

# Acute noncardiogenic pulmonary edema after neostigmine administration during the recovery period of general anesthesia

## A case report

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### Abstract

**Rationale:** Acute non-cardiogenic pulmonary edema (ANPE) is a rare but challenging complication which occurs during the perioperative period, mainly before and after the extubation in the course of the recovery period of general anesthesia. It is characterized by increased fluid in extravascular pulmonary spaces, preventing gas exchange and further resulting in respiratory failure.

**Patient concerns:** A 12-year-old boy who had undergone island skin flap in the right upper limb and who developed a unilateral pulmonary edema after the administration of neostigmine during the recovery period of general anesthesia. The neostigmine was administered to reverse neuromuscular block.

**Diagnoses:** Acute non-cardiogenic pulmonary edema.

**Interventions:** The patient was transferred to intensive care unit (ICU) and treated with mechanical ventilation (controlled mode ventilation pattern, CMV) and other supportive treatment.

**Outcomes:** The oxyhemoglobin saturation of the patient returned to the normal level with symptoms and signs of ANPE significantly alleviated. The mechanical ventilation was withdrawn by the fourth day, and no sequela of vital organs was observed.

**Lessons:** Although neostigmine is widely used for recovery from neuromuscular block and exhibits satisfactory effect in most cases, there is a potential risk of ANPE in some cases, which is rare but potentially fatal and could affect the patient outcomes. Therefore, it is necessary for anesthetists to closely monitor the vital signs of patients after administration of neostigmine in the perioperative period.

**Abbreviations:** ANPE = acute noncardiogenic pulmonary edema, BP = blood pressure, CPE = Cardiogenic pulmonary edema, ECG = electrocardiogram, HR = heart rate, NCPE = noncardiac pulmonary edema, NPPE = negative pressure pulmonary edema, Paw = airway pressure, SpO<sub>2</sub> = oxyhemoglobin saturation.

**Keywords:** acute noncardiogenic pulmonary edema, mechanical ventilation, neostigmine, perioperative period

## 1. Introduction

Pulmonary edema is a rare but potentially fatal complication, which may occur during the perioperative period. It is characterized by increased fluid in pulmonary interstitial spaces

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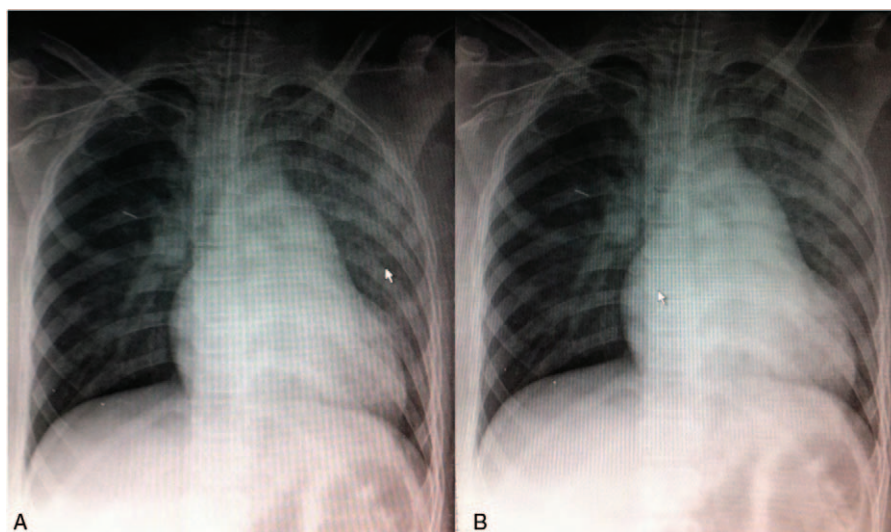
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and alveoli, which obstructs normal gas exchange and further leads to respiratory failure.<sup>[1]</sup> The common causes of pulmonary edema are left ventricular failure, trauma, sepsis, drug reaction or overdose, and so on.<sup>[2]</sup> Due to different etiology, the pathogenesis of drug-induced pulmonary edema is multifactorial and not completely understood, which may involve cytotoxicity of lung epithelial cells and relevant inflammatory response.<sup>[3]</sup> Here, we report a rare case of a 12-year-old boy with a dry gangrene who developed acute noncardiogenic pulmonary edema (ANPE) after administration of neostigmine for the reversal of neuromuscular block at the end of the surgery.

## 2. Case report

This study was approved by the Ethics Committee and Institutional Review Board of the China-Japan Union Hospital of Jilin University, and informed consent was obtained.

