The Relationship of the Colloid Osmotic–Pulmonary Artery Wedge Pressure Gradient to Pulmonary Edema and Mortality in Critically Ill Patients*

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The relationship of serum colloid osmotic pressure (COP) and pulmonary artery wedge pressure (PAWP) to pulmonary edema and mortality was investigated in 76 critically ill patients. Forty patients suffered from circulatory shock and 36 did not. The COP-PAWP gradient and radiographic evidence of pulmonary edema were measured at the time of diagnosis. The COP-PAWP gradient was markedly decreased in both shock and non-shock patients with pulmonary edema. Decrease of the COP-PAWP gradient correlated with mortality only in those patients with shock. The shock patients who died had a significantly higher incidence of pulmonary edema than those who survived, whereas there was no difference in the incidence of pulmonary edema for surviving or dying non-shock patients. We conclude that marked decreases of the COP-PAWP gradient predict pulmonary edema in the critically ill, but predict mortality only for patients with circulatory shock.

Pulmonary edema is a frequent complication encountered in the critically ill patient and ultimately results from the excessive shift of fluid from the intravascular to extravascular space.

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Starling1 was one of the first to define the colloid osmotic and hydrostatic forces regulating the transvascular flux of fluid. Guyton and Lindsay2 supported Starling’s original contentions by demonstrating in laboratory animals that major alterations of the balance between colloid osmotic and hydrostatic pressures could result in lung fluid accumulation. Since that time it has become possible to measure two of these forces in the clinical setting: serum colloid osmotic pressure (COP) and pulmonary artery wedge pressure (PAWP). Recent clinical studies have shown that increases of PAWP3 and decreases of both COP4 alone and COP-PAWP5-8 gradient correlate with the development of pulmonary edema. However, while it is widely accepted that increases of PAWP may result in pulmonary edema, there is considerable disagreement on the role of colloid osmotic pressure and the COP-PAWP gradient. Furthermore, questions have arisen regarding the clinical importance of pulmonary edema in predicting patient outcome.

The findings of the present study suggest that reductions of the COP-PAWP gradient are highly related to the development and the degree of pulmonary edema and that this occurrence in patients suffering from circulatory shock resulted in a significant increase in mortality.

Materials and Methods

The study included 76 consecutive admissions to the critical care unit who required right heart catheterization for clinical purposes. There were 39 women and 37 men whose ages ranged from 20 to 90 years (median = 62 years). The primary diagnoses of the patients and their in-hospital outcomes are listed in Table 1.

Central venous blood samples were taken from each patient for determination of serum colloid osmotic pressure at the time of right heart catheterization. The colloid osmotic pressure was directly measured using a membrane transducer system (Weil Oncometer, Instrumentation Laboratories, Lexington, Mass). Normal saline solution (0.9 percent NaCl)

Table 1—Primary Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Survived</th>
<th>No. Expired</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>3</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Septic shock</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>42</td>
<td>76</td>
</tr>
</tbody>
</table>
was used as a zero reference and 5 percent human serum albumin was used as a reference standard, as previously reported.4

Right heart catheterization was performed for clinical purposes using a triple-lumen thermodilution flow-directed catheter (Swan-Ganz, Edwards Laboratories, Santa Ana, CA). The position of the catheters was confirmed by pressure recordings and chest roentgenograms. Pressure transducers were zeroed at the mid-chest level with the patient supine. Pressure measurements were recorded with the patients off all assisted ventilation. Coincident with the PAWP measurements and blood sampling for colloid osmotic pressure, chest roentgenograms were taken with the patients in the semi-erect position (45°) at a tube-to-chest distance of 40 inches. Roentgenographic films were evaluated independently according to the criteria of Turner et al6 as adapted by Luz et al.7

The degree of pulmonary edema was graded as follows: 0, normal pulmonary vessels with orderly tapering toward the periphery; 1+, equal perfusion of upper and lower lung zones; 2+, minimal interstitial prominence and perivascular edema insufficient to obliterate vascular markings; 3+, prominent interstitial markings (Kerleys' B lines) and diffuse reticular pattern with obliteration of the vascular markings; 4+, bilateral confluent shadows of relatively uniform density but ill-defined margins. Grades 2 and 3 were considered diagnostic of interstitial pulmonary edema, and grade 4 diagnostic of alveolar pulmonary edema.

The presence of circulatory shock was determined by two or more of the following criteria: cardiac index less than 2.2 L/min/m2; systolic blood pressure less than 90 mm Hg; clinical evidence of hypoperfusion, such as decreased urine output, cool and clammy extremities, or decreased mental status; and serum arterial lactate greater than 18 mg/dl.

