# Synthetic Phenylpiperidine Derivative Meperidine as a Trigger for Type I Negative Pressure Pulmonary Edema in General Anesthesia

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*We present a case of type I negative pressure pulmonary edema in a healthy 17-year-old boy who underwent an emergent appendectomy under general anesthesia. The particularity of our case revolves around the administration of meperidine for perioperative shivering, along with other anesthetic risk factors, which may have served as the trigger of type I negative pressure pulmonary edema.We present the pathophysiological mechanisms, the formulation of clinical and paraclinical diagnosis and the principles of intensive care therapy. This was the first such case experienced in our practice, with a remarkable learning opportunity.*

*Keywords: phenylpiperidine, meperidine, negative pressure pulmonary edema, general anesthesia*

Negative pressure pulmonary edema (NPPE) is an acute, potentially life threatening, uncommon perioperative pathological entity. Two clinical types have been described: type I NPPE, associated with acute airway obstruction, and type II NPPE, associated with chronic partial upper airway obstruction. An early differential diagnosis between various pulmonary edema conditions in critically ill patients and a prompt recognition of high risk of acute morbidity are crucial in certain circumstances. We present a case of type I NPPE in a healthy 17-year-old boy who underwent an emergent appendectomy under general anesthesia. The particularity of our case revolves around the administration of meperidine, along with other anesthetic risk factors, which may have served as the trigger of NPPE.

## Experimental part

*Study case presentation*

A 17-year-old male patient without medical history presented with acute appendicitis. After evaluation in the emergency department, he was admitted for emergency appendectomy. His preoperative physical examination and laboratory tests were within normal limits except for neutrophilic leukocytosis.

Physical status: height (H) = 1.60 m; weight (W) = 50 kg; body mass index (BMI) = 19.53 kg/m$^2$; airway assessment by Mallampati classification of oral opening – Mallampati I.

Cardiovascular status: blood pressure (BP) = 117/59 mmHg; heart rate (HR) = 75 bpm; heart auscultation – normal.

Respiratory status: chest auscultation was clear bilaterally, without murmurs. His baseline pulse oximetry arterial blood oxygen saturation ($SpO_2$) was 99% on room air, with a fraction of inspired oxygen ($FiO_2$) of 0.21.

Laboratory blood investigations: hemoglobin (Hgb) = 15.2 g/L; hematocrit (Hct) = 42%; leukocytes (L) = 9,450/μL (neutrophils = 90%); platelets (PLT) = 221,000/μL; activated partial prothrombine time (aPTT) = 24.4 s; international normalized ratio (INR) = 1.09; serum proteins = 71 g/L; fibrinogen = 3.22 g/L; C-reactive protein (CRP) = 11.3 mg/L; glycemia = 110 mg/dL; serum $Na^+$ = 135 mmol/L; serum $K^+$ = 4.1 mmol/L; serum $Cl^-$ = 98,5 mmol/L; serum total calcium = 9.43 mg/dL; serum $Mg^+$ = 1.81 mg/dL; aspartate aminotrasferase (AST) = 20 U/L; alanine aminotransferase (ALT) = 18 U/L; lactate dehidrogenase (LDH) = 374 U/L; blood urea nitrogen (BUN) = 33.3 mg/dL; creatinine = 1.06 mg/dL.

The patient was accepted for general anesthesia with tracheal intubation. The patient's relative anesthetic risk was evaluated as ASA 1E, according to the American Society of Anesthesiologists (ASA) physical status classification. An 18 gauge peripheral venous cannula was inserted into the patient's left hand. 500 mL normal saline was administered before initiating the intervention. Premedication was administered 60 min before anesthesia induction and consisted of 10 mg intravenous (IV) metoclopramide and 50 mg IV ranitidine.

In the operating room, after placing ASA standard monitors, the patient was preoxygenated with 100% oxygen through a face mask for 3 minutes. General anesthesia was induced by a modified rapid induction technique with cricoid pressure and administration of 75 mg propofol (1.5 mg/kg), 60 mg rocuronium (1.2 mg/kg), 100 μg fentanyl (2 μg/kg); the trachea was intubated without problems, using a 7.5 mm oral cuffed endotracheal tube. After proper endotracheal tube placement was confirmed, it was fixed at 21 cm. The patient was connected to the anesthesia machine and anesthesia was maintained with sevoflurane 2%, $N_2O$ : $O_2$ 33 % : 66 %, fentanyl and rocuronium.

