An Analysis of Negative Pressure Pulmonary Edema Cases after Acute Upper Airway Obstruction

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Objective: Negative-pressure pulmonary edema (NPPE) occurs when significant negative intrathoracic pressure develops against an obstructed airway, causing fluid to shift into the pulmonary interstitium. NPPE is a rare complication of all anesthetics with an incidence of less than 0.1%. However, the occurrence of NPPE has been suggested to be under-reported, as it is often unrecognized or misdiagnosed. The morbidity and mortality of an unrecognized event of NPPE is as high as 40%. The present study reviews the cases of NPPE and discusses the occurrence, predisposing factors, and recommendations for treatment and prevention.

Methods: All patients with general anesthesia from January 1, 2006 through December 31, 2008 were retrospectively analyzed from our Quality Assurance (QA) anesthesiology database. NPPE was diagnosed according to the clinical findings of tachypnea, rales on lung auscultation, pink frothy sputum in the endotracheal tube, hypoxemia on pulse oximetry or on arterial blood gas determination, radiological findings of pulmonary edema, and pulmonary edema which resolved within 24 hours.

Results: Of the 126,589 patients who underwent general anesthesia with endotracheal intubation, 13 (0.01%) cases of NPPE were reported (8 males and 5 females). All cases were American Society of Anesthesiologists (ASA) physical status I or II. The age ranged from 11 months to 56 years and the body weight ranged from 9 kg to 90 kg. Most of the patients showed a rapid onset of pulmonary edema after acute upper airway obstruction in the induction and emergency periods. Resolution occurred within 24 hours after reestablishment of airway, adequate oxygenation, and positive pressure ventilation.

Conclusions: An early diagnosis of NPPE with reestablishment of the airway, adequate oxygenation, and application of positive airway pressure represent an effective treatment. NPPE can be prevented by identification of high-risk patients, gentle airway manipulation during induction, and extubation at the right time when the patient’s airway reflexes have fully recovered.

Key words: negative pressure pulmonary edema, upper airway obstruction, extubation

Introduction

Negative-pressure pulmonary edema (NPPE) is a rare clinical condition that occurs when significant negative intrathoracic pressure forms against an obstructed airway, causing fluid to shift into the pulmonary interstitium\(^{1-3}\). NPPE is most common in young, healthy male patients, capable of generating profound negative intrathoracic pressure\(^4\). Although the incidence is less than...
0.1% as a complication of all anesthetics, the occurrence of NPPE has been suggested to be under-reported since it is often unrecognized or misdiagnosed\(^5\). The morbidity and mortality of an unrecognized event of NPPE is as high as 40%\(^6\). The present study reviews the cases of NPPE and discusses the occurrence, predisposing factors, and recommendations for treatment and prevention.

**Materials and Methods**

After obtaining approval from the Review Board of Chang Gung Memorial Hospital, all patients with general anesthesia from January 1, 2006 through December 31, 2008 were retrospectively analyzed from our Quality Assurance (QA) anesthesiology database. On review of the database, NPPE was diagnosed in patients with no previous history of lung disease or no perioperative fluid overloading. In addition, airway obstruction was noted during airway management and pulmonary edema developed immediately after relief of airway obstruction. In the present study, NPPE was diagnosed according to the following conditions: (1) clinical findings of tachypnea, (2) crackles on lung auscultation; (3) pink frothy sputum in the endotracheal tube.;(4) hypoxemia on pulse oximetry or on arterial blood gas determination, (5) radiological findings of pulmonary edema with normal heart size, and (6) pulmonary edema which resolved within 24 hours. Patients were followed in the post-anesthesia care unit (PACU) or intensive care unit (ICU) until clinical improvement, normal blood gas parameters, and significant radiological clearing were achieved. Parameters including age, gender, weight, American Society of Anesthesiologists (ASA) status, type of surgery, predisposing factors, time of onset or resolution, and treatment of pulmonary edema were reviewed from anesthetic records, PACU records, and ICU records.

