Clinical Significance of Serum Colloid Osmotic Pressure in Relation to Pulmonary Edema and Coronary Instability in Patients with Unstable Angina

HIROYA TANIGUCHI, M.D., YASUO TAKAYAMA, M.D., TETSURO SUGIURA, M.D., TOSHUI IWASAKA, M.D., TERUHIRO TAMURA, M.D., SHUJI KITASHIRO, M.D., TOSHI OIZUKA, M.D., MITSUO INADA, M.D.

Second Department of Internal Medicine, Kansai Medical University, Osaka, Japan

Summary: Several investigators demonstrated that severe reduction of colloid osmotic pressure (COP) predicts a fatal outcome in patients with cardiopulmonary failure. To evaluate the clinical significance of COP in relation to pulmonary edema, we studied 117 patients with unstable angina admitted in the hospital within 24 h after the chest pain. The mean COP of all 117 patients was 24.8 ± 3.7 mmHg. COP was significantly lower in patients with pulmonary edema, according to the chest x-ray findings, compared with the patients without it. Among 26 patients with emergency coronary arteriography, a fairly good correlation was observed between coronary jeopardy score and COP (r = -0.57, p < 0.005). Furthermore, COP in patients who survived 26 months after the hospital discharge was significantly higher than that of the nonsurvivors. Thus, measurement of COP is advised for monitoring patients with unstable angina.

Key words: colloid osmotic pressure, unstable angina, pulmonary edema, prognosis

Introduction

Pulmonary edema is an important manifestation of ischemic cardiac dysfunction, both in the presence and absence of concomitant acute myocardial infarction. Starling was one of the first investigators to define the forces regulating fluid balance across the capillary membrane. Two of these forces, pulmonary artery wedge pressure and serum colloid osmotic pressure (COP), may be readily measured in the clinical setting. Several investigators demonstrated that the reduction of COP-pulmonary artery wedge pressure gradient is associated with an increased risk of developing pulmonary edema after acute myocardial infarction, and that severe reduction of COP predicts a fatal outcome in patients with cardiopulmonary failure. As it is difficult to obtain pulmonary artery wedge or left ventricular end-diastolic pressure at a time of chest pain without delay in case of unstable angina, we focused on COP as a driving force of pulmonary edema. In this study we assessed the clinical significance of COP in relation to pulmonary edema as well as coronary instability in patients with unstable angina and also evaluated the prognostic significance of COP.

Methods

Patients

From January 1986 to August 1990, we analyzed the clinical features and course of 117 patients hospitalized in the coronary care unit with a diagnosis of unstable angina. Unstable angina was defined as follows: (1) new onset or sudden worsening of effort angina without increased physical activity during the last month; (2) new onset or worsening (less than 1 month earlier) of angina at rest, still present in the week before admission. Patients with unstable...
angina developing within 2 weeks after myocardial infarction and in the presence of extracardiac condition that intensifies myocardial ischemia were excluded from this study. All the patients had chest pain together with ST-T segment changes on the electrocardiogram, but none had new Q waves or elevation of cardiac enzymes. All the patients had initial chest x-ray taken within 24 h after the onset of the chest pain. The chest x-rays were read by a radiologist who had no knowledge of the clinical condition of the patient. The lung field of the chest x-ray was graded into 4 classes: Class A, normal (no pulmonary venous congestion); Class B, pulmonary congestion (redistribution of pulmonary blood flow, defined as a greater diameter of the upper lobe pulmonary vessels), redistribution of vascularity as the only sign of pulmonary venous congestion in supine position was interpreted as normal, but the interpretation of pulmonary venous congestion was made when the loss of the hilar angle was also evident or when the heart size had increased relative to a previous control chest x-ray or to a discharge x-ray; Class C, interstitial edema (loss of definition of pulmonary vascular markings in association with Kerley’s B lines); and Class D, frank pulmonary edema (localized or diffuse alveolar edema).

