Review Article

Postpneumonectomy pulmonary edema

MARCOS NAOYUKI SAMANO[TE SBCT], LUIS MIGUEL MELERO SANCHO[TE SBPT, TE SBCT], RICARDO BEYRUTI[TE SBCT], FABIO BISCEGLI JATENE[TE SBCT]

Although pneumonectomy is a technically simple procedure, it has been associated with a high (60%) incidence of complications. Respiratory complications account for approximately 15% of such complications. Worldwide, the mortality rate among patients subjected to pneumonectomy is 8.6%. However, the rate among patients developing respiratory complications is 30%. Although postpneumonectomy pulmonary edema is rare (occurring in 3% to 5% of cases), it is a serious complication and is almost always fatal. It was first described twenty years ago and, despite these alarming statistics, little is known regarding the physiopathology of postpneumonectomy pulmonary edema. Once it has become entrenched, the condition is difficult to treat, and there is no proven efficient treatment. Various risk factors have been correlated with postpneumonectomy pulmonary edema onset. Fluid overload was the first to be identified as a factor to avoid. However, many studies have shown that there is no direct correlation between fluid overload and the development of edema. Prevention is the best way to avoid postpneumonectomy pulmonary edema and must be performed in a multidisciplinary fashion, involving the entire medical staff - from the initiation of anesthesia through the surgical procedure and extending into the critical care management phase. Equally important is early identification and testing of patients at risk for postpneumonectomy pulmonary edema when there is clinical suspicion of this serious complication.

J Bras Pneumol 2005; 31(1): 69-75.

Key Words: Pulmonary edema/complications. Pneumonectomy/adverse effects. Risk factors. Pulmonary edema/prevention & control.

*Study carried out in the Department of Thoracic and Cardiovascular Surgery of the Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP
Correspondence to: Marcos Naoyuki Samano - Rua Dr. Manoel de Paiva Ramos, 60 apto. 32D - CEP 05351-015 São Paulo, SP - Tel: 55-11-37190965 - E-mail: samanomn@terra.com.br
Submitted: 19 December 2003. Accepted, after review: 9 February 2004.

INTRODUCTION

Performing a pneumonectomy on a previously normal individual results in some physiological alterations, all aspects of which have yet to be clarified. Increased pulmonary blood flow and deviation of the mediastinal anatomy are some of the alterations to the pulmonary physiology that exemplify the possible consequences of this surgery. Some thoracic surgeons define pneumonectomy as a disease. In fact, the incidence of complications can be as high as 60%, and the perioperative mortality involved in this surgery, despite having decreased over the years, is still high, reaching 8.6% in recent studies[1]. Respiratory complications account for approximately 15% of such complications and, in this group, mortality can reach 30%[2].

The nomenclature adopted in relation to the surgical extirpation of a lung merits some mention, since the words *pneumectomia* ("pneumectomy") and *pneumonectomia* ("pneumonectomy") are used as synonyms in Portuguese and are even listed as such in the new *Dicionário Houaiss da Língua Portuguesa* (Houaiss Dictionary of the Portuguese Language)[3]. In the English language literature, however, pneumonectomy is the predominant term. Moreover, it is a MeSH term and also the search term used by the Scientific Electronic Library Online (SciELO)[4], and, for these reasons, we adopted pneumonectomy rather than pneumectomy.

The first successful pneumonectomy was performed by Graham and Singer in 1933, in order to treat a bronchogenic carcinoma[5]. Since then, this procedure has been incorporated into the treatment of pulmonary tumors, although there is a considerable amount of data in the literature regarding its mortality and complications[6]. Few studies, however, clearly focus on a quite frequent complication that occurs in these patients, postpneumonectomy pulmonary edema (PPE), perhaps because the physiopathology that leads to this complication is still unknown. Moreover, there are few professionals who are familiar with this kind of complication. Our concern is that it is often overlooked in the postoperative management of the pneumonectomized patient. A systematic review carried out by the authors of this study using SciELO to research the term pneumonectomy and its corresponding translation in Portuguese (*pneumonectomia*) resulted in only seven articles, and in none of them is PPE even mentioned as a complication[4], which reveals that this subject is yet to be approached in our milieu. This motivated the authors to carry out a broader review of the subject, addressing both the hypotheses that would explain PPE physiopathology and the preventive measures that might be taken in order to avoid this complication.

