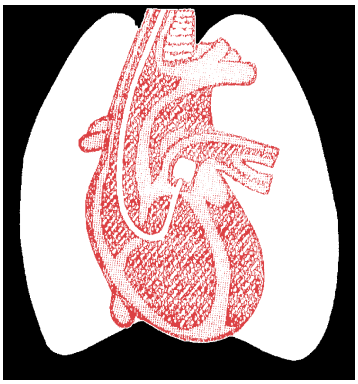

CASE CONFERENCE

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Postpneumonectomy Pulmonary Edema

John M. Alvarez, FRACS, Ranjit K. Panda, MBBS, Mark A.J. Newman, FRACS, Peter Slinger, MD, Jean Deslauriers, MD, FRCS(C), and Mark Ferguson, MD

*Case Presentations**

Idiopathic postpneumonectomy pulmonary edema (PPPE) has become recognized as a distinct pathologic syndrome.[1] However, PPPE remains a diagnosis of exclusion; hence, it is often misdiagnosed.[1] Nevertheless, it is not uncommon; the reported incidence after pneumonectomy is approximately 5% to 15%. This syndrome, despite early diagnosis and aggressive treatment, is associated with a poor prognosis.[2] Therefore, endeavors directed at minimizing the occurrence of PPPE demand analysis.

The traditional management of the pleural space after pneumonectomy has always had the potential to cause mechanical damage to the remaining lung from overdistention.[3] All cases of PPPE at the authors' institution occurred when using traditional pleural drainage.[2] The authors thought that PPPE could be induced in susceptible patients by postoperative volotrauma (hyperinflation). To test this hypothesis, the authors' changed their pleural space management technique to a balanced pleural drainage system. The impact that this sole change has had on the authors' incidence of PPPE is reported here.

CASE SERIES

All patients having pneumonectomy at the authors' institution from January 1, 1993, to December 31, 2000, were retrospectively reviewed. Two eras, according to the method used to manage the pleural space postoperatively, were identified. Group 1 (January 1, 1993-June 30, 1996) represents the traditional group. In group 1 patients, after pneumonectomy, a single intercostal catheter connected to an underwater seal drainage bottle was used. The intercostal tube was clamped and intermittently released to air, every hour for 10 seconds, for a period of 48 hours. In group 2 (July 1, 1996-December 31, 2000), a balanced drainage system (Pleurovac; Deknatel Inc., Fall River, MA, USA) was used for 48 hours postoperatively. In both groups, the intercostal catheters were removed within 48 hours after surgery.

Importantly, the perioperative anesthetic/surgical management of these patients was similar for both groups. Specifically, the anesthetic management entailed induction with intravenous thiopental and vecuronium and maintenance with inhalation enflurane and a mixture of nitrous oxide and oxygen in a ratio of 1:2. A left-sided double-lumen tube was used in all cases, delivering an inspired oxygen concentration of 66%. Cephamandole, 2 g intravenously, was administered to all patients. During surgery, the tidal volume used by the anesthesiologist ranged from 9.6 to 12.9 mL/kg.

All pneumonectomy patients had a central venous line inserted before anesthetic induction. The surgical maxim of keeping these patients "dry" is well entrenched at the authors' institution. In particular, meticulous perioperative fluid management was strictly followed. The aim was to keep the central venous pressure to the lowest level commensurate with the maintenance of stable hemodynamics (ie, systolic blood pressure $>$110 mmHg, warm well-perfused peripheries) and a satisfactory urine output (ie, $>$0.5 mL/kg/h). Diuresis with renal-dose dopamine was initiated in all patients perioperatively. Urine output was measured hourly, as was central venous pressure, and all patients received aggressive physiotherapy and bronchodilator therapy. The diagnosis of PPPE remained unchanged during the entire study period. Specifically, PPPE was defined as the development of widespread infiltrates on the chest radiograph; clinical development of respiratory distress; and the clinical exclusion of myocardial failure, aspiration, pulmonary/systemic infection, bronchopleural fistula, thromboembolism, and transfusion reactions.

Data are presented in Tables 1 and 2. Statistical comparisons for categorical parameters between groups used the chi-square and/or Fischer exact test. During this time, 57 patients underwent pneumonectomy. The 2 groups were comparable regarding number of operations, time frame of the study, type of resection, side of surgery, age, sex, tumor staging, and perioperative length of stay. There were no significant differences in the incidence of major complications (myocardial infarction, bronchopleural fistula, pulmonary embolism, and pneumonia) between the 2 eras (group 1:10.8%, group 2: 10.5%, $p = 0.72$). Importantly, no postpneumonectomy space infections occurred in either group. There were no significant differences in mor-

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Table 1. Demographic Data

	Group 1	Group 2
Era	1993-1996	1996-2000
Age (Range)	60.5 yr (39–82)	59.9 yr (40–84)
Number	28	29
Right	11	13
Left	17	16
Sex: M/F	22/6	23/6

Abbreviations: M, male; F, female.

tality rate between the 2 groups (group 1: 7.1. %, group 2: 6.9%, $p = 0.66$).

