REVIEW ARTICLE

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Perioperative Renal Dysfunction and Cardiovascular Anesthesia: Concerns and Controversies

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RENAL DYSFUNCTION remains a serious complication during the perioperative period in critically ill patients undergoing major surgery. The onset of acute renal failure (ARF) portends a poor prognosis, not only from the loss of renal function, but also from associated life-threatening complications, including sepsis, gastrointestinal hemorrhage, and central nervous system dysfunction. In high-risk patients undergoing high-risk surgery, the mortality rate from perioperative ARF has changed little during the last 3 decades, in part because the severity of disease and age of patients undergoing high-risk surgery have increased.[1-3]

Perioperative renal failure has been defined clinically either as the need for postoperative dialysis or as a postoperative serum creatinine level exceeding a predetermined preoperative value (eg, an increase of 0.5 mg/dL or of 50% or more).[4] In a recent review of postoperative renal failure, no two studies of 26 defined ARF the same way.[4] The reported frequency of ARF among all patients admitted to the hospital is 1%[5] and is 2% to 5%[6,7] during hospitalization. It is estimated that approximately 5% of the general population has renal disease severe enough to adversely affect surgical outcome.[8] The incidence of renal dysfunction after high-risk aortovascular surgery in high-risk patients has been reported to be as high as 50% in some series. The reported mortality rate from ARF once diagnosed remains between 20% and 90%.[9-15] Perioperative renal failure accounts for one half of all patients requiring acute dialysis.[16] Surgery on the infrarenal aorta has been associated with a 5% incidence of renal failure requiring hemodialysis.[17] The direct and indirect costs with respect to morbidity and mortality, with the accompanying long intensive care stay, dialysis, and other miscellaneous hospital charges, make perioperative renal failure a critical factor in maintaining a high cost for care with marginal gains to show for the efforts.

PATHOGENESIS AND CAUSES

Several mechanisms involving the renal tubule, a tubulointerstitial process, and a reduction in filtering capacity of the glomerulus have been implicated in ARF pathogenesis (Table 1). These major causes are typically classified into three broad descriptive categories: prerenal, renal, and postrenal. If clearance is limited by factors that decrease renal perfusion, then the cause is classified as prerenal failure or prerenal azotemia. If dysfunction is intrarenal, then it is designated as renal failure. If renal dysfunction is a consequence of obstruction of the urinary outflow tract, then it is classified as postrenal failure. Since World War II, it has become clear that ARF can result from decreased renal blood flow (RBF) from a myriad of causes. Unquestionably, prerenal causes are responsible for the majority of cases of perioperative ARF. Prerenal azotemia accounts for 70% of general community-acquired ARF and more than 90% of perioperative ARF.[4] When prerenal azotemia progresses to renal failure, the terms *acute tubular necrosis, vasomotor nephropathy,* or *ischemic tubular injury* are often used interchangeably in the literature.[4] In patients with inadequate blood flow (prerenal), injury is commonly caused by the added risk of drugs that alter intrarenal distribution of blood flow by abnormal hemodynamics or by pre-existing disease.[18] Patients with pre-existing renal insufficiency, for example, are especially prone to develop ARF because of cardiovascular surgery. Patients with diabetes mellitus and renal insufficiency are especially vulnerable to radiocontrast agents.[7] Intrinsic renal causes that result in ARF are described according to the primary lesion (ie, tubules, interstitium, vessels, or glomerulus). Tubular injury is the most common variation seen during the perioperative period and is most often associated with ischemic origin.[7] Prerenal azotemia and acute tubular necrosis represent extreme examples of the same problem (ie, insufficient RBF).[19] Most cases of ischemic renal failure are reversible; however, after prolonged severe ischemia, necrosis may be irreversible. Typically, an early compensatory phase of normal renal adaptation (eg, pre-prerenal failure) progresses to become decompensatory as prerenal failure ensues.[20] ARF may be characterized as an abrupt decline in renal function at this transitional stage. Depending on pre-existing reserve capacity, this stage may persist from a period of hours to days. At this point, the key decline in renal function is sufficient to result in retention of nitrogenous end products of metabolism and altered fluid and electrolyte homeostasis. Normally, the amount of blood the kidneys receive (1,000 to 1,250 mL/min) far exceeds that

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Table 1. Syndromes Associated With an Acute Decrease in GFR

Prerenal azotemia: Decrease in GFR resulting from renal hypoperfusion immediately reversed on restoration of RBF.
Acute renal failure: Decrease in GFR resulting from renal hypoperfusion (or nephrotoxin) not immediately reversed on discontinuation of the insult and associated with tubule cell damage (syndrome: acute tubular necrosis, lower nephron nephrosis, vasomotor nephropathy).
Acute interstitial nephritis: Decrease in GFR resulting from interstitial inflammation.
Acute glomerulonephritis: Decrease in GFR resulting from glomerular or vessel inflammation.
Acute renovascular disease: Decrease in GFR resulting from obstruction of renal artery or vein.
Obstructive uropathy: Decrease in GFR resulting from obstruction in the urinary collecting system (eg, postrenal azotemia)

needed to provide their intrinsic oxygen requirement. Essentially, all blood passes through glomeruli, and about 10% of RBF is filtered (a glomerular filtration rate [GFR] of 125 mL/min in the normal adult). The basal normal blood flow is 3 to 5 mL/min/g of tissue, greater than in most other organs. This average primarily reflects blood flow in the cortical glomeruli, because perfusion to the inner medulla and papilla is only about one tenth of the total flow.[21,22-25] Because the renal cortex contains most of the glomeruli and depends on oxidative metabolism for energy, ischemic hypoxia will injure the renal cortical structures, particularly the pars recta of the proximal tubules. As ischemia persists, the supply of glucose and substrates continues to decrease; glycogen is consumed, and the medulla, which depends to a greater extent on glycolysis for its energy source, becomes more adversely affected.[20,24,25]

Renal clearance is determined by the delivery of waste products to the kidney (ie, RBF) and the kidney's ability to extract them (GFR). A series of systemic and renal compensatory responses are activated to initially preserve ultrafiltration and renal clearance. The hallmark that underscores experimental models of hemodynamically mediated ARF is a reduction of renal flow (generally greater than 50%) for at least 40 to 60 minutes. Once a decrease in renal perfusion is established, then glomerular filtration is disproportionately depressed, compared with the decline in blood flow.[20,24] It has been observed that when RBF is decreased sufficiently to cause depressed glomerular filtration to less than 5% of normal, blood flow may only be depressed 25% to 50% of normal.[23,24] Hence, although decreased RBF is the initiating event most of the time, there are clearly other factors (tubular pathology) that sustain abnormal filtration besides decreased RBF.

In general, the response to renal hypoperfusion involves three major regulatory mechanisms that support renal function in the setting of decreased RBF: afferent arteriolar dilation increases the proportion of cardiac output that perfuses the kidney, efferent arteriolar resistance increases the filtration fraction, and hormonal and neural responses improve renal perfusion pressure by increasing intravascular volume, thereby indirectly increasing cardiac output. The afferent arterioles react to reductions in perfusion pressure by relaxing their smooth muscle elements to decrease renal vascular resistance. This property represents a relaxation response or myogenic reflex to reduced transmural pressure across the arteriolar wall. The kidney also possesses a tubuloglomerular feedback system, which is designed to maintain the homeostasis of salt and water excretion. Decreased solute delivery to the macula densa in the cortical portion of the thick ascending loop of Henle results in relaxation of the juxtaposed afferent arteriolar smooth muscle cells, thus improving glomerular perfusion and filtration.[25]

Reduced delivery of sodium to the macula densa also causes releases of renin from the granular cells of juxtaglomerular apparatus. Renin, in turn, catalyzes the release of angiotensin I from angiotensinogen. Angiotensin I is then transformed into angiotensin II in the lungs, catalyzed by angiotensin-converting enzyme (ACE). Finally, angiotensin II stimulates the production of aldosterone. High concentrations of aldosterone stimulate reabsorption of sodium and water, primarily in the distal tubule and collecting ducts. Initially, angiotensin II exerts a selective vasoconstrictive effect on the efferent arteriole. This occurs, in part, because during hemodynamic instability and increased adrenergic stimulation, the kidney synthesizes prostaglandins. Prostaglandin E_2(PGE_2) specifically decreases the vasoconstrictive effect of angiotensin II (a very potent vasoconstrictor) on the afferent arteriole and thereby preserves RBF. Prostaglandin synthesis is inhibited during normal states of hydration, renal perfusion, and sodium balance and, therefore, does not impact on renal function.[25,26]

A selective increase in efferent arteriole resistance decreases glomerular plasma flow, thereby preserving GFR. Glomerular filtration is augmented because capillary pressure upstream from the site of vasoconstriction tends to increase. This mechanism enables the kidney to offer high organ vascular resistance to contribute to the maintenance of systemic blood pressure without compromising its function of filtration. Studies using specific inhibitors of angiotensin II have shown that efferent arteriolar resistance is largely caused by the action of angiotensin II. At low concentrations, norepinephrine has a vasoconstrictive effect on efferent arterioles, indicating that the adrenergic system may also be important for maintaining the renal compensatory response.[24,25]

There is abundant evidence to support the notion that reductions in cardiac output are also accompanied by the release of vasopressin and by an increase in activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[25] Antidiuretic hormone (ADH), or vasopressin, acts primarily on the collecting ducts to increase water reabsorption.[27] ADH is released from the posterior pituitary gland in response to increased blood osmolarity, which stimulates osmoreceptors in the hypothalamus. ADH is inhibited by stimulation of the atrial baroreceptors or increased atrial volume. ADH release is also influenced by stress and increased $PaCO_2$. An elevated level of ADH thus results in the excretion of small volumes of concentrated urine.

Atrial natriuretic peptide causes systemic vasodilation and promotes renal excretion of sodium and water by increasing glomerular filtration. Atrial natriuretic peptide is secreted by cardiac atria and other organs in response to increased intravascular volume.[28] It decreases systemic blood pressure by relaxing vascular smooth muscle, reducing sympathetic stimulation, and inhibiting the renin-angiotensin-aldosterone system.

The common denominator of these regulatory mechanisms to

preserve RBF is salt water conservation. The control of blood delivery to the kidney, the fraction of plasma filtered, and the amount of volume returned to the systemic circulation are all determined by regulatory mechanisms within the kidney that attempt to preserve filtration function during compromised circulation. These compensatory mechanisms, however, have limits. Excess vasoconstrictive forces may eventually induce a decrease in filtration function.[24,25,29] Eventually, if left unabated, the mechanisms that influence efferent arteriolar vasoconstriction ultimately will overwhelm the system and cause afferent arteriolar vasoconstriction as well. The resulting decrease in filtration fraction is the hallmark of ischemic ARF. Histopathologic data suggest that the proximal tubules bear the brunt of the initial injury. As RBF decreases and compensatory mechanisms fail, then tubular necrotic cell debris becomes incorporated into occluding casts that lodge within the tubule lumen and cause obstruction.[25] This obstruction then causes an increase in tubular pressure that, in turn, further decreases filtration fraction and promotes back-leak upstream. Early cell changes are reversible, such as the swelling of cell organelles, especially in the mitochondria. As ischemia progresses, lack of adenosine triphosphate interferes with the sodium pump mechanism, water and sodium accumulate in the endoplasmic reticulum of tubular cells, and the cells begin to swell.[25,29,30]

The time of onset for tubular damage in experimental models of ARF is usually within 25 minutes of ischemia, as the microvilli of the proximal tubular cell brush borders begin to change. Within an hour, they slough off into the tubular lumen, and membrane bullae protrude into the straight portion of the proximal tubule. After a few hours, intratubular pressure increases and tubular fluid back flows passively. Within 24 hours, obstructing casts appear in the distal tubular lumen. Even if RBF is completely restored after 60 to 120 minutes of ischemia, GFR may not immediately improve. Ischemic tubular damage eventually may be exacerbated further by an imbalance between oxygen supply and demand. Most vulnerable to the imbalance are the thick ascending tubular cells of the loop of Henle in the medulla. In ischemia-induced ARF, lesions are unevenly distributed among the nephrons, probably reflecting variability in blood flow.

In the clinical setting of hypotension, the kidney appears to have a distinct susceptibility to injury. The reason for this susceptibility is not readily apparent, because RBF is normally high and oxygen supply exceeds by far the requirements for oxygen utilization. Although the kidneys receive nearly one quarter of the cardiac output and extract relatively little oxygen, the discrepancy between cortical and medullary blood flow and oxygen consumption is marked.[30] The apparent overabundance of blood flow to the cortex maximizes flow-dependent functions, such as glomerular filtration and tubular reabsorption. In the medulla, blood flow and oxygen supply are restricted by a tubular vascular anatomy specifically designed for urinary concentration. Normally, approximately 90% to 95% of blood flow is delivered to the cortex, compared with 5% to 10% delivered to the medulla. The selective vulnerability of the cells in the thick ascending loop of Henle is believed to result from their high oxygen consumption. Average blood flow is 5.0 mL/g/min and 0.03 mL/g/min for the cortex and medulla, respectively, whereas the oxygen extraction ratio (ie, O_2 consumption over O_2 delivery) is 0.18 and 0.79 for the cortex and medulla, respectively. Normally, the PO_2 is approximately 55 mmHg in the cortex and 8 to 15 mmHg in the medulla, making the thick ascending loop of Henle the most vulnerable to tissue hypoxia.[30]

Therefore, severe hypoxia may easily develop in the medulla with what otherwise would seem to be adequate total RBF. The initial response to decreased RBF is increased sodium absorption in the ascending loop of Henle, which coincidentally increases oxygen demand in the region most vulnerable to decreased oxygen delivery. To compensate for this, sympathoadrenal mechanisms cause cortical vasoconstriction and oliguria, which tend to redistribute blood flow away from the outer cortex to the inner cortex and medulla. At the same time, decreased sodium delivery to the macula densa causes afferent arterial constriction. With afferent arterial vasoconstriction, glomerular filtration decreases, after which solute reabsorption in the loop of Henle and oxygen consumption are thereby reduced. The severity of cellular injury appears to be related to the degree of imbalance between cellular oxygen supply and demand.[30] In the hypoperfused-kidney preparation, oxygen-enriched perfusion reduced cellular damage, hypoxic perfusion increased it, and complete cessation of perfusion (glomerular filtration zero, preventing ultrafiltration) was associated with less cellular injury than hypoxic perfusion. Afferent arterial vasoconstriction and consequent oliguria may be a normal protector response to acute tubular injury. By reducing ultrafiltration, energy-dependent ischemic injury to medullary tubular cells is prevented, even at the cost of retaining nitrogenous waste.

