Pericardial effusion causes interstitial pulmonary edema in dogs

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ABSTRACT The pulmonary effects of pericardial effusion were studied in eight anesthetized dogs, with emphasis on lung mechanics, $O_2$ exchange, and extravascular thermal lung volume (ETV) accumulation, while warm saline was instilled into the pericardium to elevate pericardial pressure. The results were compared with those from four time-controlled and sham-operated dogs. ETV, as measured by a double-indicator technique, increased from 8.1 ± 0.8 ml/kg at a pericardial pressure of 0 mm Hg to 12.9 ± 2.1 ml/kg at 11.0 mm Hg ($p < .01$). In the control group, ETV increased from 6.5 ± 0.7 to 8.2 ± 0.5 ml/kg over an equal time span. This increase in ETV in the experimental dogs was inversely related to pulmonary compliance, which decreased by 29% as ETV increased ($p < .05$), whereas in the time-controlled group of animals it decreased by 8.8%. Arterial $Po_2$ did not deteriorate during the protocol in either group. Histologic examination showed increased interstitial fluid, but neither alveolar fluid nor septal edema, and gravimetric measurements of lung liquid were also consistent with interstitial fluid accumulation in experimental but not control animals. These findings are concordant with the clinical observation that alveolar edema is rarely seen in the presence of pericardial tamponade. Conceivably, progression from interstitial to alveolar edema did not occur both because of the low pulmonary blood flow that occurs as part of pericardial tamponade physiology and/or because the hydrostatic pressures were not elevated enough to produce higher rates of fluid transudation. Circulation 76, No. 4, 843–849, 1987.

THE SYSTEMIC hemodynamic effects of pericardial effusion/tamponade are extensively studied and well documented.1–3 The pulmonary effects, however, are much less thoroughly investigated in either a clinical or a laboratory setting. This paucity of knowledge is surprising, since patients with pericardial effusions frequently present to their physicians complaining of symptoms such as tachypnea and dyspnea, which are compatible with abnormalities of lung mechanics. It is known that pulmonary edema is quite rare in these patients, perhaps because right heart filling is restricted, limiting pulmonary blood flow. Acute pulmonary edema has been reported after decompression of pericardial tamponade, related to the sudden increase in pulmonary blood flow.4

The purpose of our study was to explore the pulmonary effects of progressive pericardial effusion and tamponade in a canine preparation. The effect of increasing pericardial volume and pressure on lung mechanics, oxygen exchange, and measurements of extravascular lung thermal volume (ETV) in vivo was studied. Changes in vivo were correlated with gravimetric measurements of lung liquid and with the histologic appearance of the lung parenchyma at the end of the experimental protocol.

Methods

General preparation. Twelve mongrel dogs weighing between 17 and 33 kg were anesthetized with intravenous pentobarbital (30 mg/kg) and supplemented as necessary during the experiment. The dogs were placed supine and ventilated with room air via a cuffed orotracheal (9 mm id) tube with a Harvard animal respirator at a tidal volume of 15 ml/kg and a respiratory rate of 10 to 12 breaths/min. Via a side port in the endotracheal tube a calibrated pressure gauge measured dynamic and static airway pressures. Every 15 to 20 min the dogs' lungs were inflated to an airway opening pressure ($P_{aw}$) of 40 to 50 cm H$_2$O to minimize microatelectasis.

The dogs were then positioned in the right lateral decubitus position and a left anterior thoracotomy was performed. A small puncture was made in the pericardium and an 18-gauge catheter was brought through the chest wall and threaded into the pericardium. A purse-string suture fixed the pericardial catheter and a watertight seal was obtained with nonbiologic glue (Super Glue, Super Glue Corp.). Fifty milliliters of saline was infused

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and withdrawn to ensure freedom of the catheter in the pericardial space and to check the water seal. Positive end-expiratory pressure (PEEP) of 5 cm H₂O was used during the thoracotomy to maintain transpulmonary pressure and minimize atelectasis. Lung trauma was avoided. The chest was closed and residual air evacuated with an argyle tube that was subsequently removed.

The dogs were returned to the supine position and, via neck incisions, two Swan-Ganz catheters were passed into the venous system. One was positioned in a branch of the pulmonary artery for measurement of pulmonary arterial (Pₚa) and pulmonary wedge (Pₚw) pressures. The second was positioned in the right ventricle for monitoring of cavitary pressures. To facilitate placement of the catheter in a dependent branch of the pulmonary artery, PEEP of 10 cm H₂O, which increases the depth of West Zone I, was applied during insertion. With the catheter wedged, the Pₚw deflection was compared with Pₚa during ventilation. When the wedged catheter pressure deflections were similar to Pₚa, we inferred that the catheter was not in West Zone III and it was repositioned. The proximal port of the pulmonary arterial Swan-Ganz catheter was used for bolus injections of cold indocyanine green dye during measurements of ETV and cardiac output (Qt). An Edwards lung water catheter (Model 96-020-SF) was inserted in the right femoral artery. Figure 1 depicts the experimental preparation.

