Case in Point

Epistaxis and Death by the Trigeminocardiac Reflex: A Cautionary Report

Disha Awasthi, MD; Thomas M. Roy, MD; and Ryland P. Byrd Jr, MD

A case of trigeminocardiac reflex following nasal packing for epistaxis led to respiratory and cardiac arrest and patient death.

Epistaxis is a relatively common event that is estimated to occur at least once in 60% of the U.S. population. Epistaxis is also reported to cause 1.7 emergency department (ED) visits per 1,000 population annually.[1] Although epistaxis can occur at any age, it typically occurs with a bimodal age distribution and most commonly affects individuals aged < 18 years and adults aged > 50 years.[2] The episodes of epistaxis involving the younger age group are more often minor and self-limited. Most bleeds occur along the anterior nasal septum from Kiesselbach's plexus.

Posterior bleeds occur more often in older patients.[2] In addition, epistaxis in the older population tends to be more severe.[3] Medical intervention is required in 6% of those experiencing epistaxis. Because the median age for male veterans was 64 years in 2011 compared with a median age of 37.2 years for the average U.S. population in 2010, veterans are among those at greatest risk to develop epistaxis that requires intervention.[4,5]

Most episodes of epistaxis are not life-threatening, particularly when modern methods of diagnosis and treatment are used. Nevertheless, comorbid diseases, complications of treatment, and normal physiologic responses can sometimes combine to create an adverse outcome.[6] This report reviews the case of a veteran patient who experienced a fatal cardiopulmonary arrest after therapeutic interventions for epistaxis. It is believed that his death was due to the well-described but little known trigeminocardiac reflex (TCR).

CASE REPORT

A 65-year-old man visited the ED and reported that his nose had been bleeding intermittently for 1 day. He estimated that he had lost 1 cup of blood over a 24-hour period. He reported no rhinosinusitis, nasal congestion, or recent allergy or upper respiratory infections. He also reported no nasal trauma. In the ED, blood was oozing from his right nares and into his throat, causing him to cough. External compression failed to control the oozing. Topical vasoconstrictors were not applied.

His past medical history included a pulmonary embolism, well-controlled chronic obstructive pulmonary disease (COPD), and sleep apnea. The thrombotic site of origin for his pulmonary embolism had not been identified, despite a thorough examination. He had been on warfarin therapy for 3 months, and his international normalized ratio (INR) had been monitored in an anticoagulation clinic and was well regulated. He was also on inhaled medications for COPD (formoterol and budesonide as a combination preparation twice daily and albuterol every 6 hours as needed as a rescue medication). He adhered to his noninvasive positive airway pressure (PAP) device treatment for sleep apnea. He did not take aspirin or other antiplatelet medications. He reported no use of topical nasal preparations. He also reported no use of illicit drugs or over-the-counter

Dr. Awasthi is a pulmonary diseases and critical care medicine fellowship trainee and **Dr. Roy** and **Dr. Byrd** are professors, all at the East Tennessee State University James H. Quillen College of Medicine Division of Pulmonary Diseases and Critical Care Medicine in Johnson City. Dr. Byrd is also a staff physician in the Pulmonary Section at the James H. Quillen VAMC in Mountain Home, Tennessee.

medications, including nonsteroidal anti-inflammatory medications and herbal remedies. He reported no bleeding from other sites or easy bruising.

The patient was alert, oriented, and in no distress. His vital signs were normal. Examination of his nasal passages failed to identify an active site of bleeding. Fresh blood was present in the right nasal passage and the posterior pharynx. Examination of his chest was normal. His hemoglobin was 13.1 g/dL (13.6-17.3 g/dL) with 216 x 103/μL platelets (166-383 x 103/μL). His INR was therapeutic at 2.38. Laboratory assessments of his electrolytes, liver function, and renal function were normal. A chest radiograph demonstrated no acute process. A computed tomography failed to demonstrate sinusitis or an anatomical abnormality that could account for his epistaxis.

