Increases in Plasma Oncotic Pressure During Acute Cardiogenic Pulmonary Edema

JAIME FIGUERAS, M.D., AND MAX HARRY WEIL, M.D., PH.D.

SUMMARY Colloid oncotic pressure (COP) was measured in 95 patients with clinical and radiological evidence of acute cardiogenic pulmonary edema. Fifty patients who were admitted for coronary observation but in whom acute myocardial infarction was excluded, and 21 patients who had sustained acute myocardial infarction without evidence of left ventricular failure served as controls.

Consequently, higher values of COP, total plasma protein, and hematocrit were observed in patients with pulmonary edema. Increases in COP during pulmonary edema were best explained by transudation of hypoprotic fluid into extravascular spaces. Following treatment of pulmonary edema in 76 patients with furosemide, morphine, and oxygen, pulmonary edema was reversed in 65 patients. Reabsorption of hypoprotic fluid from extravascular sites with a significant decline in COP, total protein and hematocrit followed reversal of pulmonary edema. No significant changes in these parameters were observed in patients who failed to respond to therapy.

These observations implicate filtration of hypoprotic fluid from the intravascular compartment during onset of cardiogenic pulmonary edema and reabsorption of hypoprotic fluid into the intravascular compartment during reversal of pulmonary edema.

IN CLINICAL STUDIES previously reported from this unit,1 acute cardiogenic pulmonary edema (PE) was related either to increases in hydrostatic pulmonary capillary pressures in excess of plasma colloid oncotic pressure (COP) or to the lowering of COP. The left ventricular filling pressure alone was not a consistent indicator of the risk of pulmonary edema. In addition to COP, alterations in tissue hydrostatic pressure were recognized. The edema fluid which accumulates in the interstitium and in alveoli in this type of pulmonary edema is known to be low in protein content, usually less than one-half of that observed in plasma.3

Since as much as 3 L of fluid may extravasate following the onset of PE,3,4 hemococoncentration should be anticipated. Consequently, the red cell fraction is likely to be increased. If the extravasated fluid is lower in protein content than that of circulating blood, the protein concentration and the colloid oncotic pressure of plasma would be increased. There is both experimental and clinical evidence of such increases in hematocrit and plasma protein concentration following onset of pulmonary edema.7,8

The purpose of the present study was to investigate systematically these issues in patients following onset of acute PE. Sequential changes in hematocrit, plasma proteins, and COP were measured prior to and following emergency treatment of PE which included oxygen, morphine, and furosemide.

Methods

Patients

A total of 95 patients admitted to the University of Southern California Center for the Critically Ill between March 1972 and February 1975 were investigated. There were 52 men and 43 women ranging from 44 to 99 years (median 70) in age. In each instance, the patient presented with a past history of heart disease (86 patients) or with unequivocal clinical and electrocardiographic evidence of acute myocardial infarction (9 patients). Primary causes of heart disease in the patients are summarized in table 1. In each instance respiratory distress of sudden onset, orthopnea, and bilateral moist rales were documented. Portable anteroposterior semi-upright chest X-rays at a tube-to-chest distance of 40 inches were obtained. Radiographic criteria of interstitial or alveolar pulmonary edema with or without pleural effusion which conformed to grade 3 or 4 PE, according to the criteria of Turner, Lau, and Jacobson,9 were fulfilled. Patients in whom respiratory distress was other than of acute onset within a period of six hours prior to study or who presented with clinical signs of shock were excluded from study.

Fifty patients, including 24 men and 26 women, ranging in age from 22 to 86 years (median 62), who were admitted for coronary observation during the same interval because of chest pain, served as one control group. In each instance clinical, electrocardiographic, and routine enzyme measurements excluded the diagnosis of acute myocardial infarction. None of the patients had respiratory distress, pulmonary rales or radiographic criteria of PE. All patients survived and were discharged. These patients were designated as control group 1.

An additional group of 21 patients observed during the same interval of study, including 16 men and 5 women, ranging in age from 37 to 86 years (mean 63), who had sustained acute myocardial infarction, were designated as control group 2.2 Diagnosis was based on Q wave and associated ST and T wave abnormalities consistent with acute myocardial infarction. Characteristic increases in enzymes including creatine phosphokinase (CPK), lactic dehydrogenase (LDH), and serum glutamic oxaloacetic transaminase (SGOT) were documented. None of the patients had clinical or radiographic signs of heart failure or of PE. Two of the patients in group 2 died within an interval of two and 14 days after admission.

Methods of Study

Vital signs, fluid intake, and urine output were measured at hourly intervals. Portable chest X-ray was obtained im-
mediately following admission. Duplicate measurements of blood pH (pHa) oxygen tension (PaO2), carbon dioxide tension (PaCO2), oxygen saturation (SaO2), hematocrit, total plasma protein, plasma colloid osmotic pressure, plasma osmolality, plasma sodium, plasma potassium and arterial blood lactate (lactatea) were obtained on a single sample of 6 ml of heparinized arterial blood.

