

## Mechanisms of acute renal failure

C. J. LOTE L. HARPER AND C. O. S. SAVAGE

Acute renal failure can be defined as an abrupt decline in renal function with a decrease in glomerular filtration rate (GFR) resulting in the retention of nitrogenous waste products. Acute renal failure has conventionally been classified as (a) prerenal failure, denoting a disorder in the systemic circulation that causes renal hypoperfusion. Implicit in the prerenal classification is that the correction of the underlying circulatory disturbance (e.g. by improvement in cardiac function or repletion of volume) restores the GFR. However, prerenal failure is often followed by transition to (b) intrinsic renal failure, where correction of the circulatory impairment does not restore the normal GFR. Intrinsic renal failure generally includes tubular necrosis. (c) Postrenal failure (obstructive) is a third possibility.

Some patients with acute renal failure have oliguria (conventionally defined as a urine output of less than 400 ml day<sup>-1</sup>), but others do not. In fact, patients with acute renal failure can be divided approximately equally into oliguric and non-oliguric. The pathogenetic factors appear to be identical in both types but in general are less severe in non-oliguric acute renal failure.

Three abnormalities of renal function are present in intrinsic acute renal failure. These are (1) intratubular obstruction, (2) backleak of glomerular filtrate through damaged tubular epithelium, and (3) a primary reduction of GFR as a consequence of the release of vasoactive substances, which alter pressure, flow and filtration coefficient ( $k_f$ ) in the glomerular capillaries.

The kidneys have an enormous blood supply. They receive 20–25% of the cardiac output, but account for only 0.5% of the body weight. The renal blood supply is typically around 400 ml 100 g<sup>-1</sup> min<sup>-1</sup> compared with about 70 ml 100 g<sup>-1</sup> min<sup>-1</sup> for heart and liver. The kidneys also have a very high oxygen consumption, but because of the high blood flow, the arteriovenous oxygen difference across the kidney is small.  $P_{O_2}$  decreases from 95 mm Hg in the renal artery, to a value of about 70 mm Hg in the renal venous blood. In view of this it may seem surprising that renal ischaemia and acute renal failure are such major problems.

In this article we examine those features of the renal physiology which contribute to the (intrinsic)

failure of the kidney after renal hypoperfusion. What happens when the renal circulation is compromised, and how does this lead on to intrinsic renal failure? How can an organ which has a huge blood supply, and a very low oxygen extraction, be so susceptible to ischaemia and hypoxia? The answers are complex; they necessitate an understanding of renal haemodynamics and their control, and of the role of the kidney in circumstances in which the effective circulating volume is reduced.

### Renal blood supply

One of the first aspects of renal haemodynamics which physiology students learn is the concept of "autoregulation" (fig. 1). When mean renal arterial pressure is varied over the range 90–200 mm Hg, there is little effect on renal blood flow. The mechanism of this is still controversial; the most likely explanation is that there is a myogenic response, whereby the increased wall tension in the afferent arterioles, brought about by an increase in perfusion pressure, causes automatic contraction of the smooth muscle fibres in the vessel wall, thereby increasing the resistance to flow and so keeping the flow constant in spite of the increase in perfusion pressure. The alternative hypothesis is that a tubulo-glomerular feedback (TGF) mechanism is responsible for autoregulation, whereby increased perfusion pressure will increase filtration, increasing the tubular fluid delivery to the macula densa which then releases a factor or factors which causes vasoconstriction. Which of these hypotheses is correct is debatable [33].

However, the concept of autoregulation can be very misleading. Notwithstanding autoregulation, when effective circulating volume decreases there is a reduction in renal blood flow. This should not be surprising. It has been known for a very long time that stimulation of the renal nerves causes loss of colour from the kidney surface as a result of renal vasoconstriction [4], and this renal vasoconstriction occurs at relatively low levels of renal nerve activity (2 Hz), with increases in both afferent and efferent arteriolar resistance. Higher levels of stimulation (5–20 Hz) primarily constrict the afferent arterioles [18].

---

(Br. J. Anaesth. 1996; 77: 82–89)

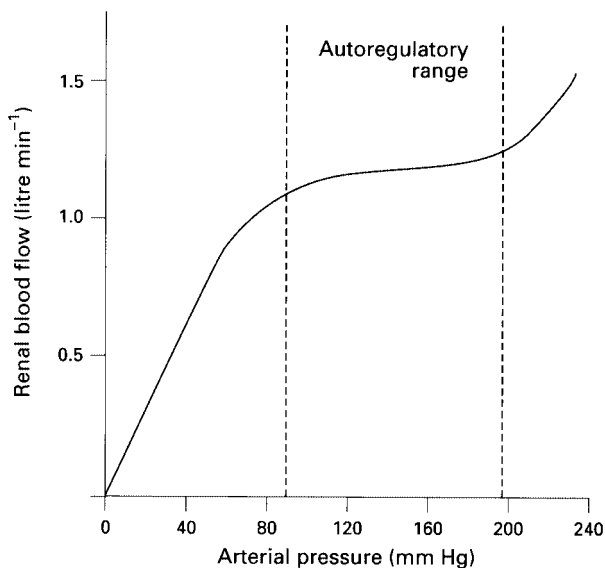
#### Key words

Kidney, failure. Kidney, blood flow. Kidney, metabolism.

---

C. J. LOTE, BSC, PHD, (Physiology Department); L. HARPER, MRCP, C. O. S. SAVAGE, PHD, FRCP, (Department of Medicine); Nephrology and CCRIS, University of Birmingham B15 2TT.

Correspondence to C. J. L.



