Review Article

Pathophysiology and prevention of acute renal failure: the role of the anaesthetist

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Ischaemic renal tubular damage in the perioperative period can lead to acute renal failure (ARF) with a very high mortality rate (60-75 per cent). Recent research suggests that this tubular injury is caused by an imbalance of the oxygen supply and demand of medullary thick ascending limb (mTAL) tubular cells. High oxygen demand is secondary to active reabsorption of solute which is increased in states of intravascular volume depletion. The restricted supply of oxygen is secondary to the organization of blood flow to the inner medulla. Because the vasa recta loop into the inner medulla and a countercurrent exchange process for oxygen is established, the oxygen tension in this area may normally be as low as 10-20 mmHg. In hypoperfusion states, mTAL injury occurs and is exacerbated by intravascular volume depletion, hypoxaemia and endothelial cell swelling which reduces perfusion of these vulnerable and metabolically active mTAL cells. The anaesthetist must prevent or attenuate postoperative renal dysfunction by identifying high-risk patients preoperatively, optimizing intravascular volume status and cardiac output in the perioperative period, as well as responding appropriately to hypoperfusion states. Therapeutic implications relate to this pathophysiological sequence and several physiological and pharmacological considerations are discussed.

L'ischémie tubulaire rénale dans la période périopératoire peut aboutir à une insuffisance rénale aigue et un taux de mortalité élevé (60-75 pour cent). Les recherches récentes suggèrent que cette lésion tubulaire soit due à un déséquilibre de la demande et

de l'apport d'oxygène dans la région médullaire des cellules du tube ascendant (mTAL). La forte demande d'oxygène est secondaire à la réabsortion active de soluté qui est augmentée dans les états d'hypovolémie. L'apport restreint en oxygène est secondaire à l'organisation du flot sanguin dans la médullaire interne. A cause de l'organisation de la vasa recta dans la médullaire interne et du contrecourant, la tension d'oxygène dans cette région peut atteindre normalement des valeurs aussi basses que 10-20 mmHg. Dans les états d'hypoperfusion, des lésions du mTAL surviennent et sont exagérées par l'hypovolémie, l'hypoxémie et l'œdème cellulaire endothélial qui réduit la perfusion de ces cellules vulnérables et mébaboliquement actives. L'anesthésiste doit prévenir ou atténuer la dysfonction rénale postopératoire en identifiant les patients à haut risque en période préopératoire, en optimalisant le volume intravasculaire et le débit cardiaque en période périopératoire et en répondant adéquatement lors des états de bas débit. Les applications thérapeutiques reliées aux conséquences pathophysiologiques et plusieurs considérations physiologiques et pharmacologiques sont discutées.

The onset of renal dysfunction in the perioperative period is a serious complication of surgery. Surgery represents a point in the disease process of critically ill patients when they are most susceptible to an ischaemic injury of vital organs. The anaesthetist is charged with the responsibility of maintaining haemodynamic stability and vital organ perfusion during this time, which may be crucial in the prevention of acute renal failure.

The severity of renal failure as a perioperative complication is emphasized by studies[1,2] which have documented that the mortality in these circumstances remains high. This high mortality persists in spite of modern monitoring and supportive techniques. The failure of intensive care and dialysis to alter the 60-75 per cent mortality when renal failure occurs in the peri-operative period emphasizes the importance of preventive measures.

The emphasis of this review is that the anaesthetist can

use an understanding of the pathophysiology of ischaemic acute renal failure to develop a treatment plan for susceptible patients and minimize perioperative renal injury.

Assessment of renal function

Acute renal failure (ARF) can be defined[3] as an abrupt decline in renal function sufficient to result in the retention of nitrogenous end-products of metabolism which is not reversible by manipulation of extra-renal factors. Note that there is no reference to urine volume in this definition. The level of nitrogenous wastes in blood depends on both production and renal clearance. Renal clearance is determined by the delivery of these waste products to the kidney (renal blood flow) and the kidney's ability to extract them (glomerular filtration rate). As well as extracting these metabolic byproducts the kidney also concentrates the ultrafiltrate. Even with maximal concentration, 400–500 ml of urine are required to clear the daily obligatory nitrogenous wastes.[3] Because creatinine production is proportional to muscle mass, many chronically ill, wasted, elderly patients have serum creatinine values in the normal range in spite of a reduced concentrating ability and glomerular filtration rate (GFR). Conversely, many critically ill patients who are at highest risk of developing ARF, have high metabolic rates (e.g., hyperalimentation, sepsis, or post-traumatic states). Therefore, these patients have higher nitrogenous waste production, requiring even higher urine flow rates to maintain normal serum creatinine concentration.

