Development of a Giant Bulla After Lung Volume Reduction Surgery*

Moeen Iqbal, MD; Leonard Rossoff, MD; Kerry McKeon, RN, RRT; Michael Graver, MD, FCCP; and Steven M. Scharf, MD, PhD

Lung volume reduction surgery (LVRS) is being evaluated in the treatment of emphysema. The proposed mechanisms of improvement are increased elastic recoil of the lung and improved mechanical efficiency of the muscles of respiration. We report a unique patient with emphysema who developed a giant bulla 3 years subsequent to LVRS. The patient underwent extensive evaluation, including measurements of lung mechanics. Bullectomy was performed, but it was unsuccessful. Although the mechanisms behind the development of giant bullous disease remain speculative, heterogeneous improvement in elastic recoil following LVRS may be one of the responsible mechanisms.

(CHEST 1999; 116:1809–1811)

Key words: elastic recoil; giant bulla; lung volume reduction surgery

Abbreviations: LVRS = lung volume reduction surgery; PV = pressure-volume; TLC = total lung capacity

Emphysema is characterized by a reduced maximum expiratory flow due to a combination of airway disease and loss of elastic recoil. The latter leads to an increase in static pulmonary compliance, static and dynamic hyperinflation, intrinsic positive end-expiratory pressure, and increased work of breathing. Chronic hyperinflation also puts the muscles of respiration at a great mechanical disadvantage.

Lung volume reduction surgery (LVRS) is currently undergoing evaluation for the treatment of pulmonary emphysema. Recent studies have documented improved quality of life and relief of dyspnea in at least some patients. Proposed mechanisms of improvement after LVRS are increased elastic recoil, decreased airway resistance, and improved respiratory muscle function.

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There are few studies describing long-term follow-up in LVRS patients. It is theoretically possible that interaction within the lung due to inhomogeneous changes in elastic recoil and airway function could result in bulla formation. The following is a case report of the development of giant bullous disease following LVRS, and we postulate that improved elastic recoil contributed to this complication.

Case Presentation

A 58-year-old white woman with severe emphysema was evaluated in our LVRS clinic. Her CT scan (Fig 1, left) showed centrilobular emphysema predominantly involving the upper lobes. After initial workup and pulmonary rehabilitation, she underwent bilateral LVRS through median sternotomy. Three months postoperatively, she improved subjectively and objectively, as shown by pulmonary function tests (Table 1). In the third year after LVRS, she gradually became more dyspneic and was referred back to the LVRS clinic. The CT scan (Fig 1, right) now showed development of a giant bulla in the right upper lobe occupying more than one third of the right hemithorax. Serial chest radiographs (not shown here) at 3 and 6 months postoperatively showed no evidence of bullous disease. Radiographs at 1 year after LVRS revealed the development of a bulla in the right upper lobe less than one third the size of the hemithorax. Subsequent films after 3 years showed the growth of the bulla. Serial pulmonary function tests are shown in Table 1. Pressure-volume (PV) curves are shown in Figure 2, top, A. Maximal static recoil pressure improved 3 months after surgery, although specific compliance remained unaltered. The 3-year curve showed decreased maximal recoil pressure compared with 3 months, but it was still greater than it was before the LVRS. Static recoil maximum flow curves (Fig 2, right, B) demonstrated improved flow rates 3 months after LVRS. However, by 3 years, there was decreased maximum expiratory flow at any given recoil pressure. An echocardiogram showed an estimated peak pulmonary systolic pressure of 40 mm Hg with normal left ventricular function. She underwent giant bullectomy but died postoperatively following massive intrathoracic bleeding and ARDS. The cause of bleeding could not be determined.

Discussion

The long-term prognosis and the effect of LVRS on the lung mechanics have not yet been characterized. This case reports the development of a giant bulla as a late complication of LVRS, a finding not previously reported.

Different mechanisms of bulla formation have been suggested. One postulate is a ball valve mechanism in a small airway subtending the distended airspace. Air is progressively trapped in alveoli distal to the obstruction and expands to form a bulla. However, bronchi connecting with bullae are patent, thus rendering this explanation implausible.

Ting et al studied isolated bullae after resection and found that bullae were very compliant with a sharp elastic limit and that the inflation pressures for bullae are less...
than they are for surrounding lungs. Morgan et al.\textsuperscript{12} measured pressures in bullae just before excision and found that the pressure was never positive during inspiration and never more positive than pleural pressure at end-expiration. Accordingly, bullae appear to be formed by emphysematous destruction of pulmonary tissue and enlarge by the retractive forces of surrounding lung parenchyma. Improved recoil after LVRS could act to exaggerate this process.

The serial PV curves of the patient mentioned above are consistent with the latter theory.\textsuperscript{12} Before bullectomy (3-year curve), there was a right shift on the normalized PV curve. This could be consistent with the presence of the large bulla. The lung would be essentially divided into two compartments: a nondeflating bulla and a normally deflating compartment. The serial static recoil and maximum expiratory flow curves initially showed improved expiratory flows at any specific elastic recoil after LVRS. This may have been due to decreased airway resistance engendered by increased recoil tethering open airways. The curve after the development of giant bulla is shifted to the right with decreased flow rates. Progressive narrowing and/or distortion of airways surrounding the expanding bulla may explain this.

The surgical removal of a giant bulla in generalized emphysema is an accepted procedure. The success depends on the size of the bulla and evidence of retraction of adjacent lung tissue.\textsuperscript{14} Long-term follow-up after a giant bullectomy reveals little recurrence and decline in pulmonary function comparable to the general population.\textsuperscript{15,16} In our case, we cannot be sure whether bulla formation represented natural disease progression or a consequence of LVRS. However, the temporal relation to the LVRS, as well as above considerations, suggest that bulla formation was a consequence of the surgery.

In conclusion, we speculate that heterogeneous improvement of elastic lung recoil after LVRS contributed to the bulla formation. The retraction of lung surrounding the bulla may have distorted or narrowed the bronchi, thus leading to decreased flow rates at comparable recoil pressures over the long term. This patient fared poorly after the bullectomy, and it is not clear if this procedure can be recommended for treatment of this possible complication of LVRS.

### Table 1—Serial Lung Function Testing\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variables for Lung Function Testing</th>
<th>Pre-LVRS</th>
<th>Post-LVRS (3 mo)</th>
<th>Pre-bullectomy (3 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>1.93 (58)</td>
<td>2.13 (61)</td>
<td>1.68 (52)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, Ls</td>
<td>0.90 (40)</td>
<td>1.18 (53)</td>
<td>0.76 (36)</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC</td>
<td>47</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>FRC, L</td>
<td>2.88 (93)</td>
<td>2.53 (82)</td>
<td>2.61 (84)</td>
</tr>
<tr>
<td>RV, L</td>
<td>2.55 (128)</td>
<td>1.52 (76)</td>
<td>2.04 (101)</td>
</tr>
<tr>
<td>TLC, L</td>
<td>4.66 (88)</td>
<td>3.66 (69)</td>
<td>3.96 (75)</td>
</tr>
<tr>
<td>TLC (by TGV), L</td>
<td>—</td>
<td>—</td>
<td>6.17 (115)</td>
</tr>
<tr>
<td>DLCO, ml/min/mm Hg</td>
<td>5.77 (24)</td>
<td>8.26 (35)</td>
<td>9.20 (40)</td>
</tr>
<tr>
<td>pH</td>
<td>7.45</td>
<td>7.45</td>
<td>7.48</td>
</tr>
<tr>
<td>P\textsubscript{CO\textsubscript{2}}, mm Hg</td>
<td>36</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>P\textsubscript{O\textsubscript{2}} (room air), mm Hg</td>
<td>72</td>
<td>72</td>
<td>45</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Values are given as No. (% predicted) or as No. FRC = functional residual capacity; RV = residual volume; TGV = thoracic gas volume; DLCO = diffusing capacity of the lung for carbon monoxide.

### References

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![Figure 1. Left: CT scan before LVRS showing bilateral, predominantly upper lobe centrilobular emphysema. Right: CT scan 3 years after LVRS with a giant bulla occupying most of the right hemithorax.](Image)

![Figure 2. Top: A: PV curves normalized to the TLC. Bottom: B: maximum flow static recoil curves. Pel = static elastic recoil pressure; V\textsubscript{max} = maximum expiratory flow.](Image)
Endobronchial Metastasis From Osteosarcoma of Bone*

Treatment With Intraluminal Radiotherapy

Nesrin Mogulkoc, MD†; Erdem Goker, MD; Alev Atasever, MD; Ali Veral, MD; Serdar Ozkok, MD; and Paul W. Bishop, BA, MB BCh

Lung parenchymal metastases are common manifestations in patients with osteosarcoma; however, spread to the major airway itself is extremely rare. We present a young man who had been previously treated with surgical resection following preoperative chemotherapy and immediate postsurgical adjuvant chemotherapy for proximal tibial osteosarcoma. He developed metastasis to the major airways. The patient was treated with intraluminal radiotherapy (ILT) for the endobronchial metastasis. This is the first report of an endobronchial osteosarcoma that was treated with ILT with a complete endoscopic response. ILT provided excellent palliation in this particular case. (CHEST 1999; 116:1811–1814)

Key words: endobronchial metastasis; intraluminal radiotherapy; osteosarcoma

Abbreviation: ILT = intraluminal radiotherapy

Osteosarcoma is the most common primary skeletal malignancy of childhood, typically occurring between the ages of 10 and 20 years. For patients treated with surgery alone or with surgery and adjuvant chemotherapy, pulmonary metastases are frequently seen (50%) as a relapse. However, metastatic malignancy rarely involves a major airway. The most common extrathoracic tumors associated with endobronchial metastasis are renal, breast, and colorectal carcinomas. Other reported primary tumors include melanoma, soft tissue sarcomas, and tumors of the uterine cervix, testis, ovary, prostate, thyroid, pancreas, and adrenal glands. Previously, only one case of endobronchial metastasis from osteosarcoma of the bone has been reported. We report such a case, highlighting the peculiar appearance of the endobronchial mass and a good clinical response to intraluminal radiotherapy (ILT).

Case Report

A 21-year-old man presented with a 2-month history of gradually increasing dyspnea, nonproductive cough, and wheeze. He gave a history of weight loss of about 15 kg over a year. He also reported 2 days of fever. Approximately 3 years (34 months) before his current problems occurred, the patient had pain and swelling in the left knee, which on excision biopsy had been proved to be caused by an osteosarcoma of the bone. At that time, CT scans of the cranium, thorax, and abdomen, along with bone scan, were negative for tumor metastasis. He had a diagnosis of nonmetastatic proximal tibial osteosarcoma and was treated with nine cycles of high-dose IV methotrexate, IV ifosfamide, and IV adriamycin followed by surgical resection. After surgery, the patient received 11 more cycles of the same drug regimen. Serial follow-up included CT scans of the thorax and abdomen together with bone scintigraphy every 3 months. CT and bone scans remained clear until 20 months after the primary diagnosis, when a CT scan of the chest showed two nodules, 5 mm in diameter, in the posterior basal segment of the left lung and lateral basal segment of the right consistent with metastatic tumor. The patient underwent resections of these pulmonary nodules via a thoracotomy. After pulmonary metastectomy, he received five courses of chemotherapy; osteosarcoma.

