Sepsis Reduces the Threshold Hydrostatic Pressure Necessary for Pulmonary Edema in Baboons

JOHN P. KOHLER, M.D., CHARLES L. RICE, M.D., POPE MOSELEY, B.S., JEFFREY SCHWARTZ, M.D., CHRISTOPHER K. ZARINS, M.D., STEVEN GOULD, M.D. AND GERALD S. MOSS, M.D.

Department of Surgery, Michael Reese Hospital, and University of Chicago, Chicago, Illinois 60616

Submitted for publication April 8, 1980

The threshold hydrostatic pressure necessary to produce pulmonary edema may be lowered by a decrease in plasma colloid oncotic pressure (COP) or an increase in capillary permeability. Sepsis is thought to increase capillary permeability. The object of this report was to assess the effect of sepsis on threshold hydrostatic pressure. In five adult male baboons a Foley catheter was inserted into the left atrium. In 1 week negative COP pulmonary artery wedge (PAW) gradients were generated by decreasing the PAW above COP in 5-mm-Hg increments from 0 to -15 in random order. At each 5-mm-Hg increment intrapulmonary shunt (Qs/Qt) was calculated from blood gases. A Qs/Qt of 15% was considered to be significant. Sepsis was then induced by the continuous infusion of E. coli. The animals then underwent a similar sequence of COP-PAW gradients and the measurements were repeated. At every COP-PAW gradient the Qs/Qt was elevated in the septic (S) period over the Qs/Qt during the nonseptic (NS) period. (0 mm Hg 32.61 k 9.02; S, 12.52 k 4.90, NS; -5 mm Hg -31.13 k 11.41, S; 13.54 k 4.23, NS (P < 0.02); -10 mm Hg -34.33 k 9.66, S, 16.95 k 8.49, NS (P < 0.02); -15 mm -31.54 k 4.87, S, 26.06 k 9.09, NS). The threshold COP-PAW gradient is raised from -10 in the nonseptic period to 0 in the septic period. Sepsis increases Qs/Qt significantly over the effect of increased hydrostatic pressure alone (linear model (P < 0.001)). Sepsis lowers the hydrostatic pressure necessary to cause pulmonary edema.

INTRODUCTION

There is controversy regarding the importance of the colloid oncotic pressure—pulmonary artery wedge pressure gradient (COP—PAW) in the production of pulmonary edema [12, 20]. In 1959 Guyton and Lindsey showed that increasing the left atrial pressure above 23 mm Hg in the presence of normal COP resulted in pulmonary edema [7]. However, when the concentration of the plasma proteins was reduced by half, the threshold left atrial pressure required to produce pulmonary edema was reduced to 13 mm Hg.

Zarins et al. have shown that when normal pulmonary capillary hydrostatic pressures are maintained, reduction in COP even to 0 mm Hg does not lead to pulmonary edema [22]. Thus with normal capillary permeability, increased capillary hydrostatic pressure is a prerequisite to the development of pulmonary edema. Increase in the pulmonary capillary permeability may be seen in sepsis and may therefore play a role in the development of the adult respiratory distress syndrome (ARDS) [1, 5]. The object of this study was to determine if sepsis reduced the threshold COP—PAW gradient necessary for pulmonary dysfunction.

MATERIALS AND METHODS

Seven adult male baboons (Papio anubis) weighing between 21 and 25 kg underwent left anterolateral thoracotomy under halo-
thane anesthesia. A No. 16 silicone rubber Foley catheter (Dover) was placed into the left atrium through the left atrial appendage. The catheter was brought out through a stab wound in the anterior thorax and tunneled subcutaneously to a pouch constructed on the anterior abdominal wall. The animals were allowed to recover for a period of 7–10 days before the second phase of the experiment was conducted.

On the day of the experiment the animals were anesthetized with intramuscular ketamine (150 mg) and atropine (0.04 mg). Anesthesia was maintained with intravenous sodium pentothal up to 15 mg/kg. Neuromuscular blockade was maintained with D-tubocurare 15 mg each hour.

A cuffed endotracheal tube was placed. The animals were ventilated with a constant-volume ventilator (Harvard) at a tidal volume of 15–18 cc/kg. The rate was adjusted so that the initial $P_aCO_2$ was maintained at 30–40 mm Hg. The $F_iO_2$ was maintained at 0.4 (Ventronics Model 5524 Oxygen Analyzer).

An arterial pressure cannula was placed in the aorta through a femoral cutdown. Arterial pressures were measured continuously. Through a femoral vein a 7-Fr balloon-tipped flow-directed catheter (Edwards Laboratories) was placed into the pulmonary artery wedge position using the characteristic wave pattern for guidance. Pulmonary artery wedge pressures were measured each half hour. Hewlett-Packard Model 1280 pressure transducers were used to measure all intravascular pressures. All intravascular pressures were recorded with a Hewlett-Packard Model 7758A eight-channel psychiograph.

