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PERIOPERATIVE MANAGEMENT OF PATIENTS WITH CHRONIC RENAL FAILURE

Siniša Šefer[1], Vlado Juranko[2], Petar Kes[3] and Vesna Degoricija[4]

[1]Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital, Zagreb; [2]Intensive Care Unit, Magdalena Special Hospital for Cardiovascular Surgery and Cardiology, Krapinske Toplice; [3]Department of Dialysis, Zagreb University Hospital Center, Zagreb; [4]University Department of Medicine, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Any surgical procedure, ranging from general operation (the most common procedures is surgical creation of arteriovenous fistula and catheter for peritoneal dialysis placement) to open heart surgery, may be performed in patients with chronic renal failure treated conservatively or with dialysis without a significant increase in the perioperative motality and morbidity in comaparation to patients without renal disease. This is possibly only with good perioperative management of these patinets and multidisciplinary collaboration of nephrologist, anesthesiologist, cardiologist, surgeon, primary care physician and nursing staff to recommend strategies for reducing cardiac and renal risk for the planned surgycal procedures.

Key words: *Kidney failure, chronic – surgery; Kidney failure, chronic – anesthesia; Preoperative care; Intraoperative care; Premedication*

Introduction

Symptoms or laboratory abnormalities suggestive of chronic renal failure (CRF) are unlikely until less than 40% of normal functioning nephrons remain. The uremic syndrome occurs with a loss of greater than 95% of functioning nephrons and requires dialysis for continued survival. Complications of CRF are multiple and often introduce significant anesthetic considerations. The perioperative management of the patients with CRF includes preoperative preparation, intraoperative and postoperative treatment. CRF may be categorized as mild (glomerular filtration rate /GFR/ of 60-89 mL/min/1.73 m^2), moderate (GFR of 30-59 mL/min/1.73 m^2), severe (GFR of 15-29 mL/min/1.73 m^2), or end-stage renal disease (ESRD) (hemodialysis /HD/ or peritoneal dialysis /PD/ is initiated as the GFR falls to <10 mL/min/1.73m^2)[1]. Some patients with CRF receive kidney transplantation before (a few cases) or after (majority of recipients) the initiation of HD or PD. The progression of renal disease from one stage to the next, the need of urgent or maintenance dialysis, prevention and management of fluid, electrolyte, and acid-base imbalances before, during and after surgery, and the high cardiac risk are issues that must be addressed before a patient with CRF proceeds for elective surgery. An early nephrologic evaluation is mandatory to assess renal function and the need of renal replacement therapy perioperatively. Based on the Croatian Registry of Renal Replacement Therapy at the end of 2002, 2,359 (76%) patients received HD, 218 (7%) patients received continuous ambulatory peritoneal dialysis (CAPD), and 532 (17%) patients had functional renal transplant[2]. In Croatia, we have not yet a CRF patient registry. It has been estimated that 5% of the adult population have a pre-existing chronic renal disease that may contribute to perioperative morbidity[3].

Correspondence to: *Siniša Šefer, M.D.*, Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: sinisa.sefer@zg.htnet.hr

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Preoperative Decision Making and Management

Preoperative evaluation and preparation of CRF patients is mandatory to minimize perioperative morbidity and mortality.

Medical history and physical examination

Thorough medical history and physical examination are essential in the evaluation of CRF patients prior to surgery. During the procedures of medical history and physical examination, information on the following should be obtained:

Blood pressure and blood sugar trends

Hypertension is found in more than 80% of CRF patients. Whether hypertension is a cause or a result of CRF remains debatable[4]. The most common cause of hypertension is volume overload. Nonvolume-dependent hypertension is related to an altered autonomic-hormonal milieu of uremia. Patients with untreated or poorly controlled hypertension have increased intraoperative hemodynamic instability and an increased risk in the presence of a preoperative diastolic blood pressure >110 mm Hg. The aforementioned complications that are associated with a decline in renal function and uncontrolled hypertension or blood sugar levels must be identified and corrected preoperatively. In a diabetic patient, intrinsic renal disease including glomerulosclerosis and renal papillary necrosis increases the risk of acute renal failure in the perioperative period. The major contributing factors are hemodynamic impairment leading to decreased renal perfusion, and urinary tract sepsis associated with stasis caused by autonomic dysfunction of the bladder and diabetic susceptibility to infections. Urinary tract infections are the most common postoperative complication in diabetic surgical patients[5].

