findings of aortic insufficiency, has been confirmed only at autopsy or operation. In this case, M-mode echocardiography performed with two-dimensional guidance was of value in the preoperative diagnosis of disruption of the aortic valve. The combination of diastolic aortic fluttering, separation of the aortic cusps in diastole, and unusually wide excursion of the cusps in systole suggested the correct diagnosis. The absence of vegetations, aortic valve thickening, or aortic root dilatation helped to exclude infective endocarditis, rheumatic heart disease, and aortic dissection as causes of aortic valve disruption in this patient.

The presence at surgery of a valve, normal morphologically except for the torn cusp, supported the echocardiographic observations.

Of importance, there was a one-year interval between the occurrence of blunt chest trauma and the occurrence of symptoms and detection of aortic insufficiency. While in some cases, severe acute aortic insufficiency may occur immediately following trauma, a variable interval of weeks to years has been noted in others. One might speculate in cases where there is delay between trauma and onset of symptoms that an initially small silent tear of the cusp at its attachment to the valve ring progressively extends as the result of ordinary hemodynamic stresses. As the valve cusp becomes separated from its anular attachment, aortic insufficiency progresses with a compensatory increase in the force of ejection and consequent increased hemodynamic stresses to the valve cusp. Eventually, even the free margin of the valve might tear, similar to the shredding of the edge of a sail when detached from its lines in a strong wind. Symptomatic deterioration would occur when aortic regurgitation becomes severe enough to cause pulmonary congestion or decreased exertional tolerance.

In summary, traumatic disruption of the aortic valve may occur without prior valvar abnormalities and may become manifest months after the traumatic event. Echocardiography can be valuable in determining the etiology as well as in functional assessment of the patient.

REFERENCES


**Adult Respiratory Distress Syndrome following Thrombolytic Therapy for Pulmonary Embolism**

Thomas R. Martin, M.D.; Robert L. Sandblom, M.D., and Richard J. Johnson, M.D.

Pulmonary edema is rare in patients with pulmonary embolism and to our knowledge has not been described in association with thrombolytic therapy. We describe a patient with massive pulmonary embolism in whom the adult respiratory distress syndrome (ARDS) developed shortly after a course of streptokinase therapy. The possible association between streptokinase therapy for pulmonary embolism and ARDS should be recognized as streptokinase gains wider clinical use.

Streptokinase is recommended for thrombolytic therapy in patients with pulmonary embolism who deteriorate despite heparin treatment. Treatment with streptokinase leads to rapid resolution of pulmonary thrombi and improvement in pulmonary hemodynamics. Reported adverse effects include bleeding (5 to 25 percent), mild allergic reactions (15 percent), and fever (33 percent).

We describe a patient in whom the adult respiratory distress syndrome (ARDS) developed shortly after streptokinase therapy for acute massive pulmonary embolism. The temporal sequence and lack of any associated causes of ARDS suggest that thrombolytic therapy may have contributed to the pathogenesis of the pulmonary vascular injury.

**Case Report**

A 63-year-old woman was seen because of the acute onset of dyspnea. Eleven years earlier, she had been treated for Hodgkin's disease (2 A) with mantle irradiation. She was in good health until three months prior to admission, when she was hospitalized with back pain due to collapse of the sixth and ninth thoracic vertebrae. A closed needle biopsy revealed osteoporotic bone and was complicated by right lower extremity paralysis and hypesthesia below the ninth thoracic dermatome on the left side (Brown-Séquard syndrome).

Four weeks later, swelling of the right leg developed, followed by the acute onset of dyspnea, aphasia, and right-sided weakness.

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Table 1—Arterial Blood Gas Values

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Pre*</th>
<th>0</th>
<th>8</th>
<th>10</th>
<th>16</th>
<th>30</th>
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<tr>
<td>FIO₂</td>
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<td>(1.0)†</td>
<td>(1.0)‡</td>
<td>1.0</td>
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<td>1.0</td>
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<tr>
<td>PaO₂ mm Hg</td>
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<td>47</td>
<td>60</td>
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<td>45</td>
</tr>
<tr>
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<td>23</td>
<td>25</td>
<td>26</td>
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<td>30</td>
</tr>
<tr>
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<td>7.48</td>
<td>7.47</td>
<td>7.46</td>
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</tr>
<tr>
<td>Therapy</td>
<td>Heparin</td>
<td>Streptokinase</td>
<td>Heparin</td>
<td>Streptokinase</td>
<td>Heparin</td>
<td>Streptokinase</td>
</tr>
</tbody>
</table>

*Pre = values obtained when the patient was clinically stable six weeks prior to the current illness.
†FIO₂ = 1.0 by face mask. The patient was intubated and pulmonary angiography was performed between the eight-hour and ten-hour blood gas determinations.

Arterial blood gas measurements (ABC) were as follows: pH, 7.50; PaO₂, 47 mm Hg (FIO₂ = 0.21); and PaCO₂, 22 mm Hg. The chest roentgenogram showed right apical pleural thickening and an elevated right hemidiaphragm. Ventilation and perfusion lung scans showed matching nonsegmental defects in the right upper, right lower, and left lower lobes. The patient did not receive anticoagulants. Her dyspnea and right hemiparesis improved.

Three months later, she again had swelling of the right calf and thigh. Two days afterward, she suddenly became dyspneic, without chest pain or new neurologic symptoms. On examination, she was anxious and diaphoretic. Her blood pressure was 120/70 mm Hg, heart rate 120 beats/minute, the respiratory rate 36/minute, and she was afebrile. Breath sounds were reduced at the right lung base. The cardiac and venous pressure examination results were normal. The right leg was swollen but nontender. She was alert and oriented, but she could not speak in complete sentences. There was a right hemiparesis and sensory loss over the left abdomen and leg.

