effects on the endocrine system are widespread. Endogenous secretion of thyroid hormones, adrenocorticotropic hormone, and steroid precursors is also diminished.<sup>25,26</sup> Our patient's history of anabolic steroid abuse may have depressed his hypothalamic-pituitary-adrenal axis, which prevented the secretion of endogenous cortisol in response to the stress of induction. The combination of a general anesthesia-induced sympathectomy coupled with adrenocortical suppression from anabolic steroid abuse and abolishment of the RAAS by an ARB may explain the persistent nature of our patient's hypotension; he had no endogenous systems available to increase blood pressure. The administration of 100 mg of hydrocortisone IV appeared to stabilize his blood pressure, which suggests that adrenocortical insufficiency may have contributed to his hypotension refractory to both conventional treatment and vasopressin. When administered exogenously, glucocorticoids have genomic, specific nongenomic, and unspecific nongenomic therapeutic effects.<sup>27</sup> Genomic effects are mediated by receptors in the cytosol and may take 30 minutes to have an effect, but the specific nongenomic effects are mediated by receptors in the cell membrane and occur in minutes.<sup>27</sup> This may explain why our patient's blood pressure stabilized shortly after starting the hydrocortisone infusion. Of note, the patient was taking sildenafil and testosterone, either of which may also have contributed to postinduction refractory hypotension. However, it is beyond the scope of this article to review the mechanisms of action for these drugs.

In summary, patients taking RAAS inhibitors may be at increased risk of hypotension after the induction of anesthesia. Anabolic steroids cause long-term cardiovascular and endocrine alterations that may contribute to and/or exacerbate postinduction hypotension. In cases of hypotension refractory to conventional treatment, vasopressin may be useful in stabilizing blood pressure because it works on receptors independent of the RAAS. If vasopressin is not successful, other causes of refractory hypotension, including hypothalamic-pituitary-adrenal axis suppression by steroid use, should be considered.

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## DISCLOSURES

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