CHRONIC RENAL FAILURE AND ANAESTHESIA

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Chronic renal failure (CRF) and end stage renal disease (ESRD) are functional diagnoses characterised by progressive decrease in glomerular filtration rate (GFR). CRF occurs where GFR has been reduced to 10% (20ml/min) of normal function and ESRD when GFR falls below 5% (10ml/min). Patients with ESRD are dependant on renal replacement therapy (RRT) to survive. The relationship between serum creatinine and GFR is not linear (figure 1) and serum creatinine does not rise until GFR has fallen below 50%. In addition, renal tubular secretion of creatinine is increased at higher serum levels.

The incidence of ESRD in the developing world is difficult to estimate and ranges from 40 per million population (pmp) to 340 pmp. The prevalence of ESRD can be more accurately recorded as the number of patients receiving RRT. It ranges from 100 pmp to 600 pmp and can be related to a countries economic wealth. In comparison, the prevalence in the United States of America (USA) is 1191 pmp.

Glomerulonephritis is the main cause of ESRD worldwide (11% – 49%). Proliferative glomerulonephritis is more common in developing countries and may be secondary to endemic infections like streptococcus, schistosomiasis, and malaria. Focal segmental glomerulonephritis is also common in Africa, while IgA nephropathy is common in Asia and Pacific regions. Amyloidosis causes a smaller proportion of glomerular disease and again may be as a result of chronic endemic infections. Interstitial nephritis, secondary to renal stones, obstruction of the urinary tract, tuberculosis and various nephrotoxins, are responsible for up to 20% of ESRD. Diabetes mellitus and hypertension remain important factors in the aetiology of ESRD, but less so in the developing world than in the USA where they account for around 65% of ESRD.
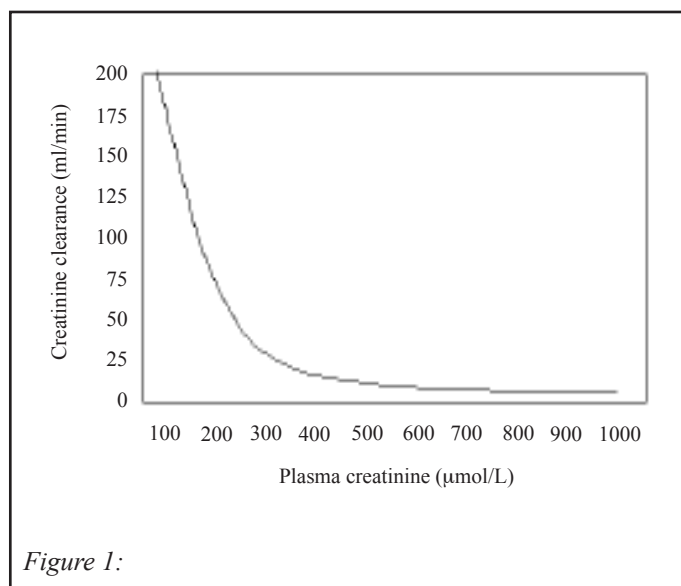

Figure 1:

Table 1 Major identified uraemic toxins

Guanidine	Benzoates
Methlguanidine	Creatine
Phenols	Creatinine
Guanidinosuccinic acid	Tryptophan
Tyrosine	Aliphatic amines
Myoinositol	Glucuronoconjugates

Patients with ESRD frequently manifest a wide range of pathological organ dysfunction either caused by the primary disease such as diabetes mellitus, the intrinsic pathological effects of uraemia or a combination of the two. Uraemia refers to the effects resulting from the inability to excrete products of the metabolism of proteins and amino acids. Some of the toxic products of amino acid metabolism are listed in table 1. 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 encountered of relevance to anaesthesia. Despite impressive medical development, 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 less than 1% being excreted. CRF can therefore be associated with sodium retention, sodium wasting or normal sodium balance, and is further influenced by factors such as diuretic use and cardiac function. Most patients however demonstrate a mild degree of sodium and water retention whist 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 and hypotension.

Potassium - 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 such as beta-blockers, potassium sparing diuretics (spironolactone), angiotensin converting enzyme (ACE) inhibitors or angiotensin antagonists, non-steroidal anti-inflammatory agents 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 0.5mmol/l for each

0.1 unit decrease in pH. For this reason hypercarbia should be avoided during general anaesthesia.

The kidney handles magnesium in a similar way to 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 or buffers such as 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 12-15mmol/l 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 $(1,25\text{-}(OH)_2D_3)$ declines causing decreased intestinal absorption of calcium. Phosphate excretion is impaired as GFR falls below 20ml/min and hyper-phosphataemia develops. As phosphate levels 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 $1\text{-}\alpha\text{-}$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 osteoblast activity causing osteitis fibrosa cystica. Patients usually tolerate hypocalcaemia remarkably well, as long as oral calcitriol is prescribed and calcium carbonate is used both as an intestinal phosphate binder and a source of calcium. The interrelationship between calcium, phosphate and parathormone in CRF is shown in figure 2.

