Prevention of Perioperative Renal Failure

Robert N. Sladen, MB ChB, MRCP, FRCPC

Pathogenesis

Oliguria and the Prerenal Syndrome

Oliguria implies "little urine." However, oliguria, like much else in life, is in the eyes of the beholder. Oliguric acute renal failure is defined as a urine output of ≤400 mL/day, i.e., a urinary flow rate ≤15 mL/h. Most anesthesiologists would describe perioperative oliguria as a urinary flow rate $\leq 0.5\ mL \cdot kg^{-1} \cdot h^{-1}$ (in an average adult, ≤30–40 mL/h). In a patient who has received mannitol (e.g., during cardiopulmonary bypass) postoperative oliguria might be considered to be a urinary flow rate ≤100 mL/h. Finally, and importantly, although intraoperative oliguria is an important indicator that the kidney is at risk, nearly 75% of cases of postoperative acute renal failure are non-oliguric, i.e., urine flow remains between 15–80 mL/h.

The etiology of oliguria traditionally has been defined as postrenal, prerenal, or intrarenal, and this simple classification still provides a useful basis for a therapeutic approach.

Postrenal oliguria implies urinary tract obstruction (renal pelvis, ureters, bladder, urethra, or urinary catheter) and typically manifests as anuria. Sudden and complete cessation of urinary flow should always trigger inspection, flushing, or changing of the urinary catheter.

In the perioperative period, oliguria should be interpreted as a physiologic response to hypovolemia (i.e., a prerenal response) (1). Hypovolemia may be absolute (acute hemorrhage, severe diarrhea, vomiting, fluid restriction), or relative (congestive heart failure, sepsis, liver failure). Dehydration, hypovolemia and hypotension trigger osmoreceptor, volume receptor, and baroreceptor reflexes that culminate in water and salt retention and vasoconstriction. There is activation of the sympathoadrenal and renin-angiotensin systems and release of aldosterone and antidiuretic hormone (arginine vasopressin, AVP). The net effect on the renal tubules is urinary concentration with avid reabsorption of water and sodium. Thus, in a prerenal state, characteristic urinary findings are oliguria with high urine osmolality and low urine sodium. When normal renal hemodynamics are restored, the stimulus to the tubules abates and normal urinary flow resumes.

In sepsis and liver failure, the above reflexes are activated but oliguria is invariably refractory to fluid replacement. These entities represent vasomotor nephropathy, which may be considered a resistant prerenal syndrome. Circulating endotoxin induces intense renal vasoconstriction characterized by oliguria with urinary sodium <10 mEq/L. It is resistant to fluid therapy and responds only to treatment of the underlying condition.

If hypovolemia is severe or combined with nephrotoxic insults, frank acute renal failure may ensue (intrarenal oliguria). In this context it is a truism that a young, healthy patient will tolerate a remarkable degree of renal insult and emerge without permanent renal injury, whereas an elderly patient at risk may develop permanent renal injury after a relatively minor insult despite all our efforts at renal protection. High risk situations and nephrotoxic insults are summarized in Tables 1 and 2.

In sum, oliguria is common but rarely implies acute renal failure (2). We should interpret oliguria as a sign of intravascular hypovolemia and treat it as prerenal until otherwise proven. Conversely, the absence of oliguria does not exclude acute renal failure. Currently, approximately 75% of acute renal failure is non-oliguric (i.e., urine flow rate 15–80 mL/h) (3), a reflection of incremental smaller insults in a protected milieu. The most reliable clinical indicator of progressive renal dysfunction and acute renal failure is a serial decline in creatinine clearance estimation, a measure of glomerular filtration rate (GFR).

The Interface Between Prerenal Syndrome and ATN

In the classic animal model of ischemic acute tubular necrosis (ATN), norepinephrine is infused into the renal artery.

Updated from: Sladen RN. Oliguria in the ICU: systematic approach to diagnosis and treatment. Anesthesiol Clin North America 2000;18:739–52. Used with permission of the publisher, Elsevier.

Table 1. Risk Factors for Perioperative Renal Failure

Advanced age
Preexisting renal insufficiency
Congestive heart failure
Diabetic nephropathy
Hypertensive nephropathy
Liver failure (hepatorenal syndrome)
Pregnancy-induced hypertension
Systemic disease (e.g., scleroderma, SLE)
Sepsis
Shock
High risk procedures
Renal revascularization
Aortic cross-clamping
Cardiopulmonary bypass
Urologic procedures
Transplantation
Nephrotoxins (see Table 2)

SLE = systemic lupus erythematosus.

Table 2. Nephrotoxins

Endogenous nephrotoxins	Exogenous nephrotoxins
Bilirubin*	Radiocontrast dyes
Myoglobin*	Fluoride (methoxyflurane, enflurane)
Hemoglobin (red cell stroma)*	Aminoglycoside antibiotics
Uric acid	Cyclosporine A, tacrolimus
	Cisplatinum
	Amphotericin B
	Low molecular weight dextrans
	NSAIDs

* Pigment nephropathy
NSAIDs = nonsteroidal anti-inflammatory drugs
Note: The risk of nephrotoxicity is low with a single insult in a healthy well-hydrated patient, but increases exponentially with the number of nephrotoxic insults, and the number of renal risk factors (e.g., diabetes, congestive heart failure, chronic renal insufficiency, and hypovolemia).

A short duration of infusion (<60 min) results in oliguria that resolves when the infusion is discontinued. This is akin to a prerenal syndrome; the renal tubules remain intact and avidly conserve salt and water in the face of sensed renal hypoperfusion. When normal renal hemodynamics are restored, urine flow returns to normal.

A longer duration of infusion (60–120 min) results in oliguria that persists when the infusion is discontinued and the animal becomes azotemic. This is akin to ATN; the renal tubules become necrotic and lose their ability to conserve salt and water. When normal renal hemodynamics are restored, urine flow remains low. The persistent reduction of GFR to <10% of baseline is ascribed to tubular obstruction by necrotic cells at *pars recta* (where the proximal tubule narrows into the descending loop of Henle). Proximal intraluminal pressure increases and lessens the glomerular-tubular gradient; GFR declines. Injury to the tubular basement membrane results in back leak of tubular fluid into the interstitial tissue (4–6).

The implication of these models is that the physiologic, reversible prerenal syndrome may deteriorate into frank ATN if the ischemic insult persists long enough. A prerenal state also sensitizes the kidney to nephrotoxic insults. Nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycoside antibiotics, IV radiocontrast dye, and cyclosporine A are much more likely to induce ATN in a dehydrated patient.

Myers and Moran emphasized the role of additive insults in causing transient renal dysfunction to deteriorate into established acute renal failure (7). They contrasted uncomplicated suprarenal aortic cross-clamping (a single limited episode of renal ischemia with recovery in 24–48 h), with poor cardiac function after cardiopulmonary bypass (poor renal function that improves if myocardial function recovers) and with superadded sepsis (additional ischemic and nephrotoxic insults resulting in dialysis-dependent acute renal failure).

