

## Kidney dysfunction in the postoperative period

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The development of perioperative acute renal failure is associated with a high incidence of morbidity and mortality. Although this incidence varies with different surgical procedures and with the definition used for renal failure, we now understand better the aetiology of the underlying problem. However, successful strategies to provide renal protection or strategies for 'rescue therapy' are either lacking, unsubstantiated by randomized clinical trials, or show no significant efficacy. The present review considers the physiology and pharmacology of the kidney; the characterization of tests of renal function; the cause of postoperative renal dysfunction; what is presently available for its prevention and treatment; and the effect of postoperative renal impairment on patient outcome.

*Br J Anaesth* 2005; **95**: 20–32

**Keywords:** complications, renal; kidney; recovery

### Renal blood flow: its control and the effects of hypoxia

In the healthy patient, the kidney receives about 20% of the total cardiac output (about 1 litre min<sup>-1</sup>), with an oxygen delivery in excess of 80 ml min<sup>-1</sup> 100 g<sup>-1</sup> tissue. The distribution of blood flow within the kidney is not uniform, with the cortex receiving more than 90% of total blood flow.

On the other hand, oxygen consumption usually does not exceed about 10% of total body utilization, such that there is a low arteriovenous oxygen content difference (1.5 ml oxygen per 100 ml blood). The low fraction of oxygen extraction by the kidney should suggest that there is an adequate and ample oxygen reserve. However, the kidney is highly sensitive to hypoperfusion, with acute renal failure (ARF) being a frequent complication of hypotension. This apparent paradox (of high blood supply and low extraction of oxygen, yet high incidence of renal damage to hypoperfusion) is related to the physiological gradient of intra-renal oxygenation with the renal medulla able to function at ambient oxygen tensions of 2–3 kPa. This low oxygen tension results from the high oxygen requirement for tubular reabsorptive activity of sodium and chloride.

Although a high percentage of blood goes to the cortex (about 5 ml min<sup>-1</sup> g<sup>-1</sup>), the cortex extracts only about 18% of total oxygen delivered to it. On the other hand, the medullary region has a far smaller blood flow (0.03 ml min<sup>-1</sup> g<sup>-1</sup>), but has a far greater extraction (of about 79% of the delivered oxygen).

Medullary oxygenation is normally strictly balanced by a series of control mechanisms, which match regional oxygen supply and consumption. Failure of these controls

renders the outer medullary region susceptible to acute or repeated episodes of hypoxic injury, which may lead to acute tubular necrosis (ATN) especially of the thick ascending limbs (the mTAL regions) and the straight proximal S<sub>3</sub> segments, or to chronic tubulo-interstitial changes respectively.<sup>13 39</sup>

### Hypoxia and renal damage

As a result of the heterogeneity of flow and oxygen requirement, the oxygen tension in the cortex is about 50 mm Hg higher than that of the inner medulla. This explains why the mTAL region is extremely vulnerable to hypoxic injury and why ATN can be induced by as little as a 40–50% decrease in renal blood flow.

Medullary hypoxic injury is characterized by necrosis of those renal tubules that are farthest away from the blood vessels. The main determinant of medullary oxygen requirement is the rate of active reabsorption of salt and water in the mTAL region. When this process is inhibited by loop diuretics, there is an increase in the medullary tissue oxygen partial pressure from 2 to about 4 kPa.

There are a number of mediators, which can affect medullary blood flow, and hence may alter the magnitude of any ischaemic injury. These include:

- (i) Vasodilators: nitric oxide, prostaglandin E<sub>2</sub>, adenosine, dopamine, urodilatin (an analogue of ANP).
- (ii) Vasoconstrictors: endothelin, angiotensin II, ADH (antidiuretic hormone or vasopressin).
- (iii) Tubulo-glomerular feedback: when there is insufficient reabsorption of sodium by the renal tubules, this reflex mechanism leads to glomerular afferent constriction,

thereby reducing filtration and hence the delivery and reabsorption of tubular solute.

- (iv) Medullary tubular growth factors: these include insulin-like growth factor I, epidermal growth factor, and tumour necrosis factor. In different animal models they have all been shown to accelerate the rate of recovery after experimental ARF. As yet, there are no data from human studies.

As the work associated with salt and water reabsorption is one factor predisposing to medullary hypoxic damage, the kidney has a major therapeutic advantage when there is adequate circulating volume and salt loading, thereby reducing the need for urine concentration. In turn, this reduces medullary oxygen utilization. In contrast, the injury associated with hypoxia will be made worse by other factors such as some antibiotics, renal hypertrophy, NSAIDs, angiotensin II, calcium ions, myoglobin, hyperbilirubinaemia, and contrast media.

Under a variety of different clinical situations, the glomerular filtration rate (GFR) may be only 10% of normal and it remains low despite a restoration of renal blood flow because of tubular obstruction and back leak. The combination of tubulo-glomerular feedback and excessive stimulation of the renin-angiotensin system will often lead to profound and prolonged ARF.

*Pharmacological control of renal blood flow*

The kidney is largely devoid of  $\beta_2$  receptors; any increase in circulating catecholamines (especially epinephrine) will cause vasoconstriction via the  $\alpha_1$ -receptors and activation of the renin-angiotensin system. As a result, despite a normal TRBF, intramedullary ischaemia may occur, especially in the region of the mTAL region where the sodium-potassium ATPase enzymes are very sensitive to the effects of ischaemia. These increases in sympathomimetic hormones lead to renal cortical vasoconstriction, which is a compensatory attempt by the body to redistribute blood flow to the renal medulla, but in fact, it causes ischaemia. As a result, there is reduced sodium reabsorption by the mTAL, leading to tubulo-glomerular feedback via the macula densa with activation of the renin-angiotensin system and glomerular mesangial constriction.

**Renal function tests**

There are a number of available renal function tests—each examining a different aspect of the kidney's function (Table 1).<sup>51</sup> The GFR is probably the single most important marker of renal function; tubular function can be assessed as urinary  $\beta$ -NAG,  $\alpha$ -1-microglobulin, retinol binding protein, and plasma pro- and anti-inflammatory cytokines.

