Pulmonary edema formation with myocardial infarction and left atrial hypertension: intravascular and extravascular pulmonary fluid volumes

ROBERT A. SLUTSKY, M.D., WALLACE W. PECK, M.D., AND CHARLES B. HIGGINS, M.D.

ABSTRACT The response of pulmonary blood volume (PBV) and extravascular lung water (EVLW) was examined by indicator-dilution techniques in 14 “open chest” dogs, seven that underwent coronary occlusion (group 2) and seven that served as controls (group 1). Data were obtained in a control stage (control stage 1) 45 min after coronary ligation (control stage 2), and 90 min after the left atrial pressure had been increased to -35 mm Hg with a left atrial balloon. In group 2 animals, EVLW increased after coronary ligation without a marked change in left atrial pressure (6.9 ± 0.4 to 8.2 ± 0.5 ml/kg mean ± SD; p < .05) and increased to 20.1 ± 1.4 ml/kg after the production of left atrial hypertension (p < .005 vs control and vs coronary ligation). In the control dogs, EVLW was unchanged 45 min after the initial data had been collected (7.1 ± 0.7 to 7.0 ± 0.8 ml/kg). After the production of left atrial hypertension in these dogs, EVLW rose (14.8 ± 1.2 ml/kg; p < .005 vs control stage 1 and control stage 2, p < .01 vs group 2 dogs). PBV did not change significantly with ligation and increased similarly in both groups during left atrial hypertension. We conclude that coronary ligation can increase EVLW, independent of microvascular hydrostatic pressure. During the production of left atrial hypertension there was greater transcapillary fluid flux in group 2 dogs at matched levels of left atrial pressure elevation. This may be due to an alteration in the permeability of the pulmonary capillary membrane during myocardial infarction and provides a partial explanation for the occasional disparity between left heart dynamics and the chest radiograph in acute myocardial infarction.

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THE CHEST ROENTGENOGRAM is used in the clinical management of patients with acute myocardial infarction in an attempt to estimate underlying left ventricular performance. However, the relationship between left ventricular filling pressure and the presence of pulmonary congestion is often unpredictable. Timmis et al. were able to demonstrate pulmonary edema in 12 infarct patients without observing a significant increase in left ventricular filling pressure. The disparity between radiographic congestion and clinical signs of pulmonary edema has been ascribed experimentally and clinically to a lag between clinical therapy and delayed radiographic clearing.

We have seen five patients with acute myocardial infarction, chest radiographs demonstrating interstitial and localized alveolar edema, and mean pulmonary capillary wedge pressures of less than 15 mm Hg; these patients had not undergone significant diuresis.

During acute experimental myocardial infarction (in the absence of elevated pulmonary hydrostatic microvascular pressure) a series of studies has demonstrated increased capillary protein permeability, increased lung lymph protein transport, and elevated extravascular lung water (EVLW). In a study by Richeson et al., EVLW accumulation after coronary ligation was significantly minimized by pretreatment with indomethacin.

The purposes of this study were to test the hypothesis that acute myocardial ischemia results in increases in EVLW in the absence of left atrial hypertension and to determine whether this disturbance in capillary fluid flux exacerbates the development of pulmonary edema during mechanical elevation in left atrial pressure.
Methods

Fourteen mongrel dogs (mean weight 26.4 kg, range 21 to 35) were preanesthetized with 2 to 5 mg/kg morphine sulfate and anesthetized 30 min later with 25 mg/kg iv pentobarbital. The animals were ventilated through a cuffed endotracheal tube with a Harvard Respirator at a rate of 14 to 16 cycles/min (tidal volume 15 cc/kg).

A No. 7 multiple side-hole injection catheter was placed through the right internal jugular vein into the pulmonary artery just above the pulmonary valve. The position of the catheter was determined from the pressure recordings and by fluoroscopy and was confirmed at postmortem examination. A polyethylene catheter was advanced through a carotid artery into the aorta for measurement of arterial pressure, and a No. 5 thermodiathermia catheter (Edwards Laboratory; Model 96-020) with a small end hole was advanced into the descending aorta from a femoral artery.