In the animal model of ischemic ATN described above, the administration of so-called renal protective agents (saline, mannitol, vasodilators) before the infusion of norepinephrine results in a less severe form of ATN. The animal becomes azotemic but urine flow rate remains normal and renal recovery is more rapid. This is a model for the clinical syndrome of non-oliguric acute renal failure. Indeed, the reason that non-oliguric acute renal failure has become the predominant manifestation of ATN is that patients are more likely to suffer a series of milder insults (e.g., hypotension, positive pressure ventilation, aminoglycoside antibiotics) in a protected milieu (saline, vasodilators, low-dose dopamine).

Impact of Resuscitation on Renal Outcome After Ischemic ATN

There are numerous examples of the beneficial effect of fluid resuscitation in the prevention of a prerenal state deteriorating to ATN or in modifying the severity of ATN.

In the 15 years between the Korean War and the Vietnam conflict the mortality of acute renal failure only decreased from 75% to 65%. However, the incidence of acute renal failure decreased threefold (from 1:200 to 1:600 casualties) as a consequence of early, rapid fluid resuscitation in the field (8). Between 1956 and 1988, the overall mortality of posttraumatic acute renal failure between remained at approximately 45%, but its incidence declined from 7.8 to only 0.9 cases per year, reflecting the importance of prompt, effective

resuscitation of injured patients (9). In a retrospective study in postoperative trauma patients Shin et al. (10) demonstrated that early diagnosis of renal dysfunction and aggressive hemodynamic intervention could attenuate the renal insult of shock. Although the incidence of acute renal failure was the same, the treatment protocol increased the proportion of nonoliguric acute renal failure from 18% to 100%, halved dialysis time, hyperkalemia, and pulmonary edema, and decreased overall mortality from 70% to 28%.

The physiological basis for the renal protective effect of aggressive fluid administration in shock was suggested 30 yr ago by Gorfinkel et al. (11), who compared hemorrhagic and cardiogenic shock in dogs. With equivalent decrease in aortic pressure and cardiac output, hemorrhagic shock decreased renal blood flow to 10% of control with cortical ischemia and progressive oliguria; in cardiogenic shock renal blood flow was maintained at 75% of control with preservation of urine flow until the preterminal phase. The difference: left atrial pressure, which was low in hemorrhagic shock but elevated in cardiogenic shock. We now know that elevated atrial pressure mediates the release of atrial natriuretic peptide, a vitally important endogenous renal vasodilator that increases GFR and sodium excretion (12,13).

Nephrotoxic Pathways to ATN

Nephrotoxic injury seldom occurs with an isolated insult, but its risk increases exponentially when multiple agents are administered in an adverse milieu; i.e., acute instability (shock, hypovolemia, congestive heart failure) or chronic instability (advanced age, diabetes, chronic renal insufficiency) (14). Nephrotoxic agents may directly injure target cells but also cause harm by disrupting renal oxygen balance. Their nexus is the medullary thick ascending loop of Henle (mTAL), an area of high metabolic activity but tenuous oxygen supply: the renal medulla receives <10% of renal blood flow and has a tissue $Pao_2 < 10$ mm Hg.

Adenosine-induced cortical vasoconstriction enhances available blood flow to the medulla, where endogenous nitric oxide and prostaglandins induce local vasodilation. Any intervention that further decreases medullary blood flow (e.g., inhibition of prostaglandin synthesis) can potentially induce mTAL injury. Nephrotoxic acute renal failure is usually nonoliguric and the decline in GFR may be missed. Without appropriate dose adjustment, renally excreted nephrotoxic drugs accumulate and thereby exacerbate renal injury; ultimately frank ATN is established. Nonetheless, the prognosis for recovery is good if nephrotoxic agents are promptly discontinued and there is no coexistent organ failure.

Table 3. Factors that Increase the Risk of Aminoglycoside Nephrotoxicity

Advanced age
Preexisting renal disease
Renal vasoconstrictive states
Sepsis
Hypovolemia
Liver disease
Congestive heart failure
Adjuvant drug therapy
Loop diuretics
Vancomycin
Cephalosporins
NSAIDs
Cyclosporine A
Tacrolimus
Amphotericin B
Electrolyte disorders
Hypokalemia
Hypomagnesemia
Hypercalcemia
Metabolic acidosis

Nephrotoxins Commonly Encountered in the Perioperative Period

Aminoglycosides. Aminoglycosides are filtered into the proximal tubule, where as cations they bind to anionic brush-border membrane phospholipids, are absorbed into intracellular lysosomes, and are then released into the cytosol. They cause injury largely by inhibiting oxidative phosphorylation and ATP synthesis (15). Nephrotoxicity is directly related to sustained high trough serum levels; factors that increase the risk of injury are listed in Table 3 (16).

Interventions to limit aminoglycoside nephrotoxicity include maintenance of adequate hydration and careful monitoring of serum levels and GFR (e.g., daily 2-h creatinine clearance). Daily administration of aminoglycosides to achieve a high therapeutic level with an adequate trough period for renal recovery may limit the occurrence of nephrotoxicity (17).

NSAIDs. Cyclooxygenase-1 (COX-1) inhibition by NSAIDs (e.g., indomethacin, meclofenamate, or ketorolac) impairs vasodilator prostaglandin synthesis for approximately 8–24 h. However, the kidney resynthesizes COX-1 within 24–48 h. During conditions of stress, impaired prostaglandin activity results in decreased renal blood flow and GFR, increased renal vascular resistance, attenuated diuretic responsiveness, and hyperkalemia (18). The risk of nephrotoxic injury is negligible with a single NSAID dose in a healthy patient, but increases exponentially with concomitant nephrotoxins (e.g., contrast dye, aminoglycosides) and in the presence of acute or chronic cardiovascular instability.

NSAIDs selective for cyclooxygenase-2 (COX-2) appear to be less likely to cause gastric irritation and erosion. However, compared with nonselective COX

inhibitors, there is as yet no evidence that they decrease the risk of nephrotoxic injury.

Calcineurin Antagonists. Calcineurin antagonists (cyclosporine A, tacrolimus) are T-cell inhibitors, and together with steroids and purine antagonists form the mainstay of current trimodal immunosuppressive regimens. These agents induce sympathetic hyperreactivity, hypertension, and renal vasoconstriction. Their effects are exacerbated by preexisting renal dysfunction, hypovolemia, and other nephrotoxic insults. Many transplant patients must tolerate a moderately elevated serum creatinine (1.5–2 mg/dL) to sustain adequate immunosuppression.

There is some evidence that calcium channel blockers provide nephroprotection against calcineurin antagonists. In patients undergoing cadaveric renal transplantation, perioperative diltiazem decreased the incidence of graft ATN and the need for postoperative hemodialysis (19). Diltiazem impairs cyclosporine metabolism so that plasma cyclosporine levels are higher but with less nephrotoxicity and fewer episodes of early acute rejection (20).

