Lung Water in Patients with Acute Myocardial Infarction

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SUMMARY
Pulmonary extravascular water volume (PEV) or lung water was measured in 45 patients with acute myocardial infarction, utilizing the double radioisotope indicator dilution technique. A PEV greater than the upper limit of normal (120 ml/m²) was found in 27 patients, 23 of whom had an elevated pulmonary wedge or pulmonary artery diastolic pressure. A significant correlation was found between PEV and pulmonary wedge or pulmonary diastolic pressure in the whole series. A progressive increase in average PEV was observed from Class I (uncomplicated) to Class IV (shock) patients. There was also a progressive increase in PEV from patients with normal chest X-ray findings to those with radiologic evidence of acute pulmonary edema. In seven of 11 patients with initial elevation of both PEV and pulmonary wedge pressure, repeat determinations demonstrated a substantial reduction in both parameters over a period of 2–4 days.

We postulate that an increased PEV in patients with acute myocardial infarction is largely due to an elevated pulmonary capillary pressure. The latter is probably a consequence of an elevated left ventricular diastolic pressure, which may be a manifestation of either left ventricular failure or a decrease in left ventricular compliance.

Additional Indexing Words:
Pulmonary extravascular water volume
Pulmonary wedge pressure
Plasma volume
Total blood volume
Pulmonary edema
Hemodynamics
Cardiac index

The measurement of pulmonary extravascular water volume (PEV) or lung water in man by the double radioisotope indicator technique has been reported by workers of several laboratories. After multiplication by a factor of 0.8, the upper limit of the normal value is estimated to be 120 ml/m², with a mean normal value of 90 ml/m². The PEV is frequently increased in patients with valvular heart disease, particularly in those with elevated left atrial or pulmonary wedge pressure. An increased PEV has been found almost uniformly in patients with pulmonary edema. Sutherland, Cade and Pain have reported increased PEV in six of fourteen patients with acute myocardial infarction. These six patients had clinical evidence of more severe left ventricular failure and greater veno-arterial shunting and hypoxemia than those in whom PEV was not elevated.

The present study was undertaken to assess the relationship of PEV with (a) clinical classification, (b) roentgenographic findings, and (c) pulmonary artery and pulmonary wedge pressures in 45 patients with documented acute myocardial infarction.

Material and Methods
Forty-five patients with acute myocardial infarction were studied in the Myocardial Infarction Research Unit (MIRU) of the University of Rochester Medical Center. There were 37 men and 8 women. Their ages ranged from 39 to 70 years. The diagnosis of acute myocardial infarction was based on a typical history, serial enzyme changes, and specific electrocardiographic criteria. Informed consent was obtained from each patient.

Following admission to the MIRU, right heart catheterization was performed under local anesthesia and fluoroscopic control. All the studies were carried out...
out without administration of specific therapeutic measures, such as administration of diuretics, acute digitalization, or phlebotomy. A cardiac catheter was introduced into the pulmonary artery via an antecubital vein. A #6 or #7F Courmand catheter was used in the first six patients, and a #6 or #7F Swan-Ganz flow-directed catheter\textsuperscript{15} was used for the last 39 patients. An 18 gauge Teflon cannula was placed in a brachial artery for measurement of systemic arterial pressure and for blood sampling.

Pulmonary artery, pulmonary wedge, and brachial artery pressures were measured through a Statham Model SP37 transducer and recorded on a Brush direct-writing recorder. Mean pressures were obtained by electronic integration. Zero reference level for pressure measurements was 5 cm below the sternal angle. The upper normal limit of pulmonary wedge and pulmonary artery diastolic pressures in our laboratory is 12 mm Hg.