A left thoracotomy was then performed through the fifth intercostal space, and a short catheter was placed into the left atrium through the atrial appendage to monitor atrial pressure. A Foley balloon catheter (30 cc) was then inserted into the left atrium in front of the mitral valve and distal (downstream) to the atrial catheter.

In each animal a suture was placed around the proximal left anterior descending coronary artery above the first major diagonal branch. A standard electrocardiograph (ECG) limb lead was continuously monitored. All pressures (aortic, left atrial, and pulmonary arterial) were measured through fluid-filled catheters with Statham p23db transducers and recorded on an eight channel (Gould 2800) strip chart recorder. Pulmonary vascular resistance (mm Hg/l/min) was calculated as

\[
PAP - LAP \quad \text{cardiac output}
\]

where PAP is mean pulmonary arterial pressure and LAP is mean left atrial pressure.

Indicators and measurements

**Pulmonary intravascular transit time and volume.** For all dogs, pulmonary blood volume (PBV) was measured with indocyanine green as the intravascular indicator (Hynson, Westcott and Dunning, Baltimore, MD). The catheters in the pulmonary artery and left atrium were preloaded with 1.5 ml of the indicator, and the green dye was rapidly flushed into the circulation (5 to 10 ml) with normal saline. Through a Y connector and pressure transducer system, the injection time was automatically recorded with the strip chart running at a paper speed of 10 mm/sec and was confirmed by an observer. Blood was sampled from the aorta (withdrawal rate 30 ml/min) and a densitometric time curve was obtained (Model DT CO-07; Electronics for Medicine, Waltham, MA).

The indicator-dilution curves were digitized at 10 samples/sec with a Talos digitizer interfaced to a Tektronix 4051 tabletop calculator. The peak of the curve was determined by the computer as the maximal deflection, and a monoeponential curve fit was applied to the downslope portion of the curve (between 30% and 70% of the way between the peak and baseline of the curve). The area under the curve was calculated and the mean transit time was obtained in the usual fashion. The densitometer was calibrated with known concentrations of indocyanine green and was found to have a linear output over the concentrations examined. The delay in transit time through the withdrawal catheter was evaluated from a step input of green dye at the withdrawal speed used in this study. All reported times have been corrected for catheter delay.

Mean circulation times could be calculated from the bolus injections of green dye into the pulmonary artery and then the left atrium. Mean pulmonary transit time (MPTT) represented the difference between the mean time obtained from the pulmonary arterial and left atrial curves. Duplicate measures were averaged and triplicate thermodiathermia measures of cardiac output (CO) (see below) were made. PBV could then be derived from the equation

\[
PBV = MPTT \times \frac{CO}{60}
\]

**EVLW.** In this study, heat was used as the diffusible indicator. The accuracy of this technique has been validated by correlation of postmortem gravimetric measures of EVLW with the values obtained from this double-indicator approach (in which indocyanine green or hypertonic saline is used as the intravascular marker). These studies in dogs,14-21 bairns,22 and humans undergoing heart and lung transplantation23 have reported correlations ranging from .81 to .99. The femoral artery thermistor has been shown to accurately measure cardiac output.24 This technique has a coefficient of variation for measuring lung water of 6% to 10%, with a 10% to 15% loss of the thermal indicator between the pulmonary artery and the left atrium.19, 24 probably caused by some heat loss into the left heart, chest wall, and nonfluid spaces in the lungs.16 Neither recirculation nor reduced flow exaggerated these heat losses significantly,24 and neither pleural nor pericardial fluid influenced measures of lung water.19

A 10 ml volume of iced saline mixed with a known amount of indocyanine green dye (2 mg) was injected into the proximal pulmonary artery (similar to the green dye injection) and simultaneous time-temperature and time-density curves were derived from the aortic thermistor. Both curves were recorded on the strip chart recorder at a rate of 10 mm/sec to confirm the integrity of the curve. The data from the thermistor and the densitometer were analyzed on-line by a specially constructed microprocessor (Model 9310; Edwards Laboratory, Santa Ana, CA). From these curves mean thermal time (MTT), mean green dye time (MPAT), and cardiac output (CO) could be derived. EVLW was calculated from the equation

\[
EVLW = (MTT - MPAT) \times \frac{CO}{60}
\]

MPAT was corrected for catheter withdrawal, and no attempt was made to control respiration during the injections. All measures were made in triplicate and averaged.