Properties of the ideal endogenous compound for the estimation of GFR should include its release into the blood stream at a constant rate; free filtration by the glomerulus; no reabsorption or secretion by the renal tubules;

**Table 1** Renal function tests available for clinical use

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Urine volume
Urine specific gravity
Urine osmolality
Serum creatinine and blood urea nitrogen
Urine/plasma creatinine ratio
Urine/plasma urea ratio
Urinary sodium excretion
Fractional excretion of sodium
Free water clearance
Creatinine clearance
Renal blood flow

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and exclusive elimination via the kidney. Until recently, measurement of the GFR was based on the plasma clearance of markers such as <sup>51</sup>Cr-EDTA or iohexol. However, both require injection of the exogenous marker; they are expensive and time consuming; and they are impractical in some patient groups. As a result, the usual rapid-estimation and first-line test of glomerular function has been creatinine clearance. The classical determination of renal function by GFR normally requires a 24-h urine collection, but changes in renal function can occur more rapidly than this. The possibility of measuring GFR more frequently led Sladen and colleagues to investigate the utility of a clearance estimate based on a 2-h urine collection.<sup>91</sup> In the intensive care unit or postoperative care area, this estimate of GFR may be a good biomarker of change in renal function.

*Cystatin C*

Although creatinine clearance is the best predictive marker of a change in renal function and the possible subsequent development of perioperative dysfunction, the test is not really practical in the operating theatre. Measurement of serum creatinine as an alternative is subject to confounding factors such as age, sex, muscle mass, and diet. Other methods of assessing GFR have therefore been investigated. Recent interest has focused on the protein cystatin C. This is an alkaline non-glycosylated protein, which is produced by virtually all nucleated cells. In the normal kidney, cystatin C is freely filtered through the glomerular membrane and then nearly completely reabsorbed and degraded by the proximal tubular cells. A recent meta-analysis by Dharnidharka and colleagues comparing serum cystatin C and creatinine as markers for GFR showed the former to be superior, and to respond more rapidly to changes in GFR than serum creatinine.<sup>25</sup> A substantial proportion of patients with a reduced GFR will have serum creatinine values within the normal range, and even a 50% reduction in GFR may be associated with normal serum creatinine concentrations.

In contrast to creatinine clearance, the reference range values for cystatin C are identical for men, women and children, and are not influenced by muscle mass. They

are not therefore altered in the elderly when muscle mass falls.<sup>40</sup>

$$\text{GFR (ml min}^{-1}\text{)}=69.3\times\text{cystatin C (mg litre}^{-1}\text{)}$$

There are no published data to date (2004) describing its utility in the perioperative period.

## Perioperative fluid balance

During the perioperative period, there is need to address two separate aspects of the normal fluid balance—the effects of preoperative fluid depletion (as a result of the routine nil-by-mouth regimens and the loss of fluid through concomitant pathology); and perioperative factors such as blood and fluid losses, and the neuroendocrine response to anaesthesia and surgery.

*Effects of anaesthesia.* Most anaesthetics (especially the volatile agents) cause peripheral vasodilatation and myocardial depression. In order to maintain organ perfusion, either vasoconstrictors or fluid replacement is needed. In the case of the kidney, there is also need to maintain adequate efferent arteriolar vasoconstriction, which is responsible for the development of the glomerular filtration pressure. This is under the control of angiotensin II; the patient receiving chronic angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonist treatment who undergoes anaesthesia may develop a significant decrease in the perfusion pressure with decreased urine production. Stimulation of a second mechanism is seen with narcotic agents, which increase the release of ADH. This response may be exaggerated by fluid depletion secondary to overnight fasting.

Neuraxial anaesthesia as well as general anaesthesia causes vasodilatation, and so augmentation of the circulating volume with i.v. fluids will be needed to maintain blood pressure.

*Effects of surgery.* This results in both an increase of catabolic hormones and cytokines. The main effect is the increased secretion of ADH, which will result in water retention. Increases in aldosterone (through activation of the renin–angiotensin system) coupled with increased glucocorticoids cause sodium and water retention and potassium loss. Plasma renin activity is also elevated as a result of a decrease in circulating blood volume. Thus, alterations in overall fluid and electrolyte homeostasis occur because of impaired water excretion, impaired sodium excretion, and increased excretion of potassium.

Perioperative fluid losses can be recorded in terms of blood and intravascular fluid losses, insensible losses, and the so-called ‘third space effect’. There is a need to replace both blood and extracellular fluid losses, as well as to maintain the normal water requirement. After surgery losses may also arise through effusions and drainage. Evaporative (or insensible) losses in major abdominal surgery may necessitate up to  $10\text{ ml kg}^{-1}\text{ h}^{-1}$  of crystalloid to be given. An

additional mechanism for increased fluid loss during general anaesthesia is artificial ventilation of the intubated patient. During intubation, the normal mechanisms for humidifying gases are bypassed. Because of the cold dry gases from the anaesthesia machine, a considerable amount of fluid can be lost through mechanical ventilation unless a humidifier is used.

Further losses occur through extravasation of fluid out of the vascular compartment (the ‘third space effect’). After the operation, this sequestered fluid is mobilized back into the vascular space, but while it is outside the vascular compartment, adequate circulating volume must be maintained by i.v. fluids. This fluid redistribution to body spaces is seen especially following intra-abdominal and intra-thoracic operations.

## Perioperative fluid requirements

(i) Intraoperatively this varies according to the extent of the surgical insult but a rough guide is: minimal trauma  $4\text{ ml kg}^{-1}\text{ h}^{-1}$ ; moderate trauma  $6\text{--}8\text{ ml kg}^{-1}\text{ h}^{-1}$ ; severe trauma  $10\text{--}15\text{ ml kg}^{-1}\text{ h}^{-1}$ . These requirements are best provided as Compound Sodium Lactate or other balanced salt solutions, as large volumes of normal (0.9%) sodium chloride may result in a hyperchloraemic metabolic acidosis.<sup>86</sup>

(ii) In the postoperative period, the standard daily needs for a 70 kg adult are a fluid intake of  $100\text{ ml h}^{-1}$ ; made up of 25–33% normal saline, 75–66% dextrose (=water) and 10–20 mmol KCl per litre of fluid. However, the clinician needs to avoid the development of hyponatraemia, which may cause serious brain damage or death.<sup>54 55</sup> This is particularly prevalent in postmenopausal women where the effect may be compounded by chronic diseases and long-term medications (especially thiazide diuretics).