When RBF is compromised, blood flow and glomerular filtration in the outer cortical nephrons decline first because of the redistribution of blood toward the inner cortical and medullary regions. This cortical-to-medullary redistribution of RBF protects the vulnerable medullary oxygen balance.[30] Decreased glomerular filtration during compromised flow thus appears to be protective because decreased urine delivery to the tubules requires less reabsorptive work and prevents further oxygen supply-demand imbalance. Modulation by various drugs or compensatory mechanisms can reduce tubular work load and prevent medullary hypoxic cellular injury. Among the compensatory mechanisms that reduce cellular injury is reduced tubular transport of glomerular filtration. Thus, in some cases, the oliguria may protect against ARF.

Surgery requiring cross-clamping of the thoracic aorta is associated with a rate of renal complications as high as 50% (depending on the definitions and criteria used to define renal insufficiency and renal failure) and is nearly always a result of acute tubular necrosis.[31] Ischemia-reperfusion injury is generally the pathogenesis for renal injury during aortic occlusive surgery. Cross-clamping of the aorta is associated with a significant increase in renal vascular resistance and decrease in RBF that persist long after the release of the aortic occlusive clamp.[32] The decrease in RBF is primarily a result of a redistribution of flow away from the outer cortex and appears to be mediated by neurohumoral disturbances unique to aortic occlusion.

Renal causes of ARF include thrombosis and atheromatous embolization, nephrotoxins, and hemolysis. Ischemia and toxic-

ity often combine to cause ARF in high-risk patients. Common toxins encountered during the perioperative period include aminoglycosides, antibiotics, radiocontrast agents, and various chemotherapy agents (cisplatin).[4-7] Acute interstitial nephritis (AIN), secondary to an acute allergic reaction, or a number of drugs, including antibiotics (penicillin, vancomycin, cefoxitin, cefazdin, etc), nonsteroidal anti-inflammatory drugs, diuretics, furosemide, thiazides, and a wide variety of other drugs commonly used in surgical candidates are other possible causes of perioperative renal failure. The true incidence of AIN is unknown because the clinical presentation is nonspecific (renal biopsy is the only true definitive diagnosis) and, most likely, mild or subclinical episodes go undetected. In a study of patients with unexplained ARF, renal biopsy showed AIN in 13% of the patients.[33] AIN is an important cause of ARF that may more significantly contribute to the differential diagnosis of perioperative ARF than previously suspected.

GENERAL CONSIDERATIONS

Risk Assessment

Perioperative renal dysfunction furnishes few warning signals. After an insult to the kidneys, the transition from compensated function to noncompensated dysfunction often goes undetected.[21] The consequences of this silent transition are usually recognized after it is too late to change the inevitable outcome. Thus, attention has been focused on predicting which patients are at greatest risk. The greater the magnitude and duration of the surgical procedure and the number of acute and chronic risk factors (Table 2), the greater the likelihood of perioperative renal compromise. Perioperative ARF is often caused by more than one insult, with one risk factor compounding the significance of another.[19] Multiple factors may influence a patient's perioperative renal function.[4] Preoperative indicators of risk for renal dysfunction perioperatively, however, are often insensitive and not always cost-effective to pursue.[23,34] History and physical examination may show associated illnesses, such as diabetes, hypertension, or congestive heart failure, that may indirectly represent stages of renal dysfunction. Advanced age also markedly decreases renal function reserve. GFR, normally about 125 mL/min in a young adult, decreases to about 80 mL/min at 60 years and 60 mL/min at 80 years.[23] Even before a patient enters the operating room, his physiology may have changed. Anticipatory stress, for example, may elevate normal levels of catecholamines and ADH, whereas fasting or extensive bowel preparations before surgery may cause the patient to become hypovolemic, with abnormal serum electrolyte levels. Relative hypovolemia also causes a compensatory redistribution of RBF away from the outer cortex to the salt-conserving and water-conserving inner cortex and medulla, which may further affect renal function reserve.[24] Inhibitors of prostaglandin synthesis (eg, salicylates, nonsteroidal anti-inflammatory agents) have been reported to cause deterioration of RBF and GFR in patients with decreased effective blood volume.[35-37] The protective vasodilator effect of indigenous prostaglandins during hypoperfusion states is attenuated. Impaired reserve capacity becomes evident only when perioperative stress severely compromises renal function. Acute risk factors, such as volume depletion, congestive heart failure, aminoglycoside use, radiocontrast dye exposure, cyclosporine use, use of ACE inhibitors or nonsteroidal anti-inflammatory drugs,[35-37] septic shock, and pigmenturia, augment, rather than induce, the risk of ARF.[4,6-8,18,19] The combined interaction of these various risk factors appears to be central in the pathogenesis of perioperative ARF.

Table 2. Risk Factors Associated With the Development of ARF

Acute
Volume depletion
Use of aminoglycosides
Radiocontrast dye exposure
Use of nonsteroidal anti-inflammatory drugs
Septic shock
Pigmenturia
Chronic
Pre-existing renal disease
Hypertension
Congestive heart failure
Diabetes mellitus
Advanced age
Cirrhosis of the liver
Intraoperative
Aortovascular surgery
Biliary track surgery
CPB and cardiac surgery
Unstable hemodynamics
Aortorenal vascular resistance maldistribution

Preoperative Evaluation

Because of the paucity of physical signs and symptoms for detecting early renal dysfunction, laboratory assessment is relied on for quantitation of renal function reserve. There is no simple, inexpensive laboratory test that adequately quantifies renal function reserve. Because acute tubular necrosis accounts for greater than 75% of the cases of perioperative renal failure, much attention has been focused on testing urine indices and serum chemistries of renal tubular function. Unfortunately, the readily available tests fail to accurately reflect the status of the kidneys in many patients, especially those who are elderly, malnourished, and dehydrated.[20] Urinalysis, for example, provides qualitative information that must be interpreted cautiously. It is best used as a screening test, because specificity for renal disease is often less than its sensitivity for renal dysfunction. Hematuria suggests glomerular disease or, in traumatized patients, injury to the kidneys or the lower urinary tract. A urine test positive for blood in the absence of erythrocytes suggests the presence of free hemoglobin or myoglobin in the urine. Pyuria suggests urinary tract infection. Cellular casts in the urine generally indicate a pathologic condition. For example, erythrocyte casts suggest glomerular bleeding or interstitial nephritis, including pyelonephritis. White blood cell casts indicate tubulointerstitial disease. Epithelial casts are often observed in acute tubular necrosis, pyelonephritis, interstitial nephritis, and renal transplant rejection. The presence of proteinuria on a routine dipstick examination may be normal or may indicate severe renal disease. In a concentrated urine sample, trace or 1+ proteinuria is a nonspecific finding, whereas 3+ or 4+ proteinuria suggests glomerular disease. The existence of glycosuria without hyperglycemia indicates proxi-

mal tubular damage. An intrinsic defect of the proximal tubule characterized by abnormal bicarbonate reabsorption causing renal tubular acidosis can also be associated with impaired reabsorption of other sodium cotransported species besides glucose, including phosphate, uric acid, and other organic acids. The condition of impaired proximal tubule transport is known as the Fanconi syndrome. This syndrome may become evident after carbonic anhydrase inhibition or gentamicin toxicity.

Both blood urea nitrogen (BUN) and serum creatinine levels offer rapid but inexact estimates of creatinine clearance.[20] Creatinine clearance measures the ability of the glomeruli to filter creatinine from plasma and approximates the GFR. The incidence and severity of postoperative ARF are usually greater when the preoperative serum creatinine concentration is greater than 2 mg/dL;[6-8] however, an isolated serum creatinine measurement is an unreliable indicator of GFR when renal function is changing. An inverse logarithmic relationship exists between GFR rate and serum creatinine concentration. Thus, the direct measurement of creatinine clearance constitutes the best overall indicator of GFR. In one study, more than one half of 131 critically ill patients had normal urine outputs and BUN and serum creatinine levels, but reduced creatinine clearance.[38] Compared with the other measurements of renal function, creatinine clearance was the best predictor of death in these patients. Creatinine is not an ideal substance with which to measure clearance, because a small amount is secreted under normal conditions. Nevertheless, the clearance of endogenous creatinine approximates that of inulin and has proved an excellent measure of filtration rate in patients with normal renal function. In patients with moderate-to-severe renal dysfunction, the creatinine-inulin clearance ratio is increased (ie, filtration rate may be overestimated). Precise measurements of creatinine clearance require that urine samples be collected over extended periods. Although reasonable correlations between 2-hour and 24-hour creatinine clearance have been reported,[39] the longer the urine collection period, the more accurate the calculation of clearance. Events such as changing hydration states, hemodynamics, and day-to-day variation can influence the result by 10% to 25%.

Other laboratory tests of tubular function, not yet widely used or economically feasible, may prove useful, such as tests for N-acetyl-beta-D-glucosaminidase[40] and β_2-microglobulin.[41] In addition, diagnostic techniques with the ambulatory renal monitor,[42] contrast ultrasonography,[43] or urine oxygen saturation,[44] may enable early recognition of deleterious shifts in regional renal perfusion heralding the onset of ARF. These techniques are currently investigational. Until then, maintaining an adequate preload, cardiac output, and distribution of blood flow and oxygen nutrients to the kidney so that glomerular filtration can be maintained remains the focus of monitoring efforts (Table 3). Until the mysteries of intrarenal blood flow distribution and the interaction among tubular function, glomerular filtration, and regional oxygen nutrient delivery and demand are better elucidated, methods for prevention are sentenced to theoretically sound but clinically unsubstantiated efforts.

Table 3. Perioperative Causes of Decreased Renal Perfusion

Intravascular volume depletion
Major trauma, crush syndrome
Hemorrhage
Vomiting, diarrhea, peritonitis, dehydration
Decreased cardiac output
Congestive heart failure or low output syndrome
Pulmonary hypertension, massive pulmonary embolism
Positive-pressure mechanical ventilation
Increased renal/systemic vascular resistance ratio
Renal vasoconstriction
α-Adrenergic agonists
Hypercalcemia, amphotericin
System vasodilation
Antihypertensive medications
Anaphylactic shock
Sepsis
Liver failure
Renovascular obstruction
Renal artery
Atherosclerosis
Embolism
Thrombosis
Dissecting aneurysm
Renal vein
Thrombosis
Compression
Glomerular and small-vessel obstruction
Disseminated intravascular coagulation
Malignant hypertension
Increased blood viscosity
Macroglobulinemia
Polycythemia
Interference with renal autoregulation
Prostaglandin synthesis inhibitors in the setting of
Congestive heart failure
Nephrotic syndrome
Cirrhosis
Hypovolemia or pre-existing renal disease
ACE inhibition in the setting of
Renal artery stenosis or cardiac failure

Premedication

Premedication before surgery may cause changes in renal function. Narcotics and barbiturates, for example, produce small decreases in GFR, urine volume, and urinary solute excretion, whereas ADH levels appear to remain unchanged. Phenothiazines act like α-adrenergic receptor antagonists in that they increase RBF by blocking α-receptors. It has been recommended that these agents be used as premedicants for the patient at risk for developing perioperative renal dysfunction. Agents that are used to control blood pressure and decrease sympathetic outflow preoperatively in cardiovascular patients, such as ACE inhibitors, calcium channel blockers, β-blockers, nitrates, diuretics, and α_2-agonists, can influence renal hemodynamics as well (Table 4). α_2-Agonists, such as dexmedetomidine, decrease heart rate, myocardial contractility, oxygen demand, and cardiac output. In a canine model, dexmedetomidine decreased RBF by 30%.[45] Conversely, a study of the α_2-agonist clonidine administered intravenously during cardiac surgery showed that 4 μg/kg of clonidine prevented deterioration of renal function after cardiac surgery in patients with normal preoperative renal function. The protective renal effect in this low-risk population was attributed to a reduction in sympathetic nervous system response.[46]

Table 4. Systemic and Renal Effects of Agents Used for Cardiovascular Patients

Agent	Systemic Effect	Renal Effect
ACE inhibitor	↓Afterload	Afferent vasodilation ↓Renin-angiotensin effect Efferent vasodilation ↓GFR
Ca^{++} channel blocker	↓Contractility	Afferent vasodilation Efferent vasodilation Mild natriuretic effect ↑GFR ↑RBF
Beta-blocker	↓Afterload ↓Inotropy ↓Heart rate	Afferent vasodilation ↓Renin-angiotensin effect ↑GFR Afferent vasoconstriction Blocking β_2 effect
Nitrates	↓Preload ↓Afterload	↓Volume: inadequate vital organ perfusion
α_2-Antagonist	↓Inotropy ↓Afterload ↓Heart rate	↓RBF ↓GFR
Mannitol	↓Preload	↑GFR ↑RBF Afferent vasodilation
Furosemide	↓Preload	↑GFR ↑RBF Afferent vasodilation

Regional and General Anesthesia

Anesthetic choice may influence intraoperative renal function. Regional anesthetics and the kidneys interact in a complex manner that varies according to the underlying cardiovascular, renal, fluid, and electrolyte status of the patient.[47] Multiple factors (eg, catecholamines, renin-angiotensin, ADH, corticosteroids, prostaglandin) determine the consequences for renal function. The effect of sympathetic blockade depends on the level of the block and underlying disease. In a patient with global systolic ventricular dysfunction because of dilated cardiomyopathy, regional anesthesia may exert the beneficial effects of an afterload- and preload- reducing agent. Conversely, regional anesthesia in a patient with hypovolemia may further compromise venous return, which could exacerbate hypotension and decrease renal perfusion. Thus, the interactions between regional anesthesia and renal function are different in patients with different underlying disease. In patients with ischemic heart disease, regional anesthesia may exacerbate regional myocardial dysfunction (through vasodilation hypotension and decreased coronary perfusion pressure) and thereby decrease renal perfusion.[48] Recall that spinal cord segments T4 through L1 contribute to the sympathetic innervation of the renal vasculature, which is innervated through sympathetic fibers from the celiac and renal plexus. Therefore, as long as flow is maintained and perfusion pressure does not decrease to less than the autoregulatory range during spinal and epidural anesthesia, there will be little change in GFR or renal vascular resistance (Fig 1). Recently, Sulerman et al[49] showed in healthy volunteers that RBF is unchanged during epidural anesthesia with a T6 sensory block. In their study, mean arterial pressure remained greater than 70 mmHg and never decreased to less than 6% of the baseline level. The sympathetic innervation of the kidney affects multiple aspects of renal function, including hemodynamics, electrolyte and water reabsorption, and renin secretion.[47] Urine volume and free-water clearance may decrease during spinal anesthesia because of increased ADH secretion.[50] Increased renal sympathomimetic activity decreases RBF through α-adrenergic mediation and increased renin release through β-adrenergic innervation directly or by interaction with the renal tubular macula densa and baroreceptor reflex mechanism.[50]