Careful assessment of the pre-operative fluid and electrolyte status is needed. Dehydration can cause further renal impairment and some patients may benefit from pre-operative intravenous saline while fasting. Patients with oliguric ESRD usually have a fluid restriction imposed. This should be enough to cover insensible losses in addition to their urine volume. When planning fluid requirements the patient's normal daily fluid allowance should be considered and potassium containing fluids should be avoided. Hourly urine volume measurement and central venous pressure monitoring may be necessary pre-operatively. Blood pressure should be kept within the patient's normal range to maintain renal perfusion.

Patients awaiting dialysis may be hypervolaemic, and those recently dialysed may be hypovolaemic. A period of 4-6 hours should ideally elapse before anaesthesia to allow fluid compartment equilibration and the clearance of residual heparin. Vascular instability may complicate induction of anaesthesia. Indications for emergency pre-operative dialysis include:

- Hyperkalaemia ($K^+ > 6.0$ mmol/L)
- Fluid overload and pulmonary oedema
- Metabolic acidosis
- "Uraemic" toxicity and coma

Haematological abnormalities

A normochromic normocytic anaemia is a common finding in CRF. Decreased renal 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. Rapid increases in haemoglobin concentration above 10g/dl often worsen hypertension and may precipitate heart failure. Compensatory mechanisms increase 2,3-diphosphoglycerate production and move the oxyhaemoglobin dissociation curve to the right thus enhancing oxygen delivery to the tissues.
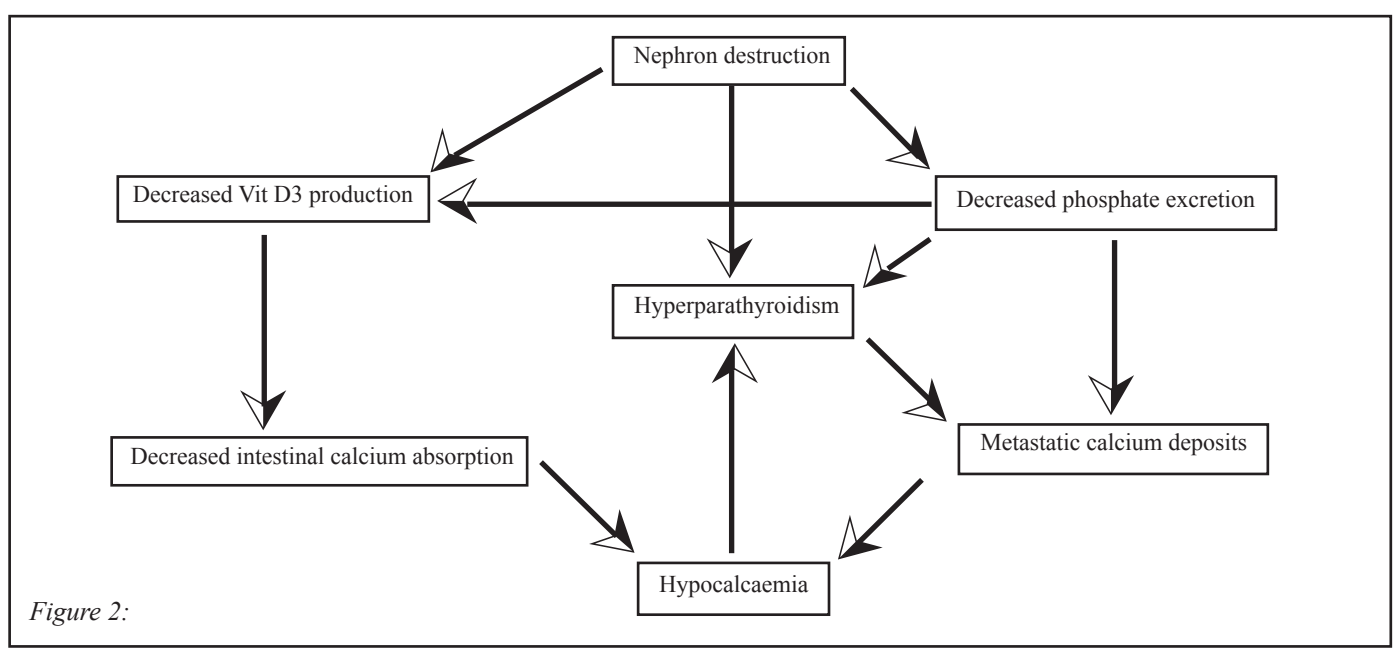

Figure 2:

Coagulopathy. Patients with CRF have a tendency to excess bleeding in the perioperative period. Standard tests of coagulation are usually normal (prothrombin time/INR, activated partial thromboplastin time) and platelet count is within normal limits. Platelet activity is however abnormal 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 β-thromboglobulin and vascular production of PGI$_2$ 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.