Data Collection

The clinical features reviewed were age, gender, presence of diabetes mellitus, prior history of hypertension, duration of chest pain, and prior myocardial infarction. All patients were treated in the usual manner for unstable angina. Our usual medication consisted of nitrates, beta-adrenergic blocking agents, Ca-antagonists, heparin, and aspirin. In 26 of 117 patients who did not improve with usual medical managements, drip infusion of nitrate and injection of beta-adrenergic blocking agents were administered, and emergency coronary arteriography was performed. Revascularization (intracoronary thrombolysis, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery) was indicated in all these patients. The coronary arteriographic findings were evaluated using jeopardy score described by Califf et al.6: the coronary circulation was considered as six arterial segments—the left anterior descending artery, its major diagonal branch, its first major septal branch, the left circumflex artery, its major obtuse marginal branch, and the posterior descending branch of right coronary artery. Each segment with a 75% or greater diameter reduction was given a score of 2 points, and each additional segment distal to such a stenosis was also given a score of 2 points. A cardiac catheterization and coronary arteriography were performed before hospital discharge in 99 patients including all of 26 patients with emergency coronary arteriography, and left ventricular end-diastolic pressure was measured to assess left ventricular function. Colloid osmotic pressure was obtained from Nitta-Staub’s equation7,8 using the measured values for total protein content, serum albumin, and serum globulin on admission:

\[
\text{colloid osmotic pressure} = a(2.8c+0.18c^2+0.012c^3)+b(0.9c+0.12c^2+0.004c^3),
\]

where \(a = \text{serum albumin fraction} \), \(b = \text{serum globulin fraction} \), and \(c = \text{total protein (g/dl)} \). None of the patients had clinical evidence of chronic protein deficiency.

Follow-Up

Follow-up data to a common termination (December 1990) were obtained from the hospital records. The mean follow-up period of these patients was 26 months, with a range of 4 to 60 months.

Statistics Analysis

Statistical analysis was performed using t-test for unpaired data. The least squares linear regression analysis was used to obtain the relationship between COP and jeopardy score or left ventricular end-diastolic pressure. Findings were considered significant if \(p<0.05 \). Results are expressed as mean \(\pm SD \).

Results

Clinical Characteristics

Clinical characteristics of COP are described in Table I. COP was significantly lower in patients with long duration of chest pain and diabetes mellitus. However, there were no significant differences in COP between patients with and without prior history of hypertension or myocardial infarction. A progressive decrease in COP from Class B to Class D was observed (Fig. 1); COP in patients with pulmonary edema was significantly lower than in those without pulmonary edema.

Correlations Between Coronary Arteriography and COP

Among 26 patients with emergency coronary arteriography, a fairly good correlation was observed between the coronary jeopardy score and COP (\(r=-0.57 \), \(p<0.005 \), COP=27.0-0.59 Jeopardy Score). In 99 patients who underwent cardiac catheterization before hospital discharge, there was no significant correlation between COP and left ventricular end-diastolic pressure.

Prognosis

Fifteen patients died and 102 patients survived during the study period. The COP of the patients who survived 26 months after the hospital discharge was significantly higher (25.1 \(\pm 3.7 \) mmHg) than that of nonsurvivors (22.6 \(\pm 2.5 \) mmHg) (\(p<0.001 \) ) (Table 1). All the patients with COP greater than 27.5 mmHg survived (Fig. 2).
### Table I  Comparison of COP on the basis of clinical characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>n</th>
<th>COP (mmHg)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78</td>
<td>24.5±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>24.4±4.5</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;30 min.)</td>
<td>58</td>
<td>26.0±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(≥30 min.)</td>
<td>59</td>
<td>23.7±3.1</td>
<td></td>
</tr>
<tr>
<td>History of previous MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>29</td>
<td>24.7±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>88</td>
<td>24.9±3.4</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>53</td>
<td>24.9±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>(-)</td>
<td>64</td>
<td>24.8±3.5</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>24</td>
<td>23.1±4.4</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>(-)</td>
<td>93</td>
<td>25.3±3.3</td>
<td></td>
</tr>
<tr>
<td>Survivor</td>
<td>102</td>
<td>25.1±3.7</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Nonsurvivor</td>
<td>15</td>
<td>22.6±2.5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COP = colloid osmotic pressure; MI = myocardial infarction; NS = not significant.