General anesthesia influences renal function primarily by affecting filtration and reabsorption. All anesthetic agents, whether volatile or intravenous, can alter renal function by changing blood pressure and cardiac output so that intrarenal blood flow is redistributed. The redistribution is accompanied by sodium and water conservation and decreased urine formation.[51] During general anesthesia, hemodynamic alterations may influence renal function reserve. All inhalation agents decrease GFR and RBF dose dependently. These can be blunted by preoperative hydration.[52] Typically, the decrease in RBF is greater than the reduction in GFR, resulting in an increase in filtration fraction.[53-55] The effect of any particular agent on autoregulation and intrarenal blood flow distribution is agent specific and dependent on renal perfusion pressure. The autoregulatory mechanisms normally preserving RBF include afferent arteriolar vasodilation and afferent vasoconstriction. When RBF decreases, so do glomerular pressure and filtration, causing overreabsorption of chloride and, consequently, a decrease in chloride ion at the macula densa; it reflexively signals the

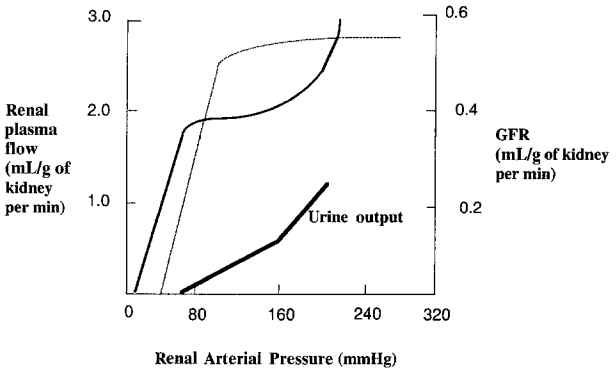

Fig 1. Relationship among RPF changes, GFR changes, and urine output changes relative to renal arterial pressure changes. Note that there is no easily recognized relationship between urine output changes and GFR or RPF.

afferent arteriole to vasodilate, thus increasing RBF and GFR back to acceptable levels. Reduced chloride in the macula densa eventually also initiates efferent arteriolar vasoconstriction by causing the juxtaglomerular cells to release renin, which facilitates the formation of angiotensin II (a potent vasoconstrictor).[20,22,24]

There is a well recognized renal nephrotoxic effect of the older fluorinated inhalation anesthetics that is attributed to serum inorganic fluoride concentration. Increased levels of serum inorganic fluoride cause polyuric renal insufficiency.[55] Methoxyflurane, which is no longer used clinically, and enflurane, when used for prolonged periods (9.6 minimal alveolar concentration [MAC] hours), cause an increase in serum inorganic fluoride.[55-57] After enflurane anesthesia, there is a decrease in maximum urinary osmolality in response to vasopressin that lasts for 5 days.[55] Sevoflurane appears to act as does enflurane with regard to the generation of inorganic fluoride as a result of metabolism.[58-61] Sevoflurane undergoes approximately 5% metabolism, and the primary metabolites are fluoride and hexafluoroisopropanol. The oxidative defluorination of sevoflurane in the liver with the liberation of free fluoride ions raised concerns that sevoflurane might have the potential, like methoxyflurane, to impair the ability of the kidneys to concentrate urine.[59] Earlier research had indicated that renal dysfunction from methoxyflurane was likely to occur when the dose or duration of methoxyflurane administration resulted in serum fluoride concentrations that exceeded 50 μmol/L.[56] This presumed threshold for toxicity has been extrapolated for other halogenated anesthetic agents, including enflurane and sevoflurane. In American Society of Anesthesiologists class I and II patients, it was shown that serum fluoride levels averaged 29 ± 2 μmol/L after 1 to 7 MAC hours of anesthesia.[62] These fluoride levels peaked 2 hours after the end of anesthesia and decreased by 50% within 8 hours. The rapid decrease in plasma fluoride level was attributed to the insolubility and rapid pulmonary elimination of sevoflurane. A study was conducted in which desmopressin testing was performed to test urine concentrating ability before anesthesia and on days 1 and 5 after 9.5 MAC hours of sevoflurane and enflurane anesthesia. Mean plasma fluoride levels were approximately twice as high in volunteers receiving sevoflurane as in those receiving enflurane, and 43% of volunteers receiving sevoflurane had plasma fluoride levels that exceeded 50 μmol/L. Despite these results, the kidneys of the volunteers receiving sevoflurane were not impaired in the ability to concentrate urine, whereas 20% of the volunteers receiving enflurane had transient concentrating deficits on day 1.[62]

Kharasch[59] explained the absence of fluoride-induced nephrotoxicity from sevoflurane by postulating that the intrarenal production of fluoride ion was a more important factor in the pathogenesis of nephrotoxicity than the association between plasma fluoride levels and nephrotoxicity. The intrarenal metabolism of methoxyflurane proved to be fourfold greater than the intrarenal metabolism of sevoflurane.

Isoflurane has a much lower rate of metabolism than does enflurane or sevoflurane. Halothane also causes minimal elevation of serum fluoride levels.[63] All anesthetic agents may indirectly influence renal function by modifying the ratio of aortic to renal artery systemic vascular resistance, thereby causing a redistribution of cardiac output away from the kidneys and an intrarenal distribution of flow away from the outer cortex.

Finally, it has been shown that all general anesthetics decrease the frequency and force of ureteral contraction.[64] Normally, ureteral peristalsis originates with electrical activity at pacemaker sites located in the proximal portion of the urinary collecting system. Basal peristalsis is influenced by the autonomic nervous system, and because all anesthetics decrease this ureteral peristalsis, the rate of urine output measured in a collecting catheter (Foley) may also be affected by the choice and dose of anesthetic (Fig 2).

Muscle relaxants are often used during general anesthesia. In general, they have minimal direct effect on the kidneys; however, they may influence renal function by changing hemodynamic parameters. For example, histamine release by curare may decrease blood pressure, or vagolysis by pancuronium may increase blood pressure, each affecting renal perfusion. Succinylcholine causes vasodilation in interlobar, afferent, and efferent arterioles.[65] This vasodilatory effect is less than that observed when acetylcholine is administered and is blocked by atropine, suggesting a muscarinic effect. Vecuronium causes selective vasoconstriction in the preglomerular but not in the postglomerular vessels.[65] This effect decreases RBF by 16% from baseline and glomerular filtration by 21% from baseline values.

Mechanical Ventilation

Mechanical ventilation with positive end-expiratory pressure (PEEP) is associated with decreased urine flow rate, creatinine clearance, and urinary sodium excretion[66-68] and elevated plasma ADH levels.[68] Elevated ADH levels during PEEP do not fully explain the decreases in urine output because consistent changes in free-water clearance are not observed. ADH release during mechanical ventilation is controlled by osmoreceptors and baroreceptors in the atria, aortic arch, and carotid sinus.[69] These receptors are stimulated when PEEP causes changes in intracardiac and systemic pressures. During mechanical ventilation, ADH maintains circulatory homeostasis, whereas the changes in free-water clearance are attributed to intrarenal mechanisms.[69] Changes in renal function during positive-pressure ventilation are attributed to decreases in intravascular volume caused by a diminished preload, with subsequent decreases leading to decreases in RBF and renal perfusion pressure.[56]

Surgical Stress Response

During surgery itself, a stress response may affect renal function by prerenal mechanisms, alterations in renal cellular activity, or by interruption of the urine collecting system. Notwithstanding that, some surgery improves renal function and integrity, such as renal artery reconstruction or relief of ureteral obstruction. In general, however, surgery induces a stress to the renal system. This stress causes increased catecholamines, even during anesthesia, which, in turn, divert blood flow away from the outer cortex.[70] Although the demonstration of perioperative stress and an outcome relationship is difficult, it has been reported that the incidence of postoperative renal

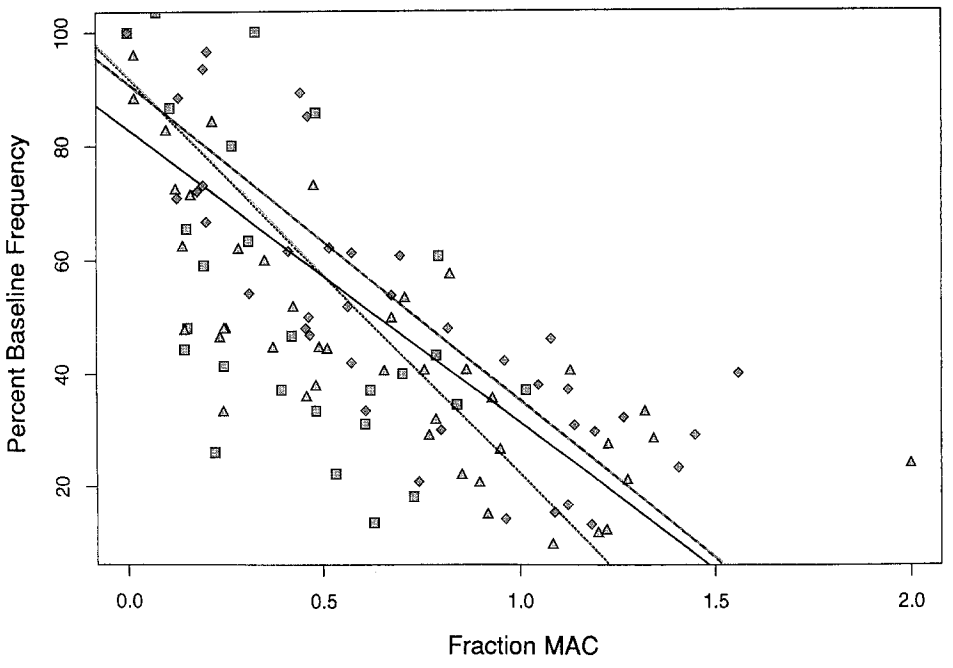

Fig 2. Peristalsis frequency as a function of MAC. The linear regression lines for each agent are shown. △, (solid line), halothone; ▨, (dotted line), enflurane; ◆, (dashed line) isoflurane. Changes in RVR, SVR, ERPF, GFR, and FF throughout the perioperative period in patients undergoing cardiac surgery with cardiopulmonary bypass. Note ECC = extracorporeal circulation. (Reprinted with permission from Young CJ, Attele A, Toledano A, et al: Volatile anesthetics decrease peristalsis in the guinea pig ureter. Anesthesiology 81:452-458, 1994.)

insufficiency may be associated with a moderate increase in intraoperative stress response. Roizen et al[71] measured intraoperative catecholamine levels (norepinephrine, epinephrine, and dopamine) in 100 patients undergoing abdominal or thoracoabdominal aortic reconstruction and noted that, of the patients who developed renal insufficiency and/or congestive heart failure in the postoperative period, the mean highest levels of norepinephrine and epinephrine were greater than those in patients who did not have renal insufficiency postoperatively.

Toxic Reactions

The controversy that has arisen concerning the relationship among sevoflurane, nephrotoxicity, and compound A deserves mention. All inhaled anesthetic agents interact with CO_2 absorbents to produce toxic compounds. In circuit systems, under conditions of high temperature and low flow rates, CO_2 absorbents interact with and degrade sevoflurane, resulting in detectable concentrations of vinyl ether compound A (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether). The degradation of sevoflurane is similar to that of halothane, which degrades in the presence of the strong base in CO_2 absorbents to 2-bromo-2-chloro-1,1-difluoroethene (BCDFE). The nephrotoxicity of both BCDFE and compound A in rats is similar. These degradation products are conjugated in the liver with glutathione. Cysteine conjugates are formed in the bile ducts and kidney by cleavage of two amino acid residues and then the conjugates are metabolized in the kidney by an enzyme (cysteine-conjugate beta lyase) to form end products that result in renal injury characterized by diuresis, glycosuria, proteinuria, and elevated serum BUN and creatinine levels. The renal injury seen in experimental rat models is a function of the concentration and duration of exposure of compound A.[72] The threshold for injury was exposure to compound A at 50 to 114 ppm for 3 hours,[73] whereas the lethal dose of compound A, from which 50% of rats died, was 331 ppm over 3 hours; 203 ppm over 6 hours; or 127 ppm over 12 hours.[73] Of the four recognized metabolic pathways for handling compound A, three do not involve renal beta lyase and do not result in organ toxicity. Beta lyase activity is 10 times greater in rats than in humans, which may account for the apparently greater toxicity of compound A in rats. A recent study[74] evaluated the safety of low-flow sevoflurane anesthesia compared with low-flow isoflurane anesthesia in 50 patients scheduled to have prolonged surgery, (ie, greater than 10 hours). The average MAC hour in the sevoflurane group was 13.1 and, in the isoflurane group, 12.1. The soda lime temperature averaged 45° ± 1.6°C. The average compound A concentration in the sevoflurane group was 24 ± 7 ppm. Markers of renal injury, including BUN, creatinine, and urinary protein glucose levels, were unaltered in either group, despite the prolonged exposure to the volatile anesthetics.

Eger et al[75] evaluated the highest concentrations of compound A possible during anesthesia (mean arterial pressure [MAP] = 56 mmHg) with sevoflurane in human volunteers. In that study, fresh CO_2 absorbent was used, sevoflurane was administered (without nitrous oxide) at 1.25 MAC, and esophageal temperature was maintained at 37°C. Volunteers were exposed to the anesthetic gas for 8 hours. The study design enabled the investigators to generate compound A levels approaching 50 ppm in the inspired limb of the breathing circuit. The volunteers were asked to bring in 24-hour urine collections for 3 consecutive days after the anesthetic exposure. In most subjects, there were transient elevations of urinary

protein, albumin, and glucose levels. No such increases were observed after a similar exposure to desflurane. They also reported that sevoflurane use was associated with transient postanesthesia albuminuria and glucosuria, as well as increased urinary α glutathione S-transferase and π glutathione S-transferase, enzymes specific to proximal and distal tubular dysfunction, respectively.

