Measurement of Pulmonary Edema in Valvular Heart Disease

By Michael McCredie, M.B., M.R.C.P., M.R.C.P. (Edin.)

SUMMARY

Pulmonary extravascular fluid volume (PEV) has been estimated by using a double isotope technique in nine normal subjects and 45 patients with valvular heart disease. The method was reproducible, the standard deviation being ± 15.2 ml/m², or 11.2% of the mean.

Groups of patients with aortic and mitral valve disease had significantly higher values of PEV than normal persons; some patients with pulmonary stenosis had subnormal values. There was a relationship between PEV and the severity of dyspnea; all patients with an abnormally high PEV were class II or worse. Of the 18 patients with abnormally high PEV, only seven had radiological evidence of chronic pulmonary edema.

PEV was independent of blood flow but was clearly related to the level of pulmonary intravascular pressure. PEV was only significantly elevated if left atrial mean pressure exceeded 12 mm Hg and was invariably raised if it exceeded 25 mm Hg. No relationship of PEV to pulmonary vascular resistance was evident in this study.

Additional Indexing Words:
Pulmonary extravascular fluid volume
Diffusible indicators
Radioisotopes
Pulmonary intravascular pressure

The use of diffusible indicators to measure pulmonary extravascular fluid volume was first suggested by Chinard in 1951 and has been used by others to quantitate pulmonary edema in animals and in man. The anatomic boundaries of the extravascular space measured by such a technique have not been delimited. On theoretical grounds it should measure the fluid surrounding the perfused pulmonary capillary bed. Its volume is less than the pulmonary parenchymal tissue volume found by a soluble gas method and corresponds to about 70% of the total water content of normal dog’s lungs at autopsy. This pulmonary extravascular volume has been shown to correlate well with the total water content of dogs’ lungs in both normal and edematous states and to be increased in patients with clinical evidence of pulmonary congestion and edema.

In the present study, pulmonary extravascular fluid volume has been measured by using a double isotope dilution technique during cardiac catheterization in normal subjects and in a group of patients with valvular heart disease. This measurement was assessed in relation to clinical features of pulmonary congestion, edema, and the hemodynamic measurements.

Methods

Nine normal subjects and 45 patients with valvular heart disease were studied. The normal subjects were patients with systolic murmurs referred for diagnosis in whom no other abnormality was detected by physical examination, radiography, electrocardiography, or cardiac catheterization. Of the patients with heart disease, 21 had mitral valve disease: 14 with dominant stenosis and seven with dominant incompetence; 18 had...
aortic valve disease: 14 with dominant stenosis and four with dominant incompetence; and six had congenital pulmonary stenosis. Clinical and radiographic assessments were made prior to study, and the diagnosis was confirmed at cardiac catheterization in all cases, and at operation in 22.

Right and transseptal left-heart catheterizations were performed in the fasting state, after premedication with papaveretum, 10 to 20 mg. Local anesthesia only was used.

Pulmonary extravascular fluid volume (PEV) was determined by a modification of the double isotope technique described by Ramsey and associates. A mixture of radioiodinated serum albumin (RISA) and tritiated water (THO) containing approximately 5 µc of 131I and 100 µc of 3H was injected into the right atrium or right ventricle. Blood samples were taken as rapidly as possible from the brachial artery with a hand-operated Aupette syringe; to the barrel of the syringe was attached a slide-wire resistance from which the timing of sample collection was recorded. Samples of approximately 1.5 ml were collected at intervals of 1.5 to 2.5 seconds. A 1-ml aliquot of each sample was transferred to a 15-ml test tube and 131I activity determined by counting for 10 minutes in a Packard autogamma counter. Standards made by diluting the injectate with known volumes of the patient’s blood were counted in the same way. The water contained in each sample was then extracted by shaking vigorously for 3 minutes with 10 ml of absolute alcohol. After centrifugation 3 ml of the clear supernatant were added to 10 ml of scintillation mixture, made up of 4 g of 2:5-diphenyl-oxazole and 0.154 g of 1:4 di [(2-5 phenyl-oxazolyl)] benzene in 1 liter of toluene. These samples were counted for 10 minutes in a Packard Tricarb Model 314 EX liquid scintillation spectrometer.

Counting rates for tritium ranged from 500 to 60,000 counts per minute above background counts of 60 to 90 counts per minute. Counts from standards prepared with known amounts of tritium in whole blood showed a linear relationship to concentration up to 200,000 counts per minute, and tritium counts were not affected by the presence of RISA in whole samples of blood. From replicate analyses, the standard errors of 131I and tritium counts were both less than ±2.5%.

