The Effect of Sepsis and Reduced Colloid Osmotic Pressure on Pulmonary Edema

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INTRODUCTION

The interrelationship of hydrostatic pressure and osmotic forces across the capillary membrane are described by the Starling equation [10]. Increasing pulmonary capillary hydrostatic pressure is a cause of pulmonary edema [3]. Pulmonary edema develops at a lower hydrostatic pressure when plasma colloid oncotic pressure is lowered suggesting that the gradient between colloid oncotic pressure (COP) and pulmonary artery wedge pressure (PAW) is an important factor in the development of pulmonary edema [3]. Decrease in plasma oncotic pressure (COP) can also result in a reduction in the COP–PAW gradient. Pulmonary edema has been attributed to the reduction of the COP alone [7, 8]. We have previously shown that reduction of the COP without elevation of the pulmonary artery wedge pressure does not result in pulmonary edema [14, 16].

Sepsis is a common denominator in patients with respiratory failure [2] and it has been suggested that altered pulmonary capillary permeability is a possible cause for the development of pulmonary edema [1]. The purpose of this investigation is to determine the effect of both reduced COP and sepsis on the development of pulmonary edema and pulmonary dysfunction in baboons.

MATERIALS AND METHODS

Nine male baboons (Papio anubis) weighing between 18 and 27 kg (mean 23 kg) were randomly assigned to one of three experimental groups: P—plasmapheresis alone, S—sepsis alone, P + S—both sepsis and plasmapheresis. Each animal was sedated with 0.1 mg/kg phencyclidine–HCl (Sernylan) with supplemental doses administered every 1–2 hr during the study. A cuffed endotracheal tube was placed and the animals were ventilated with a volume ventilator at 15 ml/kg delivered at a fractional oxygen concentration of 0.5. The rate was adjusted so that the arterial carbon dioxide was 30–40 mm Hg and was not changed thereafter for the duration of the experiment.

Incisions were made in both groins under local lidocaine anesthesia and catheters were positioned in the thoracic aorta, inferior vena cava and pulmonary artery (Edwards Laboratories). The pulmonary artery wedge pressure and arterial pressure were monitored using Statham P-23 transducers and a Brush 4-channel recorder. Blood gases were measured using the Instrumentation Laboratories Model 813 blood gas analyzer. Hemoglobin and oxygen saturation were measured using the Instrumentation Laboratories 282 COoximeter. Intrapulmonary shunt was calculated using the standard shunt equation [13]. The colloid oncotic pressure was measured by a transducer membrane system (Instrumentation Laboratories Model 186).

Sepsis was induced by the intravenous infusion of live Escherichia coli organisms over a 2-hr period. The E. coli were isolated from a neonate who died of sepsis and were further subcultured in trypticase soy broth.
The organism count was adjusted by optical density measurement and organisms were infused at a rate of 2.7 to $5.4 \times 10^9$ organisms per hour.

Plasmapheresis was accomplished by removal of 25% of estimated blood volume and reinfusion of packed red blood cells while pulmonary artery wedge pressure was maintained at a constant level by the intravenous infusion of lactated Ringer's solution. Plasmapheresis was repeated three times.

During the first 2 hr of the experiment, *E. coli* were infused in Groups S and P + S while Group P received an infusion of normal saline. During the second 2 hr, Groups P and P + S underwent plasmapheresis while Group S received a saline infusion to maintain pulmonary artery wedge pressure. All animals were observed for a final 4 hr.

After completion of the experiment the animals were returned to their cages. Blood cultures were taken at 24 hr and the animals were sacrificed. The lungs were removed immediately and dried in a hot air oven at 55°C until the weight was stable and the wet-to-dry lung weight ratio was calculated. COP, PAWP, COP-PAW, $Q_n/Q_l$, A-aDO$_2$, and wet-to-dry lung weights were compared using one way analysis of variance. The Wilcoxon's rank sum test was used to determine differences in intrapulmonary shunts between groups and the colloid oncotic pressure and the pulmonary artery wedge pressure. The multiple linear regression analysis of variance was used to determine the factors influencing the intrapulmonary shunt.

**RESULTS**

Blood cultures were positive at 24 hr in all animals that received *E. coli* infusion. In Group S, one of three animals died within 24 hr while in Groups P + S, two animals died within 24 hr.

Pulmonary artery wedge pressure remained unchanged throughout the course of the experiment (Fig. 1).