Presence of anemia

Impairment in the hormonal function of kidney results in a decrease in the production of erythropoietin (Epo) causing anemia. Chronic renal anemia is well-tolerated because tissue blood flow increases secondarily to decreased blood viscosity and increased cardiac output. A further aid to tissue oxygenation is a shift of the oxyhemoglobin dissociation curve to the right owing to metabolic acidosis and increased concentrations of 2,3-DPG. There is no conformity of opinion as to the safe hemoglobin (Hb) and hematocrit (Htc) for surgery. Generally accepted is Hb 3110 g/L and Htc 32-35%[6]. These values depend on differences among individual patients (with or without coronary artery disease /CAD/ or congestive heart failure), differences among scheduled surgical procedures and the anticipated intraoperative blood loss. Chronic normovolemic anemia is generally well-tolerated and not found to be associated with increased anesthetic morbidity and mortality for elective minor surgery. Prior to elective major surgical procedures the Hb and Htc should be corrected by adequate Epo and iron therapy. If time does not permit it, anemia must be corrected with transfusion of red blood cells (RBC). In patients with ESRD each unit of blood transfusion represents a potassium load hazard[7]. Potassium leaks out of the red cell during storage (4-8-mmol content of potassium *per* RBC unit in a 250-300 mL volume) caused by paralysis of the K/Na pump at a temperature of +4 °C and white blood cell (WBC) enzymatic damage of RBC membranes may increase the serum potassium concentration[8]. This extracellular potassium load is only a transient effect, because once infused, potassium is taken up by RBC and/or eliminated by urinary excretion secondarily to the bicarbonate production of the citrate metabolism. Transfusion-associated hyperkalemia may be observed in CRF patients with already elevated potassium levels. For this reason fresh RBC transfusion is preferable. Three-week-old blank blood may have an extracellular potassium concentration as high as 21 mmol/L. Prolongation of the last preoperative HD session may be necessary to achieve the desired postdialysis serum potassium level. By chelating calcium, citrate prevents clotting in blood products during storage. The infused citrate is rapidly metabolized and excreted primarily by the liver and then by the kidneys, with bicarbonate as the end product. Citrate toxicity can be manifested by severe hypocalcemia in primarily hypocalcemic CRF patients, neuromuscular or cardiac abnormalities[9]. Laboratory evaluations for acid-base status and ionized calcium are strongly recommended after RBC transfusion and prior to the initiation of anesthesia, as calcium imbalance is associated with significant morbidity or mortality.

Radiocontrast exposure

Radiocontrast material can induce acute deterioration of renal function, especially in CRF patients, by causing vasoconstriction and direct renal tubular epithelial cell damage. If radiocontrast material must be used preoperatively, prophylactic oral administration of the antioxidant acetylcysteine or verapamil, along with hydration (0.45% saline), and postradiologic medical procedures HD may reduce the risk of renal function impairment in CRF patients[10].

Previus surgical experiences and allergies

Inquiry about the patient's history of previous surgeries can help determine the effects of general anesthesia and the presence of allergies to medications.

Coagulation disorders

Bleeding tendencies in uremic patients rise towards platelet dysfunction and presence of deficient platelet – vessel wall interaction. Platelet dysfunction appears to be due to defective release of a macromolecular complex of von Willebrand's factor and factor VIII (VWF-VIII) from capillary endothelium. The VWF-VIII complex binds and activates platelets, and is essential for normal aggregation and clot formation[11]. The thrombocytopathy is not corrected by platelet transfusion but is improved by intensive, efficient dialysis, cryoprecipitate, 8-deamino-D-arginine vasopressin (DDAVP), and estrogen conjugates[12,13]. Before every surgical procedure coagulation tests must be performed in CRF patients. These include platelet count, activated partial thromboplastin time (APTT) and prothrombin time (PT). The bleeding time can be shortened (but not always) to the normal range by the following procedures: intensive HD or PD to maximize reversal of the uremic state, and RBC transfusion or the administration of Epo to raise Htc to at least 30%. Acetylsalicylic acid must be avoided for 2 weeks prior to operation. Heparin from previous HD may cause prolongation of bleeding time. The half-life of heparin averages one hour in dialysis patients but may be as long as 2.5 hours or more. If heparin is used for HD, then is the best to complete HD at least 12 hours prior to starting operation. If heparin-free or regional citrate technique is used, HD can be performed up to the time of surgical procedure. PD does not increase the bleeding risk and may be continued up to the time of surgery.

Use of potentially nephrotoxic drugs

Further deterioration of renal function can be avoided by identifying and eliminating potential nephrotoxic agents. This includes substitution or dosage adjustment for antibiotics (e.g., aminoglycosides, acyclovir, amphotericin), high dose of diuretics in combination with nephrotoxic antibiotics, sedatives, and muscle relaxants. The nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and radiocontrast material should be avoided[14,15]. All drug interactions and potential nephrotoxicity must be identified and stopped or the dose of the drug adjusted for the level of renal function.