Time concentration curves for both RISA and THO were plotted on semilogarithmic paper, and the cardiac output and mean transit times were determined from each curve. The more obvious recirculation of the RISA curve was used to mark the end of the downslope of the THO curve. Pulmonary extravascular volume (PEV) was calculated as the product of the mean cardiac output from the THO and RISA curves and the difference between mean transit times. To provide a comparison between subjects of widely differing body sizes, values of PEV were expressed in milliliters per square meter of body surface area. Pulmonary vascular resistance (PVR) was also related to body surface area; it was expressed in resistance units (RU.m⁻²) obtained by dividing the difference between mean pulmonary arterial pressure (P$_{PA}$) and mean left atrial pressure (P$_{LA}$) in millimeters of mercury by the cardiac index in liters per minute per square meter.

The reproducibility of measurements of PEV with this technique has been estimated by duplicate determinations during the same study of 13 patients. Functional disability judged on dyspnea was classified according to New York Heart Association criteria.

**Results**

Comparison between cardiac outputs determined independently from the RISA and THO curves in each patient showed an excellent correlation (r = + 0.921, P < 0.001); cardiac output calculated from the RISA curves was, on the average, 98.5% of that cal-

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*Clay Adams.
Table 1

Hemodynamic Data and PEV in Normal Subjects and Patients with Valvular Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>(P_{PA}) (mm Hg)</th>
<th>(P_{LA}) (mm Hg)</th>
<th>CI (L/min/m²)</th>
<th>PVR (RU/m²)</th>
<th>PEV (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>9</td>
<td>16</td>
<td>7</td>
<td>3.5</td>
<td>1.9</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±4.0</td>
<td>±3.2</td>
<td>±0.86</td>
<td>±0.93</td>
<td>±22.4</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>21</td>
<td>37</td>
<td>21</td>
<td>2.4</td>
<td>5.4</td>
<td>193</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td>±16.7</td>
<td>±8.4</td>
<td>±0.65</td>
<td>±4.34</td>
<td>±87.4</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>18</td>
<td>24</td>
<td>12</td>
<td>3.1</td>
<td>4.1</td>
<td>154</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td>±12.6</td>
<td>±7.0</td>
<td>±1.20</td>
<td>±3.20</td>
<td>±64.3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>6</td>
<td>15</td>
<td>8</td>
<td>3.5</td>
<td>2.0</td>
<td>81</td>
</tr>
<tr>
<td>stenosis</td>
<td></td>
<td>±3.3</td>
<td>±1.9</td>
<td>±0.47</td>
<td>±0.78</td>
<td>±47</td>
</tr>
</tbody>
</table>

Abbreviations: \(P_{PA}\) and \(P_{LA}\) = pulmonary arterial and left atrial mean pressures; CI = cardiac index; PVR = pulmonary vascular resistance; PEV = pulmonary extravascular fluid volume; SD = standard deviation.

Calculated from the THO curves, a difference which was not significant statistically.

From duplicate determinations on 13 patients, the standard deviation of the measurement of PEV was ±15.2 ml/m², which represented 11.2% of the mean value (fig. 1).

Mean values for PEV and hemodynamic data for normal subjects and the groups of patients are shown in table 1.

The mean value of PEV in nine normal subjects was 107 ml/m², standard deviation ±22.4 ml/m². Using these values to define the normal range (mean ±2 SD) of 62 to 152 ml/m², 18 patients, all with aortic or mitral valve disease, had abnormally high values of PEV. Four patients had abnormally low values, of whom three had pulmonary stenosis and one had severe mitral incompetence with low left atrial pressure and low cardiac output (fig. 2).

The mean ±SD for the group with mitral valve disease was 193 ±87.4 ml/m², and for aortic valve disease 154 ±64.3 ml/m². These are both significantly higher than normal (\(P < 0.01\) and \(< 0.05\), respectively), and there was no difference between those with dominant stenosis and those with dominant incompetence in either group. Mean ±SD for the six patients with pulmonary stenosis was 81 ±47.0 ml/m², which did not differ significantly from normal \((0.20 > P > 0.10)\), although three of the six had values below the normal range.

Figure 2

Values for PEV in diagnostic groups: MVD = mitral valve disease; AVD = aortic valve disease; P.S. = pulmonary stenosis. Bars and dotted lines represent mean ±SD for each group.
PEV was not related to cardiac output ($r = -0.030$) but did correlate with mean transit times for RISA ($r = +0.497$, $P < 0.001$) and for THO ($r = +0.654$, $P < 0.001$). It correlated well with mean pulmonary arterial pressure (fig. 4, $r = +0.719$, $P < 0.001$) and with mean left atrial pressure (fig. 5, $r = +0.709$, $P < 0.001$). There was no significant relationship between PEV and pulmonary vascular resistance ($r = +0.324$).

**Discussion**

The mean PEV of 107 ml/m$^2$ (sd, ±22.4 ml/m$^2$) in nine normal subjects corresponds to 2.93 ± 1.89 ml/kg of body weight and to 1.08 ± 0.72 ml/cm of height, and is in good agreement with previously reported values by the same method.$^4$-$^7$

The estimation of PEV by this technique depends on the assumption that no indicator is lost from the system between injection and sampling sites. That no significant amount of THO was lost from the circulation during a single passage through the lungs is shown by the agreement between cardiac outputs calculated independently from the RISA and THO dilution curves. Ramsey and associates$^5$ also found no THO loss, and Pearce and associates$^6$ demonstrated a very small loss of THO of about 2%. To minimize random errors from each measurement, the mean value of these two outputs was used in the calculation of PEV.

