

# Pathophysiology of chronic renal failure

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## Key points

The incidence of chronic renal failure (CRF) is increasing.

Significant pathophysiological changes affect most organ systems.

Patients with CRF are amongst the most challenging of the hospital population.

Ischaemic heart disease is often silent, even in patients who are not diabetics.

Peri-operative morbidity and mortality are high.

Chronic renal failure (CRF) and end-stage renal disease (ESRD) are functional diagnoses characterised by a progressive decrease in glomerular filtration rate (GFR). CRF occurs where GFR has been reduced to 10% of normal function ( $20 \text{ ml min}^{-1}$ ) and ESRD when GFR falls below 5% ( $10 \text{ ml min}^{-1}$ ). In 2002, approximately 37,000 patients received renal replacement therapy in the UK for ESRD. Of these, about half had received a renal transplant (46%), 37% haemodialysis and 16% ambulatory peritoneal dialysis.

The incidence of CRF is increasing in the UK by 7% per annum; the main causes of CRF are listed in Table 1. Patients with ESRD frequently manifest a wide range of pathological organ dysfunction either caused by the primary disease (e.g. diabetes mellitus), intrinsic pathological effects of uraemia or a combination of the two. Uraemia refers to the multitude of effects resulting from the inability to excrete products of the metabolism of proteins and amino acids. Certain specific metabolic products are associated with particular organ dysfunctions (e.g. guanidinosuccinic acid and platelet dysfunction) but the individual clinical picture correlates poorly

with plasma concentrations of these substances. Some of the toxic products of amino acid metabolism are listed in Table 2. The multi-organ effects of uraemia are also caused by the impairment of the wide range of metabolic and endocrine functions normally carried out by the kidney. This review will concentrate on the more common pathophysiological changes of relevance to anaesthesia. Despite impressive medical advances, the overall 4-year survival for patients with ESRD in the UK is only 48%.

## Fluid and electrolyte derangement

### Sodium

In a normal individual, more than 25,000 mmol of sodium ions are filtered daily with < 1% being excreted. CRF can be associated with sodium retention, sodium depletion or normal sodium balance and is influenced by factors such as diuretic use and cardiac function. However, most patients demonstrate a mild degree of sodium and water retention whilst the extracellular fluid volume remains isotonic. Ironically, the patient with CRF also has impaired renal concentrating mechanisms and thus extrarenal fluid losses such as vomiting, diarrhoea or pyrexia may rapidly cause hypovolaemia.

### Potassium and magnesium

Adaptive processes increase potassium secretion in the distal nephron (collecting tubules) and also in the gut. Whilst a wide range of plasma potassium concentrations can be encountered dependent on factors such as diuretic use, it tends to be elevated. Acute changes present the greatest threats to life. A range of drugs may cause acute hyperkalaemia

**Table 1** Major causes of chronic renal failure

Diabetes mellitus	30%
Hypertension	24%
Glomerulonephritis	17%
Polycystic kidney disease	4%
Chronic pyelonephritis	5%
Unknown	20%

**Table 2** Major identified toxins in chronic renal failure

Guanidine	Benzoates
Methylguanidine	Creatine
Phenols	Creatinine
Guanidinosuccinic acid	Tryptophan
Tyrosine	Aliphatic amines
Myoinositol	Glucuroconjugates

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such as  $\beta$ -blockers, potassium-sparing diuretics (e.g. spironolactone), ACE inhibitors, angiotensin antagonists, NSAIDs and nephrotoxins such as aminoglycosides and cyclosporins. Extracellular acidosis causes an exchange of intracellular potassium for extracellular hydrogen ions in an attempt to maintain electrical neutrality. In acute acidosis, the serum potassium will rise  $0.5 \text{ mmol litre}^{-1}$  for each 0.1 unit decrease in pH. For this reason, hypercarbia should be avoided during general anaesthesia.

