Pulmonary Edema Related to Changes in Colloid Osmotic and Pulmonary Artery Wedge Pressure in Patients after Acute Myocardial Infarction

By Protasio L. da Luz, M.D., Herbert Shubin, M.D., Max Harry Weil, M.D., Edwin Jacobson, M.S., and Leon Stein, M.D.

SUMMARY

Pulmonary artery wedge and plasma colloid osmotic pressures and their relationship to pulmonary edema were investigated in 26 patients with acute myocardial infarction of whom 14 developed pulmonary edema. In the absence of pulmonary edema, both the pulmonary artery wedge pressure and plasma colloid osmotic pressure were in normal range; after onset of pulmonary edema, a moderate increase in pulmonary wedge pressure and reduction in plasma colloid osmotic pressure were observed.

When the gradient between the plasma colloid osmotic pressure and the pulmonary artery wedge pressure was calculated, highly significant differences were demonstrated ($P < 0.002$). In the absence of pulmonary edema, this gradient averaged $9.7 \pm 1.7$ SEM torr; following appearance of pulmonary edema, it was reduced to $1.2 \pm 1.3$ torr. During therapy with digoxin and furosemide, reversal of pulmonary edema was closely related to a concomitant change in the colloid osmotic-hydrostatic pressure gradient.

These observations indicate that both increases in pulmonary capillary pressure and decreases in colloid osmotic pressure may follow the onset of pulmonary edema. Such decline in colloid osmotic pressure and especially the reduction in colloid osmotic-hydrostatic capillary pressure gradient may favor transudation of fluid into the lungs.

Additional Indexing Words:

Pulmonary congestion  Pulmonary pressures  Circulatory failure
Diuretic action  Colloid osmotic-hydrostatic pressure gradient

PULMONARY EDEMA after acute myocardial infarction has been attributed to an increase in the hydrostatic pressure in the pulmonary capillary bed due to left ventricular failure. The level of the left ventricular filling pressure, however, does not always correlate with radiographic signs of pulmonary edema. Guyton and Lindsey demonstrated in dogs that pulmonary edema occurred at left atrial pressure levels of 24 torr when the albumin concentration in the plasma was normal. After the albumin concentration was reduced to 47% of the control values, pulmonary edema appeared when left atrial pressure was increased above 11 torr. Levine et al., also in studies on dogs, found no consistent relationship between the gradient of capillary hydrostatic and colloid osmotic pressure with the rate of fluid extravasation into the lungs. These investigators pointed out the role of tissue hydrostatic and oncotic pressures as potentially important determinants of pulmonary edema.

Current techniques for measurements of interstitial fluid hydrostatic and colloid osmotic pressure are not, as yet, applicable for clinical investigation. However, it is now possible to obtain an estimate of pulmonary venous pressure by the use of the flow-directed pulmonary artery catheter developed by Swan and Ganz. Reliable measurements of plasma colloid osmotic pressure are also feasible by methods evolved by Prather et al. and modified by Jacobson et al. in our laboratories. It is, therefore, possible to assess simultaneous changes in the hydrostatic and colloid osmotic pressure in patients. Our investigation was directed to the practical issue of whether or not, in the absence of quantitation of tissue hydrostatic and
colloid osmotic pressure, pulmonary edema could be related to an altered plasma colloid osmotic-hydrostatic pressure gradient in the pulmonary capillaries. The problem was specifically investigated in 26 patients who had sustained an acute myocardial infarction of whom 14 developed unequivocal radiographic signs of pulmonary edema.

Material and Methods

Clinical Material

Seventeen men and nine women, whose ages ranged from 40 to 89 (median 65) years and who were admitted to the Coronary Care Unit of the University of Southern California Center for the Critically Ill between November 1971 and June 1973, constitute the subjects of this report. Diagnosis of acute myocardial infarction was based on compatible clinical history, characteristic Q waves and/or ST segment-T wave changes, significant increases in the levels of serum creatine phosphokinase, glutamic oxaloacetic transaminase and lactic dehydrogenase. Seven patients presented with clinical signs of acute perfusion failure (shock) including clammy skin, mental disorientation, reduction in intravascular systolic blood pressure to 90 torr or less, urine output less than 30 ml/hr and arterial lactate concentration exceeding 1.4 mmol/L. Only one of these patients with shock survived for more than 15 days. Pulmonary edema was observed predominantly in older patients (table 1).