Blood gases were measured by standard electrode technique utilizing a Radiometer Model pH M27 System. Oxygen saturation was measured with an Instrumentation Laboratory Coximeter Model 182. Hematocrit was measured by microhematocrit technique. Total protein was measured by refractometry (American Optical Refractometer TS meter Model 10400). Plasma colloid osmotic pressure was measured with a transducer membrane system by methods previously described.10 Plasma osmolality was measured by freezing point depression utilizing an Advanced Digimatic Osmometer Model 3D. Plasma sodium and potassium were measured with an IL Flame Photometer Model 143. Arterial blood lactate was measured by an enzymatic technique.11

Except for administration of oxygen, baseline measurements were completed prior to drug therapy. Treatment was established by protocol and included administration of oxygen by face mask or nasal cannula, furosemide 20 to 160 mg (mean 80) by intravenous injection and one or more doses of morphine sulfate in amounts ranging from 5 to 15 (mean 8) mg by intramuscular or intravenous injection. Subsequent treatment included intravenous injection of digoxin in 31 of the patients in amounts ranging from 0.25 to 1.0 mg. In 76 of the 95 patients a second series of measurements was obtained within 36 (mean 15.7) hours following start of drug treatment, when clinical improvement was regarded as maximal. Patients who were mechanically ventilated or who subsequently received infusions of blood or colloid were excluded from further study.

Differences were statistically analyzed by the Student’s t-test for paired and unpaired observations.

### Results

Tachypnea, relative hypoventilation during oxygen breathing, hypercapnia, and acidemia were observed during acute PE. In confirmation of previous reports, hypercapnia was frequently observed even though the patients had no evidence of chronic lung disease.12,13 In 74 of 95 patients (78%), arterial blood lactate was increased to levels exceeding 1.5 mM/L, an indication of perfusion failure. Although oxygen was administered, the arterial oxygen tension and saturation were reduced during PE. Differences between patients with PE and the two control groups were highly significant for each of the parameters reflecting respiratory gas exchange (table 2). There were no statistically significant differences between the two control groups.

Plasma osmolality was significantly higher in patients with acute PE. In the absence of significant differences in plasma sodium concentrations, the increase in osmolality reflects increases in glucose, urea, and/or acid metabolites. Increase in resting heart rate but no significant difference in arterial pressure was observed during PE.

The findings of specific relevance to the present study were simultaneous increases in plasma COP, plasma total protein concentration, and hematocrit in patients with PE (table 3). Increases in COP were correlated with increases in total protein (r = 0.533). There were no significant differences between male and female patients (25.9 and 25.7, respectively) in mean COP.

Patients with more advanced ventilatory defects and specifically patients in whom PaCO2 exceeded 45 torr had higher levels of total protein and COP than patients in whom PaCO2 was less than 35 torr (P < 0.05). However, no

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**Table 2. Initial Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Acute PE  (95 psa)</th>
<th>Control 1 (50 psa)</th>
<th>Control 2 (21 psa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>109 ± 2.3</td>
<td>81 ± 3.1**</td>
<td>81 ± 3.3†</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>146 ± 4.5</td>
<td>136 ± 3.6</td>
<td>129 ± 0.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84 ± 2.4</td>
<td>81 ± 2.1</td>
<td>74 ± 3.6</td>
</tr>
<tr>
<td>resp/min</td>
<td>30 ± 0.7</td>
<td>20 ± 0.5**</td>
<td>20 ± 0.6†</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.39 ± 0.001</td>
<td>0.24 ± 0.001**</td>
<td>0.29 ± 0.004†</td>
</tr>
<tr>
<td>PaO2, torr</td>
<td>79 ± 4.0</td>
<td>102 ± 5.8</td>
<td>112 ± 14.4†</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>87 ± 1.0</td>
<td>96 ± 0.3</td>
<td>96 ± 0.7†</td>
</tr>
<tr>
<td>PaCO2, torr</td>
<td>47.9 ± 1.7</td>
<td>38.4 ± 0.6**</td>
<td>39.0 ± 1.0†</td>
</tr>
<tr>
<td>pHa, units</td>
<td>7.26 ± 0.01</td>
<td>7.42 ± 0.007**</td>
<td>7.40 ± 0.009‡</td>
</tr>
<tr>
<td>HCO3(a) eM/L</td>
<td>19.7 ± 0.4</td>
<td>25.2 ± 0.4**</td>
<td>24.0 ± 0.7†</td>
</tr>
<tr>
<td>Lactate, mM/L</td>
<td>3.5 ± 0.2</td>
<td>1.0 ± 0.07**</td>
<td>0.9 ± 0.06‡</td>
</tr>
<tr>
<td>Na, mM/L</td>
<td>130 ± 0.5</td>
<td>140 ± 0.6</td>
<td>138 ± 0.4</td>
</tr>
<tr>
<td>K, mM/L</td>
<td>4.1 ± 0.07</td>
<td>3.8 ± 0.07*</td>
<td>3.9 ± 0.07</td>
</tr>
<tr>
<td>Plasma osmolality, mOsm/L</td>
<td>302 ± 1.3</td>
<td>291 ± 1.5**</td>
<td>293 ± 2.0†</td>
</tr>
</tbody>
</table>