However, there was a significant difference in the incidence of PPPE between the 2 groups (group 1:14.3%, group 2: 0%, $p = 0.001$).

Although the mortality rate was unchanged between the 2 groups, the etiologies were clearly different. In group 1, PPPE was responsible for all pneumonectomy deaths. In group 2, however, the 2 fatalities postpneumonectomy were secondary to complications from hyperosmolar, diabetic nonketotic coma, and myocardial infarction, respectively.

DISCUSSION

Since the time of Laforet,[3] it has been appreciated that air loss following pneumonectomy from the operated hemithorax may occur via the thoracotomy. Consequently, the reduction in intrathoracic pressure may induce mediastinal shift with hyperinflation of the remaining lung. The authors hypothesize that if this hyperinflation is severe enough, alveolar/capillary membrane damage can occur with subsequent activation of inflammatory mediators and neutrophils. Given the adaptive changes occurring to the heart and pulmonary circulation after pneumonectomy, this mechanical membrane damage may trigger, in susceptible patients, a cascade of relentless pulmonary edema.[1]

The precise etiology of PPPE is unclear. The prognosis, however, is poor and is associated with reported mortality rates of 50% to 100%.[1,2,4-6] The authors have been concerned that despite the traditional management technique of opening the pleural space to air once an hour, unsuspected hyperinflation of the unoperated lung was occurring postoperatively. The authors therefore retrospectively sought clinical evidence of significant hyperinflation and/or mediastinal shift in the patients who developed PPPE. Although pulmonary hyperinflation could not be specifically identified, evidence of subcutaneous emphysema (at times markedly so) on the operated side was present in all the patients who developed PPPE. Therefore, the authors believed that significant unrecognized reduction in intrathoracic pressure on the operated hemithorax because of coughing and/or expelling air through the thoracotomy could result in significant hyperinflation of the remaining lung. If postoperative hyperinflation is etiologically relevant, eliminating this process should decrease the incidence of PPPE.

Table 2. Perioperative Data

	Group 1 (%)	Group 2 (%)
Major Complications	3 (10.8)	3 (10.5) $p = 0.72$
Bronchopleural Fistula	1 (3.6)	0
Pneumonia	1 (3.6)	1 (3.5)
Pulmonary Embolism	0	1 (3.5)
Myocardial Infarction	1 (3.6)	1 (3.5)
Mortality		
Pneumonectomy	2 (7.1)	2 (6.9) $p = 0.66$
PPPE		
Pneumonectomy	4 (14.3)	0 $p = 0.001$
Right	2 (18.2)	0 $p = 0.001$
Left	2 (11.2)	0 $p = 0.001$
Length Of Stay (Days)	8.5	8.8

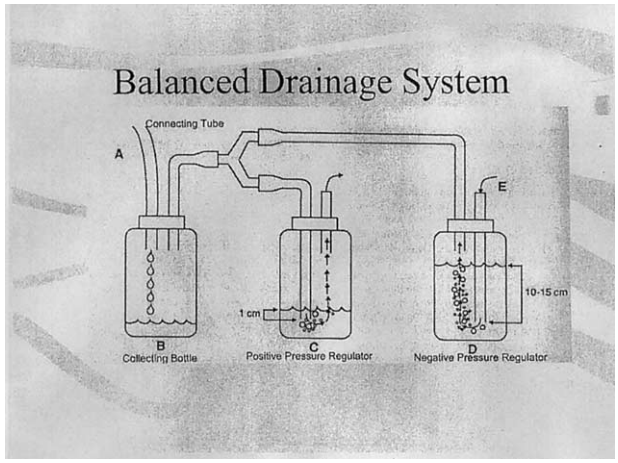

Fig 1. Balanced drainage system with (A) a connecting tube to patient, (B) a collecting bottle, (C) a positive-pressure regulator, (D) a negative-pressure regulator, (E) a tube allowing ingress of air. See text for details.