ETV measurements were made by injecting into the right atrium 10 ml of cold (0°C) saline containing 1 mg of indocyanine dye. Simultaneously blood was withdrawn by syringe pump through a densitometer cuvette (Waters, DC-410) attached to the femoral lung water catheter. A dye signal proportional to concentration was generated in the densitometer and a thermal signal proportional to temperature was generated from a thermistor on the end of the lung water catheter. Both signals were fed into a computer (Edwards Model 9310) that simultaneously determined the mean transit times (MTT) of the two indicators and the Qt. From these it derived the ETV: ETV = Qt (thermal MTT − dye MTT).

Blood pressure and heart rate were measured by a Statham P23ID transducer connected to the femoral arterial catheter. Pulmonary vascular pressures were obtained from a second P23ID transducer connected to the pulmonary arterial catheter. The vascular transducers were referenced to the left atrium (midchest). Measurements were performed during a 10 sec breath-hold at end-expiration and continuously monitored on a carrier amplifier (Electronics for Medicine Model VR-6). Mixed venous and arterial blood samples were analyzed for pH, P0₂ and PCO₂ by a Corning 165-2 analyzer and corrected for body temperature measured with the Edwards catheter. Hemoglobin (Hgb) values were measured on a Coulter hemoglobinometer and O₂ saturations (SO₂) derived from a Kelman nomogram.

Oxygen contents (Co₂) were than calculated as: Co₂ = (0.003 x P0₂) + (Hgb x SO₂ x 1.39). Venous admixture (Qva/Qt) was calculated as (Cc'O₂ - CaO₂)/(Cc'O₂ - CvO₂), where CaO₂ and CvO₂ are the calculated arterial and mixed venous O₂ contents and Cc'O₂ the end-capillary O₂ content, estimated from the alveolar gas equation assuming a respiratory quotient of 0.8. Static compliance of the respiratory system (Crs) was obtained by clamping the expiratory line at peak inspiration. Assuming the inertial pressure component to be negligible, this maneuver yields the elastic and flow resistive components of the pressure. The static compliance of the respiratory system was calculated from the tidal volume and the elastic pressure: Crs = tidal volume/elastic pressure. In three dogs an esophageal balloon was positioned in the distal third of the esophagus to estimate pleural pressure and calculate actual lung compliance (CL). In

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**FIGURE 1.** Schematic depicting the experiment preparation. See text for full description.
these dogs the airway and pleural pressures were measured via a differential air phase transducer (Validyne DP 43) and recorded on a Grass Polygraph (7D).

**Experimental protocol.** The pericardial catheter was connected to a saline-filled manometer zeroed at the level of the mid atrium. In eight dogs, body-temperature normal saline solution was infused into the pericardium to control pericardial pressure. Pressures were controlled to achieve five stages of 0, 5, 10, 15, and 20 cm of water pressure (0, 3.7, 7.4, 11, 14.7 mm Hg). Each dog was maintained at each new steady-state stage for 30 min before any measurements. At each level of pericardial pressure, systemic blood pressure, right atrial, right ventricular, \( P_{La} \), and \( P_{mv} \) pressures were measured, CL and Crs calculated, and systemic arterial and mixed venous blood samples taken. ETV and Qt determinations were made by the 9310 computer in triplicate with 3 min intervals and these values were averaged.7, 8

Four of the dogs served as time controls. All were identically instrumented and mechanically ventilated for the same time period (4 to 5 hr after the 60 to 90 min of surgical preparation) as the experimental animals but fluid was not instilled into their pericardia. All stage measurements were identical to those for the experimental dogs and were obtained every 45 to 60 min.

Lungs from six experimental and all control dogs were excised after completion of the experimental protocol to obtain lung wet weight to body weight gravimetric (ww/bw) estimates of lung water. The dogs were heparinized (200 U/kg) and their chests opened, with 5 cm PEEP added to maintain transpulmonary pressure; the animals were then rapidly exsanguinated over 5 min. the lung hilum were clamped and the lungs removed. At this time the pericardium was inspected to ensure its integrity.