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Intraoperative monitoring included: electrocardiography, non-invasive blood pressure, pulse oximetry, end-tidal capnography, body temperature.

The administration of anesthesia and the surgical procedure were uneventful. The procedure (open appendectomy) lasted about 60 minutes and a total of 400 mL of normal saline was infused. $N_2O$ was interrupted and the patient recived $O_2$ 100% at least 10 minutes before extubation. 600 mg IV acetaminophen was administred for analgesia. At the end of the surgery, the residual neuromuscular blockade was reversed with 2 mg neostigmine and 1 mg atropine. Subsequently, oropharyngeal suctioning was performed and the patient was extubated. After full recovery of consciousness and efficient spontaneous breathing, the respiratory pattern was normal and $S_pO_2$ = 100%.

Shortly after extubation, the patient developed intense shivering and 20 mg IV meperidine was administered. Immediately after administering meperidine, the patient developed sustained and intense contraction of the intercostal and sternocleidomastoid muscles (accessory muscles of respiration) and trismus, followed by rapid oxygen desaturation. 100% oxygen was administered via face mask. Ventilation was extremely difficult secondary to thoracic rigidity. 25 mg IV succinylcholine, 35 mg IV propofol, and 2 mg IV midazolam were administered with slow improvement of the muscle contracture, which progressively allowed manual ventilation and resulted in increasing oxygen saturation to 100%. 100 mg IV hydrocortisone and 150 mg IV amiophylline were then administered. After approximately 15 min the patient's respiratory pattern returned to normal. He was hemodynamically stable, coughing, and regained counsciousness.

The patient was then transferred to the postanesthetic care unit. He was tachypneic with a respiratory rate of 25-30 breaths per min; his oxygen saturation was 96% on a nonrebreather mask with 8-10 L oxygen flow per minute, and 88-90% on room air.

His cough was pesistent, with a small amount of pink frothy sputum. Bilateral disseminated crackles were audible on chest ausculation.

Electrocardiogram (ECG) and bedside 2D echocardiography were within normal limits. The antero-posterior chest X-ray showed diffuse bilateral nonhomogenous opacities, consistent with pulmonary edema (fig. 1).

The arterial blood parameters were: pH = 7.36; partial pressure of oxygen in arterial blood ($p_aO_2$) = 58 mmHg/ $FiO_2$ = 0.21; arterial blood oxygen saturation ($SaO_2$) = 88.7%; partial pressure of carbon dioxide in arterial blood ($p_aCO_2$) = 42.2 mmHg; dicarbonate ($HCO_3^-$) = 25.4 mmol/L; base excess (BE) = - 1.6 mmol/L.

The patient was admitted to the intensive care unit and maintained on oxygen therapy and bronchodilators (nebulized salbutamol) for the next 48 h. His pulmonary function continued to improve and mechanical ventilation was not needed. Throughout his stay in the intensive care unit he remained hemodynamically stable.

Serial arterial blood gases are reported in table 1. Succesive chest X-rays showed gradual resolution of pulmonary edema (figs.1, 2, 3 and 4).