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Manuscript received March 10, 1999; revision accepted June 11, 1999.

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therapy with ifosfamide plus mesna. Unfortunately, the patient was lost to follow-up for 8 months.

At the subsequent presentation, the patient was cachectic, dyspneic, and cyanotic on physical examination. His oral temperature was 38.2°C; pulse rate, 125 beats/min; and respiratory rate, 32 breaths/min. Examination of the respiratory system revealed diminished breath sounds and dullness on percussion at both lung bases. There was no peripheral lymphadenopathy. The abdomen was soft and nontender. The operation site of the extremity was free of tumor.

Laboratory test results were notable for a leukocyte count of $13.4 \times 10^9/L$ and a hemoglobin concentration of 9.9 g/dL. Erythrocyte morphology showed anisocytosis. The patient’s alkaline phosphatase was substantially increased, at 3,280 U/L (normal, 98 to 290 U/L). The serum creatinine value was 1.3 mg/dL (normal, 0.5 to 1.1 mg/dL), and the urea value was 55 mg/dL (normal, 10 to 50 mg/dL). Electrolytes and liver function test results were normal. Serum protein electrophoresis revealed an increased $a_2$ globulin value of 17 g/dL (normal, 7 to 13 g/dL). The erythrocyte sedimentation rate was increased, at 50 mm in 1 h. Arterial blood gas analysis in room air showed a $P_aO_2$ of 51 mm Hg, $P_aCO_2$ of 28 mm Hg, and oxyhemoglobin saturation of 90%.

Chest radiography revealed three soft tissue masses consistent with metastases (Fig 1). Thoracic CT additionally revealed an endobronchial metastatic tumor within the right main bronchus and the lower trachea (Fig 2). There was no mediastinal lymphadenopathy.

The patient was treated with oral antibiotics, prednisolone, and continuous nasal oxygen.

At fiberoptic bronchoscopy, a large, hard, and white endobronchial mass $> 5$ cm in length obstructed the right main and intermediate bronchi, ascending like a finger to the level of the main carina and lower trachea. Biopsy of the endobronchial tumor showed osteosarcoma (Fig 3).

The patient received a single fraction of 15-Gy ILT using an $^{192}$Ir high-dose rate source (microSelectron; Neucletron International; Veenendaal, the Netherlands) with a standard fiberoptic bronchoscopy technique. A 2-mm-diameter brachytherapy catheter was advanced via the suction channel of the bronchoscope. Because the catheter could not be passed beyond the tumor, the end of the catheter was positioned adjacent to the tumor. A guidewire was passed down the catheter, and the bronchoscope was removed. The guidewire was replaced by a wire with radiopaque markers at 1-cm intervals. Plain chest radiographs were obtained in anteroposterior and lateral planes in order to verify the position of the catheter and plan the radiotherapy treatment. The graduated wire was then removed, and the catheter was attached to the microSelectron. The radiation source was advanced in 5-mm steps every 30 s, over a distance of 10 cm, resulting in a total treatment time of 10 min. Treatment was accomplished as a day case procedure. No adverse effects occurred. The patient did not undergo any additional local therapy such as external beam irradiation, laser treatment, or surgical debulking.

He reported a decrease in cough and dyspnea during the 2 weeks following treatment. Three weeks after treatment, blood gases had improved, with a $P_aO_2$ of 68 mm Hg, $P_aCO_2$ of 28 mm Hg, and oxyhemoglobin saturation of 95% in room air. We repeated bronchoscopy 1 month later to assess actual tumor resolution following ILT. The right main and intermediate bronchi were tumor-free. Posttreatment CT scans demonstrated tumor regression (Fig 4). The patient survived 86 days after this single treatment.

**Figure 1.** Chest radiograph at presentation showing three masses consistent with metastases. The first mass is a soft tissue density, pleural-based mass in the left upper zone. The second is a heavily calcified mass, 8 cm in diameter, situated medially in the right lower lobe. The third is a huge, heavily calcified mass, $> 14$ cm in diameter, in the left lower lobe extending down behind the dome of the left hemidiaphragm.

**Figure 2.** CT scan of the thorax at the level of the carina demonstrates endobronchial metastatic tumor within right main bronchus.

**Figure 3.** Histologic section of the endobronchial lesion. Centrally, the section shows malignant osteoid. This is surrounded by necrotic tissue with an acute inflammatory cell infiltrate (hematoxylin-eosin, original $\times 180$).
metastases of osteosarcoma, the first being primary bone. In our literature, we were able to find only two endobronchial intermediate and right main bronchi, extending into the earlier on CT scan. The right-sided mass was invading the wall. Our patient had huge calcified parenchymal masses in both lungs; these masses were not present 10 months earlier on CT scan. The right-sided mass was invading the intermediate and right main bronchi, extending into the main carina and lower trachea radiologically and endoscopically. The endoscopic appearance of this endobronchial tumor looked like a finger, 5 cm in length and 9 mm in diameter. It trembled with breathing. Time from diagnosis of the primary tumor to presentation of the endobronchial metastasis was 34 months.

Differential diagnosis of endobronchial tumors is important and is influenced by an accurate clinical history and endoscopic investigation. Such tumors may give rise to symptoms identical to primary bronchial carcinoid or carcinoid, including stridor if situated in the trachea.

Various treatments are available for removal or destruction of endobronchial tumors and restoration of airway patency, including surgery and external-beam radiotherapy. Patients with endobronchial metastasis may benefit from local forms of therapy. These local forms of therapy include ILT, laser therapy, electrocautery, cryotherapy, photodynamic therapy, stents, and mechanical removal with a rigid scope. Combination of these various treatments can be complementary in some instances. Transbronchoscopic intralesional Bacille Calmette-Guérin or chemotherapeutic agents have also been described as controlling an endobronchial lesion for a short time of period in limited studies.

Our patient presented in respiratory distress, and bronchoscopy was performed on an emergency basis soon after admission. Because we do not have other therapeutic endobronchial modalities in our institution, ILT alone was used in the treatment and was found to be of benefit to the patient, although the assessment of symptom relief is complicated by the presence of untreated parenchymal lung metastases in this patient. No adverse effect was observed during or after the treatment. We did perform repeat bronchoscopic examination to assess actual tumor response to ILT by direct visualization of tumor and noted total resolution of the endobronchial tumor. Blood gas analyses and CT scans also demonstrated improvement. The patient lived for 3 months after this palliative treatment.

To our knowledge, this is the first report of ILT being applied for endobronchial osteosarcoma metastasis of the bone with a good response. We found that ILT is very useful in the palliative control of endobronchial osteosarcoma metastasis causing major obstruction of the airway.

**DISCUSSION**

We present a young man with osteosarcoma of the proximal tibia who developed extensive metastatic disease involving the lung parenchyma and, more interestingly, the major airways, and in whom ILT provided effective palliation.

It has been suggested that osteosarcoma should be regarded as a metastatic disease, even when only a single primary lesion is found at the initial presentation. Metastatic disease to the lungs is found in the majority of patients dying of osteosarcoma. However, spread to the bronchial lumen itself is very rare. It is mostly in the past 2 decades that physicians have been aware of such metastases. The incidence of solid tumor spread to the bronchial tree was described in only 2% of cases in one series. Reviewing the literature, we were able to find only two endobronchial metastases of osteosarcoma, the first being primary bone and the second being primary uterine osteosarcoma.

The endobronchial lesion may form either by invasion from surrounding tissues such as lung parenchyma, as seen in our patient, or by direct seeding within the bronchial wall. Our patient had huge calcified parenchymal masses in both lungs; these masses were not present 10 months earlier on CT scan. The right-sided mass was invading the intermediate and right main bronchi, extending into the main carina and lower trachea radiologically and endoscopically. The endoscopic appearance of this endobronchial tumor looked like a finger, 5 cm in length and 9 mm in diameter. It trembled with breathing. Time from diagnosis of the primary tumor to presentation of the endobronchial metastasis was 34 months.

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**REFERENCES**

Extensive Mediastinal Lymphadenopathy in an Adult Immunocompetent Woman Caused by *Mycobacterium avium* Complex*

Ulfr Greinert, MD; Sabine Rüsch-Gerdes, PhD; Ekkehard Vollmer, MD; and Max Schlaak, MD

We report a case of extensive mediastinal lymphadenopathy in a 29-year-old immunocompetent woman, which was thought to be caused by *Mycobacterium avium* complex (MAC). Chest radiographs showed deterioration while the patient was receiving antituberculous medication for 8 months. After isolation of *Mycobacterium avium* complex (MAC) from a lymph node aspiration biopsy and switch to a MAC-specific therapeutic regimen, the lesion almost completely disappeared within 1 year. To our knowledge, this is the first report of an extensive mediastinal lymphadenopathy caused by MAC in an immunocompetent adult.

(CHEST 1999; 116:1814–1816)

**Key words:** immunocompetence; mediastinal lymphadenopathy; *Mycobacterium avium* complex; *Mycobacterium tuberculosis*; nontuberculous mycobacteria

**Abbreviations:** MAC = *Mycobacterium avium* complex; MTB = *Mycobacterium tuberculosis*; NTM = nontuberculous mycobacteria; TB = tuberculosis

Besides pulmonary disease, lymphadenopathies are the most frequent manifestations of mycobacterial infections. An enlargement of the mediastinal lymph nodes in the course of an infection with *Mycobacterium tuberculosis* (MTB) can be diagnosed quite frequently, but to our knowledge, there is no description of mediastinal lymphadenitis caused by nontuberculous mycobacteria (NTM) in an immunocompetent adult. Even in children, this location of NTM disease is extremely rare. We report a case of a 29-year-old nurse from Turkey with a huge mediastinal mass and the diagnosis of *Mycobacterium avium* complex (MAC) disease.