In 37 mongrel dogs in our laboratory (nine control, 19 with oleic acid pulmonary injury, and the remainder with left atrial balloon pulmonary congestion) we found an excellent correlation between the thermal/green dye and gravimetric assessment of EVLW (r = .86, y = .92x + 35 ml). We also sequentially analyzed EVLW and PBV over 120 min in three anesthetized, mechanically ventilated dogs catheterized with left atrial balloons. In these animals the coefficients of variation of triplicate measures of EVLW and PBV were 5.7% and 5.1%, respectively. Four more animals were studied during the production of pulmonary edema with a left atrial balloon, and the coefficients of variation for EVLW and PBV did not differ from those above.

**Study protocol.** The 14 animals were divided into two groups; seven (group 1) served as sham controls and seven dogs underwent coronary ligation (group 2). Approximately 3 to 45 min after the induction of anesthesia, control data were obtained. In each dog, EVLW, PBV, cardiac output, and left atrial, pulmonary arterial, and aortic pressures were obtained.
All pressures represented an average of at least two respiratory cycles.

The coronary ligature was then tied in the group 2 animals and a myocardial infarction was produced. The sequence of animal selection was random, and alternate animals underwent occlusion throughout the study. Occlusion was confirmed by a change in the color of the myocardium from its usual red to a dusky blue, by ECG changes, by abnormal regional contraction in the distribution of the ligated vessel, and by postmortem gross examination of the heart.

A repeat series of measurements was obtained 45 min after coronary ligation. A second sequence of data was also obtained in the control animals 45 min after the initial sequence of studies (control stage 2). The left atrial balloon was then inflated in all 14 dogs to produce a mean left atrial pressure of approximately 35 mm Hg. Measurements were then taken exactly 90 min later. Left atrial pressure was held constant by increasing or decreasing the amount of air in the left atrial balloon catheter.

Thus data were acquired in animals with infarction (group 2) and in a sham control group (group 1) before coronary ligation (control stage 1), 45 min after coronary ligation (control stage 2), and 90 min after severe elevation of left atrial pressure with a left atrial balloon.

After the experiment, animals were killed in intravenous KCl. The chests were opened, the hila were encircled, and the lungs were removed. The lungs were then passively drained of blood, weighed, and reweighed after heated vacuum drying (Precision Vacuum Oven; GCA Corp.).

Statistics. Data within each group were compared with a repeated measures analysis of variance,25 and comparable points in time were compared between groups with an unpaired Student’s t test.

Results

The hemodynamic data are presented in table 1. There were no significant differences between the groups with respect to left atrial pressure at any of the three data collection points. After coronary ligation there was a significant decline in cardiac output and aortic pressure in group 2; however, during left atrial hypertension there was no difference in these parameters when groups 1 and 2 were compared. Pulmonary vascular resistance during atrial hypertension was greater in group 2 (13.2 ± 3.7 vs 9.3 ± 2.1 mm Hg/min; p < .05).

The changes in pulmonary fluid volumes are given in table 2 and figure 1. In group 2 there was no change in PBV after coronary ligation. Both groups had significantly increased PBV when the left atrial pressure was mechanically elevated, and there were no significant differences in PBVs between the two groups during left atrial hypertension (10.1 ± 2.1 ml/kg in group 1, 9.0 ± 1.7 ml/kg in group 2; 1 > p > .05).