Three options exist regarding the immediate management of the postpneumonectomy hemithorax. First, the most popular method uses a single clamped intercostal catheter attached to an underwater seal that is briefly released (ie, 10 seconds) to air at hourly intervals to allow realignment of the mediastinum and assess blood/air loss. Second, no drainage catheter is used, and correction of mediastinal shift is achieved by aspiration or injection of air via thoracentesis. The third and final option is using a balanced drainage system (Fig 1).[3]

A balanced drainage system allows continuous automatic adjustment of a defined pressure within the hemithorax by using a system of 3 chambers (Fig 1). The first chamber is a collecting chamber (ie, trap bottle). The remaining 2 chambers are connected in series to the trap bottle and in parallel with each other. They act as positive and negative pressure regulators. A simple underwater seal determines the positive pressure developing within the empty hemithorax. Hence, any pressure within the system exceeding a set limit (ie, 1 cm water) will be vented to air. The negative pressure within the hemithorax is regulated by a reversed underwater seal also set to a predetermined level (ie, -10 to -15 cm of water). Hence, any pressure more negative than 10 to 15 cm of water, relative to atmospheric pressure that develops in the system, will allow the ingress of air to allow compensation to the set level (ie, -10-15 cm of water). Therefore, air within the hemithorax may egress via an underwater seal chamber and ingress via a reverse

underwater seal chamber. Postoperative mediastinal shift and hyperinflation of the remaining lung are thus avoided.[3]

This retrospective case series shows that, in an intensive care unit with a heightened awareness of PPPE, the use of a balanced drainage system may help abolish PPPE. Recently, Deslauriers' group have also noted similar findings.[5] In Deslauriers' series of 291 pneumonectomies from 1988 to 1993, 13 (4.5%) patients were identified as having developed PPPE. The mortality associated with PPPE in this series was 85%. Analysis of factors associated with PPPE revealed that the type of postoperative pleural drainage system was found to be a very significant risk factor ($p = 0.009$) for the development of PPPE.[5] The incidence of PPPE was 0% (0/77 cases) versus 2.5% (2/75) versus 9.1% (11/121) for a balanced drainage system, no drainage, and clamped underwater seal with intermittent brief release, respectively.[5] Admittedly, in Deslauriers' series, patients developing PPPE had longer operating room times (184 *v* 143 minutes, $p = 0.005$), more extensive resections, and higher pleural drainage when compared with the balanced drainage group.

The limitations of this study are clear. It is retrospective in nature and thus unidentified confounding variables may occur, affecting the validity of its conclusions. Also, patient numbers are modest. All reported series involving PPPE have been retrospective in design, and thus, conclusions must be viewed with caution. Furthermore, the numbers involved from any one center, given the incidence of PPPE, and especially if there is not a heightened sense of awareness of PPPE, will be modest. Either a randomized trial and/or the development of an animal model of postoperative hyperinflation-induced PPPE will validate or repudiate the authors' hypothesis.

Volotrauma (hyperinflation) during mechanical ventilation and anesthesia is a suspected etiologic variable regarding PPPE. Slinger recommends limiting peak and plateau airway pressures during one-lung ventilation to minimize the risk of volotrauma.[1] Logically, minimizing the risk of volotrauma after pneumonectomy may be equally, if not more, important. Indirect evidence exists that hyperinflation of the remaining lung after pneumonectomy may cause significant parenchymal damage. Ramenofsky[7] induced acute respiratory distress syndrome (ARDS) in newborn beagles subjected to a left pneumonectomy managed with an underwater seal drain. ARDS was avoided if mediastinal shift was prevented by positive pressure. Raffensperger[8] showed interstitial emphysematous changes from disrupted alveoli after the removal of air from the empty hemithorax after pneumonectomy. Furthermore, mechanical disruption of the alveolar-endothelial barrier is implicated in the well-recognized phenomenon of pulmonary edema/hemorrhage after re-expansion of a chronically collapsed lung.[6]

The major potential risk of using a balanced drainage system is the possibility of introducing an infection into the pneumonectomy space. The authors, like Deslauriers' group, have not encountered this complication. In Laforet's time, PPPE was unrecognized. Laforet thus advocated a balanced drainage system on the basis of "maintaining the mediastinum in a physiologically optimal position" and effecting satisfactory drainage of the chest.[3] Laforet was aware of the potential for infection in the postneumonectomy space; however, over a 10-year period (ie, 1952-1962) this complication did not occur.[3] Importantly, postpneumonectomy empyema, unlike PPPE, can be managed successfully in the vast majority of cases.

The precise etiology of PPPE remains uncertain. Certainly, some operative factors are clinically salient; the incidence after carinal resection is 2- to 3-fold higher than noncarinal pneumonectomies.[2] Also, the incidence after a right pneumonectomy is 2-fold compared with a left pneumonectomy. However, the importance of other operative factors is not so clear (ie, extent of mediastinal lymph node resection).[2] Furthermore, although excessive perioperative fluid administration (oral and/or intravenous) is thought to facilitate the development of PPPE, it is unquestionable that PPPE can develop in so-called "dry patients."[2] Irrefutably, this syndrome continues to occur despite the maxim: "don't drown the down lung."

