Treatment of canine permeability pulmonary edema: short-term effects of dobutamine, furosemide, and hydralazine

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ABSTRACT  The effects of treatment of oleic acid pulmonary edema with dobutamine, furosemide, and hydralazine on cardiopulmonary function in 24 dogs were investigated. Pulmonary capillary wedge pressure (PCWP) was adjusted to approximately 7 mm Hg; 45 min after oleic acid (0.08 ml/kg), dogs were randomly divided into a control group, in which PCWP was maintained at approximately 7 mm Hg, and into treatment groups as described above. Mean time-averaged PCWP was 2.3 mm Hg in dogs treated with dobutamine, 4.1 mm Hg with furosemide, and 4.4 mm Hg with hydralazine. Four hours of treatment with dobutamine and furosemide significantly (p < .01) reduced accumulation of lung water compared with the control and hydralazine groups. Qs/Qt was lower (p < .05) with dobutamine and furosemide compared with the other groups. In dogs given hydralazine, cardiac output (CO) and systemic vascular resistance (SVR) remained constant over the 4 hr treatment interval. In contrast, in all other groups, SVR increased and CO decreased (both p < .05). The short-term pulmonary effects of the above drugs are probably explained by differences in PCWP and/or by regional pulmonary vascular effects.

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IN CONTRAST to cardiogenic pulmonary edema, in the adult respiratory distress syndrome severe edema develops in spite of normal or low left ventricular filling pressure. Acute respiratory failure occurs because alveolar and/or pulmonary endothelial damage results in excess accumulation of extravascular lung water, leading to alveolar edema and collapse, which causes a large right-to-left intrapulmonary shunt (Qs/Qt).^1-3^ Although therapy designed to reduce pulmonary capillary wedge pressure (PCWP) effectively treats cardiogenic pulmonary edema, this approach has only recently been tested in low-pressure pulmonary edema.^4,5^ In a canine study, phlebotomy and infusion of nitroprusside reduced PCWP from 11 to 6 mm Hg over a 4 hr period, and compared with a control group in which the 4 hr time-averaged PCWP was 11 mm Hg, pulmonary edema was significantly reduced.^5^ Although phlebotomy reduced edema, it resulted in a large fall in cardiac output (CO), an effect clearly to be avoided in critically ill patients. Although nitroprusside maintained CO despite reduced PCWP, it had adverse effects on blood pressure and gas exchange. These adverse effects were confirmed in two short-term experiments in which infusion of nitroprusside increased CO, increased Qs/Qt, and reduced PAO₂.^6,7^ Similar results with nitroprusside are reported in patients with acute respiratory failure.\(^8\)

This study was designed to determine the short-term cardiopulmonary effects of several drugs in canine low-pressure pulmonary edema induced by intravenous injection of oleic acid.

Current inotropic agents used to increase CO include dobutamine and dopamine. In patients with congestive heart failure, dopamine increased PCWP when it increased CO.\(^9,\)\(^10\) On the other hand, in the same patients, for an equal change in CO, PCWP fell with dobutamine. Because the subacute cardiopulmonary effects of dobutamine have not been investigated in a model of low pressure pulmonary edema, we chose to study this drug and test the hypothesis that PCWP and lung water will decrease with dobutamine.
Previous work in canine oleic acid edema demonstrated that over a two 2 hr interval, intravenous furosemide (1 mg/kg) improved gas exchange but did not affect formation of pulmonary edema. Most likely, edema was not reduced with furosemide because PCWP remained constant. Accordingly, in the current study, furosemide was given to reduce PCWP.

In patients with congestive heart failure, primary pulmonary hypertension and chronic obstructive pulmonary disease, hydralazine decreases resistance and increases CO. Two recent studies investigated the short-term cardiopulmonary effects of hydralazine in canine oleic acid pulmonary edema. In both, there was a small decrease in PCWP with hydralazine and an increase in CO. Lung water was not measured in these studies. Accordingly, the current study was designed to determine the subacute cardiopulmonary effects of hydralazine in low-pressure pulmonary edema.