After coronary ligation there was a small but significant (mean increase of 19 ± 3%) elevation of EVLW (6.9 ± 0.4 to 8.2 ± 0.5 ml/kg). EVLW was significantly greater in group 2 animals than in group 1 dogs at the corresponding time before left atrial pressure elevation (8.2 ± 0.5 vs 7.0 ± 0.5 ml/kg; p < .05).

This difference between the groups persisted during left atrial hypertension (14.9 ± 1.3 ml/kg in group 1 vs 20.1 ± 1.4 ml/kg in group 2; p < .01). The ratio of extravascular fluid determined at the end of the study by the indicator dilution technique (EVLW ratio group 1/group 2 = 0.74 ± 0.05) was similar to the postmortem data (weight dry weight ratio of group 1/group 2 = 0.80 ± 0.04). The group 1 animals had a wet/dry ratio at the peak elevation of left atrial pressure of 7.7 ± 0.5 g/g dry weight vs 9.6 ± 0.8 g/g dry weight in group 2 dogs (p < .05).

Discussion

Vriem et al.26 found that during cardiogenic pulmonary edema there was transudation of relatively protein-poor fluid into the interstitial and alveolar spaces in the lung and that the free interstitial, alveolar, and airway fluid protein content was roughly 50% of the corresponding plasma values. During elevations in pulmonary microvascular pressure, and in particular, in conjunction with a reduction in intravascular oncotic pressure, there is a gradual expansion of the extravascular fluid.8, 9, 27, 28 This experimental increase in interstitial fluid volume is rarely associated with pulmonary edema without significant reduction in intravascular protein,26, 29 which results in an increase in relatively protein-poor lymphatic flow from the lung.30, 31 In general these studies have involved the use of mechanical

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**Table 1**

<table>
<thead>
<tr>
<th>Hemodynamic data</th>
<th>Control stage 1</th>
<th>Control stage 2 (postligation)</th>
<th>Left atrial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>4.3 ± 1.0</td>
<td>4.2 ± 1.1</td>
<td>35.0 ± 1.6c</td>
</tr>
<tr>
<td>Group 2</td>
<td>4.0 ± 1.1</td>
<td>5.2 ± 1.0</td>
<td>34.0 ± 1.7c</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>13.6 ± 1.2</td>
<td>13.2 ± 1.7</td>
<td>49.1 ± 5.6c</td>
</tr>
<tr>
<td>Group 2</td>
<td>14.0 ± 1.0</td>
<td>15.2 ± 1.2</td>
<td>51.2 ± 6.1c</td>
</tr>
<tr>
<td>Aortic P (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>92 ± 11</td>
<td>94 ± 14</td>
<td>82 ± 10a</td>
</tr>
<tr>
<td>Group 2</td>
<td>96 ± 14</td>
<td>85 ± 10</td>
<td>79 ± 9b</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2.2 ± 0.4</td>
<td>2.0 ± 0.5</td>
<td>1.5 ± 0.3b</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.3 ± 0.5</td>
<td>1.9 ± 0.7a</td>
<td>1.3 ± 0.3b</td>
</tr>
<tr>
<td>PVR (mm Hg/l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>4.2 ± 1.0</td>
<td>4.8 ± 1.4</td>
<td>9.3 ± 2.1b</td>
</tr>
<tr>
<td>Group 2</td>
<td>4.3 ± 0.7</td>
<td>5.2 ± 1.7</td>
<td>13.2 ± 3.7b</td>
</tr>
</tbody>
</table>

LAP = mean left atrial pressure; PAP = mean pulmonary arterial pressure; Aortic P = mean aortic pressure; CO = cardiac output; PVR = pulmonary vascular resistance.

Statistical comparisons: 8p < .05 vs control; 9p < .01 vs control; 10p < .005 vs control.