A 12-year-old boy, 41 kg of weight, having his right forefinger bashed 70 days ago, underwent an island skin flap in the right upper limb under general anesthesia. He was also diagnosed of the dry gangrene in the distal limb. The preoperative blood routine, coagulation routine, chest X-ray, and electrocardiogram (ECG) examination results were normal. The patient fasted for 12 hours without transfusion before the operation.



**Figure 1.** Chest X-ray photograph findings of (A) postoperative acute pulmonary edema phase after administration of neostigmine. (B) Recovery phase on the next day.

When entering the operation room for the first time, the patient was extremely frightened and refused to receive the venipuncture, so a peripheral intravenous access was established in the ward. The patient was treated with intravenous injection of midazolam 7.0 mg and escorted into the operation room in sleep. During the process, the patient had been repeatedly beaten by his parents, which aggravated his nervousness and fright.

In the operation room, ECG, oxyhemoglobin saturation ( $SpO_2$ ), and blood pressure (BP) were monitored with anesthesia monitor (S5 TM, GE Healthcare TM, Milwaukee, WI). The general anesthesia was induced by intravenous administration of fentanyl 4  $\mu$ g/kg, cisatracurium 0.25 mg/kg, and diprivan 1.5 mg/kg. Then a tracheal intubation followed. Brachial plexus block was performed on the right upper arm with 0.375% ropivacaine (20.0 mL). All procedures were carried out smoothly, and the breath sounds of both lungs were within normal limits. General anesthesia was maintained with sevoflurane 1% to 1.5% and no additional drugs were added. During the surgery,  $SpO_2$  was 99%, airway pressure (Paw) 13 to 15 cm  $H_2O$ , tidal volume ( $V_T$ ) 300.0 mL, respiratory rate 11/min, heart rate (HR) 90 to 105/min, and BP was 90–110/65–80 mmHg. The surgery lasted for 1.5 hours and was finished uneventfully. Ringer solution 500 mL was used during the surgery, and the urine volume was 150 mL with the use of catheterization.

At the end of the surgery, the anesthetic inhalation was deactivated followed by a lung lavage. A respiratory resistance was found, so a mixture of neostigmine 1 mg and atropine 0.5 mg was given intravenously, and a manual-control breathing assistance was provided. Ten minutes later, another neostigmine 1 mg and atropine 0.5 mg mixture were given for the respiratory depression, which was still existing, then the BP decreased to 90/60 temporarily, and HR was 70 bpm. BP and HR returned to normal range within 3 minutes, while no significant improvement in respiration was observed. Mechanical ventilation proceeded in controlled mode ventilation with  $V_T$  300 mL, flux 15/min, and positive end-expiratory pressure (PEEP) 7 on 100%  $O_2$ . Ten minutes after the 2nd administration of neostigmine-atropine, massive pink and frothy sputum were sucked from the endotracheal tube. Bilateral auscultation displayed a large amount of moist rale at the left lung bases while a few were

observed at the right lung. Arterial blood gas analysis showed that Paw rose to 15 to 20 cm  $H_2O$  while  $S_pO_2$  dropped away to 93% to 97%. Then, the patient was propped up, and furosemide 20.0 mg, methylprednisolone 80.0 mg, and cedi-lanid 0.2 mg were given intravenously together with papaverine 30.0 mg intramuscularly. Right chest puncture proceeded with a 7# needle and no gas out was observed, then the needle was pulled out. After that, a chest X-ray was taken, the results of which showed significant left pulmonary edema (Fig. 1A).

Massive frothy pink sputum came from the patient's mouth. Paw increased significantly to 20 to 25 cm  $H_2O$ ,  $S_pO_2$  decreased to 85% to 93%, systolic blood pressure 140 to 160 mmHg, HR 110 to 140 bpm, and  $S_pO_2$  decreased momentarily to 65% to 75% during airway suction. After that, anisodamine 10.0 mg and furosemide 80 mg were given intravenously. Two hours later, pink frothy sputum declined significantly and breathing recovered spontaneously, but  $S_pO_2$  remained 85% to 93% and obvious breathing difficulty were observed. Then, the patient was transferred to intensive care unit to continue ventilation therapy. The chest X-ray on the next day showed left pulmonary edema, right pneumothorax, and a right thoracic drainage was given (Fig. 1B). Then, the pulmonary oxygenation improved (fraction of inspiration  $O_2$ ,  $FiO_2$ : 0.4, partial pressure of carbon dioxide,  $PaCO_2$ : 203 mmHg), and myocardial enzyme level was significantly increased, liver and kidney functions improved mildly, and thrombocytocrit became 103  $\mu$ g/L.