Methods

In nineteen patients, studies were performed during the first 24 hours following onset of severe chest pain and in seven patients, at intervals ranging from 2 to 10 days after the acute episode. Informed consent was routinely obtained. Diazepam, meperidine and/or oxygen were routinely administered prior to study; digoxin (0.5 mg) and furosemide (40 to 80 mg) had been administered to five patients (patients 1, 2, 7, 9, 19). Seven patients were mechanically ventilated after endotracheal intubation (patients 1, 2, 5, 10, 18, 23, and 25). Anteroposterior supine chest X-rays were obtained within two hours of the hemodynamic studies. Films were taken using parspeed screens and film (Kodak X-Omnicat cassette, screens and film) with 2½ minute development. Tube-to-chest distance was 40 inches. Interpretation of the chest radiographs was independently reported by two radiologists who had no prior knowledge of the clinical status of the patients. Criteria for interpretation were those proposed by Turner et al. for adapted for reading supine chest films (table 2).

After local anesthesia utilizing lidocaine, 2%, a radioopaque flow-directed catheter (Swan-Ganz catheter Model 93/110/5F or 93/111/7F, Edwards Laboratories) was surgically inserted into a basilic vein. The tip of the catheter was advanced to a position in the peripheral pulmonary artery for wedge pressure recording as initially recommended by Swan et al. The correct position was documented by chest X-ray. Proper wedging of the catheter was determined by: 1) immediate loss of typical arterial pulse morphology on inflation of the balloon, documented by the pressure recording; 2) abrupt return of typical arterial pulse morphology on deflation of the balloon; 3) appearance of wedge pressure morphology consistent with that of the left atrial pressure pulse; 4) a mean pulmonary wedge pressure equal to or less than the pulmonary artery end-diastolic pressure. A thin walled teflon catheter (Longdwell, 18 gauge, internal diameter 1.05 mm, length 20 cm, Becton, Dickinson and Company) was percutaneously inserted into a femoral artery and advanced for a distance of approximately 15 cm. A Statham P23Db pressure transducer was used in conjunction with a two channel (Model 7702B) or eight channel (Model 7878A) Hewlett Packard medical recorder. The mid chest level was established as zero reference for intravascular pressure measurements.

Cardiac output was measured by the dye-dilution technique with injection of 2.5 or 5 mg of indocyanine green dye into the pulmonary artery and withdrawal of blood from the femoral artery utilizing either a Gilson (Model 17500A) or Waters (Model PR-5M) densitometer. The area under each dye curve was calculated by numerical integration.

Table 1

<table>
<thead>
<tr>
<th>Pulmonary edema absent (12)</th>
<th>Pulmonary edema present (14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
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</tr>
<tr>
<td>40 to 68 (median 53)</td>
<td>44 to 89 (median 75)</td>
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<tr>
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<tr>
<td>Location</td>
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<td>Inferior</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

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Table 2

Criteria of Pulmonary Edema (adapted from Turner, Lau and Jacobson)
Left ventricular stroke work index (SWI) was calculated by the formula:

\[
\text{SWI} = \text{SI} \times (\text{MAP} - \text{PAWP}) \times 0.0136
\]

in which SI = stroke work index, MAP = mean arterial pressure and PAWP = pulmonary artery wedge pressure.

Samples of blood were obtained from the femoral artery within an interval of less than three minutes following insertion of the indicator dilution curve. Samples were submerged in ice water and blood gas analyses were performed within 30 min after blood withdrawal. The partial pressure of oxygen (PO\(_2\)), carbon dioxide (PCO\(_2\)) and pH were measured at 37°C with the standard electrode technique utilizing a radiometer system (Radiometer Company, Denmark, Model PHA927). The output of the pH, PO\(_2\), and PCO\(_2\) amplifiers were recorded on a strip chart recorder (Hewlett Packard, Model 680) and the appropriate meter was read after the slope of the recording was zero for 30 sec. Plasma volume was measured using radioiodinated human serum albumin (RI 1255A). Isotope activity was determined at intervals of 15, 25, 35, and 45 min with subsequent extrapolation of the values to zero time.