The values shown are mean ± standard error of mean.

*P < 0.01 (PE vs C1); **P < 0.001 (PE vs C1).

†P < 0.006 (PE vs C1); †P < 0.001 (PE vs C2).

Abbreviations: PE = pulmonary edema; HR = heart rate; S and DBP = systolic and diastolic blood pressure; resp = respiration; FIO2 = inspired oxygen fraction; PaO2 = arterial oxygen tension; SaO2 = arterial oxygen saturation; PaCO2 = arterial carbon dioxide tension; pHa = arterial pH; HCO3a = arterial bicarbonate.
significant correlation was found between the initial COP and PaCO₂, pH, plasma osmolalinity, plasma sodium and potassium, lactate, or arterial systolic and diastolic pressures.

Effects of treatment of pulmonary edema were evaluated on the basis of clinical signs including reversal of diaphoresis, warning of the skin, diminution of pulmonary rales and disappearance of orthopnea. In 65 patients in whom clinical signs of pulmonary edema were reversed, there was negative fluid balance averaging 1412 ml. Respiratory rate, blood gases, plasma osmolality and blood lactate were restored to normal within an average of 15.5 hours (table 4). A significant decline in heart rate and diastolic blood pressure were also observed. Colloid osmotic pressure, TP, and Hct decreased to levels comparable to the control group (table 5). A representative case in which changes in COP, TP, and Hct during and after reversal of PE are demonstrated is shown in figure 1.

To the contrary, no significant change in these parameters was observed in 11 patients who failed to improve. Continued lactacidemia indicated continued circulatory failure.

Of the 76 patients in whom the effects of treatment were objectively evaluated, the changes in COP were weakly correlated with simultaneous changes in plasma protein (r = 0.67) and hematocrit (r = 0.55).

Discussion

An increase in left ventricular filling pressure, and consequently, a corresponding increase in pulmonary capillary hydrostatic pressure constitute objective criteria of left ventricular failure. Providing that the integrity of the capillary membrane is not compromised, the egress of fluids into the pulmonary interstitium and subsequently into the alveoli is attributed to an increase in hydrostatic pressure and the excessive fluid influx which results from it.14-17

Experimentally, integrity of the capillary membrane as a semipermeable membrane is maintained in cardiogenic pulmonary edema when the capillary hydrostatic pressure is increased to the levels commonly observed in patients with pulmonary edema.1, 5, 16, 18, 19 The fluid which escapes from the intravascular compartment by filtration is hyponcotic with respect to plasma. COP or protein concentration measured on tracheobronchial fluid in cases of cardiogenic PE ranged from 32% to 61% of that simultaneously observed in plasma.2 Micropipette punctures of the pulmonary interstitium after cardiogenic pulmonary edema or hemodilution in experimental animals also indicate that the edema fluid has approximately one-half of the protein content of plasma.20

Since the transudate into the lung appears to be hyponcotic with respect to plasma, fluid loss from the intravascular compartment into the lung is accompanied by increases in protein concentration, COP, and red cell fraction. These were the changes observed in our patients. The findings are consistent with experimental data bearing on this issue. When PE was induced in dogs by balloon obstruction of the left atrium, Weiser and Grande2 also observed hemoconcentration. Progressive increases in pulmonary extravascular water were associated with simultaneous increases in hematocrit and plasma protein concentration.

