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Changes in pulmonary clearance of technetium labelled DTPA during haemodialysis

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ABSTRACT An index of pulmonary epithelial permeability has been studied in 12 patients with chronic renal failure during haemodialysis. It was assessed by the half time clearance from lung to blood (t½LB) of a nebulised solution containing technetium labelled diethylene triamine pentacetic acid (^{99m}Tc DTPA). Six patients were cigarette smokers and six were non-smokers. The non-smokers had greater predialysis permeability (mean 37.7, range 24–54 min) than non-smokers without renal disease (mean 60.2, range 38–99 min; $p < 0.025$). The t½LB was measured before dialysis and during the first half hour and the last half hour of dialysis in all 12 patients and also during other periods of dialysis in 10 of them. Dialysis lasted for five hours in 11 patients and four hours in one patient. There was no significant change in the t½LB of ^{99m}Tc DTPA during early dialysis; but as dialysis progressed there was a statistically significant increase in t½LB, suggesting a reduction of pulmonary epithelial permeability. These results show no increase in an index of pulmonary epithelial permeability in association with the pulmonary sequestration of neutrophils that occurs in early haemodialysis. They also suggest that in chronic renal failure the epithelial permeability is increased and that this can be modified by haemodialysis.

It is known that during the early part of haemodialysis there is a temporary profound peripheral neutropenia[1] and that this appears to be due to temporary pulmonary sequestration of neutrophils.[2] There is speculation that such pulmonary sequestration of neutrophils may be an important factor in pathophysiology of the adult respiratory distress syndrome.[3] An increase in an index of pulmonary epithelial permeability has been found in "non-haemodynamic pulmonary oedema"[4] and in patients predisposed to the adult respiratory distress syndrome[5]—namely clearance from the lungs of nebulised solution of technetium 99m attached to diethylenetriamine pentacetic acid (^{99m}Tc DTPA). Because of the similarities between the pulmonary sequestration of neutrophils during early haemodialysis and the adult respiratory distress syndrome we have studied this index of pulmonary epithelial permeability before and during dialysis in 12 patients with chronic renal failure.

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Methods

We studied 12 patients who had chronic renal failure from various causes (table 1). They gave their informed consent to take part in this study.

An index of the pulmonary epithelial permeability was measured by the half time clearance from lung to blood of a nebulised solution of ^{99m}Tc DTPA. A correction for background count and tissue perfusion was made by a method similar to that described by Jones *et al.*[6] The aerosol was generated from a Hudson nebuliser, the output of which was filtered to produce particles with a mass median diameter of 0.9 μm.

After the patient had inhaled this aerosol for two to three minutes a scintillation counter was positioned over either the right or the left upper chest on the mid clavicular line 10 cm below the clavicle, and a second scintillation counter was positioned over the right or left mid thigh pointing away from the trunk. Satisfactory counts were obtained for calculating the t½LB of ^{99m}Tc DTPA for both predialysis and early dialysis. Further inhalations were necessary for measurements later in dialysis.

Recordings were taken for one minute during every 90 seconds for a least 15 minutes to calculate the t½LB of ^{99m}Tc DTPA. After data had been recorded

Table 1 *Details of patients*

Patient No	*Smoking habit*	*Age*	*Sex*	*Weight loss during dialysis (kg)*	*Length of haemodialysis*	*Cause of chronic renal failure*
1	ns	41	F	0.7	3 m	Focal glomerulonephritis
2	ns	32	F	1.6	1 m	Adult haemolytic uraemic syndrome
3	ns	49	F	1.2	7 m	Polycystic renal disease
4	ns	54	M	0.6	6 m	Gout
5	ns	55	M	2.1	8 m	Hypertension
6	ns	66	M	1.7	5 y	Glomerulonephritis
7	s	22	F	1.6	4 m	Glomerulonephritis
8	s	54	M	1.1	2 y 6 m	Glomerulonephritis
9	s	68	M	1.0	3 m	Renal stones, hydronephrosis
10	s	45	M	1.2	5 m	Congenital absence of right kidney; left nephrectomy for trauma
11	s	40	F	Not available	8 m	Analgesic nephropathy
12	s	65	M	2.4	3 y 5 m	Adult haemolytic uraemic syndrome

ns—non-smoker; s—smoker.

for the subsequent estimation of t½LB in the last hour of haemodialysis, an intravenous injection of about 2 MBq of ^{99m}Tc DTPA was given to enable the tissue correction factor to be calculated from a hand drawn graph. The calculation of t½LB from the linear correlation between the log of the corrected lung count and time was performed on a BBC B microcomputer. All the clearances appeared linear and did not show the double exponential curve that has been described in patients predisposed to the adult respiratory distress syndrome.[5]

The t½LB for ^{99m}Tc DTPA was calculated before dialysis and during the first half hour and the last hour of dialysis in all 12 patients. In 10 of the patients the t½LB of ^{99m}Tc DTPA was also measured at other times during dialysis (table 2). The correction factor calculated from data in the last hour of dialysis was used for all clearance estimations. These values of the correction factor (mean 2.3, range 0.5–4.2) were similar to those found in 11 patients without renal disease (mean 2.6, range 1.3–3.8) and in two patients with renal disease not studied during dialysis (2.8, 1.8).