Histologic examination of lung sections was performed to determine whether interstitial or alveolar fluid was present. Lung samples were taken immediately after conclusion of the experiment and fixed overnight in buffered formalin, and paraffin embedded blocks were prepared. A 2.0 \( \times \) 1.0 \( \times \) 0.4 cm section was sampled from the dorsal aspect of the right and left cranial and caudal lobes, for a total of four samples from each lung. The dorsal aspect was selected as the dependent portion since the dogs were in a supine position during surgery. Sections were stained with hematoxylin and eosin, examined, and compared with similarly prepared sections from three normal dogs.

All animals were cared for according to the guidelines and standards of the University of Chicago for care and use of laboratory animals. For statistical interpretation of results, an analysis of variance for random block design was used, and means were compared by Scheffe’s contrast.9 Significance is attributed to \( p \) values less than .05.

**Results**

Figure 2, A, shows the effects on ETV/kg of serially elevating pericardial pressure in the experimental group and at the same time-controlled stages in the control group (figure 2, B). Values in this and subsequent figures at stage 5 were taken from the four experimental dogs that survived to that level; because of the small number, statistical comparisons were not attempted, and results are presented to show trends. ETV/kg increased by 59% in the experimental group from stage 1 to stage 4, compared with an increase of 30% for the same duration of ventilation in the control group.

Changes in Crs are also shown in figure 2. The decrease from stage 1 to stage 4 in the experimental dogs was 28.9% as compared with 8.8% in the control group. CL and Crs correlated directly in the four dogs in which both were measured.

Figure 3 shows how diastolic right ventricular and pulmonary arterial pressures and the mean right atrial pressure increased as pericardial pressure was raised in the eight experimental dogs. Table 1 shows the hemodynamic effects of the pericardial effusion. Blood pressure, heart rate, and \( P_{pa} \) did not change significantly during the experiments. Wedge pressure increased stepwise and Qt fell as pericardial pressure increased. The microvascular hydrostatic pressure (\( P_{mv} \)), calculated by the Gaar equation as expressed in the Discussion, rose sequentially at stages 3, 4, and 5.

Table 2 shows the data related to the effects of increase in pericardial pressure on pulmonary gas exchange. Arterial \( P_{O_2} \) and \( P_{CO_2} \), and pH remained stable during the experiment, but venous admixture,
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which started at a high level, decreased at stages 3, 4, and 5. Results were equivalent in the four control dogs.

The mean gravimetric value of lung liquid (ww/bw) in six experimental dogs was 11.4 ± 2.1 g/kg. It was 8.7 ± 0.9 g/kg in the four sham-operated animals, which is similar to previously obtained control values in six normal dogs after ventilation for 6 hr (8.6 ± 1.6 g/kg) and can be contrasted to values of over 20 g/kg in dogs with high permeability pulmonary edema. Histologic examination in contrast to three normal dogs showed that all six experimental animals had moderate-to-marked perivascular cuff widening in all sections, without alveolar flooding, around both arteries and veins. These changes were most evident around larger vessels. Although a clear distinction between bronchial and pulmonary arteries is difficult, the most pronounced changes were in the arteries accompanying respiratory bronchi and bronchioles. These changes have been identified as the earliest visible evidence of excess interstitial fluid. Figure 4 shows an example.

Neither intra-alveolar fluid nor septal edema was seen in any of the sections.

**Discussion**

This study was stimulated by the observation that many patients with pericardial effusion have respiratory symptoms, such as tachypnea and dyspnea without abnormalities of O₂ exchange, without a clear cause. In certain cases, other lung disease, e.g., lung cancer, chronic obstructive pulmonary disease, or radiation fibrosis, may contribute. Actual pulmonary edema, however, is rare or nonexistent in these patients. It has been postulated that protection from pulmonary edema is due to pericardial pressure limiting right heart filling and therefore lowering right heart output and pulmonary blood flow. This is a plausible hypothesis, since it has been shown in dogs that at elevated left atrial pressures, low pulmonary blood flow protects against, or does not allow, the development of typical pulmonary edema, defined as tracheal froth and large increases in gravimetrically measured lung liquid.

Presumably, the restriction of right heart filling due to tamponade effectively shifts blood from the central to the peripheral circulation. However, even at low-flow states, small increases in gravimetrically measured lung liquid can be detected when left atrial pressure is sufficiently elevated. Thus protection from gross pulmonary edema should not be equated with complete protection against smaller volumes of extravascular fluid accumulation in the lung.