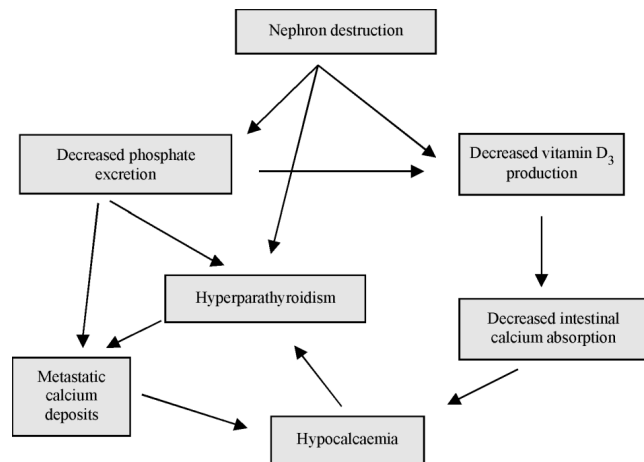
Magnesium is handled by the kidney much like potassium. Reduced excretion may cause hypermagnesaemia, muscle weakness and potentiate non-depolarising muscle relaxants.

### Acidosis

Chronic metabolic acidosis is a common feature of ESRD. The inability to secrete protons and buffers (e.g. phosphate) or to regenerate bicarbonate limits the clearance of hydrogen ions. Furthermore, reduction in glutamine utilisation reduces ammonia production and secretion into the proximal tubule. Retention of organic anions causes a progressive increase in the anion gap and a further fall in plasma bicarbonate concentration. Although plasma bicarbonate concentrations rarely fall below  $12\text{--}15 \text{ mmol litre}^{-1}$ , there is little reserve to counter acute acidosis caused by ketoacidosis or sepsis.

### Calcium, phosphate, parathormone and renal osteodystrophy

Total plasma calcium concentration is reduced in CRF. Renal production of calcitriol ( $1,25\text{-(OH)}_2\text{D}_3$ ) declines causing decreased intestinal absorption of calcium. Phosphate excretion is impaired as GFR falls below  $20 \text{ ml min}^{-1}$  and hyperphosphataemia develops. As phosphate concentrations increase, calcium phosphate is deposited in soft tissues such as skin and blood vessels further lowering plasma calcium concentration. Hyperphosphataemia also has a negative effect on  $1\text{-}\alpha$ -hydroxylase, the enzyme responsible for renal calcitriol production. Both hypocalcaemia and hyperphosphataemia are potent stimuli to parathormone secretion, leading to hyperplasia of the parathyroid gland and secondary hyperparathyroidism. This causes increased osteoclast and osteoblastic activity causing osteitis fibrosa cystica. Patients usually tolerate hypocalcaemia remarkably well, whilst oral calcitriol is prescribed and calcium carbonate is used both as an intestinal phosphate binder and a source of calcium. The inter-relationship between calcium, phosphate and parathormone in CRF is shown in Figure 1.



**Fig. 1** Calcium and phosphate homeostasis in chronic renal failure.

Careful assessment of pre-operative fluid and electrolyte status is needed. Patients awaiting dialysis may be hypervolaemic; those recently dialysed may be hypovolaemic. Ideally, a period of 4–6 h should elapse before anaesthesia to allow fluid compartment equilibration and the clearance of residual heparin. Indications for emergency pre-operative dialysis include: hyperkalaemia; fluid overload and pulmonary oedema; metabolic acidosis; and ‘uraemic’ toxicity and coma.

### Haematological abnormalities

A normochromic normocytic anaemia is a common finding in CRF. Decreased renal parenchymal erythropoietin production reduces stem cell transformation into erythrocytes, while uraemic toxins reduce red cell life. Chronic upper GI tract losses and those from dialysis further compound the problem. Dietary deficiency in iron and folate also occurs. The introduction in 1989 of synthetic erythropoietin has revolutionised the management of anaemia in these patients but a compensated relative anaemia is still to be expected. A rapid increase in haemoglobin concentration above  $10 \text{ g dlitre}^{-1}$  often worsens hypertension and may precipitate heart failure. Compensatory mechanisms increase 2,3-diphosphoglycerate production and move the oxygen-haemoglobin dissociation curve to the right.