**CASE REPORT**

A mediastinal mass was demonstrated on chest radiograph in a 29-year-old Turkish woman, and histopathologic examination of a suprACLAVICULAR lymph node diagnosed tuberculosis (TB) in May 1996. There was no proof by culture. For reasons of pregnancy, therapy was not initiated until September 1996, when isoniazid, 300 mg qd, and ethambutol, 20 mg/kg of body weight, was administered for 2 months until delivery. Then, a therapy of isoniazid; rifampicin, 600 mg; ethambutol; and streptomycin, 1 g 5 days a week for 6 months, was begun; after 4 more months, a chest radiograph did not reveal any change for the better. There was no evidence of noncompliance on the part of the patient. In March 1997, mediastinoscopy was performed, and histopathologic examination of the lymph node specimen showed typical features of active TB. Microbiological analysis of biopsy material identified acid-fast bacilli, but culture results were negative.

The patient presented at our institution in April 1997 complaining of cough and chest pain on deep inspiration, with no weight loss and no night sweats. The physical examination showed no abnormalities; laboratory analysis revealed an elevated erythrocyte sedimentation rate, an elevated C-reactive protein, and mild anemia. A skin test for recall antigens (Multitest-Mérieux; Pasteur Mérieux; Leimen, Germany) showed a positive reaction to tuberculin only. No antibodies against HIV-1 or HIV-2 were detected. Further analysis did not reveal abnormalities of humoral or cellular immunity. Chest radiographs showing the increasing size of a right-sided mediastinal mass, and imaging of the lesion by CT of the chest are shown in Figures 1–3. By ultrasound scanning of the neck, a retroclavicular lymph node of 2 cm in diameter was detected, of which a needle aspiration biopsy was done twice. Nucleic acid amplification test results for MTB complex were negative, but cultures from both specimens were positive for MAC. A chest radiograph of June 1997 showed additional pulmonary infiltration of the right upper lobe. Bronchoscopy and transbronchial biopsies as well as transtracheal needle aspiration biopsies were performed. For both sites, abortive granuloma without acid-fast bacilli were described histopathologically (Fig 4). Nucleic acid amplification test results of biopsy specimens and sputum samples were negative for MTB complex; in addition, cultures failed to detect mycobacteria. Polymerase chain reaction from a paraffin-fixed histologic specimen gained by mediastinoscopy in March 1997 has been performed, but no mycobacterial DNA sequence could be detected.

Sensitivity testing of the *M avium* strain showed resistance to all first-line drugs. After the results of combination testing were analyzed, therapy with rifabutin, 300 mg qd; clarithromycin, 500 mg bid; and prothionamide, the N-propiol derivative of ethionamide, 500 mg bid (later substituted by ethambutol), was introduced. After 6 weeks of modified treatment, chest radiograph showed marked improvement, and the size of the mediastinal mass as well as that of the pulmonary nodule decreased continuously (Fig 5). Clinical symptoms had already disappeared.
in October 1997, and therapy had been stopped in October 1998. Corticosteroids have never been prescribed for the patient.

**DISCUSSION**

We report a case of mycobacterial mediastinal lymphadenopathy caused by an infection with MAC in an immunocompetent, HIV-seronegative Turkish woman, a setting that, to our knowledge, has not been published before. The main differential diagnosis of course is infection by MTB, which usually is thought to cause mediastinal lymphadenopathy, revealing typical findings in chest CT and histologic examination of biopsy specimens. As our patient had a positive tuberculin skin test result, the diagnosis of TB seemed rather convincing.

But there are several aspects pointing to another etiologic agent, namely MAC:
- MTB has never been isolated, and we have not been successful in demonstrating DNA of MTB in any specimen.
- MAC has been isolated twice from needle-aspiration specimens of an enlarged retroclavicular lymph node.
- Lymphadenopathy by MTB is described to respond to antituberculous therapy very well, and even short...
course therapy is recommended, but our patient has been treated for about 8 months for TB and at least for 6 months using regimens containing isoniazid and rifampicin without any improvement.

- Already 6 weeks after the initiation of therapy with rifabutin, clarithromycin, and protonamide (later ethambutol), regression of the mediastinal mass could be described.
- After 6 months of antituberculous therapy, a nodular lesion persisted in the upper lobe of the right lung, pointing to a nontuberculous etiology. As pulmonary biopsy revealed abortive granuloma, there is good reason to believe in mycobacteria as the inducing pathogen. Pulmonary lesions disappeared after therapy for MAC disease.

**CONCLUSION**

In otherwise healthy adults, MAC (and maybe other NTM) may cause lymphadenopathies of the mediastinum, a site of disease being more typical for infections by MTB. In lymphadenopathy at any site that shows typical histopathologic features of TB and does not adequately respond to antituberculous therapy, NTM should be thought of as the etiologic agent. Before initiating antituberculous or other antimycobacterial therapy, definitive attempts should be made to establish a bacteriologic diagnosis.

**REFERENCES**


**Saphenous Vein Graft Infection**

**A Fatal Complication of Postoperative Mediastinitis**

Hasan B. Alam, MD; Christopher Kowalski, MD; and George A. Sample, MD, FCCP

Infection and erosion of the saphenous vein graft with mediastinal hemorrhage is a rare but highly lethal complication of cardiac surgery. This is associated with a mortality rate of 50%. We present a patient who died during the postoperative period due to this complication.

*(CHEST 1999; 116:1816–1818)*

**Key words:** coronary artery bypass grafting; graft infection; hemorrhage; mediastinitis
Mediastinitis after cardiac surgery continues to represent a major complication associated with extremely high morbidity and cost. The incidence varies between 1% and 2.8% in large series, depending on the risk factors and the nature of the operation. However, fatal hemorrhage as a result of mediastinal infection is rare. We present a case of mediastinitis complicated by profuse hemorrhaging from an infected saphenous vein graft.

**CASE REPORT**

The patient is a 72-year-old white man with a medical history significant for insulin-dependent diabetes, hypertension, and coronary artery disease. He had undergone coronary artery bypass grafting 13 years before. He presented this time with recurrent chest pain. On this admission, he underwent cardiac catheterization with angioplasty and stenting of the bypass grafts. Due to persistent symptoms, he subsequently underwent repeat coronary artery bypass surgery. Two saphenous vein grafts and a left internal mammary artery graft were used to bypass the posterior descending, obtuse marginal, and left anterior descending arteries, respectively. There were no intraoperative or immediate postoperative complications, and the patient was successfully extubated. On postoperative day 6, he had a transfusion reaction requiring steroids and ventilatory support. On postoperative day 8, while still receiving mechanical ventilation, he developed purulent drainage, which had grown *Staphylococcus aureus*, from the sternal incision. The patient began receiving IV vancomycin and was taken to the operating room the same day by the plastic surgery team (in consultation with the cardiac surgeon) for debridement of the necrotic sternal bone, removal of the sternal wires, and sternal wound irrigation. The infection involved the skin, subcutaneous tissue, and the sternal bone. There was purulent material under the skin incision that extended through the sternal bone closure. The bone showed areas of early osteomyelitis and necrosis. There was some extension into the superficial retrosternal space, but the pericardial space and deeper mediastinal structures were not involved. The mediastinal wound was left open and was packed with a saline solution-soaked sterile dressing. This dressing was changed in a sterile fashion by the plastic surgeon daily. The patient returned to the operating room for debridement and irrigation 2 days later. This time only fibrous exudate was noted in the wound with no involvement of the deeper mediastinal structures, coronary grafts and the suture lines. On postoperative day 12, the wound was closed using bilateral pectoralis major and right rectus abdominus muscle flaps. No signs of any active infection were noted at the time of the flap closure. On postoperative day 17, the patient developed a massive mediastinal hemorrhage associated with cardiovascular collapse. This hemorrhage presented as a rapidly expanding hematoma under the sternal flaps and as a hidden bright red bleeding through the previous mediastinal drainage tube tract. An emergent sternotomy was performed, and an advanced cardiac life support protocol was carried out. However, we were unable to resuscitate the patient. At the time of the sternotomy, a large amount (approximately 3 L) of fresh blood was found in the mediastinum, but the source of bleeding could not be clearly identified. An autopsy was performed that revealed focal erosion of the mid portion of the saphenous vein bypass graft (to the obtuse marginal artery) associated with purulent pericarditis. There were no ligated branch points in the vein graft at that site, and there was no operative trauma to the area during the wound debridement procedures or during the emergent sternotomy. Two independent pathologists, one from the Washington Hospital Center and one from the Armed Forces Institute of Pathology (both in Washington, DC) reviewed the autopsy findings. They concluded that the graft erosion was a result of the surrounding purulent infection.

**DISCUSSION**

Mediastinitis after sternotomy is a serious complication that affects between 1% and 2.8% of cardiac surgery patients in most of the larger series, with an overall mortality rate between 25% and 52%. The modern management of deep sternal infections with early, aggressive debridement and liberal use of muscle flap closure is thought to be responsible for the improved outcome rate reported in a recent study. A multicenter prospective trial established independent risk factors that increased the incidence of sternal infections. They included the following: obesity, coronary artery bypass grafting, reoperation, and postoperative inotropic support. Similarly, risk factors for mortality in patients who develop mediastinitis have been studied and include the following, among others: bacteremia, use of an intra-aortic balloon pump, advanced age, and prolonged mechanical ventilation. The vast majority of the deaths in these patients are secondary to sepsis and multiple organ failure. Postoperative hemorrhage remains a rare complication of mediastinitis. The possible mechanisms by which secondary hemorrhage may develop following open management of mediastinitis (debridement without flap closure) include the following: direct extension of the infection to the suture line, laceration of the myocardium by the jagged sternal edges, and intrapleural pressure forcing the heart against the open sternotomy incision. An early muscle flap closure of the sternotomy site offers protection against all of these mechanisms. The common sites of bleeding are the left heart (mostly left ventricle and occasionally the atrium) and aorta. The saphenous vein bypass grafts are an extremely rare source of bleeding, as described by Par- tanen et al. These authors reported three cases of mediastinal hemorrhage. One patient had an erosion of saphenous vein bypass graft by an irrigation catheter. This patient survived ligation of the graft and omental flap closure of the mediastinum. The other two patients had erosions of the right ventricle and the aorta.

We conducted a literature search using the MEDLINE database to identify all cases of mediastinal hemorrhage from saphenous vein grafts in the setting of postoperative infection. Only cases in which the source of bleeding was clearly described were included. Including our own case report, the literature search identified only six patients with this complication. The mortality rate was 50%. Of the three survivors, two required operative control of hemorrhaging with suture ligation of the graft. The third patient was found to have a bleeding pseudoaneurysm of the vein graft that was successfully obliterated by coil embolization during
angiography. Another patient identified during this search presented with hemoptysis instead of mediastinal hemorrhage. This patient’s coronary artery bypass surgery also was followed by protracted mediastinal infection, and a workup revealed a pseudoaneurysm of the bypass graft eroding into a segmental bronchus. A lobectomy and ligation of the graft was successful in controlling the bleeding.10

CONCLUSION

Infection and erosion of the saphenous vein graft with a mediastinal hemorrhage is a rare but highly lethal complication of cardiac surgery. Our review of the literature also suggests that hemorrhagic complications may be associated with an inability to control the local infection, leaving the mediastinum open for a prolonged period following the drainage of infection and frequent operative debridements. Our current policy in patients with postoperative mediastinitis is early debridement, the shortest possible duration of open treatment with early muscle flap closure, and 6 weeks of antibiotic treatment. However, this case is an example of a fatal complication despite aggressive treatment of the mediastinal infection. We recommend early mediastinal reexploration in high-risk patients who have signs of hemodynamic instability or unexplained falls in their hematocrit.