Subsequently, another study to evaluate the safety and efficacy of sevoflurane versus isoflurane in patients during conditions of flow of less than 2 L was conducted. In that study, more than 385 patients undergoing elective surgery lasting from 2 to 8 hours were evaluated from multiple institutions. Fresh baralyme was used for all cases, and nitrous oxide was not permitted. The use of sevoflurane averaged 1 MAC hour. No differences were found in urine albumin, glucose, or protein levels or osmolality between treatment groups. Moreover, within the sevoflurane group, there was no significant correlation between compound A levels and markers of renal tubular function.[76] Currently, although these theoretic concerns have been raised about sevoflurane and renal toxicity, it appears after extensive use that no pattern of toxicity is emerging.

A rare intraoperative event that may induce renal failure is hemoglobinuria. Hemoglobin is normally filtered at the glomerulus and enters the urine when the serum concentration is high (0.5 to 1.4 g/L). If an acute hemolytic transfusion reaction occurs during administration of blood or the inadvertent introduction of large quantities of distilled water into the blood stream while irrigating the bladder during transurethral prostatectomy occurs (causing hemolysis), a pigment load is presented to the kidney causing dysfunction.[77] Although purified hemoglobin is not nephrotoxic, hemolyzed whole blood can be less innocuous. The intravenous infusion of as little as 50 mL of hemolyzed blood can cause a decrease in RBF and GFR by as much as 50% in elderly patients because of presumed direct toxicity.[78-80] Other pigments, such as methemoglobin, bilirubin (because of obstructive jaundice), and hematin are also associated with ARF, but it is not certain whether they are directly nephrotoxic.

Myoglobin is filtered at the glomerulus at serum concentrations greater than 0.15 g/L. When rhabdomyolysis occurs during surgery, myoglobinuria may occur with or without renal dysfunction. In the operating room, rhabdomyolysis is most commonly caused by muscle ischemia. Events having the potential to cause muscle ischemia and rhabdomyolysis include arterial embolization, leading to myonecrosis, and improper positioning. About one-third of the people who develop rhabdomyolysis develop ARF. The mechanism of myoglobin nephrotoxicity remains unclear; however, both hemoglobin and myoglobin[81,82] cause vasoconstriction by inhibiting the production of endothelial relaxant factor. Hypovolemia and urinary acidification appear to be crucial precipitating factors in rhabdomyolysis-induced ARF.[83] It has been postulated that renal damage from myoglobin or hemoglobin results from an imbalance between O_2 supply (decrease by direct vasoconstriction caused by the pigment) and continued O_2 demand (caused by inefficient transport).[84,85] In addition, myoglobin (because of its O_2 binding properties) can interfere with the O_2 available in hypoxic regions of the kidney. Tubular obstruction can also have a role. Prevention or attenuation of renal injury is achieved by volume repletion, mannitol or furosemide diuresis, and alkalinization of the urine.[85] Rhabdomyolysis occurring intraoperatively may be caused by hypokalemia, hypophosphatemia, myxedema, infection, seizure, muscle compression, ethanol abuse, or malignant hyperthermia.

CARDIAC AND VASCULAR SURGERY

Aortic Occlusive Surgery

Pre-existing renal dysfunction caused by renal artery stenosis, hypertension, and diabetic nephropathy is common among all patients with vascular disease. Surgery involving occlusion of the aorta is an independent risk factor that is associated with a high rate of renal dysfunction. Postoperative ARF after aortic occlusion surgery, in particular, is associated with a mortality rate of up to 90% and is nearly always a consequence of decreased RBF and resulting acute tubular necrosis.[7,86-89] In general, infrarenal aortic occlusion is associated with increased renal vascular resistance and moderately (25%) decreased RBF. These hemodynamic changes persist after removal of the aortic occlusive clamp. Thoracic aorta occlusion is associated with up to a 95% reduction in RBF. These changes also persist after release of the occlusive clamp.[89] Accompanying the increases in renal vascular resistance and decrease in RBF that occur with occlusion of the aorta are decreases in glomerular filtration and urine output. These changes do not necessarily correlate with changes in cardiac output or systemic blood pressure.[32] Furthermore, the decrease in urine output that is typically observed does not correlate with reduction in GFR or postoperative renal function.[90,91] Finally, the changes in total RBF after aortic occlusive surgery do not directly correlate to changes in regional RBF distribution within the kidney. There is a propensity for outer cortical RBF to decrease more than inner cortical RBF, thereby causing a redistribution of blood flow within the kidney, after the application of an aortic occlusive clamp.[92]

The decrease in RBF during aortic occlusion involves many mechanical and hormonal mechanisms, including the renin-angiotensin system. Angiotensin II causes an increase in renal vascular resistance and sodium reabsorption. Aldosterone also causes increased sodium reabsorption. Evidence suggests that pretreatment with ACE inhibitors allows for complete return of RBF (compared with a 50% return without pretreatment) after the release of aortic occlusive clamps.[93] This apparent salutary effect after aortic occlusion is, however, associated with lower blood pressure during the phase of aortic occlusion. There is no evidence that low blood pressure during aortic occlusion with a consequent decrease in renal flow is poorly tolerated after the administration of ACE inhibitors.

Sympathetic blockade with β-adrenergic antagonists and the reversal of cortical ischemia during infrarenal artery occlusion are probably related to inhibition of the renin-angiotensin system more than inhibition of the sympathetic nervous system.[94] On one hand, epidural anesthesia (and consequential sympatholysis) appears to provide no significant relief of decreased GFR as long as MAP is maintained within the range needed for normal autoregulation.[47,48,95] Deep anesthesia with sufentanil, however, appears to inhibit sympathetic outflow and provide renal protection.[96] The exact contribution of inhibition of the sympathetic nervous system to renal function has yet to be elucidated.

Endothelin and prostaglandins also influence renal blood.[97] Calcium channel antagonists prevent the vasoconstriction of blood flow induced by endothelium. The intrarenal redistribution of RBF is influenced by intrarenal secretion of prostaglandin. This effect may not mimic the nonselective vasodilating effect after exogenously administered prostaglandin.

Perioperative ARF after vascular surgery (depending on its definition) results in an incidence of postoperative renal failure from 0.1% to 30%. Mortality rates after postoperative renal failure are 50% to 100%. Data continue to indicate that the development of ARF remains an ominous sign for patients in the intensive care unit. The mean survival rate is less than 25% to 35%. This troublesome and often lethal complication assumes an even greater significance in patients who develop it after distal aortic surgery. Surgery on the infrarenal aorta is associated with a 5% to 10% incidence of renal failure requiring hemodialysis. Renal function compromise after surgery on the suprarenal aorta may be as high as 15% to 30%. Surgery requiring occlusion of the thoracic aorta is associated with a rate of renal dysfunction as high as 50%.[9,98]

Cardiac Surgery

A prospective study of 500 consecutive patients during the first 24 hours after cardiovascular surgery enabled the determination of prevalence, cause, and results of therapy for postoperative ARF.[99] In that study, positive risk factors for ARF included age, active renal dysfunction, duration of cardiopulmonary bypass (CPB) and aortic cross-clamping, and total operating time. Negative risk factors for ARF after cardiac surgery included type of operation, New York Heart Association classification, diuretic therapy preoperatively, other chronic illness, and lowest mean blood pressure.[99] In general, the frequency of ARF after cardiac surgery requiring CPB is 4% to 15%.[9-11,14] The high mortality rates continue despite advances in CPB technology, intraoperative hemodynamic monitoring, intensive care management, dialysis techniques, and antibiotic therapy, most likely because the advances and willingness to provide surgery to increasingly more elderly and more critically ill patients have changed the demographics and increased the risks of perioperative ARF. Conversely, infants who undergo congenital cardiac repair are also at risk of developing ARF. Chesney et al[100] reported an 8% incidence of ARF in children with an associated high mortality rate of 65%. Gomez-Campdera et al[101] reported a 9% incidence of ARF with a mortality rate of 58% in children who underwent cardiac surgery. These figures are consistent with the reported incidence of ARF in adult cardiac surgery.

The pathogenesis of ARF in infants and children undergoing cardiac surgery is multifactorial. In healthy neonates, the GFR and total RBF/surface area are less than in older children or adults. There is also a greater distribution of juxtamedullary versus cortical blood flow.[102] In addition, cardiac failure may be worsened intraoperatively by hypoglycemia, acidosis, volume overload, hypoxia, or abnormalities of electrical conduction. Nonetheless, cardiac failure may not be the major factor in the pathogenesis of renal failure in this population after cardiovascular surgery. The presence of congenital renal abnormalities or hypotension from any cause, including cardiac arrest, tamponade, acidosis, disseminated intravascular coagulation, or septic shock may contribute to ARF postoperatively. Cold injury from deep hypothermia during pediatric cardiac surgery may also predispose to ARF.[103] In summary, ARF continues to be a serious complication of cardiac surgery. If it occurs, survival depends on the underlying pathology and complications in other organs. The high mortality rate associated with postoperative ARF is not just a consequence of the comorbid state that initially predisposed the patient to renal failure.

CPB

Overview

Because CPB poses a unique physiologic stress, a number of hemodynamic, hormonal, and pharmacologic responses to it by the kidney have been evaluated. Lema et al[104] prospectively evaluated patients who had coronary artery surgery for perioperative serum creatinine values less than 1.5 mg/dL. During hypothermic CPB, effective renal plasma flow (measured with ^{124}I-hippuran clearance) increased and then returned toward baseline during resumption of normothermia. GFR (measured with inulin) remained normal before and after surgery and decreased somewhat during the normothermic phase of CPB; filtration fraction (normal to high before surgery and after anesthesia induction) decreased during CPB, the latter suggesting vasoconstriction before CPB. Tubular dysfunction was assessed (by urine concentration of N-acetyl-β-D-glucosaminidase) and, despite minor changes observed in urinary electrolyte levels, tubular function remained essentially normal throughout CPB. The investigators concluded that the significant alterations in renal function typically found before and during cardiac surgery were not associated with CPB (Fig 3).

Neurohormonal Effects

There is a decrease in plasma concentration of atrial natriuretic factor (ANF) during CPB.[105] ANF is a polypeptide secreted by the heart in response to atrial distension and is involved in body fluid and circulatory regulation.[106] Pharmacologic doses induce vasodilation, enhance diuresis and natriuresis, and antagonize the sodium retentive and vasoconstrictive renin-angiotensin-aldosterone system.[107] Thus, ANF is therapeutic and beneficial in patients with cardiac, renal, or liver failure and in hypertensive patients.[108] During CPB, patients are exposed to an accumulation of sodium and water, hemodilution, and a decrease in atrial distension. Hynynen et al[108] studied the effects of a bolus dose and low-dose infusion of ANF in patients undergoing CPB. They found that a bolus dose led to significant decreases in MAP without a diuretic and natriuretic response, but a low-dose infusion of ANF during CPB led to significant diuresis and natriuresis without change in MAP.

Prostacyclin, because of its vasodilating property, seems to maintain organ perfusion by inhibiting vasoconstriction.[109] Prostacyclin has been used during CPB primarily for its preservation of platelet count and function and, thus, ability to decrease blood loss. It causes vasodilation and hypotension during CPB. Feddersen et al[110] reported that patients receiving a 50 ng/kg/min dose of prostacyclin during CPB had no incidence of renal failure and an increase in GFR, despite a MAP less than

the autoregulatory level. Abe et al[111] investigated the effect of prostaglandin E (PGE) on renal function after cardiac surgery and showed increased peripheral blood flow and cortical RBF. PGE infusion during CPB decreased the incidence of renal tubular dysfunction after bypass, as shown by levels of urine and serum β_2-microglobulin (measured to evaluate proximal tubule function) and urine N-acetyl-β-D-glucosaminidase (measured to evaluate dysfunction of tubular reabsorption). Gailiunas et al[112] reported that damage to the tubular epithelium caused renal tubular necrosis after cardiac surgery. During CPB, blood flow to the outer renal cortex was reduced, and intracortical and intramedullary blood flow were increased. PGE_1 increased outer cortical RBF and caused a sodium diuresis.[113] PGE_1 decreased vascular resistance, inhibited the reuptake of water, and blunted vasopressin.[114] Patients treated with PGE_1 had no change in free-water clearance on postoperative days 1, 3, or 5; thus, the renal tubular insufficiency after bypass was mitigated by PGE_1.

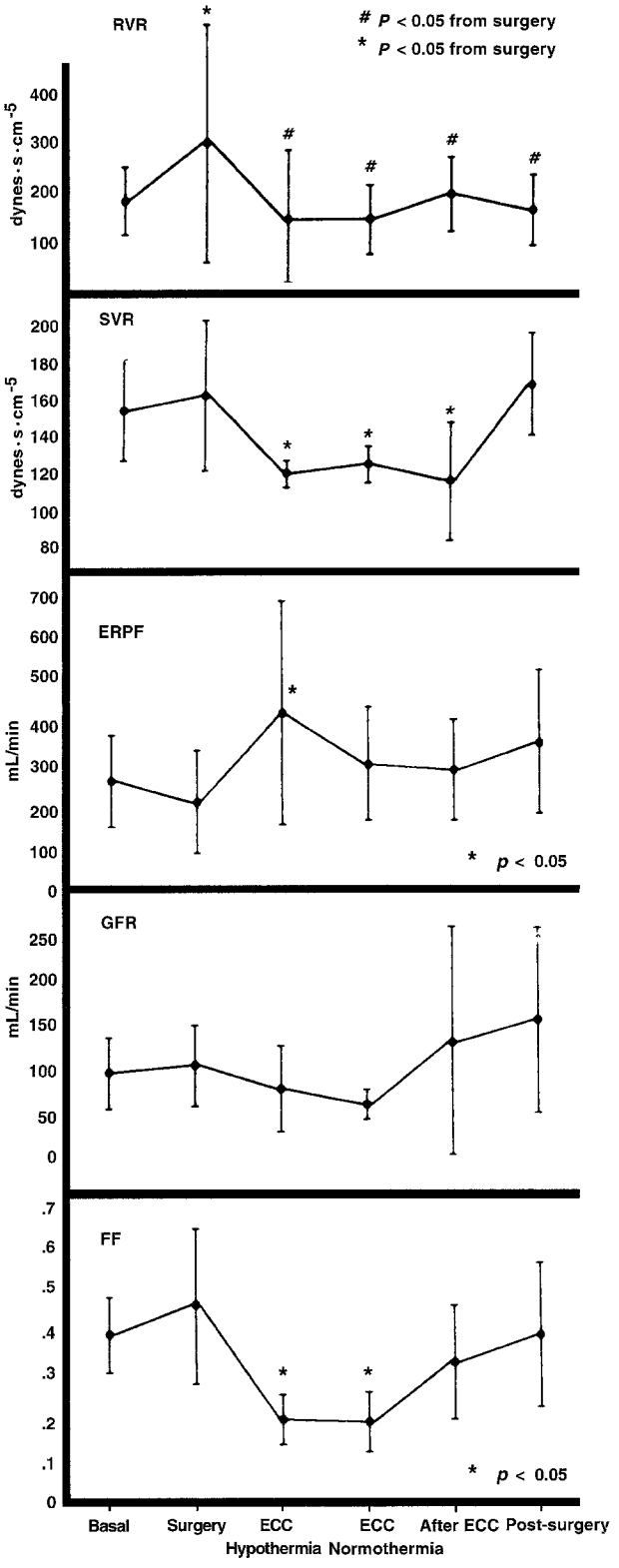

Fig 3. The evolution of ERPF, GFR, FF, RVR, and SVR during CPB. Abbreviations: RVR, renal vascular resistance; SVR, systemic vascular resistance; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; FF, filtration fraction; ECC, extracorporeal circulation). (Reprinted with permission from Lema G, Meneses G, Urzua J, et al: Effects of extracorporeal circulation on renal function in coronary surgical patients. Anesth Analg 81:448-451, 1995.[104])