## Aetiology of postoperative renal dysfunction

Renal dysfunction in the surgical patient is usually multifactorial: the commonest cause is ATN as a result of hypoxic damage to nephrons in the medullary region of the kidney secondary to hypotension, hypovolaemia, and/or dehydration. Among the common associated risk factors are: pre-existing renal insufficiency; type 1 diabetes mellitus; patient age over 65 yr; major vascular surgery; cardiopulmonary bypass times over 3 h; and recent exposure to nephrotoxic agents (such as radio-contrast dyes, bile pigments, aminoglycoside antibiotics, and NSAIDs).

The time course of factors predisposing to renal dysfunction can be divided into pre- and intraoperative.

*Preoperative.* There is good evidence that arteriopathies have a reduced renal perfusion. Other factors include the age-related decline in nephron mass (as a result of the reduced expression of vascular endothelial growth factor),<sup>48</sup> and the presence of pre-existing renal dysfunction.<sup>17 20</sup>

*Intraoperative.* There are a number of clearly defined predisposing factors.

**Hypovolaemia.** The presence of a low circulating blood volume leads to a series of vasoconstrictor, salt-retaining neurohumoral systems being activated (these include the sympathoadrenal system, angiotensin, aldosterone, and ADH). The initial response to a contracted extracellular fluid volume is a decrease in both the GFR and the filtered solute load.

These sympathoadrenal effects are mediated by increased levels of circulating epinephrine and norepinephrine release from T8–L1 nerve endings, which act on the afferent arterioles. The increased concentrations of aldosterone act on the proximal tubules, mTAL regions, and collecting ducts to enhance sodium (and water) reabsorption.

**Nephrotoxins.** These include contrast media. They act to increase intra-renal vasoconstriction and decrease medullary blood supply. They also present the medullary nephrons with an increased osmotic load leading to an increased oxygen requirement in the presence of an already low tissue oxygen tension.<sup>57</sup> Effective prevention includes avoiding contrast media in high-risk subjects if at all possible, minimization of the contrast load, hydration pre- and post-procedure, as well as considering pre-treatment with *N*-acetylcysteine.<sup>92,96</sup> Other toxins include increased serum inorganic fluoride concentrations from some volatile agents (particularly enflurane), NSAIDs, and aminoglycosides.

**Embolism.** The release following application of an aortic clamp.

**Renal ischaemia.** This is as a result of concurrent drug therapies. Cittanova and colleagues have shown that long-term ACEI therapy increases the risk of postoperative renal dysfunction as a result of a loss of ability of the renin-angiotensin system to compensate for decreases in renal perfusion.<sup>18</sup>

**Inflammation.** Gut ischaemia, impaired visceral perfusion, and portal endotoxaemia may occur during abdominal aortic aneurysm surgery. The released endotoxin load activates other vasoactive compounds, as shown by Wellborn and colleagues who found an increased pro-inflammatory cytokine response in aortic aneurysm patients.<sup>99</sup> The magnitude of the response correlated well with the period of visceral ischaemia. Increases of serum creatinine of more than 177  $\mu\text{mol litre}^{-1}$  ( $>2 \text{ mg dl}^{-1}$ ) over baseline were seen in 44% of patients undergoing conventional thoraco-abdominal aortic aneurysm surgery, compared with 25% if aortofemoral bypass was used.

**Genetic predisposition.** An association has been found between the epsilon 4 allelic variant of the apoE gene and the development of acute renal injury. However, data from Chew and colleagues suggest this polymorphism may be renoprotective in coronary artery bypass grafting (CABG) patients.<sup>17</sup>

A meta-analysis of at-risk patients has indicated a number of important predisposing factors: preoperative renal dysfunction; surgery of the aorta and CABG; and cases where there is ischaemia to the kidney. However, no two of the 28 included studies used the same diagnostic criterion for

renal failure.<sup>68</sup> Hence, there is the possibility of interaction by confounding factors leading to variable analytical bias.

### Incidence of postoperative renal dysfunction

The incidence of perioperative ARF varies according to the aetiology and definition, and type of surgery undergone; but for all causes, renal failure is associated with mortality rates of 60–90%.<sup>57,61</sup> In the cardiac surgical patient, postoperative ARF is accompanied by increased intensive care unit stay and increased overall length of hospital stay (Table 2).<sup>61</sup> The development of postoperative renal dysfunction is also accompanied by a higher incidence of gastrointestinal bleeding, respiratory infections, and sepsis.<sup>4</sup> The definition of postoperative ARF varies between studies. Three useful criteria are an increase of serum creatinine by more than 44  $\mu\text{mol litre}^{-1}$  ( $>0.5 \text{ mg dl}^{-1}$ ) over the baseline value, a serum creatinine increase of  $>50\%$  when compared with the preoperative baseline value, or a serum creatinine more than 177  $\mu\text{mol litre}^{-1}$ .<sup>33</sup>

Perioperative renal dysfunction may either remain as sub-clinical impairment or evolve into ARF. The incidence of renal impairment varies between 4 and 24% because there is no rigid definition of renal dysfunction.

### Cardiopulmonary bypass

In patients undergoing CABG on cardiopulmonary bypass, the incidence of renal dysfunction (manifest as a postoperative increase in serum creatinine or urea) varies between 1 and 15%.<sup>16,20,24,62</sup> This is associated with a mortality of up to 19%.<sup>61,62,82</sup> The incidence of cases of ARF after CABG requiring dialysis is less than 2%; but in these cases, the mortality varies between 23 and 88% (average about 50%). It is questioned as to whether there is not subclinical renal dysfunction (observed as a normal plasma creatinine or urea in the presence of elevated markers of tubular injury or dysfunction) in all these patients.<sup>47</sup> This is not associated with any apparent increase in morbidity or mortality; but are these kidneys liable to subsequent 'second hit' damage, as a result of the effects of hypotension, hypoxia, and nephrotoxins?