We emphasize that the value of observations in this study is not dependent on how closely oleic acid pulmonary edema mimics clinical adult respiratory distress syndrome; rather, our objective was to investigate several commonly used drugs in a model of permeability pulmonary edema.

Methods

Twenty-four dogs of mixed breed were anesthetized with pentobarbital (30 mg/kg) and given small maintenance doses as required. They were artificially ventilated (20 ml/kg) in the supine position via an endotracheal tube with 100% O₂. End expiratory pressure was zero. Respiratory rate was adjusted to maintain Pco₂ between 35 and 40 mm Hg. Sodium bicarbonate was given as required to correct metabolic acidosis and maintain pH above 7.3. A catheter was placed in the aorta to record blood pressure and to sample arterial blood. A Swan-Ganz catheter was flow directed into the right ventricle via the external jugular vein. A thermostippered Swan-Ganz catheter that was flow directed to the pulmonary artery through the external jugular vein was used to sample mixed venous blood and to measure pulmonary arterial pressure and PCWP. These catheters were connected to Statham P23 ID transducers and leveled to the center of the chest, and their outputs were displayed and recorded on an Electronics for Medicine oscillograph. The pressures were recorded at a sensitivity at which 1 mm Hg corresponds to a 1 mm deflection. Another catheter was placed in the right atrium for injection of boluses of saline, and a thermal dilution curve was recorded and analyzed by a cardiac output computer (Columbus Instruments). A large-bore polyethylene catheter was inserted into the superior vena cava through the external jugular vein for volume infusion and drug administration.

When the surgical preparation was completed, the PCWP was adjusted to approximately 7 mm Hg by intravenous infusion of approximately 250 ml of 6% dextran; after the preparation was stable for approximately 10 min, baseline measurements were taken. Simultaneous samples of arterial and venous blood were taken before hemodynamic measurements were obtained. They were analyzed for blood gas tension with a Corning 165/2 (Corning Scientific Instruments, Medfield, MA) and O₂ contents were measured by a carbon monoxide scrubbing technique. Qs/Qt was calculated in a standard manner as Qs/Qt = (Cvo₂ - CaO₂)/(Cvo₂ - Cvo₂).

With the animals' breath held at end expiration, heart rate, blood pressure, pulmonary arterial pressure, mean PCWP, right ventricular pressure, and CO were measured. Measurements of onotic pressure (π IV) were obtained from samples of arterial blood.

After baseline measurements, during a 20 sec breath hold, oleic acid (0.08 ml/kg) was infused into the right atrium. The PCWP was maintained at 7 to 8 mm Hg for 45 min by intravenous infusion of approximately 250 ml of 6% dextran.

Forty-five minutes after injection of oleic acid, dogs were randomized into the following groups:

(1) Untreated group. In this group, PCWP was maintained at approximately 8 mm Hg for the 4 hr treatment interval. This was achieved with infusion of 6% dextran, as required. Dogs received 250 to 400 ml of dextran over the treatment period. In all groups, measurements of PCWP, pulmonary arterial pressure, and blood pressure were obtained at 10 min intervals throughout the study. The reported values represent the mean of all measurements during the treatment period in this and the three treated groups. Furthermore, in all groups transducers were frequently balanced and the zero position confirmed during each experiment.

(2) Furosemide-treated group. Intravenous furosemide was given as required to reduce and maintain PCWP at approximately 3 mm Hg. It took approximately 20 min to reduce PCWP to the desired level, and over the 4 hr treatment interval the PCWP was stable and varied less than 2 mm Hg. Dogs received aliquots of 20 to 40 mg and the total dose received varied between 5 and 20 mg/kg. Blood pressure fell less than 10% with furosemide and it remained relatively constant over the treatment interval.

