Acute Pulmonary Edema in the Absence of Left Ventricular Failure

By Edward A. Rittenhouse, M.D., and K. Alvin Merendino, M.D., Ph.D.

SUMMARY
Two patients have been observed to develop acute repetitive pulmonary edema in the absence of left ventricular failure as evidenced by a normal or near normal left atrial pressure recorded during these periods. Continuous monitoring of the left atrial pressure was made possible by a catheter inserted during open-heart surgery. Both patients suffered brain damage, presumably secondary to cerebral air embolism, and eventually succumbed.

Although the authors think that a causal relationship between cerebral damage and pulmonary edema best explains the mechanism in these two patients, this must remain conjectural. Neurogenic pulmonary edema, however, has been assumed to be secondary to elevated left atrial and left ventricular end-diastolic pressures. If a specific relation exists in these patients, the findings herein described strongly suggest that this may not be the mechanism.

Additional Indexing Words:
- Edemas of central origin
- Cerebral air embolism
- Aortic valve replacement
- Left atrial pressure
- Intracranial lesions
- Cardiopulmonary bypass
- Congestive heart failure
- Open-heart surgery

The occurrence of acute pulmonary edema can usually be attributed to left ventricular failure or overload as a result of hypervolemia, myocardial insufficiency, or valvular malfunction. Characteristically, there is elevation of left atrial and left ventricular end-diastolic pressure with pulmonary venous congestion and exudation of fluid into the alveoli. Recently, however, we experienced two patients who had fulminant pulmonary edema in the absence of a significant elevation in left atrial pressure. Both patients had undergone aortic valve replacement with the aid of total cardiopulmonary bypass. Another common factor was severe cerebral damage believed to have resulted from air embolism at the time of surgery.

Mechanisms of development of pulmonary edema without elevated pulmonary vascular pressure are poorly understood. Changes in colloidal osmotic pressure or local factors such as alterations in capillary permeability may be contributory in some cases. Pulmonary edema can also result from neurological lesions although concomitant left atrial and pulmonary artery pressures have not been previously measured clinically. Neurogenic pulmonary edema produced experimentally is usually associated with elevated left atrial and left ventricular end-diastolic pressure.

The precise events that led to the development of pulmonary edema in our two cases and their relation to the cerebral injury cannot be stated with certainty, but it seems unlikely that the mechanism was ventricular failure.

Report of Cases

Case 1
B. G., a 30-year-old man, had acute rheumatic fever as a child but remained asymptomatic until dyspnea and an irregular heart rhythm developed
in 1966. Physical examination, cardiac catheterization, and electrocardiographic findings were all consistent with moderately severe aortic and mitral regurgitation (72% calculated from catheterization data).

Replacement of the aortic valve with a homograft and a posteromedial mitral annuloplasty was performed under halothane anesthesia on March 17, 1967. Total cardiopulmonary bypass was achieved utilizing a roller pump and disk oxygenator primed with lactated Ringer's solution and blood in a ratio of seven to one. During this procedure the coronary arteries were intermittently perfused with blood at 6 C, and the left ventricle was decompressed with a catheter. After evacuation of air from the aortic root and defibrillation, a catheter† was inserted into the left atrium for continuous pressure monitoring.

Cardiovascular status was stable at the termination of the 3 hours of bypass but as preparations were being made for chest closure acute pulmonary edema suddenly developed. Pink, frothy fluid was obtained from the endotracheal tube, and rales were heard through an esophageal stethoscope. The patient was in atrial fibrillation, with a ventricular rate of 120. Initial treatment consisted of phlebotomy, hyperventilation with 50% oxygen and digoxin (0.5 mg intravenously). During this episode the mean left atrial pressure was 8 mm Hg and central venous pressure 12 mm Hg. Both pressure tracings had normal phasic contours. Pulmonary edema gradually subsided but recurred shortly after chest closure, again without significant elevation of left atrial pressure.

The patient was transferred to the intensive care unit and continued on positive-pressure ventilation utilizing the Bird respirator.

It became apparent shortly after surgery that cerebral damage had occurred during the operative procedure. The patient did not regain consciousness and responded poorly to external stimuli. The etiology of this coma was not entirely clear, but air embolism was thought to be the most likely explanation. There were no clinical signs of increased intracranial pressure or a focal brain lesion.

Four hours after the initial episode the patient again developed acute pulmonary edema. A chest roentgenogram at that time revealed marked bilateral pulmonary edema. He was treated with phlebotomy and 25 mg of ethacrynic acid† administered intravenously. Pink, frothy fluid continued to come from the endotracheal tube but slowly resolved over the ensuing 12 hours. Throughout all bouts of pulmonary edema the mean central venous pressure never exceeded 12 mm Hg, and the mean left atrial pressure remained below 10 mm Hg (fig. 1). During this same time period serum sodium was 137, potassium 5.8, chloride 103, and bicarbonate 17 mEq/L. Total protein and serum osmolarity were not determined.