The patient was ventilated for 4 days and extubated on the 5th day after the operation. Cardiac color ultrasound, chest radiography, and bronchoscopy showed no clinical problems in vital organs, and the patient was transferred to Department of Pediatrics for further treatment.

### 3. Discussion

Pulmonary edema is a severe perioperative complication which usually happens before or after the tracheal extubation during the recovery period of general anesthesia. It is characterized by excess fluid accumulation in the tissue and air spaces of the lungs. Due to an increase in the pulmonary capillary hydrostatic pressure, pulmonary edema can be cardiogenic while noncardiogenic is

induced by increased capillary permeability.<sup>[4]</sup> It is important to understand the potential causes of pulmonary edema during the perioperative period to determine the specific therapy and prevent the disease from aggravation.

In this case, cardiogenic pulmonary edema (CPE) was first excluded. CPE may be caused by pneumothorax tension of the right lung due to vascular reactive contraction, which induces a shift to the left of the mediastinum, an obstruction of the return flow, and a vascular distortion in the left lung. At that moment, the pulmonary capillary hydrostatic pressure increases gradually and a pulmonary edema occurs. The anesthetist also considered this factor first. However, the patient had no history of cardiovascular disease, and ECG was normal throughout the process. In addition, postoperative ultrasonic cardiogram showed no compromise of cardiac functions. Therefore, the cardiogenic possibility was evaded.

Excessive infusion of liquid or rapid infusion per unit time can also lead to pulmonary edema. However, only 500 mL of lactic acid Ringer solution was infused in this case at a constant speed, thus this factor was also ruled out.

Negative pressure pulmonary edema (NPPE) often occurs in patients with acute upper airway obstruction or spontaneous breathing recovery after chronic partial airway obstruction. In the present case, NPPE can be ruled out as the patient had no history of chronic partial airway obstruction and the endotracheal catheter had not been removed.

When the endotracheal tube is inserted deeply into the right lung, it may lead to atelectasis of the left lung, resulting in reexpansion pulmonary edema. In addition, repeated stimulation to the carina with the endotracheal tube end can also induce pulmonary edema by activating the vasovagal reflex.<sup>[5]</sup> However, in the present case, these factors related to endotracheal tube localization and single-lung ventilation have been ruled out by the chest X-ray.

Considering that also the above factors have been ruled out and pulmonary edema occurred within a few minutes after the injection of neostigmine, it can be speculated that the pulmonary edema was induced by neostigmine. Neostigmine is a type of cholinesterase inhibitor that can increase the amount of acetylcholine by inhibiting the activity of cholinesterase, thereby enhancing and prolonging the cholinergic effects of acetylcholine. It is conventionally used for reversal of neuromuscular block induced by nondepolarizing neuromuscular blocking drugs at the end of surgery.<sup>[6]</sup> The use of neostigmine is known to be safe and effective for most patients. However, in recent years several cases of acute pulmonary edema due to the application of neostigmine have been reported. Raiger et al<sup>[7]</sup> reported 2 cases of ANPE after the administration of neostigmine to reverse neuromuscular block. Preeti and coworkers<sup>[8]</sup> have reported a 9-year-old boy who developed ANPE following extubation after using neostigmine. Bijapur and coworkers described a case of a 1-year-old child who developed acute pulmonary edema after the use of a neostigmine-glycopyrrolate mixture for reversal of neuromuscular block.<sup>[9]</sup> In all cases, the patients had no preexisting cardiac or respiratory diseases and underwent operation under general anesthesia. Neostigmine-induced ANPE was diagnosed based on the fact that ANPE occurred soon after the administration of neostigmine while other causes of ANPE were ruled out. Preeti et al speculated that neostigmine might induce noncardiac pulmonary edema (NCPE) by impairing the function of upper airway dilating muscle and causing upper airway to narrow which may result in NPPE. Bijapur and coworkers surmised the occurrence of NCPE might be also related to the rare anaphylaxis

of neostigmine. However, in the present case, the tracheal tube had not been removed when NCPE occurred and no allergy was observed through the process. Therefore, those mechanisms were not applicable to the present case. In addition, the patients were children under 12 years old in 3 of the 4 cases, so it can be assumed that the neostigmine-induced NCPE was more likely to happen to children.