The hematocrit reading was 32 percent; the white blood cell count, 18,500/mm³; and the platelet count, 645,000/mm³. The prothrombin time was 12.5 seconds, and the partial thromboplastin time was 24 seconds. The arterial pH was 7.40, PaCO₂ 31 mm Hg, and PaO₂ 44 mm Hg on supplemental oxygen by nasal cannula at 6 L/min. ECG showed sinus tachycardia but was otherwise normal. The chest roentgenogram showed right apical capping, an elevated right hemidiaphragm, and clear lung fields.

Pulmonary embolism was suspected, and heparin was administered as an initial bolus of 7,500 units, followed by 1,000 units/hr as a continuous infusion. A radionuclide perfusion scan disclosed no perfusion to the left lower lobe and major segmental perfusion defects in the right lung. The patient remained alert, and her blood pressure was stable, but the hypoxemia worsened steadily (Table 1).

She was intubated without complication and mechanically ventilated. Pulmonary angiography demonstrated massive emboli occluding nearly every segmental pulmonary artery in the left lung, as well as multiple segmental arteries in the right upper and right lower lobes. The pulmonary arterial pressure during angiography was 22/15 mm Hg with a wedge pressure of 15 mm Hg. A repeated chest x-ray film showed no changes.

Streptokinase was administered with an initial dose of 250,000 units intravenously (IV) over 30 minutes and 100,000 units/hr for 14 hours; the heparin therapy was discontinued. She also received methylprednisolone, 1 g IV. The thrombin time was 65 seconds (normal, 14 to 24 seconds).

During streptokinase therapy, the PaO₂ initially improved (Table 1) but then deteriorated. The pulmonary artery pressure increased to 56/21 mm Hg, and static thoracic compliance fell steadily (Table 1). The pulmonary wedge pressure was low (11 mm Hg). Bilateral pulmonary infiltrates developed and progressed (Fig 1). A sputum Gram stain revealed few cells with scant mixed bacterial flora. Gentamicin and cefazolin were administered, but two blood cultures and a urine culture were sterile; the sputum grew only mixed flora. Positive end-expiratory pressure (up to 20 cm H₂O) did not improve her oxygenation. Two units of packed RBCs were administered, increasing the hematocrit reading to 38.4 percent. A repeated lung perfusion scan showed marked improvement 30 hours after initiating streptokinase. A small amount of radioactivity was also detected over the brain. Serial ECGs and serum myocardial enzymes were normal. Despite aggressive respiratory and hemodynamic support, the patient died on the third day.

At autopsy, the lungs were edematous and weighed 1,400 g. Small, recent and organizing thrombi were found within the central pulmonary arteries. Diffuse lung injury was present microscopically.

**Figure 1.** Chest roentgenograms before and after streptokinase therapy. Left, six hours after the onset of symptoms, during heparin therapy. Right, four hours after the completion of the streptokinase infusion.
with proteinaceous alveolar exudates and hyaline membranes (Fig 2). Increased numbers of alveolar and interstitial macrophages and granulocytes were present, and proliferation of type 2 pneumocytes was observed in some areas. Alveolar hemorrhage was absent. Stains for fungi, acid-fast organisms, bacteria, and Legionella were negative. A probe-patent foramen ovale was present in the heart, which was otherwise normal. There was an old infarct in the left internal capsule of the brain. No evidence of recurrent Hodgkin’s disease was found.

DISCUSSION

This patient had massive pulmonary embolism and did not improve with heparin therapy. Streptokinase therapy was associated with prompt improvement in arterial oxygenation and the radionuclide perfusion scan; however, 12 hours after streptokinase therapy was started, the clinical signs of ARDS developed. Sepsis and gastric aspiration were unlikely, and blood products were not administered until after the patient had deteriorated. Myocardial ischemia was not evident and the pulmonary artery wedge pressure was low. The pathologic features were consistent with a primary injury to the alveolar capillary barrier.

Pulmonary edema is rare after pulmonary thromboembolism and usually occurs in patients with increased vascular pressures due either to preexisting heart disease or to a severe reduction in the pulmonary vascular bed. In our patient, however, the clinical data and histopathology suggest that the primary pathogenetic mechanism was an increase in vascular permeability. Mediators such as serotonin, histamine, and prostaglandins may account for an immediate increase in permeability after experimental pulmonary emboli. Surfactant loss, occurring 24 hours or more following pulmonary emboli, has been implicated as a delayed cause of increased permeability.

In this patient, the clinical evidence of an increase in pulmonary capillary permeability began 16 to 20 hours after the clinical embolic episode, during the latter part of the streptokinase infusion. Two potential mechanisms may account for the pulmonary injury. First, pulmonary vascular permeability may have been altered by the generation of fibrinolytic products in the pulmonary circulation. Fibrin degradation by urokinase results in the formation of low molecular weight peptides, which increase vascular permeability and are chemotactic for granulocytes. Fragment D, a peptide product of fibrinolysis, can produce diffuse pulmonary injury which resembles human ARDS after IV infusion in rabbits. Saldeen has proposed that these peptides are the mediators of lung injury in the delayed microembolism syndrome.

Alternatively, streptokinase may have caused “reperfusion” edema, as described after pulmonary embolectomy. Granger et al have proposed that the mechanism for this injury involves vascular damage by oxygen radicals generated in the hypoxic vascular bed when oxygenation is restored.

While the etiology of the ARDS in this patient cannot be proved, the potential association between streptokinase therapy and ARDS should be recognized as streptokinase therapy gains wider clinical use.

REFERENCES