Case Report



# Cardiovascular crisis after use of epinephrine: a case report and review of the literature

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**Abstract:** Diluted epinephrine is often locally used to provide hemostasis and improve visualization. However, rapid absorption or inadvertent intravascular injection of epinephrine can cause unexpected cardiovascular effects. A 28-year-old man was scheduled to undergo a nasal septoplasty. After local application of 0.01% epinephrine-soaked nasal pledgets and infiltration of 3 mL 0.001% epinephrine, the patient developed a severe hypertension of 205/126 mmHg, followed by ventricular tachycardia. Cardiac arrest ensued after intravenous injection of lidocaine and esmolol in an attempt to control ventricular arrhythmia. After successful resuscitation, the patient was transferred to the intensive care unit (ICU) and fully recovered in 5 days. While another two epinephrine-induced hypertension cases were treated smoothly without β-blockers. Although the plausible explanation of this precipitating event is the usage of β-blocker, we reviewed the previous published similar clinical reports and proposed other possible explanations and differential diagnosis. It is important to recognize this potential cardiovascular side-effect in patients administrated with topical and/or submucosal epinephrine. Drugs used to treat hypertension and/or arrhythmia needed to be appreciated.

**Keywords:** Epinephrine; hypertension; ventricular tachycardia; cardiac arrest; case report

Received: 22 November 2020; Accepted: 22 April 2021; Published: 25 October 2021.
doi: 10.21037/acr-20-161
**View this article at:** http://dx.doi.org/10.21037/acr-20-161

## Introduction

Epinephrine is commonly used in nasal surgeries to decrease bleeding in the operative site. If locally administrated epinephrine reaches the systemic circulation, however it can cause hypertensive crisis, arrhythmia, pulmonary edema and even cardiac arrest (1). Here we describe a patient who showed sudden increases in blood pressure (BP) and heart rate, followed by cardiac arrest, and we report it with a related literature review and provide the interpretation of this cardiac disaster event. This report may be helpful for the future analysis of this rare event.

We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/acr-20-161).

## Case presentation

A 28-year-old man, weighing 62 kg, was admitted for nasal septoplasty. The patient denies has any history of hypertension or cardiac disease family history, and there was no evidence of cardiac or pulmonary disease on physical and laboratory examination. After arriving at the operation room, standard monitoring and intravenous infusion of Ringer's lactate was started. General anesthesia was induced with propofol 100 mg intravenously (*iv*), sufentanil 20 μg *iv*, cis-atracurium 12 mg *iv* to facilitate tracheal intubation. Anesthesia was maintained with sevoflurane 2–3% in oxygen.

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After induction, the surgeon applied pledgets soaked with epinephrine (1:10,000) into the patient's nasal cavity and injected 3 mL epinephrine (1:100,000) locally. Within 10 to 15 minutes, the patient's BP rose from 107/68 mmHg to 205/126 mmHg, Heart Rate (HR) increased from 60 to 163 beat per minute (bpm) and end-tidal carbon dioxide ($ETCO_2$), previously around 33 mmHg, increased to 44 mmHg. ST-segment elevation and ventricular tachycardia appeared on the electrocardiograph. Initially, the inspired sevoflurane concentration was increased to 5%. Lidocaine (50 mg) was given to control ventricular tachycardia. Few minutes later, a 30 mg dose of esmolol was administered to control hypertension and tachycardia. In 5 minutes, the patient's BP dropped to 102/64 mmHg, HR decreased to 79 bpm and $ETCO_2$ fell to 13 mmHg. Ventricular fibrillation ensued. All the anesthetics and the operation were stopped. Anesthesiologist initiated chest compression immediately and delivered a biphasic defibrillation shock at 120 J within 1 minute. The patient's heart returned to sinus rhythm (124 bpm). Dopamine 5 μg/kg/min was infused to maintain the systolic BP at 100–120 mmHg. The arterial blood gas and electrolytes test performed 20 minutes after the success of cardiopulmonary resuscitation (CPR) revealed no abnormalities (pH 7.37, $PaCO_2$ 41 mmHg, $PaO_2$ 535 mmHg) except low blood potassium (2.8 mmol/L). Hypokalemia was treated with KCl 1 g. Surgery was completed uneventfully and anesthesia was maintained with propofol of 4–6 mg/kg/h.