The prognosis after the development of PPPE remains poor. The authors continue to advocate early diagnosis and aggressive management. This entails a high clinical suspicion of the existence of this syndrome, early intubation, bronchoscopy, exclusion of other potential etiologies (ie, bronchopleural fistula, pulmonary embolism, myocardial infarction, and intrapulmonary sepsis) and aggressive hemodynamic and pharmacologic support (ie, corticosteroids, histamine blockers, and pulmonary vasodilators).[2] In few and selected patients, extracorporeal circulatory support has been successful.[5] However, prevention of PPPE is clearly the best option. It is, therefore, essential that such unquestionably simple maneuvers like a balanced drainage system be put to the clinical test.

In conclusion, a balanced pleural drainage system may decrease the risk of hyperinflation of the remaining lung after pneumonectomy and have a beneficial effect on the incidence of PPPE. It is thus possible that PPPE may be an avoidable complication. Until proven otherwise, the authors therefore recommend a balanced drainage system after all pneumonectomies.

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The authors thank Mr A. Wilson, senior cardiothoracic surgeon, St Vincents Hospital, Melbourne for alerting them to the possibility that hyperinflation may be an unrecognized factor in this syndrome.

COMMENTARY†

Pulmonary edema after pulmonary resection has been described intermittently over the past 50 years.[9] Perhaps the most widely known report is a multicenter compilation of 10 cases published in 1984 by Zeldin et al.[10] After retrospective comparison with controls, they identified 3 significant risk factors for postpneumonectomy pulmonary edema: right pneumonectomy (9/10 cases), increased perioperative intravenous fluids, and increased postoperative urine output. These factors were independent of previous known factors associated with postpneumonectomy pulmonary edema including postoperative tachyarrhythmias and reoperation or hemorrhage. Zeldin et al[10] went on to further show their thesis that this complication was caused by overhydration by producing postpneumonectomy pulmonary edema in a dog model with fluid overload. In their recommendations, they

†P. Slinger

wrote "the most important thing that we can do in terms of recognizing this problem is to watch our anesthetists as they start loading the patient up with fluid."[10]

Those managing thoracic cases are well aware that fluid management is commonly a contentious issue between anesthesiologist and surgeon. Anesthesiologists tend to focus on the undesirable consequences of regional hypoperfusion of potentially compromised organs (brain, heart, and kidneys) while surgeons worry about the complications caused by volume overload on the respiratory system.

In the 18 years since Zeldin's landmark article, there have been at least a dozen similar case series reviews of this topic in the literature with varied conclusions. The largest of these reviews was a study by Turnage and Lunn.[11] In a multihospital retrospective survey of 806 pneumonectomies, these authors found 21 cases (2.5%) of postpneumonectomy pulmonary edema. Their diagnostic criteria were (1) clinical respiratory distress, (2) chest radiography consistent with pulmonary edema, (3) no indication of cardiac dysfunction, (4) no pneumonia or sepsis, and (5) no evidence of aspiration. They found no differences in perioperative fluid balance between postpneumonectomy pulmonary edema cases versus age- and sex-matched pneumonectomy controls. They confirmed the predominance of this complication in right-sided pneumonectomies (16/21). Also, they found that this complication was not associated with elevated pulmonary artery occlusion pressures (PAOP) and was resistant to treatment (mortality 21/21). The histology at autopsy showed evidence of ARDS.

The known facts about postpneumonectomy pulmonary edema at present are as follows:

1. Incidence of 2% to 4% after pneumonectomy. It does occur postlobectomy but with a lower incidence and better outcome.
2. Significantly increased incidence in right versus left pneumonectomies.
3. Symptomatic onset postoperative day 1 to 4; radiologic changes precede clinical signs by 24 hours.
4. High mortality rates (>50%) and resistance to standard therapies for pulmonary edema.
5. Associated with fluid overload but not clearly a cause-effect relationship.
6. Histologic picture of ARDS.
7. Associated with a low PAOP and high-protein edema fluid suggesting endothelial damage (low-pressure pulmonary edema).

There is no single mechanism that can fully explain all these findings and the cause must be multifactorial. Among the potential causes are fluid overload, lung lymphatic damage, altered pulmonary capillary pressure, pulmonary endothelial damage, volume-induced lung injury, right ventricular dysfunction, cytokine release, and oxygen toxicity.

Perhaps the most useful piece of information in the search for the underlying causes of postpneumonectomy pulmonary edema in the past decade comes from a study by Waller et al.[12] These authors studied the postoperative permeability, assessed by scintigraphy with technetium-99m–labeled albumin, of the nonoperated lung in pulmonary resection patients. In the early postoperative period the permeability of the nonoperated lung increased in pneumonectomy but not lobectomy patients. Even though the exact reasons may not be clear, just knowing that a pneumonectomy patient has a "leaky lung" has enormous management implications for the anesthesiologist and all reasonable efforts should be used to limit the pressures in the pulmonary vascular bed and avoid exacerbation of the lung injury.