We have demonstrated that pericardial effusion and elevation of pericardial pressure causes lung ETV to increase. This measured increase is compatible with interstitial fluid accumulation but not with pulmonary edema and alveolar flooding. This is in agreement with previous observations that the interstitium is the initial site of liquid accumulation and that this area, because of its high compliance, serves as a physiologic protective buffer zone against alveolar flooding. It is only when the capacity of the interstitium and the lymphatics is exceeded that liquid “spills over” into the alveolar septum and alveolus itself. So, as discussed below, the balance of Starling forces determines whether filtration into the interstitium will change, but pulmonary blood flow may also influence the volume that is filtered.

The cause of the early rise in ETV in our experiment is multifactorial. Although our experiment did not explore the mechanism of ETV accumulation, an important factor must be the increase in Pmv, which must always be equal to or greater than pericardial pressure. Fluid flux (Qf) at the level of the microvas-
osmotic permeability of the pericardial membrane into the interstitium is described by Starling’s fluid flux equation:

\[ Q_f = K_f [(P_{mv} - P_{pmv}) \sigma (\tau_{mv} - \tau_{pmv})] \]

where \( P_{mv} \) = microvascular hydrostatic pressure, \( P_{pmv} \) = perimicrovascular (interstitial) hydrostatic pressure, \( \tau_{mv} \) = microvascular osmotic pressure, and \( \tau_{pmv} \) = perimicrovascular osmotic pressure. \( K_f \) is the fluid filtration constant and \( \sigma \) is the protein reflection coefficient. The greater \( P_{mv} \), the greater the rate of fluid transudation into the lung interstitium. As described by Gaar et al., 18 \( P_{mv} \) is 40% of the difference between the \( P_{pa} \) and left atrial pressure plus the arterial pressure \( P_{mv} = P_{pw} + 0.4 (P_{pa} - P_{pw}) \). As \( P_{pa} \) increases then \( P_{mv} \) increases to the extent that \( P_{pa} \) is transmitted to the filtration site and fluid filtration into the interstitium is increased. This equation suggests partitioning of resistance across the pulmonary circulation and we reasoned that in our model of progressive pericardial effusion the resistance partitioning does not change. In addition, although \( P_{pw} \) never increased to the levels of pressure associated with development of pulmonary edema, it did rise and this increased \( P_{mv} \).

Another important cause of the ETV increase is that lung lymphatic drainage and clearance of interstitial fluid is diminished by the elevation of right atrial and venous pressures that accompany pericardial tamponade. It has been shown that increased systemic venous pressure causes resistance to and thereby impedes lymphatic flow from the lung, and this phenomenon contributes to the formation of interstitial edema.19

The biological significance of increasing interstitial lung liquid is lung stiffening and decreased Crs; this increases the work of breathing and may be associated with the sensation of dyspnea experienced by many patients with pericardial effusions. The fact that CL correlated directly with Crs supports the conclusion that the effect of interstitial pulmonary edema was on the lungs and not on the chest wall. An increase in lung liquid limited to the interstitial compartment would not be expected to produce abnormalities in \( O_2 \) exchange. Consequently it is not surprising that \( P_{o2} \) remained stable while \( Qva/Qt \), which was higher than normal, probably because of microatelectasis caused by opening the chest, decreased proportionally to the decreases in \( Qt \).20 Although \( O_2 \) exchange is not altered, another

### Table 1

<table>
<thead>
<tr>
<th>Stages</th>
<th>1 (0 mm Hg)</th>
<th>2 (3.7 mm Hg)</th>
<th>3 (7.4 mm Hg)</th>
<th>4 (11.0 mm Hg)</th>
<th>5 (14.7 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>128 ± 18</td>
<td>128 ± 21</td>
<td>127 ± 24</td>
<td>113 ± 41</td>
<td>111 ± 50</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>127 ± 28</td>
<td>134 ± 40</td>
<td>143 ± 41</td>
<td>148 ± 36</td>
<td>129 ± 10</td>
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<tr>
<td>Qt (l/min)</td>
<td>4.35 ± 1.22</td>
<td>3.58 ± 1.16</td>
<td>2.54 ± 0.97</td>
<td>1.95 ± 1.15</td>
<td>1.01 ± 0.76</td>
</tr>
<tr>
<td>PRV (mm Hg)</td>
<td>12.4 ± 2.4</td>
<td>13.1 ± 4.6</td>
<td>13.7 ± 3.3</td>
<td>17.5 ± 4.4</td>
<td>19.6 ± 2.0</td>
</tr>
<tr>
<td>( P_{pa} ) (mm Hg)</td>
<td>14.9 ± 3.0</td>
<td>14.7 ± 2.4</td>
<td>15.5 ± 2.1</td>
<td>16.9 ± 2.7</td>
<td>22.5 ± 6.1</td>
</tr>
<tr>
<td>( P_{pmv} ) (mm Hg)</td>
<td>3.7 ± 1.8</td>
<td>5.9 ± 1.9</td>
<td>6.8 ± 1.5</td>
<td>8.7 ± 2.5</td>
<td>14.9 ± 2.1</td>
</tr>
<tr>
<td>( P_{mv} ) (mm Hg)</td>
<td>8.2 ± 2.2</td>
<td>9.4 ± 2.3</td>
<td>10.2 ± 1.3</td>
<td>12.0 ± 2.0</td>
<td>17.9 ± 3.0</td>
</tr>
</tbody>
</table>

