The lungs in uraemia: a review[1]

Andrew Bush MA MRCP
Lung Function Unit, Brompton Hospital, London SW3 6HP
Roger Gabriel MSc FRCP
St Mary's Hospital, London W2 1NY

Introduction

When plasma urea is persistently greater than 20 mmol/l it is likely that most body systems and metabolic processes are affected, albeit often subclinically. Lung disease is known to be associated with uraemia (Hopps & Wissler 1955). Possible contributions of the uraemic state and confounding factors introduced by treatment have been the subject of only one inconclusive study (Di Paolo *et al.* 1984). Mechanisms whereby uraemic patients may develop lung disease are summarized in Table 1.

This review examines what is known of the consequences of uraemia and its treatment on lung and respiratory muscle function. Very infrequently the lungs may be severely affected by uraemia, but pulmonary abnormalities are not prominent in most patients with chronic renal failure. Multisystem diseases and pulmonary side effects of drugs such as cyclophosphamide are not discussed. The term 'uraemic lung' is not a specific entity but a phrase which loosely embraces the findings of patchy shadowing on the chest X-ray in a uraemic patient.

Effects of uraemia prior to renal replacement therapy

There are difficulties in conducting a study of pulmonary function in patients with moderate to severe impairment of renal function. As glomerular filtration rate (GFR) falls, and particularly if there is hypoproteinaemia, fluid retention becomes increasingly likely. Thus it is very difficult to exclude increased lung water as a cause of abnormal lung function. Some patients may have been given immunosuppressive drugs, a further cause of pulmonary dysfunction (Ginsberg & Gomis 1982). In a study of 55 patients with chronic renal failure of varying severity (Lee *et al.* 1975), the percentage reduction in carbon monoxide transfer (TCO) correlated weakly with creatinine clearance ($r=0.49$) and plasma urea ($r=-0.49$). These findings are difficult to explain. Eight patients had peripheral oedema and may also have had subclinical pulmonary oedema. If the figures are extrapolated backwards, a GFR of 164 ml/min or a blood urea of -63 mmol/l would be required to produce a normal TCO. Additionally, in patients having lost only half their renal function it is improbable that TCO would be 60% of normal.

Haemodialysis and the lung

Hypoxaemia during the course of haemodialysis was first noted by Sherlock *et al.* (1972). The mechanisms are unknown because of lack of good controlled studies (Garella & Chang 1984). Possible causes include ventilation-perfusion mismatch due to pulmonary microemboli; hypoventilation due to alkalosis or extracorporeal carbon dioxide loss; and a direct effect of the metabolism of acetate by Krebs' cycle enzymes. These mechanisms are considered below.

Pulmonary sequestration of leukocytes

There is persuasive evidence that white cells are important in the pathophysiology of haemodialysis hypoxia. Craddock *et al.* (1977) investigated 34 patients who developed

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Table 1. Possible reasons why pulmonary dysfunction may be found in patients with renal failure independent of any direct effect of uraemia on the lungs

Cause	Effect
Iatrogenic:	
(1) Haemodialysis	Complement activation Leukocyte sequestration Silicone emboli
(2) Peritoneal dialysis	Massive hydrothorax
Poor patient compliance	Repeated bouts of pulmonary oedema
Indirect effects	Immune suppression Respiratory muscle dysfunction Chronic acidosis, abnormal calcium and phosphorus homeostasis causing dystrophic calcification
Chance finding	Artefacts of selection and increased medical supervision