The patient was transferred to the intensive care unit (ICU) and was extubated on the second day and discharged from ICU on the fourth day without any sequel. The timeline of treatment is shown in *Table 1*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). A written informed consent was obtained from the patient.

## Discussion

A local infiltration of epinephrine mixed with saline or local anesthetic is widely used to improve the surgical field view, provide hemostasis or diminish the systemic toxic effect of local anesthetic. However, absorption or inadvertent intravascular injection of epinephrine might cause unexpected cardiovascular effects (1).

The nasal mucosa has an excellent absorbing ability. van Hasselt (2) found that following submucosal infiltration with 4.4 mL of 1:80,000 epinephrine, plasma epinephrine concentrations increased by 44 times to a peak of 9.9 nmol/L (1,800 ng/L) within one minute. While peak epinephrine levels were 2 to 4 times higher than baseline values 10 minutes after topically used of Moffett's solution containing 1 mL of 1:1,000 epinephrine (3). Increased plasma level of epinephrine was mainly due to absorption of exogenous epinephrine rather than increased endogenous production in response to stressful conditions. The incidence of hypertension and tachycardia has been shown to increase in a dose-dependent manner (2,3).

A summary of the published cardiac arrest events associated with epinephrine infiltration is shown in *Table 2* (1,4-14).

Kalyanaraman *et al*. (4) analyzed a case series of 12 cardiac arrest or pulmonary edema patients who previously received topical phenylephrine and/or submucosal epinephrine. They proposed a possible mechanism: a systemic hypertension resulted from absorbed topical vasoconstrictor could increase left ventricular afterload and decrease cardiac output, even lead to cardiac congestion and left heart failure; The ability to increase heart rate and contractility which was important to preserve cardiac output under these circumstances might be blunted by β-blocker, leading to cardiopulmonary crisis (4). A similar cycle happened in our case when an unexpected severe α-agonist-induced hypertension treated by a dose of esmolol. Although the proposed explanation of this precipitating event is most plausible, there are still 11 cardiac arrest cases (*Table 2*) which were not treated with β-blocker. We need to explore alternate etiologies of cardiac arrest for this case.

Epinephrine is known to affect plasma potassium levels. It initially causes a slight transient rise in plasma potassium mediated by α-adrenoceptors through the activation of hepatic $Ca^{2+}$-dependent-$K^+$-channels (15), then within 5 minutes, leads to a marked prolonged decrease in plasma potassium, which is due to a β2-adrenoceptors-mediated influx of potassium into liver and skeletal muscle cells through $Na^+$-$K^+$-ATPase (15).

It has been shown that acute severe hypokalemia (<2.5 mmol/L), even in the absence of heart disease, can cause serious ventricular tachyarrhythmia (16), which is commonly attributed to prolonged ventricular repolarization, slowed conduction and abnormal pacemaker activity (17). Circulating epinephrine could induce hypokalemia in a dose-related manner. A plasma epinephrine of 800 ng/L is commonly associated with hypokalemia (18). While a 15- to 30-fold increase above basal epinephrine level depresses plasma potassium by

**Table 1** Timing of clinical events

| Time | Event | Clinical signs |
|---|---|---|
| 17:00 | Patient arrive at the operation room, standard monitoring | BP 110/60 mmHg, HR 72 bpm, $SpO_2$ 100% |
| 17:10 | Anesthesia begins | BP 108/57 mmHg, HR 65 bpm, $SpO_2$ 100% |
| 17:30 | Epinephrine (1:10,000) into the patient's nasal cavity and injected 3 mL epinephrine (1:100,000) locally | |
| 17:44 | | BP 205/126 mmHg, HR 163 bpm, $SpO_2$ 100%, $ETCO_2$ 44mmHg |
| 17:45 | Increase the sevoflurane concentration to 5% | |
| 17:46 | Lidocaine 50 mg iv | |
| 17:47 | Esmolol 30 mg iv | |
| 17:49 | | BP 102/64 mmHg, HR 79 bpm, $ETCO_2$ 13 mmHg |
| 17:50 | | Ventricular fibrillation |
| 17:51 | CPR and shock of 120 J delivered | |
| 17:55 | | The patient's heart returned to sinus rhythm (124 bpm) |
| 18:00 | Dopamine 5 μg/kg/min was infused | SBP 100–120 mmHg |
| 18:10 | The arterial blood gas and electrolytes test performed | pH 7.37, $PaCO_2$ 41 mm Hg, $PaO_2$ 535 mm Hg, potassium 2.8 mmol/L |
| 18:12 | KCl 1 g ivgtt | |
| 18:30 | Continue the operation | BP 98/57 mmHg, HR 112 bpm, $SpO_2$ 100% |
| 21:00 | Transferred to ICU for further monitoring after operation | BP 115/73 mmHg, HR 91 bpm, $SpO_2$ 100% |
| Day 1 after surgery | Remove tracheal tube | |
| Day 3 after surgery | Discharged from ICU without any sequel | |