### Coagulopathy

Patients with CRF have a tendency to excessive bleeding in the peri-operative period. Standard tests of coagulation are usually normal (i.e. prothrombin time, activated partial thromboplastin

time, international normalised ratio) and platelet count is within normal limits. However, platelet activity is deranged with decreased adhesiveness and aggregation, probably caused by inadequate vascular endothelial release of a von Willebrand factor/factor VIII complex which binds to and activates platelets. Increased platelet release of  $\beta$ -thromboglobulin and vascular production of PGI<sub>2</sub> also contribute to the coagulopathy. Defects in platelet adhesion may also be related to excessive nitric oxide (NO) production. The plasma from patients with CRF has been shown to be a potent inducer of endothelial NO production.

Measured bleeding time may be prolonged beyond 10 sec. Thrombocytopenia is not corrected by platelet transfusion but, where operative bleeding is problematical, it can be improved by dialysis. Rapid improvements in coagulation require the use of pooled cryoprecipitate or DDAVP (which enhances release of von Willebrand factor). DDAVP 0.3  $\mu\text{g kg}^{-1}$  is effective within 1–2 h but has a duration of only 6–8 h and is subject to tachyphylaxis. Intravenous conjugated oestrogens have a slower onset but a longer duration of action (5–7 days). The risks of coagulopathic complications should be considered when choosing regional anaesthetic techniques in CRF.

### Cardiovascular and pulmonary abnormalities

Cardiovascular abnormalities are common in CRF and are responsible for 48% of deaths in these patients. Systemic hypertension is the most common with an incidence approaching 80%, although it is often not a feature of sodium-wasting nephropathies such as polycystic kidney disease or papillary necrosis. Plasma volume expansion resulting from sodium and water retention is the most frequent cause of hypertension; it may be improved significantly by dialysis. Some patients may require  $\beta$ -blockers, ACE inhibitors,  $\alpha$ -antagonists and vasodilators to control their blood pressure adequately. Alteration in the control of renin and angiotensin secretion may also contribute to hypertension in 30% of patients.

Ischaemic heart disease (IHD) is a frequent cause of mortality in patients with CRF. The incidence varies with patient subgroup but is present in 85% of diabetics > 45 years of age with CRF. Accelerated atherosclerosis results from a decreased plasma triglyceride clearance, hypertension and fluid overload causing left ventricular hypertrophy and failure. The elevation in plasma triglyceride concentrations is caused by a defect in lipoprotein lipase activity and reduced lipolysis.

The incidence of metastatic calcific valvular heart lesions is significantly increased. Aortic calcification occurs in up to 55% of patients with aortic stenosis being present in 13%. Mitral

valve calcification occurs in 40% (stenosis 11%). Elevation in the calcium-phosphate product and parathyroid hormone concentrations are the main cause. As a result of these lesions, bacterial endocarditis is much more common in dialysis patients than the normal population. Haemorrhagic uraemic pericarditis was often seen prior to the advent of effective dialysis. However, it is now uncommon and occurs in patients receiving inadequate dialysis. If untreated, it may rarely progress to pericardial tamponade with hypotension, elevated jugular venous pressure and signs of falling cardiac output. Pericardectomy may be required but should be reserved for those who fail to improve with immediate dialysis. Sudden death from acute cardiac arrhythmias is frequent and related to both IHD and electrolyte imbalance.

Postoperative pulmonary complications are common in patients with CRF. Fluid overload, malnutrition, anaemia, impaired humoral and cellular immune function and decreased surfactant production predispose patients to atelectasis and infection.

### Immune function

Sepsis is a leading cause of death in patients with CRF. Inhibition of cell-mediated immunity and humoral defence mechanisms occurs, with little improvement following dialysis. There is an increased production of pro-inflammatory cytokines suggesting that activation of monocytes may play a role in uraemic immune dysfunction. Superficial infections are common in fistula and catheter sites; wound healing is poor.

The incidence of viral hepatitis B has decreased somewhat following the introduction of erythropoietin and hepatitis B vaccination. There is also an increased incidence of hepatitis C infection in patients on haemodialysis and, although there is often little effect on liver function, it is of concern in patients undergoing renal transplantation and immunosuppression. Hospital staff must take precautions against blood-borne viruses in these patients.