REFERENCES


Successful Treatment of Prosthetic Aortic Valve Mucormycosis*

Angel Sanchez-Recale, MD; Jose L. Merino, MD; Francisco Dominguez, MD; Isabel Mate, MD; Jose L. Larrea, MD; and Jose A. Sobrino, MD

Mucor endocarditis after cardiovascular surgery is rare and usually fatal. We report the first known case of prosthetic aortic valve mucormycosis in a patient without predisposing risk factors who was successfully treated using a combination of early antifungal drug therapy and surgical removal of infected material. (CHEST 1999; 116:1818–1820)

Key words: amphotericin; mucormycosis; prosthetic aortic valve

Primary cardiovascular involvement in mucormycosis is rare and typically leads to death in the short term. This has been reported to be associated with immunosuppression or prolonged antibiotic therapy. We report on a patient without risk factors and with mucor prosthetic valve endocarditis shortly after aortic valve replacement. The patient received therapy with antifungal drugs for 7 days followed by surgery, and no recurrence was evident at follow-up.

CASE REPORT

A 60-year-old man underwent aortic valve replacement with a mechanical prosthesis because of degenerative aortic valve disease. Perfusion and ischemic times were 65 min and 35 min, respectively. Cefazolin and tobramycin prophylaxis against infection was administered during the first 2 postoperative days. The postoperative outcome was unremarkable. Six weeks after discharge, the patient was readmitted due to clinical deterioration, fever, and chills. An early prosthetic valve endocarditis was suspected, and the patient was empirically treated with vancomycin, gentamycin, and rifampicin without any clinical improvement. Transesophageal echocardiography showed a paraaortic abscess and a prosthetic vegetant mass (Fig 1). There was significant transvalvular flow stenosis (mean gradient, 70 mm Hg) with no regurgitation that was partially relieved (mean gradient, 45 mm Hg) following vegetation embolization (Fig 2) 1 week after admission. Left inferior limb ischemia, due to embolization, led to vascular surgery and microbiological examination of the embolus, which demonstrated hypheae. The antibiotic therapy was changed to United States Pharmacopoeia amphotericin B, 300 mg/d IV, and itraconazol, 400 mg/d orally. Two days later, he had no fever, clinical improvement was evident, and prosthetic replacement was postponed for 1 week. At surgery, several vegetations (about 1 cm in length) and an abscess were found in the aortic aspect of the aortic valve and in the aortic-mitral intervalvular fibrosa, respectively. Mucor species were demonstrated in the culture of the embolic material and by valvular

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pathologic examination. After surgery, amphotericin and itraconazole treatment were continued for 6 and 8 weeks, respectively. The patient remains asymptomatic and without clinical, analytical, or echocardiography evidence of infectious recurrence after 1 year follow-up.

**COMMENT**

Mucormycosis after cardiovascular surgery almost always results in death. It is usually associated with immunosuppression secondary to severe concomitant diseases, or prolonged therapy with steroids or broad spectrum antibiotics.1-6 Interestingly, our patient showed no concomitant diseases and received prophylactic antibiotic therapy for only 2 days.

Therapy of cardiovascular mucormycosis is controversial. Combined treatment with surgery and amphotericin is the most accepted strategy. However, the correct duration of antifungal drug therapy, both before and after surgery, is not well established.2,4 To our knowledge, there are six reported patients with mucormycosis after cardiovascular surgery.1-6 Three of them were treated with urgent cardiovascular surgery after the etiologic diagnosis was established and followed by a 5-week course of amphotericin, and two of them survived.2,4 The remainder died of fungal sepsis, and the etiologic diagnosis was first suspected at necropsy.1,3,5,6 In our patient, antifungal drug therapy was associated with significant clinical improvement. For this reason, it was decided to maintain this therapy for at least 1 week before surgery in order to reduce the potential infectious load. The outcome of our patient, together with previous experience, underlines the importance of antifungal drug therapy and suggests that it should be started before surgery whenever the clinical condition allows.

**Figure 1.** Transesophageal echocardiography: (left, A) basal short-axis view in the transverse plane showing a large aortic periprosthetic abscess (black arrows); (right, B) longitudinal axis showing a vegetation (white arrow) and abscess (black arrow). LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle; AO = aorta.

**Figure 2.** Aortic continuous-wave Doppler echocardiography from the transesophageal transgastric view before (top, A) and after (bottom, B) vegetation embolization. Note the significant decrease in aortic flow velocity: 5.5 m/s (top, A) vs 4.5 m/s (bottom, B).
Can Pleural Effusions Cause Cardiac Tamponade?*

Hasan B. Alam, MD; Adam Levetit, MD; Robert Molyneaux, PA-C; Paul Davidson, PA-C; and George A. Sample, MD, FCCP

Pleural effusion(s) can increase the pressure of an otherwise insignificant pericardial effusion to a degree that can result in cardiac tamponade. The case histories presented here illustrate the importance of recognizing this phenomenon and altering our treatment algorithm to drain the pleural effusions instead of the pericardial collections.

(CHEST 1999; 116:1820–1822)

Key words: cardiac tamponade; pericardial effusion; pleural effusion

Abbreviations: CI = cardiac index; PCWP = pulmonary capillary wedge pressure; POD = postoperative day; RVDC = right ventricular diastolic collapse

Cardiac tamponade is a life-threatening clinical syndrome that is caused by the accumulation of pericardial fluid under pressure. Animal studies have demonstrated that large pleural effusions can raise the pressure in an otherwise insignificant pericardial effusion to a degree that is sufficient to produce right ventricular diastolic collapse (RVDC).1 However, clinical cases confirming this phenomenon have rarely been reported.2,3 We present three surgical patients with pleural effusion(s) who, instead of the typical respiratory symptoms, developed a clinical picture of cardiac tamponade. The pathophysiologic mechanisms that are responsible for this event and the therapeutic implications are discussed.

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Figure 1. Chest radiograph showing left-sided pleural effusion (case 1).
subsequently underwent four-vessel coronary artery bypass graft surgery. His initial postoperative cardiac index (CI) was 1.6 L/min/m², which required dobutamine drip at 10 μg/kg/min and epinephrine at 2 μg/min. He was successfully weaned off epinephrine on POD 1. Over the next few days, the dobutamine could not be reduced due to a fixed CI of 2.1 L/min/m², with a pulmonary capillary wedge pressure (PCWP) of 16 to 18 mm Hg, a central venous pressure of 17 mm Hg, and a mixed venous oxygen saturation between 40% and 45%. On POD 6, chest radiographs showed moderate bilateral pleural effusions (Fig 3). A two-dimensional echocardiogram revealed inferior wall akinesis, decreased right ventricular function, and a left ventricular ejection fraction of 50%. There was only minimal posterior pericardial effusion. A right thoracentesis was performed with drainage of 600 mL of thick bloody fluid. There was a dramatic improvement in the hemodynamic status of the patient, with a CI of 2.7 to 2.9 L/min/m² and mixed venous oxygen saturation of 70%. The dobutamine drip was easily discontinued over the next 6 hours, and he was transferred to the step-down unit the next day. He was finally discharged to home on POD 12 in a stable condition.

Case 3

A 77-year-old man was admitted for intractable angina and mitral valve insufficiency. His medical history was significant for class III congestive heart failure, hypertension, chronic atrial fibrillation, and arrhythmias requiring insertion of a permanent pacemaker. A cardiac catheterization on admission revealed 70% and 100% occlusions of the left anterior descending and right circumflex arteries, respectively. Two-vessel coronary artery bypass graft surgery using saphenous veins and a mitral valve repair was performed. Postoperatively, the patient had low cardiac output that required inotropic support (dobutamine, 5 μg/kg/min, and epinephrine, 3 to 5 μg/min). On POD 2, 10 hours after stopping the dobutamine drip, the CI dropped from 2.4 to 1.8 L/min/m², the central venous pressure increased from 6 to 12 mm Hg to 12 to 20 mm Hg, and the PCWP increased from 12 to 16 mm Hg to 20 to 25 mm Hg. The CI failed to improve despite the addition of afterload reducers (captopril) and aggressive diuresis. The dobutamine drip was restarted at 5 μg/kg/min, and epinephrine was increased to 6 μg/min. A chest radiograph at this time showed bilateral pleural effusions (Fig 4). On POD 4, a decision was made to perform left thoracentesis that yielded 500 mL of bloody fluid. Immediately following the procedure, the CI improved to 2.7 L/min/m², PCWP decreased to 12 mm Hg, and the inotropic support was easily withdrawn over the next 6 hours. The patient still had dyspnea, but this resolved after right thoracentesis (900 mL) was performed. He was finally discharged to home on POD 13.

Discussion

Cardiac tamponade is a clinical syndrome, and its presentation can range from a minimally symptomatic pericardial effusion to a state of complete cardiovascular decompensation. The onset of RVDC during early diastole identifies a point in the progression of this syndrome when the intrapericardial (extracardiac) pressure exceeds right ventricular diastolic pressure. RVDC is a sensitive and
specific indicator for the early detection of hemodynamically important pericardial effusions. However, a similar clinical and echocardiographic picture can be seen when pressures from pleural effusions are transmitted to the pericardial space. This has been demonstrated in a canine model, where infusion of saline solution in the pleural spaces (with minimal pericardial effusion) resulted in a linear increase in the intrapericardial pressure, which in turn caused RVDC and a tamponade-like physiology.1 Interestingly, the same intrapericardial pressure was better tolerated when it was caused by pleural effusions than when it was caused by increased pericardial fluid alone.1

Only five cases of pleural effusions that caused hemodynamically significant cardiac tamponade or just an echocardiographic evidence of right atrial or ventricular collapse (with no hemodynamic compromise) have been reported in the literature. This phenomenon has not previously been reported in early post-cardiac surgery patients. We have also noted significant differences in the clinical presentations of post-cardiac surgery patients as compared to the patients in the medical literature:

1. Postoperative patients do not require large-sized pleural effusions to cause hemodynamic compromise. Two of our patients had small to moderate-sized effusions (500 mL and 600 mL). Whether this effect is due to the different nature of the effusion (blood clots) or to a poor right ventricular reserve in this group of patients is unclear.

