Extravascular Lung Water in Resting and Exercising Uraemic Patients on RDT

W A CROSBIE, V PARSONS, S SNOWDON
King's College Hospital, London, United Kingdom

Water readily accumulates in the lungs in renal failure and is often the cause of death. Measures to reverse excess fluid retention form an everyday pattern in renal units. The patient on regular dialysis therapy has provided us with a subject in whom some of the factors controlling fluid balance in the lungs can be studied. The ready access to the arterial and venous systems simplifies the normal practical procedures required for most cardio-pulmonary investigations. The changes in cardiac and pulmonary function produced by exercise allow us to study changes occurring at capillary level in the lungs. By using isotopes as tracer elements the volume and changes in distribution of water in the various fluid compartments in the lungs can be followed. This paper describes our findings in tracing the changes occurring in the lung capillary blood volume and extravascular water volume in a group of chronic dialysis patients who had developed general fluid retention.

The water in the lung tissue is derived from the blood and endogenous metabolism. The transfer of water across the capillary membrane depends upon the interplay of hydrostatic and osmotic forces (Starling, 1896). Excess water moves into the lung tissue if the rate of outflow exceeds the rate of removal from the lung tissue. Excess outflow of fluid is caused by an increased capillary pressure, decreased plasma osmotic pressure, or a change in the normal permeability of capillary walls. Decreased fluid removal from the lung tissue occurs if there is diminished lymph flow, increased interstitial osmotic pressure, or decreased tissue pressure.

In renal disease fluid accumulation in the lungs is thought to be due to a combination of heart failure, sodium retention, reduction in plasma osmotic pressure, or a change in the permeability of capillary walls.

Investigation into fluid exchange in the lungs has been hindered by the lack of some means for measuring water in the lungs. Estimation of the amount of water in the lungs in human subjects has depended upon the clinical observation of crepitations in the lungs or the interpretation of chest radio-
graphs. Such methods were incapable of measuring the actual mass of water in the lungs. Thus, measurements of changes in the amount of water in a patient or comparison of results of investigations with the reported results of other workers has been difficult. The information that does exist applies mainly to cardiac patients undergoing cardiac catheterisation; exercise studies being done while the supine subject pedalled on the catheterisation table. Cardio-pulmonary physiological data on renal patients is scarce.

By floating a fine catheter into the pulmonary artery of renal patients in pulmonary oedema Gibson (1966) found lower mean pressures than those found when pulmonary oedema develops in other conditions. Todesco et al (1970) reported that the mean pulmonary artery pressure was only moderately increased ($23.5 \pm 7.2$ mmHg) in the 10 uraemic patients they catheterised.

**METHODS**

Six patients who were being maintained on regular haemodialysis because of chronic renal failure were studied. They all had developed fluid retention as shown by a 5 kg increase in their normal dialysing weight. They all had noticed increased breathlessness on exertion and crepitations were audible in the lungs but no peripheral oedema was present. They all were anaemic. The anthropometric data is shown in Table I.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age-Years</th>
<th>Surface area m²</th>
<th>Hb g/100 ml</th>
<th>Exercise load Kgm/min</th>
<th>Cardiac output ml/sec</th>
<th>Pulmonary extravascular water volume ml</th>
<th>Pulmonary Capillary blood volume ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td>39</td>
<td>1.83</td>
<td>5.5</td>
<td>300</td>
<td>100</td>
<td>180</td>
<td>480</td>
</tr>
<tr>
<td>AD</td>
<td>51</td>
<td>1.75</td>
<td>9.5</td>
<td>150</td>
<td>135</td>
<td>150</td>
<td>450</td>
</tr>
<tr>
<td>NH</td>
<td>40</td>
<td>1.68</td>
<td>8.5</td>
<td>150</td>
<td>174</td>
<td>125</td>
<td>594</td>
</tr>
<tr>
<td>RB</td>
<td>47</td>
<td>1.77</td>
<td>8.1</td>
<td>150</td>
<td>170</td>
<td>116</td>
<td>316</td>
</tr>
<tr>
<td>FW</td>
<td>45</td>
<td>2.12</td>
<td>6.5</td>
<td>300</td>
<td>150</td>
<td>224</td>
<td>800</td>
</tr>
<tr>
<td>AM</td>
<td>52</td>
<td>1.52</td>
<td>9.5</td>
<td>100</td>
<td>100</td>
<td>110</td>
<td>237</td>
</tr>
</tbody>
</table>

The studies were made in the clinical investigation laboratory. The measurements at rest were made with the patient sitting upright in a chair. The exercise measurements were made while the subjects pedalled upright on a bicycle ergometer. The exercise load was chosen to suit the physical state of the patient and is specified in Table I. The aim was to find a steady state load the subject could maintain comfortably for 12 minutes. The measurements were made between the 10th and 12th minute.

The volume of blood (ml) in the lung capillary bed (Vc) was measured by partitioning the carbon monoxide transfer factor at two oxygen levels (McNeil et al, 1958). Three measurements were made with the subject resting and the results were averaged. Corrections for anaemia were
applied in each subject as demanded by the method. In normal adult males there is about 90 ml of blood in the lung capillary bed at any one time (Comroe et al, 1962). The volume of water (ml) in functional contact with perfused lung capillaries was measured using the double indicator dilution technique (Chinard, 1966). $^{125}$Iodine labelled human serum albumin (2.5/μCi) was used as the intravascular tracer. Tritiated water (150/μCi) was used as the extravascular indicator. Thirty individually timed samples of blood were collected from the arterial line of a Scribner shunt using an automated fraction collector (Crosbie & Wyatt, 1971). The amount of each indicator injected and collected was measured by radio-chemical analysis. Time/recovery fraction curves were constructed for each indicator. From this data the blood flow through the lungs, the mean transit time of each indicator, and the excess volume of distribution available to the water during one transit of the lungs was calculated. This volume is called the pulmonary extravascular water volume ($\text{PEVW}_V$) and in normal resting man is about 200 ml and increases by about 40% under exercise conditions (Crosbie et al, 1971, Marshall et al, 1971).