(3) Hydralazine-treated group. Intravenous hydralazine was initially given in 2 mg aliquots until mean blood pressure had fallen approximately 15%. This was usually achieved in less than 20 min at an average dose of 12 mg. Subsequently, the drug was given by continuous infusion at a rate of 2 to 4 mg/hr. At this rate of infusion the mean blood pressure and PCWP remained relatively stable.

(4) Dobutamine-treated group. Dobutamine was infused at an increasing rate until mean blood pressure decreased by 15%, until mean heart rate increased by approximately 15 beats/min, or until PCWP fell to approximately 3 mm Hg. PCWP always fell with dobutamine and the desired reduction in left ventricular filling pressure was always achieved within 20 min. The rate of infusion varied among dogs between 8 to 15 μg/kg/min.

After dogs had been treated for 4 hr and just before they were killed, 100 ml of blood was taken and weighed. Twenty-five microcuries of chromium-51 tagged to autologous red blood cells was then injected into the right atrium. After adequate mixing, 9 ml of blood was withdrawn and divided into 3 x 3 ml aliquots. The dogs were then killed by an intravenous bolus of concentrated KCl, and almost immediately the chests were opened, the hila clamped, and the lungs removed. The lungs were then homogenated and blood was taken and counted in a gamma camera.

The lungs and 100 ml of blood were placed in a vacuum-sealed oven at 60°C and dried over the next few days. Lungs and blood were weighed each day until weights changed less than 1 g in 2 consecutive days. The following formulas were used to calculate lung composition: (1) lung blood weight = (count in homogenate sample)/(count in blood sample) x (volume blood)/(volume homogenate) x density of homogenate; (2) lung wet weight blood free (LWWBF) = lung wet weight - lung blood weight; (3) extravascular lung water (EVLW) = LWWBF - lung dry weight blood free.
TABLE 1
Short-term cardiopulmonary effects of oleic acid

<table>
<thead>
<tr>
<th></th>
<th>CO (l/min)</th>
<th>BP (mm Hg)</th>
<th>Ppa (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>SVR (mm Hg/1/min)</th>
<th>PVR (mm Hg/1/min)</th>
<th>PO2 (mm Hg)</th>
<th>Qs/Qt (%)</th>
<th>PCWP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.0</td>
<td>140</td>
<td>17.2</td>
<td>18.6</td>
<td>4.3</td>
<td>25.3</td>
<td>2.0</td>
<td>502</td>
<td>17</td>
</tr>
<tr>
<td>±1.2</td>
<td>±4.9</td>
<td>±2.3</td>
<td>±1.9</td>
<td>±0.9</td>
<td>±4.4</td>
<td>±6.7</td>
<td>±0.2</td>
<td>±17.6</td>
<td>±3.1</td>
</tr>
<tr>
<td>45 min</td>
<td>5.3</td>
<td>133</td>
<td>15.9</td>
<td>18.5</td>
<td>4.1</td>
<td>28.0</td>
<td>1.9</td>
<td>239^</td>
<td>37.4^</td>
</tr>
<tr>
<td>±0.9</td>
<td>±7.8</td>
<td>±2.2</td>
<td>±2.4</td>
<td>±0.8</td>
<td>±3.2</td>
<td>±4.1</td>
<td>±0.1</td>
<td>±14.3</td>
<td>±5.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD for all 24 dogs.

OA = oleic acid; BP = blood pressure; Ppa = pulmonary arterial pressure; PO2 = partial pressure of oxygen in arterial blood.

*p < .05 compared with preceding value.

Results

Table 1 depicts measured values before and 45 min after oleic acid. Analysis of variance showed no significant differences among the five groups for any of the measured variables in either baseline or 45 min measurements. Oleic acid caused a marked deterioration in gas exchange, i.e. mean Qs/Qt more than doubled (p < .05, paired t test). There was no significant change in the values of CO, πIV, PCWP, pulmonary arterial pressure, and systemic (SVR) or pulmonary vascular resistance (PVR) with oleic acid.