2. Secondly, because of the postoperative mediastinal changes, a two-dimensional echocardiogram cannot be relied on completely to rule out cardiac tamponade. Although it was not performed in these patients, transesophageal echocardiography appears to be a better choice.

Based on our experience, we believe that an increased intrapleural pressure is transmitted to the pericardial space. This can result in impaired cardiac filling and a tamponade-type physiology. However, this phenomenon is rare enough to pose a diagnostic challenge and can lead to misdiagnosis of an otherwise insignificant pericardial effusion. Once recognized, we recommend that thoracentesis followed by reevaluation should precede an attempt at pericardial drainage.

REFERENCES

Pine Oil Ingestion*
A Common Cause of Poisoning

James A. Welker, DO; and Gary P. Zaloga, MD, FCCP

Pine oil is a common component of household cleaning solutions. We present the case of an elderly woman with dementia who ingested a household cleaning solution that contained pine oil and review the treatment of pine oil ingestion. The patient developed CNS depression and respiratory failure that required intubation and mechanical ventilation. A chest radiograph revealed diffuse alveolar interstitial infiltrates consistent with pneumonitis. The patient improved with supportive care. However, she developed nosocomial pneumonia, sepsis, and multiple organ failure and subsequently died. This case is illustrative of the increased risk for ingestion of toxic household compounds in the growing population of elderly and demented individuals, who are being cared for in the home. Pine oil ingestions are one of the most common accidental ingestions encountered in clinical practice. Clinical features of ingestion include depressed mentation, respiratory failure, and GI dysfunction. The treatment is supportive, and the ingestions are rarely fatal.

(CHEST 1999; 116:1822–1826)

Key words: dementia; elderly; hydrocarbons; pine oil; pneumonia; poisoning; respiratory failure

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of readily available compounds and an increasing population of elderly and demented individuals makes encounters between the two likely.

In 1997, the poison control center registry (United States) reported 10,232 ingestions of solutions containing pine oil. The true incidence of ingestions (since many are unreported) is likely to be much greater. Although many pine oil ingestions are not lethal, ingestions still represent an important health hazard. The goals of this report are to increase the awareness of ingestions of pine oil and other readily available household toxins, to review the clinical presentation of pine oil ingestion, and to discuss the treatment of this type of poisoning.

**Case Report**

An 88-year-old woman with a history of Alzheimer’s disease who was living at home with her grandson presented to the emergency department following the ingestion of approximately 10 oz of a cleaning solution containing pine oil (Pine-Sol; Clorox Company, Oakland, CA). She ingested the solution when a bottle was left unattended for a short period of time (approximately 5 min) during bathroom cleaning. Functionally, the patient was capable of dressing herself, feeding herself, and ambulating about the home. Mentally, the patient was disoriented, incapable of complex calculations, unable to remember recent events, and incapable of proper interpretation of situations. She could follow simple commands and carry on conversations. The patient had no other medical problems, took no medications, and had no known allergies.

The patient was found in the bathroom in a state of confusion that exceeded her usual state of dementia. Adjacent to her was an empty bottle of pine oil cleaning solution, which earlier had contained approximately 10 oz of cleaning fluid. The smell of pine oil was noticed on her breath, and the family called emergency medical services. On arrival at her home, the emergency medical services personnel found the patient to be unresponsive to voice commands and to painful stimuli and found her respirations to be depressed. The patient was ventilated and oxygenated via a face mask and was transported to the emergency department.

On initial examination in the emergency department, the patient was unresponsive to voice commands and to painful stimuli, and had inadequate respirations. She was intubated and ventilated. Measurement of vital signs revealed a BP of 100/45 mm Hg and a heart rate of 96 beats/min. The patient was transported to the ICU and began receiving mechanical ventilation. On arrival in the ICU, the patient’s BP had decreased to 40/20 mm Hg, heart rate was 95 beats/min, and temperature (rectal) was 35°C. The patient was administered an IV saline solution and was begun on a dopamine infusion, resulting in an improvement in BP to 90/40 mm Hg. Physical examination revealed the patient to be unresponsive to voice commands and to painful stimuli. Her pupils were at midposition and were reactive to light, corneal response was present, and gag reflex was intact. Deep tendon reflexes were slightly diminished but symmetrical. There was no evidence of head or other bodily trauma.

The remainder of her examination was significant for the smell of pine oil on the breath and scattered rhonchi on chest examination. The patient was rewarmed with a heating blanket. Initial laboratory data are presented in Table 1. An arterial blood gas measurement while the patient was receiving 100% oxygen revealed the following: pH, 7.30; PaO₂, 44 mm Hg; PaCO₂, 413 mm Hg; tidal volume, 450 mL; respiratory rate, 12 breaths/min; and positive end-expiratory pressure, 5 cm H₂O. Her inspired oxygen concentration level was decreased to 40%, with maintenance of oxygen saturation by pulse oximetry > 90%. A chest radiograph revealed a right lower lobe infiltrate that was felt to be secondary to aspiration.

The patient was administered activated charcoal via nasogastric tube, subcutaneous vitamin K, and IV potassium, and was maintained on an IV saline solution and a dopamine infusion. Her ventilatory depression was supported with mechanical ventilation. The dopamine was tapered and discontinued over 18 h, and the patient maintained a BP > 100/50 mm Hg. The patient’s serum bicarbonate level normalized over the first 24 h of ICU care, and her anion gap decreased from 13 to 5 mEq/L. Creatinine level decreased to 0.8 mg/dL.

By the second day in the ICU, the patient was alert, following simple commands, and breathing spontaneously. Her chest radiograph revealed mild pulmonary vascular congestion with resolution of the right lower lobe infiltrate. The patient was successfully extubated. She developed rapid atrial fibrillation, which was controlled with IV diltiazem. Her family felt that she was functioning at her baseline mental status. Unfortunately, over the next 8 h, the patient developed increasing respiratory distress (rapid ventilations) associated with hypoxemia and a respiratory acidosis. She was reintubated and began receiving mechanical ventilation again. The patient’s BP was 110/60 mm Hg, heart rate was 130 beats/min, respiratory rate was 25 breaths/min, and temperature was 37.2°C. A chest radiograph revealed worsening diffuse pulmonary infiltrates consistent with diffuse lung injury, despite a negative fluid balance of 650 mL. However, the patient’s PaO₂ level was 443 mm Hg while receiving 100% oxygen. The possibility of sepsis with diffuse capillary leak was considered. Blood, urine, and suctioned pulmonary secretions were sent for culturing, and the patient was started on empiric antibiotics (pipercillin and tazobactam). Feedings through an enteral tube were begun.

By the fourth day in the ICU, the patient continued to require mechanical ventilation. Her oxygen saturation, as measured by pulse oximetry, was 90%. A chest radiograph revealed a right lower lobe infiltrate that was felt to be secondary to aspiration.

![Table 1—Admission Laboratory Data*](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21934/)

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Data</th>
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<tbody>
<tr>
<td>Sodium</td>
<td>145 mEq/L</td>
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<tr>
<td>Potassium</td>
<td>3.4 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>115 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>17 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>20 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.6 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>171 mg/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>7.9 mg/dL</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.4 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>4.6 mg/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>35%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.1 g/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>12,900 cells/µL</td>
</tr>
<tr>
<td>Platelets</td>
<td>197,000 cells/µL</td>
</tr>
<tr>
<td>PT</td>
<td>16 s</td>
</tr>
<tr>
<td>PTT</td>
<td>29 s</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.9 mg/dL</td>
</tr>
<tr>
<td>Alkaline phospha-</td>
<td>83 IU/L</td>
</tr>
<tr>
<td>tase</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>47 IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>12 IU/L</td>
</tr>
<tr>
<td>LDH</td>
<td>263 IU/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.6 g/dL</td>
</tr>
</tbody>
</table>

*PT = prothrombim; PTT = partial thromboplastin time; AST = serum aspartate aminotransferase; ALT = serum alanine aminotransferase; LDH = lactate dehydrogenase.
substances) accounted for 66,000 toxic exposures in 1997. Selected Reports

...demented patients. Of all toxic exposures in 1997, 88.1% solutions arise in the growing population of elderly and (Table 2). Particular concerns about ingestion of such
tures subsequently grew the results of bacterial cultures were pending. Pulmonary cul-
temperature was 38.6°C. The patient was treated empirically for rate was 100 beats/min, respiratory rate was 38 breaths/min, and
WBC count was 8,200 cells/...now revealed a new left upper lobe infiltrate, and testing of pulmonary secretions demonstrated many WBCs and Gram-negative bacteria. The patient was felt to have pneumonia. The WBC count was 8,200 cells/mL, BP was 100/50 mm Hg, heart rate was 100 beats/min, respiratory rate was 38 breaths/min, and temperature was 38.6°C. The patient was treated empirically for nosocomial pneumonia with vancomycin and ciprofloxacin while the results of bacterial cultures were pending. Pulmonary cultures subsequently grew Pseudomonas aeruginosa. Vancomycin was discontinued, and cefazidime was added to ciprofloxacin. The patient’s BP transiently decreased to 60/30 mm Hg but normalized with the infusion of an IV saline solution.

The patient’s subsequent course in the ICU was characterized by decreasing mental function (coma), progressive appearance of pulmonary infiltrates with worsening respiratory status, fever with rising WBC counts, and progressive renal failure. Bilirubin and liver enzymes were within normal ranges. However, the albumin level had decreased to 1.6 g/dL. The patient was thought to have pneumonia with sepsis and progressive multiple organ failure secondary to sepsis. The patient died on her 16th day in the ICU.

**DISCUSSION**

The patient in this report ingested Pine-Sol, a cleaning solution containing both pine oil and isopropyl alcohol. Although most ingestions of solutions containing pine oil are not lethal, our patient died from complications (ie, pneumonia, sepsis, and multiple organ failure) during treatment.

Pine oil ingestion is an alarmingly common event. Pine oil is among the most common ingredients found in household cleaning solutions and is readily available in stores. It is found in cleaning solutions such as Pine-Sol. In 1997, the poison control registry reported that cleaning solutions were the most common toxic substances ingested. Hydrocarbon ingestion (with pine oil and similar substances) accounted for 66,000 toxic exposures in 1997. Pine oil ingestion was only exceeded by gasoline ingestion (Table 2). Particular concerns about ingestion of such solutions arise in the growing population of elderly and demented patients. Of all toxic exposures in 1997, 88.1% took place in the patient’s own residence. While only approximately 5% occurred in the elderly, this number is anticipated to increase with the growing elderly population and the increased number of individuals being cared for in the home. Dementia renders many of these individuals incapable of distinguishing safe from unsafe household substances. Demented elderly individuals are much like children, who account for the majority of toxic ingestions. Common to both these populations is the physical ability to move about the home associated with reduced cognitive function.