Fluid status

CRF patients may be overhydrated or dehydrated. Overhydration should be completely corrected prior to surgery with intensive diuretic therapy or preoperative dialysis. Overhydration will impede tissue approximation, suturing, and wound healing. Dehydration may lead to severe hypotension during induction of anesthesia and the subsequent surgery.

Nutritional status

CRF patients are at risk during the period when the GFR falls below 10 mL/min but prior to the initiation od dialysis. The nutritional status of CRF patients can be estimated from serum albumin level. Most CRF patients are on a protein-restricted diet and may have a depleted lean body mass. CRF is categorized according to abnormal substrate utilization. These patients are prone to hyperglycemia and hypertriglyceridemia because of increased peripheral insulin resistance and decreased lipoprotein lipase activity. Homocysteine concentration is high in CRF patients[16]. A direct consequence of the combination of uremia and anemia with poor nutritional status is a decreased resistance to infection. WBC dysfunction (phagocytosis, chemotaxis) and immunosuppression (cell-mediated immunity and hypogammaglobulinemia) coexist. This contributes to the malnutrition-inflammation-atherosclerosis syndrome (MIA) with a high incidence of CAD, cerebral and peripheral artery disease (PAD)[17]. Daily loss of protein in CAPD patients is up to 15 g and may increase to 30-40 g/day during acute peritonitis. Serum albumin has been shown to be a very strong predictor of mortality in HD patients. Patients with serum albumin levels above 40 g/L have lowest mortality. When the serum albumin level falls below 30 g/L, the increase in the mortality rate is quite dramatic[18]. These patients have low colloid oncotic pressure (<15 mm Hg) and are prone to the formation of interstitial and pulmonary edema. Functional residual capacity and ventilatory reserve are decreased and the risk of postoperative pulmonary edema is increased. Serum albumin of less than 30 g/L must be substituted with 20% human albumin to the range of 340 g/L prior to surgery[19]. As albumin exerts osmotic activity, slow infusion is recommended due to the possible risk of heart failure and pulmonary edema. Hypoalbuminemia will impede wound healing and wound suturing dehiscence as a consequence of depleted lean body mass and catabolic effects of uremia. The adverse consequences of the poor nutritional state include increased mortality, increased susceptibility to infection, malaise, and poor postoperative rehabilitation.

Functional capacity

The patient's functional capacity should be assessed by using simplified questions about the usual daily activi-

ties (e.g., climbing flights of stairs, shoveling snow in winter). Functional capacity is defined in metabolic equivalents (METs), which are usually self-reported. However, this capacity can also be assessed based on the results from exercise treadmill testing. Patients who achieve at least 7 METs have a significantly better prognosis. Strenuous activities such as swimming or tennis, have estimated energy requirements of at least 10 METs. Patients with poor functional capacity should be evaluated with noninvasive testing methods, while patients with good functional capacity can proceed to surgery[20].

Extent of uremia

Based on the updated American College of Cardiology/American Heart Association Task Force on Practice Guidelines guidelines on perioperative cardiovascular evaluation of noncardiac surgery[21], pre-existing renal disease (preoperative serum creatinine levels between 123.7 and 176.8 mmol/L or above) has been identified as a risk factor for postoperative renal dysfunction and increased long-term morbidity and mortality compared with patients without renal disease[22]. In coronary artery bypass patients who are more than 70 years old, preoperative creatinine levels >229.8 mmol/L place the patient at a much greater risk of chronic dialysis postoperatively than those with creatinine levels L229.8 mmol/L[23]. One large study has shown that a preoperative creatinine level >176.8 mmol/L is a significant independent risk factor for cardiac complications after major noncardiac surgery[24].