Due to the amount of blood loss by epistaxis complicated by anticoagulation for his recent pulmonary embolism, the patient was admitted to the hospital for observation. Reversal of the anticoagulation was considered by the admitting service, but because the patient was only oozing blood, this intervention was not undertaken. Instead, he was continued on warfarin, was treated with an oral antibiotic, and was continued on his inhaled medications for his COPD. He also used his noninvasive PAP device to sleep.

The next day, the patient began to bleed freely from his right nares. The bleeding was initially controlled with compression and positioning and resolved without additional intervention. An otolaryngologist performed silver nitrate cauterization of Kiesselbach's plexus. The patient experienced no further bleeding, and his hemoglobin remained stable.

The next day, his nose began to bleed briskly. He passed large clots from his nose and mouth. The patient was alert and oriented. He remained hemodynamically stable. His INR was 2.1. Nasal packing was proposed, and the procedure, including the risks and benefits, were explained to the patient.

After obtaining consent from the patient, the nasal mucosa was prepared with topical 2% lidocaine and 1% phenylephrine. Anterior and posterior nasal packing was successfully achieved with paraffin gauze. This procedure was completed in a monitored environment by an experienced otolaryngologist. However, the patient became agitated 15 to 20 minutes after the nasal packing had been accomplished. He rapidly became apneic, bradycardic, and hypotensive. His oxygen saturation on room air as measured by pulse oximetry decreased precipitously to 50%. These developments were quickly followed by asystole.

Advanced cardiac life support measures were initiated. His airway was secured by oral endotracheal intubation, and oxygen was delivered at 100% fraction of inspired oxygen by bag ventilation. At intubation, only a few small clots were present in the posterior pharynx. No blood was suctioned from the endotracheal tube; therefore, active bleeding was not suspected. The nasal packing remained in place and was not removed. The patient failed to regain spontaneous circulation and died. An arterial blood gas analysis obtained during cardiopulmonary resuscitation demonstrated no methemoglobin on co-oximetry.

If mechanical stimulation to the trigeminal nerve is anticipated, continuous monitoring of hemodynamic parameters may allow the clinician to more readily identify the TCR and immediately interrupt the inciting stimulus.[24]

DISCUSSION

Because of the high prevalence of epistaxis in the general population, many health care providers (HCPs) are confronted with this problem. Epistaxis in most patients remits without consequence. However, HCPs may be required to intervene. Treatment modalities include simple compression and positioning maneuvers, the application of topical medications, anterior and posterior nasal packing, chemical cauterization, endoscopic electric cauterization, embolization therapy, and surgical arterial ligation.[7] The choice of therapy depends on several factors, including the site of the bleeding, the severity of the bleeding, the availability of resources, and the expertise of the HCP. A localized cause of epistaxis is discovered in only 15% of patients, making a conservative therapeutic approach an attractive initial intervention.[8]

Nasal packing is a successful intervention in 70% of patients with posterior epistaxis. In addition, nasal packing is the preferred method for hemostasis in anterior epistaxis when cauterization fails.[3,9] This patient failed simple compression and positioning maneuvers as well as chemical cauterization. For this reason, nasal packing was proposed as a therapeutic intervention. He was hemodynamically stable when the nasal packing procedure was initiated.

Although epistaxis may often have the appearance of significant blood loss and can be frightening for both

the patient and HCP, most episodes are not life threatening. Death, when it occurs in association with epistaxis, is very rarely due to exsanguination.[3] More commonly, death from epistaxis is related to complications of the treatment intervention or to an exacerbation of an underlying comorbid disease.[10] The external overt blood loss in this patient was not significant enough to explain his cardiopulmonary collapse. Although he had experienced a recent pulmonary embolism, he had been on continuous anticoagulation for 3 months and remained adequately anticoagulated during his hospitalization. It therefore seems unlikely that he had experienced a recurrent pulmonary embolism.

Complications

The treatment of epistaxis can be associated with serious infectious complications, including toxic shock syndrome due to nasal packing and infective endocarditis.[11,12] Because patients with malignancies, autoimmune disorders, or organ failure may have epistaxis from decreased platelet production or increased platelet destruction, an infection can be devastating. Many HCPs anticipate this occurrence and provide the patient with epistaxis prophylactic antibiotics.[13] Life-threatening infectious complications are usually delayed events and are generally easily recognized. An infectious process was not suspected in this patient. Nevertheless, he was treated with an oral antibiotic.