Death following toxin ingestion is unusual and occurs in < 0.1% of reported cases. The elderly comprise 17.4% of these fatalities, and mortality from ingestion increases with age (Table 3). Thus, approximately 4% of patients ingesting a toxin who are > 60 years old are likely to die from the ingestion. Increased mortality in the elderly has many causes (Table 4). The elderly have a decreased volume of distribution for most toxins. In addition, hepatic metabolism and renal clearance of toxins are decreased in the elderly. As a result, the elderly are more likely to achieve higher circulating levels of toxins and to be exposed to such toxins for longer periods of time than their younger counterparts. Skin, mucous membranes, and the gut barrier are diminished in the elderly and may allow for increased absorption of toxins. Organ function is frequently diminished in the elderly, impairing their ability to heal and respond to exogenous insults. Immune function is depressed, and this limits the response to secondary infections acquired after toxin ingestion (ie, pneumonia or urinary tract infections).

Despite the frequency of cleaning solution ingestions, many medical practitioners are unaware of the components of such solutions and of the treatment for their ingestion. Thus, the goal of this report is to increase the awareness of such ingestions in both the young and old and to discuss the specific evaluation and treatment of pine oil intoxication.

**Table 2—1997 Hydrocarbon Exposures**

<table>
<thead>
<tr>
<th>Substance</th>
<th>No. of Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasoline</td>
<td>14,146</td>
</tr>
<tr>
<td>Pine oil</td>
<td>10,232</td>
</tr>
<tr>
<td>Fluorochlorocarbons/propellants</td>
<td>7,185</td>
</tr>
<tr>
<td>Mineral spirits/varsol</td>
<td>5,499</td>
</tr>
<tr>
<td>Lubricating oils/motor oil</td>
<td>4,421</td>
</tr>
<tr>
<td>Lighter fluid/naphtha</td>
<td>3,861</td>
</tr>
<tr>
<td>Toluene/xylene</td>
<td>2,201</td>
</tr>
<tr>
<td>Kerosene</td>
<td>1,732</td>
</tr>
<tr>
<td>Turpentine</td>
<td>1,139</td>
</tr>
<tr>
<td>Diesel fuel</td>
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</tr>
<tr>
<td>Halogenated hydrocarbon</td>
<td>965</td>
</tr>
<tr>
<td>Mineral seal oil</td>
<td>234</td>
</tr>
<tr>
<td>Benzene</td>
<td>174</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>43</td>
</tr>
</tbody>
</table>

*Data from Litovitz et al.

**Table 3—1997 Mortality Rates For Toxic Exposure**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Age Group, yr</th>
<th>No. of exposures</th>
<th>Total no. of mortalities</th>
<th>Mortality rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 19</td>
<td>19–60</td>
<td>&gt; 60</td>
<td></td>
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<tr>
<td>No. of exposures</td>
<td>1,467,524</td>
<td>550,717</td>
<td>81,191</td>
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<tr>
<td>Total no. of mortalities</td>
<td>77</td>
<td>572</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>3.7</td>
<td></td>
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</tbody>
</table>

*Data from Litovitz et al.
Pine oil and turpentine are distillates of pine wood. They are hydrocarbons similar in structure to petroleum distillates such as gasoline, mineral spirits, and mineral oil. While hydrocarbons may differ slightly in structure, the management of hydrocarbon ingestion is similar for all agents. However, agents may differ in their absorption characteristics and propensity to be aspirated. Pine oil has low viscosity and high volatility. Low viscosity contributes to aspiration, while high volatility contributes to inhalation injury and asphyxiation. Fortunately, the pine oil formulation used in cleaning solutions has additives that increase viscosity and decrease volatility, reducing its toxic risks.

Following ingestion or aspiration, pine oil is readily absorbed into the systemic circulation. A strong pine aroma may appear on the breath. This is a specific finding of ingestion, since few other toxins produce this smell. The smell even occurs following rectal administration of pine oil (ie, due to pulmonary elimination of the agent). The systemic effects of pine oil primarily involve the CNS, GI tract, and respiratory systems. The onset of effects occurs within 24 h of ingestion and usually resolves over the next 48 h. Within 90 min of clinically significant ingestions, most patients develop CNS depression and/or pneumonitis. The CNS effects include headache, ataxia, blurred vision, dizziness, lethargy, stupor, and coma. Injury to the lungs results in a pneumonitis that is characterized by diffuse pulmonary infiltrates. Patients may develop diffuse noncardiogenic pulmonary edema and may go on to develop ARDS, requiring intubation and mechanical ventilation. Bronchospasm also may occur. The injection of pine oil into animals resulted in pulmonary edema as its primary toxic effect. When orally administered to humans, there was associated oropharyngeal and GI toxicities characterized by sore throat, nausea, vomiting, abdominal pain, and diarrhea. Cardiovascular effects are characterized by bradycardia and hypotension. Metabolic acidosis is uncommon but, when present, is usually associated with acute renal failure. Fever may occur as a result of cytokine release from tissue injury or secondary infection. Ventricular arrhythmias are rare following pine oil intoxication, and catecholamines are recommended for cardiovascular support following fluid resuscitation. On the other hand, following ingestion of petroleum distillates, there is a sensitization of the myocardium to catecholamines that may predispose the patient to ventricular arrhythmias.

Death due to pine oil ingestion is rare and is reported to be approximately 0.02%. In 1997, there were only two deaths reported as a result of pine oil ingestion. Both were the result of attempted suicide. One death resulted from prehospital cardiac arrest. Most deaths from pine oil ingestion occur as a result of complications from supportive care of the patient. Death has been reported with as small an ingestion of pine oil as 8 oz.

The diagnosis of pine oil ingestion is based primarily on the history of exposure and the aroma of pine on the breath. It should be suspected in individuals presenting with unknown causes for stupor, coma, and respiratory depression or failure. There are no tests readily available to confirm the ingestion of pine oil. However, the alpha-terpineol found in pine oil can be measured by gas chromatography. Toxic levels have not been established and are not clinically useful. Initial evaluation should include hematocrit, WBC count, platelet count, prothrombin and partial thromboplastin time, serum electrolyte levels, glucose level, BUN and/or creatinine levels, renal and hepatic function studies, myoglobin, arterial blood gas measurements, and a drug screen. Patients should receive ECG monitoring and a chest radiograph.

Following diagnosis, disposition is based on the amount of pine oil ingested and the clinical condition of the patient. Patients who have ingested a small amount (< 6 oz of 20% solution) can be cared for at home if they are asymptomatic, have easy access to health care, and have someone at home to monitor them, and if there is no evidence of suicidal ideation or child abuse. Patients ingesting larger amounts should receive gastric decontamination with activated charcoal and should be observed for at least 6 h prior to discharge. If symptoms develop, patients should be hospitalized. Patients who have attempted suicide or who are suspected of pine oil substance abuse also require hospitalization. In one large series of 184 accidental hydrocarbon ingestions, none of the 120 patients who were asymptomatic at the initial presentation developed symptoms during follow-up.

The safety and benefit of gastric evacuation must be individualized. The low toxicity following absorption of hydrocarbons must be weighed against their high risk for aspiration and pulmonary toxicity. Clearly, there is little need to evacuate the stomach in patients who have vomited. In addition, vomiting should not be induced in patients with depressed mentation. Most studies do not favor the administration of ipecac to awake patients due to the risk of aspiration. In addition, the risk of aspiration may be increased due to development of CNS depression following the administration of ipecac. The use of gastric lavage is also controversial for the same reasons as gastric evacuation via vomiting. Lavage is safer in patients who are intubated but should only be considered in patients within 1 to 2 h of ingestion. Patients should receive activated charcoal to diminish absorption of the hydrocarbon from the GI tract.

Following GI decontamination, the treatment of pine oil ingestion is supportive. There is no specific antidote. Of primary importance is support of the respiratory and cardiovascular systems. Adequate cardiovascular support is mandatory to increase clearance of the toxin and to prevent secondary organ injuries. IV fluids are usually required to support intravascular volume, and vasopressor and inotropes may be required if hypotension and cardiac contractile failure occur. Intubation and mechanical ventilation may be required to maintain the airway, deliver oxygen, and support ventilation. Acute lung injury usually reaches its maximum over 72 h and improves over a few
days. Other supportive care includes nutrition support, prophylaxis against deep vein thrombosis, and maintenance of body temperature.

In summary, we present the case of a demented elderly patient who died following ingestion of a household cleaning solution that contained pine oil. We emphasize the common occurrence of such ingestions and discuss the specific physiologic effects of pine oil. Finally, we review the medical treatment for pine oil ingestion.

REFERENCES


**Exacerbation of Acute Pulmonary Edema During Assisted Mechanical Ventilation Using a Low-Tidal Volume, Lung-Protective Ventilator Strategy**

**Richard H. Kallet, MS, RRT; James A. Alonso, RRT; John M. Luce, MD, FCCP; and Michael A. Matthay, MD, FCCP**

**Study objectives:** To assess the magnitude of negative intrathoracic pressure development in a patient whose pulmonary edema acutely worsened immediately following the institution of a low-tidal volume (VT) strategy.

**Design:** Mechanical lung modeling of patient-ventilator interactions based on data from a case report.

**Setting:** Medical ICU and laboratory.

**Patient:** A patient with suspected ARDS and frank pulmonary edema.

**Interventions:** The patient’s pulmonary mechanics and spontaneous breathing pattern were measured. Samples of arterial blood and pulmonary edema fluid were obtained.

**Measurements:** A standard work-of-breathing lung model was used to mimic the ventilator settings, pulmonary mechanics, and spontaneous breathing pattern observed when pulmonary edema worsened. Comparison of the pulmonary edema fluid-to-plasma total protein concentration ratio was made.

**Results:** The patient’s spontaneous VT demand was greater than preset. The lung model revealed simulated intrathoracic pressure changes consistent with levels believed necessary to produce pulmonary edema during obstructed breathing. A high degree of imposed circuit-resistive work was found. The pulmonary edema fluid-to-plasma total protein concentration ratio was 0.47, which suggested a hydrostatic mechanism.

**Conclusion:** Ventilator adjustments that greatly increase negative intrathoracic pressure during the acute phase of ARDS may worsen pulmonary edema by increasing the transvascular pressure gradient. Therefore, whenever sedation cannot adequately suppress spontaneous breathing (and muscle relaxants are contraindicated), a low-VT strategy should be modified by using a pressure-regulated mode of ventilation, so that imposed circuit-resistive work does not contribute to the deterioration of the patient’s hemodynamic and respiratory status.

