Rev Bras Anestesiol. 2019;69(2):222–226

Sociedade Brasileira de Anestesiologia

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

CLINICAL INFORMATION

Negative pressure pulmonary edema: report of case series and review of the literature

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Received 5 June 2018; accepted 5 November 2018
Available online 12 January 2019

KEYWORDS
Pulmonary edema;
Negative pressure pulmonary edema;
Negative pressure;
General anesthesia;
Airway obstruction

Abstract
Background and objectives: Negative pressure pulmonary edema occurs by increased intrathoracic negative pressure following inspiration against obstructed upper airway. The pressure generated is transmitted to the pulmonary capillaries and exceeds the pressure of hydrostatic equilibrium, causing fluid extravasation into the pulmonary parenchyma and alveoli. In anesthesiology, common situations such as laryngospasm and upper airway obstruction can trigger this complication, which presents considerable morbidity and requires immediate diagnosis and propaedeutics. Upper airway patency, noninvasive ventilation with positive pressure, supplemental oxygen and, if necessary, reintubation with mechanical ventilation are the basis of therapy.
Case report: Case 1: Male, 52 years old, undergoing appendectomy under general anesthesia with orotracheal intubation, non-depolarizing neuromuscular blocker, reversed with anticholinesterase, presented with laryngospasm after extubation, followed by pulmonary edema.

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https://doi.org/10.1016/j.bjane.2018.12.002

Case 2: Female, 23 years old, undergoing breast reduction under general anesthesia with orotracheal intubation, non-depolarizing neuromuscular blocker, reversed with anticholinesterase, presented with inspiration against closed glottis after extubation, was treated with non-invasive ventilation with positive pressure; after 1 hour, she had pulmonary edema. Case 3: Male, 44 years old, undergoing ureterolithotripsy under general anesthesia, without neuromuscular blocker, presented with laryngospasm after laryngeal mask removal evolving with pulmonary edema. Case 4: Male, 7 years old, undergoing crude fracture reduction under general anesthesia with orotracheal intubation, non-depolarizing neuromuscular blocker, presented with laryngospasm reversed with non-invasive ventilation with positive pressure after extubation, followed by pulmonary edema.
Conclusions: The anesthesiologists should prevent the patient from perform a forced inspiration against closed glottis, in addition to being able to recognize and treat cases of negative pressure pulmonary edema.

PALAVRAS-CHAVE
Edema pulmonar;
Edema pulmonar por pressão negativa;
Pressão negativa;
Anestesia geral;
Obstrução de vias aéreas

Edema pulmonar por pressão negativa: relato de casos e revisão da literatura

Resumo
Justificativa e objetivos: O edema pulmonar por pressão negativa ocorre por aumento da pressão negativa intratorácica após inspiração contra via aérea superior obstruída. A pressão gerada é transmitida aos capilares pulmonares e supera a pressão de equilíbrio hidrostático, o que causa extravasamento de líquido para o parênquima pulmonar e alvéolos. Em anestesiologia, situações comuns como laringoespasmo e obstrução de via aérea superior podem desencadear essa complicação, que apresenta considerável morbidade e exige diagnóstico e propedêutica imediatos. A desobstrução das vias aéreas superiores, ventilação não invasiva com pressão positiva, oxigênio suplementar e, se necessário reintubação com ventilação mecânica são a base da terapia.
Relato de caso: Caso 1: Masculino, 52 anos, submetido a apendicectomia sob anestesia geral com intubação orotraqueal, uso de bloqueador neuromuscular adespolarizante, revertido com anticolinesterásico; apresentou laringoespasmo após extubação, seguido de edema pulmonar. Caso 2: Feminino, 23 anos, submetida a mamoplastia redutora sob anestesia geral com intubação orotraqueal, bloqueador neuromuscular adespolarizante revertido com anticolinesterásico, apresentou inspiração contra glote fechada após extubação, tratada com ventilação não invasiva com pressão positiva; após uma hora apresentou edema pulmonar. Caso 3: Masculino, 44 anos, submetido a ureterolitotripsia sob anestesia geral, sem bloqueador neuromuscular, apresentou laringoespasmo após retirada de máscara laríngea e evoluiu com edema pulmonar. Caso 4: Masculino, sete anos, submetido a redução cruenta de fratura sob anestesia geral com intubação orotraqueal, uso de bloqueador neuromuscular adespolarizante; apresentou laringoespasmo revertido com ventilação não invasiva com pressão positiva após extubação, seguido de edema pulmonar.
Conclusões: O anestesiologista deve evitar que o paciente faça inspiração forçada contra glote fechada, além de ser capaz de reconhecer e tratar os casos de edema pulmonar por pressão negativa.