Dislodgement of the nasal packing with resultant aspiration and asphyxiation has been described as a fatal complication associated with the treatment of epistaxis.[14] This complication was not observed in this patient. The otolaryngologist responsible for the placement of the nasal packing was in attendance during the cardiopulmonary resuscitation and insured oral pharyngeal airway patency. Moreover, endotracheal intubation also failed to identify an upper airway obstruction. Aspiration of the packing material was not the cause of this patient's hemodynamic collapse.

Epidemiology

Florian Kratschmer (1843-1922) was the first researcher to provide a comprehensive analysis of changes in breathing, blood pressure, and heart rate that can occur when mucosa of the nasal airways are stimulated mechanically or chemically.[15] His report is considered the first description of trigeminal-mediated bradycardia and asystole, a phenomenon that is sometimes referred to as Kratschmer's reflex. In current terminology, it is referred to as the nasopulmonary reflex or TCR.

The trigeminal nerve is the largest of the cranial nerves. It provides sensory innervation to the face, scalp, and mucosa of the nose and mouth. The TCR may occur with manipulation of the branches of the trigeminal nerve anywhere along its intracranial or extracranial course. The TCR is described as a sudden onset of parasympathetic arrhythmia, sympathetic hypotension, or apnea elicited by central or peripheral stimulation of any of the sensory branches of the trigeminal nerve.[16] The TCR may result in an immediate decrease of the mean arterial blood pressure and heart rate of > 20% when compared with the baseline levels with surgical, mechanical, electrical, or chemical stimulation of the central part of the sensory branches of the trigeminal nerve.[17] The TCR represents one of the most powerful autonomous reflexes.[18,19]

Stimulation of trigeminal receptors that innervate the nose and nasal passage in animals can be an important stimulus for respiratory dysfunction and cardiac arrhythmias.[15,16] However, the inability to accurately document the neuroanatomy of this reflex coupled with its variable and rare expression in humans has hindered the appreciation of the importance of the TCR. These observations have led some researchers to dismiss the reflex as inconsequential in humans. However, other physicians, particularly surgeons who manipulate craniofacial structures, have witnessed the effects of the TCR firsthand.[20-25]

In studies of neurosurgical procedures utilizing the nasal passages and transsphenoid approaches, the TCR has occurred in 10% to 18% of patients.[16,24] The TCR has been consistently, although infrequently, noted by otolaryngologists in the management of epistaxis.[10,26] Even when performed properly, posterior nasal packing has been reported to cause apnea, hypoxemia, and dysrhythmia.[10] Although there has been debate about the importance of the TCR in humans, this response explains the sequence of events in and the death of this patient.[27]

The mechanism of the TCR is not well understood. The available data suggest that the response of the TCR when triggered by peripheral stimulation is different from the response when the TCR is triggered by central stimulation.[18] There is additional anatomic evidence that different areas can be distinguished within the nasal mucosa with regard to stimulation site and stimulus properties.[25] Specifically, it has been demonstrated in animals that mechanoreceptors are not equally sensitive throughout the nasal mucosa. The most sensitive areas for mechanical stimuli are located in the posterior parts of the nasal passages. In many animals, including humans, pronounced respiratory and cardiovascular responses can be elicited by appropriate

stimulation of the nasal mucosa. These responses have been studied by many researchers in various animals and may be evoked by mechanical, electrical, and chemical stimuli.[18,25]

Risk Factors

Several risk factors for heightening the TCR have been described.[25] Risk factors known to enhance the expression of TCR include hypercapnia, hypoxemia, light general anesthesia, the nature of provoking stimulus, the strength and duration of the stimulus, and medications. The specific pharmaceutical agents known to increase the manifestation of the TCR are narcotics, such as sufentanil and alfentanil, beta blockers, and calcium channel blockers.[16,24] This patient was not on any of these medications. In addition, he had not been hypoxemic. He had no known risk for elevation of the TCR.