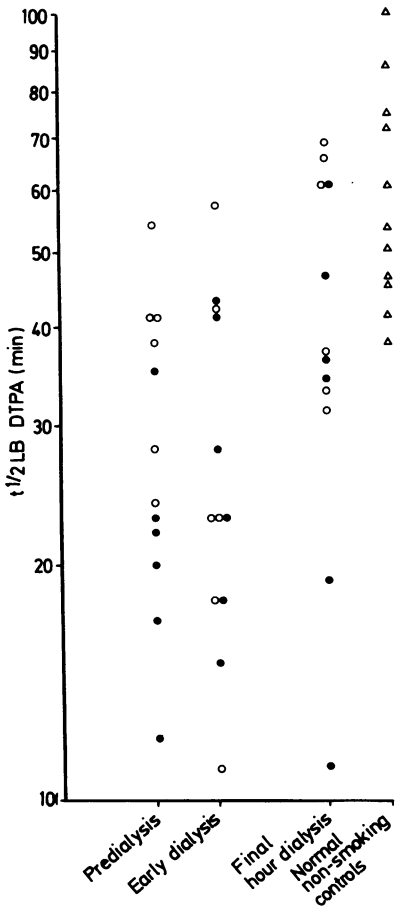
The t½LB of DTPA is not known to be influenced by age.[7] All patients had been having haemodialysis for at least one month. They used a dialysis fluid containing acetate with a new cuprophane membrane for each dialysis. All used Gambro Lundia membranes except patients 4 and 10, who used membranes manufactured by ASAHI. No patient had had corticosteroids or other immunosuppressive drugs for at least three months. Six were current smokers, four were lifelong non-smokers, and the other two had not smoked for three years and one year.

Blood samples were taken just before dialysis, 15–20 minutes after the dialysis blood pumps had been switched on (midway through recording the early dialysis clearance of ^{99m}Tc DTPA), and during the last hour of dialysis in 10 patients. Comparison of the neutrophil counts was by the Student's *t* test for paired data. The comparison of t½LB ^{99m}Tc DTPA values was performed after log transformation of the data by paired and unpaired *t* tests as appropriate. Four normal non-smoking subjects aged 21–36 years had their DTPA clearance measured several times

Table 2 *Pulmonary epithelial permeability expressed as the half time clearance from lung to blood technetium labelled diethylene triamine pentacetic acid during haemodialysis*

Patient No	*Before dialysis*	*Period of dialysis*				
		0–40 min	*1–2 h*	*2–3 h*	*3–4 h*	*Final hour*
1	28	23	—	40	41	33
2	38	12	17	—	46	37
3	54	23	44	35	—	65
4	41	57	52	—	47	68
5	24	18	22	23	28	31
6	41	42	—	—	—	60
7	20	28	38	—	—	34
8	35	43	37	48	60	60*
9	23	15	—	—	—	46
10	17	23	22	—	19	12
11	12	18	20	—	15	19
12	22	41	39	52	30	36

*All patients had dialysis for five hours except patient 8, who had it for four hours.



Changes in pulmonary clearance of diethylene triamine pentacetic acid (DPTA) labelled with technetium during haemodialysis: half time DTPA clearance during dialysis and in normal non-smoking controls. Filled circles represent smokers, open circles non-smokers, and triangles control subjects. Early dialysis measurements were made during the first 40 minutes of dialysis.

over four to five hours in a similar fashion.

Results

Measurements of DTPA clearance before and during dialysis are shown in the figure and table 2. The baseline values in the six smokers were similar to published values[6 8] and to previously obtained values for smokers without renal failure in our laboratory. The clearance times for the six non-smokers (mean 37.7 range 24–54 min) were, however, significantly shorter than our results for 11 healthy non-smokers aged 18–38 years (mean 60.2, range 38–99 min; $p < 0.025$).

Table 3 *Neutrophil count per microlitre during haemodialysis*

Patient No	*Before dialysis*	*15–20 min from start*	*Final hour*
1	4725	1620	4400
2	2860	280	2928
4	3540	504	3150
6	4940	765	3710
7	2451	260	4180
8	2480	1254	2460
9	4290	558	3116
10	6968	490	5700
11	3480	360	2880
12	3604	459	2747
Mean	3934	655	3527
SE	433	141	312

There was no significant change in the clearance of DTPA during the first half hour of dialysis in the 12 subjects or in the smokers and non-smokers considered separately. There was a significant decrease in DTPA clearance by the last hour of dialysis in all 12 subjects ($p < 0.005$) and in smokers ($p < 0.05$) and non-smokers ($p < 0.025$) analysed separately. These changes appear to develop through dialysis but the data at intermediate time points are too few to be analysed separately. The clearances during the last hour of dialysis in the six non-smokers were not significantly different from the values for our group of 11 healthy non-smokers.