Colloid osmotic pressure was measured with a transducer membrane system, utilizing a modification of methods proposed by Prather et al.\(^\text{10}\) A Diatray Fl ultrafilter 10PM30 (Amicon, Lexington, Massachusetts) was rigidly mounted above an airtight saline chamber. The membrane is specified to be impermeable to molecules larger than 30,000 MW. The oncometer incorporated a Statham P23Db strain gauge pressure transducer in conjunction with a differential amplifier of our own design and Hewlett Packard Model 7100 OM ten inch recorder. The transducer was calibrated from 0 to 40 torr by use of a saline column and precisely spaced platforms; the fluid column was lowered in steps of 13.6 cm (10 torr). Zero reference was obtained by pipeting 0.3 ml of saline solution into the chamber above the membrane. Since the lower chamber also contained saline there was no osmotic gradient across the membrane. The saline was then absorbed with a pledget of gauze and 0.3 ml of the patient’s plasma was delivered into the chamber; the plasma was obtained from blood anticoagulated with sodium heparin in amounts of less than 100 units/ml. All measurements were made at room temperature, ranging from 25 to 28°C.

The validity of the method was confirmed by measurements of colloid osmotic pressure of crystalline bovine albumin in concentrations of 1 to 7% and by measurements on normal ambulatory and supine subjects. Within the range of 3 to 6 gm % of albumin concentration, the colloid osmotic pressures were plotted against the albumin concentrations. This demonstrated a linear regression line. The values of the small F-statistic for testing the hypothesis of linearity [F(2, 4) = 1.349] and the large P value (close to 0.50) incite that the data do not contradict the hypothesis of a linear regression model. In 19 ambulatory subjects, colloid osmotic pressure was 25.4 ± 2.3 torr and in 14 subjects who had been at bed rest for more than 12 hours, colloid osmotic pressure was 21.6 ± 3.6 torr. These results were comparable to those previously reported.\(^\text{14}\) Refrigerated 5% human serum albumin (Hyland Laboratories, Costa Mesa, California) was used as a reference prior to each measurement. Stability and reproducibility of the reference measurements were demonstrated over a 10 month period; the mean colloid osmotic pressure of 45 reference measurements was 19.3 torr and the maximum deviation was less than ± 1 torr. Duplicate measurements on 40 samples in which colloid osmotic pressure ranged from 4 to 29 torr, revealed an average difference of less than ± 0.1 torr and a correlation coefficient of 0.999.\(^\text{15}\)

The two-tailed Student’s t-test was used for statistical comparison of the data.

### Results

1. **Radiographic Interpretation**

Chest roentgenograms were classified in severity groups 0 and 1 in 12 cases, and for purposes of statistical analysis these were designated as cases of uncomplicated acute myocardial infarction. ‘Early’ signs of interstitial edema were observed in the two cases classified in category 2 and more advanced stages of pulmonary edema were observed in twelve additional patients. For purposes of statistical analysis, these 14 patients were designated as cases of acute myocardial infarction complicated by pulmonary edema (table 2).

2. **Hemodynamic Measurements**

The mean arterial pressure and heart rate were within normal range in both groups of patients (table 3). Although the cardiac index and stroke work index were reduced in both groups of patients, no significant difference was observed after the onset of pulmonary edema.

Pulmonary artery systolic, mean, diastolic and wedge pressures were slightly but significantly higher in patients with pulmonary edema (table 4). The wedge pressures averaged only 15.7 (± 1.5 SEM) torr in patients with pulmonary edema and 11.0 (± 1.2) torr in the absence of pulmonary edema. In the absence of pulmonary edema, the arterial oxygen tension was 124 torr and in patients with pulmonary edema, it was 96 torr. Although the oxygen content of inspired gas was an uncontrolled variable, anoxemia was excluded as a mechanism accounting for the relatively higher pulmonary artery pressures values observed among patients with pulmonary edema.