The preceding article on postpneumonectomy pulmonary edema by Alvarez et al in this issue of the *Journal of Cardiothoracic and Vascular Anesthesia* introduces another new piece that may fit into the puzzle of this complication. They theorize that the tendency of the lung to hyperinflate, pushing the mediastinum laterally (or being pulled by the negative pressure into the operative hemithorax), causes volume-induced trauma of the residual lung after a pneumonectomy. It has been repeatedly shown in studies of intensive care unit patients that acute lung injury is severely exacerbated by hyperinflation,[13] and it is reasonable to assume that this would also apply to the "leaky lung" of the postpneumonectomy patient.

Alvarez and his coworkers used a chest tube drainage system with parallel high- and low-pressure underwater relief valves to maintain the pressure in the postoperative hemithorax within set limits that keep the mediastinum in a "balanced" physiologic position and prevent overdistention of the remaining lung. These chest drainage systems are now commercially available as single disposable units specifically for pneumonectomies.

Alvarez et al found that they had no cases (0/29) of postpneumonectomy pulmonary edema after they began using this chest drainage system. They compared this with a historical control group in which they found this complication in 4 of 28 pneumonectomies with a "traditional" chest drainage system. The caveats of using historical controls and the small number of cases are acknowledged by the authors.

An uncontrolled factor that may have changed in the period of the study is the intraoperative tidal volumes that the anesthesiologists used during one-lung ventilation. The authors report tidal volumes of 9.6 to 12.9 mL/kg during surgery but do not specify if this was during two-lung ventilation, one-lung ventilation, or both. Traditionally, anesthesiologists have been taught to use such large tidal volumes during one-lung anesthesia to prevent atelectasis in the dependent lung. This practice is still followed in many centers.[14]

However, peak inspiratory pressures exceeding 40 cm H_2O during one-lung ventilation have been associated with an increased incidence of postpneumonectomy pulmonary edema.[15] Also, many anesthesiologists have become aware of the fact that most patients during one-lung ventilation develop auto-PEEP and have an elevated functional residual capacity. The use of a large tidal volume in a lung that is starting at an elevated volume can lead to end-inspiratory lung volumes that approach the theoretical limits associated with ventilator-induced lung injury. Because of this concern, some anesthesiologists have backed down from the traditional large tidal volumes for one-lung anesthesia and are using more physiologic volumes (eg, 5 mL/kg), adding PEEP to those patients without auto-PEEP and limiting plateau inspiratory pressures to <25 cmH_2O. Because the data of the current study were collected retrospectively, it is difficult to be certain that the same tidal volumes were used for one-lung anesthesia during the entire 7-year period of the survey.

Table 3. Possible Causes and Prophylaxis of Postpneumonectomy Edema

Possible Cause	Possible Prophylaxis
Increased pulmonary capillary (Pc) and filtration pressure	Fluid restriction and diuretics; if BP and urine output are low, use inotropic agents instead of extra amounts of fluid
Acute hyperinflation of remaining lung	Avoid excessive mediastinal shift by using balanced drainage systems or no drainage
Microaspiration due to excessive analgesia	Improve patient awakeness; keep patient sitting up in bed and NPO for at least 24 hours
Endothelial damage and increased vascular permeability	Fluid restriction
Right ventricular dysfunction	None
Mediastinal lymphatic interruption and lung operation	Avoid extended surgeries and mediastinal lymphadenectomy

Another factor that may limit the applicability of the results in other centers is that the authors' "traditional" method of chest drainage, which was used in the controls, is not applied universally. There seems to be little consensus among thoracic surgeons on the correct way to manage the chest drain after a pneumonectomy. Alvarez et al's "traditional" method was to connect a clamped single intercostal catheter to an underwater seal and release the clamp for 10 seconds hourly for 48 hours and then remove the catheter. They do not mention the concept of "balancing" the mediastinum by injecting or withdrawing air as practiced by some surgeons. Some surgeons do not place a chest drain at all after a pneumonectomy. Others may leave the drain open to an underwater seal or unclamp it only if indicated, and the time to removal varies between surgeons.

In summary, this study provides data that are suggestive that the incidence of postpneumonectomy pulmonary edema can be decreased by managing the chest drainage system to avoid hyperinflation of the remaining lung. Because of the use of historical controls and the small numbers of patients and cases, it is impossible to be certain of the conclusions at this time. However, based on the limited understanding of the etiology of this complication, specifically the fact that after pneumonectomy there is a degree of endothelial injury in the nonoperated lung in the early postoperative period, and knowing the susceptibility of a "leaky lung" to further injury from overdistention, following the suggestions of Alvarez et al to avoid hyperinflation of the remaining lung is a commonsense approach to postpneumonectomy management with a low risk/benefit ratio.