The impact of primary disease and presence of comorbidity

The cause of CRF also has a considerable impact on clinical management. Patients with primary renal disease (e.g., IgA nephropathy) are likely to be younger and have good cardiopulmonary reserve. Older patients with CRF secondary to diabetes mellitus or hypertension may suffer the ravages of diffuse atherosclerosis and heart disease. CRF secondary to systemic lupus erythematosus or vasculitis implies multisystem involvement and dysfunction. CRF patients with significant comorbid diseases should be evaluated carefully. Comorbid diseases (e.g., pulmonary disease, history of stroke, transient ischemic attacks, hematologic, gastrointestinal or endocrine diseases) increase the risk of surgery in CRF patients. The symptoms and signs of central nervous system (CNS) disorders depend on the rapidity of progression of uremia rather than the level of blood urea nitrogen (BUN). If it develops slowly over time, the levels of BUN of more than 43 mmol/L or serum creatinine of 884-1060 mmol/L are tolerated with remarkably well preserved sensorium. However, uremic encephalopathy may manifest after an acute event such as major surgery, gastrointestinal bleeding, or infection[25]. Peripheral sensorimotor neuropathy with "glove and stocking" distrubation is a common complication of CRF and an important indication for dialysis initiation[26]. The presence of peripheral neuropathy should alert one to the strong likelihood of coexistent autonomic neuropathy. Important consequences include silent myocardial ischemia, impaired gastric emptying and increased aspiration risk, orthostatic hypotension, and impaired circulatory response to anesthesia. Urea appears to act as a mucosal irritant, and in uremic enteropathy the entire gastrointestinal tract may become inflamed and irritable. Anorexia, hiccups, nausea, and vomiting are hallmarks of the uremic syndrome. These symptoms can be controlled by protein restriction and dialysis, but they may recur when uremic patients present for surgery for acute problems. Peptic ulcer disease occurs in up to 25% of CRF patients, even when uremic symptoms are well controlled by regular dialysis[27]. There is an increased risk of regurgitation and aspiration during induction and emergence of anesthesia. Enteropathy, ulceration, and bleeding are exacerbated by perioperative stress, uremic coagulopathy, and heparinization during HD. Because of the frequent exposure to blood and blood products, the incidence of hepatitis B and C in patients on chronic dialysis is high. Many patients become asymptomatic carriers without jaundice and with minimal abnormality of liver function tests. All patients on dialysis should be treated as potentially infected, and medical personnel should take precautions against exposure, including hepatitis B vaccine and protective clothing, especially during anesthesia and surgery. The most common diseases are PAD and CAD. PAD is a significant risk marker for the presence of CAD. Epidemiologic studies have shown the incidence of CAD in patients with PAD to be 25%-90%, depending on age group. CAD is largely asymptomatic in more than 50% of patients with PAD, largely due to the limited functionality of these patients and the presence of intermittent claudication and congestive heart failure. Using a noninvasive diagnostic test, the ankle-branchial index (ABI), the prevalence of PAD was 2.5% in patients younger than 60 years and 18.8% in patients older than 70 years[28]. Thorough physical examination should be performed, particularly to obtain evidence of volume overload and cardiovascular abnormalities (e.g., murmurs, carotid bruits, pericardial effusion, abnormal peripheral pulses). Note the presence or absence of hair

on the lower extremities because this information may herald undiagnosed PAD and record all extremity blood pressures, and calculate the ABI. Abnormal calcium metabolism is observed in secondary and tertiary hyperparathyroidism, which is prevalent in CRF patients. In one retrospective study, the annual incidence of severe valvular heart disease was estimated at 15-19 cases *per* 10,000 patients who were on dialysis. In these patients, the most common etiology was calcific valvular disease, found in 69%[29]. Calcific valvular disease manifested primarily as aortic stenosis and mitral regurgitation, which could be due primarily to calcific valvular disease or secondarily to endocarditis; therefore, a history of syncope, heart failure, or chest pain should imply not only ischemic heart disease but also the possibility of significant aortic valvular disease[30]. These patients may benefit from preoperative noninvasive imaging, i.e. echocardiography.

Preoperative Laboratory Studies and Other Tests

Suggested laboratory studies

- Perform RBC count and Hb, particularly to investigate for the presence of anemia of CRF, which can be treated with Epo therapy or RBC transfusion. Epo therapy helps optimize the Hb value prior to elective surgery and RBC transfusion prior to emergency surgery.
- Conduct iron studies to determine if iron deficiency or anemia is present, which can be treated with intravenous iron. Also perform thorough gastrointestinal and gynecologic evaluation to investigate the possible cause of iron deficiency.
- Study the patient's serum chemistry results, including potassium, magnesium and phosphate concentrations, BUN and serum creatinine to establish the level of renal function and electrolyte concentrations. A recent change is most important. Also obtain digoxin and other drug levels.
- Perform urinalysis to detect urinary infection or active glomerular disease (WBC or RBC casts).
- Coagulation studies: platelet count, bleeding time, PT, TT, APTT.
- Perform a baseline electrocardiogram (ECG) to investigate for arrhythmias, conduction system abnormalities (e.g., left bundle-branch block), evidence of silent myocardial infarction (MI) or ischemia, electrolyte abnormalities (e.g., hypokalemia, hyperkalemia, hypocalcemia or hypercalcemia).