3. **Colloid Osmotic Pressure and Its Relationships to Pulmonary Artery Wedge Pressure**

In the absence of pulmonary edema, colloid osmotic pressure was 20.8 (± 1.0) torr but it was reduced to 16.9 (± 1.1) torr in patients with pulmonary edema (P < 0.02).

Among the 14 patients who had pulmonary edema, six also were in shock and plasma colloid osmotic pressure averaged 15.5 (± 1.40) torr; in the remaining eight patients, in whom pulmonary edema was observed in the absence of shock, the plasma colloid osmotic pressure averaged 18.0 (± 1.59) torr, a statistically insignificant difference for this small group.

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Table 3

Hemodynamic and Respiratory Measurements

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR (beat/min)</th>
<th>MAP (torr)</th>
<th>CI (L/min/m²)</th>
<th>SWI (gm/m²)</th>
<th>PaO₂ (torr)</th>
<th>pHa (units)</th>
<th>PaCO₂ (torr)</th>
<th>FIO₂</th>
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<td>96.3</td>
<td>7.40</td>
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</table>

P value | NS | NS | NS | NS | NS | NS | NS | NS

Abbreviations: HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SWI = stroke work index; pHa = arterial pH; PaO₂ = arterial PO₂; FIO₂ = inspired oxygen fraction (1-room air; 2-room air + O₂ by mask ranging from 2 to 10 L/min; 3–100% O₂).

When both colloid osmotic pressure and pulmonary artery wedge pressure were taken into account for estimation of the net effects of these forces on fluid transfer between the intravascular and extravascular compartments, highly significant differences were demonstrated. In 13 normal supine individuals previously studied in this laboratory, the plasma colloid osmotic pressure averaged 20.6 (± 3.9 sd) torr; the pulmonary artery wedge pressure normally ranges from 4 to 12 torr. Based on these values, and without reference to changes in interstitial colloid and hydrostatic pressure or alterations in membrane permeability, a gradient of 9 to 17 torr normally favors the retention of fluid within the intravascular compartment. Among the patients without pulmonary edema, the colloid osmotic-hydrostatic pressure gradient averaged 9.7 (± 1.7) torr, a low normal value. In 14 patients with pulmonary edema, however, this gradient was reduced to 1.2 (± 1.3) torr (P < 0.002) and it exceeded 3 torr in only three cases (fig. 1).

4. Fluid Balance and Intravascular Volume

Patients with pulmonary edema had a positive fluid balance of 598 ± 231 ml in the eight hours preceding the study. In three of these patients, the positive fluid balance was not associated with a reduction in colloid osmotic pressure. A positive fluid balance of 116 ± 183 ml also was documented among the patients without pulmonary edema. There was no

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Table 4

<table>
<thead>
<tr>
<th>Patient</th>
<th>$P_{PA}$</th>
<th>$P_{PA}$</th>
<th>$P_{PPA}$</th>
<th>$P_{PFW}$</th>
<th>$P_{PFW}$</th>
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<td>23</td>
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<td>AMI + pulmonary edema</td>
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<td>35</td>
<td>27</td>
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<td>AMI, uncomplicated vs AMI + pulmonary edema</td>
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<td>$P$ value</td>
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</table>

Abbreviations: AMI = acute myocardial infarction; $P_{PA}$ = systolic pulmonary artery pressure; $P_{AP}$ = mean pulmonary artery pressure; $P_{PPA}$ = diastolic pulmonary artery pressure; $P_{PFW}$ = pulmonary artery wedge pressure; $P_{COP}$ = plasma colloid osmotic pressure.

*Further complicated by acute circulatory failure (shock).
†Left ventricular end-diastolic pressure (torr).

A significant difference in the positive fluid balance between the two groups of patients. In addition, no significant differences in plasma volume and plasma sodium were detected (table 5).