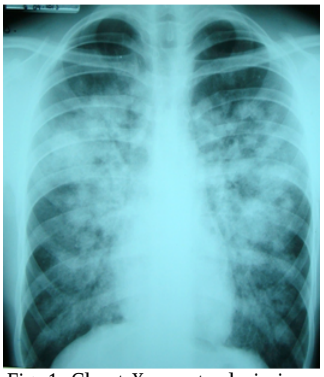

Fig. 1. Chest X-ray at admission to the intensive care unit

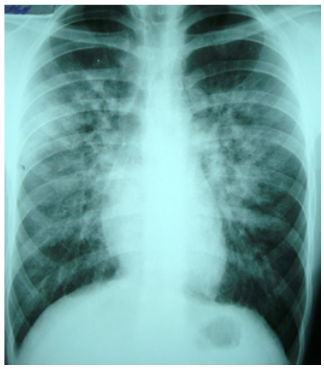

Fig. 2. Chest X-ray 24 h later

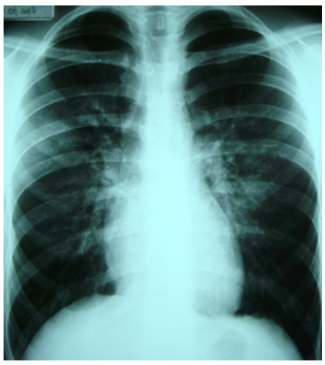

Fig. 3. Chest X-ray 48 h later

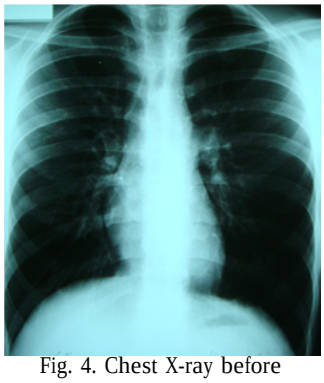

Fig. 4. Chest X-ray before discharge

## Results and discussions

With regard to our patient, the onset of the signs and symptoms, the radiologic appearance and clinical evolution support the diagnosis of type I negative pressure pulmonary edema. In the context of general anesthesia, the differential diagnosis includes other life threatening conditions: aspiration pneumonitis, acute respiratory distress syndrome (ARDS), postoperative residual curarization, cardiogenic pulmonary edema, neurogenic pulmonary edema, pulmonary embolism, anaphylaxis, drug induced pulmonary edema [1] and pulmonary edema secondary to diabetic decompensated cardiomiopathy [2].

As already mentioned above, NPPE is classified as type I NPPE and type II NPPE. The etiology of type I NPPE is associated with forceful inspiratory effort in the context of an acute upper airway obstruction: laryngospasm, epiglottitis, croup, foreign body aspiration, strangulation, laryngeal tumor, goiter, postoperative vocal cord paralysis, near drowning, endotracheal tube obstruction, intraoperative suctioning through the endotracheal tube,

**Table 1**
BLOOD GASES/ACID – BASE EQUILIBRUM

| Parameter/time | 1 h | 6 h | 12 h | 18 h | 24 h | 36 h |
|---|---|---|---|---|---|---|
| pH | 7.36 | 7.34 | 7.36 | 7.7 | 7.42 | 7.40 |
| $P_aO_2$ (mmHg) | 58 | 81 | 61 | 81 | 63 | 61 |
| $S_aO_2$ (%) | 88.7 | 95.1 | 90 | 95.5 | 92.5 | 91 |
| $P_aCO_2$ (mmHg) | 42.2 | 44.7 | 45.5 | 46.1 | 39.1 | 42.4 |
| $HCO_3^-$ (mmol/L) | 25.4 | 24.1 | 26.2 | 27.4 | 25.5 | 26.4 |
| BE (mmol/L) | - 1.6 | - 1.9 | + 0.2 | + 1.3 | + 0.9 | + 1.2 |

*$p_aO_2$ = partial pressure of oxygen in arterial blood; $SpO_2$ = pulse oximetry arterial blood oxygen saturation; $p_aCO_2$ = partial pressure of carbon dioxide in arterial blood; $HCO_3^-$ = bicarbonate; BE = base excess*

laryngeal mask airway (LMA) displacement, migration of a Foley catheter balloon used to tamponade the nose in epistaxis [3]. Type II NPPE can result after relief of a chronic partial upper airway obstruction: adenoidectomy, tonsillectomy, laryngeal mass resection, correction of choanal stenosis, reduction of a hypertrophic redundant uvula [4].

The incidence of this uncommon, but potentially life threatening condition has been reported to be 0.05 – 0.1% in healthy adults undergoing general anesthesia [1, 4].