Imaging studies and other specific noninvasive testing

- Obtain a chest radiograph to rule out volume overload or active pulmonary disease, pleural, pericardial effusion, and left ventricular hypertrophy.
- Conduct noninvasive diagnostic testing in patients who are about to receive intermediate-risk procedures and have a poor functional capacity or in patients with minor clinical predictors who are about to receive high-risk surgery and have poor functional capacity. Noninvasive assessment can be achieved using the tests :
  - Exercise ECG testing: patients who are able to achieve more than 85% of the maximal predicted heart rate with good exercise capacity (>6 METs) without showing ischemic changes in the ECG findings or developing hypotension are at a very low risk of perioperative MI. Test results also help estimate the functional capacity of the patient. Limitations include difficulty in interpreting ECG findings in the presence of left bundle block, hypertensive ECG changes, and the effect of digoxin. The test has a sensitivity and specificity of 68% and 77%, respectively. However, in CRF patients this testing is much less applicable because of limitations in exercise capacity and baseline ECG abnormalities[20].
  - Stress thallium testing: advantages of this test are its applicability in patients with abnormal ECG findings, left ventricular hypertrophy, or documented CAD. A positive test result is documented as perfusion defects on images in combination with ECG findings. This combination of findings bolsters the clinical picture and has an overall sensitivity and specificity of 92% and 93%, respectively. This study has limitations in patients who are unable to attain their target heart rates, and some clinicians consider the findings to be of low predictive value in patients with diabetes and ESRD[31].
  - Dipyridamole pharmacologic myocardial perfusion imaging with thallium: this study is used in patients who are unable to exercise and/or are undergoing major vascular or orthopedic procedures. Positive test results are quantified as reversible defects. Fixed defects do not convey risk. The finding of a reversible dilated left ventricular cavity is also considered a high-risk profile. Several randomized studies have shown that the results of this test may help predict the risk of a perioperative cardiac event

in patients with ESRD[32]. Limitations include patients with pulmonary obstructive disease, use of theophylline, and critical carotid stenosis.

- Dobutamine stress echocardiography: this test is used to detect wall motion abnormalities on echocardiography findings after infusing dobutamine to increase the heart rate to at least 85% of the maximal heart rate. Findings include wall motion abnormalities and ECG changes at different infusion rates. Limitations include patients who are obese, have severe chronic obstructive pulmonary disease, and have severe hypertension and arrhythmias. In one study, a negative test result in selected patients helped identify a very low-risk population, with a 97% probability of no cardiac complications after surgery[33].

Specific noninvasive testing

- Coronary angiography: the investigation is indicated in patients with profoundly abnormal stress test results, evidence of significant left ventricular dysfunction after echocardiography testing, the possibility of significant aortic valvular pathology, and symptoms suggestive of worsening chronic angina pectoris.

Cardiovascular and Renal Risks of Anesthesia and Surgery in CRF Patients: Assessment and Intervention

Cardiovascular risk

CRF is an important risk factor for the development of heart diseases. CRF patients have an accelerated rate of atherosclerosis, and death rates due to cardiac disease increase dramatically with age in these patients. Because of improved diagnostic and therapeutic capabilities, life expectancy was increased in these patients. Cardiac disease continues to be a major cause of death in CRF patients and is responsible for up to 60% of all causes of death[34]. Hyperlipidemia, hypertension, renal anemia, increased volume load caused by arteriovenous shunts, platelet dysfunction, and abnormalities in the metabolism of calcium and triglycerides, and malnutrition are the main factors that increase the incidence of atherosclerosis and cardiac diseases in HD patients. Clinical predictors of preoperative cardiovascular risk (e.g., MI, chronic heart failure /CHF/, death) can be described as major, intermediate, or minor risk factors[35].

Major predictors

- Unstable coronary syndromes - recent MI with evidence of important ischemic risk based on clinical symptoms or the results of noninvasive testing or unstable or severe angina (Canadian Heart Association class III or IV)
- Decompensated CHF
- Significant arrhythmias – high-grade atrioventricular block, symptomatic ventricular arrhythmias in the presence of underlying heart disease, supraventricular arrhythmias with uncontrolled ventricular rate
- Severe valvular disease

Intermediate predictors

- Mild angina pectoris (Canadian Heart Association class I or II)
- Prior MI based on history findings or the presence of pathologic Q waves
- Compensated or prior CHF
- Diabetes mellitus

Minor predictors

- Advanced age
- Abnormal ECG findings (e.g., left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities)
- Rhythm other than sinus (e.g., atrial fibrillation)
- Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)
- History of stroke
- Uncontrolled systemic hypertension

Surgical risk for noncardiac procedures can be divided into high-risk, intermediate-risk, or low-risk surgery[36]. The type of surgery, the duration of the surgical procedure, and the choice of anesthesia can make difference in patient outcome. Allowing the anesthesiologist to choose the mode of anesthesia is always advisable.