Radiocontrast Dyes. Hyperosmolar radiocontrast agents induce osmotic diuresis that exacerbates hypovolemia, red cell crenation that obstructs the microcirculation, and free oxygen radical release that results in direct tubular toxicity. The risk of contrast nephropathy is markedly increased in diabetic renal insufficiency, hypovolemia, congestive heart failure, and myeloma (21). Azotemia commences 24 to 48 h after exposure and peaks at 3 to 5 days.

Prevention of nephrotoxicity depends on adequate hydration and deferral of elective surgical procedures until the effects of the dye have been evaluated and treated (22). Nonionic, low-osmolar radiocontrast agents are less nephrotoxic but are expensive and offer optimal cost-benefit ratio only when used in high-risk situations, e.g., diabetic nephropathy (17).

A Clinical Approach to Oliguria

General Principles

An algorithmic approach to oliguria is shown in Figure 1.

1. Assume that Oliguria is Prerenal. Oliguria should be assumed to be attributable to intravascular hypovolemia until otherwise proven (23). The finding of a prerenal pattern on urine analysis (Table 4) supports this assumption. If clinical assessment does not suggest fluid overload, it is reasonable to first administer serial fluid challenges guided by vital signs (1). Diuretic therapy should be deferred unless there are unequivocal signs of fluid overload, oliguria persists despite fluid challenges and restoration of stable hemodynamics, or there is evidence of pigment nephropathy.

2. Evaluate and Treat Intravascular Volume. In difficult cases appropriate hemodynamic and urinary monitoring is essential to properly identify and treat intravascular hypovolemia and oliguria. Central venous pressure and intra-arterial monitoring is indicated when large fluid shifts are anticipated. Pulmonary artery catheterization should be considered with preexisting renal dysfunction, sepsis, severe pulmonary disease, or congestive heart failure.

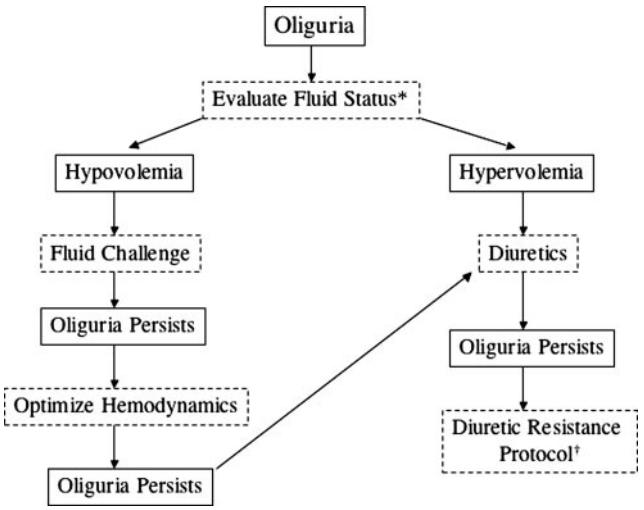

Figure 1. An algorithmic approach to the evaluation and management of oliguria. Complete boxes = observation, dashed boxes = appropriate action. Used with permission of the publisher, Elsevier, from Sladen RN. Oliguria in the ICU: systematic approach to diagnosis and treatment. Anesthesiol Clin North America 2000;18:743 (Fig. 1).

Table 4. Evaluation of Oliguria

	Prerenal	ATN
U:P osmolality	>1.4:1	1:1
U:P creatinine	>50:1	<20:1
Urine Na (mEq/L)	<20	>80
FENa (%)	<1	>3
C_{CR} (mL/min)	15–20	<10

U:P = urine: plasma; Na = sodium; FENa = fractional excretion of sodium; ATN = acute tubular necrosis; C_{CR} = creatinine clearance.

3. Maximize Renal Blood Flow. Standard hemodynamic management to optimize cardiac function includes normalization of cardiac rhythm and rate, maintenance of adequate preload, judicious use of inotropic support (including dopamine if appropriate), and afterload reduction with vasodilator or inodilator agents.

This is particularly important in ensuring renal recovery after ischemic or nephrotoxic insults. Premature withdrawal of inotropic support such as milrinone or dobutamine in patients with hemodynamically mediated renal dysfunction may result in return of oliguria and renal deterioration.

4. Maintain Renal Perfusion Pressure. It is essential to maintain renal perfusion pressure in situations where autoregulation is attenuated or absent—notably, sepsis and acute renal failure itself. Vasopressor

therapy with norepinephrine is not only important to maintain adequate blood pressure but can also dramatically improve renal function when oliguria occurs in the setting of vasodilated hypotension (24). Arginine vasopressin (1–6 U/h) has even greater potential benefit because it preferentially constricts the efferent arteriole (25), thereby maintaining glomerular filtration pressure in the face of decreased arterial pressure.

5. Diuretic Therapy.

a. *Therapeutic*. In general, diuretic therapy should be reserved for oliguria that persists despite optimization of intravascular volume, hemodynamic status, and renal perfusion pressure (1). Administration of diuretic agents to "make urine" in the face of intravascular hypovolemia or hypotension will either be unsuccessful or will result in a short-lived diuresis that simply exacerbates volume depletion and increases the risk of renal injury.

b. *Prophylactic*. Diuretic agents may confer benefits on renal function in a number of ways. These include renal cortical vasodilation (dopaminergic agents, loop diuretics), prevention of tubular obstruction (osmotic, loop diuretics), suppression of reflex vasoconstrictive responses (dopaminergic agents, ANP), and decreased tubular oxygen consumption (dopaminergic agents, loop diuretics). By inhibiting the active sodium pump in the medullary thick ascending loop of Henle (mTAL), diuretics could theoretically enhance renal tubular oxygen balance, thereby conferring protection against ischemic or nephrotoxic injury (26). However, experimental data suggest that renal tubule oxygen delivery and consumption differ markedly from systemic indices (27).

Prophylactic diuretic therapy is commonly used in situations of intraoperative renal risk such as aortic cross-clamping, cardiopulmonary bypass, and transplantation. In pigment nephropathy (rhabdomyolysis, intravascular hemolysis, jaundice) there is abundant anecdotal evidence of the benefit of prophylactic diuresis combined with volume loading (28). However, there are few if any controlled prospective data that demonstrate a positive impact on renal outcome or that diuretic therapy is more effective in maintaining GFR than aggressive volume loading alone (29–31).

