Case in Point

Epistaxis and Death by the Trigeminocardiac Reflex: A Cautionary Report

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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. 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. 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. 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.

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. 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 antplatelet medications.

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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 10^3/μL platelets (166-383 x 10^3/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 scan 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 anticoagulant, and was continued on his inhaled medications for his COPD. An antibiotic, and was continued on his warfarin, was treated with an oral anticoagulant. The patient was alert and oriented. His hemoglobin was 13.1 g/dL (13.6-17.3 g/dL) with 216 x 10^3/μL platelets (166-383 x 10^3/μL). His INR was therapeutic at 2.38. Laboratory assessments of 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.

**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. 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.

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. 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 exsanguina-
tion.10 More commonly, death from epistaxis is related to complications of the treatment intervention or to an exacerbation of an underlying co-
morbid disease.10 The external overt blood loss in this patient was not sign-
nificant enough to explain his cardio-
pulmonary collapse. Although he had experienced a recent pulmonary embolism, he had been on continuous anticoagulation for 3 months and remained adequately anticoag-
ulated 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, autoim-
mune disorders, or organ failure may have epistaxis from decreased plate-
let production or increased platelet destruction, an infection can be dev-
astating. Many HCPs anticipate this occurrence and provide the patient with epistaxis prophylactic antibiot-
ics.13 Life-threatening infectious compi-
ications are usually delayed events and are generally easily recognized. An infectious process was not sus-
pected in this patient. Nevertheless, he was treated with an oral antibiotic.

Dislodgement of the nasal pack-
ing with resultant aspiration and as-
phyxiation has been described as a fatal complication associated with the treat-
ment of epistaxis.14 This compi-
cation was not observed in this patient. The otolaryngologist respon-
sible for the placement of the nasal packing was in attendance during the
cardiopulmonary resuscitation and insured oral pharyngeal airway pa-
tency. 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 com-
prehensive analysis of changes in breathing, blood pressure, and heart rate that can occur when mucosa of the nasal airways are stimulated me-
chanically or chemically.15 His report is considered the first description of trigeminal-mediated bradycardia and asystole, a phenomenon that is some-
times referred to as Kratschmer's reflex. In current terminology, it is referred to as the nasopulmonary reflex or TCR.

The trigeminal nerve is the larg-
est 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 para-
sympathetic arrhythmia, sympathetic hypotension, or asystole elicited by central or peripheral stimulation of any of the sensory branches of the tri-
geminal nerve.10 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 recep-
tors that innervate the nose and nasal passage in animals can be an important stimulus for respiratory dysfunction and cardiac arrhyth-
mias.15,16 However, the inability to accurately document the neuroanat-
omy of this reflex coupled with its variable and rare expression in hu-
mans has hindered the appreciation of the importance of the TCR. These observations have led some researc-
chers to dismiss the reflex as inconsequen-
tial in humans. However, other physicians, particularly surgeons who manipulate craniofacial structures, have witnessed the effects of the TCR firsthand.20–23

In studies of neurosurgical pro-
cedures utilizing the nasal passages and transsphenoid approaches, the TCR has occurred in 10% to 18% of patients.10,24 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 asystole, hypoxemia, and dys-
rhythmia.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 re-
sponse when the TCR is triggered by central stimulation.18 There is addi-
tional anatomic evidence that differ-
ent areas can be distinguished within the nasal mucosa with regard to stimu-
lation site and stimulus properties.25

Specifically, it has been demonstrated in animals that mechanoreceptors are not equally sensitive throughout the nasal mucosa. The most sensi-
tive areas for mechanical stimuli are located in the posterior parts of the nasal passages. In many animals, in-
cluding humans, pronounced respira-
tory and cardiovascular responses can be elicited by appropriate

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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.\(^{23}\) 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 hypoxic. 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 vasoressors 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**

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REFERENCES