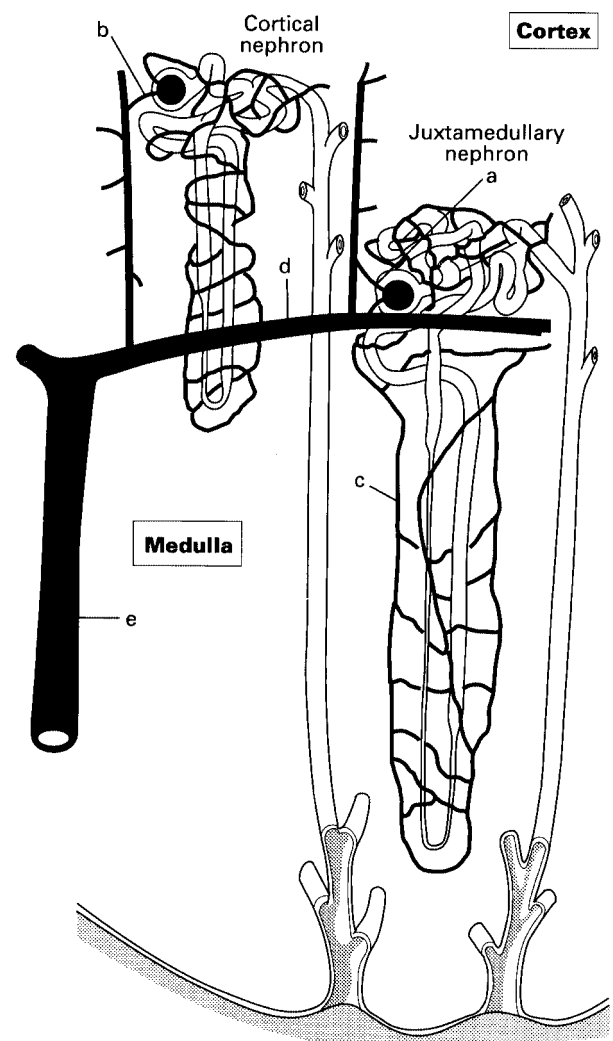
**Figure 1** The autoregulation of renal blood flow. In the "autoregulatory range" (90–200 mm Hg), a change in the mean renal perfusion pressure has little effect on the blood flow. The graph can be misleading, since *in vivo* the kidneys do not respond passively to changes in blood pressure, but are active components of blood pressure regulation. (From ref. [22].)

As mentioned above, the kidneys, relative to their size, receive a huge fraction of the cardiac output (20–25%), and in times of stress, sympathetically mediated renal vasoconstriction can shunt the large blood flow to extrarenal sites. Thus, whereas the autoregulation diagram gives the impression that the kidneys *react* to changes in blood pressure, the reality is that the kidneys play a major role in the *regulation* of blood pressure, and many authors have emphasized that renal blood flow decreases whenever cardiac output is decreased secondary to volume depletion [24], although there is continuing controversy over the magnitude of the decrease.

Thus systemic blood pressure is not a good guide to the adequacy of renal perfusion. If there is a decrease in the effective circulating volume (for whatever reason), there may be catastrophic underperfusion of the kidneys, even though blood pressure is in the "autoregulatory" range; this is by virtue of the fact that it may be intense renal vasoconstriction that is the reason for the blood pressure being maintained. So, overt hypotension is not a prerequisite for the development of acute renal failure, and modest reductions in cardiac output, with maintained blood pressure, can imply substantial renal ischaemia. But, if the kidneys normally have such a large blood supply, why does ischaemic damage occur so readily?

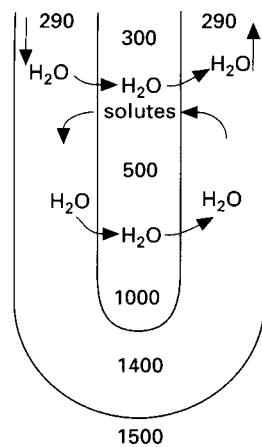
### The renal medullary blood supply

The function of the renal medulla is to maintain a high osmolality (produced by solute transport out of the ascending limb of the loop of Henle), in order to allow the tubular fluid to be concentrated by the osmotic abstraction of water from the collecting ducts. This function demands a specialized blood supply; conventional capillaries traversing the renal medulla would instantaneously dissipate the cortico-

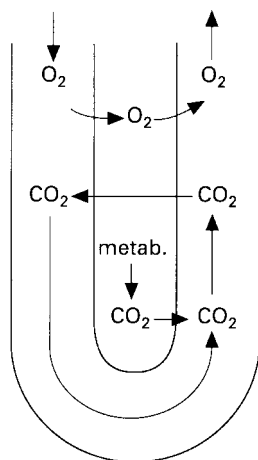


**Figure 2** Diagram to show the anatomical arrangement of the blood supply to the nephrons. For clarity, venules and veins are omitted. A typical juxtamedullary nephron (15% of the total) and cortical nephron (85% of the total) are shown on the right and left respectively. Note that the afferent arterioles of the juxtamedullary nephrons (labelled a) leave the interlobular artery at a retrograde angle, whereas the afferent arteriole of the cortical nephron (labelled b) leaves at a shallow angle. Thus, plasma skimming is more likely in the blood to the juxtamedullary nephron, the efferent arteriole of which supplies the vasa recta (c). Only two nephrons are shown complete. Other afferent arterioles are shown, but not the glomeruli. Other labels: arcuate artery (d) running along corticomedullary boundary. Interlobar artery (e).

medullary solute gradient. The specialization is the countercurrent arrangement of the vasa recta (fig. 2), which minimizes washout of solutes from the medullary interstitium. However, for vasa recta countercurrent exchange to operate, it is essential that the haematocrit of the blood entering the vasa recta should be low. If it were not, then the osmotic removal of water from the descending vasa recta (fig. 3) would dramatically increase the blood viscosity. Even with a low haematocrit, there is a considerable increase in viscosity due to the increase in intravascular protein concentration brought about by the countercurrent exchange of water. Furthermore, since the blood entering the descending vasa recta is derived from efferent arterioles and is unlikely to have gained any tubular fluid reabsorbate, the