An important predisposing risk factor in the development of perioperative ARF is preoperative renal function, which may not be obvious from a single creatinine measurement. Since there is an inverse logarithmic relationship between GFR and serum creatinine concentration, a halving of GFR results in a doubling of serum creatinine. If a patient with a preoperative serum creatinine of 60 μmol·L^{-1} has GFR reduced by half after an intraoperative ischaemic injury the serum creatinine will increase to only 120 μmol·L^{-1} which is still in the normal range. This would not be as obvious to the clinician as the same halving of GFR in a patient with a preoperative concentration of 120 μmol·L^{-1} which would increase to 240 μmol·l^{-1} after the same insult. Both situations demonstrated a 50 per cent reduction in renal function, but only the latter creatinine values were outside the normal range.

It should be emphasized that urine volume is determined by a variety of factors independent of glomerular filtration rate and that a normal hourly urine output does not preclude the presence of renal failure. These factors include tubular handling of solute and water which are determined by local and systemic levels of renin and ADH.

Patients in the operating room are often not in a stable haemodynamic state and may have fluctuating renin, ADH and catechol concentrations which can alter GFR.[4,5] Anaesthetists are not able to use standard tests of renal function, such as creatinine clearance, which are of considerable value to nephrologists, who evaluate renal function over longer periods in patients under stable haemodynamic conditions. Instead we must rely on indirect variables to assess renal blood flow. We often measure urine volume which may not bear a reliable relationship to GFR and renal function under these unstable intraoperative conditions.

Historical perspective

Our understanding of the natural course of the disease process has been assisted by studies performed during several armed conflicts of this century.[6] During World War II the mortality of injured soldiers when renal failure occurred approached 90 per cent.[6] With the institution of dialysis before the Korean War, it was hoped that this mortality would be substantially reduced. In fact, the mortality remained high (53 per cent).[6] During the Vietnam conflict the emphasis was clearly on the prevention of ARF by early resuscitation at or near the site of injury. During the Vietnamese War the mortality of injured soldiers when ARF was present remained about 65–75 per cent,[6] suggesting that advances made in the interim had not reduced the outcome once ARF was present.

Studies performed in civilian practice[1,2,6] demonstrate a similar trend of decreasing incidence but fixed mortality rate. With the improvement in perinatal care the incidence of ARF after childbirth is very rare. Werb[1] reported that 72 per cent of patients developing ARF in intensive care had had recent surgery. The mortality was 85 per cent in this group. In our recent experience,[2] 65 per cent of patients requiring dialysis in our multidisciplinary Intensive Care Unit were surgical patients. The associated mortality for this group was 72 per cent. Today, the anaesthetist participates in the care of the majority of patients developing ARF, and this complication is still associated with a high risk of death.

Causes of acute renal failure

For normal renal activity the kidney must perform three basic functions in the excretory process. The process begins with glomerular ultra-filtration and progresses to selective tubular reabsorption and tubular secretion. When ARF is present these processes are deficient, making the maintenance of the body's normal homeostasis impossible.

The initiating factors responsible for ARF are classified as either pre-renal (inadequate perfusion), renal (intrinsic kidney disease), or post-renal (obstructive uropathy).

The obstructive causes may originate in the ureter, bladder or urethra. Blocked urinary catheters have caused perioperative oliguria and must always be ruled out as a source of obstruction. For the purposes of this review, the pathophysiology of the resulting renal disease process known as "acute tubular necrosis" will be discussed in detail. It is important to emphasize that this disease of the tubulo-interstitial region of the nephron, commonly caused by ischaemia and occasionally by renal toxins, is not synonymous with ARF but rather is the most common and important of the renal causes of ARF especially in the critically ill patient.

The ischaemic causes of acute tubular necrosis (ATN) include all hypoperfusion states as well as embolic occlusion of the renal arteries. Renal hypoperfusion may be related to intravascular volume depletion, maldistribution of systemic flow away from the renal vascular bed, cardiogenic shock, and obstructive vascular conditions such as pulmonary emboli, cardiac tamponade, and tension pneumothorax. The most common of the maldistribution states is sepsis. Severe hypoxia will also contribute to ischaemic damage.

The toxic renal causes of ATN include such commonly used drugs as antibiotics (aminoglycosides, amphotericin B), and radiocontrast agents. Other endogenously produced substances can contribute to the development of ARF and are of specific interest to the anaesthetist. These include haemoglobin after a transfusion reaction, myoglobin from rhabdomyolysis of massive trauma and myeloma renal damage.

The anaesthetist's aim must be to prevent any avoidable hypoperfusion or hypoxic causes of ATN and minimize exposure to toxic factors.