Why does renal dysfunction and/or ARF occur after CABG (Table 3)? The ischaemic-reperfusion injury occurs post-CABG because of the combination of low cardiac output and hypovolaemia. Under normal circumstances, regional blood flow keeps the outer renal medulla in a borderline

**Table 2** Influence of renal dysfunction and ARF on the incidence (%) of mortality, and duration of intensive care unit and hospital stay (in days) after coronary revascularization. (Adapted from Mangano and colleagues<sup>61</sup>)

	Mortality (%)	ICU stay (days)	Hospital stay (days)
Normal renal	0.9	3.1	10.6
Renal dysfunction	19.0	6.5	18.2
ARF	63.0	14.9	28.8

**Table 3** Aetiological factors associated with renal dysfunction following cardiopulmonary bypass

Non-bypass factors
1. Significant surgical trauma.
2. Shed blood management.
3. Anaesthesia—increases the pro-inflammatory cytokines (IL-1, IL-8, TNF $\alpha$ , also IL-1ra, CD11b, HLA-DR expression).
4. Heparin–protamine interactions activate complement, also pro-cytokines.
Patient-related factors
1. Genotype—apolipoprotein E4 allele.
2. Pre-morbid conditions—congestive heart failure; diabetes mellitus.
3. Drugs—use of $\beta$ -agonists/antagonists; use of ACEI.
Bypass related
1. Contact activation.
2. Ischaemia.
3. Endotoxin translocation from the gut to the kidney.

hypoxic condition. Nephrons here have a high oxygen need and high oxygen extraction. Hence they are vulnerable to changes in oxygenation. Again under normal circumstances, intra-renal blood flow distribution is aimed at protecting filtration rather than maintaining tubular function.

Hence ARF was originally thought to be the result of tubular injury and damage; but it is now recognized that injury to the intra-renal vasculature may also contribute significantly.<sup>58</sup> The development of renal failure is associated with a 40–50% decrease in total renal blood flow (TRBF). Alone, this is not enough to account for the observed decrease in GFR. The decrease in TRBF is resistant to improvements in cardiac output (even when the TRBF is restored to normal, there may still be some evidence of intra-renal ischaemia as a result of alterations in the regional blood flow).

Why does this occur? First, there is increased vasoconstriction (as a result of increased concentrations of endothelin [ET]1)-coupled with an augmented response to constrictor agents and diminished response to dilator agents. The increase in intracellular calcium after ischaemia causes an increased release of ET. Ischaemia also interferes with the dilator system via the nitric oxide pathway.

Secondly, the kidney shows evidence of vascular obstruction and congestion, which arises both within and without the renal vessels. Within the vessels, there are a number of separate mechanisms occurring.

- (i) Reduced blood flow in capillaries.
- (ii) Endothelial dysfunction.
- (iii) An up-regulation of adhesion molecules, with increased levels of ET1, which promotes adhesion.
- (iv) A reduction in nitric oxide production (which inhibits adhesion).

Outside the vessels, there is epithelial cell swelling and interstitial oedema. In addition, there are other bypass and non-bypass factors, as well as patient-related factors (Table 3).

Despite the observations of Chertow and colleague, and Conlon and colleagues that the duration of bypass was

independently associated with the development of acute renal dysfunction and/or renal failure needing dialysis, the recent introduction of off-pump coronary artery surgery has shown no decrease in either of these two morbidities.<sup>16,20</sup>

In an observational prospective study, Gamoso and colleagues found comparable renal dysfunction rates in patients undergoing cardiac surgery under bypass (7.7%) and off-pump (8.9%).<sup>29</sup> However, further randomized studies are clearly needed to confirm this position. Recent data suggest that off-pump cardiac surgery may better preserve renal function, but there are few randomized comparative data.

### *Aortic surgery involving the thoracic aorta or suprarenal aortic clamping*

Following vascular surgery involving either suprarenal cross-clamping of the aorta, or thoracic or thoraco-abdominal aortic surgery, there is a similarly high incidence of acute tubular necrosis. Svensson and colleagues found an overall hospital incidence of dialysis requiring ARF of 5.5%, with an in-hospital mortality of 63%.<sup>93</sup> The most important predictors of ARF were pre-existing renal dysfunction; evidence of diffuse atherosclerosis; use of intra-operative pump bypass; and haemodynamic instability. This study also showed no evidence of any protective effect from ACE inhibitors.

Following cross-clamping of the aorta above the renal arteries, even in the presence of mannitol to attempt protection of the kidneys, there is still a period of reduced renal function with the GFR 2 h after clamp release being only 39% of figures seen after infra-renal clamping (23 vs 60 ml min<sup>-1</sup>).<sup>66</sup> This abnormality takes about 48 h to correct.

Overall, studies in patients undergoing suprarenal aortic clamping show that the decrease in renal blood flow does **not** correlate well with any measured decrease in cardiac output or change in mean arterial pressure; and the decrease in urine output does not correlate with the degree of reduction in GFR. **Similarly the magnitude of the decrease in urine output does not predict the occurrence, or not, of post-operative renal dysfunction.**

### *Abdominal aortic surgery*

Infra-renal aortic cross-clamping leads to a reduction in renal blood flow by up to 40%, as a result of an increase in renal vascular resistance of up to 75%.<sup>30</sup> The reduction in renal blood flow in turn reduces the GFR and hence the rate of urine formation. The mechanism underlying this increased resistance is uncertain but may, in part, be a result of the associated decrease in cardiac output during aortic cross-clamping, as well as because of humoral mechanisms, which lead to increased release of renin. After declamping, there is a maldistribution of renal blood flow away from the cortex for at least 60 min. Deterioration in both RBF and GFR (compared with preoperative values) may persist for some time after the period of hospitalization;

Awad and colleagues found evidence of impairment up to 6 months later.<sup>5</sup>

In patients undergoing abdominal aortic surgery, there are even fewer data to provide a clear statement of the incidence of postoperative renal dysfunction. A study of 666 patients undergoing elective surgery for non-ruptured aneurysms by Johnston and colleagues, reported a renal dysfunction rate (defined as an increase in preoperative creatinine or urea by  $\geq 20\%$ ) of 5.4%, but only 0.6% of the population received dialysis.<sup>45</sup> The need for dialysis is a poor outcome predictor. Braams and colleagues observed a 69% mortality among 42 patients who experienced renal failure and required dialysis after aortic surgery.<sup>11</sup> Similar mortality rates were reported by Levy and colleagues in a case-control study of 183 patients with contrast-media associated renal failure.<sup>57</sup> The death rate was 34% in the renal failure group compared with 7% in the controls.

Although less invasive than open surgery, endovascular repair may also be associated with renal impairment (possibly due, in part, to the contrast media used intraoperatively). Just as in the case of thoracoabdominal aneurysms, patients undergoing endovascular abdominal aortic repair and suffering renal impairment show a reduced 1-yr survival.<sup>59</sup>

#### *Surgery for relief of obstructive jaundice*

The association between renal dysfunction and obstructive jaundice was first recognized in 1910 by Clairmont and von Haberer;<sup>19</sup> subsequent studies have suggested causative factors to include hyperbilirubinaemia; increased serum level of bile salts; endotoxaemia, and renovascular fibrin deposition; as well as the influence of fluid volume status and alterations in systemic and renal haemodynamics.