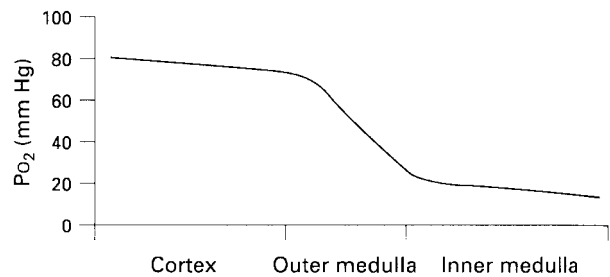
**Figure 3** Countercurrent exchange of water and solutes in the vasa recta. The osmotic gradient in the renal medulla/papilla, set up by extrusion of sodium and chloride from the thick ascending limb of the loop of Henle (not shown), causes solute to enter the descending vasa recta limb (on left), and water to leave, so that there is equilibration with any level of the interstitium. The removal of water from the descending limb raises the plasma protein concentration and concentrates the erythrocytes. Hence a low haematocrit at the beginning of the vasa recta is necessary. (From ref. [22].)



**Figure 4** Countercurrent exchange of oxygen and carbon dioxide in the vasa recta. The diffusion gradient causes oxygen to leave the descending limb and enter the ascending limb, and vice versa for carbon dioxide. Thus the cells deep in the renal medulla/papilla have a hypoxic and hypercapnic environment. (From ref. [22].)

increased viscosity which will have occurred because of glomerular filtration will still be present in the blood entering the vasa recta.

Most measurements of the haematocrit for the blood entering the inner medullary descending vasa recta give values of about 10% [31]. Why is the haematocrit low in the blood entering the vasa recta? The vasa recta are derived from the efferent arterioles of juxtamedullary nephrons, which are the first nephrons to be supplied by the interlobular arteries (fig. 2). There are some obvious differences between the afferent arterioles of juxtamedullary glomeruli when compared with other glomeruli. The afferent arterioles of the juxtamedullary glomeruli, as they branch from the interlobular arteries, do so at right angles or even at retrograde angles [21]. This leads to plasma skimming [2] so the blood which enters the



**Figure 5** The  $PO_2$  (mm Hg) from cortex to medulla, showing the dramatic decreases in  $PO_2$  in the inner medulla as a result of countercurrent exchange of oxygen in vasa recta (as shown in fig 4).

branch vessel (the afferent arteriole) is likely to have a reduced haematocrit. The important point is that the volume of the blood flow into the medulla is not a good indication of the adequacy of the blood supply for tissue metabolism, because of the low haematocrit and hence low oxygen-carrying capacity of the blood. This situation is then further exacerbated by the countercurrent exchange process in the vasa recta, because oxygen and carbon dioxide take part in this countercurrent exchange (fig. 4) [22]. Consequently, the cells of the renal papilla live in a remarkably hostile environment, with high (and labile) osmolality, poor oxygen delivery, and poor carbon dioxide removal. The degree of hypoxia in this part of the kidney is shown in figure 5.

Thus, although the blood flow rates in the renal medulla and papilla are well within the range found in other metabolically active tissues, the low haematocrit and countercurrent exchange of oxygen lead to very low oxygen availability for the papillary cells.

### The renal cortical blood supply

The obvious specialization of the cortical blood supply is the fact that there are two capillary beds in series—the glomerular capillaries and the peritubular capillaries. These are linked by the efferent arterioles which thus constitute portal vessels. There are a number of reports that the  $PCO_2$  is high in the renal cortex (e.g. ref. [9]) and it is suggested that this is because countercurrent exchange can occur in the cortical peritubular capillaries, as it does in medullary vasa recta. However, others have found typical tissue values of  $PCO_2$  in the renal cortex [25], and at the time of writing the question of whether renal cortical tissue  $PCO_2$  is atypically high remains unresolved.

### The kidneys as guardians of the effective circulating volume

Renal tissue damage will occur when the renal blood supply is insufficient to sustain the metabolic demands of the cells. Hypoxia limits ATP production, and hence impairs those cells dependent on oxidative metabolism [35]. Changes of cellular pH as a consequence of oxygen deprivation can also impair glycolytic (anaerobic) metabolism [27].

Although it might be supposed that the renal sites which have the highest oxidative metabolism (i.e. proximal tubule), would be the ones most affected by

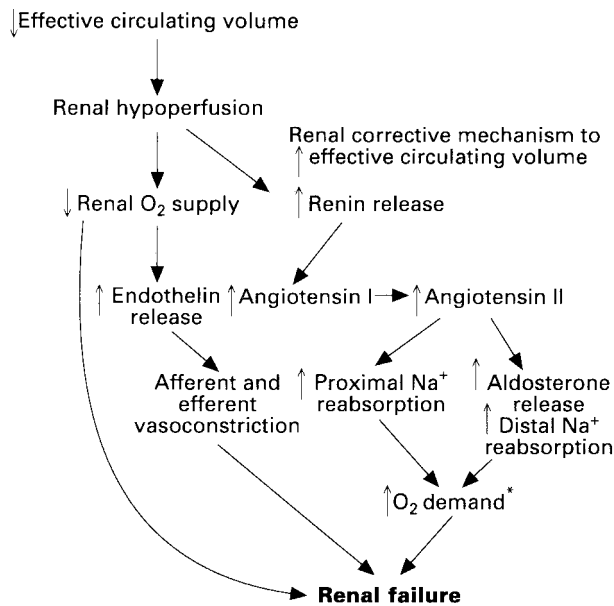


Figure 6 The typical sequence of events leading to acute ischaemic renal failure. \* Na<sup>+</sup> transport by the Na<sup>+</sup>/K<sup>+</sup> ATPase accounts for 80 % + of renal oxygen consumption.