Pathophysiology of ATN

The normal kidney can autoregulate both its blood flow and glomerular filtration rate (GFR) in response to changes in cardiac output and/or perfusion pressure. This autoregulation is controlled by neural and humoral mechanisms which mediate intrarenal adjustment of vascular resistance and blood flow.[8,9] When the limits of autoregulation are exceeded, ischaemic renal injury can result. Some interesting pathophysiological data explain the rather paradoxical sensitivity of this extremely well-perfused organ to an ischaemic insult. The anaesthetist, by understanding this pathophysiology, can develop an approach to understanding the process that results in ATN.

The factors contributing to ischaemic renal damage are summarized on Table I and discussed in detail. The answer to both the inhomogeneity of histologic renal damage in ATN,[10,12] as well as the paradoxical sensitivity of the kidney to ischaemia, requires an understanding of the distribution of intra-renal blood flow. The key concept

TABLE I Proposed factors which initiate ischaemic renal tubular damage

A Decreased oxygen supply:
   a Hypoperfusion
   b Hypoxaemia
   c Endothelial cell swelling
   d Erythrocyte aggregation (sludging)
   e Organization of medullary blood flow

B Increased cellular oxygen demand:
   a Active transport of solute
   b High demand – persisting GFR

in understanding the pathophysiology is that factors leading to the onset of ATN from ischaemic causes (initiation phase) must be differentiated from those that maintain the state of renal failure during the healing process (maintenance phase).

Initiation phase

A major paradox in our classical understanding of the renal response to ischaemia is the fact that early and severe hypoperfusion damage occurs in such a well-oxygenated vital organ. The normal kidney receives approximately 20 per cent of the cardiac output. This far exceeds the kidney's oxygen requirement and accounts for the fact that the normal renal venous oxygen saturation is much higher than the total body mixed venous oxygen saturation. This high-flow state is needed to ensure optimal clearance of all wastes and drugs. Studies[13-15] have demonstrated marked inhomogeneities of tissue oxygen availability within the kidney. A cortico-medullary gradient of oxygen exists (Figure 1) that under normal circumstances results in a medullary tissue PO_2 as low as 10 mmHg. This gradient has been demonstrated in a variety of animal species[14,15] both in vivo and in isolated perfused kidneys. Thus, normal medullary cells exist in a state of vulnerability, on the brink of hypoxaemia, in spite of the high total renal blood flow.

This intra-renal PO_2 gradient (Figure 1) has been attributed to the organization of vessels within the medulla.[16,17] The inner medulla is perfused by the vasa recta which form loops (Figure 2) and are responsible for the counter-current mechanism in which solute is pumped out of tubular cells to dilute ultrafiltrate and maintain the hypertonicity of the medullary interstitium. Brezis et al.[18] postulate that this counter-current principle also functions in the renal medulla to maintain a low partial pressure of oxygen. This allows counter-current exchange of oxygen from the descending to ascending branch of the loop, as shown in Figure 2. This maintains the state of relative tissue hypoxia in the interstitium most marked in the inner medulla. This vascular organization within the kidney is designed to maximize the "flow-dependent clearance of
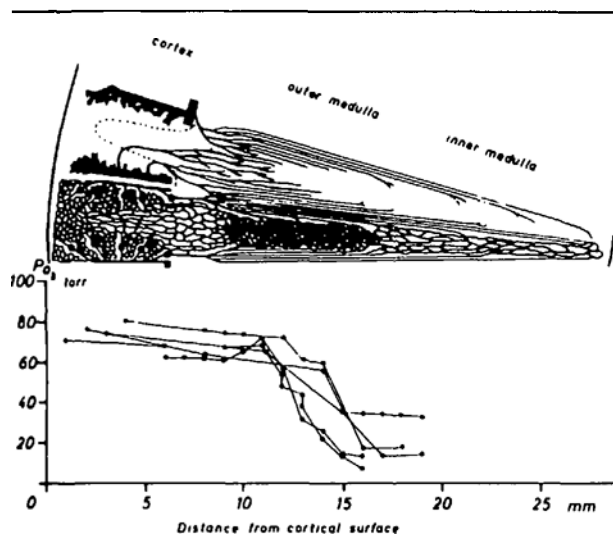
FIGURE 1   Renal tissue oxygen tension (PO₂) at various locations within the kidney identified by distance from cortical surface.
Above the data is a schematic of the renal vascular pattern illustrating the source of blood flow to inner medulla by vasa recta.
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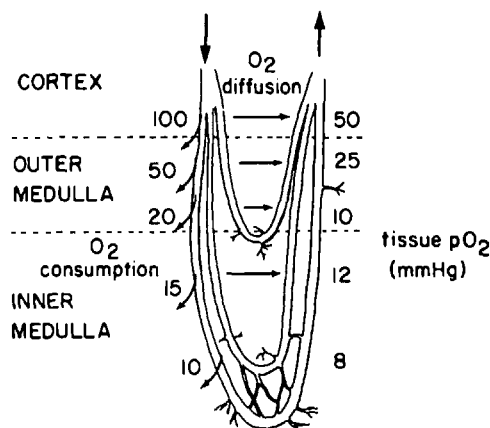