neutropenia (white cell count falling by 80%) in the first 30 minutes of haemodialysis. Neutropenia was associated with consumption of C3 and Factor B, and caused hypoxaemia with an increased alveolar-arterial oxygen gradient, decreased TCO and increased closing volume, presumably at least partly related to ventilation-perfusion mismatch. Interestingly, a single patient who had agranulocytosis due to aplastic anaemia was dialysed four times against identical membranes and developed none of the above abnormalities. It has been shown that if animal serum is incubated with the cellophane membranes of a dialyser, or with zymosan to activate complement, and is then returned to the animal, leukopenia, hypoxaemia, increased pulmonary lymph flow and pulmonary hypertension develop (Craddock *et al.* 1977). These abnormalities were not found if complement was inactivated or the animals were previously rendered neutropenic. Craddock *et al.* (1977) suggested that the fall in white cell count was a response to intrapulmonary sequestration of neutrophils and the phlogistic consequences of complement consumption. They were unable to demonstrate the site of white cell aggregation. Abu-Handon *et al.* (1984) have observed correlations between initial white cell count and hypoxaemia during dialysis. Repeated use of the same dialyser resulted in progressively less complement activation (Stroncek *et al.* 1984, Arnaout *et al.* 1985). Subsequently an increase in granulocyte-adhesion-promoting surface glycoprotein has been demonstrated in dialysis patients (Arnaout *et al.* 1985). This is mediated in part by C5a and may promote intrapulmonary leukocyte sequestration. However, the model does not wholly account for the experimental observations. Polyacrylonitrile (PAN) membranes have been shown to activate complement without resulting neutropenia or changes in lung function (Aljama *et al.* 1978*a*, Vaziri *et al.* 1984). Furthermore, ultrafiltration with cuprophane membranes (no exposure to dialysate) does not cause arterial hypoxaemia (Dumler & Levin 1979, Brautbar *et al.* 1980). The precise relationship between dialysis membrane structure, activation of complement, white cell aggregation and pulmonary function abnormalities remains to be clarified.

Extracorporeal formation of microemboli

Bischel *et al.* (1975) demonstrated amelioration of some of the pulmonary complications of haemodialysis by filtering blood before returning it to the patient. Conversely, Aurigemma *et al.* (1977) were unable to reproduce these findings and thus the importance of this mechanism, together with the need for blood filters in the venous line, is controversial.

Correction of acidosis

An important determinant of respiratory drive is arterial pH. It is possible that partial, intermittent correction of chronic acidosis by haemodialysis might cause hypoventilation by removing this drive to breathing (Torrance *et al.* 1975). This is unlikely to be the only

mechanism, because dialysis-related hypoxaemia may occur in the face of unchanged pH (Carlon *et al.* 1979).

Elimination of carbon dioxide by the dialyser

Hypoventilation due to loss of respirator drive has been attributed to loss of carbon dioxide with the dialyser acting as a 'third lung'. Carbon dioxide loss has been difficult to measure and there is a lack of reliable information on oxygen consumption and carbon dioxide production during haemodyalysis. Acetate buffered dialysis appears to cause less carbon dioxide loss through the lungs, a greater reduction in ventilation and more severe hypoxia than bicarbonate dialysis which prevents carbon dioxide loss across the dialyser. This suggests that carbon dioxide elimination by the dialyser is also an important cause of hypoxaemia (Garella & Chang 1984).

Acetate metabolism

Acetate is broken down by Kreb's cycle enzymes (Oh *et al.* 1979, Burns & Scheinhorn 1982).

$$CH_3COO^- + CO_2 + H_2O \rightarrow CH_3COOH + HC_3^- \quad \ldots\ldots (1)$$

$$CH_3COOH + 2O_2 \rightarrow 2CO_2 + 2H_2O \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

The net result of (1) and (2) is the production of only one carbon dioxide molecule for two oxygen molecules consumed, giving the low respiratory quotient (carbon dioxide production/oxygen consumption) of 0.5. The diminished carbon dioxide production might be important in causing hypoventilation.

Despite considerable research, the cause or causes of dialysis-related hypoxaemia are not known. There is a dearth of well controlled studies.

'First use syndrome'

This syndrome is characterized by the development of chest pains, dyspnoea and hypotension when a patient is first dialysed against a cuprophane membrane. Hakim *et al.* (1984) studied 16 patients of whom 6 had experienced severe 'first-use syndrome'. All 6 had higher serum activities of the anaphylotoxins C3a and C5a whilst symptomatic, compared with asymptomatic controls. The cuprophane dialyser membrane was thought to have activated the complement cascade via the alternative pathway since C4a activity was not increased. Cuprophane is a polysaccharide and is structurally similar to other *in vivo* alternative pathway activators (Eknoyan 1984). The blood lines of an extracorporeal dialysis circuit probably do not activate complement. It is not known why there is individual variation in complement activation. Patients' sera could be screened for complement activation by cuprophane and other membranes and if complement were activated either peritoneal dialysis or PAN membranes could be used in those whose sera reacted. A similar syndrome has been described in a patient only on re-use of membranes (Stein *et al.* 1985).