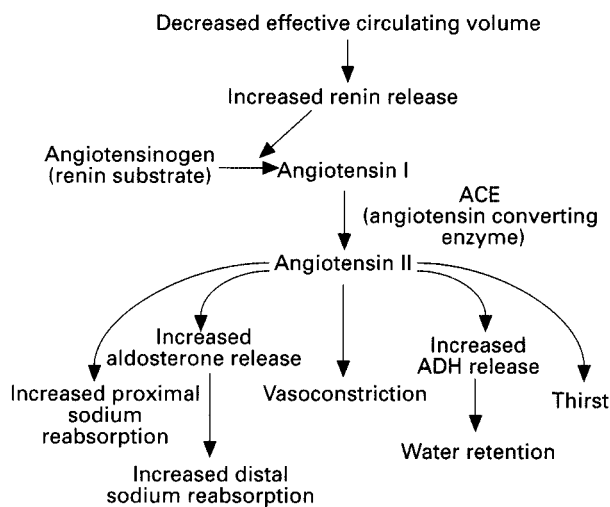


Figure 7 The role of the renin-angiotensin system in the maintenance of effective circulating volume.

hypoxia, the structural factors considered earlier also have a major bearing. The proximal convoluted tubules have the highest Na<sup>+</sup>-K<sup>+</sup>-ATPase activity. However, the S3 segment (pars recta—the part of the proximal tubule which descends into the medulla), and the medullary thick ascending limb of Henle (both of which have considerable glycolytic capability) are the sites commonly damaged in ischaemic acute renal failure. These sites, while having important transport roles, are also affected by the oxygen shunting in the vasa recta.

Eighty percent of the renal oxygen consumption is utilized to drive the Na<sup>+</sup>-K<sup>+</sup>-ATPase on the basal side of the tubule cells which is responsible for nephron sodium reabsorption. Many of the other transport processes along the nephron (e.g. glucose reabsorption, amino acid reabsorption, organic acid secretion) are secondary active processes which are

driven by the gradient for sodium entry across the apical membrane. Thus, there would be almost no transport across the tubular cells without Na<sup>+</sup>-K<sup>+</sup>-ATPase activity. However, there are differences in the properties of the Na<sup>+</sup>-K<sup>+</sup>-ATPase in different nephron segments. For example, the Na<sup>+</sup>-K<sup>+</sup>-ATPase is 10–30 times more sensitive to ouabain in the collecting tubule (where the final adjustments to sodium excretion occur) than in the proximal tubule [8]. These differences raise the possibility of different control mechanisms over Na<sup>+</sup>-K<sup>+</sup>-ATPase activity in different nephron segments. This is discussed in more detail below.

As the foregoing has demonstrated, decreases in effective circulating volume lead to a reduction in renal perfusion, and this threatens the kidneys by further reducing the blood supply to sites where it is only just adequate. However, renal hypoperfusion is a signal of hypovolaemia to the kidneys, and brings into play renal correcting mechanisms to increase sodium and water reabsorption, and hence restore effective circulating volume. But for the kidneys to do this, their oxygen consumption must increase. This sequence of events, potentially leading to renal failure, is shown in figure 6.

Renal hypoperfusion is a powerful stimulus to renin release from the renin-containing granular cells of the afferent arteriole. Three main signals mediate this release.

(1) *The afferent arteriolar “baroreceptor” mechanism.* Decreased wall tension in the afferent arterioles as a consequence of decreased renal perfusion, increases renin release.

(2) *The sympathetic innervation to the granular cells.* Systemic baroreceptor reflexes activated by decreased effective circulating volume (and consequent decreased blood pressure) increase the activity in these nerves, increasing renin release.

(3) *The macula densa.* This is a sensor in the early part of the distal tubule (which is in close proximity to the afferent arteriole), which responds to decreased sodium chloride delivery into the distal tubule by increasing renin release. Sodium chloride delivery to this site decreases when there is a decrease in effective circulating volume, as a consequence of several factors, including decreased GFR, and decreased peritubular capillary hydrostatic pressure which leads to increased proximal tubular reabsorption.

The consequences of increased renin release are shown in figure 7 where it can be seen that the effects of increased angiotensin II production serve to increase effective circulating volume. Incidentally, the renal vasoconstriction induced by angiotensin II is predominantly of the efferent arteriole, but the renal vasoconstrictor effect of angiotensin II is anyway markedly attenuated because angiotensin II is a powerful stimulus for the production of vasodilator prostaglandins (see below). Thus, the vasoconstrictor effect of angiotensin II is primarily, (though not exclusively) systemic rather than renal.

However, another vasoconstrictor peptide, endothelin-1 may act more locally. Its release and the tissue sensitivity to its effects are both enhanced by hypoxia [17]. Endothelin-1 mediates afferent and

efferent arteriolar vasoconstriction, reducing renal plasma flow and glomerular filtration rate (fig. 6).

The sequence of events shown in figure 6 might seem to indicate that renal failure would be inevitable whenever there is a decrease in effective circulating volume, and this is obviously not the case. This is because there are intrinsic renal protective mechanisms. To a large extent, these are dependent on arachidonic acid metabolism.

### Protective role of renal arachidonic acid metabolism

There are many excellent recent reviews of renal arachidonic acid metabolism [23]. This section will therefore focus on those aspects of arachidonate metabolism which have particular relevance to renal function in hypoxia and ischaemia.

The availability of free arachidonic acid as a substrate for the enzymes which convert it to active products, is very limited, since most of the esterified arachidonic acid which is converted to free arachidonic acid by phospholipase A<sub>2</sub> is normally re-esterified. This requires ATP, and hence is oxygen dependent, so hypoxia and ischaemia are powerful stimuli for renal prostaglandin synthesis. An alternative or additional possibility is that a hypoxia-induced increase in intracellular (cytosolic) Ca<sup>2+</sup> concentration enhances phospholipase A<sub>2</sub> activity [23].