FIGURE 2   A schematic of the countercurrent exchange of oxygen within the inner medulla by the vasa recta. The hair-pin conformation of the vasa recta prevents the dissipation of cortico-medullary gradient of osmolality, but at the cost of counter-current diffusion of O_2 between arterial (descending) and venous (ascending) limbs. The high oxygen consumption of the inner medulla keeps medullary PO_2 low and is almost undisturbed by high total renal blood flow. Reproduced with permission of Plenum Press from the work of Brezis et al.[19]

wastes" at the price of medullary hypoxaemia. The low medullary blood flow rate prevents the washout of the hypertonic interstitium preserving the osmotic gradient on which normal renal function depends.

Hypoxic perfusion of an isolated kidney preparation[19] has demonstrated that the medullary thick ascending limb (mTAL) cells of the loop of Henle are extremely vulnerable to hypoxaemic damage. This mTAL damage is patchy, being most evident in tubules located at a distance from a vessel. The selective vulnerability of the mTAL cell is thought to result from their high oxygen consumption resulting from active reabsorption of solute (Na, K, Cl).[18] Ischaemic renal damage may reflect the effect of deep medullary hypoxic injury to mTAL cells that are metabolically active. The normal homeostatic response to systemic hypoperfusion (pre-renal ARF) is characterized by active mTAL sodium and chloride reabsorption. This metabolic response results in high mTAL cellular oxygen demand at the time of maximal cellular hypoxic vulnerability.

Of interest to the anaesthetist is the suggestion[18] that oxygen-enriched perfusion of hypo-perfused kidney preparations reduces the cellular damage, and hypoxic perfusate increases the extent of injury. However, complete vascular occlusion which reduces GFR to zero preventing glomerular ultra-filtration seems to be associated with less cellular damage than hypoxic perfusion.[18] It is therefore possible that the severity of cell injury is related to the

energy expenditure at the time of cellular hypoxia. This may explain differences between various models[10-12] of ischaemic ARF as well as suggesting appropriate pharmacological interventions. These interventions would reduce oxygen demand by either decreasing glomerular filtration prior to an ischaemic injury or decreasing cellular work of active transport to protect the mTAL from subsequent hypoxic damage.

Our understanding of the initiating factors in the pathogenesis of ATN then suggests a process essentially similar to that in other vital organs exposed to hypoxaemia. In discussing the response of the heart and brain to ischaemia we commonly use the concept of the balance between oxygen supply and demand. Renal hypoperfusion reflects a state of "renal angina"[20] most marked in the vulnerable medullary area. The term vasomotor nephropathy has been used in place of ATN, since this term emphasizes the vascular aetiology of the initiating events.

Afferent arteriolar vasoconstriction[21] may represent a normal protective renal response to an acute tubular injury. By reducing ultrafiltration, any further energy expenditure by the already ischaemic mTAL cells would be prevented. Afferent arteriolar vasoconstriction may also produce feedback inhibition of glomerular filtration, perhaps mediated by intra-renal renin release.[22] The result of both mechanisms would be reduced ultrafiltrate formation. Decreased ultrafiltrate formation would reduce the oxygen consumption of mTAL cells secondarily preserving tubular integrity at the cost of retaining

nitrogenous wastes. Since the loss of tubular concentrating ability is the earliest functional defect noted after an ischaemic injury, the reduced GFR could also protect intravascular volume from rapid and inappropriate depletion.

Mason[23,24] has described an additional hypothesis which provides important insight into these pathophysiological factors responsible for the initiation phase of ATN. Early after ischaemia the inner glomeruli which supply blood to the inner medulla are hypoperfused and a marked vascular congestion[25,26] with erythrocyte aggregation[27] in the vessels of the inner medulla has been found. This erythrocyte aggregation or "sludging" occurs during the ischaemic period and persists into the maintenance phase of ARF. This sludging process perpetuates the state of renal medullary ischaemia in ARF. Sludging can be prevented in the renal ischaemic model by either raising perfusion pressure or reducing the viscosity of the perfusate by hemodilution.[23] Both of these interventions may be of specific interest to the anaesthetist in providing a rationale for therapy. Mason[23] also speculated on the cause of erythrocyte aggregation, suggesting that vascular congestion was related to endothelial cell oedema and swelling which follow the ischaemic damage to membrane function. Endothelial cell swelling was most marked in the poorly perfused outer medulla and was reduced by the administration of mannitol prior to the insult.[24] The degree of renal functional impairment was related to the amount of vascular congestion present.[27] This suggests that therapy should also focus on reducing cell swelling thus improving perfusion to the ischaemic medullary region.