Evidence suggests that the intensity of the TCR corresponds with the intensity of the mechanical stimulation of the trigeminal pathway.[24] Abrupt and sustained traction is more likely to evoke the TCR than is smooth and gentle manipulation. Immediate cessation of the stimulus, such as removal of the nasal packing, may be helpful in the prevention of fatal complications.[16] Unfortunately, this was not accomplished in this patient. Other interventions, including the administration of atropine, local anesthetic infiltrations, or blockage of the nerve, may be helpful in preventing fatal complications.

The TCR may be elicited without prior hemodynamic changes. Nevertheless, it is important to anticipate hypoxemia and bradycardia as the first indication of a cardiopulmonary response.[26] Administration of the anticholinergic atropine may be required in some cases where bradycardia is severe or persists despite cessation of the stimulus. However, premedication with intramuscular administration of an anticholinergic medication has not been effective in preventing this reflex. Moreover, the TCR may at times be refractory to the conventional methods of treatment, and use of vasopressors and immediate cardiac life support may be required. Thus, if mechanical stimulation to the trigeminal nerve is anticipated, continuous monitoring of hemodynamic parameters may allow the clinician to more readily identify the TCR and immediately interrupt the inciting stimulus.[24]

This patient was being monitored, but his cardiopulmonary collapse occurred suddenly and rapidly. He received immediate resuscitation following advanced cardiac life support protocols. Unfortunately, there was no attempt to remove the material that had been employed as packing to control his epistaxis. It remains conjecture whether removal of this material could have altered his outcome. However, the gauze probably should have been removed to maximize his chance of survival.

CONCLUSION

This case demonstrates the clinical importance of the TCR to providers in the VA health care system, particularly to those who treat epistaxis. Because they are typically older, veterans are a high-risk group. Age is important due to the higher incidence of epistaxis in the older populace, and interventions are more often necessary in older patients with epistaxis. In addition, posterior bleeds occur more frequently in older patients. The resulting stimulation of the trigeminal nerve from interventions to control a posterior bleed may be a more potent provocation for the TCR. Finally, older patients often have comorbid illnesses requiring medications that may augment the TCR. Therefore, the veteran's age and comorbid illnesses and medications may lead to greater susceptibility of a poor outcome, should the TCR occur as a result of interventions undertaken to control epistaxis.

VA practitioners should, therefore, be aware of the possible occurrence of the TCR in all patients with epistaxis, particularly when invasive manipulations of areas innervated by the trigeminal nerve are required. Evidence suggests that complications of the TCR range from mild bradycardia that responds to simple maneuvers to severe bradycardia and asystole requiring intervention with vagolytics. In rare cases, cardiac dysfunction may lead to death if the TCR is not suspected and early appropriate measures, such as removal of packing materials, are not undertaken.

Although the estimated complication rate of epistaxis and its treatment remains low (about 3%), the authors hope that this report will alert HCPs and that they will remain aware of the TCR as a potentially serious occurrence, even with mild to moderate manipulation of areas innervated by the trigeminal nerve.[6] ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and*

adverse effects—before administering pharmacologic therapy to patients.