### Discussion

The increase in left ventricular end-diastolic pressure accounts for elevation in left atrial pressure and in pulmonary venous pressure in patients with acute myocardial infarction. Transient increase in left ventricular diastolic pressure relative to volume has been described repeatedly in patients with angina pectoris. McKay et al. described that pacing-induced angina was associated with an increase in left ventricular end-diastolic pressure and a widening of atriovenous oxygen difference. This increase in hydrostatic pressure is generally regarded as the main cause of pulmonary edema after myocardial ischemia. However, increase in left ventricular filling pressure does not always explain the presence of pulmonary edema. The Starling fluid transport equation describes the net flux of fluid across a capillary membrane under steady state conditions. The movement of fluid is believed to be a function of balance between transcapillary colloid osmotic and hydrostatic pressures and integrity of the capillary membrane:

$$Q_f = \frac{K_f}{\sigma} \left( P_c - P_i - \frac{\pi_c - \pi_i}{\sigma} \right)$$

where $Q_f$ is 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; $\pi_c$ and $\pi_i$ are the COP in the capillary and interstitial spaces, respectively. Two of these factors $P_c$ (pulmonary artery wedge pressure) and $\pi_c$ (COP) can be measured and calculated in the clinical setting. Several investigators demonstrated that reduction of COP-pulmonary artery wedge pressure gradient increases the risk of developing pulmonary edema. Luz and co-workers demonstrated that the COP averaged only 16.9 mmHg in 14 patients who developed pulmonary edema after myocardial infarction, whereas the COP averaged 20.8 mmHg in 12 patients with uncomplicated acute myocardial infarction. Increase in pulmonary artery wedge pressure and...
decrease in COP are associated with the onset of pulmonary edema after myocardial infarction, and such decline in COP may favor transudation of fluid into the lungs. As it is difficult to obtain pulmonary artery wedge pressure at a time of the chest pain without delay in patients with unstable angina, we focused on COP as a driving force of pulmonary edema.

A fairly good correlation was observed between the coronary jeopardy score and COP in 26 patients with emergency coronary arteriography, which indicates that COP reflects coronary instability in unstable angina. In addition, COP was markedly reduced in patients complicated with pulmonary edema. The mechanism by which the COP decreases in patients with pulmonary edema after myocardial ischemia remains unclear, but earlier studies indicate that myocardial ischemia contributes to increased capillary permeability of the heart and lungs. In permeability types of edema, experimental and clinical studies have revealed that microvascular barrier loses its sieving properties. Some investigators found that the total protein of the edema fluid in patients with myocardial ischemia was higher than that found in patients without myocardial ischemia. As a result, a greater leakage of protein into the lung fluid may decrease serum COP. Therefore, one of the possible mechanisms of pulmonary edema in patients with unstable angina was due to increased pulmonary vascular permeability manifested as decreased COP.

Morissette and co-workers and Rackow and co-workers have stated that reduction of COP and COP-pulmonary artery wedge pressure gradient is an important indicator for the development of pulmonary edema and subsequent cardiopulmonary death in the critically ill patients. However, to our knowledge, none of the studies have evaluated COP as a prognostic indicator in patients with unstable angina. Our data revealed that COP was significantly lower in the patients who eventually died, and none of the patients with a COP greater than 27.5 mmHg died. Thus, the decrease in COP may be an important prognostic indicator for the development of pulmonary edema in patients with unstable angina.

Limitation of This Study

We could not assess left ventricular end-diastolic pressure in the acute phase, because drip infusion of nitrate and injection of beta-adrenergic blocking agents were administered in all 26 patients with emergency coronary arteriography. It was suggested that left ventricular end-diastolic pressure decreased under the influence of these agents and was far from the value at a time of chest pain. However, as there was no relation between left ventricular end-diastolic pressure in the late hospital phase and initial COP, it may be concluded that left ventricular function was not the major factor affecting COP.

Conclusion

Measurement of COP, because it is easily obtained at small cost, is advised for the monitoring of patients with unstable angina.

References

1. Starling EH: On the absorption of fluids from the connective tissue spaces. J Physiol 19, 312 (1896)
4. Rackow EC, Fein IA, Leppo J: Colloid osmotic pressure as a prognostic indicator of pulmonary edema and mortality in the critically ill. Chest 72, 709 (1977)