Pulmonary edema may occur after any type of surgical procedure and is usually related to pre-existing heart disease. Pulmonary edema may also follow pulmonary thromboembolism, acute respiratory distress syndrome (ARDS) resulting from sepsis, pneumonia, aspiration and bronchopleural fistula. When pulmonary edema follows pneumonectomy, assuming that none of these other determinants are present, it is known as PPE.

The PPE condition was first described by Gibbon and Gibbon in 1942, when they observed that transfusion of plasma or blood in animals submitted to lobectomy caused pulmonary edema, respiratory insufficiency and death, whereas such transfusions were well tolerated by normal animals[7]. However, only recently has this complication been studied further.

Incidence and clinical profile

Several studies have shown that PPE occurs in approximately 3% to 5% of patients submitted to pneumonectomy[7], although the incidence may be as high as 12.2%[8]. Pulmonary edema is not exclusive to pneumonectomized patients, since it may also follow minor resections, such as lobectomies[9,10]. Mortality ranges from 80% to 100%. Some authors have reported a lower mortality rate, possibly related to the inclusion of milder cases of PPE in the diagnosis[11]. Classically, PPE occurs within two to three days after a complication-free postoperative period, the so-called "honeymoon". However, PPE may also occur from twelve hours to six days after pulmonary resection. Clinically, the patient presents dyspnea, hypoxia and difficulty in expelling secretions. Progressive worsening follows, and all patients evolve to requiring positive-pressure ventilation within 12 hours. Initially, there might be no clinical or radiological signs of pulmonary edema, but infiltrated alveolar walls rapidly evolve to clinically evident ARDS. Patients may also present fever[7,12].

Turnage and Lunn[13] adopted the following criteria for PPE diagnosis: respiratory difficulty upon clinical examination; progressive pulmonary infiltration seen on serial chest X-rays; not meeting the criteria for heart failure; no signs of pneumonia, sepsis or aspiration. Deslauriers[7] adopts a similar definition. Van de Werff, in a retrospective study using radiographic analysis, classified PPE as pre-manifest or manifest, the latter presenting more radiological signs of pulmonary edema[8]. Therefore, there is no consensus as to the diagnosis of PPE in the literature.

RISK FACTORS

Not only is right pneumonectomy a risk factor for increased morbidity and mortality, but previous studies have revealed a higher incidence of PPE in right resections as well[13-15]. However, more recent studies have shown that there is no significant difference regarding laterality[7,8].

According to some studies[14,15], excess volume administered in the perioperative period has a significant relationship with PPE development, which inspired the expression used by Mathru: "don't drown the down lung", emphasizing that a highly positive fluid balance was the primary factor battled against in this sort of operation[9]. Subsequent to these studies, other authors questioned this assertion[7,10,13]. However, as Parquin et al.[11] admit, perhaps the care taken to maintain the fluid balance of patients close to zero might be one of the reasons why more recent studies do not show significant differences regarding fluid overload.

Other determinants related to the development of PPE are intraoperative administration of fresh frozen plasma and use of high-pressure ventilation[8], as well as surgical time, the extent of the surgery, and the sort of drainage system used (balanced or not)[7].

PHYSIOPATHOLOGY

Although the physiopathology of PPE has yet to be completely established, some determinants seem to contribute, to a greater or lesser degree, to the development of edema. These include increased pulmonary capillary pressure, endothelial damage with greater vascular permeability, and failure of the lymphatic drainage system of the lung (Table 1).

Fluid overload and increased hydrostatic pressure

Zeldin et al. were pioneers in the study of PPE associated with perioperative excess volume. They analyzed the data set of a group of pneumonectomized patients who had developed PPE and found a significant difference in the volume of fluid received within the first 24 hours, when compared with another group that had not developed edema. In addition, their experimental modeling with dogs revealed increased pulmonary capillary pressure in the dogs that developed PPE, which led to the conclusion that PPE is caused by elevated pulmonary capillary hydrostatic pressure, which increases filtration forces, leading to transudation of fluid into the pulmonary interstitium and alveoli[15]. More recently, Parquin et al. also correlated PPE with hyperhydration (above 2000 mL) in the intraoperative period[11].