Introduction

Negative-pressure pulmonary edema (NPPE) may develop in patients after inspiratory effort against an obstructed upper airway,[1] which causes very negative intrathoracic pressure, leading to leakage of fluid into the interstitium,[2] pulmonary edema and hypoxemia.[1] The present review aims to report four cases of NPPE that occurred during the anesthetic practice.

Case report

Case 1

A 52-year-old male patient was admitted with suspected acute uncomplicated appendicitis. In the preanesthetic evaluation (PAE), anamnesis and physical examinations revealed no abnormalities and complementary exams were normal and appropriate to the case. He was under adequate

fasting and his physical status was classified as P1-E. In the operating room, venoclysis and automatic monitoring with non-invasive blood pressure, pulse oximetry, continuous cardioscopy at CM5 lead, parameters derived from the electroencephalogram, analysis of anesthetic gases, and capnography-capnometry after tracheal intubation were performed. Metoclopramide (20 mg), clonidine (90 mcg), ketoprofen (100 mg), dexamethasone (10 mg), and ceftriaxone (1 g) were given intravenously. Epidural puncture was performed at the T12-L1 interspace with a Tuhoy 16G needle and epidural administration of 0.25% bupivacaine (50 mg) combined with morphine (2 mg). Venous induction was then performed with dextroketamine (50 mg), propofol (200 mg) and cisatracurium (10 mg). Tracheal intubation was uneventful. Anesthesia was maintained with oxygen, medical air and sevoflurane in a circle system with carbon dioxide absorber and volume-controlled mechanical ventilation with protective parameters. At the end of the uneventful surgery, the patient had the neuromuscular block reversed with neostigmine (2 mg) combined with atropine (1 mg). Fluid replacement was performed with warm Ringer's lactate solution (2500 mL). He was responsive to verbal command, on adequate spontaneous ventilation, and was extubated. The patient evolved with laryngospasm and received 100% oxygen through face mask and manual positive pressure. The patient breathed against the closed glottis for about 1 min, until the airway became patent again. There was no drop in oximetry until then, but there was a sudden decrease (less value 69%), despite the supply of pure oxygen under a face mask. He had a productive cough, with pink frothy discharge from the mouth. Pulmonary auscultation revealed diffuse rales; the patient was placed in the head-up position, maintaining the face mask with pure oxygen; and reintubation was considered. However, blood pressure kept its normal values, and progressive improvement of his condition began to occur. In 90 min, the oximetry reached 92% with ambient air alone. The patient was then taken to the post-anesthesia care unit (PACU), from where he discharged to bed with 10 points on the modified Aldrette Scale. Chest X-ray post-PACU was normal. The patient was discharged from the hospital on the second postoperative day.