Table 2 summarizes the mean (± SD) values for PCWP, right ventricular end-diastolic pressure (RVEDP), and πIV for each group over the 4 hr treatment intervals. Analysis of variance demonstrated a highly significant F ratio for PCWP. Duncan’s multiple comparison test confirmed that PCWP was significantly lower in the treated groups compared with the untreated group. Also note that, compared with hydralazine, dobutamine produced lower PCWP values.

Values for πIV were similar in all groups and RVEDP was reduced in two groups.

Table 3 illustrates the effects of treatment on formation of pulmonary edema.

Lung weights are normalized for body weight. Analysis of variance of lung wet weight (WW)/body weight (BW) ratios resulted in a significant F statistic. Dogs treated with furosemide and dobutamine had a significantly smaller WW/BW ratio compared with the hydralazine and control groups by analysis of variance and Duncan’s test (p < .01). In the same groups there was also a significant reduction (p < .01) in the ratio of LWWBF to BW.

When groups were compared by EVLW/BW ratios, the F statistic was again significant. Compared with the control and hydralazine groups, treatment with furosemide and dobutamine significantly (p < .05) reduced this ratio. Compared with controls, all treatments except hydralazine significantly (p < .05) reduced the EVLW/BF dry lung ratio. The compara-

TABLE 2
Effects of treatment on ventricular filling pressures and oncotic pressure

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>H</th>
<th>F</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 min after OA</td>
<td>7.4±0.8</td>
<td>7.3±0.4</td>
<td>7.7±0.5</td>
<td>7.1±0.4</td>
</tr>
<tr>
<td>4 hr</td>
<td>7.4±0.7</td>
<td>4.4±0.3^A.C</td>
<td>4.1±0.2^A,D</td>
<td>2.3±1.1^A.B,D</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 min after OA</td>
<td>5.0±1.4</td>
<td>4.8±2.4</td>
<td>3.5±1.0</td>
<td>4.0±1.7</td>
</tr>
<tr>
<td>4 hr</td>
<td>5.2±2.3</td>
<td>4.0±2.8</td>
<td>1.8±1.7^A.D</td>
<td>0.5±1.2^A.C</td>
</tr>
<tr>
<td>πIV (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 min after OA</td>
<td>18.3±3.2</td>
<td>22.5±1.5</td>
<td>17.0±6.4</td>
<td>17.3±2.8</td>
</tr>
<tr>
<td>4 hr</td>
<td>18.3±4.7</td>
<td>16.0±2.8</td>
<td>14.3±3.3</td>
<td>14.4±1.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

H = hydralazine; F = furosemide; D = dobutamine; OA = oleic acid.

^Significant difference (p < .05) compared with controls.

^Significant difference (p < .05) compared with hydralazine.

^Significant difference (p < .05) compared with 45 min values.

^Significant difference (p < .01) compared with 45 min values.
tively low ratio obtained with hydralazine is explained by the high value for lung dry weight in two dogs that had marked edema as assessed by the other indexes.

The nonsignificant F statistic from analysis of variance of lung dry weight to BW suggested no difference among groups. However, mean values were highest in controls and in dogs given hydralazine.

Table 4 illustrates effects of oleic acid and treatment on gas exchange. Compared with the 45 min values, there was a large (p < .05, paired t test) increase in Qs/Qt over the treatment interval in the control group and in dogs treated with hydralazine. In contrast, mean Qs/Qt remained constant in dogs treated with furosemide and dobutamine. Analysis of variance of measurements obtained after 4 hr of treatment resulted in a significant F ratio. Compared with the other groups, Duncan’s test confirmed that Qs/Qt was lower (p < .05) in groups treated with furosemide and dobutamine. Edema and Qs/Qt at 4 hr were similar in the latter two groups. In the control group and in dogs given hydralazine, the deterioration in gas exchange paralleled the increase in lung water. Changes in PaO₂ followed the trend for Qs/Qt but no significant differences were detected by analysis of variance.