COMMENTARY‡

Postpneumonectomy edema is a clinical condition in which an early (2-3 days) postpneumonectomy patient experiences rapidly progressing shortness of breath and hypoxemia and in which the contralateral lung develops radiologic infiltrations suggesting interstitial pulmonary edema. To make that diagnosis, there should be no clinical or radiologic evidence of aspiration; bacterial pneumonia; heart failure; thromboembolism; bronchopleural fistula; or of other causes of ARDS such as blood transfusion, shock, or overwhelming sepsis. One of the most interesting clinical features of postpneumonectomy edema is that once the process has begun, no conventional therapy seems to improve the patient's condition. Diuretics, oxygen, fluid restriction, and positive-pressure ventilation often aggravate the hypoxia rather than improve it. Ultimately, the mortality associated with this complication is in the range of 80% to 100%.

Because postpneumonectomy edema is primarily a diagnosis of exclusion and because the condition was not clearly defined until the 1980s, its true incidence is difficult to extrapolate from the literature. In the authors' series of 1,046 consecutive pneumonectomies done for lung cancer over a 20-year period (1980-1999), 26 cases of postpneumonectomy edema were identified, for an incidence of 2.5%. Nineteen of these 26 patients (73%) eventually died of respiratory insufficiency or multiorgan failure.

Although the pathogenesis of postpneumonectomy edema is not fully understood, several factors (Table 3) are likely to interact to cause this complication. Obviously, the knowledge that some of these factors are significant could lead to the use of prophylactic measures that could decrease the incidence of the complication.

Ever since the original work of Zeldin et al[10] in the early 1980s, fluid overload and increased pulmonary capillary hydrostatic pressure (Pc) have been thought to be the driving force in the pathogenesis of postpneumonectomy edema. Based on some experimental work, these authors concluded that after pneumonectomy, the remaining lung has to accommodate the whole cardiac output, and this may result in a net increase in fluid filtration pressures that could cause postpneumonectomy edema. Because of this work, most surgeons now advocate to keep the pneumonectomy patient "dry" with fluid restriction and diuretics. Unfortunately, this concept of keeping the patient "dry" has never been challenged, even if several retrospective series, including the authors',[5] have shown no significant differences in fluid balance between patients with or without postpneumonectomy edema. Indeed, it is the authors' belief that because of possible volotrauma and air-block syndrome, the pulmonary capillary bed should at least be kept "filled up."

In this article by Alvarez et al, the authors postulate that acute hyperinflation of the remaining lung causes stretching of the alveoli (volotrauma) and this likely promotes interstitial accumulation of fluid. Although the series is retrospective and includes very few patients, the analysis shows that the type of postoperative drainage is a very significant risk factor for the occurrence of postpneumonectomy edema. The rationale is that

‡J. Deslauriers

with an underwater seal type of drainage, the air will be expelled quickly from the pleural space, thus creating a vacuum that will cause excessive mediastinal shift toward the operated side. The remaining lung will then overexpand very rapidly. In their series of 57 patients, 4 of 28 (14.3%) with underwater seal drainage developed postpneumonectomy edema, whereas none of the 29 with balanced drainage had the complication. As a conclusion, Alvarez and colleagues advocate the use of a balanced drainage system[3] designed to maintain optimal physiologic position of the mediastinum in the critical early postoperative period.

Numerous factors favor interstitial accumulation of fluid in acute overinflation of the lung. These include increased pulmonary artery pressure, which is proportional to lung volume overdistention and permits a net increase in capillary and filtration pressures, widening of the intercellular junction of the capillary endothelium, facilitating protein and fluid flux, or decreased lymphatic drainage. In 1979, Ramenofsky[7] did a very interesting experiment in newborn beagle puppies. After left pneumonectomy had been performed, the animals were separated into 1 of 2 groups. In group 1, the thoracostomy tube was attached to a waterseal drainage unit; in group 2 animals, the tube was attached to a pressure manometer, and air was insufflated into the hemithorax until the mediastinum was positioned in the midline. By 24 hours postoperatively, all group 1 animals had died of ARDS, as compared with none in group 2. The histologic appearance of the lung in group 1 animals showed the presence of hyaline membranes, thickened alveolar septa, and distention of alveoli, whereas the lung of group 2 animals revealed a normal architecture. Indirect evidence that acute overdistention of the lung may be an important factor in the pathogenesis of postpneumonectomy edema is that this complication was not seen in the series of 47 patients who had pneumonectomy for benign disease, presumably because the remaining lung had already been overexpanded for several years before pneumonectomy.