If it is measured, bleeding time may be prolonged beyond the normal. Platelet dysfunction is not corrected by platelet transfusion, but if operative bleeding occurs, it can be improved by dialysis. Rapid improvements in coagulation require the use of cryoprecipitate or DDAVP (which enhances release of von Willebrand factor). DDAVP (0.3mcg/kg) is effective within 1-2 hours but has a short duration of only 6-8 hours, and is subject to tachyphylaxis. Intravenous conjugated oestrogens have a slower onset but a longer duration of action (5-7 days). The risks of bleeding complications should be considered when deciding to use regional anaesthetic techniques in CRF.

Cardiovascular and pulmonary abnormalities

Cardiovascular abnormalities are very common in CRF, and represent 48% of the causes of death 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, and may be significantly improved by dialysis. Some patients may require beta-blockers, ACE inhibitors, alpha-blockers and vasodilators to adequately control their blood pressure. 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, for example it is present in 85% of diabetics older than 45 years with CRF. Accelerated atherosclerosis results from decreased plasma triglyceride clearance, hypertension and fluid overload causing left ventricular hypertrophy and failure. The elevation in plasma triglyceride levels is caused by a defect in lipoprotein lipase activity and reduced lipolysis.

The incidence of metastatic calcific valvular heart lesions is increased. Aortic valve 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, but is now uncommon and occurs in patients on inadequate dialysis regimen. If untreated, it may 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 abnormalities.

Pulmonary complications are common in patients with CRF in the postoperative period. 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 the instigation of 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, and 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 be balanced against the risks of difficult intubation in chronically ill patients with poor dentition. Suxamethonium will increase the plasma potassium concentration by approximately 0.5mmol/L and this 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. CNS changes have a wide spectrum from mild personality alterations to asterixis, myoclonus, encephalopathy and convulsions. Peripheral neuropathy is common in advanced stages of the disease and is initially a distal "glove and stocking" sensory loss progressing later 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 levels at the commencement 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 diabetics, 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 may be important when assessing fever.

Altered drug handling in CRF

A wide range of pharmacokinetic changes occurs in drug handling in patients with CRF. The volume of distribution is usually decreased, but may be increased if there is fluid retention. Hypoalbuminaemia and acidosis increase the free drug availability of highly protein bound drugs. These changes may require an alteration in the loading dose of a drug. The doses of benzodiazepines and thiopentone may need to 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 may also be appropriate. The elimination of highly ionised, water soluble drugs such as gallamine or atropine are 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. Dialysis can only partially compensate for the loss of excretory ability of the kidney.

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. Morphine is metabolised to morphine-6-glucuronide, a more potent analgesic and respiratory depressant. The interval between doses will need to be increased because of its reduced renal clearance. Metabolism of pethidine produces norpethidine, which can cause seizures. Although fentanyl undergoes hepatic metabolism and is not thought to have active metabolites, its clearance is decreased in severe uraemia. Alfentanil can be used as normal.

The elimination of volatile anaesthetic agents is not dependent on renal function and their activity is unaffected by CRF. The hepatic metabolism of both enflurane and sevoflurane will theoretically produce nephrotoxic fluoride ions and their use should be discouraged for prolonged durations. Metabolism of halothane produces fluoride ions when the liver is hypoxic but has been used safely in patients with renal disease. It has a greater myocardial depressant effect and causes more arrhythmias than other inhalational agents and caution should be observed when used in CRF patients with cardiovascular impairment. Isoflurane, although more expensive, may be the agent of choice as it undergoes less metabolism to fluoride ions. Nitrous oxide has little effect on the kidney. Older agents such as cyclopropane, ether and trichloroethylene are not recommended as they cause renal vasoconstriction.

Atracurium and cisatracurium are obvious choices for muscle relaxation. Around 90% is metabolised by ester hydrolysis and Hofmann elimination. Plasma cholinesterase activity is not thought to be affected by CRF and therefore mivacurium and suxamethonium (in the absence of hyperkalaemia) may be used. Limited doses of vecuronium and rocuronium are acceptable alternatives. Acidosis prolongs the action of all muscle relaxants except gallamine. The excretion of anticholinesterases and anticholinergic agents will be prolonged as they are highly ionised and water soluble.

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

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with CRF. NSAIDs inhibit the production of renal prostaglandins PGE_2 and PGI_2, which are responsible for maintaining renal blood flow during hypovolaemia and in the presence of vasoconstrictors, and could precipitate acute renal failure.

Conclusions

The incidence of chronic renal failure is increasing throughout the world. The effects of CRF are multiple and widespread beyond the confines of the kidney. The function of many organ systems of great interest to anaesthetists are adversely affected by a range of accumulated toxins. Great improvements in nephrology and transplantation mean that many more patients with CRF are living much longer. Their appearance on both renal and unrelated operating lists will continue to increase.

Further reading

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