Diuretic Resistance

Types of Diuretic Resistance.

a. *Acute Tolerance*. Also known as the "braking phenomenon", this manifests as tachyphylaxis, i.e., a decreased saluretic response with repeated doses of diuretic agent. It is probably a result of extracellular fluid contraction induced by diuresis because it can easily be counteracted by fluid repletion (32). The mechanism appears to be activation of sodium retention via the sympathoadrenal and renin-angiotensin-aldosterone systems (33). However, acute tolerance can be induced *ab initio* by intravascular hypovolemia. Fluid-restricted surgical patients are resistant to the natriuretic effects of low-dose dopamine because activation of tubular sodium reabsorption overcomes its diuretic effect (34). Caveat: in oliguria, low dose dopamine is not a substitute for rehydration!

b. *Chronic Tolerance*. This describes the gradual tachyphylaxis encountered with long-term administration of loop diuretics. It is attributable to compensatory hypertrophy of the distal tubule because mTAL blockade allows increased concentrations of sodium to reach this segment (35). Concomitant administration of thiazide diuretics, which block sodium reabsorption at the distal tubule, restores diuresis.

c. *Refractory Disease States*. Generalized edema refractory to diuretic therapy is encountered in acute and chronic renal insufficiency, congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. Resistance occurs because of altered diuretic pharmacokinetics through decreased diuretic or sodium delivery to the luminal border of the mTAL or altered pharmacodynamics, i.e., decreased natriuretic response to a given concentration of drug in the urine. In uremia, endogenous organic acids compete with loop diuretics for active transport sites at the proximal tubule and less diuretic reaches the mTAL (32). Renal clearance of furosemide is inversely proportional to the BUN and GFR (36). In cirrhosis, congestive heart failure and nephrotic syndrome, the depleted intravascular volume markedly increases sodium reabsorption at the proximal tubule, restricting the sodium available for diuretic action at the mTAL (37). In liver failure diuretic action at the mTAL site is impaired.

Strategies for Overcoming Diuretic Resistance.

1. *Restore normal hemodynamics*. Hypovolemia or hypotension induce proximal tubule sodium reabsorption and decrease the filtered load of sodium and tubular diuretic delivery. The diuretic response will be predictably improved by normalizing preload and by judicious use of inotropic agents (e.g., dopamine, dobutamine, milrinone) (32,35).

2. *Administer higher doses of diuretic agent*. The quantity of diuretic agent reaching the mTAL is decreased in CHF and renal insufficiency. When GFR is very low, only 20% of a dose of furosemide and 10% of bumetanide reaches the urine (32). Doses should be increased accordingly (i.e., furosemide from 20 mg to 100 mg, bumetanide from 0.5 mg to 5 mg).

3. *Concomitant administration of human albumin*. Loop diuretics are highly protein bound. In hypoalbuminemic patients, administration of human albumin to markedly increases the diuretic efficacy of furosemide (38).

4. *Continuous diuretic infusion*. Continuous furosemide infusion achieves effective diuresis in patients with CHF at blood concentrations considerably lower than those of bolus doses (39–41). After a small loading dose (10–20 mg), an infusion of 2.5–10 mg/h is administered.

The pharmacodynamic explanation is that the duration of delivery of diuretic into the urine is the critical determinant of diuretic response. In comparison with bolus doses, continuous infusion provides a more consistent and sustained diuresis, avoids high peak doses that induce toxic side effects, decreases the potential for rebound sodium retention, and facilitates titration to effect (35,42). However, there is also the risk of excessive diuresis with its attendant consequences of hypovolemia, hypokalemia, hypomagnesemia, and supraventricular arrhythmias (43).

5. *Segmental nephron blockade*. The combination of low doses of a loop diuretic and a thiazide is more effective than high doses of either agent used alone (37). As described earlier, inhibition of sodium absorption at both the mTAL and at the distal tubule effectively blocks two segments of the nephron and induces a synergistic diuretic response.

In the ICU we commonly administer metolazone (2.5 to 5.0 mg PO), a thiazide-like diuretic, together with IV furosemide (20–40 mg) or bumetanide (2.5–5 mg). Gastrointestinal absorption of metolazone is unpredictable; it is usually given at least 30–60 min before the loop diuretic and may take 12–48 h for full effect (35). A large (and possibly excessive) diuresis can be generated even in states of very low GFR, and almost all metolazone is excreted unchanged by the kidney; it accumulates in renal insufficiency.

Pharmacologic Interventions to Prevent and Reverse ARF

Mannitol

Mannitol is an "inert" sugar that has been used for many years as a renal protective agent. Once administered it is not metabolized but expands the intravascular volume and induces an osmotic diuresis. Renal protection occurs via several mechanisms, including a direct hemodynamic effect (increased preload and cardiac output), release of ANP and intrarenal prostaglandins, prevention of tubular obstruction, and attenuation of reperfusion injury (scavenging of free radicals, prevention of postischemic cell swelling and the "no-flow" phenomenon). For the greatest effect it should be present at the time of the renal insult (44).

In high-risk situations, mannitol (6.25–12.5 g) is given 15 min before a defined insult (e.g., aortic cross-clamping) and repeated if necessary every 4–6 h. Alternatively, 10% mannitol can be continuously infused at 50 mL/h. Rapid volume expansion can precipitate pulmonary edema and, to avoid a hyperosmolar syndrome (serum osmolality >320 mOs/kg), the 24-h cumulative dose should be limited to 1.5 g/kg.

The routine inclusion of mannitol in the pump prime during cardiopulmonary bypass does not prevent tubular enzymuria (an indicator of subclinical renal injury) (45), but acute renal failure in normal patients after uncomplicated cardiac surgery occurs in <2% of cases. The true role of mannitol-induced renal protection is unknown. Mannitol (or dopamine) does not prevent a decline in GFR and tubular injury after suprarenal aortic cross clamping (46,47). Although a considerable diuresis is induced during infrarenal cross-clamping, it is no more effective than volume loading in attenuating the decline in GFR (29). In the treatment of pigment nephropathy, mannitol confers protection by "washing out" the tubule but must be accompanied by volume loading to avoid dehydration that could exacerbate nephrotoxic injury.

Loop Diuretics

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) are potent inhibitors of sodium reabsorption at the mTAL and can induce diuresis even with marked renal impairment. If administered before a renal ischemic or nephrotoxic insult, furosemide attenuates renal injury (48), probably through the mechanisms described above. However, in clinical practice loop diuretics are usually given *post hoc*; they must be given within 18 h for any protective effect to be obtained.

The practice of administering high-dose (2–10 mg/kg) furosemide IV to "convert" oliguric to non-oliguric acute renal failure is based on a single study that claimed a reduction in mortality from 50% to 26% but that specifically excluded patients with shock or perioperative acute renal failure (49). In dialyzed patients high-dose furosemide does not alter morbidity or mortality and may cause permanent ototoxicity (50,51). Low-dose furosemide is a useful adjunct to hydration and mannitol in pigment nephropathy.

Loop diuretics may induce acute hypotension as a result of systemic venodilation at high doses, and excessive diuresis my result in hypovolemia (and renal injury), sodium and potassium wasting, and metabolic alkalosis. The potential for ototoxicity should limit individual doses of furosemide to ≤250 mg, especially with aminoglycoside antibiotics.