High risk (reported cardiac risk often >5%)

- Emergency operations, particularly in elderly persons
- Aortic and other major vascular procedures
- Peripheral vascular procedures
- Anticipated prolonged surgical procedures associated with large fluid shifts, blood loss, or both

Intermediate risk (reported cardiac risk generally)

- Carotid endarterectomy
- Head and neck procedures
- Intraperitoneal and intrathoracic procedures

- Orthopedic procedures
- Prostate surgery

Low risk (reported cardiac risk generally)

- Endoscopic procedures
- Superficial procedures
- Cataract surgery
- Breast surgery

Patients with major clinical predictors of cardiac morbidity who are undergoing elective surgery can be treated by identifying their risk profile for surgery and their risk of the intended procedure, as indicated above. Patients with decompensated heart failure or unstable coronary syndromes should have their procedures postponed until their medical management is optimized. Patients with intermediate or minor clinical predictors who are undergoing elective noncardiac surgery should be evaluated based on their functional capacity and type of surgery.

Renal risk

Patients with CRF treated conservatively

Patients with preoperative renal insufficiency are more likely to develop postoperative renal failure than those with normal preoperative renal function. Both of these groups may benefit from optimizing intraoperative renal perfusion because not all preoperative renal risk factors are easily diagnosed[37]. Rapidly establish the duration of CRF, level of renal function impairment; and whether the elevation in BUN and creatinine is prerenal, renal, postrenal, or a combination of these. Patients who are normovolemic, responsive to diuretic therapy, and/or have no significant electrolyte and acid-base status abnormalities or bleeding tendencies are uncomplicated and do not require dialysis before surgery[38]. Patients with edema, CHF, or pulmonary congestion or those who are responsive to diuretic therapy require further cardiovascular evaluation. If the results of the cardiovascular evaluation are optimal, then fluid overload can be attributed to CRF. Combination diuretic therapy can help treat these patients to achieve normovolemia prior to surgery. Patients with diabetes have a greater tendency of having volume overload or cardiovascular disease. CRF may be so advanced that the patient develops diuretic resistance, with progressive edema. Preoperative dialysis may be considered in these patients. If the patient has a high serum potassium level, any drugs that may cause hyperkalemia must be excluded (Table 1). The presence of severe uremia prior to surgery may adversely affect platelet function, fibroblast response to tissue injury, and many aspects of the immune system. If an elective surgical procedure is being planned, the patient should be dialyzed well preoperatively. It may be necessary to administer two or three successive daily HD sessions to achieve a well-dialyzed status in patients whose uremia has not been in an optimal state of control. If repeated, intensive dialysis is performed preoperatively, then dehydration, hypokalemia, and hypophosphatemia must be avoided. If the predialysis serum level of potassium is in the low or low-normal range, the risk of hypokalemia can be minimized by adding an appropriate amount of potassium to the dialysis solution. If postoperative dialysis is imminent, the anesthesiologist should be advised to place a temporary central venous catheter for HD preoperatively. The jugular site should generally be preferred because it is associated with the lowest incidence of delayed central venous stenosis compared to subclavian access, and low rates of blood recirculation compared to subclavian and femoral site access[39]. Subclavian-vein cannulation is burdened with a 40%-50% risk of subclavian-vein stenosis or occlusion. Chronic obstruction of a subclavian vein, of course, will

Table 1. Drugs that may cause hyperkalemia

- Drugs that inhibit renin-angiotensin-aldosterone system
  - **Inhibitors of renin synthesis:** beta-blockers (e.g., metoprolol, atenolol), clonidine, methyldopa, nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen, naproxen), cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib, rofecoxib)
  - **Inhibitors of angiotensin II synthesis:** ACE inhibitors (e.g., enalapril, fosinopril)
  - **Inhibitors of aldosterone synthesis:** angiotensin II receptor blockers (e.g., losartan, candesartan), heparin, low molecular weight heparin (e.g., enoxaparin, nadroparin calcium), immunosuppressive drugs (e.g., cyclosporin, tacrolimus)
  - **Inhibitors of aldosterone receptor:** potassium-sparing diuretics (e.g., spirolactone)
  - **Blockers of distal Na^+/K^+ channels:** potassium-sparing diuretics (e.g., triamterene, amiloride), antibiotics (e.g., trimethoprim/sulfamethoxazole, pentamidine)
- **Drugs that cause release of K^+ from muscles:** succinylcholine, antipsychotics (e.g., haloperidol)
- **Others:** digoxin (overdose)

complicate later construction of a peripheral arteriovenous access on that arm[40]. Permanent vascular access placement can then be arranged when the patient is more stable.