Cardiac output was measured by the indicator dilution technique, derived from the indocyanine green dilution curves. Arterial blood was continuously withdrawn by a Harvard pump from the brachial artery cannula and through a Gilford cuvette densitometer at the rate of 45.9 ml/min; a rapid injection of 3 ml (7.5 mg) of indocyanine green dye into the right atrium or pulmonary artery was rapidly followed by a saline flush. Analog-to-digital conversion of the indicator dilution curves was performed on-line at a rate of 160 samples/sec by an XDS Sigma 3 computer. The computer averaged the 16 time-concentration values obtained during each 0.1 sec, and the resulting values (10 for each second) were used to calculate cardiac output, using the gamma variate technique.\textsuperscript{18} In each patient 2 to 4 determinations of cardiac output were made in rapid succession. After each determination, withdrawn blood was reinfused in order to avoid excessive blood loss. The reported cardiac output in each patient is the average of 2 to 4 determinations done in rapid succession.

Within 10 minutes after completion of cardiac output determinations, PEV was measured by the double radioisotope technique described by Chinard. The indicators were radio-iodinated serum albumin (RISA) and tritiated water (THO), in a solution of 5 ml of normal saline containing 7 \( \mu \text{c} \) I\textsuperscript{131} and 80 \( \mu \text{c} \) H\textsuperscript{3}. Before injection of the indicators, blood samples were collected for background counts. As soon as the solution of indicators was injected through the cardiac catheter into the pulmonary artery (39 patients) or right atrium (6 patients), arterial blood was sampled using a machine designed especially for this purpose. This machine contains a piston-driven syringe which automatically withdraws and ejects 1.0 ml of blood every two seconds. A one-way valve with an attached one-way sidearm was interposed between the sampling syringe and the arterial line, so that the sampling syringe withdrew blood from the arterial line, and ejected it via the sidearm. Blood was collected using a special drum which contained 30 two ml centrifuge tubes; the drum made a 1/30 turn every two seconds, so that a maximum of 30 ml of blood could be collected each minute. Usually 15–20 samples of blood were collected from each patient. Immediately following the collection of samples, the tubes were inverted in order to mix the blood thoroughly with heparin. Twenty minutes later, two more blood samples were obtained for comparison with the background counts as well as for estimation of plasma volume.

The blood samples were then centrifuged. From each sample an aliquot of 0.5 ml of supernatated plasma was carefully pipetted and transferred to a 20 ml capped bottle containing 10 ml of Beckman special scintillation solution. Beta radiation emissions from both I\textsuperscript{131} and H\textsuperscript{3} were counted simultaneously at ambient temperatures through separate counting ports in a Beckman LA 250 scintillation counter. Counting ratio of tritium ranged from 1,000 to 50,000 counts/min with background counts of 50-200 counts/min. Counts from standards prepared with known amounts of tritium (H\textsuperscript{3}) in whole blood showed a linear relationship to concentration up to 50,000 counts/min. The tritium counts were not affected by the presence of RISA in the blood.

Time-concentration points for both RISA and THO were punched onto data cards after subtracting background counts from the actual counts. Cardiac outputs and mean transit times were derived from both RISA and THO curves using the aforementioned cardiac output computer program. The values of mean transit times determined from indocyanine green and RISA curves in 31 patients were compared (fig. 1). The average mean transit time from RISA was about 0.5 second longer than that from indocyanine green. Although there was a slight systematic difference, it was considered of no practical importance. The PEV was calculated according to the following formula:

\[
\text{PEV} = \frac{\text{CI}}{60} \left[ T_{\text{mTHO} (PA-R)} - T_{\text{mRISA} (PA-R)} \right]
\]

Where \( \text{PEV} = \) pulmonary extravascular water volume (ml/m\textsuperscript{2})

\( \text{CI} = \) cardiac index (ml/m\textsuperscript{2}/min)

\( T_{\text{mTHO} (PA-R)} = \) mean transit time of tritiated water from pulmonary artery to brachial artery (sec)

\( T_{\text{mRISA} (PA-R)} = \) mean transit time of radio-iodinated serum albumin from pulmonary artery to brachial artery (sec).

In this formula, it is implied that the expression \( \frac{\text{CI}}{60} \times T_{\text{mRISA} (PA-R)} \) represents the distribution volume of water in blood. Since blood is heterogeneous and contains elements other than water, this assumption may be incorrect. The water fraction of plasma and that of red cells are not the same, so the water content of whole blood would naturally be influenced by the number of red cells or hematocrit. The PEV may be overestimated because of the difference in plasma and red cell water fractions. A correction factor of 0.8 was used, as suggested by Chinard et al.\textsuperscript{18} All the values of PEV determined in this series of patients.