Free arachidonic acid can be metabolized via three routes, as shown in figure 8. The major cyclo-oxygenase products have renal tubular and renal vascular actions, both of which are important in the renal response to ischaemia and anoxia. Non-steroidal anti-inflammatory drugs (such as indomethacin) which are cyclo-oxygenase inhibitors, have little or no effect on renal blood flow (RBF) or GFR in healthy subjects, but cause marked decreases in RBF and GFR when the renal circulation is compromised, for example by haemorrhage [6]. This indicates that vasodilator products of the cyclo-oxygenase enzyme (mainly prostaglandin E<sub>2</sub> and prostacyclin PGI<sub>2</sub>) play an important role in maintaining blood flow and GFR in these circumstances.

In addition to these haemodynamic vasodilator actions, PGE<sub>2</sub> also reduces sodium reabsorption in

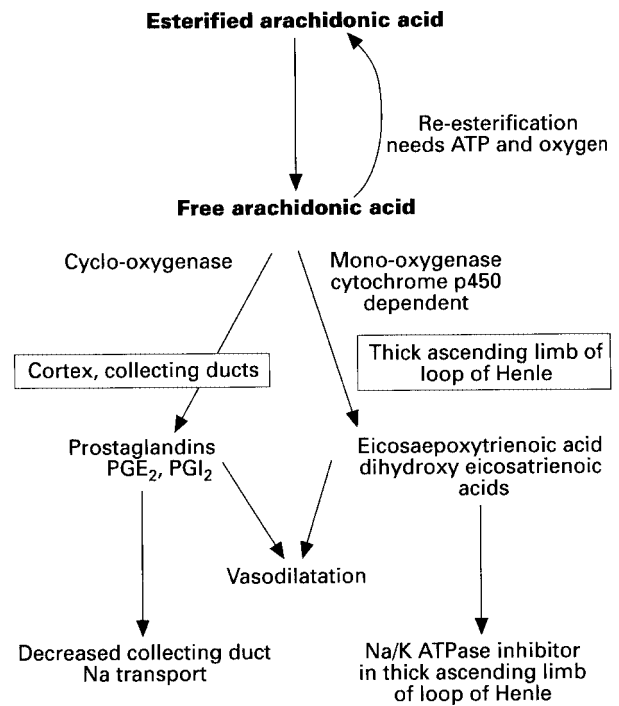


Figure 9 The renal protective effects of arachidonic acid metabolism.

the thick ascending limb of the loop of Henle [32] and the collecting duct [19] and hence reduces the oxygen consumption of the cells at these sites [20].

Products of the cytochrome P450-dependent mono-oxygenase enzyme may also be important in the ischaemic kidney. One product of this enzyme, probably a derivative of 11, 12-dihydroxyeicosatrienoic acid, produced in cells of the thick ascending limb of Henle, is a sodium potassium ATPase inhibitor at this site, and another (5,6-eicosapoxytrienoic acid) is a vasodilator [5].

The renal protective actions of the arachidonic acid products are summarized in figure 9.

### Other protective mechanisms

It was mentioned earlier that there are differences in the control over Na<sup>+</sup>-K<sup>+</sup>-ATPase activity at different sites in the nephron, and this fact will have been apparent from the foregoing section. However, arachidonic acid products are not the only humoral agents which influence Na<sup>+</sup>-K<sup>+</sup>-ATPase activity. The effects of aldosterone are predominantly on the activity of Na<sup>+</sup>-K<sup>+</sup>-ATPase in the collecting tubule, where it acts by inducing the synthesis of new transporter molecules [12]. However this, of course, increases oxygen demand. There are other agents which reduce oxygen demand, important among which are atrial natriuretic peptide and its renal analogue, renal natriuretic peptide (urodilatin) [14, 36] (fig. 10). There are high affinity binding sites for these peptides in the collecting ducts, binding to which leads to an increase in intracellular cGMP, which in turn inhibits ouabain-sensitive oxygen consumption [36] and this is assumed to inhibit sodium transport.

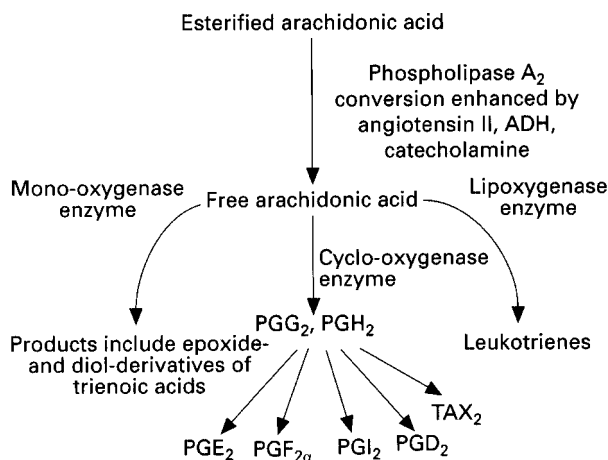


Figure 8 Renal arachidonic acid metabolism.

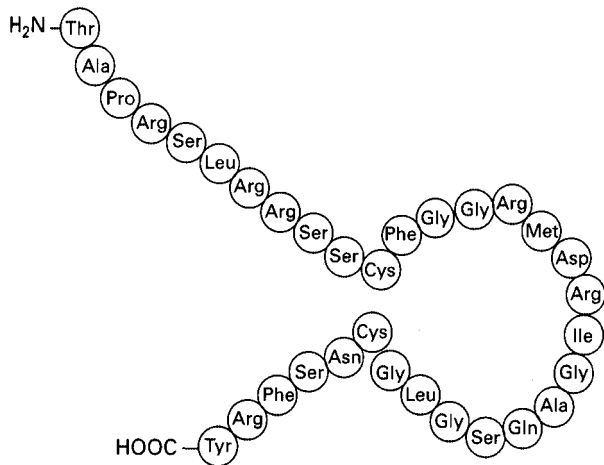


Figure 10 Renal natriuretic peptide (urodilatin). The major circulating form of atrial natriuretic peptide,  $\alpha$ -human ANP, is identical except that it does not contain the 4 N-terminal amino acids (Thr, Ala, Pro, Arg).