In this case, a 12-year-old boy developed NCPE following the use of neostigmine for reversal of neuromuscular block before extubation. The autonomic nervous system of the child has not developed well. Meanwhile, the child was in a state of irritation before the surgery because of the fear of the operation and the abuse of his parents. Also, the patient has a history of gangrene, and the absorption of toxins can also induce the sympathetic nervous system to an excited state. It is known that the application of neostigmine may further activate the sympathetic nervous system. In our case, neostigmine was administered twice with a total dose of 50 µg/kg, which could be considered as high dose (although not over-dose) for a child. High dose of neostigmine can inhibit the activity of cholinesterase, and lead to an accumulation of acetylcholine at cholinergic nerve terminals. The accumulated acetylcholine can then stimulate the N1 receptor, induce the excitation of autonomic ganglion, and upregulate the excitement of sympathetic nervous system. Moreover, the sympathetic nervous system was over-excited after the administration of neostigmine together with atropine. Atropine is routine use in preventing the bradyarrhythmia effects of neostigmine, because it acts by inhibiting M receptor in the parasympathetic postganglionic postsynaptic membrane. The regulation of peripheral vessels is mainly accomplished by the binding of acetylcholine to N receptor in the postsynaptic membrane of the sympathetic nervous system, while atropine does not bind to the N receptor or affect the sympathetic transmission process. In brief, atropine used in this case was clinical doses, which has been proved no effect on ventricular function and peripheral blood vessels mainly due to the lack of parasympathetic domination of the M receptors.<sup>[10]</sup> Therefore, the role of atropine in sympathetic hyperexcitability and pulmonary edema could be excluded and the over-excited state of sympathetic nervous system was mainly due to the administration of neostigmine.

The excessive excitation of sympathetic nervous system has a lot to do with the occurrence of pulmonary edema.<sup>[11,12]</sup> It has been reported that the significant activation of the sympathetic nervous system is a necessary precondition of neurogenic pulmonary edema in rats with spinal cord injury.<sup>[13]</sup> The significant increase of catecholamine including norepinephrine and adrenaline in the blood is closely related to the development of neurogenic pulmonary edema. It can be speculated that due to the over-excitation of the sympathetic nervous system, a surge of catecholamine, including epinephrine and norepinephrine, was released into the bloodstream and induced systemic vasoconstriction and rapid changes in hemodynamics, which then induced a sudden increase of arterial BP and a large amount of blood in the pulmonary circulation. On one hand, the effective filtration pressure of pulmonary capillary bed increased sharply and a large amount of fluid accumulated in the lung clearance, resulting in the formation of pulmonary edema. On the other hand, the impact of blood flow induced the injury of vascular endothelial cells and the release of vasoactive substances (such as histamine, etc.), which resulted in increased vascular permeability and extravasation of massive plasma protein and further aggravated acute pulmonary edema.

In view of the diagnosis and treatment process of ANPE in our case, several tips were summarized as follows to effectively prevent, diagnose, and treat acute pulmonary edema during the perioperative period.

- (1) Routine medication may also induce rare but fatal complications such as ANPE in some cases especially when patients are in an irritable or infectious state. This phenomenon may have individual differences and should draw enough attention.
- (2) The sympathetic nervous system of children has not well developed and is more likely to be over-excited by the external environment. When using neostigmine for children, it is necessary to appropriately regulate the dose and closely monitor the vital signs for the effective prevention and prompt diagnosis of pulmonary edema.
- (3) The diagnosis of drug-induced pulmonary edema is difficult due to the lack of detection methods. If pulmonary edema occurs soon after the administration of drugs with other factors ruled out, drug-induced pulmonary edema should be considered.
- (4) The treatment of pulmonary edema should be based on mechanical ventilation and other supportive treatment such as a cardiac stimulant, diuretics, and other symptomatic treatment should be applied when necessary.

#### 4. Conclusion

In conclusion, we report a case of pulmonary edema caused by neostigmine during the period of general anesthesia recovery. There was no drug induced allergy in this case report and the dose of neostigmine was relatively high but not over dose. This complication is unpredictable and challenging which could affect the prognosis of patients, and careful attention should be paid on the administration of neostigmine for the reversal of neuromuscular block, especially for young patients or those in an irritable state. Once the pulmonary edema occurs, mechanical ventilation and other appropriate supportive treatment should be provided in accordance with the severity of the conditions.

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#### Author contributions

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**Resources:** Guoqing Zhao.

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