The Student two tailed t test, paired sample analysis, chi-square test, and multiple analysis of variance were used for statistical evaluation of data. All data are reported as mean ± standard error of the mean (SEM).

RESULTS

The COP-PAWP gradient was determined at the time of initial right heart catheterization for each patient and bore a distinct relationship to the absence or presence of pulmonary edema. The COP-PAWP gradient was markedly decreased in patients with pulmonary edema as compared with those patients without pulmonary edema (Fig 1). Furthermore, the COP-PAWP gradient was significantly lower (p < 0.001) for patients with radiographic evidence of alveolar pulmonary edema as compared to patients with interstitial pulmonary edema (Fig 2). These findings were true for both shock and nonshock patients (40 and 36 patients, respectively).

There was no significant difference in the COP-PAWP gradient between shock and nonshock patients (5.3 ± 0.8 mm Hg vs 6.7 ± 1.7 mm Hg, respectively). When COP-PAWP gradients were related with in-hospital mortality for the entire group, no significant associations were apparent. However, when only shock patients were examined, analysis

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21316/ on 03/31/2017

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21316/ on 03/31/2017

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Pulmonary Edema and Mortality in Critically Ill (Rackow, Fein, Siegel)
revealed that decreases of COP-PAWP gradient were associated with increases in mortality (Fig 3).

Pulmonary edema occurred in 52.6 percent of all patients. Both pulmonary edema and shock each adversely affected mortality to the same degree (67.5 percent mortality when either is present, \( p < 0.05 \)). When shock patients were examined alone, there was a marked increase in mortality among those with either interstitial or alveolar pulmonary edema as compared with those with no pulmonary edema (Fig 4). Overall, a significantly higher incidence of pulmonary edema was found in patients dying in shock than those surviving (74 percent vs 31 percent, respectively, \( p < 0.05 \)), whereas there was no difference in pulmonary edema incidence for nonshock patients (47 percent vs 43 percent, respectively).

If pulmonary edema in the face of PAWP \( \leq 15 \) mm Hg is considered noncardiogenic, then the 76 patients may be separated into no pulmonary edema (NPE), cardiogenic pulmonary edema (CPE), and noncardiogenic pulmonary edema (NCPE) groups (Table 2). Multivariate analysis revealed that the COP-PAWP gradient independently identified patients with pulmonary edema. Noncardiogenic pulmonary edema (NCPE) was further identified by a decrease in COP and a normal PAWP, while CPE was characterized by a normal COP and an increase in PAWP. While COP distinguished NCPE patients and PAWP identified CPE patients, the COP-PAWP gradient reliably identified pulmonary edema in both groups in this series.

The presence of sepsis or septic shock did not affect the incidence of pulmonary edema. Chi-square analysis revealed no significant difference in the incidence of sepsis between the patients with NPE and those with NCPE (33 percent vs 50 percent, respectively). Furthermore, while serum COP was decreased for the NCPE group as a whole, the presence of sepsis did not affect the level of COP in either that group or the patients with NPE (Ta-

### Table 2—The Colloid Osmotic Pressure (COP)—Pulmonary Artery Wedge Pressure (PAWP) Gradients in All 76 Critically Ill Patients

<table>
<thead>
<tr>
<th></th>
<th>COP, ( \text{mm Hg} )</th>
<th>PAWP, ( \text{mm Hg} )</th>
<th>COP-PAWP, ( \text{mm Hg} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>edema</td>
<td>36 20.4±0.6</td>
<td>7.1±1.0</td>
<td>13.0±0.9</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary</td>
<td>24 21.7±0.8</td>
<td>24.3±1.0*</td>
<td>-2.7±1.2*</td>
</tr>
<tr>
<td>edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiogenic</td>
<td>16 14.3±0.7*</td>
<td>12.2±0.8*</td>
<td>1.9±0.5*</td>
</tr>
</tbody>
</table>

Mean ± SEM

\( *p < 0.001 \) compared to no pulmonary edema group

\( \dagger p < 0.001 \) compared to cardiogenic pulmonary edema group
Table 3—The Colloid Osmotic Pressure (COP) Pulmonary Artery Wedge Pressure (PAWP) Gradients in Septic and Non-Septic Patients

