

# Intraoperative Pulseless Electrical Activity and Acute Cardiogenic Shock After Administration of Phenylephrine, Epinephrine, and Ketamine

Alan D. Kaye, MD, PhD,\* Alecia L. Sabartinelli, MD,†‡ Adam M. Kaye, PharmD,§  
Alan M. Holtzman, CRNA,|| Paul L. Samm, MD†

\*Department of Anesthesiology, School of Medicine, and

†School of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA

‡Department of Anesthesiology, School of Medicine, University of Miami, Miami, FL

§Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences,  
University of the Pacific, Stockton, CA

||University Hospital Staff, New Orleans, LA

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## ABSTRACT

The use of phenylephrine has been well described as a potential cause of morbidity and mortality. A thorough literature review of phenylephrine use is presented in this article. The use of ketamine and epinephrine with phenylephrine can precipitate an even more potentially lethal and catastrophic syndrome. We present the case of a 21-year-old man with Hodgkin's lymphoma and lupus who experienced an abrupt hypertensive crisis followed by pulseless electrical activity and cardiogenic shock after application of 2.5% phenylephrine-soaked nasal pledgets prior to excision of a large nasopharyngeal tumor. This case report adds to the current literature on the potential dangers of phenylephrine in clinical practice and describes a case of reversible severe left ventricular dysfunction in the setting of excessive pharmacologically induced sympathetic stimulation.

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## INTRODUCTION

Phenylephrine is an  $\alpha$ -agonist with a wide array of effects on the body. The drug has multiple indications

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Address correspondence to:

Alan D. Kaye, MD, PhD

Professor and Chair

Department of Anesthesiology

School of Medicine

Louisiana State University Health Sciences Center

1542 Tulane Avenue, Room 659

New Orleans, LA 70112

Tel: (504) 568-2315

Fax: (504) 568-2317

Email: akaye@lsuhsc.edu, alankaye44@hotmail.com

Key Words: Cardiogenic shock, Hodgkin's lymphoma, lupus, phenylephrine

Dr. Alan Kaye serves on the Baxter Speakers Bureau.

and is employed in varied medical disciplines. Intraoperative use of topical  $\alpha$ -agonist agents for vasoconstriction is common in ear, nose, and throat (ENT)<sup>1</sup> and ophthalmologic<sup>2</sup> procedures and has been increasingly used in arthroscopic surgeries.<sup>3</sup> Use of this drug is not without risks because severe cardiopulmonary complications can occur if local administration reaches the systemic circulation. Such an occurrence comprises the case reported here. We present a case of pulseless electrical activity (PEA) and cardiogenic shock following hypertensive crisis induced by absorption of 2.5% phenylephrine, an  $\alpha$ -agonist, soaked onto nasal pledgets. This drug was administered in preparation of an ENT nasopharyngeal tumor excision in a 21-year-old man without known preexisting cardiac dysfunction. Signed consent was obtained from the patient in question prior to writing this case report.

## CASE REPORT

A 21-year-old man (57 kg, 180 cm) was scheduled for surgical debulking and excisional biopsy of an aggressive nasopharyngeal mass under general anesthesia. The procedure was intended to establish a definitive diagnosis and to establish a nasal airway. The patient had a history of multiple tumors with a nondiagnostic biopsy in the emergency department. His past medical history was also significant for anemia (hematocrit 28% after transfusion) and thrombocytopenia (156/mm<sup>3</sup> after transfusion) requiring recent blood transfusion, systemic lupus erythematosus treated with prednisone (30 mg/d and hydroxychloroquine 200 mg/d), and recent excision of a necrotic pelvic mass that was later diagnosed as nonsclerosing Hodgkin's lymphoma. The patient complained of persistent breathing difficulties, altered speech, and dysphagia. On examination, he was awake, spontaneously mouth breathing, and resting comfortably. Airway evaluation revealed bilateral nasal airway obstruction approaching 100%. The

oropharynx was obstructed by a large mass measuring approximately 8 cm that was abutting the soft palate. The patient could open his mouth to 3 fingerbreadths but was unable to fully extend his neck. The remainder of the physical examination was unremarkable except for a mild tachycardia of 104 beats per minute (bpm). Preoperative evaluation, including complete blood count, electrolyte studies, coagulation studies, and electrocardiogram, revealed no additional abnormalities. No additional cardiac work-up was performed or deemed warranted.