TABLE 1

Factors involved in the physiopathology of postpneumonectomy edema

Probable factors	Fluid overload
	Increased pulmonary capillary pressure and filtration pressure
	Reduced reabsorption capacity of lymphatic vessels
	Barotrauma
	Endothelial damage
Possible factors	Right ventricular dysfunction
Questionable factors	Oxygen toxicity
	Cytokines

Endothelial damage and increased vascular permeability

The high protein content in the pulmonary edema fluid suggests some degree of endothelial damage, contributing to the development of PPE. Mathru et al., analyzing a small sample of patients with postresection pulmonary edema, observed that the relationship between the protein levels in the pulmonary edema fluid and the serum levels of those proteins was greater than 0.6, which reinforces the hypothesis of increased vascular permeability. However, they did not rule out hyperhydration as a contributing factor in PPE genesis[9].

Waller et al. analyzed a group of patients who had undergone pulmonary resection (lobectomy or pneumonectomy) and studied vascular permeability using technetium-99-labeled human albumin, followed by scintigraphic detection. The authors observed albumin accumulation in the remaining lung at eight hours after pneumonectomy, which supports the hypothesis that hyperpermeability may contribute to the development of PPE[10]. Hemodynamic data showed no increase in mean pulmonary artery pressure or mean pulmonary capillary pressure. However, there was an increase in pulmonary vascular resistance. The explanation derived from these findings for the increase in vascular permeability is that the increase in resistance is followed by an increase in blood flow, resulting in stress and damage to the endothelium.

Despite the increase in capillary permeability, experimental studies have shown that alveolar fluid clearance is time-dependent, i.e. there is no absorption through the respiratory epithelium in the acute phase[16].

Interrupted mediastinal lymphatic drainage

Although the mechanisms that balance oncotic and hydrostatic pressure in the pulmonary capillaries are responsible for controlling fluid accumulation in the lung, the lymphatic vessels also seem to play an important role. It is estimated that, under normal conditions, there might be a seven- to ten-fold increase in the flow through the lymphatic vessels. However, when there is an increase in hydrostatic pressure resulting from pulmonary resection, lymphatic drainage will prove to be inefficacious, resulting in fluid accumulation in the interstitium[7].

Pulmonary hyperinflation

Deslauriers et al. stress the importance of mediastinal deviation and pulmonary hyperinflation (barotrauma) as causes of PPE. In their series, a conventional drainage system was used with practically all of the patients (11/13). However, of the patients in which a balanced drainage system or no drain was used, only two developed PPE. The authors also stated that the mediastinum and the heart offer more resistance to deviation after left pneumonectomies, which is why PPE is more common after right pneumonectomies[7].

Several determinants seem to be associated with fluid accumulation in the hyperinflated lung, among them the enlargement of intercellular junctions of the capillary endothelium, which facilitates the extravasation of the edema.

The hyperinflation of the remaining lung may result in a process called air block syndrome, in which air fistulas in the interstitium result in accumulation of air in the perivascular cuff, causing compression of the vascular structures and pulmonary hypertension, thereby resulting in PPE. In two studies, the animals who had undergone pneumonectomy and developed barotrauma suffered architectural alterations in the alveolar histology and died of ARDS, whereas the animals in whom mediastinal deviation was controlled presented normal evolution[7].

Right ventricular dysfunction

In their study, Reed et al.[17] demonstrated that patients who had undergone pulmonary resection developed right ventricular dysfunction. There was increase in the right ventricular end-diastolic volume and decrease in the right ventricular ejection fraction in the second postoperative period. Although central venous pressure was unaltered in this group, the authors asserted that right ventricular dysfunction results in reduced lymphatic drainage. In contrast to the findings of other authors[10,13], they observed no increased pulmonary vascular resistance in their study.

TREATMENT

The treatment of patients with PPE begins with early identification of the disease. Being aware of the high mortality rate associated with this

complication, the doctor who is attending the patient ought to always bear this hypothesis in mind during the postpneumonectomy period. After the "honeymoon" period, any clinical sign, such as dyspnea, hypoxia or tachycardia, must be regarded as a warning. A chest X-ray should be requested daily and compared to the previous X-rays, searching for signs of pulmonary congestion.