As illustrated in figure 1, mean CO expressed as a percent of the 45 min (control) value fell over the treatment interval in all groups except that given hydralazine. Comparing values obtained at 4 hr with those obtained at 45 min, CO decreased in all dogs (p < .05, paired t test) except those treated with hydralazine.

Over the treatment interval, mean arterial blood pressure remained constant with dobutamine and in controls but tended to decrease in other groups (table 5). Over the 4 hr interval, SVR increased in all groups (p < .05, paired t test) except those dogs treated with hydralazine. The initial high value for SVR in the hydralazine groups is explained by the observation that two dogs in this group had low CO and thus high SVR 45 min after oleic acid. Values for blood pressure, pulmonary arterial pressure, and PVR were similar between groups after 4 hr of treatment and there were no differences by analysis of variance.

**Discussion**

This study confirms previous work describing the pathophysiology of oleic acid pulmonary edema.\(^5\)\(^6\) Despite normal PCWP, 45 min after oleic acid, mean

### Table 3

**Effects of treatment on lung water**

<table>
<thead>
<tr>
<th></th>
<th>WW/BW (g/kg)</th>
<th>WWBF/BW (g/kg)</th>
<th>EVLW/BW (ml/kg)</th>
<th>EVLW/BF DL (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>47.3 ± 12.2</td>
<td>41.0 ± 6.2</td>
<td>38 ± 5</td>
<td>11.4 ± 1.2</td>
</tr>
<tr>
<td>Furosemide</td>
<td>32.6 ± 6.8 (^{B,D})</td>
<td>25.0 ± 3.6 (^{B,D})</td>
<td>22 ± 5.7 (^{A,C})</td>
<td>8.1 ± 1.3 (^{A})</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>32.0 ± 4.0 (^{B,D})</td>
<td>27.2 ± 3.9 (^{B,D})</td>
<td>26 ± 4.9 (^{A,C})</td>
<td>9.7 ± 1.7 (^{A})</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>43.8 ± 8.6</td>
<td>36.0 ± 6.6</td>
<td>32 ± 6.2</td>
<td>9.7 ± 3.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

BW = body weight; WW = wet weight; WWBF = wet weight blood free; EVLW = extravascular lung water; BFDL = blood free dry lung.

\(^{A}\) Difference from control group (p < .05).

\(^{B}\) Difference from control group (p < .01).

\(^{C}\) Difference from H group (p < .05).

\(^{D}\) Difference from H group (p < .01).

### Table 4

**Effects of treatment on gas exchange**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>H</th>
<th>F</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qs/Qt (%) 45 min after OA</td>
<td>37 ± 15</td>
<td>37 ± 18</td>
<td>31 ± 13</td>
<td>34 ± 8</td>
</tr>
<tr>
<td>4 hr</td>
<td>58 ± 12 (^{B})</td>
<td>50 ± 7 (^{B})</td>
<td>30 ± 16 (^{A})</td>
<td>33 ± 12.7 (^{A})</td>
</tr>
<tr>
<td>Pao₂ (mm Hg) 45 min after OA</td>
<td>239 ± 135</td>
<td>278 ± 140</td>
<td>284 ± 126</td>
<td>236 ± 84</td>
</tr>
<tr>
<td>4 hr</td>
<td>76 ± 66 (^{B})</td>
<td>97 ± 49 (^{B})</td>
<td>159 ± 143 (^{B})</td>
<td>147 ± 92 (^{B})</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Abbreviations as in table 2.

\(^{A}\) p < .05 compared with controls and hydralazine.

\(^{B}\) p < .05 compared with 45 min value.
FIGURE 1. Effects of treatment on CO. CO increased at 1 and 2 hr after treatment in dogs given hydralazine. Although CO decreased progressively in controls and in dogs given furosemide, in those treated with dobutamine and combination therapy, CO remained constant over the first 2 hr. For further discussion, see text.