RESULTS

Table I shows that all 6 patients had abnormally increased volumes of capillary blood and extravascular water in the lungs in the resting state. The cardiac output was increased in 5 of the patients most likely due to the concomitant anaemia. Figure 1 shows the close correlation ($r = 0.96, P < 0.01$) between the lung capillary blood volume ($V_C$) and the pulmonary extravascular water volume ($\text{PEVW}_V$). In addition the normal 1 to 2 proportion of the two lung fluid compartments appears to be maintained even when there is a four-fold increase in both parameters. Figure 2 shows the changes we found in the pulmonary extravascular water volume when the 6 subjects exercised. In 4 patients the $\text{PEVW}_V$ decreased during exercise. There is no significant relationship between the changes in $\text{PEVW}_V$ and cardiac output.

DISCUSSION

When a patient in chronic renal failure retains excess body fluid the lungs share in the redistribution of water and blood. A correlation between the amount of blood in the lungs and the radiographic appearance produced by left heart failure in cardiac patients has been recognised for some time (McNeil et al, 1958; Bates et al, 1960). The association in renal disease has not been so well recognised where fluid retention rather than left heart failure is the likely pathophysiological process. When the lungs contain excess blood they also contain excess water in the extravascular tissue. In addition the normal 1 to 2 proportion of the two fluid compartments is maintained. Since water and solutes readily exchange across capillary walls
PULMONARY EXTRAVASCULAR WATER VOLUME (PEVW) and CAPILLARY BLOOD VOLUME (VC) in 6 RENAL PATIENTS with CONGESTED LUNGS.

Figure 1

CHANGES IN PULMONARY EXTRAVASCULAR WATER SPACE IN 6 RENAL PATIENTS WITH CONGESTED LUNGS, AT REST AND ON EXERCISE.

Figure 2
these findings would help to confirm that physico-chemical forces alone control fluid transfer in the lungs. This state may only apply so long as the capillary walls retain their normal permeability.

The increased volume of blood in the lung capillaries must help to compensate for the anaemia which is a constant finding. It would also compensate for the shorter time each red blood cell spends in the lung capillary bed when the cardiac output is increased (Roughton, 1945). The structural change in the alveolar-capillary membrane by additional fluid must also retard the normal transfer of oxygen molecules from the alveolar air into the capillary blood. The interaction of these factors helps to explain the relative infrequency of desaturation of the arterial blood in this clinical state.

The changes in the PEVW on exercise in renal patients with congested lungs were unexpected. Theoretically, exercise should raise the capillary pressure in the lungs since the blood flow is increased. The ability of the transpulmonary vascular pressure to fall must be seriously impaired when the lungs are congested. If the heart is failing then lung capillary pressure will rise and even more fluid will pass out through the capillary walls into the lung tissue. Instead the PEVW decreased during exercise in 4 patients. Since we contend that physico-chemical forces alone control fluid exchange in the lungs we must explain this anomaly. Changes in the plasma or interstitial oncotic pressure on exercise seem unlikely to produce a rapid effect of this magnitude, neither would the changes in the lung tissue pressure.

The lung lymphatic vessels drain excess fluid from the lung interstitium into the great veins and this flow is stimulated by respiratory movements in the animal species studied (Courtice & Steinbeck, 1950). When pulmonary oedema is produced in animal preparations there is a marked increase in lymph flow from the lungs (Warren & Drinker, 1942). While the lung lymph flow is only about 2–9 ml/hour (Courtice, 1963) in the dog a 30 fold increase in this value can be produced when recurring bouts of lung congestion are produced over several months (Uhley et al, 1961). It is just possible that patients in chronic renal failure who are subject to repeated episodes of sodium retention with excess fluid gathering in their lungs may also develop this ability to increase pulmonary lymphatic flow. This mechanism may protect the renal subject from developing overt pulmonary oedema especially on exertion.

ACKNOWLEDGMENTS

May we express our appreciation to Dr P Hugh-Jones for the facilities and encouragement he provided enabling us to complete these studies. We also wish to thank Mr Len Smith and Miss Margaret Rusbridge for their skilful technical help for the production of the illustrations and to Miss Mary Howell for typing the manuscript.
REFERENCES

Courtice, F. C. (1963) British Medical Bulletin, 19, 76
Crosbie, W. A. and Wyatt, C. (1971) Medical and Biological Engineering, 9, 725
Starling, J. (1895) Journal of Physiology, 19, 323

OPEN DISCUSSION

B LINDQVIST (Umea): There must be some other factors influencing pulmonary oedema in uraemia besides those you have shown, because both in animals and in human beings, the frequency of pulmonary oedema increases as you increase the severity of the uraemic toxic state. Maybe surface tension is decreasing or something like that. What do you think?

CROSBIE: I think I answered some of this question when I commented on Dr Kramer's paper. We found that if we traced the sodium flux across the capillary membranes in the lungs when the patients developed pulmonary oedema there was an increased leakage of sodium compared with the normal state. We feel there is some change in the permeability of lung capillaries when the patients develop pulmonary oedema. This we think is not haemodynamic, we think it is due to some metabolite that is released.