REFERENCES

1. Pallin DJ, Chng YM, McKay MP, Emond JA, Pelletier AJ, Camargo CA Jr. Epidemiology of epistaxis in US emergency departments, 1992 to 2001. *Ann Emerg Med.* 2005;46(1):77-81.
2. Viducich RA, Blanda MP, Gerson LW. Posterior epistaxis: clinical features and acute complications. *Ann Emerg Med.* 1995;25(5):592-596.
3. Manes RP. Evaluating and managing the patient with nosebleeds. *Med Clin North Am.* 2010;94(5):903-912.
4. National Center for Veterans Analysis and Statistics. Profile of veterans: 2011. Data from the American Community Survey. http://www.va.gov/vetdata/docs/SpecialReports/Profile_of_Veterans_2011.pdf. Published March 2013. Accessed May 4, 2015.
5. U.S. Census Bureau. Age and sex composition: 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf. Issued May 2011. Accessed May 4, 2015.
6. Pollice PA, Yoder MG. Epistaxis: a retrospective review of hospitalized patients. *Otolaryngol Head Neck Surg.* 1997;117(1):49-53.
7. Kucik CJ, Clenney T. Management of epistaxis. *Am Fam Physician.* 2005;71(2):305-311.
8. Kotecha B, Fowler S, Harkness P, Walmsley J, Brown P, Topham J. Management of epistaxis: a national survey. *Ann R Coll Surg Engl.* 1996;78(5):444-446.
9. Gifford TO, Orlandi RR. Epistaxis. *Otolaryngol Clin North Am.* 2008;41(3):525-536.
10. Fairbanks DN. Complications of nasal packing. *Otolaryngol Head Neck Surg.* 1986;94(3):412-415.
11. Aeumjaturapat S, Supanakorn S, Cutchavaree A. Toxic shock syndrome after anterior-posterior nasal packing. *J Med Assoc Thai.* 2001;84(3):453-458.
12. Jayawardena S, Eisdorfer J, Indulkar S, Zarkaria M. Infective endocarditis of native valve after anterior nasal packing. *Am J Ther.* 2006;13(5):460-462.
13. Derkay CS, Hirsch BE, Johnson JT, Wagner RL. Posterior nasal packing. Are intravenous antibiotics really necessary? *Arch Otolaryngol Head Neck Surg.* 1989;115(4):439-441.
14. Koudounarakis E, Chatzakis N, Papadakis I, Panagiotaki I, Velegrakis G. Nasal packing aspiration in a patient with Alzheimer's disease: a rare complication. *Int J Gen Med.* 2012;5:643-645.
15. Kratschmer F. On reflexes from the nasal mucous membrane on respiration and circulation. *Respir Physiol.* 2001;127(2-3):93-104.
16. Spiriev T, Sandu N, Arasho B, Kondoff S, Tzekov C, Schaller B. A new predisposing factor for trigeminocardiac reflex during subdural empyema drainage: a case report. *J Med Case Reports.* 2010;4:391.
17. Schaller B. Trigemino-cardiac reflex during microvascular trigeminal decompression in cases of trigeminal neuralgia. *J Neurosurg Anesthesiol.* 2005;17(1):45-48.
18. Schaller B, Cornelius JF, Prabhakar H, et al; Trigemino-Cardiac Reflex Examination Group (TCREG). The trigemino-cardiac reflex: an update of the current knowledge. *J Neurosurg Anesthesiol.* 2009;21(3):187-195.
19. Sandu N, Spiriev T, Lemaitre F, Filis A, Schaller B; Trigemino-Cardiac Reflex Examination Group (TCREG). New molecular knowledge towards the trigemino-cardiac reflex as a cerebral oxygen-conserving reflex. *Sci World J.* 2010;10:811-817.
20. Nirmala J, Dilip KK, Padmaja D, Gopinath R. "Kratschmer" reflex during rhinoplasty. *Anesth Analg.* 2006;103(5):1337-1338.
21. Jacobs JR, Levine LA, Davis H, Lefrak SS, Druck NS, Ogura JH. Posterior packs and the nasopulmonary reflex. *Laryngoscope.* 1981;91(2):279-284.
22. Larsen K, Juul A. Arterial blood gases and pneumatic nasal packing in epistaxis. *Laryngoscope.* 1982;92(5):586-588.
23. Loftus BC, Blitzer A, Cozine K. Epistaxis, medical history, and the nasopulmonary reflex: what is clinically relevant? *Otolaryngol Head Neck Surg.* 1994;110(4):363-369.
24. Arasho B, Sandu N, Spiriev T, Prabhakar H, Schaller B. Management of the trigeminocardiac reflex: facts and own experience. *Neurol India.* 2009;57(4):375-380.
25. Schaller BJ, Filis A, Buchfelder M. Trigeminocardiac reflex in humans initiated by peripheral stimulation during neurosurgical skull-base operations. Its first description. *Acta Neurochir (Wien).* 2008;150(7):715-717; discussion 718.
26. Stemm RA. Complications of nasal packing. *Ear Nose Throat J.* 1981;60(10):461-462.
27. Widdicombe J. Reflexes from the lungs and airways: historical perspective. *J Appl Physiol (1985).* 2006;101(2):628-634.