Dopaminergic Agonists

Dopamine receptors are classified into DA_1 and DA_2 subtypes. Stimulation of DA_1 receptors causes renal vasodilation and inhibition of active sodium transport in the proximal tubule, leading to natriuresis and diuresis (52). Stimulation of presynaptic DA_2 receptors inhibits norepinephrine release and promotes peripheral vasodilation but appears to attenuate the beneficial effects of DA_1 effectors on renal blood flow. Dopamine is a nonselective DA_1 and DA_2 agonist; this

may explain why its effect on renal blood flow is less potent than that of fenoldopam, a selective DA_1 agonist. Dopexamine is an investigative nonselective dopaminergic agonist with about one third the effect of dopamine. It is a potent β_2-adrenoceptor agonist that shows promise in the treatment of congestive heart failure. Haloperidol, chlorpromazine and metoclopramide are nonselective dopaminergic antagonists.

Dopamine

Despite the lack of definitive evidence (53), "low-dose" dopamine (0.5–3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) has been widely used as a renal protective agent. However, plasma dopamine levels vary markedly (up to 10-fold) in different individuals (54), and it is likely that in many cases dopamine benefits the kidney by its β-adrenergic actions (increased cardiac output, renal blood flow, and perfusion pressure) (55,56).

Dopamine has been demonstrated to increase the renal clearance of aminoglycosides, reverse low renal blood flow caused by oral cyclosporine A, and prevent renal injury induced by recombinant interleukin-2 therapy (52). However, in many other situations, including cardiopulmonary bypass, aortic cross-clamping, and liver and renal transplantation, there are no data that demonstrate a positive impact on renal outcome (57–59). There is some evidence that low-dose dopamine can increase renal blood flow when administered simultaneously with norepinephrine (60) and increase GFR in compensated sepsis, but it does not appear to be effective in septic shock (61), and a large-scale prospective study in septic patients demonstrated no benefit of prophylactic dopamine on dialysis requirement or outcome (62).

Although there is no justification for its prophylactic use, dopamine remains a useful inotropic agent and may enhance renal function by increasing cardiac output and renal perfusion pressure (56). It has a reliable and reproducible diuretic effect in critically ill patients, as long as they are well hydrated (63,64). The addition of low-dose dopamine to furosemide therapy is often successful in reversing unresponsive oliguria, although most reports are anecdotal in nature (65). Like furosemide, dopamine must be administered within 24 h of the onset of oliguria to achieve benefit. Low-dose dopamine can increase urine flow in chronic renal insufficiency (66), but its effect on GFR is negligible when baseline GFR is $\leq$50 mL/min/1.73M (2).

The use of low-dose dopamine may be limited by tachycardia and supraventricular and ventricular arrhythmias (67), which likely represents the achievement of β-adrenergic plasma levels in individuals with slower hepatic dopamine clearance.

Fenoldopam

Fenoldopam is a dopamine analog in which a phenol group is attached to the basic dopamine structure (68). It is the first selective DA_1-receptor agonist (69). IV it has a relatively rapid onset and offset, with an elimination half-life of 10 min. At infusion rates of 0.03–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (i.e., a potency 10–100 times that of dopamine), it induces dose-dependent increases in renal blood flow.

Initial clinical studies showed it to be as effective as sodium nitroprusside for control of accelerated hypertension (70) but with dramatically increased urine flow, sodium excretion, and creatinine clearance (71). In 1998 fenoldopam was approved in the United States for the short-term parenteral treatment of hypertension, but because of high acquisition cost it has not gained widespread acceptance in this role.

As a consequence, interest developed in the use of low-dose (<0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$) fenoldopam infusion as a renal protective agent and diuretic. In this dose range it seldom induces a decrease in blood pressure. Potential advantages over dopamine include increased dopaminergic potency, lack of tachycardia or tachyarrhythmias, and the ability to safely infuse via a peripheral IV catheter (72). Although there is some evidence that it may attenuate cyclosporine A-induced vasoconstriction and nephrotoxicity (73), its initial promise of renal protection during cardiopulmonary bypass (74) has never been confirmed. Similarly, preliminary data suggestive of a renoprotective effect in contrast nephropathy (75) have not been confirmed by a large randomized controlled study (76).

N-Acetylcysteine

N-Acetylcysteine has long been used as an aerosolized mucolytic agent and, because of its antioxidant properties, as an antidote to acetaminophen toxicity. A landmark study demonstrated that prophylactic oral administration n-acetylcysteine (600 mg twice daily) markedly attenuated renal injury in high-risk patients undergoing contrast radiography (77). However, in a subsequent study, n-acetylcysteine provided better protection than saline alone only when a low dose of contrast dye was used (78). In another randomized prospective study, the authors concluded that neither n-acetylcysteine nor fenoldopam offered any benefit over saline (79). One must conclude that the evidence of benefit of n-acetylcysteine in prevention of radiocontrast nephropathy is at the very least equivocal, and there is as yet no evidence whatsoever to support its prophylactic use in other types of renal injury.

Natriuretic Peptides

The natriuretic peptides are formed by the endogenous synthesis of chains of 22–32 amino acids of similar structure. They specifically oppose the sympathoadrenal, renin-angiotensin, aldosterone, and arginine vasopressin systems via multiple mechanisms (12). They thereby counteract the vasoconstrictor and anti-natriuretic responses induced by hypovolemia and induce vasodilation and natriuresis that protect against hypervolemia and hypertension. The vasodilator and renal effects of the natriuretic peptides are mediated by cyclic guanosine monophosphate (cGMP), which increases glomerular filtration fraction by afferent arteriolar vasodilation. They are rapidly inactivated by natriuretic peptide C-type receptors and cellular neutral endopeptidases.

Atrial (A-type) natriuretic peptide (ANP) is synthesized by modified atrial myocytes and released by atrial stretch; plasma ANP increases *pari passu* with central venous pressure (13). Brain (B-type) natriuretic peptide (BNP) is synthesized in the right and left ventricles and is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) has become established as an emergency room diagnostic tool for acute cardiac failure, and BNP levels correlate with outcome in acute myocardial ischemia as well as heart failure. C-type natriuretic peptide (CNP) is synthesized in the endothelium of the great vessels. Urodilatin, a 22-amino acid peptide, is synthesized in the kidney and appears to have less vasodilator activity than ANP.

Anaritide. Anaritide is the human recombinant formulation of ANP. IV administration decreases systemic blood pressure by arterial and venodilation, increases GFR, induces natriuresis, and reverses renovascular hypertension.