Prior to induction, standard American Society of Anesthesiologists monitors were applied and initial vital signs were stable (blood pressure [BP], 117/90 mmHg; heart rate, 112 bpm; respiratory rate, 14 breaths per minute; and oxygen saturation, 100%). Midazolam, 2 mg intravenously (IV), was administered to the patient in the holding area to allay preoperative anxiety. Methylprednisone, 125 mg IV, was administered for adrenal insufficiency prophylaxis prior to induction. Ketamine, in divided doses totaling 100 mg, and a dexmedetomidine infusion, in a dose range of 1 to 3  $\mu\text{g}/\text{kg}$ , were started prior to induction, and both transtracheal and superior laryngeal blocks were performed using 4% and 1% lidocaine, respectively. A fiberoptic intubation was done using a 7.0-mm oral RAE tube. Anesthesia induction was facilitated with an additional dose of ketamine, 100 mg IV; rocuronium, 50 mg IV, was administered to facilitate paralysis. Maintenance of anesthesia was facilitated with sevoflurane, in a dose range of 1.8% to 2%.

The surgeon prepared the patient's nose and oral cavity, applied approximately 5 to 10 mL of 2.5% phenylephrine-soaked pledgets into the nasal cavity after injecting a total of 6 mL of 1% lidocaine with epinephrine bilaterally into the sphenopalatine region with obvious blanching of the palate. Within 10 to 15 minutes, the patient's systolic BP rose to 190 mmHg and his pulse to 130 bpm. The elevated BP was initially treated with divided doses of propofol (total 200 mg) and 150  $\mu\text{g}$  of fentanyl, with no significant hemodynamic response. In the 10-minute period following, the end-tidal carbon dioxide level fell to 10 mmHg. Concurrently, BP and pulse plummeted to 70 mmHg and 55 bpm, respectively, and radial, femoral, and carotid pulses were absent. Resuscitation was then initiated; Advanced Cardiac Life Support protocol was followed with the onset of cardiopulmonary resuscitation. Resuscitation was achieved with administration of 150  $\mu\text{g}$  of sodium bicarbonate, 4 mg of 1:10,000 epinephrine (including 1 via the endotracheal tube, for a total of 40 mL delivered), 1 mg of atropine, and 1 g of calcium chloride during approximately 10 minutes of cardiopulmonary resuscitation. The heart rate increased to

130 bpm and the BP to approximately 180/110 mmHg. An epinephrine infusion was started to maintain the patient's pressure. The procedure was cancelled, and the patient was transported to the surgical intensive care unit for immediate cardiologic evaluation.

An arterial blood gas analysis on 100% oxygen sampled in the operating room immediately after resuscitation revealed no abnormalities (pH, 7.464;  $\text{Pco}_2$ , 32.6 mm Hg;  $\text{Po}_2$ , 460.1 mm Hg;  $\text{HCO}_3$ , 23.1 mmol/L; and BE,  $-0.5$ ). A potassium level of 2.7 mmol/L was corrected in the intensive care unit, and other electrolytes remained unremarkable. The electrocardiogram revealed sinus tachycardia with nonspecific T-wave abnormality unchanged from prior studies. A transesophageal echocardiogram demonstrated left ventricular ejection fraction at 10%. The patient was initially placed on 2  $\mu\text{g}/\text{h}$  of dobutamine infusion and was titrated upward to 10  $\mu\text{g}/\text{h}$  for presumed cardiogenic shock during the first day of treatment. The patient's neurologic and cardiac function improved over the next several days—he became more responsive to verbal commands—and his left ventricular ejection fraction increased to 15%, 30%, and then 55% on postoperative days 1, 2, and 4. The surgical intensive care unit staff discontinued the dobutamine infusion 5 days after the event, and the patient's functional status improved enough to reattempt the tumor excision.

Seven days later, the patient underwent the previously scheduled procedure without complication. A preventive tracheostomy was placed during surgery, and the patient was able to breathe without the assistance of a ventilator the following day. This tracheostomy was performed because of the concern of local spread of tumor. Pathologic analysis of the mass revealed nonsclerosing Hodgkin's lymphoma. In light of the recent history of a necrotizing iliac mass of unknown etiology and the nasopharyngeal mass, it was determined that this patient had an aggressive stage IV Hodgkin's lymphoma and would receive chemotherapy once he regained full cardiac function. He remained in the hospital for several more weeks for initiation of chemotherapy. At the time of his discharge, his cardiac status was fully recovered and he was well underway with his cancer treatment.

## **DISCUSSION**

Cardiopulmonary events and ensuing shock are rare in minimally invasive ENT surgeries but can occasionally occur after systemic absorption of local vasoconstrictive agents. We report a case of 10 to 15 minutes of PEA following a severe hypertensive episode in a 21-year-old man with both systemic lupus erythematosus and Hodgkin's lymphoma and no known cardiac dysfunction. The patient was

prepared to undergo excision of a nasopharyngeal mass. He received ketamine, had preoperative local anesthetic with epinephrine injection, and an unintended systemic absorption of 2.5% phenylephrine, which initiated the described events. The absorption of phenylephrine caused a dramatic increase in vascular resistance and afterload, which led to acute left ventricular failure and cardiogenic shock. This was further enhanced with the injection containing epinephrine and ketamine. The pharmacologic mixture—ketamine, epinephrine, and nasal phenylephrine—can form a potentially catastrophic mixture when combined, resulting in sympathetically induced reversible left ventricular dysfunction.