Recent evidence suggests that atrial natriuretic peptide is primarily a cardiovascular regulator and relatively unimportant for sodium excretion, whereas renal natriuretic peptide is more likely to participate in the intrarenal regulation of sodium excretion [13]. The renal natriuretic peptide is synthesized in the distal cortical nephron, and may be secreted into the cortical peritubular capillaries, or directly into the tubular lumen [36].

### Role of endotoxins, inflammatory mediators and nitric oxide in acute renal failure

Sepsis is a common cause of acute renal failure and septicaemia is a common event in patients with acute renal failure, particularly those requiring intensive care. Infective agents may exert their effects by both direct and indirect mechanisms. Many of the indirect effects are mediated through the potent bacterial product, endotoxin or lipopolysaccharide (LPS). LPS may act on many cell types, particularly endothelial cells, monocytes and neutrophils. It can bind directly to, and activate cells via the glycosyl-phosphoinositol-anchored membrane protein CD14; interactions between LPS and CD14 are facilitated by serum factors including LPS binding protein.

The endothelial cell phenotypic changes induced by LPS are almost identical to those induced by the cytokines TNF and IL-1 [7, 28] and include: (a) the upregulation of cell surface adhesion molecules such as E-selectin, ICAM-1 and VCAM-1 that promote leucocyte adhesion and transmigration; (b) the development of a procoagulant surface through enhanced expression of tissue factor, enhanced release of von Willebrand factor from internal stores in response to agonists (e.g. thrombin), increased secretion of plasminogen activator inhibitor-1 (with subsequent reduced fibrinolytic capacity) and reduced expression of thrombomodulin (with reduced activation of the protein C, protein S pathways); (c) the induction of inflammatory mediator secretion from endothelial cells, including prostacyclin (PGI<sub>2</sub>) platelet activating factor (PAF), nitric oxide (NO) and endothelin-1; and (d) the secretion of growth

factors, secondary cytokines, leucocyte chemoattractants and enzymes related to matrix degradation.

In addition to its effects on endothelial cells, endotoxin may also activate neutrophils and monocytes, while within the kidney it may induce adhesion molecule upregulation on renal epithelial and mesangial cells. Injection of endotoxin into baboons caused acute renal failure and dramatic upregulation within glomeruli of the adhesion molecule E-selectin (that binds ligands on neutrophils, monocytes and some T-cells) [28]. Accumulated activated neutrophils secrete proteases and free oxygen radicals which damage the glomerular basement membrane and nearby cells. Activated monocytes express tissue factor (favouring coagulation) and secrete further cytokines including IL-1 and TNF that potentiate the effect of endotoxin.

Many of the secondary inflammatory mediators induced by endotoxin can have far reaching effects. Thus, PAF is a product of arachidonic acid metabolism that is released by vascular endothelial cells and which, among its many functions, is a potent platelet activator. The two vasodilators PGI<sub>2</sub> and NO may be released from endothelial cells in response to LPS, while LPS-stimulated monocytes and mesangial cells are a further source of NO [30]. The induction of NO by endotoxin in these cell types differs, reflecting the predominant NO synthase (NOS) enzyme present; NOS generate NO from the terminal guanidino nitrogen of L-arginine. Endothelial NOS is a constitutive enzyme that is dependent on calcium and calmodulin for activity and it continuously produces nmol quantities of NO. Macrophage NOS is not calcium/calmodulin dependent and is induced by endotoxin and certain cytokines such as TNF and IL-1; this induction occurs over hours as it requires new protein synthesis but it leads to sustained production of mmol quantities of NO. Endotoxin and cytokine upregulation of NO from endothelial cells occurs because these factors increase the levels of tetrahydrobiopterin, an essential cofactor, although recently an inducible NOS has been described in endothelial cells also. An inducible NOS is present too in glomerular mesangial cells. NO inhibits platelet aggregation (as does PGI<sub>2</sub>) and adhesion to collagen, effects which may be renal protective. However, excess NO levels in sepsis are blamed for the negative inotropic effects on cardiac muscle and for the profound vasodilatation (often resistant to vasoconstrictors) that occurs in septic shock. Nitric oxide has complex interactions with other vasoactive systems—angiotensin II, sympathetic nervous system catecholamines, endothelin I, and prostaglandins; a detailed description of these effects is beyond the scope of this article but they are reviewed in ref. 30.

In parallel with the enhanced NO production, endotoxin may also upregulate the potent constrictor peptide, endothelin [17]. Local endothelin I production may contribute to the renal vasoconstriction that occurs during septic shock since administration of anti-endothelin immunoglobulin directly into the renal artery completely reverses endotoxin-induced renal vasoconstriction.

## Prevention of acute renal failure

Prevention of acute renal failure is clearly a better option than treatment. Patients at risk of acute renal failure can be identified and certain simple measures may help to prevent the subsequent development of acute renal failure.

The following conditions predispose to development of acute renal failure:

- (1) pre-existing renal impairment
- (2) diabetes mellitus (both insulin-dependent and non-insulin dependent)
- (3) hypertension and/or vascular disease, particularly renal vascular disease
- (4) jaundice
- (5) multiple myeloma
- (6) age.

The incidence of acute renal failure in the above groups of patients is high after the use of i.v. contrast media, use of nephrotic drugs (e.g. non-steroidal anti-inflammatory drugs, gentamicin, amphotericin) and surgery. Measures that may be taken to reduce the risk of acute renal failure include discontinuation of nephrotoxic agents wherever possible (such as non-steroidal anti-inflammatory drugs) or monitoring levels carefully to avoid toxic concentrations (as with gentamicin).