Silicone accumulation

A further pulmonary complication of haemodialysis is the formation of silicone emboli from blood pump tubing (Leong *et al.* 1982). Particles of silicone can be demonstrated in lung capillaries, intravascular giant cells and alveolar macrophages. Granulomata and fibrosis were not seen. The clinical relevance of these findings is unknown but silicone-induced alveolitis, adult respiratory distress syndrome and pulmonary granulomas complicated injections of liquid silicone to augment breasts or buttocks (Chastre *et al.* 1983), presumably due to silicone emboli to the lungs.

Miscellaneous reactions

Anaphylactic reactions have been recorded during dialysis but are very rare (Villarroel 1984). By inducing the release of mediators (Stenson & Parker 1980) intrapulmonary micro-

aggregates of leukocytes may account for the reported cases of provocation of bronchial asthma by haemodialysis (Aljama *et al.* 1978*b*).

Overt pulmonary complications during haemodialysis are very infrequent. It is possible that repeated subclinical events affect lung function, may be common and contribute to the impairment of lung function.

Studies of lung function between dialysis periods

The most consistent abnormality of lung function measured between dialyses is reduced TCO. Daum *et al.* (1966) demonstrated a mean 55% reduction in TCO in 15 patients with acute and 2 with chronic renal failure. Zidulka *et al.* (1973) studied 6 fluid-overloaded patients immediately before haemodialysis. All had reduced lung volume and TCO. After dialysis, closing capacity decreased significantly in 5, with improved basal ventilation and perfusion. The authors suggested that the changes were due to dialysable pulmonary oedema and irreversible uraemic lung fibrosis, although figures for removal of fluid during dialysis were not given. Crosbie & Parsons (1974) found reduced TCO in 3 out of 6 fluid-overloaded patients with chronic renal failure. Forman *et al.* (1981) demonstrated a 59% reduction in TCO in 18 haemodialysis patients after correction for anaemia by the method of Cotes *et al.* (1972). More severe abnormalities were found by Lee *et al.* (1975).

Pulmonary abnormalities found at post-mortem in haemodialysis patients

The post-mortem findings in the lungs of 46 haemodialysis patients have been retrospectively studied (Fairshter *et al.* 1982). There was no control group. Only one subject had normal lungs; 26 different diagnoses were made, acute and chronic diseases being found in 44 and 37 patients respectively.

The most common acute disease was pulmonary oedema which was found in 19 patients. Fluid overload, left ventricular failure and probably hypoproteinaemia and increased capillary permeability may have contributed (Rackow *et al.* 1978). Pulmonary fibrosis and metastatic calcification were the most common of the chronic diseases. Eleven patients had pulmonary arteriosclerosis thought to reflect pulmonary hypertension. Predisposing causes include elevated left atrial pressure, chronic acidosis, hypoxaemia during haemodialysis and thromboembolism.

Some of the above abnormalities may have been a consequence of haemodialysis, the lack of patient compliance with drug therapy and fluid restriction, or chance findings. The difficulty in finding adequate controls for dialysis patients who are a selected group and under close supervision has been discussed (Kinlen *et al.* 1980, Bush & Gabriel 1984).

Peritoneal dialysis

Acute renal failure

The pulmonary effects of intraperitoneal dialysate were first studied in patients with acute renal failure undergoing dialysis with semi-rigid peritoneal catheters (Berlyne *et al.* 1966). Infection, lower lobe collapse and effusions were common and thought to be due to splinting of the diaphragm and sputum retention in immobile patients. Goggin & Joekes (1971) showed that hypoxaemia developed or worsened when acute peritoneal dialysis began. Freedman & Maberley (1971) suggested that intra-abdominal dialysate caused airway closure during tidal breathing. It was therefore considered that pre-existing lung disease was a contraindication to peritoneal dialysis (Berlyne *et al.* 1966) and by extrapolation to continuous ambulatory peritoneal dialysis (CAPD) (Lameire *et al.* 1981).

Chronic renal failure

There have been few systematic studies of the effects of CAPD on the lungs. Thieler *et al.* (1980) studied spirometry, lung volumes and static and dynamic compliance in 10 patients whilst standing, sitting and lying. With the abdomen full, there were significant changes in dynamic compliance in all 3 positions. Thoracic gas volume and vital capacity fell whilst lying.