Case 2

Female patient, 23 years old, admitted for reduction mammoplasty due to Grade III breast hypertrophy in an outpatient setting. In the PAE, there were no noteworthy reports during anamnesis and physical exams and the complementary exams were appropriate to the case and normal. The patient was under adequate fasting and her physical status was classified as P1. In the operating room, venoclysis and monitoring with continuous cardioscopy at DII and V5 leads, capnography-capnometry, and automatic non-invasive artery pressure by oscillometry were performed. After denitrogenation, venous induction was performed with midazolam (2.5 mg), fentanyl (250 mcg), propofol (200 mg), and rocuronium (37.5 mg). Tracheal intubation was uneventful, and anesthesia was maintained with O_2 + isoflurane, in a circle system with carbon dioxide absorber and volume-controlled mechanical ventilation with protective parameters. In the perioperative period, dipyrone (2.5 g slow IV), dexamethasone (10 mg slow IV), tenoxicam (4 mg slow IV), and standard heparin (5000 IU sc) were given. The surgery was uneventful, with a 2.5 h duration. At the end of surgery, the patient received neostigmine (2 mg slow IV) combined with atropine (1 mg slow IV) and was subsequently extubated when presented with a mild upper airway obstruction. She breathed against the closed glottis for about 120 s. An oropharyngeal cannula was placed and O_2 was given via face mask and positive pressure for approximately 4 min. When the patient was fully awake, she was taken to the PACU only with O_2 supplementation via nasal catheter. After 40 min in the PACU, she was discharged to bed with 10 points on the modified Aldrette Scale. She had received up to 2000 mL of warm Ringer's lactate solution. Approximately 1 h after discharge from PACU, already in bed, the patient complained of nausea and, 30 min later, evolved with progressive dyspnea, tachypnea, psychomotor agitation, peripheral cyanosis, pink frothy discharge from the mouth, and rhonchi and rales on auscultation. She was medicated by the attending clinician with O_2 via Hudson mask, placed in the head-up position, received hydrocortisone (1.5 g IV) and furosemide (40 mg IV), and was taken back to PACU for monitoring and support. She maintained her hemodynamic stability and gradually regained respiratory stability. She received bladder catheterization and 2000 mL of Ringer's lactated solution. After another 3 h in the PACU, the patient reached and maintained 10 points on the modified Aldrette Scale and was discharged to the bed. She was discharge from hospital on the following uneventful day, after the postoperative follow-up without complaints.

Case 3

A 44-year-old male patient admitted for laser nephrolithotripsy under balanced general anesthesia. In the PAE, the patient had poorly controlled hypertension, was taking oral candesartan (16 mg twice daily), nebivolol (5 mg.day^{-1}), and hydrochlorothiazide (25 mg.day^{-1}). Complementary exams were appropriate and normal. His physical status was classified as P3 and he was under proper fasting. In the operating room, venoclysis and monitoring with pulse oximetry, cardioscopy at DII and V5 leads, capnography-capnometry, and automatic non-invasive artery pressure were performed. Venous induction was performed with fentanyl (250 mcg and propofol (200 mg). Laryngeal mask passage was uneventful, and anesthesia was maintained in a circle system with carbon dioxide absorber and volume-controlled mechanical ventilation with protective parameters (sevoflurane and O_2). Neuromuscular blocker was not used. At the end of the procedure, the laryngeal mask was removed and the patient presented with respiratory obstruction in the upper airway. The patient was hypertensive and about 20 min after LM removal he developed acute negative pressure edema, with productive cough, and pink frothy discharge from the mouth. He was treated with noninvasive ventilation, placed in a seated position and supplied with 100% O_2 via face mask. He received intravenous furosemide (40 mg), oral captopril (25 mg), and was taken to the intensive care unit for further care. Hospital discharge occurred after 24 h.

Case 4

A 7-year-old male patient was admitted for a crude reduction of humeral supracondylar fracture under general anesthesia with OTI. His ASA physical status classification was P1. On preanesthetic evaluation, he had no history of comorbidities or allergies, no history of upper airway infection in the four weeks prior to the procedure, and he was under adequate fasting. In the operating room, monitoring with cardioscopy at DII and V5 leads, pulse oximetry, capnography-capnometry, and automatic non-invasive artery pressure were performed. Inhaled induction (sevoflurane and O_2) was performed followed by venoclysis and intravenous administration of fentanyl (80 mcg) and cisatracurium (3 mg). Orotracheal intubation was uneventful and the maintenance of anesthesia was done with O_2 and sevoflurane in a circle system with carbon dioxide absorber and mechanical ventilation with adequate parameters. At the end of the procedure, neuromuscular block was reversed with neostigmine (500 mcg) and atropine (25 mcg), and the patient was extubated. Then, the patient presented with laryngospasm, which was reversed with positive pressure ventilation via face mask. About 5 min after the laryngospasm reversal, the child began to show psychomotor agitation, productive cough, and pink frothy discharge from the mouth. He was intubated and maintained sedated and mechanically ventilated for approximately 2 h, when he was extubated. Hospital discharge occurred after 48 h.