5. Effects of Therapy

In nine patients with pulmonary edema, measurements were repeated at an average interval of 26 hours for the purpose of evaluating changes in colloid osmotic pressure and pulmonary artery wedge pressure following treatment with digoxin and furosemide. In three patients in whom pulmonary edema was reversed, the plasma colloid osmotic pressure remained in the normal range or increased. A decline in pulmonary wedge pressure was also observed (fig. 2). In six cases in which the clinical treatment failed to reverse pulmonary edema, plasma colloid osmotic pressure was either unchanged or further reduced. The effects on pulmonary artery wedge pressure were variable. Nevertheless, a close relationship between the course of pulmonary edema and changes in the colloid osmotic-hydrostatic pressure gradient was demonstrated (fig. 3). This gradient increased in each of the patients in whom pulmonary edema was reversed. However, the

Table 5

<table>
<thead>
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<th>Intravascular Volume and Fluid Balance</th>
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<tbody>
<tr>
<td>Positive fluid balance</td>
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<td>AMI + pulmonary edema</td>
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</table>

Abbreviation: AMI = acute myocardial infarction.

Numbers in parentheses represents total of observations in each group.

*Mean = SEM.
COLOID OSMOTIC PRESSURE AFTER INFARCTION

Changes in pulmonary artery wedge pressure (left) and colloid osmotic pressure (right) in relation to the course of pulmonary edema in 9 patients.

gradient remained below 4 torr or was further reduced when treatment proved ineffective.

**Discussion**

Experimental ligation of a coronary artery or acute myocardial infarction in patients is followed by increases in left ventricular end-diastolic pressure. The fact that these increases account for elevation in left atrial pressure and in turn pulmonary venous pressure is also well established. This increase in hydrostatic pressure is generally regarded as the main cause of pulmonary edema after acute myocardial infarction.

However, increases in left ventricular filling pressure do not always explain the presence of pulmonary edema. Forrester et al. in their study of fifty patients with acute myocardial infarction, consistently observed radiographic signs of pulmonary edema when pulmonary artery wedge pressures exceeded 17 torr. McHugh et al., in a subsequent report, proposed 22 to 25 torr as the critical range of pulmonary artery wedge pressure for appearance of alveolar pulmonary edema. In the majority of patients reported by Lassers et al. a good correlation between the level of pulmonary artery wedge pressure and the presence or absence of pulmonary edema was also found. However, these authors were unable to explain pulmonary edema in three patients in whom the pulmonary artery wedge pressure was lower than 16 torr. A recent report by Kostuk et al. included 86 patients who had sustained acute myocardial infarction. The level of pulmonary capillary wedge pressure correlated with the radiographic findings in fewer than one-half of their cases. Of 32 patients with interstitial pulmonary edema, wedge pressure was equal to or less than 18 torr in 18 cases. On the other hand, in 17 patients, the chest X-ray was normal despite persistent elevation of the wedge pressure for six to 24 hours.

When the left ventricular end-diastolic pressure was measured directly following retrograde catheterization of the aorta, similar discrepancies were noted. Hamosh and Cohn studied 40 patients with acute myocardial infarction; in six of these cases, elevations in the left ventricular end-diastolic pressure to levels ranging from 25 to 40 torr were observed, and yet clinical signs of pulmonary edema were absent. Nixon, the other hand, reported pulmonary edema in the absence of an increase in left ventricular end-diastolic pressure in one patient with acute myocardial infarction.

In our series a similar discrepancy was observed. Pulmonary artery wedge pressure averaged only 15.7 (± 1.5) torr among the 14 patients with pulmonary edema. However, when both plasma colloid osmotic pressure and pulmonary wedge pressure were taken into account by computing an oncotic-hydrostatic gradient, a more sensitive index for separating patients with and without pulmonary edema emerged. All patients with pulmonary edema had a gradient of less than 9 torr, and in only three instances was it less than 8 torr in the absence of pulmonary edema. The same applied when pulmonary edema was reversed by therapy. When pulmonary edema was reversed, the gradient increased to 7 torr or more. When treatment failed to reverse pulmonary edema the gradient remained less than 2 torr.