In a review in 1985, Pain and colleagues reported that operative procedures in patients with obstructive jaundice were followed by a high incidence of postoperative complications including renal dysfunction (up to 60%).<sup>69</sup> The latter was associated with a significant mortality (the mean of several series being 68%). However, in a prospective series of 59 jaundiced patients, Parks and colleagues showed that prophylactic fluid preoperatively (3 litres crystalloid) reduced the subsequent incidence of perioperative renal failure (10.2%) and mortality (3.4%).<sup>73</sup> Further research by Pain and colleagues indicated that additional protection in these patients might be afforded by the preoperative administration of lactulose or sodium deoxycholate.<sup>70</sup>

Both Gubern and colleagues, and Wahbah and colleagues have examined the effects of mannitol, and furosemide and dopamine on postoperative renal function in jaundiced patients.<sup>34,98</sup> Gubern showed that mannitol resulted in a poorer creatinine clearance on the second postoperative day in a small randomized controlled study of 31 patients undergoing surgical intervention for the relief of obstructive jaundice. This further supports the findings of Paul and colleagues.<sup>74</sup>

More recently, Wahbah and colleagues studied 40 jaundiced patients randomized to receive either preoperative hydration (1 litre crystalloid overnight and 1 litre in morning) alone, or fluid followed by either dopamine  $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$  for 48 h; or dopamine plus mannitol  $0.25 \text{ g kg}^{-1}$  every 12 h for 48 h; or furosemide  $1 \text{ mg kg}^{-1}$  every 12 h for 48 h.<sup>98</sup> They found no added renal protection of dopamine, dopamine plus mannitol, or furosemide over hydration alone. Similarly Parks and colleagues showed no effect of perioperative dopamine alone by infusion.<sup>72</sup>

### **Prevention of renal dysfunction and renal protection**

Most current practices used to provide 'renal protection' are based on tradition, anecdotal information, or extrapolation from animal models. There are few double-blinded, randomized studies in man of sufficient power to allow a definitive assessment of efficacy. However, logic suggests that the aim of the anaesthetist during the perioperative period should be to maintain a urine flow greater than  $0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$ ; although there are no randomized studies to confirm this assertion.

A number of possible strategies aimed at alleviating the development of renal dysfunction are shown in Table 4. Although commonly used approaches to prevent ARF (not specifically in the perioperative period) have included adequate hydration, mannitol, 'renal doses' of dopamine, and loop diuretics.<sup>37,71</sup> Examination of the evidence does not support the continued adoption of all these regimens.

#### *Adequate hydration*

The most extensive evidence for the role of fluid balance in the development of renal dysfunction is based on studies of radiocontrast nephropathy. These dyes can cause severe intra-renal haemodynamic disturbances, which may result in an ischaemic injury comparable with that seen after CPB and aortic surgery. One of the important conclusions of these studies is that pre-contrast hydration reduces the incidence of renal injury.

**Table 4** Aims of and treatment modalities to reduce or prevent the development of postoperative renal dysfunction

1. Maintain adequate oxygen delivery—by ensuring adequate cardiac output, adequate oxygen carrying capacity, and proper haemoglobin saturation.
2. Suppression of renovascular constriction—by ensuring adequate volume preload, use of infusions of mannitol, calcium entry block, and angiotensin converting enzyme inhibitors.
3. Renal vasodilation—by dopaminergic agents, prostaglandins, and atrial natriuretic peptide.
4. Maintain renal tubular flow—by loop diuretics and mannitol (which may act to prevent tubular obstruction which can cause cellular swelling, ischaemia and death).
5. Decrease oxygen demand—by use of loop diuretics and mild cooling.
6. Attenuate ischaemic reperfusion injury—as a result of the release of oxygen free radicals and calcium ions.

Solomon and colleagues compared the effects of hydration alone with hydration plus mannitol, and hydration plus loop diuretics in high-risk patients undergoing coronary angiography.<sup>92</sup> The pre-angiography creatinine clearances were all less than  $60 \text{ ml min}^{-1}$ . Preoperative hydration strategy was saline 0.45% administered at  $1 \text{ ml kg}^{-1} \text{ h}^{-1}$  for 12 h for all patients; the mannitol-hydration group received mannitol 25 g as well, while the hydration-diuretic group received furosemide 80 mg. Renal dysfunction defined as an increase in serum creatinine more than  $0.5 \text{ mg dl}^{-1}$  ( $>44 \text{ } \mu\text{mol litre}^{-1}$ ) occurred in 11% of the hydration only group; 28% in the hydration and mannitol group; and 40% in the hydration plus frusemide group. However, a major criticism of the study is the small sample size (78 patients overall), and a failure to make allowance for the co-administration of ACEIs or NSAIDs.

There are also some data indicating that saline-based fluids in both man and experimental animals may alter renal function.<sup>101</sup> Studies in dogs have shown that a raised serum chloride can reduce renal blood flow, GFR, and urine formation;<sup>102</sup> while Reid and colleagues showed, using a cross-over study in nine volunteers, that infusion of 2 litres of normal saline when compared with Compound Sodium Lactate resulted in a hyperchloraemia of more than  $105 \text{ mmol litre}^{-1}$ .<sup>81</sup> In a further study, Bennett-Guerrero and colleagues examined the results of different infusion solutions in 200 patients undergoing coronary artery bypass grafting (viz. 5% albumin in saline; 6% hetastarch in saline; Hextend, a colloid; or Compound Sodium Lactate) on the serum creatinine at 1 week post-surgery.<sup>10</sup> Highest postoperative plasma creatinine concentrations were seen in the albumin and hetastarch groups (both made up in saline); furthermore, six patients needed postoperative haemodialysis—again all six had received saline-based solutions. More data are clearly needed to determine whether infusions of saline are indeed associated with the development of renal dysfunction.