There was considerable neutropenia 15–20 minutes after the dialysis blood pumps had been switched on (table 3). Predialysis neutrophil counts were not significantly different from those taken in the last hour of dialysis. In four normal subjects the mean baseline clearance half time was 51 (range 37–79) minutes. After a further inhalation of ^{99m}Tc DTPA at four to five hours the mean half time was 52 (range 37–95) minutes. The mean coefficient of variation for these four subjects over five hours was 15%.

Discussion

The pulmonary sequestration of neutrophils has been suggested as playing a part in tissue injury.[9] This injury could be produced by the generation of harmful reduced oxygen radicals, the release of catalytic enzymes, or the release of arachidonic acid metabolites.[3] Pulmonary sequestration of neutrophils is often regarded as important in the pathophysiology of the adult respiratory distress syndrome.[3 10] Pulmonary epithelial permeability is increased in this syndrome[11] and this might reflect damage to the alveolar capillary barrier induced by the sequestrated neutrophils. Temporary pulmonary sequestration of neutrophils occurs in the early part of haemodialysis.[2] Our findings show that temporary pulmonary seques-

tration of neutrophils did not cause an increase in the DPTA clearance during dialysis. This suggests that other factors, possibly interacting with the neutrophil sequestration, are necessary to produce acute lung injury[12] and the increase in DTPA clearance seen in adult respiratory distress syndrome. Since these patients were having haemodialysis, conceivably the initial fast clearance in non-smokers could have been a late effect related to the previous haemodialysis. It seems unlikely, however, that this would improve during further dialysis. Capillary endothelial damage does not explain the increased baseline clearance since the endothelium is only responsible for a small part of the alveolar capillary barrier to DTPA.[5 6 13]

The decrease of DPTA clearance during dialysis suggests that dialysis might be removing a circulating factor related to renal failure that is responsible for the abnormal baseline clearance in non-smokers. Such an abnormality in permeability might explain the development of pulmonary oedema in uraemic patients without raised pulmonary capillary pressure.[14] Although changes in blood volume and pulmonary blood flow may occur during haemodialysis, they are not of the order necessary to affect DTPA clearance, which depends primarily on the resistance of the membrane across which it must diffuse.[5 6 13]

The predialysis clearances of our non-smokers were significantly slower than those of our smokers ($p < 0.005$). The clearances of the smokers were similar to the published data on smokers[6 8] and our own data on apparently healthy smokers. Smoking increases pulmonary epithelial permeability as assessed by the decrease of the t½LB of DTPA,[6] and this abnormality shows a rapid improvement within one week of abstention from cigarette smoking.[8] Some component of the gas phase of the smoke appears to be responsible for this change in clearance in smokers.[15]

The method used to measure permeability was similar to that used in previous studies, except that only one intravenous injection of DTPA was given. This was given in the last hour of dialysis since an earlier injection would have interfered with subsequent measurements of clearance. The calculated single correction factor was then applied to all the clearance measurements. With this technique clearances were unchanged over five hours in four normal subjects. Conceivably fluid shifts during dialysis would mean that the correction factor might change. The values we found (mean 2.3, range 0.5–4.2) are, however, similar to those we have previously obtained from normal subjects (mean 2.6, range 1.3–3.8) and from two patients with renal failure but not during dialysis (2.8 and 1.8). Changes in the correction factor and therefore blood distribution would have to be very large either to mask a clearance change in early dialysis or to explain the changes in late dialysis. Nevertheless, we have also calculated the t½LB of ^{99m}Tc DTPA without the use of a correction factor, and these data again showed no significant change in t½LB of ^{99m}Tc DTPA in early dialysis but showed a significant increase in the t½LB of ^{99m}Tc DTPA in later dialysis.

As dialysis proceeds with an acetate buffered dialysate ventilation may fall owing to loss of carbon dioxide into the dialysate.[16 17] Such modest variations in tidal volume of frequency do not affect DPTA clearance.[18] Changes in lung volume can influence the clearance of DPTA,[18] but functional residual capacity is not known to change in chronic renal failure or haemodialysis.

Our findings suggest that some circulating factor in renal failure increases pulmonary epithelial permeability. Such an abnormality in permeability might be responsible for these patients having an increased propensity to develop pulmonary oedema. The abnormality is temporarily corrected by haemodialysis. These findings do not support the suggestion that pulmonary sequestration of neutrophils on its own produces lung damage and an increase in epithelial permeability.

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