In patients with cardiogenic pulmonary edema, increases in hematocrit and plasma proteins have also been documented, especially following acute myocardial infarction.8 The coincidence of hypovolemia and pulmonary edema with increases in plasma proteins and hematocrit was interpreted by these authors as an indication of plasma water loss.21, 22

In addition, systemic venous hypertension and increased sympathetic stimulation by which capillary filtration pressures are augmented may also account for egress of fluid from systemic capillaries and therefore hemoconcentration.23-25 Loss of plasma water may also be accentuated by hyperventilation,26, 27 or muscular exertion28-30

In a complementary study reported from this unit, pul-

### Table 3. Specific Measurements of Oncotic Pressure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Acute PE (95 pts)</th>
<th>Control 1 (50 pts)</th>
<th>PE vs C1 P value</th>
<th>Control 2 (21 pts)</th>
<th>PE vs C2</th>
<th>C1 vs C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>COP, mmHg</td>
<td>25.6 ± 0.4</td>
<td>25.5 ± 0.4</td>
<td>&lt;0.001</td>
<td>23.3 ± 0.4</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>TP, %</td>
<td>7.8 ± 0.1</td>
<td>7.1 ± 0.1</td>
<td>&lt;0.001</td>
<td>7.2 ± 0.1</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Hct, %</td>
<td>44.3 ± 0.7</td>
<td>41.7 ± 0.8</td>
<td>&lt;0.02</td>
<td>42.9 ± 1.0</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values shown are mean ± SEM. Abbreviations: COP = colloid osmotic pressure; TP = total protein; Hct = hematocrit.

### Table 4. Effects of Therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Improved (65 pts)</th>
<th>Not Improved (11 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Treatment</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>108 ± 2.8</td>
<td>92 ± 2.2</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>146 ± 5.6</td>
<td>140 ± 6.0</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>84 ± 3.0</td>
<td>75 ± 1.8</td>
</tr>
<tr>
<td>Resp/min</td>
<td>31 ± 0.8</td>
<td>22 ± 0.5</td>
</tr>
<tr>
<td>PaO₂, torr</td>
<td>75.8 ± 4.2</td>
<td>97.4 ± 4.5</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>87 ± 1.2</td>
<td>96 ± 0.2</td>
</tr>
<tr>
<td>PHa, units</td>
<td>7.26 ± 0.02</td>
<td>7.44 ± 0.009</td>
</tr>
<tr>
<td>PaCO₂, torr</td>
<td>49.4 ± 2.1</td>
<td>39.4 ± 0.8</td>
</tr>
<tr>
<td>Lactate, mM/L</td>
<td>3.4 ± 0.3</td>
<td>1.4 ± 0.07</td>
</tr>
<tr>
<td>HCO₃, mEq/L</td>
<td>20.2 ± 0.5</td>
<td>26.5 ± 0.5</td>
</tr>
<tr>
<td>Plasma osmolality, mOsm/L</td>
<td>302 ± 1.5</td>
<td>295 ± 1.6</td>
</tr>
</tbody>
</table>

The values shown are mean ± SEM. For abbreviations see table 2.
monary edema was often associated with a reduction in plasma volume. Following diuresis induced by furosemide, an increase rather than a decrease in plasma volume was observed during reversal of PE. Olesen had previously observed that during diuresis with furosemide the edema fluid that is cleared from the lungs is returned to the intravascular compartment. This explains, at least in part, the prompt decline in COP observed by us after treatment.

The immediate therapeutic effects of loop diuretics include a reduction of systemic venular and arteriolar tone. The resulting increase in vascular capacitance is also observed after administration of morphine. The consequent decrease in venous return accounts for a decrease in left ventricular filling; with the increase in COP such a lowering of hydrostatic pressure favors reabsorption of plasma water. The observed decreases in heart rate and diastolic pressure with increased plasma water following effective treatment (table 4) would be consistent with a reduction in sympathetic activity. This process is analogous to the "capillary refill" that ensues after blood loss. In instances in which therapy failed to reverse pulmonary edema in patients herein reported, COP, total protein, and hematocrit are unchanged or increased. The evidence therefore implicates ingress of fluid of low protein content during reversal of pulmonary edema.

The possibility that the reduction in TP and COP following reversal of PE may be due to selective escape of albumin from the intravascular compartment cannot be entirely excluded. However, such "capillary leaks" are more likely to be maximal prior to therapy when capillary hydrostatic pressure is maximal. To the contrary, COP declines during therapy as these hydrostatic forces are decreased. Moreover, the concomitant and comparable decrease in hematocrit during reversal of pulmonary edema makes hemodilution a more likely mechanism.

The results of the present study in patients with cardiogenic pulmonary edema contrast with those previously reported from this center on patients with pulmonary edema following protein dilution after infusion of large amounts of crystalloid fluid. Pulmonary edema in the present series of patients was primarily of hydrostatic cause due to left ventricular failure. In such patients, COP was increased rather than reduced.

The present report therefore provides additional insight into the nature of the fluid shifts between the intravascular and extravascular compartments during acute cardiogenic pulmonary edema and following its reversal. The observation of hemococoncentration and increases in oncotic pressure during onset of pulmonary edema is best explained by the transudation of fluid which is low in protein content into the lung. The hemodilution which is associated with reversal of PE represents redilution of red cells and proteins after hypooncotic edema fluid is reabsorbed from the interstitial compartment.

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