Another possible, but not yet documented, cause for postpneumonectomy edema is occult microaspiration possibly related to “too much” analgesia. In this situation, pain control may be at the expense of patient’s awakeness and ability to prevent the consequences of aspiration by adequate coughing. Whether routine use of drugs given by an epidural catheter somehow increases the risk of respiratory complications after pneumonectomy by favoring microaspiration is an interesting question that must be looked at very carefully.

The finding of high levels of protein in postpneumonectomy edema fluid suggests that some degree of endothelial damage must occur and probably contributes to the production of low-pressure pulmonary edema. The cause of this increased permeability is still unclear, although high pulmonary pressures have been shown to cause capillary stretching and damage to junctions between endothelial cells. It is also possible that because of increased linear velocity of blood flow, actual injury to endothelial cells may occur. According to Slinger,[17] this increased permeability may explain the delay of the syndrome until the second or third postoperative day, when “increased cardiac output is seen as patients begin to mobilize their fluids.”

Other possible factors for postpneumonectomy edema include transient right ventricular dysfunction, which has been shown to develop on the second postpneumonectomy day. It also includes mediastinal lymphatic interruption with secondary lymph pump capacity reduction to an amount proportional to the amount of lung that has been removed and to the extent of mediastinal lymphadenectomy. Extended pneumonectomies and long operations are also associated with an increased incidence of postpneumonectomy edema.

In summary, postpneumonectomy edema is a major complication that occurs in 3% to 4% of all pneumonectomies. Although its true cause is unknown, it is likely to be multifactorial, with acute hyperinflation probably being an important risk factor. Prophylaxis is possible but often inefficient, as is management by conventional methods.

COMMENTARY§

Alvarez and coauthors provide an interesting and clinically useful assessment of a challenging surgical complication. Pulmonary edema is a frequently fatal but fortunately uncommon complication that occurs primarily after pneumonectomy but has also been described after lesser resections including lobectomy and pulmonary wedge resection. It is initially recognized as a minimally symptomatic pulmonary infiltrate that develops within the first 24 hours postoperatively. Its florid clinical presentation, which consists of rapidly worsening dyspnea and hypoxemia, develops during the second or third postoperative day. Conventional therapy often appears to aggravate the hypoxia.[5] Mortality is caused by respiratory insufficiency, with historical death rates reported as high as 80% to 100%.

PPPE is likely the same clinical entity as noncardiogenic pulmonary edema and postpneumonectomy ARDS. The etiology of PPPE is not yet well understood. Proposed causes include an extended duration of operation, administration of excess perioperative fluids, barotrauma from elevated intraoperative airway pressures, surgically induced release of vasoactive mediators, right heart failure resulting in back pressure on pulmonary lymphatics, interruption of mediastinal lymphatics limiting lymphatic drainage pathways and causing restricted lymph flow from the remaining lung, and alveolar-endothelial membrane damage because of volotrauma as suggested by Alvarez and coauthors in the accompanying article. It is likely that more than one of these etiologies is active in the development of this challenging clinical problem (Fig 2).

The 2-fold higher incidence of postpneumonectomy pulmonary edema after right lung resection compared to left lung resection is similar to the increased incidence of right heart failure associated with that operation, suggesting a possible shared causal relationship between these pathologies. That pulmonary edema occurs more often after right pneumonectomy than after left has sometimes confused surgeons and critical care physicians. In a healthy person the right lung comprises up to 55% of the lung volume, meaning that only 45% of the original pulmonary capillary volume is available for blood flow through the lung after right pneumonectomy. This, coupled with the fact that more severe volotrauma is likely to occur based on the greater amount of overdistention that is possible after right rather than left pneumonectomy, is sufficient to