It is important to eliminate dehydration in "at risk" individuals by evaluating fluid status (if necessary with a central venous catheter) and administering fluid (if necessary i.v. using normal saline in preference to 5% dextrose in patients with renal impairment). Adequate extracellular volume status before major surgery is an excellent preventative measure particularly in the jaundiced patient or those undergoing aortic surgery [3]. Recently, in a prospective study, patients with a mildly elevated creatinine who underwent coronary angiography were hydrated with 0.45% saline before and after angiography. Saline alone significantly reduced the risk of renal failure induced by radiocontrast agents compared with saline and furosemide or mannitol [34].

The role of dopamine as a renoprotective agent is controversial. Dopamine is used widely in the dose range 2–5  $\mu\text{g kg}^{-1} \text{min}^{-1}$  and is said to act as a renal vasodilator. There is significant overlap in the stimulation of beta-adrenergic and alpha-adrenergic receptors even at these doses. The increased blood flow is probably the result of the inotropic effects of dopamine and can be reproduced by other non-dopaminergic inotropes. In a randomized double-blind trial [11], dopamine and dobutamine were compared for their ability to improve renal function. Dopamine acted as a diuretic and did not improve creatinine clearance. Dobutamine, a non-dopaminergic inotrope, improved creatinine clearance without a change in urine output [11].

The diuresis commonly seen after administration of dopamine is probably the result of a direct tubular effect. However, dopamine impairs the important tubuloglomerular feedback mechanism which may adversely affect the oxygen supply and demand balance, possibly promoting the development of

acute tubular necrosis [10]. Dopamine is commonly used to prevent acute tubular necrosis. The evidence supporting this is poorly controlled and often anecdotal. A recent well designed trial [1] showed no benefit in the prevention of renal dysfunction in well hydrated patients undergoing elective abdominal surgery receiving dopamine [1]. In another controlled study, patients undergoing coronary artery bypass surgery failed to derive any benefit from prophylactic dopamine [26]. There is one study in which dopamine protected against radiocontrast-induced renal failure in patients with pre-existing renal impairment; however, no diabetics were included [16].

Mannitol is an osmotic diuretic which if administered prophylactically to patients undergoing surgery can reduce the incidence of acute renal failure. However a recent prospective trial found no additional benefit beyond adequate hydration [15]. The beneficial effects of mannitol are thought to be due to decreased intratubular obstruction and improved renal haemodynamics secondary to an increase in medullary blood flow and cellular protection.

At present there is no acknowledged treatment which reduces duration or mortality of acute renal failure since the advent of dialysis. However, recent animal studies have indicated that atrial natriuretic peptide (ANP) attenuates the severity and/or accelerates the recovery in experimental models of acute renal failure [29]. ANP increases GFR in pathological states, by increasing the glomerular capillary perfusion pressure and has a direct diuretic and natriuretic effect on the distal tubule as described earlier. In a randomized blinded study in humans, ANP appeared to reduce the need for dialysis and increased creatinine clearance when given parenterally to those patients with established intrinsic acute renal failure. There was no improvement in mortality [15]. This study needs to be reproduced in larger trials before definitive conclusions on the use of ANP in acute renal failure can be made.

## Conclusions

The structural specialization of the renal circulation is necessary for its function, but some features of the specialization make the kidneys prone to ischaemic and/or hypoxic failure. Most importantly, despite the low oxygen extraction overall, the renal blood supply is not excessive, and indeed is barely adequate in some areas. Excessive reliance on blood pressure measurements (indicating a pressure in the "autoregulatory range") overlooks the fact that the renal blood flow is labile since the kidneys contribute to the regulation of blood pressure.

So, is there an easy way of assessing whether the kidneys are failing after an ischaemic episode? Urinary measurements are a useful indicator. If the effective circulating volume has been reduced the kidneys, if functioning normally, will be maximally reabsorbing sodium and water. Consequently, the urine volume will be small, urine osmolality will be high (e.g. over 800 mosmol/kg  $\text{H}_2\text{O}$ ), and the urinary sodium concentration will be low (e.g. less than

25 mmol litre<sup>-1</sup>). In contrast, if the decreased effective circulating volume has induced renal failure, then urine volume will be small (or there may be no urine produced at all) as a consequence of decreased GFR; but if any urine is produced, it is likely that the urine osmolality will be close to the plasma osmolality (300 mosmol kg<sup>-1</sup> H<sub>2</sub>O) and the urinary sodium will be around 140 mmol litre<sup>-1</sup>. This is because in acute renal failure, renal concentrating ability is lost. However, there can be considerable overlap between urinary values in prerenal and intrinsic renal failure, and although it is true that most oliguric patients with urine osmolalities below 350 mosmol kg<sup>-1</sup> H<sub>2</sub>O will have intrinsic renal failure, and most with osmolalities over 500 will have prerenal failure, values in between can occur in both conditions.