In animal models of ischemic (80) or nephrotoxic (81) acute renal failure, anaritide demonstrated great promise as a rescue agent, reversing established ATN. A preliminary human study (82) was equally promising, but a subsequent large, 504-patient randomized multicenter study had equivocal results (3). After a 24-h infusion of anaritide, patients with oliguric ATN (urine output $<$400 mL/day) had significantly improved dialysis-free survival but outcome was actually worse in patients with non-oliguric acute renal failure. The disparity in these results may be attributed to the hypotensive effect of ANP, which was greater in the non-oliguric patients and may have injured intact or partially damaged nephrons. Finally, a randomized prospective study that focused on 222 patients with oliguric acute renal failure only found no difference in renal outcome between anaritide and placebo (83). The only difference was that patients receiving anaritide were significantly more hypotensive. These data appear to emphasize the importance of maintenance of renal perfusion pressure in acute renal failure because renal autoregulation is impaired (84).

Nesiritide. Nesiritide is the human recombinant formulation of BNP, and has been approved by the FDA for the parenteral treatment of patients with decompensated heart failure. In these patients it provides preload and afterload reduction, enhances cardiac function, and also can promote a sustained diuresis with improvement in pulmonary congestion, edema, and anasarca (85). The major adverse effect is dose-related hypotension, which can impair renal function (86).

There is as yet no evidence for a protective role for nesiritide in acute renal injury, but there is considerable current interest in its role in hemodynamic function and renal protection in high-risk patients undergoing cardiac surgery.

Vasoconstrictor Therapy and Dysautoregulation

Renal autoregulation maintains renal blood flow and GFR over a wide range of renal arterial pressures. In certain situations, notably ATN itself (84), severe sepsis (24), and possibly during cardiopulmonary bypass (87), autoregulation appears to be lost or attenuated. Hypotension results in strikingly decreased renal blood flow, which is restored by normalization of renal perfusion pressure—even if this is achieved by vasoconstrictor therapy.

Acute Renal Failure. During the Vietnam conflict, Conger noted that soldiers who died while on hemodialysis had postmortem evidence of acute ATN up to 3 wk after the initial renal injury (Conger, J., personal communication). He subsequently found that in acute renal failure there is an almost complete loss of renal autoregulation (84) and concluded that hypotension during intermittent hemodialysis represents a repetitive ischemic insult to the kidney that is likely to delay or even prevent renal recovery from ATN. His group also demonstrated that in ischemic ATN, the renal vasculature develops a smooth muscle injury that renders it relatively unresponsive to the vasoconstrictor effect of norepinephrine (88).

This evidence strongly suggests that during intermittent hemodialysis, blood pressure should be supported with appropriate fluid administration or even pressor therapy because of the loss of autoregulation. It also provides a theoretic argument for aggressive hemodynamic management (e.g., inotropic therapy) and the use of continuous venovenous hemodialysis in hemodynamically unstable patients in ARF so as to minimize further insults to the kidney and increase the likelihood of renal recovery.

Vasodilated Shock. Renal dysfunction is a consistent component of sepsis and septic shock and is multifactorial in nature. A primary insult is intravascular hypovolemia and hypotension and the systemic vasoconstrictor responses these evoke. However, even aggressive fluid therapy may not reverse oliguria because of coexistent vasomotor nephropathy. This is characterized by intense renal vasoconstriction and a prerenal state with oliguria and very low urinary sodium excretion that correlates with the severity of sepsis and plasma renin activity (89). Afferent arteriolar constriction, mesangial contraction, and direct nephrotoxic injury are all induced by endotoxin itself as well as by various vasoactive compounds activated by it, including endothelin, thromboxane A_2, prostaglandin F_2, and leukotrienes (90).

In addition, loss of autoregulation in severe sepsis is implicated by the dramatic improvement in renal function that may be observed when blood pressure is normalized by the use of vasopressor therapy in patients with septic shock, profound hypotension, and oliguria.

Norepinephrine. The beneficial effects of norepinephrine on renal function in vasodilated shock were demonstrated in hypotensive septic patients who remained oliguric despite high-dose dopamine (24). An infusion of norepinephrine that increased mean arterial pressure from 50 to 70 mm Hg tripled urine flow rate and doubled the creatinine clearance. In this situation norepinephrine appears to increase the SVR with little change in cardiac index or Do_2 (91).

Arginine Vasopressin. Landry et al. (92) observed that in patients with vasodilated shock with profound hypotension despite catecholamine infusion, there is remarkable sensitivity to the vasoconstrictor effects of infused arginine vasopressin (AVP). With AVP infusion rates as low as 2.4 U/h, systolic blood pressure increased dramatically, catecholamine infusions could be tapered or discontinued, and urine flow rate tripled in some patients (93).

In septic shock plasma AVP concentrations are remarkably low, approximately 3 pg/mL, compared with concentrations in patients in acute cardiogenic shock (approximately 20 pg/mL). This is attributable to sustained baroreceptor-mediated AVP release during the initial hypotensive stages of sepsis, with subsequent AVP depletion of posterior pituitary stores (94). Infusion of low-dose AVP restores plasma levels to those (30–100 pg/mL) that stimulate V_1 receptors in smooth muscle to enhance hypotension-induced vasoconstriction.

There is clinical evidence that AVP infusion improves renal function in patients in vasodilatory shock (95). In addition to restoring renal perfusion pressure in the face of abnormal autoregulation, AVP preferentially constricts the efferent arteriole, thereby improving glomerular filtration pressure, filtration fraction, and GFR (96). It appears prudent to infuse low-dose AVP (1–6 U/h) whenever sepsis is associated with hypotension and oliguria despite a high cardiac index and an increasing dose of norepinephrine. It may also be useful in other forms of vasodilatory shock, such as that seen with high-dose milrinone for severe ventricular failure and in the systemic inflammatory response syndrome after placement of a left ventricular assist device (97).