Patients already on chronic dialysis

For patients already on dialysis, dialysis adequacy, preoperative dialysis needs, postoperative dialysis timing, and dosage requirements for all medications should be determined. Patients on HD usually require preoperative dialysis within 24 hours before surgery to reduce the risk of volume overload, hyperkalemia, and excessive bleeding. The serum potassium value in a dialysis patient who will undergo major surgical procedure is of great concern. The ideal serum potassium concentracion at the time of surgery is at the lower range of normal (about 4.0 mmol/L). In patients with no residual renal function consuming a typical diet, the serum potassium level will usually increase by 1.0-1.5 mmol/L/day. To achieve a serum potassium level of 4.0 mmol/L at time of surgery, the postdialysis serum potassium level on the day prior to operation should be about 3.0 mmol/L. The HD solution potassium level should be 2.0 mmol/L or the last preoperative HD session should be longer than usual. In patients receiving digitalis, the postdialysis serum potassium level of 4.0 mmol/L is desirable. In a severely catabolic state (sepsis, extensive trauma) or internal bleeding, the rise od serum potassium value may be greater than 1.5 mmol/L/day. In these cases potassium-binding resins may be administered (Sorbisterit, Kayexalate) in adition to prolonged HD. Progress in lowering the serum potassium concentration should be monitored by frequent blood sampling[11]. Less commonly, dialysis patients scheduled to undergo surgery are hypokalemic. In such patients the serum potassium level should be increased to at least 3.5 mmol/L before induction of anesthesia to limit the risk of cardiac arrhythmia. Preoperative hypokalemia is hazardous in patients with poor cardiac function and in patients receiving digitalis. Mild hyponatremia is common in severely ill patients. The presence of hyponatremia preoperatively is undesirable because the administration of sodium-poor fluids during and after operation will result in further fall in the serum sodium level. In the correction of the acid-base balance, the goal is to correct the patient's pH and not necessarily the plasma bicarbonate concentration. A mild preoperative acidosis may be safer than a severe preoperative alkalosis. Severe alkalemia can occur due to hyperventilation during anesthesia or in the postoperative period. Alkalemia can predispose to cardiac arrhythmias.

Although CAPD patients generally have a constant higher serum creatinine level (often >800 mmol/L) in relation to HD patients whose postdialysis serum creatinine level is often <400 mmol/L, in the absence of overhydration signs and electrolyte disbalance, and with an acceptable dialysis efficacy measured with Kt/V, any surgical procedure can be performed in CAPD patients without an increased incidence of anesthetic morbiditiy and mortality risk. Patients with CAPD who are undergoing abdominal surgery should be switched to HD until wound healing is complete[41]. CAPD should be continued in those undergoing nonabdominal surgery but should be restarted postoperatively only when it can be assured that the patient's ventilatory status will tolerate abdominal distension and high diaphragmatic pressure. The use of CAPD has some advantages over HD in the early postoperative period. CAPD can be initiated with minimal equipment and does not require specialy trained personnel. It also avoids the potential complications of abrupt hemodynamic changes or the risk of heparin-associated bleeding that may occur with the use of HD. However, CAPD may be contraindicated after cardiac surgery when there is a continuity of the thorax or pericardium (or both) with the abdominal cavity. The risks of peritonitis, respiratory disturbances, and protein loss are other drawbacks of the CAPD.

Patients who have a renal transplant

Because of complicated drug interactions and immunosuppressive dosing, monitoring, and adjustment, a nephrologist with specialized knowledge of renal transplantation should be included in the preoperative evaluation of CRF patients who have received kidney transplant. Cyclosporine or tacrolimus taken by renal transplant recipients for immunosuppression are metabolized by the cytochrome P-450 system in the liver and thus interact with a wide variety of agents. Diltiazem, hepatic 3-methylglutaryl coenzyme A reductase inhibitors, macrolides, and antifungal drugs inhibit the system, elevate immunosuppressive drug levels, and can precipitate nephrotoxicity. Other agents, such as carbamazepine, barbiturates, and theophylline, induce the system, reduce immunosuppressive drug levels, and can precipitate transplanted kidney rejection. Drug levels must be monitored in this setting. Intravenous cyclosporine or tacrolimus should be given at one-third oral dose until the patient is able to tolerate oral medications[42].