Progressive renal failure, requiring hemodialysis, developed over the third and fourth postoperative days. Generalized convulsions occurred on the fifth postoperative day, followed by unresponsive hypotension and death.

At postmortem examination the heart was enlarged, weighing 1,100 g. The aortic valve homograft and mitral valve both appeared competent, and a mural thrombus was present in the left atrium. On microscopical examination of the heart, mild mitral valvulitis was observed. The lungs were grossly edematous, and microscopical examination revealed alveolar hemorrhage and edema. Areas of hyaline membrane formation and micro-abcesses were also found. The pulmonary arterioles had mild periadventitial and intimal fibrosis. Some degree of intimal proliferation was observed in many of the small arteries and veins suggestive of moderate pre-existing pulmonary hypertension. Unfortunately, permission for examination of the brain was denied.

Comment: The pressure catheter inserted during surgery was extremely valuable in documenting left atrial pressure during the repetitive episodes of pulmonary edema in this patient. The finding of a normal left atrial pressure and poor response to the usual form of therapy clearly documents the absence of left ventricular failure.

†Merck, Sharp and Dohme Co.

Figure 1

Left atrial pressure, central venous pressure, and drug therapy during the course of pulmonary edema in patient B. G.
Case 2

W. C., a 46-year-old man, suffered multiple episodes of acute rheumatic fever at ages 18 and 20 but remained well compensated until several years prior to admission. Dyspnea and decreasing exercise tolerance prompted cardiac work-up, including right heart and retrograde left heart catheterization. The findings were consistent with moderately severe aortic regurgitation and mitral regurgitation.

On July 25, 1967, under halothane anesthesia, full cardiopulmonary bypass was established by means of a roller pump and disk oxygenator primed with lactated Ringer's solution and blood in a ratio of 7.5 to 1 plus 130 g of mannitol.* The diseased aortic valve was resected and replaced with a homograft pulmonic valve followed by posteromedial annuloplasty of the mitral valve. During aortic valve replacement, the coronary arteries were perfused intermittently with blood at 6 C, and the left ventricle was decompressed with a catheter. The heart was defibrillated after rewarming; it immediately took over support of the circulation. Total bypass time was 3 hours and 8 minutes. Prior to chest closure a catheter was inserted into the left atrium for continuous pressure monitoring.

The patient was comatose immediately after surgery and did not regain consciousness before death, on the eleventh postoperative day. This neurological injury was believed to have resulted from cerebral air embolism at the time of the operative procedure. There was never clinical evidence of a focal lesion or increased intracranial pressure.

Oliguria and hyperkalemia developed on the first postoperative day. Intravenous administration of ethacrynic acid (100 mg) and mannitol (12.5 g) failed to promote a diuresis, so peritoneal dialysis was begun. Arterial blood pressure was maintained at normal levels by careful attention to fluid and electrolyte balance. Mean central venous pressure ranged from 7 to 14 mm Hg, and mean left atrial pressure from 8 to 17 mm Hg.

The patient remained quite stable until the early morning of the fifth postoperative day, when pulmonary edema developed. The lungs became congested, and rales were heard at both bases. There was copious production of pink frothy fluid. At that time the patient was in atrial fibrillation with a ventricular rate of 82. The mean left atrial pressure was noted to be 17 mm Hg, and central venous pressure 13 mm Hg. The phasic tracings of both left atrial and central venous pressure exhibited a normal wave contour. Marked bilateral pulmonary edema was confirmed by chest x-ray. Morphine sulfate (4 mg) was given intravenously, resulting in moderate improvement. At the onset of pulmonary edema serum sodium was 139, potassium 5.0, chloride 87, and bicarbonate 23 mEq/L; the total protein was 5.7 g/100 ml (albumin 3.4 and globulin 2.3). Serum osmolarity was not determined. Pulmonary edema recurred the following day and was associated with a mean left atrial pressure of 16 mm Hg and central venous pressure of 12 mm Hg. The left atrial catheter became occluded on the seventh postoperative day and was removed. Pulmonary edema occurred three more times (table 1). With each episode morphine sulfate and positive-pressure ventilation were helpful forms of therapy.

The patient became progressively jaundiced followed by septicemia. On the eleventh postoperative day his blood pressure gradually decreased and became unresponsive to high doses of Levophed.† He died later that day.

At autopsy the heart was enlarged (1220 g) and on microscopical examination of the myocardium there were interstitial fibrosis, subendocardial hemorrhage, and focal necrosis. The aortic

---

*Merck, Sharp and Dohme Co.