(CHEST 1999; 116:1826–1832)

**Key words:** acute pulmonary edema; assisted mechanical ventilation; lung model; lung-protective ventilation strategy; work of breathing

**Abbreviations:** AMV = assisted mechanical ventilation; CPAP = continuous positive airway pressure; Cts = respiratory system compliance; f = respiratory frequency; FIO2 = fraction of inspired oxygen; Paw = airway pressure; PEEP = positive end-expiratory pressure; ΔPt = maximal negative pressure developed in the thoracic compartment; FTP = pressure-time product; Spo2 = pulse oximeter estimate of arterial oxygen saturation; VC = volume control; VT = inspiratory flow rate; VT = tidal volume; WOB = work of breathing

S ome have suggested limiting tidal volume (VT) delivery to 6 mL/kg to avoid ventilator-induced lung injury in patients with ARDS. However, during assisted mech-

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Manuscript received February 17, 1999; revision accepted July 15, 1999.

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1826

Selected Reports
Intrathoracic pressure swings, associated with upper airway obstruction, may lead to hydrostatic pulmonary edema. Limiting pulmonary edema is another therapeutic objective in the treatment of ARDS. Damage to the capillary endothelium and alveolar epithelium in ARDS results in a permeability pulmonary edema from leakage of protein-rich plasma into the interstitial and alveolar spaces, thus reducing the protein osmotic gradient opposing edema formation. Subsequently, the magnitude of pulmonary edema formation depends primarily on the pressure gradient between the microvascular and perimicrovascular space. Excessive fluid administration in ARDS will aggravate pulmonary edema by increasing the pulmonary microvascular pressure and the transvascular pressure gradient. Likewise, high negative intrathoracic pressure swings, associated with upper airway obstruction, may lead to hydrostatic pulmonary edema by raising the transvascular pressure gradient.

During AMV in the volume control mode, VT and Vt settings that do not exceed patient VT and Vt demand results in imposed resistive work of breathing (WOB). This may mimic the cardiothoracic relationships present during partial upper airway obstruction, and result in a widening hydrostatic pressure gradient. Therefore, patient-ventilator dyssynchrony could aggravate pulmonary edema and gas exchange dysfunction in patients with ARDS. We encountered a patient with suspected ARDS in whom pulmonary edema was exacerbated by the institution of a low-Vt ventilation strategy during AMV. We measured the pulmonary mechanics and breathing pattern of the patient, and collected a sample of pulmonary edema fluid. By using a standard WOB lung model, we provide evidence that using a set VT slightly lower than patient demand during AMV can result in negative intrathoracic pressure swings sufficient to account for the exacerbation of pulmonary edema in this case.

**Case Report**

A 26-year-old man presented to the emergency department with severe tonsillitis and a temperature of 103°F. His previous medical history was significant only for adrenal insufficiency, for which he had been noncompliant with glucocorticoid therapy. The patient was in severe respiratory distress with a BP of 70/30 mm Hg (mean, 43 mm Hg). A chest radiograph revealed bilateral infiltrates. During emergent endotracheal intubation, the patient suffered cardiovascular collapse and required high doses of dopamine, phenylephrine, and epinephrine to maintain a systolic pressure of 70 mm Hg. Within a 1-h period, the patient also received 7 L of normal saline. Treatment with clindamycin and cefuroxime, in addition to dexamethasone and methylprednisolone, was initiated.

On arrival in the ICU, the patient was placed on a Dräger E-1 ventilator (Dräger, Inc/Critical Care Systems; Telford, PA) in the pressure control mode, with a fraction of inspired oxygen (FiO2) of 1.0 and a positive end-expiratory pressure (PEEP) of 10 cm H2O. Fentanyl, midazolam, and propofol drips were required to maintain patient-ventilator synchrony. A repeat chest radiograph showed progressive, diffuse bilateral infiltrates, and moderate amounts of pulmonary edema fluid were aspirated during suctioning. Diuretics were administered; fluid balance 10 h later was positive 5 L. By this time, the PaO2/FiO2 had improved from 141 to 322, respiratory system compliance (Crs) increased from 17 to 67 mL/cm H2O, and pulmonary edema fluid was no longer present in the endotracheal tube aspirate. The patient was ventilated in the volume control (VC) mode because of his improving pulmonary status.

However, the patient’s pulmonary status again deteriorated despite relative cardiovascular stability and no change in total fluid balance. The PaO2/FiO2 fell to 128, and Crs decreased to 36 mL/cm H2O. This coincided with a temperature elevation to 39°C. Concurrently, the patient was enrolled into the National Institutes of Health ARDS Network study of mechanical ventilation and randomized to a lung-protective strategy requiring use of the VC mode. An attempt was made to reduce the VT from 580 mL (11.1 mL/kg) to 450 mL (7.4 mL/kg). As the patient was triggering the ventilator, the respiratory frequency (f) was increased to 35 breaths/min and the peak VT was raised to 110 L/min to compensate for the decrease in VT. Trigger sensitivity was increased from −2 to −1 cm H2O.

Within 10 min, the pulse oximeter estimate of arterial oxygen saturation (SpO2) had decreased from 94% on an FIO2 of 0.50 and a PEEP of 10 cm H2O to 79% on an FIO2 of 0.70 and a PEEP of 10 cm H2O. The patient was triggering the ventilator at an f of 40 breaths/min, and dyssynchrony was apparent by a “saw-tooth” way pressure waveform (ie, during inspiration, the way pressure waveform had alternating negative deflections and positive inflections). Physical examination of the patient’s ventilatory pattern revealed pronounced inspiratory effort throughout the inspiratory phase. Despite 10 cm H2O PEEP, copious amounts of frothy, serosanguineous, pulmonary edema fluid suddenly filled the ventilator tubing. The heart rate rose to 128 beats/min, and the mean BP decreased to 56 mm Hg. The VT was increased to 600 at an f of 35 breaths/min. The patient quickly became synchronous with the ventilator and ceased triggering breaths within a few minutes. Within 10 min, the SpO2 rose to 100% and pulmonary edema fluid no longer accumulated in the ventilator tubing. A sample of pulmonary edema fluid was obtained using the method described below.

After 30 min of stabilization, the patient’s pulmonary mechanics and spontaneous breathing pattern were measured in order to assess the prudence of pursuing a lung-protective ventilator strategy. During a period of controlled ventilation, Crs was found to be 33 mL/cm H2O and the airways resistance was 13 cm H2O/L/s (measured at 60 L/min square-wave inspiratory flow pattern). The ventilator then was set at an FIO2 of 1.0 for 10 min, followed by a brief period (approximately 30 s) of continuous positive airway pressure (CPAP) at 10 cm H2O. The patient immediately began to breathe at an f of 35 breaths/min and a VT of 500 mL. The flow waveform graphics on the ventilator displayed the patient’s flow pattern as a fast rising half sine, with a peak VT of approximately 60 L/min and an inspiratory-expiratory ratio of approximately 1:1. SpO2 remained stable at 98% during spontaneous breathing.

The VC mode was reinitiated, and oxygenation remained stable. On the next day, the patient’s BP improved so that the level of sedation could be increased, allowing the VT to be decreased to 6 mL/kg without provoking spontaneous inspiratory efforts. Over the next several days, fluid intake and output were balanced, and the patient’s pulmonary gas exchange function markedly improved. The patient was weaned to CPAP 6 days after intubation, and was successfully extubated 2 days later. Hospital discharge followed 5 days later.
Pulmonary Edema Fluid Collection and Analysis

Once the patient’s SpO₂ had stabilized at a Vt of 600 mL, the airway was suctioned for pulmonary edema fluid using a previously described method. Arterial blood was obtained for comparison of pulmonary edema fluid protein concentration to plasma protein concentration. Measurement of the total protein in the pulmonary edema fluid and plasma samples was done by the biuret and bromocresol green dye-binding technique. Measurement of the total protein concentration in the edema fluid and the plasma correctly characterizes the type of pulmonary edema that results from either hydrostatic or increased permeability.

Lung Model Study

Because an esophageal balloon was not in place at the time pulmonary edema developed, we reproduced the ventilator settings, pulmonary mechanics, and spontaneous breathing pattern of the patient with a lung model to estimate the intrathoracic pressure swings that may have occurred. A standard WOB lung model based on the design of Katz and colleagues was used to recreate the observed patient-ventilator interactions (Fig 1). A Dräger E-1 ventilator and a Hamilton Veolar (Hamilton Medical, Inc; Reno, NV) ventilator were attached to separate ports of a Vent AID Training Test Lung (Michigan Instruments, Inc; Grand Rapids, MI). Two 32-cm long, 7.0-mm inner-diameter endotracheal tubes with 15-mm adapters at both ends were used to connect each ventilator to the lung compartment of the model (Fig 1). Both compartments were connected by a bar so that one ventilator acted as the patient’s inspiratory muscles and the other as the patient’s thorax. The positive pressure created during inflation of the muscle pump created a corresponding negative pressure in the thorax. The rate of change in pressure, flow, and displacement of the thoracic unit was used as an analog for the performance of the inspiratory muscles.

The Dräger E-1 was adjusted to the ventilator settings that were used when pulmonary edema developed. The Veolar ventilator was used to reproduce the spontaneous breathing pattern documented shortly after the incident of alveolar pulmonary edema. The Veolar was set in the VC mode incorporating a modified sine wave that approximated the inspiratory flow waveform and rise time percentages documented both in normal humans and in those with diseases characterized by increased elastic recoil. Measurements made from scalar tracings of the modified sine flow waveform revealed that peak Vt occurred at approximately 25% of the inspiratory phase. An inspiratory resistor (Rp5; Michigan Instruments, Inc; Grand Rapids, MI) was added to both endotracheal tubes in order to achieve an airways resistance of 13 cm H₂O/L/s (measured at 60 L/min square-wave inspiratory flow pattern). The f on the Veolar was set at 40 breaths/min with an inspiratory duty cycle of 0.40. Preset Vt was adjusted to create a Vt demand of 500 mL and a peak Vt of 60 L/min on the thoracic compartment. Inspiratory time was confirmed by measurement of the inspiratory flow profile from a calibrated scalar tracing. Both ventilators were set at a PEEP of 10 cm H₂O so that the end-expiratory compartment volumes were equal.