Since the postoperative behavior of hemodynamic pressure variables in the pneumonectomized patient is still undefined, simple measurements such as that of central venous pressure are not dependable parameters for use in patient management. Only a few parameters seem to be well established. Pulmonary artery pressure is unaltered[10,17], although it increases during exercise[18]. There seems to be an increase in pulmonary vascular resistance[10,13], although some authors contest this finding[17,18]. Pneumonectomy seems to result in right ventricular dysfunction, characterized by reduced right ventricular ejection fraction, as well as increased right ventricular end-diastolic volume. However, this dysfunction is not sufficient to alter the central venous pressure, perhaps because the diastolic volume acts as a reservoir, which expands in order to adapt to the afterload increase[17,18]. Pneumonectomy may result in misleading "pulmonary wedge pressure", as demonstrated by Wittnich et al.[19]. Inflation of the Swan-Ganz balloon-tipped catheter may reduce the filling of the left chambers, resulting in falsely low left atrial pressure readings. Correct measurement could be obtained by advancing and wedging the catheter into a peripheral branch.

Despite the difficulty in interpreting the data obtained with thermodilution catheters, they are still the best method for understanding the adaptation of the heart to a single lung. It is understood that the patient who presents signs of PPE onset and whose condition does not improve should be submitted to invasive hemodynamic monitoring. According to Miller[17], there is less PPE in patients whose right ventricular end-diastolic volume was kept low. Therefore, this might also be a useful parameter for better understanding this disease. According to Zeldin et al.[15], we can control the pressure of the pulmonary artery and cardiac insufficiency with the Swan-Ganz, maintaining the cardiac index at approximately 2.5 to 3 L/min/m^2.

Although some authors have found no correlation between fluid excess and the development of edema[7,8,13], there is a consensus as to the fluid restriction in the patients who have undergone pneumonectomy, perhaps because this is one of the few easily applicable measures and also because of its great impact on such a serious complication. The total volume infused into the patient within the first 24 hours should not exceed 20 mL/kg, and should preferably be given in the form of crystalloid solutions (< 2 L during surgery and < 50 mL during the postoperative period). Inotropic agents should be chosen over fluid overload in the event of hypotension or decreased diuresis. Maintaining diuresis at 0.5 mL/kg/h is sufficient in the immediate postoperative period.

Adequate analgesia should be provided in order to lower catecholamine levels (higher levels being related to increased pulmonary vascular resistance), maintaining the patient in dorsal decubitus, elevated to 35° and lying over the operated side in order to lower the gravitational effect. Excessive mediastinal deviation and hyperdistention of the remaining lung must be avoided. Balanced drainage may be used, although we prefer intermittent clamping of the pleural drain.

It is common practice among anesthesiologists to adopt the same volumetric parameters for both single-lung ventilation and two-lung ventilation. If this occurs, it naturally results in increased functional residual capacity of the remaining lung and consequently barotrauma. In addition, there is increased pulmonary vascular resistance, which might contribute to the development of pulmonary edema. Therefore, some adjustments must be made intraoperatively[20,21].

In a recent study, Cerfolio et al.[22] presented the use of corticoids as a preventive measure against PPE. By administering 250 mg of solumedrol immediately before ligation of the pulmonary artery, the authors obtained favorable results regarding PPE development (0% in the group treated with solumedrol vs. 16% in the control group). There were no incidences of bronchopleural fistulas in the group treated with corticoids, and the length of hospitalization was slightly reduced.

Once PPE has become entrenched, it is treated in the same fashion recommended for ARDS, maintaining adequate oxygenation, either through

the use of a continuous positive airway pressure mask or through orotracheal intubation. Positive end-expiratory pressure can be used to reduce the shunt and the fraction of inspired oxygen, which, on occasion, might need to be between 80% and 100% in these patients. High peak pressure has to be avoided, thus preventing barotrauma and bronchial stump dehiscence (Table 2). In addition, nutritional support and adequate physical therapy to help clear secretions should also be provided. Diuretics are usually administered but have resulted in little clinical improvement in these patients.