Winchester & Taveira de Silva (1981) reported significant reduction in forced vital capacity (FVC) in 12 patients studied sitting and lying. The variables were measured again 6 months later; abnormalities persisted only when patients were supine. Statistically significant reductions in total lung capacity, residual volume and FVC were found by Epstein *et al.* (1982) who concluded that the changes were not clinically important. Effects of CAPD volume upon respiratory mechanics are potentially important and Rebuck (1982) emphasized the need for detailed studies of diaphragmatic and chest wall function.

In a recent study of 29 patients on CAPD, spirometry, lung volumes, TCO and sniff transdiaphragmatic pressures sitting and lying were performed together with maximal inspiratory and expiratory mouth pressures whilst sitting (Bush *et al.* 1985). In addition, optical contour mapping of the thoracoabdominal wall was carried out by the method of Peacock *et al.* (1984). No clinically important change was found in any variable upon filling or emptying the abdomen with dialysate. Compensatory abdominal distension was predominantly below the umbilicus. The abdomen and not the chest is the cavity predominantly affected by CAPD. The frequent occurrence of abdominal herniae in CAPD patients (Schleifer *et al.* 1984) also tends to support this suggestion. Bush *et al.* (1985) concluded that fluid volumes used for CAPD do not acutely impair lung function.

Studies on patients receiving chronic intermittent peritoneal dialysis show that FVC, residual volume and total lung capacity decreased significantly upon first filling the abdomen and reverted to pre-dialysis values at the end of the dialysis period (generally of 18 to 24 hours' duration). These changes could be due to fluid removal during the dialysis period (Ahluwalia *et al.* 1982).

Miscellaneous complications

Massive hydrothorax is an occasional complication of CAPD (Rudnick *et al.* 1979). The condition is probably due to passage of dialysate across small diaphragmatic defects. Treatment is usually by pleurodesis and the patient is retained on haemodialysis until the pleural space has been obliterated (Scheldewaert *et al.* 1982).

Indirect effects of uraemia

Immune system

Both B and T cell function is abnormal in uraemia (Raska *et al.* 1983, Giacchino *et al.* 1982). The abnormalities may be less pronounced in patients receiving CAPD (Giacchino *et al.* 1982). Staphylococcal septicaemia occurs in haemodialysis patients and is related to skin bacteria gaining access to the circulation during puncture of the arteriovenous fistula prior to dialysis. Lung abscess may result. Uraemic patients may thus be particularly prone to infection and diagnosis may be difficult (Gabriel 1984).

Muscle disease

There have been two small studies of respiratory muscle function in uraemia. Gomez-Fernandez *et al.* (1984) found reduction in inspiratory mouth pressures in patients on CAPD compared with controls. Mouth pressures were independent of the presence of fluid in the abdomen. We studied 10 patients and found that sniff transdiaphragmatic pressures (Miller *et al.* 1985) and inspiratory and expiratory mouth pressures (Black & Hyatt 1969) were within normal limits for our laboratory (Miller *et al.* 1985, Bush *et al.* 1985). We are currently conducting further studies to assess respiratory muscle function in uraemia.

Transplantation and the lung

There is little data on pulmonary physiological variables in patients with an uncomplicated course after renal transplantation (Doak *et al.* 1973). Lee *et al.* (1975) reported that reduced TCO persisted for 3 years after successful transplantation. From our own preliminary studies (unpublished) we have found that this variable may never return to normal. Possibly micro-embolic lesions having developed during dialysis leave irredeemable pulmonary damage. Lung

function in patients treated only by CAPD and then transplanted does not appear to have been reported.

Conclusion

The nature and severity of the functional damage done to the lungs by uraemia is unknown. In patients studied while on haemodialysis the main abnormality is a reduced TCO. An isolated reduction in TCO is commonly seen in patients who have suffered multiple pulmonary emboli (Davies 1982), which suggests that blockage of the microcirculation by white cells, thromboemboli or even silicone may be of central importance. The confounding effect of possible chronic intermittent increases in lung water has yet to be clarified. The permanence of this damage after renal transplantation has also not been established. Subtle changes may gradually develop and thus be difficult to diagnose. Whether lung damage is an invariable accompaniment of the uraemic state is not yet known.

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