Maintainance phase

Studies[10] of renal pathology after an ischaemic insult demonstrate histologically normal glomeruli and patchy tubular cell necrosis. Cellular debris from tubular necrosis were found in dilated renal tubules. This histological evidence of tubular necrosis and subsequent obstruction with dilatation of the tubular lumen led investigators to use the term Lower Nephron Necrosis as a synonym for ATN. The histological appearance of the kidney in ischaemic ARF is not well correlated with the degree of renal failure.[10-12] The classical delay in the recovery of renal function (7-21 days) after an ischaemic event is believed to be evidence for regeneration of tubular cells in the healing process.

In established ATN the clearance of markers of glomerular filtration was reduced to values approximately five per cent of normal, whereas total renal blood flow had returned to 25-50 per cent of baseline value.[30-32] This suggested that factors other than the vasomotor response were important in sustaining the state of ARF. Oliver et
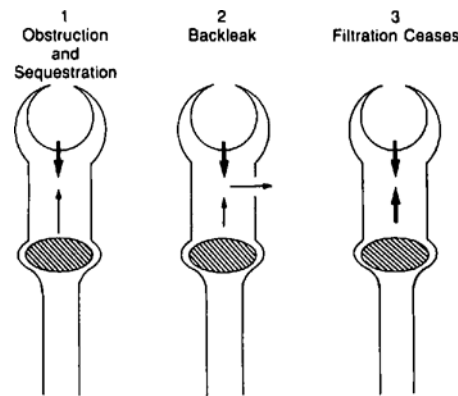

FIGURE 3   Classical explanation for maintenance phase of ARF illustrating obstruction of tubules with necrotic cellular debris causing (1) proximal tubular dilatation and sequestration of ultrafiltrate, (2) leakage into the interstitium and ultimately (3) rising intratubular pressure to cause cessation of ultrafiltration with balancing of hydrostatic pressure gradient across the glomerular membrane.

al.[28] suggested that the cause of the persistent oliguria was the presence of tubular obstruction with necrotic cellular debris. This debris results in cellular casts in the urine sediment characteristic of established ATN. The presence of tubular obstruction initiates a cascade of events that culminate in oliguria, reduced GFR, and prolonged renal failure.

Tubular obstruction results in dilatation and sequestration of ultra-filtrate within the tubule. As intra-tubular pressure rises the balance of Starling forces determining GFR are altered such that the hydrostatic pressure across the glomerulus is balanced and ultra-filtration eventually will cease (Figure 3).[33]

After obstruction, the damaged tubular wall is exposed to higher intra-tubular pressures and "backleak" of ultra-filtrate out of the tubule into the oedematous interstitium has been documented.[34-35] The ultra-filtrate that leaks into the interstitium is reabsorbed into the circulation. The result of decreased ultra-filtration, backleak and vascular re-absorption is no net excretion of filtered solute, hence no detectable clearance of nitrogenous waste.

Therapeutic implications for the anaesthetist

The prevention of pre-renal causes of ATN must begin before surgery. In our experience[36] with patients presenting for aortic aneurysm resection, preoperative intravascular volume depletion was a frequent occurrence. The preservation of renal function in high-risk patients should begin at the preoperative visit where risk is assessed and perfusion is optimized. In high-risk patients this should mandate an intravenous infusion the night before surgery. The maintenance of renal function after an ischaemic

TABLE II   Patients at high risk of intraoperative renal ischaemic injury

I	Preoperative renal disease
2	Preoperative hypoperfusion (shock) states
3	Cirrhosis
4	Biliary obstruction
5	Sepsis
6	Multiple system trauma
7	Multiple organ system failure
8	Cardiac failure
9	Extra-cellular fluid volume deficit
10	Elderly patients
11	Aorto-renal vascular disease

FIGURE 4   Pattern of measured GFR (ml·min^{-1}·1.73 m^{-2}) during aortic reconstructive surgery in nine patients treated with intravenous saline (▲) to increase PCWP > 12 mmHg and in similar ECF volume-expanded patients (n = 9) who were treated with dopamine (3 μg·kg^{-1}·min^{-1}) and mannitol (25 g bolus and 200 mg·kg^{-1}·hr^{-1} infusion) during aortic cross-clamping (●).

insult appears to be critically dependent on the speed with which perfusion is re-established.[19]

High-risk patient groups include those listed on Table II. Clearly the intraoperative maintenance of cardiac output in these patients is the responsibility of the anaesthetist. Whether monitoring with invasive devices such as pulmonary artery catheters, arterial cannulae, or even urinary catheters actually reduces the incidence of ARF has never been demonstrated. The overwhelming consensus among clinicians is that these devices have improved our ability to maintain perfusion during major surgery. However, it must be emphasized that unless data from invasive monitoring is appropriately used to maintain perfusion, the risk of complications (e.g., sepsis) may negate any benefits.