### Drug therapies

**Dopamine.** In healthy non-anaesthetized subjects, low doses of dopamine (range  $0.05\text{--}2.5 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) result in renal vasodilatation and predominantly reduce the activity of the  $\text{Na}^+/\text{K}^+$  ATPase in the proximal tubule (so reducing the proximal tubular reabsorption of sodium). At higher doses ( $>5\text{--}10 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) there is an increase in cardiac output. The net sum of these actions is an increase in renal blood flow; and increases in GFR, diuresis, and natriuresis.

However, in the critically ill and anaesthetized subjects, the picture is less clear. The influence of dopamine on renal function is controversial as it is uncertain whether the decline in function following infra-renal clamping can be alleviated by infusion of dopamine.

Paul and colleagues found no clinically important benefit in patients undergoing infra-renal aortic surgery of the

combination of dopamine and mannitol over extravascular volume expansion alone if the pulmonary artery wedge pressure (PAWP) is maintained at 12–15 mm Hg.<sup>74</sup> However, Salem and colleagues demonstrated a positive advantage of low-dose dopamine ( $2 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) when given in combination with fluid loading using Hartmann's solution ( $15 \text{ ml kg}^{-1} \text{ h}^{-1}$ ) again during aortic cross-clamping.<sup>83</sup> There were postoperative increases in urine volume, creatinine clearance, and sodium and potassium output.

In a further study of 37 patients, Baldwin compared low-dose ( $3 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) dopamine or placebo on renal function after elective vascular surgery.<sup>6</sup> Sufficient crystalloid was given to achieve normovolaemia, and to maintain a urine output of more than  $1 \text{ ml kg}^{-1} \text{ h}^{-1}$  for the first 24 h after surgery. Dopamine had no effect on postoperative plasma creatinine concentrations, creatinine clearance, or total urine output at 24 h and 5 days.

More recent findings by Girbes and colleagues suggest that a low-dose infusion of dopamine ( $2\text{--}4 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) can cause an increase in renal blood flow and GFR (of up to 20 and 21%, respectively) in patients undergoing aneurysmectomy under general anaesthesia supplemented by epidural analgesia.<sup>32</sup> From this uncontrolled study of seven haemodynamically stable patients, the authors concluded that dopamine at  $4 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$  was the optimum regimen. However, how does it produce its effects at this dose? At lower doses ( $0.5\text{--}3 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ) dopamine augments renal blood flow by  $\text{DA}_1$  receptor-mediated intra-renal vasodilatation, and possibly the contributory engagement of  $\text{DA}_2$  receptors on pre-synaptic sympathetic nerve terminals leading to inhibition of norepinephrine release. At intermediate doses ( $3\text{--}10 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ ), dopamine augments renal perfusion by improving cardiac output via  $\beta_1$  adrenoceptor stimulation.

However, we should note that all these findings were made in normovolaemic subjects. What about the patient who may be hypovolaemic and hypothermic? In the study of Girbes and colleagues, the effect of low-dose dopamine in increasing renal blood flow was secondary to an increase in cardiac output. Plasma renin activity was unaltered, but plasma aldosterone concentrations were decreased.<sup>32</sup> Thus, the findings are at variance with the earlier cited studies of Paul, Salem and Baldwin.<sup>6,74,83</sup> The low doses of dopamine used by Girbes probably acted to increase urine output by a diuretic effect with an accompanying natriuresis and kaliuresis, through a combination of some inotropic activity and renal vasodilator properties.<sup>32</sup>

Recently, two very important papers have confirmed the absence of any renal protective affect of infusions of dopamine both in the surgical patient and in the intensive care unit. The ANZICS Clinical Trial Group examined data from 24 studies and in a meta-analysis of over 1000 patients, and found no effect.<sup>9</sup> A second meta-analysis covering 15 studies with 970 patients has also found no benefit of so-called renal doses of dopamine.<sup>63</sup> Furthermore, Perdue and colleagues have reported 'renal doses' of dopamine to

be associated with an increased incidence of arrhythmias and worsening renal function.<sup>76</sup>

*Dopexamine.* This synthetic sympathomimetic agonist has a number of different properties but is mainly a  $\beta_2$  agonist. In volunteers, dopexamine acts as a positive inotrope to increase the heart rate and decrease the systemic vascular resistance.<sup>28</sup> However, its renal effects differ between species. In animals, dopexamine increases renal blood flow by  $DA_1$  agonism to cause intra-renal vasodilatation; an increased cortical but not medullary blood flow; and an increase in urine flow as a result of increased renal blood flow and thence GFR. However, in man the effects on diuresis and natriuresis are small, and may solely reflect the increase in renal blood flow from the increased cardiac output. This results in an improved oxygen supply-demand balance compared with dopamine where the increased natriuresis is secondary to  $DA_2$  activity, which increases oxygen requirements. Dopexamine also decreases gut permeability and may reduce bacterial translocation and endotoxaemia.

Although Welch and colleagues concluded that dopexamine in patients undergoing aortic artery surgery might offer some renal protection,<sup>100</sup> this has not been confirmed in two other more recent and larger studies.<sup>123</sup>

*Loop diuretics.* Drugs such as furosemide cause renal vasodilation as well as increasing sodium, potassium, and urine output and creatinine clearance. High-dose furosemide has been shown to decrease the duration of oliguria and need for dialysis in patients with ARF, but has no effect on mortality.<sup>15</sup> There are no controlled trial data to show the efficacy of continuous infusions of loop diuretics in overcoming diuretic tolerance or resistance; or in the treatment of refractory patients in the ICU.<sup>8</sup>

Furthermore, recent studies by Lassnigg and colleagues have shown furosemide (at a dose of  $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$  for 48 h) to have no renal protective effect after cardiac surgery, and to, perhaps, be causative of renal impairment.<sup>56</sup> Prophylaxis using loop diuretics is, however, effective against pigment nephropathies.<sup>41</sup>

*Mannitol.* Mannitol acts by a number of separate mechanisms: first, as an osmotic diuretic, it causes renal vasodilation through increased prostaglandin production and thereby promotes renal tubular urine flow. This protects against injury by reducing tubular obstruction. It also acts as a free radical scavenger, reducing the effects of hydroxyl and other free radicals in causing ischaemia-reperfusion injury.<sup>60</sup>

The protective effect of mannitol in treating ischaemic renal damage is well described by Barry and colleagues, and Payne and colleagues.<sup>775</sup> However, recently Nicholson and colleagues conducted a randomized prospective clinical trial in 28 patients undergoing infra-renal aortic surgery.<sup>67</sup> The combination of mannitol ( $0.3 \text{ g kg}^{-1}$ ) and saline (in an equal volume) resulted in no differences in postoperative serum

creatinine or urea, or creatinine clearance. However, the mannitol group had a greater first day diuresis and less glomerular and tubular damage. It is obvious that there is a clear need for a large randomised trial of the effect of mannitol in patients undergoing aortic surgery and in CABG patients.