Pharmacology

Among the commonly used pharmacologic renal protective strategies administered during CPB, low-dose dopamine and mannitol have been extensively studied. Myles et al[115] investigated the effect of routine prophylactic administration of low-dose dopamine versus placebo on renal impairment in patients undergoing coronary artery bypass graft surgery (CABG). The incidence of renal impairment was similar in both groups. Dopamine improved hemodynamics, but did not change urine output, creatinine clearance, or free-water clearance up to 24 hours.[115] Routine use of low-dose dopamine during CABG did not significantly improve or prevent renal failure in that study. High-risk patients (those with pre-existing renal dysfunction or poor ventricular function) were not included in the study. Davis et al[116] studied adult cardiac surgical patients with left ventricular dysfunction and postoperative oliguria. Patients who were administered low-dose dopamine had increased urine flow, osmolar and free-water clearances, and urinary sodium concentration.[116] No adverse hemodynamic effects were noted. Hollenberg et al[117] found that low-dose dopamine increased the cortical component of RBF with the xenon washout technique compared with low-dose dobutamine infusion in children undergoing CPB; however, no improvement in renal function was found.[118] The mystique that surrounds dopamine's effectiveness is largely based on anecdotal reports and poorly controlled studies. Dopamine was first synthesized in the early 1900s. However, its unique renal effects were not appreciated until the 1960s, when Horwitz et al[119] showed that low-dose dopamine, in contrast to other catecholamines, increased renal plasma flow, GFR, and urinary sodium excretion. The multiplicity of the receptors activated by dopamine and the wide interpatient variability of responses have made it difficult to determine before use the precise infusion rate required for each patient to achieve low-dose dopamine. Thus, the maximum dose at which dopamine affects only dopamine receptors is still in question

and must be individually determined. In addition, upregulation and downregulation of receptors occur, so that in any one patient the appropriate dose for a given action can vary even from hour to hour when other factors such as preload, cardiac output, etc, vary. Low doses of dopamine increase RBF and GFR and directly inhibit proximal tubular sodium reabsorption. This combination of events results in increased sodium excretion when dopamine is infused in euvolemic patients with normal renal function. Importantly, this response diminishes with prolonged infusion. Recognizing that dopamine can be natriuretic, it is equally clear that dopamine is not always natriuretic in most critically ill patients.[120-122] The regulation of renal sodium excretion depends on an intricate interaction between natriuretic vasodilatory and antinatriuretic vasoconstrictive influences. The use of a single natriuretic vasodilatory hormone, such as dopamine, is unlikely to counteract the effects of multiple effects that may have been activated to induce sodium conservation. Although dopamine causes an increase in glomerular filtration in patients with normal renal function, patients with a baseline GFR of less than 70 mL/min do not show an increase in glomerular filtration with low-dose dopamine infusions.[122] This lack of response may be attributed to exhaustion of the renal reserve capacity in these patients with depressed renal function.

There is considerable disagreement concerning the effect of low-dose dopamine on urine output. It can be concluded that low-dose dopamine increases urine output in some oliguric patients and in patients with good renal function who are adequately hydrated; however, until more definitive studies are available, it would be premature to conclude that dopamine is advantageous in the treatment of oliguric renal failure. The use of low-dose dopamine to protect the kidney from ischemic or toxic insult is based on even more dubious data. Although dopamine has been shown to preserve blood flow in animal models treated with norepinephrine, the implication for this finding for critically ill hypotensive humans is unclear.[123] In the few studies that have examined the effects of dopamine in patients with ARF, there is no evidence that dopamine preserves or improves renal function. If dopamine-induced natriuresis produces intravascular volume depletion, the kidney may actually be made more susceptible to ischemic injury.[124] Despite the variability and lack of sensitivity used to measure renal function outcome, there is a paucity of evidence supporting the theoretic advantages of routinely using prophylactic low-dose dopamine. Furthermore, dopamine may increase the potential for ventricular arrhythmias[124] and myocardial ischemia by causing a deleterious shift in the balance of myocardial oxygen supply and demand. In addition, respiratory depression by intravenous dopamine has been described in animals, as well as in man. Apparently, the renal-dose range reduces arterial PO_2 through peripheral chemoreceptors. Therefore, the authors do not routinely use low-dose dopamine as prophylaxis against developing postoperative ARF and believe its unproven benefit must be carefully weighed against its potential harm.

Mannitol is also commonly used for renal tubular protection during CPB. Mannitol has many real and theoretic renal protective effects during cardiovascular surgery.[125] It decreases proximal tubular reabsorption of sodium and water, which is an energy-consuming process. It also decreases sodium reabsorption in the thick ascending loop of Henle, medullary tonicity, renin production, and vascular congestion and consequent edema in the endothelial cells. Mannitol increases RBF by increasing prostaglandin formation and promoting intravascular volume retention. Carcoana et al[126] measured β_2-microglobulin excretion in patients undergoing CPB as a measure of renal tubular dysfunction and found dysfunction was significantly lower compared with controls 1 hour after bypass when mannitol was administered during CPB, thus indicating renal tubular protection. Utley et al[127] studied the effects of albumin and mannitol in CPB priming solutions and found that albumin decreased urine flow, urine sodium, and free-water clearance. Mannitol, in contrast, had no significant effect on renal flow, renal plasma flow, or renal clearance. In children undergoing CPB, the prophylactic administration of mannitol, 0.5 g/kg, was associated with significantly lower plasma creatinine concentrations and urinary albumin excretion when compared with controls.[128] Mannitol, an osmotic diuretic that promotes free-water diuresis by acting as a nonreabsorbable solute (primarily in the proximal tubule), has been the focus of mechanistic and outcome research for several decades. Mannitol effectively causes an expansion of extracellular volume by shifting fluid from the intracellular fluid compartment to the extracellular volume compartment with consequent increases in the flow in the renal tubule.[129] An infusion of mannitol is associated with increases in RBF and glomerular filtration. It effectively vasodilates afferent arterioles and thereby increases intratubular pressure and filtration. Mannitol affects the pressure-flow relationship in the kidney such that higher RBF values result at similar (or lower) levels of renal perfusion pressures. However, the mechanism of mannitol's ability to increase RBF, or its exact consequence, is still unknown. Mannitol's effect on RBF has been attributed to the release of intrarenal prostaglandins or atrial natriuretic peptide, decrease in intravascular cell swelling or renin production, and an increase in intravascular volume. The question regarding the effect of increasing RBF also remains unanswered. Although it is tempting to presume (albeit in a simplistic way) that increasing RBF is a good thing, especially when oxygen nutrient delivery is compromised, it may not necessarily be so. Thus, another critical question that remains unanswered is mannitol's effect on changes in distribution of intrarenal blood flow. Clearly, the inner cortex and medulla would stand to benefit the most from increases in oxygen nutrient delivery at a time when the kidney is susceptible to hypoxic injury, whereas increases in RBF to the outer cortex may tax the kidney at a time when it is least affordable.

After many years of clinical trials, the jury is still out on the benefits of mannitol in preserving renal function outcome in clinical practice. In one study, during CPB mannitol use suggested some renal tubular protection 1 to 3 hours after bypass.[126] However, increasing RBF may not be an obvious benefit of mannitol's presumed positive effect. Mannitol's other mechanism of action, coupled with an understanding of the pathophysiology that is associated with perioperative ARF, most likely explains its positive effect. Mannitol reduces reabsorption of sodium chloride, potassium, calcium, phosphates, and water in the proximal tubule; sodium chloride in the thick ascending limb of the loop of Henle; as well as water reabsorption from the collecting duct; all of which are energy-

consuming processes. In addition to preserving oxygen balance by decreasing demand, mannitol may relieve the vascular congestion and endocellular cell edema that may result from hypoperfusion to the medulla. Therefore, given the paucity of clinical data showing the benefit of mannitol on preserving renal function outcome, it is necessary to carefully weigh its risks (ie, intravascular volume depletion after acute volume overload, hyperosmolarity, hypokalemia, and hyponatremia) against its theoretic benefit.[129-132]

Although mannitol and furosemide have been shown in animals to help protect the kidney against ischemic injury, most studies of humans have failed to show the effectiveness of these agents in the prevention or treatment of ischemic or toxic ARF. Both mannitol and loop diuretics, if administered early in the course of ischemic ARF, can convert an oliguric to a nonoliguric state. Although nonoliguric ARF is generally associated with a lower mortality rate, there is little evidence that conversion from an oliguric to a nonoliguric state decreases the mortality rate. Patients with a response to diuretics may have less severe renal damage at baseline than those with no response. Finally, diuretics can be detrimental in ARF induced by radiocontrast agents. At this time, the use of loop diuretics can only be justified to increase urine output for fluid management, with no expectation that these agents will improve outcome.

Another diuretic, furosemide, has been found to have a dilating effect on cortical vessels and tubules.[133,134] Nuutinen et al[135] reported that patients administered furosemide prophylactically had a higher creatinine clearance on the second postoperative day than equally matched controls. Renal artery blood flow increased and cortical and medullary tissue oxygen tensions improved with furosemide administration.

The administration of corticosteroids during cardiac surgery and CPB has been recommended by some clinicians because of the beneficial effects on multiple organ systems, including the kidney. Fecht et al[136] administered methylprednisolone sodium succinate to 25 of 50 patients undergoing CABG in a double-blind study to ascertain the effects of the glucocorticoid in decreasing ischemic injury to the heart. Steroids were administered before CPB and repeated one time during the surgery. The investigators showed that circulatory function after CPB was improved, as evidenced by modest increases in arterial blood flow and coronary graft flow. Urine output in the first 24 hours was 67% higher in the treated group.[136] Glucocorticoids are known to prevent platelet aggregation, stabilize lysosomal membranes, protect the capillary endothelium of the microcirculation, and prevent the formation of toxic factors during low-flow states.[137-140] Any or all of these mechanisms could be operational on the cardiac, pulmonary, and renal systems during CPB. In another investigation, dexamethasone was also shown to affect renal function. Administered in massive doses, dexamethasone increased urine output because of solute diuresis. GFR and RBF during CPB remained stable, presumably because of the decreased renal vascular resistance observed with dexamethasone.[141]

Two other agents commonly used during cardiac surgery that may have some effect on renal perfusion are nitrous oxide and neosynephrine. It was reported that air, when compared with nitrous oxide, was associated with a greater free-water clearance. In addition, creatinine clearance and urine flow were lower when nitrous oxide was used, and urine osmolality was higher.[92] It was suggested that low-molecular-weight inhalation agents, such as nitrous oxide, represent, in anesthetic concentrations, a sufficient osmolal stimulus for the release of ADH by the posterior pituitary.[142] Vasoconstrictors, such as phenylephrine, are commonly used during CPB to improve systemic perfusion pressure. Comparing the effect on RBF of administering neosynephrine versus increasing pump flow, it has been shown that RBF is pressure sensitive with a reduction at low perfusion pressures. Regional perfusion to the kidneys is improved only when aortic pressure is increased by adjusting pump flow, not when phenylephrine is infused.[143]

Hemodynamics

MAP management during CPB has an effect on renal function. When MAP was maintained with vasoactive drugs at 80 to 100 mmHg in one group and at 50 to 60 mmHg in a second group, during moderate hypothermic conditions (flow rates maintained at 1.6 L/min/m^2 during cooling and 2.4 L/min/m^2 during rewarming), renal circulation was preserved as long as MAP was maintained at greater than 50 mmHg.[144] Nevertheless, many clinicians maintain that the pathogenesis of ARF after cardiac surgery appears to be more appropriately ascribed to perioperative hemodynamic instability (eg, low cardiac output syndrome) and that the institution of CPB or specific management strategies of CPB deserve less importance. Valentine et al[145] compared CPB flow rates fixed at 2.4 L/min/m^2 to a bypass flow tailored to maintain venous return oxygen saturation at 75% to 80%. Vasoactive drugs were used to maintain perfusion pressure between 50 to 80 mmHg. An overall decline in postoperative renal function compared with preoperative levels (based on creatinine clearance and serum creatinine levels) was observed with no significant difference between the two groups.[145] Other studies provide conflicting results on the effect of CPB flows and pressure management strategies on postbypass renal function. Koning et al[146] retrospectively showed a relationship between low flow during CPB and increased serum creatinine levels postoperatively. Yeboah et al,[147] in a retrospective study of 430 patients, showed that the incidence of renal failure was reduced when perfusion pressure was maintained at greater than 80 mmHg. Bhat et al,[148] also in a retrospective analysis of 490 patients, found no correlation between renal failure and management of MAP and mean flow rate during CPB. They showed that the duration of CPB was the factor most predictive of postoperative renal failure.[148] Urzua et al,[149] in a prospective study, found no postoperative differences in renal function between those patients with untreated arterial blood pressure during CPB and those who received vasopressors. Abel et al,[9] who evaluated 500 patients prospectively, found no correlation between postoperative renal failure and lowest and mean blood pressures or flow rates during CPB, whereas others have shown the effectiveness of low-flow (30 to 50 mL/kg) and low-pressure (30 to 65 mmHg) management in preserving postoperative renal function. Recently, CPB flow was safely lowered using oxygen saturation monitoring of venous return to gauge metabolic demand and vasoconstrictors to maintain perfusion pressure at 50 to 80 mmHg.[99]

In the early twentieth century, a number of investigators reported that pulsatile perfusion improved urine output.[150,151]

Controversy arose five decades later when other investigators contradicted the findings.[152-154] By the mid-1980s, numerous studies published on this topic suggested that pulsatile perfusion preserved renal function better, maintained normal renal metabolism, reduced renal renin release, preserved outer cortical flow, and prevented ischemic changes (especially during longer periods of perfusion).[155-157] Many experimental and clinical studies, however, failed to show beneficial effects in the kidneys with pulsatile perfusion. Louagie et al[158] studied 100 patients undergoing CABG and randomly assigned one half of them to standard nonpulsatile perfusion and one half to pulsatile perfusion. CPB flow rate was maintained at the standard 2.4 L/min/m^2 with MAP at 50 to 80 mmHg. Although urinary output was lower during CPB in the pulsatile group (presumably because of the low MAP), blood creatinine levels and creatinine clearance did not differ between the groups postoperatively. These investigators disputed the superiority of pulsatile flow in preserving renal function during CPB and suggested that modern techniques of CPB are much less injurious to renal function than older ones. They pointed out that at high flow rates any effects of pulsatile blood flow on cardiovascular hemodynamics are far overshadowed by other perfusion variables.[158]

Acid-Base Management

Badner et al[159] compared the renal effects of pulsatile versus nonpulsatile perfusion during alpha-stat and pH-stat management. Mean urine output and fractional excretion of sodium and potassium increased during the study period, whereas mean postoperative creatinine and BUN levels decreased compared with preoperative values. No differences were reported between the groups. They concluded that, in patients with normal preoperative renal function undergoing hypothermic CPB, neither the mode of perfusion nor the method of acid-base management influenced preoperative renal function.[159] The best prediction of postoperative renal failure in this study was preoperative renal insufficiency and postoperative circulatory dysfunction.[159] The influence of acid-base management on renal function has been examined by others.[160,161] Michielon et al[160] studied 201 patients and, although they noted increased urine output, they could not conclude that alpha-stat management was superior. Tuppurainen et al[161] found no difference in inulin clearance between alpha-stat and pH-stat management techniques during CPB. Badner et al[159] showed that alpha-stat management resulted in slightly lower mean postoperative creatinine values compared with pH-stat management.[128] The advantage of alpha-stat versus pH-stat management for postoperative renal outcome has not been conclusively shown.