Qs/Qt had more than doubled. The deterioration in gas exchange most likely resulted from accumulation of excess lung water, which occurred because oleic acid disrupted pulmonary vascular integrity. Two of our interventions caused a small but significant decrease in a normal left ventricular filling pressure and substantially decreased accumulation of lung water. In an earlier study of canine oleic acid edema, phlebotomy and a 4 hr infusion of nitroprusside decreased PCWP from 11 to 6 mm Hg and significantly reduced pulmonary edema. Other canine studies have also demonstrated that relatively small changes in PCWP may induce accumulation of lung water when vascular permeability is increased.

We emphasize that because the pathophysiology of oleic acid pulmonary edema is different from clinical acute respiratory failure, direct clinical extension of the current results is limited. However, the adult respiratory distress syndrome is also characterized by increased pulmonary vascular permeability, and in this condition relatively small changes in PCWP may influence accumulation of pulmonary edema.

A previous study demonstrated that despite no effect on edema, furosemide improved gas exchange in canine oleic acid pulmonary edema. The improvement in gas exchange was attributed to pulmonary vasoactive effects of the drug. In that study, the dose of furosemide was relatively low (0.1 mg/kg) and had no effect on PCWP. Most likely, edema was not reduced because PCWP remained constant. In the current study, furosemide decreased PCWP from 7 to 4 mm Hg and significantly reduced pulmonary edema.

Compared with the control group and dogs treated with hydralazine, gas exchange did not deteriorate over 4 hr in dogs given furosemide. As reflected in figure 1, corresponding to the decrease in PCWP, there was a large fall in CO over the treatment interval. The decrease in CO with furosemide is explained by a decrease in ventricular preload and by an increase in SVR. Note that despite constant ventricular filling pressures and unchanged PVR, CO fell over the 4 hr interval in controls. The decrease in flow in this group may be explained by the increase in systemic resistance. Since SVR increased a similar amount in controls and in dogs given furosemide, the greater decrease in mean flow in the treated group (29% vs 19%)

### TABLE 5

<table>
<thead>
<tr>
<th>Hemodynamic effects of oleic acid and treatment</th>
<th>Control</th>
<th>H</th>
<th>F</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (l/min)</td>
<td>5.6 ± 1.2</td>
<td>4.2 ± 1.1</td>
<td>5.1 ± 0.5</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>45 min</td>
<td>4.7 ± 0.4(^A)</td>
<td>4.4 ± 0.2</td>
<td>3.6 ± 0.4(^A)</td>
<td>3.8 ± 0.6(^A)</td>
</tr>
<tr>
<td>4 hr</td>
<td>140 ± 30</td>
<td>132 ± 26</td>
<td>141 ± 19</td>
<td>133 ± 11</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>140 ± 32</td>
<td>103 ± 20</td>
<td>131 ± 14</td>
<td>133 ± 23</td>
</tr>
<tr>
<td>Ppa (mm Hg)</td>
<td>18 ± 2.8</td>
<td>16 ± 4.0</td>
<td>17 ± 3.0</td>
<td>16 ± 1.7</td>
</tr>
<tr>
<td>45 min</td>
<td>20 ± 3.8</td>
<td>16 ± 4.1</td>
<td>14 ± 3.5</td>
<td>15 ± 4.1</td>
</tr>
<tr>
<td>4 hr</td>
<td>2.1 ± 0.5</td>
<td>1.8 ± 1.4</td>
<td>1.7 ± 0.44</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td>PVR (mm Hg l/min)</td>
<td>3.0 ± 0.3</td>
<td>2.8 ± 0.4</td>
<td>2.9 ± 0.4</td>
<td>3.4 ± 0.8</td>
</tr>
<tr>
<td>45 min</td>
<td>24 ± 5</td>
<td>32 ± 4</td>
<td>26 ± 5</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>4 hr</td>
<td>31 ± 3(^A)</td>
<td>24 ± 4</td>
<td>38 ± 5(^A)</td>
<td>35 ± 3(^A)</td>
</tr>
</tbody>
</table>

BP = blood pressure; Ppa = pulmonary artery pressure; other abbreviations as in table 2.