Changes in simulated thoracic pressure and airway pressure (Paw) were measured using an automated pulmonary mechanics monitor (Bicore CP-100; Allied Healthcare Products, Inc—Ventilation Products; Riverside, CA). Validation of this monitor has been previously documented. Changes in simulated thoracic pressure and airway pressure (Paw) were measured using an automated pulmonary mechanics monitor (Bicore CP-100; Allied Healthcare Products, Inc—Ventilation Products; Riverside, CA). Validation of this monitor has been previously documented. Changes in simulated thoracic pressure and airway pressure (Paw) were measured using an automated pulmonary mechanics monitor (Bicore CP-100; Allied Healthcare Products, Inc—Ventilation Products; Riverside, CA). Validation of this monitor has been previously documented. Changes in simulated thoracic pressure and airway pressure (Paw) were measured using an automated pulmonary mechanics monitor (Bicore CP-100; Allied Healthcare Products, Inc—Ventilation Products; Riverside, CA). Validation of this monitor has been previously documented. Changes in simulated thoracic pressure and airway pressure (Paw) were measured using an automated pulmonary mechanics monitor (Bicore CP-100; Allied Healthcare Products, Inc—Ventilation Products; Riverside, CA). Validation of this monitor has been previously documented. Changes in simulated thoracic pressure and airway pressure (Paw) were measured using an automated pulmonary mechanics monitor (Bicore CP-100; Allied Healthcare Products, Inc—Ventilation Products; Riverside, CA). Validation of this monitor has been previously documented.

The pulmonary mechanics monitor calculated Vt from flow and time measurements and excluded circuit compression volume. Because we were primarily interested in the effects of patient-ventilator interactions on intrathoracic pressure changes, we expressed WOB as the pressure-time product (PTP). The pulmonary mechanics monitor calculated PTP as the integral of the negative changes in Pt during inspiration, taking into account inspiratory time and assuming normal chest wall compliance. PTP, or peak inspiratory effort, was measured by the pulmonary mechanics monitor as the nega-
tive change in pressure from the end-expiratory pressure plateau to the minimum value. The data from 10 consecutive breaths were averaged and used for analysis.

**Results**

**Pulmonary Edema Fluid Analysis**

The pulmonary edema fluid-to-plasma total protein concentration ratio was 0.47. Initial ratios < 0.65 are characteristic of hydrostatic pulmonary edema, whereas initial ratios between 0.75 and 1.0 are characteristic of increased-permeability pulmonary edema.\(^{12}\) The pulmonary edema fluid-to-plasma total protein ratio found in this case was in the range recently reported during postobstructive pulmonary edema.\(^{10}\)

**Lung Model**

Re-creation of the patient-ventilator interactions with the lung model resulted in a mean \(\pm\) SD \(\Delta P\)it of 35 \(\pm\) 0 cm H\(_2\)O per breath with a PTP of 535 \(\pm\) 12 cm H\(_2\)O/s/min. The mean inspiratory pressure per breath (PTP \(\times f\)) was 12.4 \(\pm\) 0.3 cm H\(_2\)O. Inspection of the scalar Paw tracings revealed the same saw-tooth pattern seen during the episode of alveolar pulmonary edema (Fig 2). The contribution of imposed work from the inspiratory valve was assessed from measurements of the negative \(\Delta\) Paw and PTP taken at the wye-adapter.

These results were a \(\Delta\)Paw of 22 \(\pm\) 0 cm H\(_2\)O with an imposed PTP of 130.6 \(\pm\) 4.5 cm H\(_2\)O/s/min. To put this in perspective, a mean total PTP of 150 cm H\(_2\)O/L/s has been reported in patients recovering from acute respiratory failure and breathing on CPAP.\(^{18}\) An imposed PTP value that is 87% of the total value for patients being weaned from mechanical ventilation represents a high degree of imposed WOB.

**Discussion**

We have reported a case in which exacerbation of acute pulmonary edema coincided with the institution of a lung-protective strategy. The fact that pulmonary edema quickly appeared and resolved with the institution and removal of a low-Vt ventilation strategy led us to suspect that vigorous inspiratory efforts were responsible for the sudden deterioration in the patient’s cardiorespiratory status. This impression was supported by the fact that the patient had been consistently triggering the ventilator at a higher Vt for several hours prior to the event. During that time period, there was no pulmonary edema fluid in the tracheal aspirate, nor was there further deterioration in Cts (Cts, 39 mL/cm H\(_2\)O prior to the onset of pulmonary edema, and 24 mL/cm H\(_2\)O in the hours following the episode).

We recently demonstrated in a lung model that imposed resistive work in the VC mode increases exponentially when Vt demand equals or exceeds Vt delivery.\(^{4}\)

**Figure 2.** Scalar tracings of Vt (flow), Vt, Paw, and simulated intrathoracic pressure recorded from the lung model using the patient’s spontaneous breathing pattern and the ventilator settings measured around the time that pulmonary edema developed. The saw-tooth appearance of the Paw waveform reflects the following events: a represents the initial drop in Paw associated with simulated patient effort to trigger the ventilator into inspiration; b represents the rapid rise in Paw as ventilator Vt delivery exceeds simulated Vt demand; c represents a secondary drop in Paw as simulated patient effort continues after Vt delivery; and d represents the secondary rise in Paw with the cessation of simulated effort and the cycling of the ventilator into expiration. The pressure spike above PEEP reflects initial expiratory valve resistance at peak expiratory flow.
Conscious of this fact, we attempted to compensate by using a very high $V_t$ (110 L/min) and increasing the trigger sensitivity. However, respiratory distress and pulmonary edema developed despite the fact that the patient appeared capable of generating a spontaneous peak $V_t$ of only 60 L/min. We believe that if a patient’s $V_t$ demand is higher than preset $V_t$, then high initial peak $V_t$ delivery alone may not be sufficient to prevent respiratory distress because inspiratory effort will continue beyond the ventilator-delivered $V_t$. This point was illustrated in the lung model when the $V_t$ and $V_t$ waveforms for the ventilator and simulated patient are superimposed (Fig 3).

We reasoned that imposed resistive work from the inspiratory valve of the ventilator produces the same breathing conditions that occur during partial upper airway obstruction. There has been speculation regarding the transpulmonary pressure changes necessary to produce pulmonary edema during upper airway obstruction. Both Galvis et al. and Younker et al. speculated that negative pleural pressures of $\geq 30$ cm H$_2$O may occur during upper airway obstruction resulting in pulmonary edema. Newton-John reported mean, peak-negative, intratracheal pressure swings of 37 cm H$_2$O in an infant with severe croup. He believed that these negative pressure swings could account for at least the development of interstitial pulmonary edema. Stalcup and Mellins reported mean negative intraesophageal pressures of 29 cm H$_2$O during tidal breathing and 39 cm H$_2$O during forced inspiration in children with severe asthma. However, because of the emergent nature of upper airway obstruction, there have been no reports in the literature in which intrathoracic pressures have been measured under conditions severe enough to produce pulmonary edema. To address this, Loyd and colleagues measured lung lymph flow and lymph-to-plasma protein concentration ratio during resistive breathing in an animal model. Inspiratory resistive loads of 20 cm H$_2$O caused a decrease in mean central $P_{aw}$ of 12 cm H$_2$O. In normal sheep lungs,

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Scalar tracings of $V_t$, $V_t$, $P_{aw}$, and simulated intrathoracic pressure recorded from the lung model superimposing the simulated patient’s spontaneous breathing pattern (measured on CPAP on ventilator pattern in AMV in the VC mode). The $V_t$ waveforms show the continuation of simulated patient effort beyond ventilator $V_t$ delivery. The slope of the rise in ventilator delivered $V_t$ exceeds that of the simulated patient $V_t$ because of the higher peak $V_t$ and square-wave delivery pattern. However, by the end of inspiration, spontaneous $V_t$ exceeds the ventilator-delivered $V_t$. The saw-tooth appearance of the $P_{aw}$ waveform results from the interactions of $V_t$ and $V_t$ performance between the ventilator and simulated patient demand. The differences in $P_{aw}$ over the course of inspiration reflect the changing characteristics of imposed resistive work during AMV and the difference in trigger levels ($-1$ cm H$_2$O set during AMV and a built-in trigger level of $-0.2$ cm H$_2$O during CPAP). Note that the rapid rise in $P_{aw}$ above baseline after the onset of ventilator-delivered $V_t$ was not reflected in the pressure changes in the thoracic compartment. In addition, an intrathoracic pressure plateau below baseline is noted when $V_t$ demand continues past ventilator $V_t$ delivery.
this was enough to cause a twofold increase in lung lymph flow and a decrease in lymph-to-plasma protein concentration ratio. These results suggest that increasingly negative intrathoracic pressure resulting from mild obstructive breathing is sufficient to cause an increase in the transvascular hydrostatic pressure gradient with resulting fluid extravasation. Our lung model provided an approximation of the intrathoracic pressure swings that might have occurred during the development of pulmonary edema. Our results are similar to both the clinical and laboratory measurements of mean and peak transpulmonary pressure gradients suggested as being sufficient to produce fluid extravasation and pulmonary edema during obstructive breathing.

Our patient was more susceptible to developing pulmonary edema during a low-Vt ventilation strategy because of fluid overload, possible pulmonary hypertension from large infusions of phenylephrine and epinephrine, and possible sepsis-induced acute lung injury. As Stålup and Mellins observed, the effects of vigorous fluid therapy on transvascular hydrostatic pressure in the development of pulmonary edema can be potentiated by more negative pleural pressure swings.

The significance of this report is that careful assessment of a patient’s spontaneous Vt capacity must be taken into consideration before a low-Vt strategy is employed. This becomes especially important if high sedation or neuromuscular blocking agents cannot be used to suppress spontaneous breathing efforts. We refrained from increasing sedation and using neuromuscular blockage in our patient because of persistent hypotension (despite high-dose vasopressor support) and concurrent glucocorticoid therapy. In this situation, a low-Vt strategy using a pressure-regulated mode of ventilation may either have prevented or attenuated the exacerbation of pulmonary edema. Preliminary lung model results have demonstrated that both pressure-control ventilation and VC-autoflow ventilation reduce WOB compared with VC ventilation because of their ability to augment both Vt and Vt when patient demand for both increases. The ability of pressure-regulated modes to augment both Vt and Vt delivery reduces simulated negative intrathoracic pressure swings and, therefore, should reduce the pulmonary transvascular pressure gradient favoring pulmonary edema formation. Therefore, we recommend the use of a pressure-regulated mode of ventilation during use of a low-Vt strategy in ARDS when spontaneous breathing efforts cannot be adequately suppressed with sedation and neuromuscular blockade must be avoided.

The fact that gross pulmonary edema occurred in this case most likely resulted from the combination of acute lung injury, fluid overload, and probable pulmonary hypertension. However, this case serves as a salient reminder that spontaneous breathing efforts during ARDS may enhance pulmonary edema and worsen gas exchange. This deterioration may be mistakenly attributed to either fluid therapy or a worsening of the patient’s disease process. Therefore, spontaneous breathing efforts during mechanical ventilation in ARDS should be evaluated clinically in the same manner as fluid therapy, because both factors are important in determining the transvascular hydrostatic pressure gradient responsible for pulmonary edema.

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