Time Management

An additional factor believed to predispose cardiac surgery patients to postoperative renal dysfunction is CPB time.[135,148] Nuutinen et al[135] compared renal function variables after bypass surgery when CPB lasted less than 60 minutes or more than 60 minutes. Creatinine clearance, free-water clearance, and excretion of sodium and potassium were significantly greater if CPB time was less than 60 minutes versus greater than 60 minutes. However, patients in the group requiring more than 60 minutes for CPB were older and had a higher preoperative serum creatinine value than the patients with shorter perfusion time. Weinstein et al[162] concluded that modern techniques of CPB are not injurious to renal function. Urine output and creatinine clearance are decreased before CPB, probably because of preoperative dehydration; loop diuretics in the postoperative period increase both urine output and creatinine clearance for as long as 6 hours after administration. Mazzarella et al[163] concluded that CPB probably causes renal damage, but not sufficient to influence routine renal function. Free plasma hemoglobin elastase, endothelin, and free radicals generated during CPB may induce injury to the renal brush border membrane.[164,165] As with any surgical procedure, hydration is a critical factor to prevent renal hemodynamic suppression.[166]

Temperature and Hemodilution Management

Hypothermia is another factor believed to have adverse effects on the kidney. Utley et al[167] found that hypothermia increased urine potassium and filtration fraction and diminished renal free-water clearance, RBF, and osmolar clearance. Hypothermia decreased the activity of renal tubules and elevated the excretion of filtered sodium and water.[167] Ischemia in the outer renal cortex has been recognized during CPB (hypothermia decreases outer and inner cortex blood flow and oxygen delivery).[167] Hemodilution during CPB protects the integrity of renal tubules postoperatively by improving urine flow and decreasing urine osmolarity and combating the effects of hypothermia. Regragui et al[168] studied the associated risk of renal dysfunction during CABG surgery at three different CPB temperatures (28°C, 32°C, and 37°C). They found no significant difference in the renal function tests (creatinine clearance, urinary albumin-creatinine ratio) among the three groups and concluded that CPB perfusion temperature does not influence renal function in patients with normal preoperative creatinine levels. The observed uniform increase in urinary albumin and total protein levels at 24 hours suggests that there is a potentially deleterious effect of CPB on glomerular function at all temperatures. The increase in urinary retinol binding protein on postoperative day 3 in all three groups suggests a longer lasting alteration in proximal tubular function after CPB than in glomerular function. Normothermic CPB was associated with the same degree of renal functional changes as hypothermic CPB. The oncotic pressure of perfusate during CPB has also been studied. Whereas tissue edema and metabolic acidosis increase with decreased colloid oncotic pressure, urinary excretion and glomerular filtration rate improve. The safety margin for renal function during CPB widens when the protein content of perfusate is decreased. Thus, 16 mmHg and 4.2 g/dL were believed to be the optimal levels of perfusate oncotic pressure and protein content, respectively, during CPB.[169] Hemodilution during CPB improves urine flow, increases renal free-water clearance, and decreases urinal osmolarity and filtration fraction, thus protecting the integrity of the renal tubules postoperatively.[167] Outer cortical flow in the kidney also increases, but oxygen delivery to the outer and inner cortex is diminished with hemodilution.[167] Decreased cortical flow may be caused by microemboli formed within the oxygenator itself, which then

are distributed to the terminal arteriolar branches of the kidney. Hessel et al,[170] in a prospective study to evaluate the between-membrane and bubble oxygenators, found a higher relative platelet count after CPB with the membrane oxygenator and no significant differences in bleeding or pulmonary, renal, or cardiac function between groups. In that study, renal function was monitored with BUN and urine flow data.

The Inflammatory Reaction

Aprotinin is a proteinase inhibitor with effects on a number of biochemical systems. In patients undergoing cardiac surgery with CPB, aprotinin has been shown to inhibit plasma-mediated and kallikrein-mediated fibrinolysis and to decrease the formation of fibrin degradation products.[171-176] In addition to effects on contact activation and fibrinolytic pathways, aprotinin improves hemostasis during and after CPB by preserving the platelet membrane adhesive receptor (glycoprotein Ib).[171] Aprotinin undergoes active reabsorption by the proximal tubules and is gradually metabolized by lysosomal enzymes in the kidney. Two large clinical trials using aprotinin have shown an incidence of renal dysfunction (renal failure or temporary elevation of plasma urea or creatinine levels) of about 1% to 2%.[160-162] In a multicenter study using aprotinin in 671 patients undergoing cardiac surgery in the United Kingdom, there was a 0.4% incidence of renal failure, 1% incidence of renal dysfunction, and a temporary postoperative increase in postoperative BUN or creatinine levels in 0.6%.[173] In a German study of 1,784 patients receiving aprotinin, elevated postoperative creatinine levels were independently associated with preoperative plasma creatinine levels, the age of the patient, and duration of surgery.[172] In that study, no detrimental effect of aprotinin on renal function could be established. Higher mean urine output in patients receiving aprotinin versus placebo has been reported. Of 80 patients who underwent primary CABG operations, urine output was significantly elevated during the initial 6 postoperative hours in the intensive care unit.[173] Patients receiving aprotinin have shown changes in biochemical markers of tubular damage without clinical evidence of renal dysfunction.[175]

Four placebo-controlled studies with aprotinin have been conducted in the United States. During cardiac valve surgery, the incidence of elevations of plasma creatinine concentration of 70.5 mg/dL ($\geq$44 μmol/L) greater than baseline was 21% for patients receiving high-dose aprotinin, 18% for low-dose aprotinin, and 14% for patients receiving placebo.[177] Renal dysfunction, however, was not severe in the majority of patients and was reversible. In another study of 100 patients undergoing CABG or valve replacement, serum creatinine levels were elevated greater than 1.3 mg/dL (>115 μmol/L) in a high-dose aprotinin group versus a placebo group, but no significant difference (>1.7 mg/dL) was noted between groups.[176] Lemmer et al[178] found no differences in clinically significant adverse events related to renal function between high-dose aprotinin and placebo in patients who underwent primary or repeated CABG surgery and had baseline normal creatinine levels. Some investigators have suggested that patients with diabetes and those undergoing hypothermic arrest[179] receiving high-dose aprotinin have an increased risk of renal dysfunction during and after CPB. The proximal tubular epithelial cells in the kidney take up small proteins, such as aprotinin and insulin, to recycle the amino acids and the kidneys become overwhelmed. Feindt et al[180] found that patients with normal renal function who underwent CABG surgery with aprotinin had temporary tubular damage compared with a placebo group. Renal dysfunction increased β_2-microglobulin levels and increased renal tubular protein load for 5 days, with maximum dysfunction on postoperative day 3. This finding was confirmed in a retrospective study in which moderate impairment in tubular function was noted in children who had undergone cardiac surgery.[181]

SUMMARY

In patients with renal disease undergoing cardiovascular surgery, perioperative management continues to be a challenge. Traditional answers have turned into new questions with the introduction of new agents and the redesign of old techniques.

For ARF prevention, early recognition of pending deleterious compensatory changes is critical. Theoretically, therapeutic intervention designed to prevent ischemic renal failure should be designed to preserve the balance between RBF and oxygen delivery on one hand and oxygen demand on the other. Maintenance of adequate cardiac output distribution to the kidney is determined by the relative ratio of renal artery vascular resistance to systemic vascular resistance. Indeed, it should not be surprising to learn that norepinephrine (despite its vasoconstricting effect) has been reported to have no deleterious renal effects in patients with low systemic vascular resistance.[182]

Until recently, strategies for the treatment of ARF have been directed to supportive care with dialysis (to allow tubular regeneration). Various therapeutic maneuvers have been introduced in an attempt to accelerate the recovery of glomerular filtration, including dialysis, nutritional regimens, and new pharmacologic agents. A recent small prospective trial of low-dose dopamine in the prophylaxis of ARF in patients undergoing abdominal aortic aneurysm repair showed no benefit in those patients receiving dopamine.[183] Conversely, the effects of intravenous atrial natriuretic peptide in the treatment of patients with ARF appear to offer benefit in patients with oliguria. Among 121 patients with oliguric renal failure, 63% of those who received a 24-hour infusion of atrial natriuretic peptide required dialysis within 2 weeks compared with 87% who did not.[184] Whether this effect will be borne out in the future remains to be determined. The administration of epidermal growth factor after induction of ischemic ARF in rats has been shown to enhance tubular regeneration and accelerate recovery of kidney function.[185,186] Human growth factor administration has been shown to increase GFR 130% greater than baseline in patients with chronic renal failure, but no data for clinical ARF have been reported.

In addition, there have been significant improvements in dialysis technology in the treatment of ARF. Modern dialysis uses bicarbonate as a buffer as opposed to acetate, which reduces cardiovascular instability, and has more precise regulation of volume removal.[181] Dialysate profiles and temperatures improve hemodynamics and reduce intradialytic hypotension. Techniques of hemodialysis without anticoagulation have re-

duced bleeding complications. Finally, dialysis membranes activate neutrophils and complement less with the biocompatible membranes used today that reduce recovery time and dialysis treatment.[188,189] Evidence indicates that activation of complement and neutrophils by older dialysis membranes caused a greater incidence of hypotension, adding to ischemic renal injury. It remains to be determined whether early and frequent dialysis with biocompatible membranes, as well as other therapeutic interventions, will increase the survival of patients with perioperative ARF.