Discussion

NPPE is one of the clinical forms of non-cardiogenic pulmonary edema[1] and may be classified into two types.[3] Type I occurs when the patient, generally adult, after inspiration against a closed glottis, generates more negative intrathoracic pressure and this negativity is transmitted to the pulmonary capillaries, causing imbalance of hydrostatic forces and leading to capillary extravasation. Type II is common in children who have chronic upper airway obstruction and over time develop more positive intrathoracic pressures by creating positive pressures at the end of expiration. Thus, acute removal of the obstruction makes the intrathoracic pressure suddenly lower and this negativity is transmitted to the pulmonary capillaries, resulting in extravasation of fluid into the interstitium.[3]

The incidence of NPPE ranges from 0.1% to 11%.[1] After laryngospasm, the incidence of NPPE reaches 3%. The incidence is higher in men (80%) and ASA physical states PI and PII (73%). This is possibly due to the fact that the healthy ones are capable of generating more negative intrathoracic pressures.[1] The most common causes of Type I NPPE are upper airway infections and tumors, laryngospasm, endotracheal tube biting, epiglottitis, and foreign body aspiration.[1] Type II NPPE may occur after tonsillectomy and adenoidectomy, upper airway tumor surgery, choanal atresia, and increased uvula repair. And, in general, procedures in the oropharynx are at increased risk for NPPE.[3]

It is important to consider the residual neuromuscular blockade as the cause of NPPE when using nondepolarizing neuromuscular blockers, since diaphragmatic recovery occurs before the pharyngeal muscles. Thus, the patient may present with upper airway obstruction by tongue drop and diaphragmatic inspiratory effort, which favors the NPPE pathophysiological mechanism.[4]

NPPE pathophysiology is related to the generation of more intrathoracic negative pressures when the patient exerts inspiratory effort against an obstructed glottis (modified Müller's maneuver)[1] or when chronically positive intrathoracic pressures become acutely less severe.[5] During an inspiratory effort against a closed glottis, for example, an adult is able to generate pressures between -50 and -100 cm H_2O (normal breathing: -4 to -7 cm H_2O).[3] The Starling equation demonstrates the factors that determine the edema formation: $Q = K\,[(Pmv - Pi) - \sigma\,(\pi mv - \pi i)]$ where Q is the flow between capillary membranes; K is the permeability coefficient between membranes; Pmv is the hydrostatic pressure of capillary membrane; Pi is the hydrostatic pressure of the alveolar interstitium; σ is the reflection coefficient (ability of membranes to prevent the passage of proteins); πmv is the osmotic pressure of microvascular proteins; and πi is the osmotic pressure of interstitial proteins.

Normally, with the balance of hydrostatic pressures, the fluid flow from the capillaries to the pulmonary interstitium is minimal, where it will be reabsorbed by the lymphatic vessels.[2] When the rate of interstitial fluid formation is greater than the resorption capacity, edema is formed, clinically manifested by the expectoration of pink secretion and alveolar infiltrate on the chest X-ray.[2]

Laboratory analysis of pulmonary secretion allows us to obtain important information. First, the pulmonary fluid protein rate is measured and the value is divided by the plasma protein rate. Values less than 0.65 suggest hydrostatic mechanisms (with lower protein concentration), as occurs in NPPE. Higher values indicate increased permeability of capillary membranes (with higher protein concentration), as occurs in adult respiratory distress syndrome. The serial analysis allows quantification of the clearance rate of interstitial proteins. In NPPE, it ranges from 14% to 17%/h and in ARDS it is around 6%/h. This reinforces the pathophysiological hypothesis that edema occurs due to variations in intrathoracic pressures, to the detriment of pulmonary capillary lesions.[2]