When there is clinical suspicion of bronchopneumonia, broad spectrum antibiotic therapy treatment must be introduced. Waiting for the results of cultures or leukocyte counts is not recommended since delayed treatment of PPE is fatal for the patient. The use of pulmonary vessel dilators in the treatment of PPE has also been proven to increase pulmonary vascular resistance[9]. Decreased blood flow resulting from increased pulmonary vascular resistance reduces endothelial stress, leading to lower endothelial permeability. The use of nitric oxide in ARDS seems to increase oxygenation, improving perfusion of the well-ventilated areas and consequently gas exchange. Regarding PPE, Mathisen reported the successful treatment of eight patients and suggested treatment with nitric oxide (10-20 ppm) for all patients with this condition[23]. More recently, Rabkin et al. reported that they had successfully treated a patient through the use of nitric oxide for 72 hours[24].

Extracorporeal membrane oxygenators have been used in the treatment of ARDS. This treatment has also been successfully used in a patient with PPE,

TABLE 2
Individualized ventilation during pneumonectomy (Excerpted from Slinger[21])

		ADJUSTMENT
Total volume	5-7 mL/kg	PIP < 35 cmH_2O Pplat < 25 cmH_2O
PEEP	5 cmH_2O	Add PEEP for patients without auto-PEEP (not COPD)
Respiratory frequency	12/min	Maintain $PaCO_2$ at 35-45 mmHg
Mode	Controlled volume	Controlled Pressure

PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; Pplat: end-inspiratory plateau pressure; COPD: chronic obstructive pulmonary disease

TABLE 3
Preventive and therapeutic measures in postpneumonectomy pulmonary edema

MEASURE	ADJUSTMENT
Volume	Intraoperative: < 2000 mL Immediate postoperative: < 50 mL/h or < 20 mL/kg within the first 24 h Prefer crystalloids
Urinary flow rate	> 0.5 mL/kg/h is excessive
Decubitus	35°, on the operated side
Catecholamine reduction	Control of pain, decreasing PAP
Supplementary Oxygen	Decrease PVR
Ventilation	Airway pressure < 40 cmH_2O Low tidal volume PEEP only if oxygenation worsens
Hemodynamic monitoring	If there are signs of low debit
Echocardiogram	Useful in diagnosis of RV failure
Central venous pressure	Not dependable
RV failure	Inotropics and pulmonary vasodilators
Drainage intermittent clamping	Early drain removal, balanced drainage or

PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; PEEP: positive end-expiratory pressure; RV: right ventricular.

as related by Verhelst et al., who suggested it as a promising treatment[25]. However, there have been few, if any, studies corroborating this statement.

CONCLUSION

Twenty years have elapsed since the first cases of pulmonary edema related to pulmonary resection were reported. Despite the studies carried out, however, little progress has been made in the treatment of this condition. The use of prophylactic corticotherapy has shown promising results, although only one study has been published to date. When PPE has become entrenched, treatment with nitric oxide also shows satisfactory results, as does the use of extracorporeal membrane oxygenators.

Prevention is still the best means of reducing mortality. Until the physiopathology of PPE is thoroughly understood, prevention must be performed in a multidisciplinary fashion, attempting to assimilate all of the positive results obtained by the various authors who have studied this condition (Table 3). Nevertheless, equally as important as prevention is early clinical suspicion, identifying the patients at risk for developing this serious complication.