**Results**

Of the 126,589 patients who underwent general anesthesia with endotracheal intubation, 13 (0.01%) cases of NPPE were reported (8 males and 5 females). All cases were American Society of Anesthesiologists (ASA) physical status I or II with no history of cardiac disease. The age ranged from 11 months to 56 years and the body weight ranged from 9 kg to 90 kg (Table 1). In case 1 to case 6, upper airway obstruction developed after extubation. Pink frothy sputum was recognized immediately to 10 minutes after relief of upper airway obstruction. Chest X-ray (CXR) showed bilateral perihilar airspace consolidation (Fig. 1). Case 1 and case 3 were re-intubated and mechanically ventilated with positive end-expiratory pressure (PEEP) in addition to drug treatment with intravenous furosemide 20 mg and morphine 5 mg. Case 2 and case 6 were treated with continuous positive airway pressure (CPAP) without re-intubation. Case 4 and case 5 were treated with intravenous furosemide 20 mg and morphine 5 mg in addition to simple oxygen mask. They improved quickly and the follow-up CXR showed resolution of alveolar changes within 3 to 8 hours. They were discharged from hospital without any sequela.

In case 7 to case 10, NPPE was suspected and noted in the anesthetic records by the anesthesiologists. These patients had no history of cardiac disease or blood transfusion and no fluid overload during anesthesia. Cough with pink sputum was observed at the postoperative recovery room after 10 to 30 minutes. CXR showed bilateral perihilar airspace changes with normal heart size. These patients were diagnosed with pulmonary edema and treated with intravenous furosemide 20 mg and morphine 5 mg in addition to simple oxygen mask, except for case 8 who was treated with CPAP. Pulmonary edema resolved in these patients within 24 hours.
Case 11 had a history of asthma and developed severe asthmatic attack upon intubation. Pulmonary edema was noted 1 hour after intubation. PEEP was added on the mechanical ventilation in addition to the drug treatment. Case 12, an 11-month-old infant with a body weight of 9 kg, developed laryngospasm and hypoxemia during induction with mask ventilation. Frothy sputum was evident immediately after endotracheal intubation. CXR revealed pulmonary edema and the patient was sent to ICU for further treatment. Pulmonary edema was resolved 6 hours after mechanical ventilation with PEEP and drug treatment. Case 13, a 6-year-old girl with a weight of 23 kg, developed pulmonary
edema after airway obstruction due to the biting of endotracheal tube. After 24 hours of treatment with drugs and mechanical ventilation with PEEP, pulmonary edema resolved without any sequela.

**Discussion**

**Negative pressure pulmonary edema** (NPPE) has also been known as ‘post-obstructive pulmonary edema’ and ‘laryngospasm-induced pulmonary edema’\(^{(1-3)}\). The exact mechanism of NPPE still remains unknown. It may be caused by the considerable negative intrathoracic pressure generated due to forceful inspiratory effort against an obstructed upper airway, resulting in a decrease in interstitial pressure. This favors transudation of edema fluid from pulmonary capillaries, leading to pulmonary edema. At the same time, decreased interstitial pressure may cause an increase in pulmonary blood flow due to increased venous return to the right side of the heart, further precipitating edema\(^{(7,10)}\).

Although negative intrathoracic pressure is the primary pathological event in the genesis of NPPE, other factors may also play an important role in the development of edema with upper airway obstruction\(^{(11,12)}\). Hypoxia, hypercarbia, acidosis, and hyperadrenergic state contribute to its development. Hypoxic vasoconstriction may increase capillary pressure and favor movement of fluid into the interstitium. Hypoxemia alters the capillary integrity and precipitates a hyperadrenergic state. The hyperadrenergic state is associated with peripheral vasoconstriction and increased venous return to the right side of the heart, which could further increase pulmonary blood flow, thus contributing to edema.