References

1. Dishart MK, Kellum JA. An evaluation of pharmacological strategies for the prevention and treatment of acute renal failure. Drugs 2000;59:79–91.
2. Alpert RA, Roizen MF, Hamilton WK, et al. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery 1984;95:707.
3. Allgren RL, Marbury TC, Rahman SN, et al. Anaritide in acute tubular necrosis. N Engl J Med 1997;336:828–34.
4. Arendshorst WJ, Finn WF, Gottschalk CW. Pathogenesis of acute renal failure following temporary renal ischemia in the rat. Circ Res 1975;37:558.
5. Wilkes BM, Mailloux LU. Acute renal failure: pathogenesis and prevention. Am J Med 1986;80:1129–36.
6. Myers B, Chui F, Hilberman M, Michaels A. Transtubular leakage of glomerular filtrate in human acute renal failure. Am J Physiol 1979;237:F319–25.
7. Myers BD, Moran SM. Hemodynamically mediated acute renal failure. N Engl J Med 1986;314:97–105.
8. Butkus DE. Post traumatic acute renal failure in combat casualties: a historical review. Milit Med 1984;149:117–24.
9. Guly UM, Turney JH. Post-traumatic acute renal failure, 1956–1988. Clin Nephrol 1990;34:79–83.
10. Shin B, MacKenzie CF, McAslan TC, et al. Postoperative renal failure in trauma patients. Anesthesiology 1979;51:218–221.
11. Gorfinkel HJ, Szidon JP, Hirsch LJ, et al. Renal performance in experimental cardiogenic shock. Am J Physiol 1972;222:1260–8.
12. Laragh J. Atrial natriuretic hormone, the renin-angiotensin axis, and blood-pressure electrolyte homeostasis. N Engl J Med 1985; 313:1330–40.
13. Maack T, Camargo MJF, Kleinert HD, et al. Atrial natriuretic factor: structure and functional properties. Kidney Int 1985;27: 607–15.
14. Brezis M, Rosen S. Hypoxia of the renal medulla: its implications for disease. N Engl J Med 1995;332:647–55.
15. Wardle N. Acute renal failure in the 1980s: the importance of septic shock and of endotoxemia. Nephron 1982;30:193–200.
16. Zager RA. Endotoxemia, renal hypoperfusion, and fever: interactive risk factors for aminoglycoside and sepsis-associated acute renal failure. Am J Kidney Dis 1992;20:223–30.
17. Wetzels JF, Burke TJ, Schrier RW. Prevention and attenuation of acute renal failure. Curr Opin Nephrol Hypertens 1992;1:133–40.
18. Clive D, Stoff J. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1984;310:563–72.
19. Kunzendorf U, Walz G, Brockmoeller J, et al. Effects of diltiazem upon metabolism and immunosuppressive action of cyclosporine in kidney graft recipients. Transplantation 1991;52:280–4.
20. Neumayer HH, Kunzendorf U, Schreiber M. Protective effects of calcium antagonists in human renal transplantation. Kidney Int 1992;Suppl 36:87–93.
21. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency or both: a prospective, controlled study. N Engl J Med 1989;320:143.
22. Eisenberg RL, Bank WO, Hedgecock MW. Renal failure after major angiography can be avoided with hydration. Am J Radiol 1981;136:859.

23. Sladen RN: Perioperative renal protection. In: Murray MJ, Coursin DB, Pearl RG, Prough DS, eds. Critical care medicine: perioperative management. New York: Raven Press, 1996:551–64.
24. Desjars PH, Pinaud M, Bugnon D, et al. Norepinephrine has no deleterious renal effects in human septic shock. Crit Care Med 1989;17:426–9.
25. Edwards RM, Trizna W, Kinter LB. Renal microvascular effects of vasopressin and vasopressin antagonists. Am J Physiol 1989; 256:F274–8.
26. Brezis M, Rosen S, Epstein F. The pathophysiologic implications of medullary hypoxia. Am J Kidney Dis 1989;13:253–8.
27. Haywood GA, Tighe D, Moss R, et al. Goal directed therapy with dobutamine in a porcine model of septic shock: effects on systemic and renal oxygen transport. Postgrad Med J 1991; 67(S1):S36.
28. Ron D, Taitelman U, Michaelson M, et al. Prevention of acute renal failure in traumatic rhabdomyolysis. Arch Intern Med 1984;144:277.
29. Paul MD, Mazer CD, Byrick RJ, et al. Influence of mannitol and dopamine on renal function during elective infrarenal aortic cross-clamping in man. Am J Nephrol 1986;6:427–34.
30. Parks RW, Diamond T, McCrory DC, et al. Prospective study of postoperative renal function in obstructive jaundice and the effect of perioperative dopamine. Br J Surg 1994;81:437–9.
31. Plusa SM, Clark NW. Prevention of postoperative renal dysfunction in patients with obstructive jaundice: a comparison of mannitol-induced diuresis and oral sodium taurocholate. J Roy Coll Surg Edin 1991;36:303–5.
32. Brater DC. Diuretic resistance: mechanisms and therapeutic strategies. Cardiology 1994;84(suppl 2):57–67.
33. Sjostrom PA, Odlind BG, Beermann BA, Hammarlund Udenaes M. On the mechanism of acute tolerance to furosemide diuresis. Scand J Urol Nephrol 1988;22:133–40.
34. Bryan AG, Bolsin SN, Vianna PTG, Haloush H. Modification of the diuretic and natriuretic effects of a dopamine infusion by fluid loading in preoperative cardiac surgical patients. J Cardiothorac Vasc Anesth 1995;9:158–63.
35. Sica DA, Gehr TW. Diuretic combinations in refractory oedema states: pharmacokinetic-pharmacodynamic relationships. Clin Pharmacokinet 1996;30:229–49.
36. Rose HJ, O'Malley K, Pruitt AW. Depression of renal clearance of furosemide in man by azotemia. Clin Pharmacol Ther 1976; 21:141–6.
37. Knauf H, Mutschler E. Functional state of the nephron and diuretic dose-response: rationale for low-dose combination therapy. Cardiology 1994;84(suppl 2):18–26.
38. Inoue M, Okajima K, Itoh K, et al. Mechanism of furosemide resistance in analbuminemic rats and hypoalbuminemic patients. Kidney Int 1987;32:198–203.
39. Copeland JG, Campbell DW, Plachetka JR, et al. Diuresis with continuous infusion of furosemide after cardiac surgery. Am J Surg 1983;146:796–9.
40. Lawson DH, Gray JMB, Henry DA, Tilstone WJ. Continuous infusion of frusemide in refractory oedema. BMJ 1978;2:476.
41. van Meyel JJ, Smits P, Russel FG, et al. Diuretic efficiency of furosemide during continuous administration versus bolus injection in healthy volunteers. Clin Pharmacol Ther 1992;51: 440–4.
42. Rudy DW, Voelker JR, Greene PK, et al. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. Ann Intern Med 1991;115:360–6.
43. Wilson NJ, Adderley RJ, McEniery JA. Supraventricular tachycardia associated with continuous furosemide infusion. Can J Anaesth 1991;38:502–5.
44. Behnia R, Koushanpour E, Brunner EA. Effects of hyperosmotic mannitol infusion on hemodynamics of dog kidney. Anesth Analg 1996;82:902.
45. Ip-Yam PC, Murphy S, Baines M, et al. Renal function and proteinuria after cardiopulmonary bypass: the effects of temperature and mannitol. Anesth Analg 1994;78:842–7.
46. Pass L, Eberhart R, Brown J, et al. The effect of mannitol and dopamine on the renal response to thoracic aortic cross-clamping. J Thorac Cardiovasc Surg 1988;95:608–12.
47. Myers BD, Miller DC, Mehigan JT, et al. Nature of the renal injury following total renal ischemia in man. J Clin Invest 1984; 73:329–41.
48. Brezis M, Rosen S, Silva P, et al. Transport activity modifies thick ascending limb damage in the isolated perfused kidney. Kidney Int 1984;25:65.
49. Anderson R, Linas S, Berns A, et al. Nonoliguric acute renal failure. N Engl J Med 1977;296:1134–7.
50. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, et al. Furosemide in acute oliguric renal failure: a controlled trial. Nephron 1976;17:51.
51. Brown C, Ogg C, Cameron J. High dose furosemide in acute renal failure: a controlled trial. Clin Nephrol 1981;15:90–6.
52. Lokhandwala MF, Amenta F. Anatomical distribution and function of dopamine receptors in the kidney. FASEB J 1991;5: 3023–30.
53. Burton CJ, Tomson CR. Can the use of low-dose dopamine for treatment of acute renal failure be justified? Postgrad Med J 1999;75:269–74.
54. MacGregor DA, Smith TE, Prielipp RC, et al. Pharmacokinetics of dopamine in healthy male subjects. Anesthesiology 2000;92: 338–46.
55. Bailey JM. Dopamine: one size does not fit all. Anesthesiology 2000;92:303–5.
56. Davis RF, Lappas DG, Kirklin JK, et al. Acute oliguria after cardiopulmonary bypass: renal functional improvement with low-dose dopamine infusion. Crit Care Med 1982;10:852–6.
57. Costa P, Ottino GM, Matani A, et al. Low-dose dopamine during cardiopulmonary bypass in patients with renal dysfunction. J Cardiothoracic Anesth 1990;4:469–73.
58. Swygert TH, Roberts LC, Valek TR, et al. Effect of intraoperative low-dose dopamine on renal function in liver transplant recipients. Anesthesiology 1991;75:571–6.
59. De los Angeles A, Bacquero A, Bannett A, Raja R. Dopamine and furosemide infusion for prevention of post transplant oliguric renal failure. Kidney Int 1985;27:339–44.
60. Schaer GL, Fink MP, Parrillo JE. Norepinephrine alone versus norepinephrine plus low-dose dopamine: enhanced renal blood flow with combination pressor therapy. Crit Care Med 1985;13: 492–6.
61. Lherm T, Troche G, Rossignol M, et al. Renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines. Intensive Care Med 1996;22:213–9.
62. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139–43.
63. Duke GJ, Briedes JH, Weaver RA. Renal support in critically ill patients: low-dose dopamine or low-dose dobutamine? Crit Care Med 1994;22:1919–25.
64. Flancbaum L, Choban PS, Dasta JF. Quantitative effects of low-dose dopamine on urine output in oliguric surgical intensive care unit patients. Crit Care Med 1994;22:61–8.
65. Schwartz LB, Gewertz GL. The renal response to low-dose dopamine. J Surg Res 1988;45:574–88.
66. Ter Wee PM, Smit AJ, Rosman JB, et al. Effect of intravenous infusion of low-dose dopamine on renal function in normal individuals and in patients with renal disease. Am J Nephrol 1986;6:42–6.
67. Chiolero R, Borgeta A, Fisher A. Postoperative arrhythmias and risk factors after open heart surgery. Thorac Cardiovasc Surg 1991;39:81–4.
68. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. Drugs 1997;54:634–50.