Physiological considerations

Blood gas tensions

Decreases of arterial oxygen tension alter renal blood flow by either local (direct) effects or by the secondary haemodynamic response to hypoxaemia.[37] Severe arterial hypoxaemia to PaO$_2$ values less than 40 mmHg are associated with decreases of renal blood flow[38] and enhanced renal vasoconstriction.[39] Hypercapnia has also been associated with decreased sodium excretion, and renal blood flow[40] in patients requiring mechanical lung ventilation. Thus, the maintenance of perioperative renal blood flow is best accomplished if the anaesthetist ensures adequate ventilation preventing hypoxaemia and hypercarbia.

Positive pressure ventilation (PPV)

Several studies have documented a consistent decrease in renal plasma flow and sodium excretion associated with positive intra-thoracic pressure. This has been attributed to the reflex (hormonal) systemic response to a reduced cardiac output.[41] Augmentation of circulating intravascu-
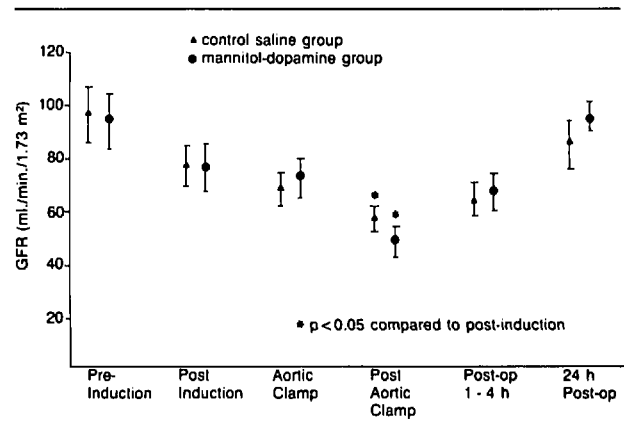
lar blood volume attenuates these haemodynamic changes as well as the hormonal and renal response to PPV.[42]

In 27 intravascular volume-expanded patients (PCWP > 12 mmHg), the induction of anaesthesia with positive pressure ventilation did not cause a significant decrease in GFR in our study (Figure 4).[36] Deterioration of renal function[4,5] is not an invariable consequence of anaesthesia or positive pressure ventilation if perfusion is maintained.

Perfusion pressure

The anaesthetist must rely on his clinical estimate of cardiac output and must attempt to keep mean systemic perfusion pressure at a minimum value of approximately 70–80 mmHg in high-risk patients (Table I). Stone and Stahl[8] studied the renal effects of haemorrhage in normal humans and concluded that a decrease in mean perfusion pressure from 80 mmHg to 62 mmHg resulted in a reduction of renal blood flow of about 30 per cent without an autoregulatory response of the renal vasculature. Although some authors[9] have used these data to suggest that renal blood flow declines precipitously when mean systemic blood pressure drops below 80 mmHg, this has not been demonstrated under anaesthesia with maintenance of cardiac output. A high perfusion pressure may also help to minimize vascular congestion and improve perfusion of the inner medulla. In chronically hypertensive individuals who have altered vascular autoregulation this minimal perfusion pressure may be higher. Since renal function in the unstable intraoperative period[4,5] is influenced by numerous haemodynamic and hormonal factors, attempting to generalize perfusion pressure requirements for all patients is impossible.

Intra-abdominal pressure

Tense abdominal distension has been associated with decreased renal function. This is a complex response to intravascular volume depletion, reduced cardiac output and increased renal vein and inferior vena cava pressure.[43] Savino et al.[44] have improved renal function by paracentesis in critically ill cirrhotic patients with elevated intra-abdominal pressure. These authors suggested that measurement of intra-abdominal pressure using a transurethral catheter in this patient group is a useful quantitative monitor and the haemodynamic and renal consequences of ascites may be evaluated.

Preservation of the transplanted kidney

The maintenance of perfusion to the "donor" kidney prior to removal is the primary aim of the anaesthetist. All means of support including augmented intravascular volume, inotropic agents and even blood administration to a brain-dead donor may be required to maintain a functioning kidney. If a reduction in mTAL oxygen consumption is important in renal tubular preservation, the inhibition of tubular transport with diuretics prior to removing the donor kidney may improve preservation. However, no studies have demonstrated effectively improved post-transplant renal function if a potent loop diuretic is given to the donor. Haemodilution (by perfusing the renal artery with blood-free solution) and renal artery clamping (effectively preventing ultrafiltrate formation) will also decrease mTAL oxygen consumption. Mannitol administration to the recipient coupled with haemodilution and maintenance of renal perfusion at a mean arterial pressure >80 mmHg should provide the transplanted kidney with a hyperosmotic ultrafiltrate that will flush tubules of cellular debris.

