Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure

G M ROCKER, A G MORGAN, D PEARSON, G S BASRAN, D J SHALE

From the Respiratory Medicine Unit, University of Nottingham, and the Renal Unit and Department of Medical Physics, City Hospital, Nottingham

ABSTRACT Thirteen patients with renal failure and pulmonary oedema were assessed for evidence of increased pulmonary vascular permeability to protein by a double isotope technique. Comparison was made with 10 patients with cardiogenic pulmonary oedema, 11 healthy volunteers, and 10 patients with the adult respiratory distress syndrome. There was no significant difference in the accumulation of a radiolabelled plasma protein (transferrin) in patients with renal or cardiogenic pulmonary oedema and normal volunteers. Patients with adult respiratory distress syndrome showed significantly greater protein permeability (p < 0.001). In pulmonary oedema associated with renal failure managed by current regimens there was no evidence of increased permeability to transferrin.

The mechanisms underlying the pulmonary oedema of renal failure are unknown, but fluid overload, left ventricular failure, and increased pulmonary microvascular permeability secondary to uraemia have all been invoked. There is increased endothelial permeability to sodium and water in pulmonary oedema, including that associated with renal failure, and alveolar epithelial permeability to technetium-99m labelled diethylenetriamine pentaacetic acid (99mTc DTPA, 492 daltons) was increased before and reduced during haemodialysis.

Histological studies of uraemic lung showed the presence of a proteinaceous oedema fluid but many of the subjects had intra-alveolar haemorrhage. Direct sampling of oedema fluid by endotracheal aspiration in two patients showed a raised protein content, suggesting increased pulmonary vascular permeability to plasma proteins in renal failure, although the lack of change in the volume of distribution for albumin in the lung suggests the opposite.

To investigate the possibility that increased vascular permeability to plasma protein occurs in pulmonary oedema associated with renal failure, we determined the accumulation of radiolabelled transferrin in the lung. Patients with renal and cardiac failure associated pulmonary oedema were compared with healthy controls and patients with high permeability pulmonary oedema.

Methods

SUBJECTS We studied 23 patients with pulmonary oedema—13 with renal failure and 10 with left ventricular failure after myocardial infarction or excessive postoperative fluid replacement (tables 1 and 2). Pulmonary oedema was diagnosed according to standard clinical and radiological criteria (dyspnoea and the finding of crackles on auscultation, alveolar shadowing with or without effusions, and pulmonary venous congestion). Transferrin accumulation in these patients was compared with that in 11 healthy volunteers (10 non-smokers) and 10 patients with the adult respiratory distress syndrome, where evidence of increased microvascular permeability would be expected. The diagnosis of adult respiratory distress syndrome was made according to the standard criteria of an accepted risk factor, no prior lung disease or evidence of left ventricular failure, bilateral multiple lobe involvement on the chest radiograph, and an arterial oxygen tension to inspired oxygen concentration ratio (Pao2:Fio2) of < 20 (kPa: O2% × 10^-2). All patients with adult respiratory distress syndrome had histological evidence at necropsy of diffuse alveolar damage; and all of them required intermittent positive pressure ventilation, while only three cardiac and one renal patient needed ventilation. The study had the approval of the local ethical committee and informed consent was obtained from all subjects or their closest relative if appropriate.
Double Isotope Technique

Pulmonary accumulation of protein was determined by a double isotope method, modified and described in detail by Basran et al. In this technique increased permeability to protein is detected by accumulation of transferrin (labelled in vivo with indium-113m (20 MBq)) by comparison with an intravascular control marker (red blood cells labelled in vivo with technetium 99mTc (12 MBq)). In vivo labelling of transferrin with 113mIn is highly efficient at 30 minutes and red blood cell labelling efficiency at 3 hours was 92% (D Pearson, unpublished data). The radiation dose equivalent for each patient did not exceed 0.2 mSv (20 rem).

External detection of both isotopes from the upper lobe of the lung was compared with external detection from over the heart during a series of 30 second count periods for each site with monitoring for one hour. This was achieved by using a single probe with three fixed lights attached, which allowed accurate repositioning by refocusing the lights on to markings on the chest. For each count period the following ratio was calculated:

\[
\frac{\text{In lung counts}}{\text{Tc lung counts}} \div \frac{\text{In heart counts}}{\text{Tc heart counts}}
\]

A fitted regression line for these data against time was derived. The protein accumulation index (PAI) was numerically equal to the gradient of this line. The ratio of lung to heart counts corrects for radioactive decay, changes in blood volume, and loss of transferrin to other extra vascular compartments. Examples of PAI calculations are given in figure 1.

Colloid Osmotic Pressure

An estimate of colloid osmotic pressure was determined from serum albumin and globulin concentration for the groups with renal and cardiac disease.

Statistics

Data throughout are expressed as means with standard deviations in parentheses. The significance of differences between groups was assessed by analysis of variance. All PAI values given are the higher measurement if a bilateral study was performed.

Results

The mean PAI of the patients with renal failure was not significantly different (p > 0.05) from that of the cardiac group or a healthy control group. The mean PAI values for all three groups were significantly lower than for the adult respiratory distress syndrome group (p < 0.001) (fig 2). The mean arterial oxygen tension ratio for the cardiac group was significantly less than that of the renal group (p < 0.01; tables 1 and 2) and that of the patients with adult respiratory distress syndrome (mean 13.2 (SD 3.4)) was...
Derivation of a protein accumulation index (PAI) from protein and red blood cell counts in patients with adult respiratory distress syndrome (ARDS) (a) and left ventricular failure (b). Isotope counts—lung:heart ratio: indium, technetium; indium:technetium ratio: ooo. PAI is the gradient of the regression line computed for the indium:technetium ratio. To avoid overlap technetium counts from the patients with adult respiratory distress syndrome have been lowered with the ratio axis to the right.

Protein accumulation index (PAI) in pulmonary oedema of renal, cardiac, and non-cardiac origin (adult respiratory distress syndrome—ARDS) compared with healthy normal controls. Individual results are given plus the mean and standard deviation for each group.

Discussion

A common feature of pulmonary oedema is increased permeability to water and low molecular weight solutes, probably attributable to haemodynamic factors and associated hydration of the alveolar interstitium and basement membrane. In renal failure there is additional evidence suggesting increased pulmonary microvascular permeability to protein. The main evidence comes from histological studies of patients with uraemic lung. The alveoli of patients with this complication of end stage untreated renal failure appeared to be filled with proteinaceous fluid. Additional support comes from a study of two critically ill patients with severe pulmonary oedema,
Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure

We would like to thank Mrs CB Richards, medical physics technician, for assistance with radioisotope studies and the physicians at the City Hospital, Nottingham, for permission to study patients under their care. This study was supported by a Chest, Heart, and Stroke Association award to DJS and the City Hospital Kidney Fund.

References

Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure.

G M Rocker, A G Morgan, D Pearson, G S Basran and D J Shale

*Thorax* 1987 42: 620-623
doi: 10.1136/thx.42.8.620

Updated information and services can be found at:
http://thorax.bmj.com/content/42/8/620

These include:

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/