\textsuperscript{15} Chinard, ET AL.
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Plot of the mean transit times of the two indicator-dilution curves (indocyanine green and RISA) obtained in 31 patients with acute myocardial infarction.

were corrected by multiplying by this factor of 0.8. Thus, the corrected values would be 20% less than the determined values. Values of PEV were expressed in terms of square meters of body surface area.

The initial determination of PEV was made in 34 patients on the first day, eight patients on the second day, two patients on the third day, and one patient on the sixth day of hospitalization. A second determination of PEV was made in 21 patients 2-4 days after the initial measurement.

The reproducibility of the technique was established by duplicate measurements made in ten patients with valvular heart disease studied in our cardiac catheterization laboratory.9 Duplicate studies of PEV within 30 min of each other were also made on five patients with acute myocardial infarction. In all patients, differences between the first and second determinations were less than 10%. We use 120 ml/m² as the upper limit of normal value.

The volume from the pulmonary artery to the brachial artery was designated as central blood volume (CBV) and was calculated as the product of cardiac output and the mean transit time from the pulmonary artery to brachial artery. Plasma volume (PLV) was calculated from the I¹³¹ counts obtained from samples drawn 10 min after the PEV determination. Total blood volume was calculated using the following formula:

\[ TBV = \frac{PLV}{1.0 - Hct} \]

where TBV = total blood volume (ml/m²)

PLV = plasma volume (ml/m²)

Hct = hematocrit.

An unpaired t-test was used to compare the differences between groups of patients. Correlation coefficients between various parameters were calculated, using standard techniques.17

The patients were grouped into four clinical classes according to the following definitions adopted by the Myocardial Infarction Research Units: Class I, uncomplicated patients; Class II, patients with S₃ gallop and pulmonary rales; Class III, patients with frank pulmonary edema; and Class IV, patients with cardiogenic shock.18

Roentgenograms of the chest were read by a radiologist who had no knowledge of the clinical condition of the patient or results of the hemodynamic studies. The changes were described under four classes: Class A, normal; Class B, pulmonary congestion; Class C, interstitial edema; and class D, frank pulmonary edema.

Results

The routine clinical and laboratory data in 45 patients are shown in table 1 and the hemodynamic data are presented in table 2. A PEV greater than 120 ml/m² was found in 27 patients. In 23 of these 27 patients, pulmonary wedge or pulmonary diastolic pressure was elevated. In four patients (G.D., H.McC., J.H. and D.M.), PEV was increased despite a normal pulmonary wedge pressure.

There is a progressive increase in the average PEV from Class I to Class IV patients (fig. 2). The mean values of Class I and Class II are not significantly different, but the mean values of both Class III and Class IV patients are significantly higher than those of either Class I or Class II patients.

A progressive increase in the average PEV is observed from Class A to Class D patients according to the roentgenographic findings (fig. 3). Statistically significant differences (P < .001) were noted between Classes A and B and Classes C and D. A significant positive correlation was observed between the pulmonary wedge pressure and PEV (fig. 4).

A second determination of PEV was made in 21 patients two to four days after the first determination (fig. 5). The initial PEV was elevated in 11 patients and normal in 10 patients. In 7 of the 11 patients with initial elevation of both PEV and pulmonary wedge pressure, repeat determinations showed a reduction in both parameters. In 9 of the 10 patients with normal initial PEV, a decrease in pulmonary wedge pressure was associated with no appreciable change in PEV.

A significant correlation was found between the PEV and the following parameters (table 3): (a) pulmonary wedge pressure (r = +.51, P < 0.001),
(b) pulmonary arterial diastolic pressure 
\( (r = +.58, P < 0.001) \), (c) pulmonary arterial mean pressure 
\( (r = +.54, P < 0.001) \), (d) central blood volume 
\( (r = +.43, P < 0.01) \), (e) total blood volume 
\( (r = +.41, P < .05) \), and (f) plasma volume 
\( (r = +.35, P < .05) \). There was no correlation between PEV and the following parameters: cardiac index, systemic arterial mean pressure, and pulmonary vascular resistance.