To be effective, the mannitol must be given before the ischaemic episode. However, mannitol can be injurious in large doses causing intra-renal vasoconstriction.<sup>26</sup>

*Calcium channel entry blockers.* Arteriolar vasoconstriction is mediated by increases in cytoplasmic calcium. Hence calcium antagonists might affect renal vascular tone and GFR. Duggan and colleagues showed verapamil to significantly reduce the incidence of ATN following kidney transplantation by presumably increasing renal blood flow and GFR.<sup>27</sup> There are, however, few data examining the possible effects of calcium channel blocking drug on postoperative renal dysfunction in patients undergoing aortic or cardiopulmonary bypass surgery. Two small series of CABG patients suggest diltiazem to produce a beneficial effect on either postoperative renal function,<sup>2</sup> or renal tubular integrity.<sup>78</sup>

*ACE inhibitors.* Joob and colleagues<sup>46</sup> showed that increases in renal vascular resistance associated with cross-clamping can be prevented by pre-treatment with ACEIs; however, further double-blind controlled studies are needed to support these data and show whether these drugs alter the incidence of perioperative renal dysfunction.

*Atrial natriuretic peptide.* Atrial natriuretic peptide increases the GFR by vasodilation of the afferent arterioles and constriction of the efferent arterioles. This leads to an increase in the glomerular filtration pressure. Atrial natriuretic peptide also increases glomerular permeability and promotes tubular sodium and water loss. To date there are two studies evaluating the effects of infusions of ANP. Rahman and colleagues gave an infusion of ANP to 53 patients with ischaemic ARF in a randomized controlled trial.<sup>79</sup> Fewer patients in the treatment group required dialysis (23 vs 52%). However, there was no difference in patient mortality, and a significant disadvantage of ANP by infusion was the tendency to cause systemic hypotension. In a second study in patients receiving a cadaveric renal transplant, there was no advantage seen in those patients receiving an infusion of ANP commenced after revascularization.<sup>84</sup>

The synthetic agent urodilatin has ANP-like activity, but is more haemodynamically stable. There have been a number of studies examining its utility in post-cardiac bypass surgery, but no studies to date (2004) of its efficacy in patients undergoing other high-risk surgeries.

*Other possible therapies.* Future therapeutic advances in the treatment of renal ischaemic damage after aortic surgery



may be made in the areas of ET antagonism, prostaglandins, and dopamine agonists:

(i) ET antagonists. ET are potent vasoconstrictor peptides secreted by many types of cells. In the kidney, ET1 causes dose-dependent vasoconstriction. In low doses, ET affects equally both the afferent and efferent arterioles, so leaving the glomerular filtration pressure unchanged; at higher doses, afferent arteriolar constriction predominates, so leading to a reduction in the GFR.

Several authors have found high concentrations of ET1 in the plasma of patients with ARF, with restoration to normal values after correction of the renal dysfunction.<sup>97</sup> Furthermore, cross-clamping can increase plasma ET concentrations, the resulting renal vasoconstriction being preventable by nifedipine.<sup>3</sup> Thus either ET receptor antagonists or ET antibodies might offer amelioration of hypoxic renal injury.<sup>65</sup>

(ii) Prostaglandin E<sub>1</sub>. This is an endogenous renal vasodilator; but evaluation of three dosage regimens in patients with chronic renal insufficiency undergoing radiocontrast studies showed no effect on creatinine clearance, although the serum creatinine increased more in the placebo group.<sup>53</sup>

(iii) Dopaminergic drugs. There are two DA receptors with different functional activities (Table 5). Fenoldopam is a selective DA<sub>1</sub> agonist, introduced principally as an antihypertensive agent. It reduces blood pressure in a dose-dependent manner while preserving renal blood flow and GFR.<sup>64</sup> As a DA<sub>1</sub> agonist, it acts postsynaptically to cause vasodilatation and so increase renal blood flow. Fenoldopam also improves creatinine clearance. It has no effect on myocardial contractility (i.e. it does not act as an inotrope as does dopamine), but is a selective vasodilator of both renal and mesenteric beds. It may also cause an increase in intra-ocular pressure. Fenoldopam has no  $\beta$ -effects; and is therefore less arrhythmogenic than dopamine. Increasing doses of fenoldopam do not cause tachycardia or tachyarrhythmias (as the agent has no action on  $\beta$  or  $\alpha$  receptors). However, a tachycardia may occur if there is rapid vasodilatation. It is not presently licensed in the UK.

In dogs, fenoldopam acts to increase both renal medullary and cortical blood flow; it also inhibits sodium transport in the mTAL region of the nephron, thereby reducing

oxygen utilisation.<sup>52</sup> Most renovasodilators (such as ANP and dopamine) do not increase medullary blood flow, and may actually increase blood flow away from the medulla to the well-perfused cortical regions. Use of fenoldopam in man was approved by the FDA for the treatment of accelerated hypertension in 1998; there has been increasing use of its renoprotective effects (in doses ranging from 0.03 to 0.05  $\mu\text{g kg}^{-1} \text{min}^{-1}$ ).

There are, however, few randomized trials of fenoldopam in renal protection. In a study of 58 patients undergoing thoracoabdominal aortic aneurysm surgery, the use of fenoldopam resulted in a more rapid return of renal blood flow; a lower mortality in the fenoldopam group; a reduction in the need for dialysis postoperatively; and shorter ICU and hospital stays.<sup>90</sup> Fenoldopam also had beneficial effects in a small study of patients undergoing abdominal aortic aneurysmectomy<sup>35</sup> on the postoperative serum creatinine level. A recent prospective observational study in 70 cardiac surgery patients with one or more risk factors for renal dysfunction has examined the utility of a per- and early postoperative infusion of the agonist at 0.03  $\mu\text{g kg}^{-1} \text{min}^{-1}$ . No patient developed renal failure requiring dialysis, but 7.1% of patients (each with two or more risk factors) had a deterioration in renal function.<sup>31</sup>