§M. Ferguson

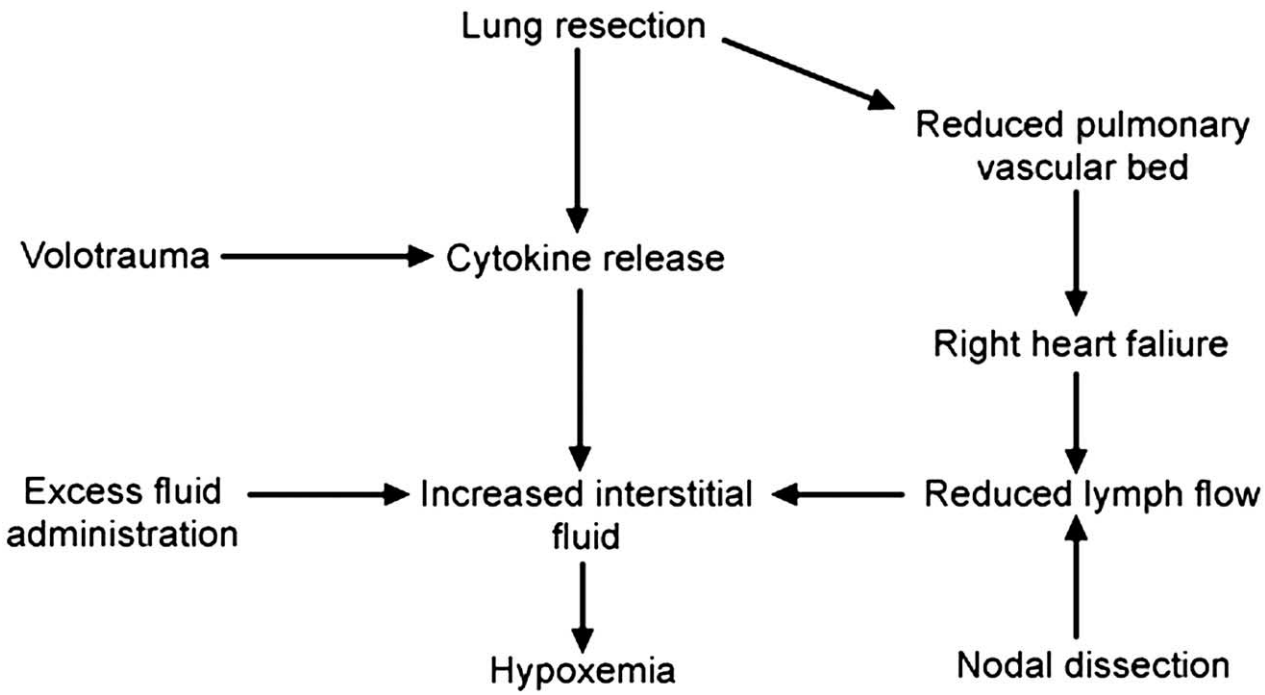

Fig 2. The interaction of a variety of factors is likely necessary for the development of postpneumonectomy pulmonary edema.

explain the higher reported incidence of postpneumonectomy edema that occurs after right lung resection.

It is important to prevent PPPE because success in managing this problem once it develops is far from satisfactory. Algorithms for predicting preoperatively which patients are at increased risk have not been developed. Therefore, the onus is on the surgeon, anesthesiologist, and intensive care specialist to provide intraoperative and postoperative therapy that does not increase a patient's risk. The appropriate management of the postpneumonectomy space has been somewhat overlooked in this regard. Alvarez and his colleagues provide an important study that reinforces the contention that underwater seal drainage may facilitate the development of PPPE because of volotrauma. Surgeons are wisely cautioned to avoid the use of this drainage technique in the management of the pneumonectomy patient. Stabilization of the mediastinum in the midline at the time of chest closure without tube drainage is usually sufficient for most pneumonectomy patients. When the possibility of rapid fluid accumulation arises because of less-than-adequate hemostasis or other factors, use of a balanced drainage system is appropriate. Both techniques appear to substantially reduce the risk of volotrauma in this patient population.

Once PPPE develops, standard management includes supplemental oxygen, intravenous fluid restriction, diuresis, positive-pressure ventilation, and administration of pulmonary vasodilators. Antibiotics and systemic steroids are of questionable utility. Use of extracorporeal oxygenation has been successful in anecdotal reports, but many medical centers lack the technical expertise to provide this therapy.

One new treatment that recently has been suggested is inhaled nitric oxide (NO). Mathisen and coauthors[18] described administration of NO to 8 pneumonectomy patients as soon as the diagnosis of PPPE was made, resulting in a mortality rate of only 25%.[3] Neither of the deaths was directly attributable to PPPE. This outcome was substantially better than in their historical controls who experienced an 86% mortality rate in the absence of NO administration. That NO is possibly effective in the management of PPPE should not be surprising. Smoking is associated with a decreased level of endothelial nitric oxide synthase (eNOS).[19] Pulmonary and mediastinal lymph flow is regulated in part by NO.[20] Endothelial damage from cytokine release and volotrauma likely decrease eNOS further. Supplementing NO levels causes pulmonary and lymphatic vascular dilation, reducing right heart strain and permitting increased lymph flow from the remaining lung.

Further studies of the unusual and challenging problem of PPPE are warranted to provide a better understanding of its etiology and to further define appropriate management. At present, limiting fluid administration and avoidance of barotrauma and volotrauma in the pneumonectomy patient are useful adjuncts to standard postoperative therapy of the lung resection patient. The use of inhaled NO in managing noncardiogenic postoperative pulmonary edema appears promising.

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