In addition to the errors and limitations inherent in any indicator-dilution method for the measurement of flow and volume, the effect of uneven distribution of blood flow as occurs in pulmonary vascular disease should be considered. If part of the blood flow through the lungs bypasses the capillary bed, then no THO will diffuse out into a perivascular space and in this part of the system THO would have the same distribution volume as RISA. Theoretically this could affect the calculation of PEV. If this occurs through an intracardiac shunt, the early appearance would be obvious in both dilution curves. Early appearance, however, did not occur in this series. If a shunt occurs through non-capillary vessels in the lungs, it does not

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**Figure 3**

*Relationship of PEV to functional classification. Bars and dotted lines represent mean ±sd for each group. Open circles are normal subjects. Patients with pulmonary stenosis, all asymptomatic, are included with the normal group (dots).*
Measurement of Pulmonary Edema

Figure 4

Relationship of PEV to mean pulmonary arterial pressure (Pπ). Open circles represent normal subjects; dots, patients with valvular heart disease; dots surrounded by a larger circle represent patients with pulmonary vascular resistance over 4 RU.m². This correlation for the whole group is highly significant (r = +0.719, P < 0.001).

produce any error in the calculated PEV provided that the flow to volume ratio is approximately the same (that is, similar transit time). If the flow-to-volume ratio is higher in this segment, it can produce an underestimate of PEV. It can be shown that a 50% shunt with double the flow-volume ratio would produce only a 20% underestimate of PEV. But right-to-left shunts of this magnitude would produce gross arterial desaturation; this did not occur in this series. Thus systematic errors from maldistribution are unlikely to have affected the present results.

As pointed out before, difficulty is often encountered in separating recirculation from the primary dilution curve when it is rather flat. This happens particularly with THO curves in those patients with large central blood volumes or low outputs, or both. This problem is partly overcome by using the more obvious recirculation of the RISA curve to mark the end of the downslope of the THO curve. Although there was a correlation between slow mean transit time and elevation of PEV, one would expect a slow circulation time in patients with more severe valvular heart disease and there was no reason to suspect a systematic error from this source affecting these results. PEV was not related to blood flow in the group. This confirms the finding of Levine and associates in dogs that PEV is independent of wide variations in blood flow, which suggests that it would provide a useful index of water content of the lungs even in patients with the slow circulation and low cardiac output of heart failure.

Ramsey and associates showed the relationship between functional class and PEV in patients with heart disease, and this is confirmed here (fig. 3). In none of our patients was there clinical evidence of pulmonary edema at the time of study, but as shown previously, determination of PEV is a reliable method for detecting abnormal quantities of water in the lungs and is more sensitive than clinical or radiological methods.

Increase in PEV was related to both pulmonary arterial and left atrial pressures (figs. 4 and 5); this relationship presumably reflects increased transudation of fluid due to increased intracapillary pressure. The fluid in the interstitial space surrounding pulmonary capillaries should increase when the effective capillary pressure exceeds the effective plasma osmotic pressure; with normal plasma proteins, the latter should be about 25 mm Hg.

Figure 5

Relationship of PEV to mean left atrial pressure (Pπ). Symbols as in figure 4. This correlation is highly significant (r = +0.709, P < 0.001).

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Pulmonary capillary pressure must be at least as high as left atrial pressure, but it has frequently been noted that many patients with mean left atrial pressures higher than 25 mm Hg at cardiac catheterization do not develop clinical signs of intra-alveolar pulmonary edema. It has been suggested that thickening of the capillary walls protects the lungs from edema,12 or that the stress of cardiac catheterization produces an acute rise in left atrial pressure in these patients, which does not reflect their normal resting state.13 However, in this group, PEV was invariably grossly elevated when mean left atrial pressure exceeded 25 mm Hg and was also raised in about half the patients whose mean left atrial pressure was between 12 and 25 mm Hg. If a raised PEV is an index of interstitial pulmonary edema, then all patients in whom hydrostatic pressure exceeded the effective osmotic pressure in the capillaries did in fact have edema.

There was no significant relationship between PEV and pulmonary vascular resistance in this series. If the development of a high PVR protected the lungs from pulmonary edema, one might expect a low PEV relative to left atrial pressure, that is, the patients with high resistance would fall below the regression line in figure 5. On the other hand, if, as West and associates14 suggested from isolated lung experiments, perivascular edema may itself cause an increase in PVR, one might expect a high PEV relative to left atrial pressure, that is, these high resistance cases would fall above the regression line in figure 5. In fact, the patients with high PVR are fairly evenly scattered about the regression line and there is no real evidence for either mechanism being the predominant one.

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References


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