## Sequelae of postoperative renal dysfunction

The presence of an abnormal GFR is coupled with an increased incidence of adverse drug reactions. There may be kinetic effects with prolongation of the half-life of both drugs and metabolites; changes in bioavailability; changes in apparent volumes of drug distribution; and changes in plasma protein binding.<sup>87</sup> Drugs affected include the opiates, morphine and meperidine,<sup>14 22 36 77 87 88 95</sup> and the neuromuscular blocking drugs, succinylcholine, pancuronium, doxacurium, pipercuronium, and possibly vecuronium.<sup>87</sup>

Postoperative renal dysfunction is also associated with an increased morbidity and mortality (Table 6). The incidence of ARF requiring dialysis varies with the underlying surgical operation (e.g. CABG 1.1 vs 0.6% in general surgical patients).<sup>16</sup> Novis and colleagues examined 26 studies to identify those preoperative risk factors predictive of postoperative ARF; only preoperative renal dysfunction, advanced age, and cardiac dysfunction were of importance.<sup>68</sup> If the preoperative serum creatinine was more than 1.5–3.9  $\text{mg dl}^{-1}$ , there was a poorer outcome.<sup>57</sup>

There have been a number of studies looking at the influence of different surgical operations. Breckwoldt and colleagues studied 205 patients undergoing surgery involving either infra- or supra-renal aortic clamping.<sup>12</sup> In the infra-renal population, there was a 10% incidence of transient renal dysfunction, compared with 28% after supra-renal clamping; but there was no difference in the percentage of patients (2–3%) in the two groups who required long-term haemodialysis.

**Table 5** Sites of action of dopaminergic receptor agonists/antagonists and their agonist effects

Receptor	Site	Effects
DA <sub>1</sub>	Renal and splanchnic beds	Vasodilation, increased renal blood flow, natriuresis
	Proximal renal tubule	
DA <sub>2</sub>	Postganglionic sympathetic nerves	Inhibits presynaptic norepinephrine release; decreases renal blood flow

**Table 6** Incidence of acute renal dysfunction and outcome after aortic surgery. TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm; Aortic Diss., aortic dissection repair; AAA, abdominal aortic aneurysm (with SR=suprarenal clamping; IR=infra-renal clamping); ARD, acute postoperative renal dysfunction; HD, % patients with ARD needing haemodialysis. NA, not available or calculable

Study	Type of surgery	Number of patients	Incidence of ARD (%)	HD (%)	Overall mortality (%)	Mortality associated with ARD (%)
Chertow <sup>16</sup>	Cardiac	42313	1.1	NA	NA	63.7
Mangano <sup>61</sup>	Cardiac	2222	7.7	17.5	3.0	19.0
Conlon <sup>20</sup>	Cardiac	2672	7.9	9.0	1.2	26.3
Ryckwaert <sup>82</sup>	Cardiac	591	15.6	8.7	2.7	12.0
Svensson <sup>94</sup>	TAAA	1509	17.8	50.6	8.2	30.9
Kashyap <sup>49</sup>	TAA/ TAAA	183	11.5	NA	NA	NA
Godet <sup>33</sup>	TAA/ TAAA/ AAA	475	25	32.2	25.5	43.8
Cittanova <sup>18</sup>	TAAA/ AAA	249	24	NA	NA	NA
Huynh <sup>44</sup>	TAAA	450	13	12.8	14.6	NA
Coselli <sup>21</sup>	TAAA	1415	15.9	32.2	3.1	NA
Rectenwald <sup>80</sup>	TAAA	101	27.8	NA	17.8	NA
Kazui <sup>50</sup>	Aortic Diss.	130	9	NA	19.2	NA
Breckwoldt <sup>12</sup>	AAA (SR/IR)	205	20.5	2.0	1.5	NA
Hertzer <sup>38</sup>	AAA (IR)	1135	1.7	31.6	1.2	NA

In a prospective study of 475 patients undergoing thoraco-abdominal aortic aneurysm surgery, Godet and colleagues reported an incidence of renal failure of 20–25%. There was an 8% incidence of postoperative dialysis, and a higher mortality in these patients.<sup>33</sup>

Rectenwald and colleagues have similarly reported increases in the serum creatinine of more than 2 mg dl<sup>-1</sup> over baseline value in 28% of patients undergoing thoracic abdominal aortic aneurysm surgery;<sup>80</sup> while Huynh and colleagues reported a 13% incidence in 540 patients undergoing thoracic aneurysmectomy who required postoperative dialysis.<sup>44</sup> In a separate study, Kashyap and colleagues on 183 thoraco-abdominal aortic aneurysm patients, with an 11.5% incidence of renal impairment and a dialysis rate of 2.7%.<sup>49</sup> The death rate in those patients with renal failure was 9.2 times that in patients not receiving dialysis. Similar incidences of renal impairment have been reported in the studies of Hertzer and colleagues, and Kazui and colleagues in aortic surgery and aortic dissection patients respectively.<sup>38,50</sup> More importantly, the development of renal dysfunction has been shown to be an independent predictor of poor quality of life and mortality.<sup>12 16 18 20 21 33 38 44 49 50 61 80 82 85 94</sup>

However, the trend towards an association between postoperative renal complications and mortality is not limited just to patients undergoing CABG or aortic surgery. Using data from the Oxford Record Linkage Study Database, we found that pre-existing renal dysfunction (defined as a pre-operative serum creatinine of  $\geq 150 \mu\text{mol litre}^{-1}$ ) was associated with cardiac death within 30 days of a variety of

elective surgical operations but not after urgent/emergency surgery.<sup>42,43</sup> For patients undergoing elective surgery and urgent/emergency surgery, the conditional logistic regression odds ratios (with their 95% CI) were 3.56 (1.04–12.18) and 2.96 (0.87–10.1), respectively, after adjustment for confounding factors. The importance of pre-existing renal dysfunction as a causation of mortality in elective surgical cases is further supported when data for 1991–8<sup>89</sup> are added in giving a crude odds ratio from 209 cases and controls of 4.00 (1.71–10.90).

## Conclusions

The development of postoperative renal impairment following cardiovascular or other surgeries is a major cause of perioperative morbidity and mortality. The type of surgery being undertaken is important, as is the presence of pre-existing renal dysfunction. **Although a number of preventative strategies have been described, none apart from maintenance of normovolaemia appears to be effective.** A number of new therapies have been identified, but these must await the outcome of randomized clinical trials with large numbers of patients.

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