Negative pleural pressures are also transmitted to the heart and, consequently, cause cavitary distension, increase post-load and venous return, which further favors the increase of transcapillary pressure gradient and fluid leakage.[3]

In addition, sympathetic hyperactivity (agitation) may occur, which releases catecholamines and secondary hypertension, which adds to the mechanisms already mentioned. In the cases reported here, we noticed that the patients were quite distressed with the airway obstruction. The increased post-load due to sympathetic hyperactivity further favors right ventricle distension, dislocating the interatrial septum, and favors the occurrence of pulmonary edema.[1] These effects also decrease left ventricular performance, and hemodynamic instability may occur.[1]

NPPE initially presents with agitation, hypoxemia, pink expectoration and radiographic alterations.[2] Clinically, it is possible to observe wheezing on pulmonary auscultation, use of accessory musculature in the inspiration, tachypnea, paradoxical breathing, tachycardia, and

hypercarbia. Pulmonary edema causes imbalance in the ventilation/perfusion ratio, which can cause severe hypoxemia. Chest X-ray usually shows diffuse interstitial infiltrate of central distribution and non-dependent. The onset of symptoms usually occurs up to 1 h after the event, but may occur late, as in one of the reported cases. Electrocardiographic changes (arrhythmias, ST segment elevation, and branch block) may suggest cardiogenic pulmonary edema.[5] Other differential diagnoses need to be made, such as volume overload, neurogenic hypertension, and anaphylactic reaction.[5] If the patient has undergone neuromuscular blockade without neuromuscular transmission monitoring, the hypothesis of residual neuromuscular blockade should also be proposed.[4] In none of our cases was it employed.

The basis of the NPPE treatment is to maintain the upper airway patency and provide supplemental oxygen therapy. In some cases it is necessary to use breathing-aid devices, such as oro- or nasopharyngeal cannula and the association with non-invasive ventilation with positive pressure.[1] If these devices are insufficient, tracheal intubation should be performed to ensure patient airway patency and oxygenation through protective mechanical ventilation. Positive-pressure ventilation (PPV) exerts a beneficial effect in edema resolution, as positive pressure helps to normalize the pulmonary hydrostatic pressures, contributes to the resorption of interstitial fluid.[1,2,5]

From a pharmacological standpoint, muscle relaxation with low doses of succinylcholine (0.1–0.2 $mg.kg^{-1}$) is able to relieve laryngospasm and/or tracheal tube biting, in addition to facilitate airway maneuver, such as PPV via face mask.[6] The use of diuretics is controversial,[1,2,6] as in NPPE the fluid overload is not usually the causal factor it should not be used in hemodynamically unstable patients.[1] Corticosteroids showed no benefits in NPPE, whereas β2-agonists may be useful, as they aid in the transport of transmembrane ions, facilitating the clearance of the pulmonary interstitial fluid.[1]

Careful management of the airway, reduction of tracheal irritation, and extubation of the patient in an adequate anesthetic plane reduce the occurrence of laryngospasm and, therefore, NPPE.[6] In the hypothesis of residual neuromuscular blockade, it is possible to reverse the nondepolarizing neuromuscular blocker with anticholinesterase drugs (neostigmine, glycopyrrolate) or, in the case of rocuronium and vecuronium, it is also possible to use sugammadex for the direct reversal of the drug.[4]

Observation and monitoring of patients at risk for NPPE (post-laryngospasm, post-upper airway obstruction) is recommended for 2–12 h at PACU or intensive care unit. NPPE resolution occurs from 24 to 48 h in most cases, usually without the need for additional therapies or prolonged hospital stay.[6]

Conclusion

Anesthesiologists should avoid situations that may lead to NPPE, recognize and treat this complication promptly, as it presents considerable morbidity and results from relatively common situations in the anesthetic practice.

Conflicts of interest

The authors declare no conflicts of interest.

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