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CIRCULATION
TABLE 2

Changes in pulmonary fluid volumes

<table>
<thead>
<tr>
<th></th>
<th>Control stage 1</th>
<th>Control stage 2 (postligation)</th>
<th>Left atrial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBV (ml/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>6.6±1.0</td>
<td>6.4±1.0</td>
<td>10.1±2.1^</td>
</tr>
<tr>
<td>Group 2</td>
<td>6.4±2.1</td>
<td>6.1±1.8</td>
<td>9.0±1.7^</td>
</tr>
<tr>
<td>EVLW (ml/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>7.1±0.5</td>
<td>7.0±0.5^</td>
<td>14.9±1.3^</td>
</tr>
<tr>
<td>Group 2</td>
<td>6.9±0.4</td>
<td>8.2±0.5</td>
<td>20.1±1.4</td>
</tr>
<tr>
<td>Wet weight/dry weight (g/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>7.7±0.5^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>9.6±0.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical comparisons: ^p<.01 vs control; ^p<.05 group 1 vs group 2; *p<.01 group 1 vs group 2.

or volume-expanding techniques to alter pulmonary pressures and fluid dynamics.

Left ventricular mechanical failure during acute myocardial infarction has been assumed to be the sole cause of pulmonary congestion. In essence, systolic and diastolic dysfunction are presumed to result in hydrostatic congestion. In clinical practice, radiographic edema and left ventricular filling pressure have often been found to correspond poorly. To a large extent, chest x-ray “lag” has been blamed for this disparity, i.e., therapy alters intravascular volume and pressure before mobilization of extravascular fluid.

Two clinical studies have examined the ratio of the protein content of airway edema fluid to that of blood and found that in patients with acute myocardial infarction, this ratio ranked somewhere between that reported in normal subjects and individuals with capillary endothelial leak syndromes. Four recent studies have demonstrated experimental evidence of pulmonary capillary disruption during myocardial infarction. Collins et al. demonstrated an increase in both lung lymph flow and lung lymph protein clearance after coronary occlusion. Similar observations were made by Spath and Gee, who also found significant differences in lymphatic protein content in ani-

![CHANGE IN EXTRAVASCULAR LUNG WATER](image-url)

**FIGURE 1.** Individual changes in EVLW in both groups. Note the increase in EVLW after occlusion and the greater increase with hypertension in group 2 dogs.
mals with infarction and volume overload. Gee et al.\textsuperscript{10} found greater elevations in EVLW content in dogs that underwent coronary ligation compared with those in a control series of dogs. They concluded that myocardial ischemia altered the vascular permeability of the lung. Richeson et al.\textsuperscript{12} found essentially similar data and observed that this pulmonary protein leakage was minimized with the infusion of indomethacin. They speculated on the potential direct and indirect effects that prostaglandin and prostaglandin metabolites might have in provoking this condition. It has already been demonstrated that prostaglandins E and F are released after coronary ligation in the dog.\textsuperscript{35}

Transcapillary fluid flux depends on the character and surface area of the capillary membranes and on a variety of hydrostatic factors. Indicator-dilution and the postmortem techniques used in this study indicate only changes in the water content of an incompletely (in this study) characterized anatomic space. In theory, an expansion of the surface area permeability product of the lung might result in greater water flow. Indeed, a number of studies have proposed the use of $^{14}$C-labeled urea as a single transit indicator of the lung surface area permeability product.\textsuperscript{36,38} These studies found no correlation between surface area permeability product and pulmonary microvascular pressure. In fact, pulmonary vascular pressures in dogs were not found to significantly alter the surface area permeability product. In the present study, the surface area permeability product was not measured. However, after coronary ligation, extravascular water increased without any change in PBV, implying that permeability rather than surface area was altered.

In conclusion, there are significant differences in extravascular water accumulation at rest and after mechanical left atrial obstruction when dogs with infarctions are compared with matched control dogs. The data in this study lend support to the hypothesis that a component of the pulmonary extravascular fluid collection that often occurs after myocardial infarction may not be caused by elevation in pulmonary microvascular pressures alone. The occasional disparity between left heart pressures and the chest roentgenogram after myocardial infarction can often be explained both clinically and experimentally by therapeutic "laf," but the effects of altered capillary permeability need further consideration.

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