NPPE has been well-documented in young, athletic male patients, during or shortly following anesthetic extubation because of their well-compliant, muscular chest walls that are capable of generating significant negative intrapleural pressure\(^{(4)}\). Pediatric patients are also at risk because of their extremely compliant chest walls that can generate large negative intrapleural pressure\(^{(12)}\). Within our group of patients, children
with 9 kg and 23 kg also developed NPPE. Smooth airway manipulation is particularly important in these two patient populations.

In our anesthesiology department, we had criteria for extubation for most of the patients, these included: regular respiratory pattern, respiratory rate between 10 to 25/min, tidal volume > 5 ml/Kg and obey simple commands (ability to open eyes, take a deep breath, make a hand fist, head lift for 5 seconds to verbal commands). However, to achieve smooth emergence from anesthesia, a number of techniques has been used in our department. These included removal of the endotracheal tube while the patient is still deeply anesthetized or administration of a last dose of opioid to prevent involuntary movement. On the other hand, two of our patients developed pulmonary edema during induction, not extubation. Therefore, smooth airway manipulation is the most important way to prevent NPPE.

Incomplete neuromuscular recovery and residual anesthetic effect are known to be an important contributing factor to adverse respiratory events such as upper airway obstruction due to reduced pharyngeal muscle tone. In this retrospective study, the patient's anesthetic records were demonstrated that the last dose of neuromuscular blocking agent was not given at least 45 min prior to extubation. The proper dose of reversal agents was routinely administered when restoration of regular spontaneous respiration or responsive to simple commands, e.g. eyes opened to verbal command, sustained head lift for 5 seconds. However, concentration of inhalational anesthetic agent was not recorded in anesthetic charts. Upper airway obstruction was still possible due to residual anesthetic, e.g. opioid or inhalational agent after extubation. TOF-based evaluation of residual paralysis is advised to determine the appropriate timing (suggested TOF count of 4) for reversal of neuromuscular blockage, then clinically significant postoperative residual neuromuscular blockade should be a rare event\(^{(14)}\). Recording the concentration of inhaled anesthetic agent allows anesthesiologists to better understand residual anesthetics effect.

Clinical manifestations of NPPE usually present immediately but can occur several minutes to hours later\(^{(5)}\). Signs and symptoms of respiratory distress are often present, but frothy, pink sputum is the hallmark sign of NPPE. Auscultation reveals rales and occasional wheezes from fluid-compressed airways. The chest radiograph typically shows diffuse interstitial and alveolar infiltrates as well as normal cardiac size without hypervolemia. Resolution of the clinical and radiological changes is rapid, usually within 24 hours\(^{(5)}\).

Conditions that need to be considered in the differential diagnosis of NPPE include aspiration pneumonitis, transfusion-related acute lung injury, cardiogenic pulmonary edema, fluid overload, and anaphylaxis. The clinical picture of aspiration pneumonitis is very similar to patients with NPPE. However, rapid onset and resolution of radiological changes is not a feature of aspiration pneumonitis, which normally requires more than three days for resolution\(^{(15)}\). Furthermore, all of our patients had normal heart size shown by CXR, no history of cardiac disease, or blood transfusion, and no fluid overloading during surgery. Therefore, transfusion-related acute lung injury, cardiogenic pulmonary edema, and fluid overload are unlikely in these patients. No patient had any evidence of anaphylaxis.

Most patients with diffuse alveolar hemorrhage (DAH) also present with dyspnea, cough, hemoptysis and new alveolar infiltrate. In DAH, stretching force caused pulmonary capillary damage, and mechanical rupture of the alveolar capillary membrane led to diffuse alveolar lesion. Generally, DAH was associated with underlying condition: e.g. vasculitis or capillaritis, infection, toxin or drugs. Laboratory data in DAH also
revealed chronic anemia, leukocytosis, elevated erythrocyte sedimentation rate and elevated C-reactive protein. Renal function abnormalities were also found in DAH which may complicate several pulmonary-renal syndrome. Clinically, NPPE developed without any underlying condition and patients will not associated with laboratory data abnormality. Increased in capillary permeability in NPPE could also cause rupture of alveolar membrane, however, it rarely leads to diffuse alveolar hemorrhage. Moreover, similar to our patients, NPPE developed and resolved rapidly without any sequela, though its onset may be delayed up to one hour after airway obstruction in some patients.