This patient presented with a unique assortment of medical conditions that provides clues as to why the phenylephrine underwent enhanced systemic absorption. Although initially undiagnosed, the mass was later identified as nonsclerosing Hodgkin's lymphoma. Preoperative imaging revealed a large 8 × 8 cm mass obstructing the nasopharynx. The presence of this tumor is significant for 2 reasons. First, we hypothesize that the greater absorption of phenylephrine was secondary to resulting changes in the mucosal barrier and the lack of significant understanding of the impact the tumor had on absorption.<sup>4</sup> The possibility exists for an increased permeability of phenylephrine due to the pathophysiologic changes of the increased dermal surface area from the lymphoma. Overall, the amount of local phenylephrine that is absorbed is unpredictable,<sup>5</sup> but logically the amount should be proportional to the extent of mucosal surface area with which the drug makes contact.<sup>1</sup> Second, blood flow changes, due to increased surface area and vascularization, in the skin and mucosa can have profound effects on dermal pharmacokinetics and relative processes of local and systemic solute distribution.<sup>6</sup> Thus, a highly vascularized lymphoma provides additional access into the systemic circulation.

On review of the literature, several case reports were found that document adverse intraoperative events associated with use of these agents. Kalyanaraman et al<sup>5</sup> reported a case series of 12 healthy patients undergoing ENT surgery who received topical phenylephrine and/or submucosal epinephrine. Hypertension, with BP levels reaching >200/100 mmHg, developed after such administration and was treated with a  $\beta$ -blocker or calcium channel blocker in 7 of the 12 patients. All 7 patients developed pulmonary edema, and 3 developed left ventricular dysfunction, cardiac arrest, and died.<sup>5</sup> Two other similar cases are described that occurred from the intranasal administration of 0.5% phenylephrine spray during awake-nasal intubation.<sup>7,8</sup> In both cases, hypertension and tachycardia were treated with

esmolol, which induced pulmonary edema requiring extended intubation and intensive care unit stays. Treatment of the  $\alpha$ -agonist-induced hypertension with a  $\beta$ -blocker creates worsened outcomes by directly blocking  $\beta$ -agonist-induced vasodilation. This leads to unopposed  $\alpha$ -receptor activation, flash pulmonary edema, and severe cardiopulmonary consequences. As early as 1979, scientists warned of the dangerous interaction between topically applied phenylephrine and  $\beta$ -blocking agents used for hypertension.<sup>9</sup>

One particular case involving the death of a 4-year-old child prompted the New York State Department of Health to establish the Phenylephrine Advisory Committee to review phenylephrine-associated morbidity in pediatric ENT cases. Groudine et al<sup>10</sup> found 9 additional patients who had displayed similar constellations of events following topical phenylephrine administration. Of those 9 patients, 8 received  $\beta$ -blocker treatment; the 3 patients who subsequently developed cardiac arrest and died had all been treated with labetalol. In the case review, those with hypertensive crises treated by methods other than  $\beta$ -blockade tended to fare better without developing further pulmonary edema or cardiac compromise.<sup>10</sup>

Among certain specialists it is common practice to use topical  $\alpha$ -agonists as vasoconstrictive agents to decrease bleeding and to improve surgical visibility.<sup>1</sup> It should be noted that concentrations and volumes of phenylephrine vary tremendously depending on facility, procedure, and specialty training. Riegle et al<sup>1</sup> explain that topical doses exceed those given intravenously because of the theory that very little is absorbed.<sup>1</sup> Currently there seems to be little consensus on dosages; however, guidelines have been recently published.<sup>10</sup> Most ENT cases report administration of the  $\alpha$ -agonist in concentrations of 0.5% (0.25%–1%).<sup>1</sup> Ophthalmologic personnel use concentrations of 10% intraocularly or via pledgets.<sup>11–13</sup> Phenylephrine spray for nasal intubations is given in lower volumes than those soaked into cotton pledgets.<sup>7,8</sup> In the present case, pledgets were soaked with 2.5% phenylephrine. In the case reports involving similar nasal administration, the concentration of phenylephrine was typically 0.5%; volumes are not documented. It is worth noting that reports of cardiopulmonary collapse have been described from phenylephrine use in lower concentrations than that placed into our patient.<sup>10</sup>

Case reports involving local epinephrine administration are also found in the ENT<sup>14</sup> and orthopedic literature.<sup>15,16</sup> One case report describes the onset of PEA and acute cardiogenic shock in a patient undergoing an elective ENT procedure. Schwalm et al<sup>14</sup> describe a 29-year-old man undergoing elective nasal septoplasty. Administration of 1:1,000 epinephrine-soaked nasal pledgets induced hypertension that