**Discussion**

It is assumed that the transudation of fluid from the pulmonary capillaries to the interstitial or alveolar space in patients with acute myocardial...
infarction is largely due to abnormally increased pulmonary capillary pressure as a consequence of elevated left ventricular end-diastolic pressure. An elevated left ventricular end-diastolic pressure may be a result of either left ventricular failure or a decrease in left ventricular compliance.\textsuperscript{19-25}

Other important factors which may influence the volume of lung water include decreased osmotic
pressure in the capillary bed, increased permeability of the alveolar capillary membrane, and impairment of lymphatic drainage.

Total serum protein was measured in 26 patients of the present series. Both total serum protein and serum albumin were normal in all the patients in whom the measurements were made. In none of the 45 patients was there a significant reduction in hematocrit or hemoglobin. Thus, it is unlikely that a decrease in osmotic pressure contributed to the genesis of increased PEV in our patients.

Hypoxemia per se may cause significant capillary damage, which in turn facilitates transudation of fluid from the pulmonary capillary bed to the interstitial space of the lungs. Severe hypoxemia has been postulated as one of the mechanisms for high altitude pulmonary edema, in the presence of a normal pulmonary wedge pressure.\(^{26, 27}\) In our patients, marked reduction of arterial oxygen tension was infrequent. Therefore, hypoxemia is probably not an important determinant of increased PEV in acute myocardial infarction in the patients in our series.

Impairment of the pulmonary lymphatic drainage may contribute to the accumulation of excessive fluid in the interstitial and alveolar spaces.\(^{28, 29}\) We have no information regarding the contribution of lymphatic obstruction to the elevation of PEV in our patients.

The hypothesis that an elevated pulmonary capillary pressure contributes to excessive lung water in our patients is supported by: (a) an elevated pulmonary wedge pressure in 23 of 27 patients with increased PEV, (b) a positive correlation between pulmonary wedge pressure and PEV, and (c) concordant reduction in pulmonary wedge pressure and PEV within a few days after

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**Figure 2**

PEV in patients with acute myocardial infarction classified according to the clinical criteria. The mean value in each class of patients is represented by the horizontal line and the designated figure. Note progressive increase in PEV from Class I to Class IV patients.

**Figure 3**

PEV in patients with acute myocardial infarction classified according to changes of the chest roentgenograms. The mean value in each class of patients is presented by the horizontal bar and the designated figure. Progressive increase in PEV is observed from Class A to Class D patients.

**Figure 4**

Correlation between PEV and pulmonary wedge pressure (PW) in patients with acute myocardial infarction \((r = +0.511, \ P < 0.001)\). The regression is \(\text{PEV} = 3.2 \times \text{PWP} + 87.9\).
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Figure 5
First and second determinations of PEV and PW in 21 patients with acute myocardial infarction. The first determination was made on the day of admission, while the second determination was obtained 2-4 days after the initial measurement. The dotted lines indicate the upper limit of normal pulmonary wedge pressure (PW) and PEV.

The onset of illness. In a previous paper from our laboratory, we were surprised to find that there was no correlation between PEV and pulmonary vascular pressures in 11 patients with acute myocardial infarction. However, in the present series of 45 patients, including three of the previous 11 patients, a significant correlation was observed between PEV and both pulmonary wedge and pulmonary artery pressures. This discrepancy between the findings reported in the previous paper and the findings in this paper may be due to a larger number of patients included in the present series.

Although there was a considerable overlap of PEV values in clinical Class I and Class II patients, a significant increase in PEV was observed in Class III and Class IV patients. Similarly, PEV was usually normal or slightly increased in most of the Class A and Class B patients according to changes in the chest roentgenograms but a significant increase in PEV was recorded in virtually all Class C and Class D patients. Thus, the data have confirmed numerically the presence of excessive interstitial and alveolar fluid in the lungs of most patients with acute myocardial infarction who showed clinical and radiologic evidence of pulmonary edema.