Medical history: 28-year-old man, Preoperative diagnosis: deviation of nasal septum. Deny the family history of hypertension and heart disease, and there was no obvious abnormality in preoperative examination. BP, blood pressure; HR, Heart rate; ETCO2, end-tidal carbon dioxide; SBP, systolic blood pressure; bpm, beats/min; ivgtt, intravenously guttae; CPR, cardiopulmonary resuscitation; ICU, intensive care unit.

approximately 0.8 mmol/L (15). In this case, low plasma potassium of 2.8 mmol/L was detected about 30 minutes after epinephrine administration. Since the plasma epinephrine usually reach peak concentration in less than 10 minutes after infiltration, followed by a gradual decrease (19), a much lower potassium level might be identified in this patient when ventricular arrhythmia and cardiac asystole happened. In 7 published cases with clear time records of epinephrine-associated cardiac arrest, five ones (4,8,10,11) developed cardiac crisis in 5–10 minutes after epinephrine administration which was exactly when plasma potassium dropped to the lowest value (19).

After this case, another two patients developed hypertension [systolic blood pressure (SBP) >200 mmHg] after nasal infiltration of 2–3 mL epinephrine (1:100,000) in our hospital. Fortunately, BP returned to normal in 10 minutes without any treatment. Blood samples were collected immediately and again in half an hour. Hypokalemia, accompanied by ST segment depression, was found in both patients (3.0 and 2.9 mmol/L) during hypertensive episode and half an hour later (both were 3.3 mmol/L). Preoperative blood potassium of those two patients was 4.13 and 4.12 mmol/L, respectively. Although none of two patients developed ventricular arrhythmia, this acute hypokalemia still poses a threat of dangerous arrhythmias.

Nine of the ten patients received isoflurane, sevoflurane or nitrous oxide during surgery. Volatile anesthetics can depress myocardial contractility, as well as potentiate the arrhythmogenic effects of epinephrine via a synergistic

**Table 2** Summary of published cardiac arrest cases associated with epinephrine

| NO. | Age (year) | Gender | Inhaled anesthetic | Submucosal epinephrine (μg) | Submucosal/ intravenous lidocaine | Topical epinephrine | Cardiac arrest time (min) | β blocker | Hypokalemia | Depressed LV cardiac | Recovery |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 (1) | 12 | Female | Halo/$N_2O$ | 240 | Yes | No | Unknown | No | Unknown | Unknown | 3 days |
| 2 (4) | 6 | Male | Iso | 400 | No | No | 10 | Esmolol | Unknown | EF =38% | Unknown |
| 3 (4) | 15 | Unknown | Iso/ $N_2O$ | Yes | Yes | No | Unknown | Labetalol | Unknown | Unknown | Unknown |
| 4 (5) | 14 | Female | Unknown | 30 | No | No | Unknown | Propranolol | Unknown | Unknown | Unknown |
| 5 (6) | 52 | Female | Iso/$N_2O$ | Subacromial 400 | No | Yes | Unknown | No | In ICU, $K^+$ 2.9 mmol/L | Unknown | 2 days |
| 6 (7) | 29 | Male | Sevo | 20 | Yes | Yes | 30–40 | Metoprolol | Unknown | EF <20% | 5 weeks |
| 7 (8) | 21 | Male | Sevo | 60 | Yes | No | 10 | No | In ICU, $K^+$ 2.7 mmol/L | EF =10% | 4 days |
| 8 (9) | 51 | Female | Iso | 90 | Yes | No | 3–5 | No | Unknown | Unknown | 4 days |
| 9 (10) | 27 | Male | Sevo | 20 | Yes | No | 5–10 | No | Unknown | EF =35% | 6 days |
| 10 (11) | 19 | Male | Sevo/$N_2O$ | No | No | Yes | 5 | No | Unknown | EF <39% | 5 days |
| 11 (11) | 49 | Female | Sevo/$N_2O$ | No | Yes | Yes | 5 | No | Unknown | EF <30% | 5 days |
| 13 (12) | 35 | Male | Desf | 75 | Yes | No | 10 | No | Unknown | Unknown | Unknown |
| 14 (13) | 33 | Female | Unknown | 600 | Yes | No | 3–5 | No | Unknown | EF 10–15% | 2 days |
| 15 (14) | 22 | Female | No | 90 | Yes | No | 1 | No | Unknown | Unknown | 5 days |