**Table 1. Differential Diagnosis for Pulseless Electrical Activity<sup>a</sup>**

5 Hs	5 Ts
Hypoxemia	Tension pneumothorax
Hydrogen ion (acidosis)	Tamponade (cardiac)
Hypokalemia/hyperkalemia	Trauma
Hypovolemia	Toxic/therapeutic substances
Hypoglycemia	Thrombus (coronary or pulmonary)

<sup>a</sup> Modified from Desbiens<sup>17</sup> and American Heart Association Guidelines for Cardio-pulmonary Resuscitation and Emergency Cardiovascular Care.<sup>18</sup>

was treated with metoprolol, pulmonary edema, PEA, and cardiogenic shock. It is likely that, as in our case, the patient developed a significant  $\alpha$ -agonist-induced cardiac workload that resulted in left ventricular dysfunction followed by PEA and shock, but the worse outcome associated with  $\beta$ -blocker treatment of the hypertensive crisis is due to unopposed  $\alpha$ -receptor stimulation and a blunting of compensatory mechanisms.<sup>10</sup> Inasmuch as a significant dose of ketamine was administered at the time of induction, this may well have caused additional  $\alpha$ -mediated agonist effects and should be considered in this newly described syndrome. Ketamine is well established as possessing central stimulation of the sympathetic nervous system and inhibition of norepinephrine reuptake. It should also be noted that the patient received bilateral sphenopalatine ganglion blocks with lidocaine and epinephrine. Epinephrine, a potent vasopressor, could have been partially absorbed systemically and contributed to some of the increases in afterload, in heart rate, and in BP initially seen prior to the decompensation of the patient intraoperatively. It is likely that the 3 agents—phenylephrine nasally, ketamine IV, and dermal epinephrine—caused the catastrophic decompensation of this patient.

The differential diagnosis resulting in PEA and cardiogenic collapse is lengthy (Table 1); however, in this case, other reasons for PEA were excluded. The patient was given hydrocortisone prior to induction to prevent adrenal insufficiency and Addisonian crisis. Systemic lupus erythematosus can result in numerous cardiac sequelae; however, given the fact that the patient had a normal ejection fraction at the time of discharge, it is unlikely that he had baseline cardiac disease prior to the induction of anesthesia. He did have a mild tachycardia, which most likely can be explained by his anemia and underlying lymphoma. Pheochromocytoma and undisclosed cocaine abuse were excluded with urine analysis.

In summary, we present a near-fatal case of a complex patient who received phenylephrine intranasal pledgets and experienced severe cardiac dys-

**Table 2. Phenylephrine Advisory Committee Guidelines<sup>a</sup>**

Dosing	Adults: not to exceed 0.5 mg (4 drops 0.25% solution) Children (up to 25 kg): not to exceed 20 mcg/kg
Minimal amounts needed to produce vasoconstriction	Monitor BP and pulse closely after administrations
Route of administration	Use calibrated syringe, verified by a physician
Awareness	Anesthesiologist should be aware of all administered perioperative medications
Monitoring	Mild to moderate hypertension: should be monitored up 10 to 15 min prior to treating Severe hypertension: treat immediately, along with its adverse effects (ECG changes, pulmonary edema) Consider use of direct vasodilators or $\alpha$ -antagonists to treat hypertension
$\beta$ -Blockers/Ca <sup>+</sup> channel blockers	Avoid using with prior phenylephrine administration; may worsen cardiac output, resulting in pulmonary edema
If $\beta$ -blocker was used	Consider administration of glucagon to counteract cardiac effects

Abbreviations: BP, blood pressure; ECG, electrocardiogram.

<sup>a</sup> Modified from Groudine et al.<sup>10</sup>

function. This case discussion highlights the potential risks, including cardiogenic shock and possible death, of vasoconstrictive agents. Acute awareness always needs to be maintained when intraoperative  $\alpha$ -agonists are used and to avoid use for  $\beta$ -blockers as antihypertensive agents. The present case strongly suggests avoidance of ketamine and epinephrine in this setting. The clinical anesthesiologist should be prepared for the possibility of severe hypertensive response, even in the absence of epinephrine and ketamine, and the appropriate treatment necessary to prevent worsening outcomes and morbidity (eg, avoidance of  $\beta$ -blockers). The Phenylephrine Advisory Committee guidelines list 7 key recommendations, including suggested dosing for adult and pediatric populations (Table 2). These guidelines are based on IV doses and assume 100% absorption,<sup>10</sup> which is a change from prior discussions.<sup>1</sup> This case report adds to the current literature on the potential dangers of phenylephrine in clinical practice and reveals a case of reversible severe left ventricular dysfunction in the setting of excessive pharmacologically induced sympathetic stimulation.



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