### Gastrointestinal abnormalities

Gastrointestinal abnormalities are frequent with anorexia, nausea and vomiting contributing to malnutrition. Urea is a mucosal irritant and bleeding may occur from any part of the GI tract. Gastric emptying is delayed, residual volume increased and pH lowered. Peptic ulcer disease is common and most patients will receive proton pump inhibitors. The use of a rapid sequence induction technique needs to be balanced against the risks of difficult intubation in chronically ill patients with poor dentition. Succinylcholine will increase the plasma potassium concentration by approximately

0.5 mmol litre<sup>-1</sup> and is not reliably prevented by precurarisation with a non-depolarising agent. Patients with diabetes mellitus have an increased incidence of difficult intubation and autonomic gastric paresis even in the absence of CRF. In practice, rapid sequence induction is restricted to patients who are inadequately fasted or have symptoms of gastric reflux and a low serum potassium.

### Neurological abnormalities

Many patients with CRF have abnormalities in central (CNS) and peripheral nervous system function. There is a wide spectrum of CNS changes, for example, from mild personality alterations to asterixis (i.e. lapse of posture, usually manifest by bilateral flapping tremor), myoclonus, encephalopathy and convulsions. Peripheral neuropathy is common in advanced stages of the disease. Initially, it presents as a distal 'glove and stocking' sensory loss but then progresses to motor changes. Both dialysis and renal transplantation may improve the neuropathy. The presence of a peripheral neuropathy should alert the anaesthetist to the presence of an autonomic neuropathy with delayed gastric emptying, postural hypotension and silent myocardial ischaemia. Two types of neurological disturbances are unique to patients on dialysis. Dialysis dementia with dyspraxia, myoclonus and dementia occurs in patients on dialysis for many years and may be related to aluminium toxicity. The dialysis disequilibrium syndrome is associated with rapid initial reduction in plasma urea concentrations at the start of dialysis.

### Endocrine disturbances

Changes in parathyroid function and lipid clearance have been noted above. Glucose tolerance is impaired but there is a reduced requirement for exogenous insulin in diabetic patients, probably related to the reduced metabolism of insulin by the failing kidney. Patients with CRF have abnormalities of temperature regulation with reduced basal metabolic rate and a tendency to hypothermia. This is may be important when assessing fever.

### Pharmacokinetic changes

There are many pharmacokinetic changes in patients with CRF. Hypoalbuminaemia and acidosis increase free-drug availability

of highly protein bound drugs. The doses of benzodiazepines and thiopental should be reduced by 30–50%. Although the pharmacodynamics of propofol are unchanged in CRF and the metabolites lack sedative activity, changes in volume of distribution and mental state mean that a reduction in induction dose is also appropriate. The elimination of highly ionised, lipid-insoluble drugs is partially or completely dependent on renal excretion and may be markedly reduced. However, the duration of action of a single loading dose will be dependent on redistribution rather than excretion.

Most lipid-soluble analgesics are metabolised by the liver to water-soluble metabolites for renal excretion. Some of these metabolites may have far greater activity than the parent drug (e.g. morphine-6-glucuronide) or significant side-effects (e.g. nor-pethidine). Although fentanyl undergoes hepatic metabolism and is not thought to have active metabolites, its clearance is decreased in severe uraemia.

The elimination of volatile anaesthetic agents is not dependent on renal function and their activity is unaffected by CRF. The metabolism of both enflurane and sevoflurane will theoretically produce nephrotoxic fluoride ions and their use should be discouraged for prolonged durations. Nitrous oxide has little effect on the kidney. Atracurium and cisatracurium are obvious choices for muscle relaxation but limited doses of vecuronium and rocuronium are acceptable alternatives. Plasma cholinesterase activity is not thought to be affected by CRF. The excretion of anticholinesterases and anticholinergic agents will be prolonged.

Local anaesthetics are valuable agents for peri-operative pain control in CRF but their duration of action is reduced. Maximum doses of local anaesthetics should also be reduced by 25% because of reduced protein binding and a lower CNS seizure threshold.

### Key references

- Iohom G. Renal function. *Bull R Coll Anaesth* 2001; **7**: 311–5
- Sladen RN. Anaesthetic considerations for the patient with renal failure. *Anesth Clin North Am* 2000; **18**: 863–82
- Sprung J, Kapural L, Bourke D, O'Hara J. Anaesthesia for kidney transplant surgery. *Anesth Clin North Am* 2000; **18**: 919–43

See multiple choice questions 91–94.