REFERENCES

1. McCarthy JT: Prognosis of patients with acute renal failure in the intensive care unit: A tale of two eras. Mayo Clinic Proc 71:117-126, 1996
2. Maher ER, Robinson KN, Scoble JE, et al: Prognosis of critically ill patients with acute renal failure. APACHE II score and other predictive factors. Q J Med 72:857-866, 1989
3. Beaman M, Turney JH, Rodger RS, et al: Changing pattern of acute renal failure. Q J Med 62:15-23, 1987
4. Novis BK, Roizen MF, Aronson S, et al: Association of perioperative risk factors with postoperative acute renal failure. Anesth Analg 78:143-149, 1994
5. Kaufman J, Dhakal M, Patel B, et al: Community-acquired acute renal failure. Am J Kidney Dis 17:191-198, 1991
6. Hou SH, Bushinsky DA, Wish JB, et al: Hospital-acquired renal insufficiency: A prospective study. Am J Med 74:243-248, 1983
7. Shusterman N, Strom BL, Murray TG, et al: Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. Am J Med 83:65-71, 1987
8. Charlson ME, MacKenzie CR, Gold JP, et al: Postoperative changes in serum creatinine. When do they occur and how much is important? Ann Surg 209:328-333, 1989
9. Abel RM, Wick J, Beck CH Jr, et al: Renal dysfunction following open-heart operations. Arch Surg 108:175-177, 1974
10. Casali R, Simmons RL, Najarian JS, et al: Acute renal insufficiency complicating major cardiovascular surgery. Ann Surg 181:370-375, 1975
11. Hilberman M, Myers BD, Carrie BJ, et al: Acute renal failure following cardiac surgery. J Thorac Cardiovasc Surg 77:880-888, 1979
12. Stott RB, Cameron JS, Ogg CS, et al: Why the persistently high mortality in acute renal failure. Lancet 2:75-79, 1972
13. Wilkes BM, Mailloux LU: Acute renal failure. Pathogenesis and prevention. Am J Med 80:1129-1136, 1986
14. Yeboah ED, Petrie A, Pead JL: Acute renal failure and open heart surgery. Br Med J 1:415-418, 1972
15. Abreo K, Moorthy AV, Osborne M: Changing patterns and outcome of acute renal failure requiring hemodialysis. Arch Intern Med 146:1338-1341, 1986
16. Kasiske BL, Kjellstrand CM: Perioperative management of patients with chronic renal failure and postoperative acute renal failure. Urol Clin North Am 10:35-50, 1983
17. McCombs PR, Roberts B: Acute renal failure following resection of abdominal aortic aneurysm. Surg Gynecol Obstet 148:175-178, 1979
18. Davidman M, Olson P, Kohen J, et al: Iatrogenic renal disease. Arch Intern Med 151:1809-1812, 1991
19. Kellen M, Aronson S, Roizen MF, et al: Predictive and diagnostic tests of renal failure: A review. Anesth Analg 78:134-142, 1994
20. Badr KF, Ichikawa I: Prerenal failure: A deleterious shift from renal compensation to decompensation. N Engl J Med 319:623-629, 1988
21. Oken DR: Hemodynamic basis for human acute renal failure (vasomotor nephropathy). Am J Med 76:702-710, 1984
22. Bonventure JV: Mechanism of ischemic acute renal failure. Kidney Int 43:1160-1178, 1993
23. Aronson S: Monitoring renal function, in Miller RD (ed): Anesthesia (ed 4). New York, NY, Churchill Livingstone, 1994, pp 1293-1317
24. Myers BD, Moran SM: Hemodynamically mediated acute renal failure. N Engl J Med 314:97-105, 1986
25. Thadhani R, Pascual M, Bonventre JV: Acute renal failure. N Engl J Med 334:1448-1460, 1996
26. Levenson DJ, Simmons CE Jr, Brenner BM: Arachidonic acid metabolism, prostaglandins and the kidney. Am J Med 72:354-374, 1982
27. Shaw SG, Weidmann P, Hodler J, et al: Atrial natriuretic peptide protects against acute ischemic renal failure in the rat. J Clin Invest 80:1232-1237, 1987
28. Rahman SN, Batt AT, Dubose TD, et al: Differentiating clinical affects of ANP in oliguric and non-oliguric ATN. J Am Soc Nephrol 6:474A, 1995
29. Levinsky NG: Pathophysiology of acute renal failure. N Engl J Med 296:1453-1458, 1977
30. Brezis M, Rosen S, Silva P, Epstein FH: Renal ischemia, a new perspective. Kidney Int 26:375-383, 1984
31. Abbott WM, Austen WG: The reversal of renal cortical ischemia during aortic occlusion by mannitol. J Surg Res 16:482-489, 1974
32. Gamulin Z, Forster A, Morel D, et al: Effects of infrarenal aortic cross-clamping on renal hemodynamics in humans. Anesthesiology 61:394-399, 1984
33. Wilson DM, Turner DR, Cameron JS, et al: Value of renal biopsy in acute intrinsic renal failure. Br Med J 2:459-461, 1976
34. Aronson S: Tests of renal function, in Roizen MF, Fleisher LA (eds): Essence of Anesthesia (ed 1). Philadelphia, PA, Saunders, 1996, p 573
35. Ciabattoni G, Ciniotti GA, Pierucci A, et al: Effects of sulindac and ibuprofen in patients with chronic glomerular disease. Evidence for dependence of renal function on prostacyclin. N Engl J Med 310:279-283, 1984
36. Lifschitz MD: Renal effects of the newer nonsteroidal anti-inflammatory agents. J Lab Clin Med 102:313-323, 1983
37. Galler M, Folkert VW, Schlondorff TB: Reversible acute renal insufficiency and hyperkalemia following indomethacin therapy. JAMA 246:154-155, 1981
38. Wilson RF, Soullier G, Antonenko D: Creatinine clearance in critically ill surgical patients. Arch Surg 114:461-467, 1979
39. Sladen RN, Endo E, Harrison T: Two-hour versus twenty-two–hour creatinine clearance in critically ill patients. Anesthesiology 67:1013-1016, 1987
40. Price RG: Measurement of N-acetyl-beta-glucosaminidase and its isoenzymes in urine methods and clinical applications. Eur J Clin Chem Biochem 30:693-705, 1992
41. Schardijn GH, Statius van Eps LW: $Beta_2$-microglobulin: Its significance in the evaluation of renal function. Kidney Int 32:635-641, 1987
42. Rabito CA, Moore RH, Bougas C, et al: Noninvasive, real-time monitoring of renal function: The ambulatory renal monitor. J Nucl Med 34:199-207, 1993
43. Aronson S, Thistlethwaite RJ, Walker R, et al: Safety and feasibility of renal blood flow determination during kidney transplant surgery with perfusion ultrasonography. Anesth Analg 80:353-359, 1995
44. Kainuma M, Yamada M, Miyake T: Continuous urine oxygen tension monitoring in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 10:603-608, 1996

45. Lawrence CJ, Prinzen FW, deLange S: The effect of dexmedetomidine on nutrient organ blood flow. Anesth Analg 83:1160-1165, 1996

46. Kulka PJ, Tryba M, Zenz M: Preoperative alpha$_2$-adrenergic receptor agonists prevent the deterioration of renal function after cardiac surgery: Results of a randomized, controlled trial. Crit Care Med 24:947-952, 1996

47. Kennedy WF Jr, Sawyer TK, Gerbershagen HY, et al: Systemic cardiovascular and renal hemodynamic alterations during epidural anesthesia in normal men. Anesthesiology 31:414-421, 1969

48. Sadda M, Duval AM, Bonnet F, et al: Abnormalities in myocardial segmental wall motion during lumbar epidural anesthesia. Anesthesiology 71:26-32, 1989

49. Sulerman MY, Passannante AN, Onder RL, et al: Alteration of renal blood flow during epidural anesthesia in normal subjects. Anesth Analg 84:1076-1080, 1997

50. Halperin BD, Feeley TW: The effect of anesthesia and surgery on renal function. Int Anesthesiol Clin 22:157-168, 1984

51. Brezis M, Rosen S: Hypoxia of the renal medulla—Its implications for disease. N Engl J Med 332:647-655, 1995

52. Sladen RN: Effects of anesthesia and surgery on renal function. Crit Care Clin 3:373-393, 1987

53. Deutsch S: Kidney function during anesthesia and hemorrhage. Int Anesthesiol Clin 12:109-125, 1974

54. Deutsch S, Goldberg M, Stephen GW, et al: Effects of halothane anesthesia on renal function in normal man. Anesthesiology 27:793-804, 1966

55. Mazze RI, Calvey RK, Smith NT: Inorganic, fluoride nephrotoxicity: Prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46:265-271, 1977

56. Mazze RI, Shue GL, Jackson SH: Renal dysfunction associated with methoxyflurane anesthesia. A randomized prospective clinical evaluation. JAMA 216:278-288, 1971

57. Mazze RI, Trudell JR, Cousins MJ: Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. Anesthesiology 35:247-252, 1971

58. Kharasch ED: Metabolism and toxicity of the new anesthetic agents. Acta Anaesthesiol Belg 47:7-14, 1996

59. Kharasch ED: Biotransformation of sevoflurane. Anesth Analg 81:S27-S38, 1995 (suppl 6)

60. Kenna JG, Jones RM: The organ toxicity of inhaled anesthetics. Anesth Analg 81:S51-S66, 1995 (suppl 6)

61. Malan TP Jr: Sevoflurane and renal function. Anesth Analg 81:S39-S45, 1995 (suppl 6)

62. Frink EJ Jr, Malan TP, Atlas M, et al: Clinical comparison of sevoflurane and isoflurane in healthy patients. Anesth Analg 74:241-245, 1992

63. Bastron RD, Pyne JL, Inagaki M: Halothane-induced renal vasodilation. Anesthesiology 50:126-131, 1979

64. Young CJ, Attele A, Toledano A, et al: Volatile anesthetics decrease peristalsis in the guinea pig ureter. Anesthesiology 81:452-458, 1994

65. Inman SR, Stowe NT, Albanese J, et al: Contrasting effects of vecronium and succinylcholine on the renal microcirculation. Anesth Analg 78:682-686, 1994

66. Baratz RA, Philbin DM, Patterson RW: Urinary output and plasma levels of antidiuretic hormone during intermittent positive-pressure breathing in the dog. Anesthesiology 32:17-22, 1970

67. Jarnberg PO, deVillota ED, Eklund J, et al: Effects of positive end-expiratory pressure on renal function. Acta Anesthesiol Scand 22:508-514, 1978

68. Kumar A, Pontoppidan H, Baratz RA, et al: Inappropriate response to increased plasma ADH during mechanical ventilation in acute respiratory failure. Anesthesiology 40:215-221, 1974

69. Berry AJ: Respiratory support and renal function. Anesthesiology 55:655-667, 1981

70. Truniger B, Rosen SM, Grandchamp A, et al: Redistribution of renal blood flow in hemorrhagic hypotension. Role of renal nerves and circulating catecholamines. Eur J Clin Invest 1:227-280, 1971

71. Roizen MF, Lampe GH, Beuefiel DJ, et al: Is increased operative stress associated with worse outcome? Anesthesiology 67:3A:A1, 1987 (abstr)

72. Gonsowski CT, Laster MJ, Eger EI II, et al: Toxicity of compound A in rats. Effect of a 3-hour administration. Anesthesiology 80:556-565, 1994

73. Gonsowski CT, Laster MJ, Eger EI II, et al: Toxicity of compound A in rats. Effects of increasing duration of administration. Anesthesiology 80:566-573, 1994

74. Bito H, Ikeuchi Y, Ikeda K: Effects of low-flow sevoflurane anesthesia on renal function: Comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. Anesthesiology 86:1231-1237, 1997

75. Eger EI II, Koblin DD, Bouland T, et al: Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 84:160-168, 1997

76. Kharasch ED, Frink EJ, Zager R, et al: Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. Anesthesiology 86:1238-1253, 1997

77. Schmidt PJ, Holland PV: Pathogenesis of the acute renal failure associated with incompatible transfusions. Lancet 2:1169-1172, 1967

78. Knochel JP, Schlein EM: On the mechanism of rhabdomyolysis in potassium depletion. J Clin Invest 51:1750-1758, 1972

79. Honda N, Kurokawa K: Acute renal failure and rhabdomyolysis. Kidney Int 23:888-898, 1983

80. Gabow PA, Kaehny WD, Kelleher SP: The spectrum of rhabdomyolysis. Medicine 61:141-152, 1982

81. Edwards DH, Griffith TM, Ryley HC, Henderson AH: Haptoglobin-hemoglobin complex in human plasma inhibits endothelium dependent relaxation: Evidence that endothelium-derived relaxing factors acts as a local autocoid. Cardiovasc Res 20:549-556, 1986

82. Lowenstein J, Faulstick DA, Yiengst MJ, Shock NW: The glomerular clearance and renal transport of hemoglobin in adult males. J Clin Invest 40:1172-1177, 1961

83. Knochel JP: Rhabdomyolysis and myoglobinuria. Annu Rev Med 33:435-443, 1982

84. Braun SR, Weiss FR, Keller AI, et al: Evaluation of the renal toxicity of heme proteins and their derivatives: A role of the genesis of acute tubular necrosis. J Exp Med 131:443-460, 1970

85. Ron D, Taitelman U, Michaelson M, et al: Prevention of acute renal failure in traumatic rhabdomyolysis. Arch Int Med 144:277-280, 1984

86. Chawla SK, Najafi H, Ing TS, et al: Acute renal failure complicating ruptured abdominal aortic aneurysm. Arch Surg 110:521-526, 1975

87. Luft FC, Hamburger RJ, Dyer JK, et al: Acute renal failure following operation for aortic aneurysm. Surg Gynecol Obstet 141:374-378, 1975

88. Gelman S: The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 82:1026-1060, 1995

89. Roberts AJ, Nora JD, Hughes WA, et al: Cardiac and renal responses to cross-clamping of the descending thoracic aorta. J Thorac Cardiovasc Surg 86:732-741, 1983

90. Alpert RA, Roizen MF, Hamilton WK, et al: Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery 95:707-711, 1984

91. Knos GB, Berry AJ, Isaacson IF, Weitz FI: Intraoperative urinary output and postoperative blood urea nitrogen and creatinine levels in

patients undergoing aortic reconstructive surgery. J Clin Anesth 1:181-185, 1989

92. Abbott WM, Austen WG: The reversal of renal cortical ischemia during aortic occlusion by mannitol. J Surg Res 16:482-489, 1974

93. Joob AW, Harman PK, Kaiser DL, Kron IL: The effect of renin-angiotensin system blockade on visceral blood flow during and after thoracic aortic cross-clamping. J Thorac Cardiovasc Surg 91:411-418, 1986

94. Gamulin Z, Forster A, Simonet F, et al: Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. Anesthesiology 65:688-692, 1986

95. Cunningham FO, Egan JM, Inahara T: Continuous epidural anesthesia in abdominal vascular surgery. A review of 100 consecutive cases. Am J Surg 139:624-627, 1980

96. Roizen MF: Anesthesia goals for surgery to relieve or prevent visceral ischemia, in Roizen MF (ed): Anesthesia for Vascular Surgery. New York, NY, Churchill Livingstone, 1990, pp 171-196

97. Remuzzi G, Bergni A: Endothelins in the control of cardiovascular and renal function. Lancet 342:589-593, 1993

98. Svensson LG, Crawford ES, Hess KR, et al: Experience with 1509 patients undergoing thoracoabdominal aortic operations. J Vasc Surg 17:357-370, 1993

99. Abel RM, Buckley MJ, Austen WG, et al: Etiology, incidence, and prognosis of renal failure following cardiac operations. Results of a prospective analysis of 500 consecutive patients. J Thorac Cardiovasc Surg 71:323-333, 1976

100. Chesney RW, Kaplan BS, Freedom RM, et al: Acute renal failure: An important complication of cardiac surgery in infants. J Pediatr 87:381-388, 1975

101. Gomez-Campdera FJ, Maroto-Alvaro E, Galinanes M, et al: Acute renal failure associated with cardiac surgery. Child Nephrol Urol 9:138-143, 1988-1989

102. Spitzer A: Renal physiology. Impact of recent developments on clinical nephrology. Pediatr Clin North Am 18:377-393, 1971

103. Subramanian S: Early correction of congenital cardiac defects using profound hypothermia and circulatory arrest. Ann R Coll Surg Engl 54:176-188, 1974

104. Lema G, Meneses G, Urzua J, et al: Effects of extracorporeal circulation on renal function in coronary surgical patients. Anesth Analg 81:446-451, 1995

105. Hynynen M: Atrial natriuretic factor and cardiopulmonary bypass. Can J Anaesth 34:488-489, 1990

106. McIntyre RW, Schwinn DA: Atrial natriuretic peptide. J Cardiothorac Anesth 3:91-98, 1989

107. Espiner EA, Richards AM: Effect of atrial natriuretic peptide in normal and hypertensive humans, in Samson WK, Quirion R (eds): Atrial Natriuretic Peptides. Boca Raton, FL, CRC Press, 1990, pp 243-260

108. Hynynen M, Palojoki R, Heinonen J, et al: Renal and vascular effects of atrial natriuretic factor during cardiopulmonary bypass. Chest 100:1203-1209, 1991

109. Aren C, Feddersen K, Radegran K: Effects of prostacyclin infusion on platelets and hemodynamics in coronary bypass surgery. Thorac Cardiovasc Surg 32:81-84, 1984

110. Feddersen K, Aren C, Granerus G, et al: Effects of prostacyclin infusion on renal function during cardiopulmonary bypass. Ann Thorac Surg 40:16-19, 1985