Plasmapheresis alone (Group P) caused a 47% decrease in COP. In the group with sepsis and plasmapheresis (Group S and P), there was a 60% reduction. In the group that was septic alone (Group S) there was a 32% decrease of the COP without plasmapheresis (Fig. 2).

The COP–PAW gradient in the group with plasmapheresis alone (Group P) decreased from $12.7 \pm 4.5$ to $1.2 \pm 1.7$ mm Hg ($P < 0.05$). In the group with sepsis followed by plasmapheresis the COP–PAW gradient was reduced from $14.7 \pm 4.2$ to $1.1 \pm 1.1$ mm Hg ($P < 0.05$).

The COP–PAW gradient fell from 17.3...
Baseline After Infusion After Plasmapheresis

FIG. 2. The colloid oncotic pressure in mm Hg in the three groups plasmapheresis resulted in a significant reduction of colloid oncotic pressure.

± 0.9 to 8.4 ± 3.2 mm Hg (P < 0.05) in the group with sepsis alone (Group S) (Fig. 3). While this reduction in Group S was significantly lower than the baseline, it was also higher than the COP–PAW gradients in the other two groups (P < 0.05). Intrapulmonary shunt did not change in any group during the course of the experiment (Fig. 4). Linear regression analysis revealed that the magnitude of the shunt was unrelated to the COP or COP–PAW gradient.

The calculated wet-to-dry lung weight ratios were quite similar in all three groups (P: 3.5 ± 0.5; S: 2.4 ± 0.1; P and S: 3.3 ± 0.7). When these data were examined using the one-way analysis of variance, there was no significant differences between the groups.

**DISCUSSION**

The most common form of clinical pulmonary edema is that associated with left ventricular failure. It is due to an increase in the hydrostatic pressure as demonstrated by Guyton and Lindsey [3]. The hydrostatic pressure must be raised to a threshold pressure of 25 mm Hg before pulmonary edema ensued. Guyton and Lindsey [3] also found that if the level of plasma colloids

FIG. 3. The colloid oncotic pressure in pulmonary artery wedge pressure gradient was significantly reduced with Plasmapheresis.
were reduced by half, the threshold pressure necessary for formation of pulmonary edema fell to 11–13 mm Hg. Reduced colloids did have an effect on the development of pulmonary edema, but it was still necessary for hydrostatic pressure to be raised above a threshold for pulmonary edema to occur.

This observation of Guyton and Lindsey [3] was applied to the treatment of respiratory failure by Skillman [9]. He advocated raising the colloid level with infusion of colloid, but there was no striking and consistent improvement in pulmonary function with this treatment.

Mere reduction of the COP does not lead to pulmonary dysfunction or pulmonary edema. Zarins [16] reduced the colloid oncotic pressure in baboons to near 0 mm Hg through plasmapheresis without the development of pulmonary edema or increase in the intrapulmonary shunt. In his experiment, the pulmonary artery wedge pressure was kept below 10 mm of mercury which is below the threshold of Guyton. Thus reduction of the colloid oncotic pressure without an increase in intravascular pressure does not lead to pulmonary edema.

Morissette and Weil [7] and Rackow and Fein [8] have stated that reduction of the COP and the COP–PAW gradient is an important prognostic indicator for the development of pulmonary edema and subsequent cardiopulmonary death. However, in their studies they used radiographic data, usually insensitive to early changes and not readily quantifiable, for the determination of pulmonary edema. Their colloid oncotic pressure determinations were made at unspecified times after admission to the ICU, and it is difficult to single out decreased COP as the primary predisposing cause of pulmonary edema.

Brigham [1] showed that with the infusion of live Pseudomonas into sheep, there was a drop in the arterial oxygen tension and an increase in the pulmonary extravascular water measured noninvasively. However, at the end of the experiment, there was no gravimetric evidence for pulmonary edema with sepsis. This lack of clear evidence for pulmonary edema is reiterated in our experiment. The lung weight ratios were well below the normal baboon wet–dry lung weight of 5.5 for this laboratory. It is possible that interstitial pulmonary edema may have been detected by a more sensitive technique. This discrepancy with a strong clinical association of sepsis with respiratory failure and previously reported primate studies by Hinshaw [4] may be the result of differences in the strain of E. coli and in the dosage. At present, we cannot ascribe pulmonary dysfunction or pulmonary edema to sepsis.

In the present experiment, there is no synergistic relationship between the ef-
fect of sepsis and reduction of the colloid oncotic pressure. However, reduction of the colloid oncotic pressure and colloid oncotic pressure—pulmonary artery wedge gradient to extremely low levels did not result in pulmonary dysfunction.

REFERENCES