69. Murphy MB, McCoy CE, Weber RR, et al. Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine-1 agonist fenoldopam. Circulation 1987;76:1312–8.
70. Oparil S, Aronson S, Deeb GM, Epstein M, et al. Fenoldopam: a new parenteral antihypertensive: consensus roundtable on the management of perioperative hypertension and hypertensive crises. Am J Hypertens 1999;12:653–64.
71. Panacek EA, Bednarczyk EM, Dunbar LM, et al. Randomized, prospective trial of fenoldopam vs sodium nitroprusside in the treatment of acute severe hypertension. Fenoldopam Study Group. Acta Emergency Medicina 1995;2:959–65.
72. Singer I, Epstein M. Potential of dopamine A-1 agonists in the management of acute renal failure. Am J Kidney Dis 1998;31: 743–55.
73. Brooks DP, DePalma PD, Cyronak MJ, et al. Pharmacology of SK&F R-105058 and R-106114, N-ethyl carbamate ester prodrugs of fenoldopam. Pharmacology 1990;41:299–308.
74. Garwood S, Davis E, Hines RL. Fenoldopam: an effective renal preservation agent in cardiac surgery? Anesthesiology 1999;91: A154.
75. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J 2002;143:894–903.
76. Stone GW, McCullough PA, Tumlin JA, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA 2003;290:2284–91.
77. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343:180–4.
78. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. J Am Coll Cardiol 2002;40:298–303.
79. Allaqaband S, Tumuluri R, Malik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheter Cardiovasc Interv 2002;57:279–83.
80. Atanasova I, Girchev R, Dimitrov D, et al. Atrial natriuretic peptide and dopamine in a dog model of acute renal ischemia. Acta Physiol Hung 1994;82:75–85.
81. Seki G, Suzuki K, Nonaka T, et al. Effects of atrial natriuretic peptide on glycerol induced acute renal failure in the rat. Japan Heart J 1992;33:383–93.
82. Rahman SN, Kim GE, Mathew AS, et al. Effects of atrial natriuretic peptide in clinical acute renal failure. Kidney Int 1994;45:1731–8.
83. Lewis J, Salem MM, Chertow GM, et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am J Kidney Dis 2000;36:767–74.
84. Kelleher SP, Robinette JB, Miller F, Conger JD. Effect of hemorrhagic reduction in blood pressure on recovery from acute renal failure. Kidney Int 1987;31:725–30.
85. Mills RM, LeJemtel TH, Horton DP, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. J Am Coll Cardiol 1999;34:155–62.
86. Colucci WS. Nesiritide for the treatment of decompensated heart failure. J Card Fail 2001;7:92–100.
87. Mackay JH, Feerick AE, Woodson LC, et al. Increasing organ blood flow during cardiopulmonary bypass in pigs: comparison of dopamine and perfusion pressure. Crit Care Med 1995;23: 1090–8.
88. Conger JD, Hammond WS. Renal vasculature and ischemic injury. Ren Fail 1992;14:307–10.
89. Cumming AD, Driedger AA, McDonald JW, et al. Vasoactive hormones in the renal response to systemic sepsis. Am J Kidney Dis 1988;11:23–32.
90. Badr KF. Sepsis-associated renal vasoconstriction: potential targets for future therapy. Am J Kidney Dis 1992;20:207–13.
91. Hesselvik JF, Brodin B. Low-dose norepinephrine in patients with septic shock and oliguria: effects on afterload, urine flow and oxygen transport. Crit Care Med 1989;17:179–180.
92. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med 1997;25: 1279–82.
93. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95:1122–5.
94. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588–95.
95. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002;96:576–82.
96. Edwards RM, Rizna W, Kinter LB. Renal microvascular effects of vasopressin and vasopressin antagonist. Am J Physiol 1989; 256:F526–34.
97. Argenziano M, Choudri AF, Oz MC, et al. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997;96[suppl II]:II-286–90.