Pulmonary edema is the result of extravascular fluid accumulation in the lung. The flow of liquid across the capilary endothelium is described by Starling's equation: $Q = Ak \times [(h_c - h_i) - \delta(\pi_p - \pi_i)]$, where: Q = net flow of fluid, A = the surface area of the alveolar-capillary barrier, k = capillary filtration coefficient, $h_c$ = capillary hydrostatic pressure, $h_i$ = interstitial fluid hydrostatic pressure, $\pi_p$ = plasma colloid osmotic pressure, $\pi_i$ = interstitial fluid colloid osmotic pressure, $\delta$ = reflection coefficient [5].

Pulmonary edema occurs when the lymphatic flow capacity is exceeded and evolves along four stages: stage I – only interstitial pulmonary edema is present; stage II – fluid fills the interstitium and begins to fill the alveoli; stage III – alveolar flooding occurs; stage IV – alveolar flooding spills over into the airways as froth [6].

In general anesthesia, the common trigger for NPPE is acute laryngospasm induced airway obstruction. The central pathogenetic mechanism is the Muller maneuver – inspiratory effort against a closed glottis. During Muller maneuvre, the intrapleural pressures decrease at – 50 to – 100 $cmH_2O$ (normal baseline – 5 $cmH_2O$) and will result in a sudden increase of venous return associated with increased left ventricle afterload (interventricular interdependence and increased wall tension) [7-11]. Increased pulmonary capillary hydrostatic pressure and decreased intraalveolar pressure will result in interstitial and alveolar edema [12, 13]. Hypoxemia will initiate a hyperadrenergic state which increases the pulmonary vascular resistance [3, 14]. Increased capillary transmural pressures augment the linear endothelial cellular stretch which results in loss of capillary integrity because of mechanical and oxidative stress injury mechanisms [10, 12].

Young, healthy, athletic, muscular men are more frequently prone to NPPE because of their ability to generate high negative intrathoracic pressures during upper airway obstruction, due to a strong diaphragm and thoracic musculature. Other predisposing factors with impact in the perioperative period are: obesity, sleep apnea, acromegaly and a short neck [15]. Prone position of the patient on the table during general anesthesia has also been reported as a risk factor [16].

Opioids may induce muscle rigidity, a potentially serious side effect of this class of drugs, well known in anesthesia clinical practice. It is more commonly associated with phenylpiperidines, and the risk is increased with increasing opioid dose and the use of nitrous oxide [17-20]. This can induce chest wall rigidity, which can do bag and mask ventilation impossible. Ventilation difficulty is the result of vocal cord rigidity and closure [21]. The effect is mediated via the *nucleus raphe magnus,* by MOP (ì-opioid peptide), GABA (gamma-aminobutyric acid) and dopaminergic receptors. It can be reversed by the administration of naloxone and benzodiazepines. Also, muscle relaxants may eliminate muscle rigidity [22].

The clinical picture includes stridor, suprasternal and supraclavicular retractions, and the use of accessory muscles of inspiration. After NPPE develops, chest auscultation reveals crackles and occasionally wheezes and the patient develops decreased oxygen saturation, pink frothy sputum and demonstrates radiological abnormalities [3, 12].

After establishing the diagnosis, the purpose of therapy is to relieve laryngospasm, to maintain the airway patency and to reverse hypoxia [23-26]. Administration of beta – agonists enhances reabsorption of pulmonary edema fluid due to increased active cation transport. Intravenous diuretics have not demonstrated clear clinical benefits, since the mechanism of NPPE involves intrapulmonary fluid redistribution, not global fluid overload [27]. Severe cases, which are resistent to this supportive and pharmacologic treatment, require noninvasive continuous positive airway pressure (CPAP) ventilation or reintubation and invasive mechanical ventilation with positive end-expiratory pressure (PEEP) [4, 12, 28].

## Conclusions

NPPE is a rare, severe, and potentially life threatening perioperative complication. For anesthesia providers, prevention or early recognition of this complication is essential. Unfortunately, the standard reference anesthesia textbooks do not sufficiently address NPPE. However, for those in the clinical practice of anesthesia and intensive care, the signs and symptoms must represent a red flag and should lead to early recognition and rapid intervention. With respect to our clinical case, administration of meperidine, associated with the aforementioned other risk factors, was the trigger for type I NPPE. This was the first such case experienced in our practice, representing a remarkable learning opportunity.

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