REFERÊNCIAS

1. Kopec SE, Irwin RS, Umali-Torres CB, Balikian JP, Conlan AA. The postpneumonectomy state. Chest. 1998;114:1158-84.
2. Aubrée N, Grégoire J, Jacques LF, Piraux M, Guojin L, Lacasse Y, et al. Respiratory complications after pneumonectomy. An analysis of incidence, risk factors and outcome. In: 83rd AATS Annual Meeting; 2003; Boston.
3. Houaiss A, Villar MS, Franco FMM. Dicionário Houaiss da língua portuguesa. Rio de Janeiro: Objetiva; 2001. p.2242.
4. Scientific Eletronic Library Online (Scielo). Disponível em: http://www.scielo.br.
5. Graham EA, Singer JJ. Successful removal of an entire lung for carcinoma of the bronchus. JAMA. 1933;101:1371.
6. Fuentes PA. Pneumonectomy: historical perspective and prospective insight. Eur J Cardiothorac Surg. 2003;23:439-45.
7. Deslauriers J, Aucoin A, Grégoire J. Postpneumonectomy pulmonary edema. Chest Surg Clin N Am. 1998;8:611-31.
8. van der Werff YD, van der Houwen HK, Heijmans PJM, Duurkens VAM, Leusink HA, van Heesewijk HPM, de Boer A. Postpneumonectomy pulmonary edema. A retrospective analysis of incidence and possible risk factors. Chest. 1997;111:1278-84.
9. Mathru M, Blakeman B, Dries DJ, Kleinman B, Kumar P. Permeability pulmonary edema following lung resection. Chest. 1990;98:1216-8.
10. Waller DA, Keavey P, Woodfine L, Dark JH. Pulmonary endothelial permeability changes after major lung resection. Ann Thorac Surg. 1996;61:1435-40.
11. Parquin F, Marchal M, Mehiri S, Hervé P, Lescot B. Post-pneumonectomy pulmonary edema: analysis and risk factors. Eur J Cardiothorac Surg. 1996;10:929-33.
12. Shapira OM, Shahian DM. Postpneumonectomy pulmonary edema. Ann Thorac Surg. 1993;56:190-5.
13. Turnage WS, Lunn JJ. Postpneumonectomy pulmonary edema. A retrospective analysis of associated variables. Chest. 1993;103:1646-50.
14. Verheijen-Breemhaar L, Bogaard JM, van den Berg B, Hilvering C. Postpneumonectomy pulmonary oedema. Thorax. 1988;43:323-6.
15. Zeldin RA, Normandin D, Landtwing D, Peters RM. Postpneumonectomy pulmonary edema. J Thorac Cardiovasc Surg. 1984;87:359-65.
16. Sakuma T, Sagawa M, Hida M, Nambu Y, Osanai K, Toga H, et al. Time-dependent effect of pneumonectomy on alveolar epithelial fluid clearance in rat lungs. J Thorac Cardiovasc Surg. 2002;124:668-74.
17. Reed CE, Spinale FG, Crawford FA. Effect of pulmonary resection on right ventricular function. Ann Thorac Surg. 1992;53:578-82.
18. Okada M, Ota T, Okada M, Matsuda H, Okada K, Ishii N. Right ventricular dysfunction after major pulmonary resection. J Thorac Cardiovasc Surg. 1994;108:503-11.
19. Wittnich C, Trudel J, Zidulka A, Chiu RCJ. Misleading "pulmonary wedge pressure" after pneumonectomy: it's importance in postoperative fluid therapy. Ann Thorac Surg. 1986;42:192-6.
20. Slinger PD. Fluid management during pulmonary resection surgery. Ann Cardiac Anaesth. 2002;5:220-4.
21. Slinger PD. Perioperative fluid management for thoracic surgery: the puzzle of postpneumonectomy pulmonary edema. J Cardiothorac Vasc Anesth. 1995;4:442-51.
22. Cerfolio RJ, Bryant A, Thurber J, Bass CS, Bartilucci A. Intra-operative solumedrol helps prevent post-pneumonectomy pulmonary edema. In: 39th Meeting of the Society of Thoracic Surgeons; 2003; San Diego.
23. Mathisen DJ, Kuo EY, Hahn C, Moncure AC, Wain JC, Grillo HC, et al. Inhaled nitric oxide for adult respiratoy syndrome after pulmonary resection. Ann Thorac Surg. 1998;66:1894-902.
24. Rabkin DG, Sladen RN, DeMango A, Steinglass KM, Goldstein DJ. Nitric oxide for the treatment of postpneumonectomy pulmonary edema. Ann Thorac Surg. 2001;72:272-4.
25. Verhelst H, Vranken J, Muysoms F, Rondelez L, Schroe H, de Jongh R. The use of extracorporeal membrane oxygenation in postpneumonectomy pulmonary o edema. Acta Chir Belg. 1998;98:269-72.