After NPPE has been diagnosed, treatment is directed toward reversing hypoxia and decreasing the fluid volume in the lungs. The use of diuretic therapy (eg, furosemide, 1 mg/kg) to remove excess intrapulmonary fluid is controversial. In our cases, some of the patients were treated only with CPAP. Outcome of the patients with or without diuretic therapy had no difference. Maintaining the airway and providing supplemental oxygen are necessary. If oxygenation does not improve in the non-intubated patient, immediate intubation with positive pressure ventilation and PEEP is necessary. Similarly, if oxygenation does not improve in the intubated patient, PEEP should be administered to promote alveolar expansion. A small dose of succinylcholine (0.1-0.2 mg/kg) is needed to release the patient’s bite on the endotracheal tube.

**Conclusion**

NPPE is a rare clinical condition that may be under-reported due to misdiagnoses or failure in recognizing mild cases. The morbidity and mortality of an unrecognized event of NPPE is as high as 40%. In addition to the usual NPPE occurrence reported by most literature in young, healthy males capable of generating profound negative intrathoracic pressure, pediatric patients are also at risk for NPPE. The condition can be prevented by identification of high-risk patients, gentle airway manipulation during induction, and extubation at the right time when the patient’s airway reflexes have fully recovered. Management of NPPE is usually supportive. Oxygen administration via nasal cannula or non-rebreathing mask is effective in patients with mild clinical symptoms. However, re-intubation with application of positive end-expiratory pressure or continuous positive airway pressure is required in patients with severe clinical symptoms. Basic knowledge of this condition facilitates anesthesiologists to recognize the signs and symptoms of NPPE for proper diagnosis and ensures prompt treatment.

**References**

上呼吸道阻塞引起負壓性肺水腫的案例分析

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背景：負壓性肺水腫(NPPE)是一種罕見的臨床症狀，其發生於呼吸道阻塞時，所引起的胸內負壓增加，造成水分向肺組織瀰漫。而在所有的麻醉併發症中，其發生率是低於0.1%，但如果未被立即發現、確認，其死亡率可高達40%。因此在這項研究中，我們回顧這些案例，探討其發生原因、誘發因素，並提出療護及預防的建議方式。

材料與方法：在通過長庚醫院倫理委員會之審議後，我們透過麻醉品質管理的資料庫中，回顧分析從2006年1月至2008年12月31日所有接受全身麻醉的患者，並依據下列情況確認其診斷為負壓性肺水腫：(1)呼吸速率變快；(2)肺部聽診為爆裂音；(3)氣管內管內有粉紅色泡沫狀痰液；(4)脈動氧血紅素飽和度或動脈血氧分析結果為低血氧；(5)胸部X光呈現肺水腫；(6)在24小時內可解決的。同時，在術後我們也會持續追蹤在恢復室或加護單位觀察的患者，一直到症狀改善、氧氣交換參數正常及胸部X光正常。

結果：在126,589個接受氣管插管全身麻醉的件數中，有13個(0.01%)確認為負壓性肺水腫的案例，其中男性8例、女性5例，均為ASA I或II，年齡分布於11個月至56歲，體重則為9.90公斤。大多數出現肺水腫的案例是發生於氣管插管時或全身麻醉拔管後所引發的上呼吸道阻塞，當重新建立呼吸道，適當的給氧及正壓輸氣管使用，症狀可在24小時內解決。

結論：在這次研究中，我們說明了早期被診斷出來、呼吸道重新建立、適當的給氧及正壓給氣器使用，是有效的治療。當病人呼吸道反射完全恢復時，可以藉由事先鑑別出高危險患者、麻醉誘導時，執行技術輕柔，並在正確的時機拔管，是及早及早預防發生的。

關鍵詞：負壓性肺水腫，上呼吸道阻塞，拔管