111. Abe K, Fujino Y, Sakakibara T: The effect of prostaglandin E_1 during cardiopulmonary bypass on renal function after cardiac surgery. Eur J Clin Pharmacol 45:217-220, 1993

112. Gailiunas P Jr, Chawla R, Lazarus JM, et al: Acute renal failure following cardiac operations. J Thorac Cardiovasc Surg 79:241-243, 1980

113. Goto F, Otani E, Kato S, et al: Prostaglandin E_1 as a hypotensive drug during general anesthesia. Anaesthesia 37:530-535, 1982

114. Lum GM, Aisenbrey GA, Dunn MJ, et al: In vivo effect of indomethacin to potentiate the renal medullary cyclic AMP response to vasopressin. J Clin Invest 59:8-13, 1977

115. Myles PS, Buckland MR, Schenk NJ, et al: Effect of "renal-dose" dopamine on renal function following cardiac surgery. Anaesth Intensive Care 21:56-61, 1993

116. Davis RF, Lappas DG, Kirklin JK, et al: Acute oliguria after cardiopulmonary bypass: Renal functional improvement with low-dose dopamine infusion. Crit Care Med 10:852-856, 1982

117. Hollenberg NK, Epstein M, Rosen SM, et al: Acute oliguric renal failure in man: Evidence for preferential renal cortical ischemia. Medicine 47:455-474, 1968

118. Wenstone R, Campbell JM, Booker PD, et al: Renal function after cardiopulmonary bypass in children: Comparison of dopamine with dobutamine. Brit J Anaesth 67:591-594, 1991

119. Horwitz D, Fox SM III, Goldberg LI: Effects of dopamine in man. Circ Res 10:237-243, 1962

120. Goldberg LI, Rajfer SI: Dopamine receptors: Applications in clinical cardiology. Circulation 72:245-248, 1985

121. Goldberg LI, McDonald RH Jr, Zimmerman AM: Sodium diuresis produced by dopamine in patients with congestive heart failure. N Engl J Med 269:1060-1064, 1963

122. 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 6:42-46, 1986

123. Casson IF, Clayden DA, Cope GF, Lee MR: The protective effect of gamma-glutamyl L-dopa on the glycerol-treated rat model of acute renal failure. Clin Sci 65:159-164, 1983

124. Chiolero R, Borgeat A, Fisher A: Postoperative arrhythmias and risk factors after open heart surgery. Thorac Cardiovasc Surg 39:81-84, 1991

125. Behnia R, Koushanpour E, Brunner EA: Effects of hyperosmotic mannitol infusion on hemodynamics of dog kidney. Anesth Analg 82:902-908, 1996

126. Carcoana OV, Kates RA, Panagopaulos G: The effect of cardiopulmonary bypass on renal tubular function: Does mannitol provide renal tubular protection? Anesth Analg 80:SCA29, 1995

127. Utley JR, Stephens DB, Wachtel C, et al: Effect of albumin and mannitol on organ blood flow, oxygen delivery, water content, and renal function during hypothermic hemodilution cardiopulmonary bypass. Ann Thorac Surg 33:250-257, 1982

128. Rigden SP, Dillon MJ, Kind PR, et al: The beneficial effect of mannitol on postoperative renal function in children undergoing cardiopulmonary bypass surgery. Clin Nephrol 21:148-151, 1984

129. Behnia R, Koushanpour E, Brunner EA: Effects of hyperosmotic mannitol infusion on hemodynamics of dog kidney. Anesth Analg 82:902-908, 1996

130. Morris CR, Alexander EA, Bruns FJ, Levinsky NG: Restoration and maintenance of glomerular filtration by mannitol during hypoperfusion of the kidney. J Clin Invest 51:1555-1564, 1972

131. Barry KG, Cohen A, Knochel JP, et al: Mannitol infusion II. The prevention of acute functional renal failure during resection of an aneurysm of the abdominal aorta. N Engl J Med 264:967-971, 1961

132. Burke TJ, Cronin RE, Duchin KL, et al: Ischemia and tubule obstruction during acute renal failure in dogs: Mannitol in protection. Am J Physiol 238:F305-F314, 1980

133. Birtch AG, Zakheim RM, Jones LG, et al: Redistribution of renal blood flow produced by furosemide and ethacrynic acid. Circ Res 21:869-878, 1967

134. Cantarovich F, Galli C, Benedetti L, et al: High-dose furosemide in established acute renal failure. Br Med J 4:449-450, 1973

135. Nuutinen LS, Kairaluoma M, Tuononen S, Larini TK: The effect of furosemide on renal function in open-heart surgery. J Cardiovasc Surg 19:471-479, 1978

136. Fecht DC, Magovern GJ, Park SB, et al: Beneficial effects of

methylprednisolone in patients on cardiopulmonary bypass. Circ Shock 5:415-422, 1978

137. Pierce CH, Briggs BT, Gutelreus JR: Methylprednisolone and phenoxybenzamine in experimental shock: Cardiovascular dynamics and platelet function, in Forscher BK, Lillehei RC, Stubbs SS (eds): Shock in Low and High-Flow States. Amsterdam, The Netherlands, Excerpta Medica 1972, p 183

138. Weissmann G: The effects of steroids and drugs on lysosomes, in Dingle JR, Fell HB (eds): Lysosomes in Biology and Pathology. New York, NY, American Elsevier, 1969, p 276

139. Motsay GJ, Alho AV, Deitzmen RH, et al: Forelimb, small intestine, and pulmonary vascular beds in canine endotoxin shock, in Glen TM (ed): Steroid and Shock. Baltimore, MD, University Park Press, 1974, p 151

140. Lefer AM: Blood-borne humoral factors in the pathophysiology of circulatory shock. Circ Res 32:129-139, 1973

141. Nonoyama A, Katsuda H, Nakahashi M, et al: Studies on the massive administration of corticosteroid during open-heart surgery. Its effect on renal function. Jpn Circ J 34:711-724, 1970

142. Nuutinen LS: The effect of nitrous oxide on renal function in open heart surgery. Ann Chir Gynaecol 65:200-206, 1976

143. O'Dwyer C, Lin C, Woodson L, et al: Phenylephrine increases aortic pressure but not regional perfusion during porcine bypass. Anesth Analg 80:SCA 71, 1995

144. Yao FS, Hartman GS, Thomas SJ, et al: Does arterial pressure during cardiopulmonary bypass affect renal and pulmonary complications following coronary artery surgery? Anesth Analg 80:SCA113, 1995

145. Valentine S, Barrowcliffe M, Peacock J: A comparison of effects of fixed and tailored cardiopulmonary bypass flow rates on renal function. Anaesth Intensive Care 21:304-308, 1993

146. Koning HM, Koning AJ, Defauw JJ: Optimal perfusion during extra-corporeal circulation. Scand J Thorac Cardiovasc Surg 21:207-213, 1987

147. Yeboah ED, Petrie A, Pead JL: Acute renal failure and open heart surgery. Br Med J 1:415-418, 1972

148. Bhat JG, Gluck MC, Lowenstein J, et al: Renal failure after open heart surgery. Ann Intern Med 84:677-682, 1976

149. Urzua J, Troncoso S, Bugedo G, et al: Renal function and cardiopulmonary bypass: Effect of perfusion pressure. J Cardiothorac Vasc Anesth 6:299-303, 1992

150. Hooker DR: A study of the isolated kidney: The influence of pulse pressure upon renal function. Am J Physiol 27:24-44, 1910

151. Gesell RA: On the relation of pulse pressure to renal secretion. Am J Physiol 32:70-93, 1913

152. Goodyer AVN, Glenn WL: Relation of arterial pulse pressure to renal function. Am J Physiol 167:689-697, 1951

153. Ritter ER: Pressure flow relations in the kidney: Alleged effects of pulse pressure. Am J Physiol 168:480-489, 1952

154. Thompson DD, Pitts RF: Effects of alterations of renal arterial pressure on sodium and water excretion. Am J Physiol 168:490-499, 1952

155. Hickey PR, Buckley MJ, Philbin DM: Pulsatile and nonpulsatile cardiopulmonary bypass: A review of a counterproductive controversy. Ann Thorac Surg 36:720-737, 1983

156. Chiu IS, Chu SH, Hung CR: Pulsatile flow during routine cardiopulmonary bypass. J Cardiovasc Surg (Torino) 25:530-536, 1984

157. Mori A, Watanabe K, Onoe M, et al: Regional blood flow in the liver, pancreas, and kidney during pulsatile and nonpulsatile perfusion under profound hypothermia. Jpn Circ J 52:219-227, 1988

158. Louagie YA, Gonzalez M, Collard E, et al: Does flow character of cardiopulmonary bypass make a difference? J Thorac Cardiovasc Surg 104:1628-1638, 1992

159. Badner NH, Murkin JM, Lok P: Differences in pH management and pulsatile/nonpulsatile perfusion during cardiopulmonary bypass do not influence renal function. Anesth Analg 75:696-701, 1992

160. Michielon P, Zanardo G, Calo M, et al: Renal effects of pH-stat/alpha-stat strategy during cardiopulmonary bypass. J Cardiothorac Anesth 3:57, 1989 (suppl 1)

161. Tuppurainen T, Settergren G, Stensved P: The effect of pHa and whole-body oxygen uptake on renal function during hypothermic cardiopulmonary bypass in man. J Cardiothorac Anesth 3:56, 1989 (suppl 1)

162. Weinstein GS, Rao PS, Vretakis G, et al: Serial changes in renal function in cardiac surgical patients. Ann Thorac Surg 48:72-76, 1989

163. Mazzarella V, Gallucci T, Tozzo C, et al: Renal function in patients undergoing cardiopulmonary bypass operations. J Thorac Cardiovasc Surg 104:1625-1627, 1992

164. Hashimoto K, Miyamoto H, Suzuki K, et al: Evidence of organ damage after cardiopulmonary bypass. The role of elastase and vasoactive mediators. J Thorac Cardiovasc Surg 104:666-673, 1992

165. Hashimoto K, Nomura K, Nakano M, et al: Pharmacological intervention for renal protection during cardiopulmonary bypass. Heart Vessels 8:203-210, 1993

166. Barry KG, Mazze RI, Schwartz FD: Prevention of surgical oliguria and renal hemodynamic suppression by sustained hydration. N Engl J Med 270:1371-1377, 1964

167. Utley JR, Wachtel C, Cain RB, et al: Effects of hypothermia, hemodilution, and pump oxygenation on organ water content, blood flow and oxygen delivery, and renal function. Ann Thorac Surg 31:121-133, 1981

168. Regragui IA, Izzat MB, Birdi I, et al: Cardiopulmonary bypass perfusion temperature does not influence perioperative renal function. Ann Thorac Surg 60:160-164, 1995

169. Schupbach P, Pappova E, Schilt W, et al: Perfusate oncotic pressure during cardiopulmonary bypass. Optimum levels as determined by metabolic acidosis, tissue edema, and renal function. Vox Sang 35:332-344, 1978

170. Hessel EA II, Johnson DD, Ivey TD, et al: Membrane versus bubble oxygenator for cardiac operations. A prospective randomized study. J Thorac Cardiovasc Surg 80:111-122, 1980

171. Davis R, Whittington R: Aprotinin. A review of its pharmacology and therapeutic efficacy in reducing blood loss associated with cardiac surgery. Drugs 49:954-983, 1995

172. Dietrich W, Barankay A, Hahnel C, et al: High-dose aprotinin in cardiac surgery: Three years' experience in 1,784 patients. J Cardiothorac Vasc Anesth 6:324-327, 1992

173. Bidstrup BP, Harrison J, Royston D, et al: Aprotinin therapy in cardiac operations: A report on use in 41 cardiac centers in the United Kingdom. Ann Thorac Surg 55:971-976, 1993

174. Bidstrup BP, Royston D, Sapsford RN, et al: Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). J Thorac Cardiovasc Surg 97:364-372, 1989

175. Blauhut B, Gross C, Necek S, et al: Effects of high-dose aprotinin on blood loss, platelet function, fibrinolysis, complement, and renal function after cardiopulmonary bypass. J Thorac Cardiovasc Surg 101:958-967, 1991

176. Swart MJ, Gordon PC, Hayse-Gregson PB, et al: High-dose aprotinin in cardiac surgery—A prospective randomized study. Anaesth Intensive Care 22:529-533, 1994

177. Miles Incorporated: Aprotinin Prescribing Information. New Haven, CT, 1994

178. Lemmer JH Jr, Stanford W, Bonney SL, et al: Aprotinin for coronary artery bypass grafting: Effect on postoperative renal function. Ann Thorac Surg 59:132-136, 1995

179. Sundt TM III, Kouchoukos NT, Saffitz JE, et al: Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. Ann Thorac Surg 55:1418-1424, 1993

180. Feindt PR, Walcher S, Volkmer I, et al: Effects of high-dose

aprotinin on renal function in aortocoronary bypass grafting. Ann Thorac Surg 60:1076-1080, 1995

181. Ranucci M, Corno A, Pavesi M, et al: Renal effects of low-dose aprotinin in pediatric cardiac surgery. Minerva Anestesiol 60:361-366, 1994

182. Schaer GL, Fink MP, Parillo JE: Norepinephrine alone versus norepinephrine plus low-dose dopamine: Enhanced renal blood flow with combination pressor therapy. Crit Care Med 13:492-496, 1985

183. Baldwin L, Henderson A, Hickman P: Effect of postoperative low-dose dopamine on renal function after elective major vascular surgery. Ann Intern Med 120:744-747, 1994

184. Rahman SN, Butt AR, DuBose TD, et al: Differential clinical effects of anaritide atrial natriuretic peptide (ANP) in oliguric and non-oliguric ATN. J Am Soc Nephrol 6:474, 1995

185. Hammerman MR, Miller SB: Therapeutic use of growth factors in renal failure. J Am Soc Nephrol 5:1-11, 1994

186. Miller SB, Martin DR, Kissane J, Hammerman MR: Insulin-like growth factor I accelerates recovery from ischemic acute tubular necrosis in the rat. Proc Natl Acad Sci U S A 89:11876-11880, 1992

187. Sadowski RH, Allred EN, Jabs K: Sodium modeling ameliorates intradialytic and interdialytic symptoms in young hemodialysis patients. J Am Soc Nephrol 4:1192-1198, 1993

188. Schiffl H, Lang SM, Konig A, et al: Biocompatible membranes in acute renal failure: Prospective case-controlled study. Lancet 344:570-572, 1994

189. Yoshioka T, Ichikawa I: Glomerular dysfunction induced by polymorphonuclear leukocyte–derived reactive oxygen species. Am J Physiol 257:F53-F59, 1989