Halo, Halothane; N2O, nitrous oxide; Iso, isoflurane; Sevo, sevoflurane; Desf, desflurane; EF, ejection fraction.

interaction between α1- and β-adrenoceptors. Also, it can slow the automaticity of the sino-atrial node and myocardial conduction, leading to atrial or ventricular arrhythmias, which could be further potentiated by epinephrine (20). In our case, sevoflurane was increased to 5% till the BP decreased. Thus, the influence of the volatile anesthetic in this situation may have worsened the depressed myocardial contractility and arrhythmogenicity of epinephrine.

Lidocaine is commonly added to infiltrating epinephrine because of its protective action against cardiovascular complications as it stabilizes the myocardium by blocking sodium channels (21), and it can provide analgesia at the time of incision. However, human and animal tests found that administration with lidocaine/epinephrine mixture could lead to a transient hypotensive effect and decreased cardiac output, which is less significant when lidocaine or epinephrine used alone (21,22). Although the exact mechanism of this synergistic effect is not clear, worsen cardiovascular function at least partly results from lidocaine in treatment of ventricular arrhythmia.

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy, is a clinical syndrome characterized by acute transient apical ventricular dysfunction without obstructive coronary disease (23). It is precipitated by emotional or physical stress and can be triggered by exogenous epinephrine (24). It typically involves new ST-segment elevation and/or T-wave inversion, mild elevation of cardiac troponin, and dyskinesia of left ventricular mid-segments (25). Most of the patients completely recover within days or weeks (23). It has been reported that nasal administration of epinephrine could lead to Takotsubo cardiomyopathy (26,27). If Takotsubo cardiomyopathy is suspected, echocardiography and coronary angiography are urgently warranted to rule out an ACS and confirm the diagnosis. Some supportive treatments might be helpful and ACE inhibitors and angiotensin receptor blockers are associated with improved survival (27). In conclusion, we have described a case of cardiovascular crisis which took place after a small amount of epinephrine was injected in a healthy patient without any heart disease. The complex cardiovascular interactions of treatment with β-blockers and, possibly, lidocaine, must be appreciated in order to prevent severe complications such as pulmonary edema and cardiac arrest. When ventricular arrhythmia

occurred, it might be sensible to identify and correct a possible hypokalemia. Both surgeons and anesthesiologists should be familiar with this possible cardiovascular side-effect in patients administrated with topical and/or submucosal epinephrine.

The strengths and limitations of this manuscript: This case report review the previous published reports and proposed the common mechanisms and reasonable treatment. Considering the complexity of the patients with wide range of pathologies, further studies are warranted. The high level of clinical evidences is still needed to draw a final conclusion.

## Acknowledgments

*Funding:* This research was supported by the National Natural Science Foundation of China (Grant no. 81701116).

## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/acr-20-161

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/acr-20-161). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). A written informed consent was obtained from the patient.



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doi: 10.21037/acr-20-161
**Cite this article as:** Ren Y, Wang Y, Yan H, Chen L, Mao Q. Cardiovascular crisis after use of epinephrine: a case report and review of the literature. AME Case Rep 2021;5:31.