Arterial and mixed venous blood gases were measured using the Instrumentation Laboratories Model 113 blood gas analyzer. The hemoglobin concentration and oxygen saturation were measured using the Instrumentation Laboratories Model 182 CO-Oximeter.

Colloid oncotic pressure was measured with an Instrumentation Laboratories Model 186 oncometer [3]. The gradient between COP and PAW was determined by simple subtraction.

Intrapulmonary shunt was calculated by the standard equation [10].

Each animal underwent two experimental periods: nonseptic and septic. During each of the periods the animals underwent a predetermined sequence of differing COP–PAW gradients: 0, −5, −10, and −15 mm Hg. The order of application of these gradients was randomized according to the Latin square technique [4]. The gradients were obtained by increasing the volume of the left atrial balloon with normal saline. After the desired pulmonary artery wedge pressure was reached an equilibration period of ½ hr was maintained. At the end of this period arterial and mixed venous blood gases were sampled and the intrapulmonary shunt ($Q_s/Q_t$) was calculated. The left atrial balloon was emptied and another equilibration period of ½ hr was observed before application of the next pressure in the sequence. After the sequence was completed during the nonseptic period the animals were given a continuous infusion of live Escherichia coli. The strain of E. coli was kindly supplied by Dr. Lerner B. Hinshaw, and prepared according to a previously described method [2]. The organisms were grown overnight on trypticase soy agar slants. They were washed with saline and the optical density was adjusted to 1.50 at 550 nm. The dosage of organisms varied between $10^6$ and $10^8$ organisms per kilogram.

After completion of the initial 2 hr of bacterial infusion the random sequence of COP–PAW gradients was repeated and intrapulmonary shunt was calculated.

At the conclusion of the experiment the animals were sacrificed with an overdose of potassium chloride. The lungs were excised and allowed to drain by gravity for 5 min. The lungs were weighed and then dried in a hot air oven at 65°C until constant weight was achieved. A wet-to-dry lung weight ratio was then calculated.

Student's $t$ test was used to assess dif-
RESULTS

The mean ± standard error of the mean $Q_s/Q_t$ at each COP–PAW gradient is shown in Fig. 1. At each gradient point the average $Q_s/Q_t$ of the septic period is higher than that of the nonseptic period. The $Q_s/Q_t$ values were significantly higher in the septic period than in the nonseptic period at COP–PAW gradients of 0 and −10 mm Hg. At each COP–PAW gradient the septic group has an average $Q_s/Q_t$ over 15%, a level generally agreed upon to represent clinically significant pulmonary dysfunction [6]. In the nonseptic period, the intrapulmonary shunt exceeds 15% only when the COP–PAW gradient is lowered to −10 mm Hg.

The mean ± standard error of the mean COP and PAW values in each COP–PAW gradient is shown in Table 1. COP differed significantly at all gradients except −15 mm Hg. There was no statistically significant difference between the PAW in the septic and the nonseptic period except at −5 mm Hg. The linear model regression analysis indicated that the effect of sepsis significantly increases the $Q_s/Q_t$ over and above the effect of COP–PAW gradient ($P < 0.005$).

The average wet-to-dry lung weight ratio of these animals is 7.72 ± 0.77. The control

### TABLE 1

COP AND PAW THROUGHOUT EXPERIMENT

<table>
<thead>
<tr>
<th>COP–PAW</th>
<th>0 mm Hg</th>
<th>−5 mm Hg</th>
<th>−10 mm Hg</th>
<th>−15 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonseptic</td>
<td>14.4 ± 0.8</td>
<td>15.0 ± 1.8</td>
<td>13.8 ± 0.7</td>
<td>9.8 ± 1.8</td>
</tr>
<tr>
<td>Septic</td>
<td>10.8 ± 1.5</td>
<td>9.4 ± 0.8</td>
<td>10.0 ± 0.5</td>
<td>7.1 ± 0.6</td>
</tr>
<tr>
<td><em>P &lt; 0.05</em></td>
<td><em>P &lt; 0.02</em></td>
<td><em>P &lt; 0.001</em></td>
<td>NS*</td>
<td></td>
</tr>
<tr>
<td><strong>PAW</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonseptic</td>
<td>13.0 ± 1.1</td>
<td>19.6 ± 2.4</td>
<td>20.2 ± 2.3</td>
<td>24.8 ± 3.1</td>
</tr>
<tr>
<td>Septic</td>
<td>10.6 ± 1.0</td>
<td>14.0 ± 0.7</td>
<td>20.5 ± 0.6</td>
<td>20.5 ± 1.9</td>
</tr>
<tr>
<td>NS</td>
<td><em>P &lt; 0.05</em></td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

* NS = Not significant.
value in this laboratory is 5.55 ± 0.33. The wet-to-dry lung weight ratio of the animals in this study were significantly above control using Student’s t test (P < 0.01).