The findings of an increased PEV and normal pulmonary wedge pressure in four of our patients deserves comment. It is possible that in these patients immediately after the onset of acute myocardial infarction the left ventricular diastolic and pulmonary capillary pressures were elevated to cause filtration of water from the capillaries to the interstitial spaces. Before the time of study the pressures may have declined to much lower values and left behind a substantial increase in PEV. This delay in shift of PEV from the interstitial space to the intravascular compartment may be a conse-

Table 3

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<th>Correlation Coefficients</th>
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* = P < 0.05.
† = P < 0.01.

Abbreviations: CI = cardiac index; SV = stroke volume; PAM = pulmonary artery mean pressure; PWP = pulmonary wedge pressure; SAM = systemic artery mean pressure; PVR = pulmonary vascular resistance; TBV = total blood volume; PLV = plasma volume; CBV = central blood volume.

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quence of a "sponge effect" of the collagen tissue in the interstitial space to which the excessive fluid is bound. It is also conceivable that during the acute phase of myocardial infarction the pulmonary perfusion may be sufficiently disturbed to reduce surfactant production in some regions of the lung and thus result in increased surface tension. This alteration in surface tension may facilitate the filtration of water from intravascular compartments to interstitial spaces despite a relatively low hydrostatic pressure in these regions.

The presence in ten patients of a normal PEV associated with an elevated pulmonary wedge or pulmonary artery diastolic pressure also deserves comment. First, the determination of pulmonary extravascular lung water is dependent on capillaries which are open and perfused. It is possible that in several of these patients a considerable portion of the capillary bed was closed during the time of study. Second, there may be redistribution of capillary flow away from the bases of the lungs where there is increased pulmonary vascular resistance. Third, there may be an uneven distribution of edema fluid within the two lungs. Fourth, it is possible that during the time of study the left ventricular diastolic or pulmonary wedge pressure may be transiently elevated because of the excitement of the procedure.

Certain potential errors and limitations may exist in the double indicator-dilution technique for the measurement of PEV. These have been well discussed by Chinard, Goresky and others. First, there are uncertainties in regard to the degree of equilibrium achieved between the THO and the extravascular fluid in one passage through the lungs. If equilibrium could not be fully achieved in one passage, the difference between the mean transit time of THO and that of RISA would be inaccurate and the estimated value of PEV would be unreliable. However, the available evidence indicates that THO crosses capillary endothelium at an extremely rapid rate and that it would be expected to equilibrate with total water volume of tissue surrounding perfused, permeable vessels in one transit through the pulmonary circulation. Second, the anatomical localization and quantity of the PEV measured depends upon the perfused areas of the lungs. PEV would be underestimated in areas of the lungs which are previously embolized or functionally restricted because of reduced blood flow and little or no mixing of THO with tissue water in those areas.

Another limiting factor is the position of the cardiac catheter in the pulmonary artery. Due to the necessity of intermittent inflation of the catheter balloon for recording pulmonary wedge pressure, we routinely placed the tip of the Swan-Ganz catheter in the proximal portion of one of the two pulmonary arteries. It is conceivable that the bulk of the indicators might have been injected into one lung and only a small portion into the other lung. If the water content is equal in both lungs, injection of the indicators into only one lung will not appreciably influence the calculated values of PEV. If, on the other hand, the water content in one lung is significantly different from the other lung, injection of the bulk of indicators into one lung only will either under- or overestimate the PEV. Injection of the indicators into the right atrium and pulmonary artery in a separate study of 13 other patients did not alter the results in PEV, however. We have found an average difference of only 0.5 sec between the mean transit time of Cardiogreen curves and that of RISA curves in a group of 31 patients with acute myocardial infarction (fig. 1); therefore, it would appear that the sampling technique used in this study is adequate. Lastly, based upon the results of animal experiments, PEV estimated by the radioisotopic technique is only about one-half to two-thirds of the actual amount of lung water after drying of the lungs. We are not certain whether the same findings can apply to man. It is possible that the numerical value of PEV reported in man may be only a portion of the true lung water.

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