The possibility that increases in pulmonary capillary pressures preceded the onset of pulmonary edema and that lowering of colloid osmotic pressure was the result rather than the cause of pulmonary edema can not be excluded. Patients with pulmonary
edema were older and more often presented with clinical signs of circulatory shock; the low perfusion state itself may increase permeability of the alveolar-capillary membrane with consequent leakage of plasma fluid into pulmonary interstitium. This could alter both hydrostatic and colloid osmotic interstitial pressures; in the absence of these measurements, however, the role of these variables remains speculative.

Nevertheless, the reduction of colloid osmotic pressure regardless of cause would of itself facilitate transudation of fluid into the pulmonary interstitium and alveoli at relatively low left ventricular filling pressure. Since in this series measurements were performed when the patients were in pulmonary edema rather than preceding it, a cause-effect relationship between decreased colloid osmotic pressure and the development of pulmonary edema was not demonstrated. However, the data are unequivocal with respect to changes that follow treatment of pulmonary edema. It is the combined effects of changes in pulmonary hydrostatic pressure and plasma colloid osmotic pressure that correlate with reversal or persistence of pulmonary edema. These initial observations make it likely that substantial increases in precision for quantifying the risk of pulmonary edema will emerge from the concurrent measurement of colloid osmotic pressure and pulmonary artery wedge pressure. Of equal importance, these measurements provide opportunity for further studies of the mechanisms of pulmonary edema both in the presence and absence of heart failure.

The mechanism by which the colloid osmotic pressure decreased in patients with pulmonary edema remains unexplained. Among the possible causes, increases in capillary permeability to albumin have already been cited. Experimentally, the infusion of crystalloids may provoke pulmonary edema without consistent elevation in pulmonary artery wedge pressure. In patients without heart failure the development of pulmonary edema after fluid administration in association with lowering of colloid osmotic pressure, has been recently reported by our group. Although no consistent relationship between the volumes of fluid administered and reductions in colloid osmotic pressure could be demonstrated in this series, we cannot exclude the possibility that the infusion of crystalloids may have contributed to lowering of osmotic pressure on a dilutional basis.

No clinical evidence of malnutrition or renal losses of protein were observed in our patients and therefore chronic protein deficiency cannot be implicated as a factor in the genesis of pulmonary edema.

The present data should not distract from the fact that left ventricular dysfunction is the major and possibly initial factor accounting for pulmonary edema after acute myocardial infarction. What is known from this study is that after acute myocardial infarction, pulmonary edema develops in close quantitative relationship with simultaneous changes in both colloid osmotic and hydrostatic pressures.

Therapeutic Implications

The administration of fluids using a well regulated technique of fluid challenge has been demonstrated to be an effective method for reversing shock following acute myocardial infarction. Admittedly, it reversed shock in only a minority of patients. The pulmonary artery wedge pressure serves as the primary monitor for assessing the response to volume loading. McHugh et al. suggested the level of 18 torr as a safe level for fluid challenge. On the basis of the present study, we would regard concomitant measurements of colloid osmotic pressure and pulmonary artery wedge pressures as a more reliable basis for guiding fluid challenge. Optimally, the colloid osmotic-wedge pressure gradient should be calculated. When this gradient declines below 9 torr, there is a substantial risk of pulmonary edema if fluid infusion is continued.

Acknowledgment

We are grateful to Doctors John Cerrone, James O'Dea and Dalvin Smolin for interpretation of radiographs; Mrs. Vinnie Liu for assistance in statistical analyses and Mrs. Linda Bowen and Miss Mary Armato for assistance in preparation of this report. The colloid osmometer (Oncometer) was developed with the aid of Mr. Joe Bisera and Mr. Michael Chaffee.

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COLLOID OSMOTIC PRESSURE AFTER INFARCTION


Pulmonary edema related to changes in colloid osmotic and pulmonary artery wedge pressure in patients after acute myocardial infarction.

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