[Table 1]

Data on Patient W. C. during the Acute Episodes of Pulmonary Edema

<table>
<thead>
<tr>
<th>Time</th>
<th>5th</th>
<th>6th</th>
<th>8th</th>
<th>9th</th>
<th>9th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>160/98</td>
<td>160/100</td>
<td>124/80</td>
<td>130/100</td>
<td>110/78</td>
</tr>
<tr>
<td>Heart rate</td>
<td>82</td>
<td>75</td>
<td>90</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Rhythm</td>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
<td>2° Heart block</td>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>17</td>
<td>16</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Mean central venous pressure (mm Hg)</td>
<td>13</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

* Left atrial pressure catheter had ceased functioning.
valve homograft had several large vegetative lesions on its surface, extending down into the sinuses of Valsalva. The lungs were grossly edematous, and on microscopic examination the alveoli were filled with proteinaceous material, red blood cells, fibrin, and large vacuolated macrophages. Interstitial edema, fibrosis, atelectasis, and small pulmonary emboli were also present in some areas. A mild degree of medial hypertrophy was observed in the small pulmonary arteries. Both the arteries and veins had intimal proliferation. These were believed to be the pathological changes of pre-existing mild pulmonary hypertension.

Sectioning of the brain revealed many small, widely scattered, cerebral infarcts. There was a 1 cm infarct on the inferior surface of the left cerebellar cortex and several small foci in the left occipital pole and right frontal cortex. Coronal section of the cerebral hemispheres revealed infarcts within the basal ganglia and junction of white and gray matter. No lesions were seen on horizontal section of the brainstem or spinal cord.

Comment: This patient had recurrent pulmonary edema over a 5-day period. Continuous left atrial pressure monitoring revealed that at no time did the mean pressure rise above 17 mm Hg, a pressure generally below the accepted level for the development of pulmonary edema.

Discussion

Elucidation of mechanisms other than left ventricular failure which can cause pulmonary edema has been hampered by a lack of clinical data.

The patients herein described developed fulminant pulmonary edema following cardiopulmonary bypass for open-heart surgery. Pulmonary lesions arising from extended perfusion often consist of gross and microscopic pulmonary edema. Pulmonary venous obstruction with loss of capillary integrity has been considered as one possible mechanism. However, the clinical picture in such situations is usually that of progressive respiratory insufficiency with hypercapnea, lactic acidosis, and hypoxia rather than recurrent pulmonary edema. It would seem highly unlikely that cardiopulmonary bypass played any role in the second case (W. C.), since respiratory difficulties were not encountered until the fifth postoperative day.

Alterations in serum osmolarity could favor the exudation of fluid into alveoli. Unfortunately, this determination was not carried out in either patient, but in the presence of a normal serum sodium (in both patients) it is unlikely that osmolality was grossly abnormal.

Acute pulmonary edema can result from a variety of neurologic lesions and specific areas of the brain such as the preoptic area and vagal nuclei (ala cinerea) have been shown to be centers responsible for development of neurogenic pulmonary edema. The mechanism is assumed by some to be peripheral vasoconstriction with left ventricular overload causing an elevated left atrial and left ventricular end-diastolic pressure. It has also been suggested that capillary permeability is increased in this form of pulmonary edema, but with little supporting evidence. Others cite pulmonary arterial hypertension as the important event. In retrospect, determination of pulmonary artery pressure may have been helpful in clarifying the mechanism involved in our cases. Although the regions cited above were not examined in detail at brain sectioning in our patient (W. C.), many widely scattered infarcts were observed.

Unknown factors may also have been involved in these two patients, since pulmonary edema without left atrial pressure elevation has been observed in other conditions. Nixon reported a patient who was found to have a mean left atrial pressure of 12 mm Hg during an episode of pulmonary edema following myocardial infarction. He made no attempt to explain the possible mechanism. The pulmonary edema associated with massive pulmonary embolism may be caused by pulmonary venous constriction, in which case left atrial pressure might not be increased.

The conventional treatment of pulmonary edema, which is directed at lowering blood volume in the pulmonary circulation and decreasing diastolic pressure within the left heart, may have to be modified if left atrial pressure is not elevated. Digitalis and other cardiotonic agents may not be beneficial since myocardial insufficiency does not appear to
exist. One of our patients (B. G.) responded poorly to rapid digitalization, phlebotomy, and diuretics. He exhibited repeated episodes of pulmonary edema over a 12-hour period despite intensive therapy. Morphine seemed moderately effective in one patient (W. C.) but this drug is probably best avoided in the unconscious individual.

References
Acute Pulmonary Edema in the Absence of Left Ventricular Failure
EDWARD A. RITTENHOUSE and K. ALVIN MERENDINO

Circulation. 1969;40:823-827
doi: 10.1161/01.CIR.40.6.823

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/40/6/823