<table>
<thead>
<tr>
<th></th>
<th>COP, mm Hg</th>
<th>PAWP, mm Hg</th>
<th>COP-PAWP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pulmonary Edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>septic</td>
<td>12</td>
<td>19.0±0.9</td>
<td>7.8±0.9</td>
</tr>
<tr>
<td>nonseptic</td>
<td>24</td>
<td>21.1±0.7</td>
<td>6.8±1.3</td>
</tr>
<tr>
<td>Noncardiogenic Pulmonary Edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>septic</td>
<td>9</td>
<td>13.9±1.0</td>
<td>11.3±1.3</td>
</tr>
<tr>
<td>nonseptic</td>
<td>7</td>
<td>14.8±1.1</td>
<td>13.3±0.7</td>
</tr>
</tbody>
</table>

Mean ± SEM
*p<0.001 compared to no pulmonary edema groups

3). The PAWP was higher in the NCPE group, but as with COP, was not affected by the presence of sepsis. There was no significant difference in PAWP between septic and nonseptic patients in either the NPE or NCPE groups.

DISCUSSION

In 1896, Starling1 defined the forces regulating the translocation of fluid between the intravascular and extravascular compartments. The movement of fluid is now believed to be largely a function of the balance between transcapillary colloid osmotic and hydrostatic pressures2 and the integrity of the capillary membrane:10,11

\[ Q_t = K_f (P_c - P_i) - K_f \sigma (\pi_c - \pi_i) \]

where \( Q_t \) is the net transcapillary fluid flux; \( K_f \) is the filtration coefficient which defines the fluid conductance across the capillary membrane; \( \sigma \) is the reflection coefficient that defines the effectiveness of the membrane in preventing protein leakage from the capillary; \( P_c \) and \( P_i \) are the hydrostatic pressures in the capillary and interstitial spaces, respectively; and \( \pi_c \) and \( \pi_i \) are the colloid osmotic pressures in the capillary and interstitial spaces, respectively. Two opposing forces, \( \pi_c \) and \( P_c \), can be readily measured in patients at the bedside as the serum COP and PAWP. Assuming a normal COP of 22-25 mm Hg12 and a normal PAWP of 6 to 15 mm Hg,13 there is a COP-PAWP gradient ranging from 7-19 mm Hg favoring the retention of fluid in the pulmonary intravascular compartment. When that gradient is reduced by either elevation of PAWP, reduction of COP, or both, increased fluid flux into the pulmonary extravascular space may occur.14

This study, which examines a series of patients at a single point in time, i.e., the time of right heart catheterization, shows that decreases in the COP-PAWP gradient are associated with the development of both cardiogenic and noncardiogenic pulmonary edema. Furthermore, as may be inferred from the Starling "law," this series of patients demonstrates that the greater the decrease of the COP-PAWP gradient, the more severe the radiographic evidence of pulmonary edema. Guyton and Lindsay4 demonstrated in dogs that the severity of pulmonary edema was proportional to the gradient between plasma COP and left atrial pressure. Studies in baboons by Zarins et al15 have shown that reduction of the COP-PAWP gradient secondary to decreases in COP after plasmapheresis results in a seven-fold increase in pulmonary lymph flow, but without evidence of overt pulmonary edema. Recently, Harms and associates16 documented in sheep a three-fold acute increase in lung lymph flow after plasmapheresis. These findings appear to support the role of the COP-PAWP gradient in the intercompartmental shift of fluid, as originally suggested by Starling.1

The presence of pulmonary edema had a significant adverse effect on mortality only in patients with circulatory shock. The shock patients in this study who died had a significantly higher incidence of pulmonary edema than those who survived, whereas there was no difference in the incidence of pulmonary edema for surviving or dying nonshock patients. In our study, the presence of sepsis did not appear to influence the development of pulmonary edema. There was no significant difference in COP among septic and nonseptic patients. On the other hand, significantly decreased COP characterized patients with noncardiogenic pulmonary edema, and the COP-PAWP gradient was significantly reduced in both the septic and nonseptic patients. These findings contradict investigations by Tranbaugh, Lewis et al10 which related the development of pulmonary edema to sepsis in burn-injured patients. Experimental studies in sheep by Brigham et al11,17 suggest that bacteremia and endotoxemia increase lung microvascular permeability and transvascular fluid flow. Nevertheless, Rice et al18 could not document that experimental sepsis increases lung water in baboons.

We conclude that the marked decrease of the COP-PAWP gradient predicts pulmonary edema in the critically ill and mortality in those patients in shock. However, the development of pulmonary edema in nonshock patients does not appear to adversely influence survival.

REFERENCES

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8 Rackow EC, Fein IA. Fulminant noncardiogenic pulmonary edema in the critically ill. Crit Care Med 1978; 6:360-63