## References

- Balwin J, Henderson A, Hickman P. Effect of low dose dopamine on renal function after elective major vascular surgery. *Annals of Internal Medicine* 1994; **120**: 744–747.
- Bankir L, Trinh Trang Tan MM, Grunfeld JP. Measurement of glomerular blood flow in rabbits and rats. Erroneous findings with 15 µm microspheres. *Kidney International* 1979; **15**: 126–133.
- Barry KG, Mazze RI, Schwartz FD. Prevention of surgical oliguria and renal haemodynamic suppression by sustained hydration. *New England Journal of Medicine* 1964; **270**: 1373–1381.
- Block MA, Wakim KG, Mann FC. Circulation through kidney during stimulation of the renal nerves. *American Journal of Physiology* 1952; **169**: 659–669.
- Carroll MA, Schwartzman M, Baba M, Miller MJS, McGiff JC. Renal cytochrome P-450-related arachidonate metabolism in rabbit aortic co-arcuation. *American Journal of Physiology*, 1988; **255**: F151–F157.
- Corwin HL, Bonventre JV. Renal insufficiency associated with nonsteroidal anti-inflammatory agents. *American Journal of Kidney Diseases* 1984; **4**: 147–152.
- Cotran RS, Pober JS. Effects of cytokines on vascular endothelium: Their role in vascular and immune injury. *Kidney International* 1989; **35**: 969–975.
- Doucet A, Barlet C. Evidence for differences in the sensitivity to ouabain of Na<sup>+</sup>-K<sup>+</sup>-ATPase along the nephrons of rabbit kidney. *Journal of Biological Chemistry* 1986; **261**: 993–995.
- Dubose TD, jr, Cafilisch CR, Bidani A. Role of metabolic CO<sub>2</sub> production in the generation of elevated renal cortical pCO<sub>2</sub>. *American Journal of Physiology* 1984; **246**: F592–F599.
- Duke GJ, Bersten AD. Dopamine and renal salvage in the critically ill patient. *Anaesthesia in Intensive Care* 1992; **20**: 277–302.
- Duke GJ, Briedis JH, Weaver RA. Renal support in critically ill patients: Low dose dopamine or low dose dobutamine? *Critical Care Medicine* 1994; **22**: 1919–1925.
- El Mernissi G, Doucet A. Specific activity of Na<sup>+</sup>-K<sup>+</sup>-ATPase after adrenalectomy and hormone replacement along rabbit nephron. *Pflügers Archives* 1984; **402**: 258–263.
- Goetz KL. Renal natriuretic peptide (urodilatin?) and atriopeptin: Evolving concepts. *American Journal of Physiology* 1991; **261**: F921–F932.
- Greenwald JE, Needleman P, Wilkins MR, Schreiner GF. Renal synthesis of atriopeptin-like protein in physiology and pathophysiology. *American Journal of Physiology* 1991; **260**: F602–F607.
- Gubern JM, Sancho JJ, Simo J, Sitges-Serra A. A randomised trial on the effect of mannitol on post-operative renal function in patients with obstructive jaundice. *Surgery* 1988; **103**: 39–44.
- Hall KA, Wong RW, Hunter GC, Camazine BM, Rappaport WA, Smyth SH, Bull DA, McIntyre KE, Bernhard VM, Misiorowski RC. Contrast induced nephrotoxicity: the effects of vasodilatory therapy. *Journal of Surgical Research* 1992; **53**: 317–320.
- Haynes WG, Webb DJ. The endothelin family of peptides; local hormones with diverse roles in health and disease? *Clinical Science* 1993; **84**: 485–500.
- Hermansson K, Larson M, Kallskog O, Wolgast M. Influence of renal nerve activity on arteriolar resistance, ultrafiltration dynamics and fluid reabsorption. *Pflügers Archives* 1981; **389**: 85–90.
- Holt WF, Lechene C. ADH-PGE<sub>2</sub> interactions in cortical collecting tubule 1. Depression of sodium transport. *American Journal of Physiology* 1981; **241**: F452–F460.
- Jabs K, Zeidel ML, Silva P. Prostaglandin E<sub>2</sub> inhibits Na<sup>+</sup>-K-ATPase activity in the inner medullary collecting duct. *American Journal of Physiology* 1989; **257**: F424–F430.
- Jamison RL, Kriz W. *Urinary Concentrating Mechanism*. New York; Oxford University Press, 1982: 233–242.
- Lote CJ. *Principles of Renal Physiology*, 3rd ed. London: Chapman and Hall, 1994.
- Lote CJ, Haylor J. Eicosanoids in renal function. *Prostaglandins, Leukotrienes and Essential Fatty Acids Reviews* 1989; **36**: 203–217.
- Madias NE, Donohue FJ, Harrington JT. Postischemic acute renal failure. In: Brenner BM, Lazarus JM, eds. *Acute Renal Failure*, 2nd ed. New York: Churchill Livingstone, 1988: 251–278.
- Mello Aires Mde, Lopes MJ, Malnic G. PCO<sub>2</sub> in renal cortex. *American Journal Physiology* 1990; **259**: F357–F365.
- Myles PS, Buckland MR, Schenk NJ, Cannon GB, Langley M, Davis BB. Effect of renal dose dopamine on renal function following cardiac surgery. *Anaesthesia in Intensive Care* 1993; **21**: 56–61.
- Neely JR, Grotyohann LW. Role of glycolytic products in damage to ischemic myocardium. *Circulation Research* 1984; **55**: 816–824.
- Pearson JD, May MJ. Regulation of endothelial cell function by cytokines. In: Savage COS, Pearson JD, eds *Immunological Aspects of Vascular Endothelium*. Cambridge: CUP, 1995: 20–42.
- Rahman SN, Kim GE, Mathew AS, Goldberg CA, Allgen R, Schrier RW, Conger JD. Effects of atrial natriuretic peptide in clinical acute renal failure. *Kidney International* 1994; **45**: 1731–1738.
- Raij L, Baylis C. Glomerular actions of nitric oxide. *Kidney International* 1995; **48**: 20–32.
- Rasmussen SN. Effects of osmotic diuresis and water diuresis on intrarenal red cell and plasma volumes in the rat. *Pflügers Archives* 1974; **1**: 1–11.
- Reeves WB, Molony DA, Andreoli TE. Diluting power of thick limbs of Henle III. Modulation of in vitro diluting power. *American Journal of Physiology* 1988; **255**: F1145–F1154.
- Steinhausen M, Endlich K, Wiegman DL. Glomerular blood flow. *Kidney International* 1990; **38**: 769–784.
- Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol and frusemide on acute decreases in renal function by radiocontrast agents. *New England Medical Journal* 1994; **331**: 1414–1416.
- Weinberg JM. The cell biology of ischemic renal injury. *Kidney International* 1991; **39**: 476–500.
- Zeidel ML, Silva P, Brenner BM, Seifter JL. cGMP mediates effects of atrial peptides on medullary collecting duct cells. *American Journal of Physiology* 1987; **252**: F551–F560.