Aortic cross-clamping

Gamulin et al.[45] have demonstrated that decreases in GFR and renal perfusion during and after infra-renal aortic cross-clamping can occur in humans. In our study[36] of 27 patients after infra-renal aortic cross-clamping and aggressive intravascular volume expansion (PCWP >12 mmHg), we could not demonstrate a reduction in GFR with cross-clamping. However, GFR decreased after removing the cross-clamp (Figure 4) in the control group given only saline to maintain intravascular volume. This is haemodynamically the most unstable intraoperative period as bleeding is often temporarily uncontrolled. Prophylactic administration of mannitol and low-dose dopamine (3 µg·kg⁻¹ min⁻¹) during time of aortic cross-clamping did not improve renal function during the cross-clamp nor prevent the decrease in GFR after clamp release. In a third group of patients the continuation of mannitol and dopamine during the post-clamp release

period was associated with the maintenance of GFR. Since the GFR of all patients returned to the preoperative level 24 hours after surgery, we do not conclude that these prophylactic measures (i.e., mannitol and low-dose dopamine) prevent a deterioration in renal function after clamp release. Rather, this study showed that high-risk patients may have major surgery without perioperative renal dysfunction, if haemodynamic stability is aggressively maintained. It is possible that high-risk patients will benefit from prophylactic pharmacologic measures if haemodynamic stability cannot be maintained.

Cardiopulmonary bypass (CBP)

Although oliguria[46] is common and renal blood flow is reduced[47] during CPB, overt post-CPB renal failure is uncommon. Abnormal intra-renal distribution of blood flow in the perioperative period may be caused by CPB-induced vasoconstriction. Preservation of renal function may be enhanced by the haemodilution and hypothermia accompanying CPB. Non-pulsatile blood flow of CPB contributes to the reduced GFR (30 per cent) and renal plasma flow (25 per cent).[48] The duration of extracorporeal perfusion, which correlates with the degree of haemolysis, and perioperative haemodynamic stability are the major factors determining the development of ATN. The prevention of ARF after CPB is non-specific and includes:[49] intraoperative maintenance of high perfusion rates, adequate oxygenation and perfusion pressure, minimizing CPB duration and haemolysis as well as optimizing myocardial protection.

Pharmacological considerations

Mannitol

Experimental data[50] suggest that the administration of hypertonic mannitol prior to an ischaemic insult will effectively reduce renal damage. There are several proposed mechanisms for this protective effect that relate to the pathophysiology of ARF. The ability of mannitol to be filtered and not reabsorbed, thus remaining within the tubule, increases distal tubular sodium delivery. This "flushing" effect of mannitol prior to an ischaemic injury would reduce inspissation of necrotic cellular debris within the tubule. Once tubular obstruction has occurred one would not expect an effective amelioration of the maintenance phase from an osmotic diuretic.

Mason[23] proposed a second rationale for the effectiveness of mannitol. The mannitol-induced hyperosmotic state may reduce endothelial cell swelling thus reducing the accompanying vascular congestion which limits flow to the inner medulla. The initial intravascular volume expansion which results from mannitol would lower the haematocrit, and viscosity of blood in the area of cell

swelling thus improving intra-renal blood flow.[51,52] If this hypothesis is correct, then mannitol given before and during an ischaemic period would reduce the degree of vascular congestion. However, any subsequent volume depletion secondary to mannitol should be aggressively avoided. Mannitol may also function as an oxygen free-radical scavenger.[53] The concentration of these reactive oxygen products increases after an ischaemic insult,[23] and may cause further damage by lipid peroxidation of cell membranes. The normal activity of oxygen free-radicals is kept low by endogenous scavengers. These are reduced after an ischaemic injury. Oxygen free-radical scavengers reduce vascular congestion in animal models after ischaemia perhaps by preventing further cell damage.[54]

Prostaglandins

Intra-renal prostaglandin release may be an important mechanism of renal autoregulation producing vasodilatation during stress.[55] During haemodynamic instability, prostaglandins may modulate the action of vasoconstricting adrenergic stimuli to preserve renal blood flow and function. Inhibition of cyclooxygenase enzyme by nonsteroidal anti-inflammatory drugs and aspirin may attenuate the normal renal prostaglandin protective mechanisms and accentuate catechol-mediated renal vasoconstriction. Therefore, patients on such drugs must be considered at risk of renal failure if haemodynamic compromise occurs. Prostaglandin therapy[56] may prove beneficial after ischaemic ATN.