\(^A\)p < .05 compared with 45 min value.
may be explained by the fall in preload with furosemide. Other studies have described similar changes in CO after oleic acid and attributed the decrease in flow to increased systemic resistance.\(^6\)\(^7\)

A 4 hr continuous infusion of dobutamine maintained mean time-averaged PCWP at 2.3 mm Hg, and compared with controls and dogs given hydralazine, dobutamine substantially reduced formation of pulmonary edema. Corresponding to the reduction in edema, gas exchange did not deteriorate over the treatment interval. Note that lung water and values for Qs/Qt and Pao\(_2\) were similar in dogs given dobutamine and in those treated with furosemide. Despite a significant fall in PCWP, after 2 and 3 hr of treatment, mean CO remained constant with dobutamine. In contrast over the same interval, despite constant PCWP in the controls, CO decreased. In patients with established left ventricular failure, CO increases when PCWP decreases with dobutamine.\(^10\)

The different effects of dobutamine are probably explained by the marked differences in subjects, i.e. patients with left ventricular failure vs dogs with oleic acid pulmonary edema and low PCWP. The improvement in left ventricular pump performance with dobutamine is most likely explained by its positive inotropic effects. That is, with respect to the current study, the increased contractile state allowed increased ventricular shortening to a smaller end-systolic volume so that stroke volume and CO remained constant despite a decrease in ventricular preload. Note that compared with controls, RVEDP also decreased with dobutamine, signaling an improvement in right ventricular pump performance. After 4 hr of treatment CO decreased. The fall may in part be explained by an increase in systemic resistance. SVR increased (p < .05) from 29 mm Hg/liter/min at baseline to 38 mm Hg/liter/min after 4 hr of treatment. Compared with other groups by analysis of variance, dobutamine did not affect other cardiopulmonary parameters. Although cardiovascular effects of dobutamine have been carefully investigated in patients with left ventricular failure,\(^9\)\(^10\) the current study is one of first to systematically investigate subacute effects of this agent on cardiopulmonary function in a model of low-pressure pulmonary edema.

Hydralazine is commonly used to decrease afterload and improved left ventricular function in patients with long-term left ventricular failure.\(^13\)\(^14\) One study of patients with congestive heart failure demonstrated that the increase in CO with hydralazine was greater when ventricular end-diastolic dimensions were larger.\(^18\) Furthermore, oral hydralazine has also been shown to be effective in decreasing resistance and increasing CO in patients with primary pulmonary hypertension and in patients with raised pulmonary artery pressure secondary to chronic pulmonary disease.\(^13\)\(^14\)

In two recent canine studies, we demonstrated that in the presence of oleic acid edema, hydralazine acutely decreased SVR and increased CO.\(^6\)\(^15\) In both studies, there was a small decrease in PCWP with hydralazine. In this study, despite a decrease in left ventricular filling pressure and in contrast to controls and treatment with furosemide and dobutamine, CO did not decrease with hydralazine. Compared to other groups, the most likely explanation for the improvement in left ventricular function with hydralazine is that the drug prevented the increases in systemic resistance. However, an increased inotropic state with hydralazine cannot be ruled out.

Although all indexes of lung water (table 3) were consistently lower in dogs treated with hydralazine than in controls because of the variability within groups, those changes were not significant. Since PCWP decreased a similar amount with all interventions, the failure of edema to decrease with hydralazine indicates that in addition to changes in PCWP, other factors influence formation of pulmonary edema in this model. For example, CO was highest in those dogs given hydralazine and the increased flow in concert with regional vascular effects of the drug could have resulted in higher intravascular pressures in damaged areas. Such changes could increase local lung water accumulation and offset effects of a lower mean PCWP. In this regard, the decrease in lung water seen with furosemide and dobutamine may also be partially explained by local pulmonary vascular effects of the drugs.

Current results indicate that in permeability pulmonary edema, relatively small changes in PCWP and/or regional pulmonary vascular effects of certain drugs may affect accumulation of lung water.

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