**DISCUSSION**

The sum of forces across the normal pulmonary capillary membrane tends to keep the pulmonary interstitium dry [17]. The pulmonary artery wedge pressure in healthy baboons ranges from 5 to 10 mm Hg; the colloid oncotic pressure of normal baboons averages 15–20 mm Hg. The COP–PAW gradient is thus normally positive, which has led some investigators to conclude the maintenance of a positive COP–PAW gradient is the key element in maintaining a relatively dry pulmonary interstitium. Specifically, these workers have stated that decrease of the COP is a significant risk factor leading to pulmonary edema [12, 14].

Other investigators dispute that mere reduction of COP leads to pulmonary edema. Virgilio studied crystalloid and colloid resuscitation in major surgery [20]. The crystalloid group had a fall in COP at an average of 8 mm Hg; however, there was no difference in the pulmonary function of either group. In experimental animals, Zarins et al. [22] reduced the COP to 0 mm Hg in some instances. The hydrostatic pressure was kept within normal limits and there was no evidence of pulmonary edema.

When capillary permeability is normal, the hydrostatic pressure in the pulmonary capillary must be raised above a threshold pressure before pulmonary edema may occur. Guyton and Lindsay demonstrated that with normal capillary permeability and normal concentration of plasma proteins, the left atrial pressure must be raised above 23 mm Hg before pulmonary edema is developed [7]. In the present investigation, clinically significant arteriovenous admixture occurred only at a COP–PAW gradient of −10 mm Hg, which corresponded to a PAW of 24 mm Hg in most instances.

There was a drop in the COP from the nonseptic to the septic period. Previous studies in this laboratory have shown that reduction of the COP in septic animals does not lead to increased pulmonary dysfunction. It is doubtful whether the drop in the colloid oncotic pressure contributed to the increased pulmonary dysfunction in the septic period.

Increased pulmonary capillary permeability has been cited as an important pathophysiological mechanism in the development of pulmonary edema [18]. Sepsis is believed to increase pulmonary capillary permeability. Brigham et al. [1] infused live *Pseudomonas* into sheep and showed increased passage of fluid and protein into the lung lymph. In this study there was an abrupt and significant decrease in $P_{O_2}$ following the infusion of live organisms and the pulmonary extravascular water increased above baseline. The experiments of Coalson et al. [2] and previous studies in our laboratory have demonstrated that infusion of live *E. coli* leads to pulmonary dysfunction.

Intrapulmonary shunt is used as a measure of pulmonary edema. The wet-to-dry lung weights indicated severe pulmonary edema. Because of the random sequence of COP–PAW gradients the lung weights cannot be attributed to any particular gradient. Increased shunting can also occur with atelectasis or bronchoconstriction. In animals that had the infusion of *E. coli* alone without increase of hydrostatic pressure the $Qs/Qt$ did not exceed 20%. At high levels of shunting, as in this study, Warhica et al. found that $Qs/Qt$ correlated well with EVLW [21]. Hill et al. [8] performed a study similar to ours in dogs. They also infused *E. coli* and increased hydrostatic pressure. Their data show a rise in the EVLW during the experiment that paralleled the rise in $Qs/Qt$ of the present study. It is interesting to note that for the nonseptic period the arteriovenous admixture sharply increased at 20–25 cm: precisely the threshold level for pulmonary edema observed by Guyton and Lindsey [7]. Thus,
at least in the nonseptic period, there is strong inferential evidence that the increase in intrapulmonary shunt can be accounted for by pulmonary edema. Sepsis reduced the threshold COP–PAW gradient necessary for the development of pulmonary edema. In the nonseptic period \( Q_s/Q_t \) over 15% did not occur until gradients of \(-10\) mm Hg were reached. During sepsis \( Q_s/Q_t \) was greater than 15% with a gradient of 0 mm Hg. This study has potentially important clinical implications. In clinical states with normal pulmonary capillary permeability, increased hydrostatic pressure is a prerequisite to pulmonary edema. With an intact pulmonary capillary membrane the PAW should be kept within normal limits, but a greater range seems to be permissible without the development of pulmonary edema. In the patient with sepsis, hypoproteinemia, or at risk for ARDS from other causes our study suggests that even greater attention must be paid to left atrial filling pressure. There may be a synergistic relationship for pulmonary dysfunction between pulmonary capillary damage and volume loading, as suggested by Peters and Hogan [13].

Other clinical implications pertain to the choice of fluid therapy. Skillman et al. recommended colloid infusion for therapy of respiratory failure although the improvement in pulmonary function in his patients was not consistent [16]. Strum et al. found that if septic shock is treated with colloid infusion there is much greater passage of colloid and fluid into the pulmonary interstitium [19]. Efforts to increase COP with exogenous colloid are generally futile because colloid passes quickly into the interstitium and increases in plasma COP are small and transient [15].

This experiment shows that in the nonseptic state the COP–PAW gradient must be lowered to at least \(-10\) mm Hg for clinically significant pulmonary dysfunction to occur. Sepsis raises the \( Q_s/Q_t \) above 15% at all COP–PAW gradients measured. Thus, sepsis reduced the threshold COP–PAW gradient necessary for pulmonary dysfunction.

REFERENCES