All values are mean ± SD from eight dogs, except for stage 5, in which only four animals were studied.

### Table 2

<table>
<thead>
<tr>
<th>Stages</th>
<th>1 (0 mm Hg)</th>
<th>2 (3.7 mm Hg)</th>
<th>3 (7.4 mm Hg)</th>
<th>4 (11.0 mm Hg)</th>
<th>5 (14.7 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( PaO_2 ) (mm Hg)</td>
<td>90 ± 8</td>
<td>88 ± 7</td>
<td>90 ± 11</td>
<td>90 ± 12</td>
<td>83 ± 7</td>
</tr>
<tr>
<td>( PaCO_2 ) (mm Hg)</td>
<td>34 ± 5</td>
<td>34 ± 4</td>
<td>32 ± 4</td>
<td>30 ± 6</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>pHa</td>
<td>7.35 ± 0.06</td>
<td>7.33 ± 0.04</td>
<td>7.35 ± 0.05</td>
<td>7.33 ± 0.07</td>
<td>7.31 ± 0.07</td>
</tr>
<tr>
<td>( Qva/Qt ) (%)</td>
<td>19.3 ± 3.3</td>
<td>19.9 ± 5.2</td>
<td>14.2 ± 3.3</td>
<td>13.4 ± 4.9</td>
<td>12.3 ± 3.0</td>
</tr>
<tr>
<td>Temp. (°C)</td>
<td>37.5 ± 1.0</td>
<td>37.6 ± 0.9</td>
<td>37.7 ± 1.0</td>
<td>37.6 ± 1.1</td>
<td>37.1 ± 0.2</td>
</tr>
</tbody>
</table>

All values are mean ± SD from eight dogs, except for stage 5, in which only four animals were studied.

*Different from stages 0 and 5 (p < .01). Random block, Scheffe.*
factor contributing to dyspnea in patients undoubtedly is the decrease in CaO₂ due to the decrease in Qt, compromising O₂ delivery to the respiratory muscles.²¹

It is possible to question the validity of the double indicator method in this preparation, where fluid is placed in the pericardium and in contact with the descending aorta. We took care to have all instilled fluid at body temperature so its presence would not
affect the accuracy of the technique. Additionally, previous investigators have found that instillation of fluid into the pericardial or pleural spaces does not affect ETV measurement by the double indicator technique.22

Because gravimetric measurements of lung water require lung excision, it was not possible to determine gravimetric values at each level of pericardial pressure. Postmortem gravimetric determinations of lung water and histologic examinations in six experimental dogs that showed perivascular cuff widening but neither septal edema nor alveolar filling were compatible with increased interstitial lung fluid, which supports the increased intrathoracic fluid. Additional studies are needed to validate the technique in experimental animals with pulmonary edema caused by volume overload.16, 22 Furthermore, it is clearly useful in defining trends of ETV accumulation.

A possible limitation of this study is that the cardiac filling pressures at the start of the experiment were either normal or slightly low. Patients with chronic pericardial effusions/tamponade retain fluid to elevate central venous pressures and filling pressures to maintain an adequate Qt. Regardless of the initial hemodynamic state, however, when pericardial pressure increases, then \( P_{nv} \) rises because of increases in both \( P_{pa} \) and \( P_{pvt} \) leading to increases in ETV. Also, the increase in systemic venous pressures impairs lymphatic clearance, favoring formation of lung edema.

We conclude that the accumulations of pericardial fluid sufficient to raise pericardial pressure can create an imbalance in the Starling forces in the pulmonary vasculature that will favor increased filtration into the interstitium. The high pericardial pressure retards pulmonary lymphatic drainage and also contributes to formation of edema. This elevation in pericardial pressure also restricts right heart filling and lowers Qt; this limits the volume of filtration into the interstitium and the final result is increased interstitial fluid but not frank pulmonary edema.

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