Potent loop diuretics

Cell death after an ischaemic injury can also be reduced by decreasing cellular metabolic activity prior to the insult. Furosemide has been used to inhibit active cellular transport and has been effective in reducing the mTAL damage in hypo-perfused kidney preparations, when given before the ischaemic event. The efficacy of diuretics in the prevention and treatment of ARF in the critically ill remains controversial. Attempts to "convert" oliguric renal failure into the non-oliguric form, which is associated with lower morbidity and mortality, have not reduced the number of dialyses, duration of renal failure or mortality when compared with untreated controls.[58] In a prospective study using furosemide to enhance urine output and renal function, Brown et al.[58] did not demonstrate a significant benefit. Since patients with oliguric renal failure have a greater reduction in filtration and tubular function than non-oliguric subjects, the response to diuretics is probably limited to patients with less severe tubular injuries. Those patients who do respond to diuretics are certainly easier to treat, providing

an opportunity for early alimentation, and augmentation of circulating red cell mass by transfusion.

Indiscriminate use of the potent loop diuretics can cause subsequent intravascular volume depletion if not combined with aggressive maintenance of intravascular volume. During the perioperative period, with its inherent danger of intravascular volume loss, this risk is substantial. Treatment should focus on maintaining renal blood flow and oxygen delivery, by increasing cardiac output, maintaining oxygen content of blood and ensuring optimal ventilation. Damage to mTAL cells is time-dependent,[23] and a prompt response to hypo-perfusion injuries intraoperatively must remain the anaesthetist's priority.

Vasodilators

Circulating catecholamine concentrations are normally high in all hypoperfusion and hypoxic states. The redistribution of renal blood flow from cortex to the juxtamedullary region accompanies these low-flow states and can be produced by catechols.[59] Brezis[60] suggested that vasodilators such as adenosine, prostaglandins and dopamine enhance renal function after ischaemia. Adenosine, which is a product of cellular ATP breakdown during ischaemia, may reduce anoxic tubular cell injury by reducing transport, vasodilating the vasa recta and enhancing tubuloglomerular feedback. Therefore, adenosine may reduce ultrafiltrate volume available for active transport.[60] Similarly, prostaglandin E_2 inhibits active transport of the mTAL cells, thus decreasing cellular oxygen consumption while enhancing medullary blood flow.[60] Whether vasodilators can mobilize aggregated erythrocytes in the vessels of a congested renal medulla has not been demonstrated.

Dopamine ($0.5-3$ $\mu g \cdot kg^{-1} \cdot min^{-1}$) increases renal blood flow by stimulating specific renal receptors (DA_1). One study of patients in acute renal failure[61] demonstrated improved renal function with low-dose dopamine administration. Although other studies[61,63] have suggested a synergistic beneficial effect between dopamine and furosemide, the response seems to be dependent on the severity of renal failure and the duration of oliguria. No randomized controlled studies have demonstrated a reduction in the incidence of ATN when low-dose dopamine is used early in a haemodynamically unstable patient.

Non-specific parenteral vasodilators such as nitroglycerine and nitroprusside result in no specific renal benefit other than maintaining perfusion when used appropriately.

Since renal vascular autoregulation is dependent on the balance of afferent and efferent arteriolar tone and angiotensin II is the prime constrictor of the efferent

vessel, inhibitors of angiotensin converting enzyme (e.g., captopril) have been investigated. They have not been shown be valuable in ATN. In renal artery stenosis, the decrease in perfusion pressure caused by captopril can precipitate renal failure. This autoregulatory function is partially calcium-dependent. Calcium channel blockers have not been thoroughly investigated to determine their efficacy in preventing ischaemic ATN. However, it has recently been reported that verapamil has a direct protective effect on renal epithelium subjected to an hypoxic stimulus.[64]

Specific toxins
Recent data on renal failure associated with radiocontrast agents,[65] multiple myeloma,[65] and rhabdomyolysis[66] suggest that intravascular volume depletion, tubular stasis, and medullary injury often co-exist. Early, aggressive volume replacement can virtually eliminate renal failure after crush injuries and rhabdomyolysis, and significantly decrease ARF after radiocontrast administration.

Conclusion
The pathophysiology of ARF following ischaemia is not yet fully understood. Therefore, many of the concepts outlined in this review are incomplete explanations for clinical and experimental data. The determinants of renal function are complex and are profoundly altered in the perioperative period. As we understand the pathophysiology of the renal response to ischaemia and the control of renal blood flow more completely, the clinician will focus on the maintenance of the oxygen supply and demand balance in the vulnerable renal tubular cells.

The continuing high mortality rate for patients developing ARF in the course of a critical illness suggests that present renal replacement therapy is not optimal. New modalities of therapy, such as continuous arterio-venous haemodialysis and slow, continuous ultra-filtration, may reduce this mortality and have been reviewed recently.[67] However, the focus of our efforts must be to prevent ATN. The anaesthetist has an unique opportunity to reduce the perioperative mortality of high-risk patients from renal failure by anticipating problems preoperatively and responding aggressively to unanticipated complications during the critical perioperative period. This can best be accomplished if the clinician understands the pathophysiological basis of the disease process.

Acknowledgements

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