Effect of Anesthesia and Pharmacologic Alterations in CRF Patients

Virtually all anesthetic drugs and techniques are associated with decreases in renal blood flow, GF rate and urine output reflecting multiple mechanisms (decreased cardiac output, altered autonomic nervous system activity, neuroendocrine changes, positive pressure ventilation). Renal blood flow (15% to 25%) of the cardiac output by far exceeds renal oxygen needs but ensures optimal clearance of wastes and drugs. The administration of general anesthesia may induce a reduction in renal blood flow in up to 50% of patients, resulting in an impaired excretion of nephrotoxic drugs[43]. Surgery is a major insult on the human body regardless of the anesthesia provided. The information obtained from the patient preoperatively is used to devise a safe anesthetic plan. The anesthetic agents we plan for intraoperative use are aimed at minimizing the body's stress response to surgery, maintaining homeostasis while considering the patient's chronic medical problems, managing fluid shifts and losses, and providing postoperative pain control. The decreasing incidence of anesthetic morbidity and mortality over the past decades has coincided with the adoption of practice standards, and new pharmacological agents. Drugs normally excreted by the kidney accumulate in CRF patients, exerting their toxicity. Therefore, dosage adjustment or drug avoidance is a key pathophysiologic principle in CRF patients (Table 2).

Premedication

CRF patients have a high susceptibility to excessive sedation and respiratory depression, thus premedication should be kept to a minimal level and omitted in the presence of uremic encephalopathy. A short-acting anxiolytic (e.g., midazolam) in a small dose is appropriate for the oriented, anxious, and alert patient. Glycopyrolate is preferred to atropine and scopolamine to minimize anticholinergic CNS effects. In patients with normal renal and hepatic function, the meperidine half-life is 3-5 hours. Normeperidine, an active metabolite of meperidine, is about half as potent as meperidine, but it has a twofold ability to stimulate the CNS. The half-life of normeperidine is substantially longer (15-30 hours). Accumulation after repeated or high doses, especially in patients with hepatic or renal impairment, should be considered. Patients with normal urine pH excrete about 30% as active metabolite and about 5% as unchanged parent drug. Acidification of the urine greatly enhances the excretion of both meperidine and normeperidine.To decrease the risk of nausea, vomiting, and aspiration, an H_2-blocker, proton pump blocker plus metoclopramide may be helpful. Cimetidine may decrease renal blod flow and is not recommended.

Regional anesthesia

The most common procedure in CRF patients is surgical creation of arteriovenous fistula (AVf). Regional an-

Table 2. Pharmacokinetics of anesthetic drug

Drug	Elimination	Metabolites	Metabolite activity
Anticholinergic agents			
Atropine	PR		
Glycopyrolate	PR		
Cholinergic agents			
Edrophonium	PR		
Neostigmine	PR		
Pyridostigmine	PR		
Barbiturates			
Methylphenobarbiton	PR		
Methohexital	PR		
Phenobarbital	PR		
Thiopental	PR		
Benzodiazepines			
Diazepam*&	PR	Oxazepam	Sedative
Lorazepam	PR		
Midazolam*&	PR	1-Hydroxy-midazolam	Sedative

Drug	Elimination	Metabolites	Metabolite activity
Oxazepam	PR		
Opioides			
Alfentanil	PR		
Fentanyl	PR		
Sufentanil	PR		
Remifentanil	PR		
Pethidine	PR	Norpethidin	Neuroexcitatory
Nelbufin	PR		
Pentazocin	PR		
Hydromorphine	PR	Hydromorphone-3-glucuronide	Analgesic
Morphine	PR	Morphine-3-glucuronide Morphine-6-glucuronide Normeperidin	Antalgesic Analgesic (40xmorphine) neuroexcitatory
Meperidin*	PR		
Muscle relaxant			
Atracurium	Hoffman		
Rocurium	PR		
Mivacurium	PR		
Doxacurium	PR		
Cis-Atracurium	Hoffman		
Vecuronium*	PR H/R	Desacetyl-vecuronium	Relaxant
Pipecuronium	PR		
Pancuronium*	DR	3-Hydroxy-pancuronium	Relaxant
d-tubocurarine	PR		
Succinylcholine	PR		
Gallamine	DR		
Demethyltubocurarine	DR		
Hypnotic agents			
Etomidate	PR		
Droperidol	PR		
Ketalar	PR		
Propofol	Hoffman		
Inhalation anesthetic agents			
Enfluran*	PR	Fluoride	Nephrotoxic
Desfluran	PR		
Izofluran	PR		
Sevofluran	PR	Fluoride	Nephrotoxic

DR=drug predominantly dependent on renal elimination; the loading dose is unaltered but maintenance doses are drastically reduced;

PR=drug partially dependent on renal elimination; the loading dose is unaltered but maintenance doses should be decreased by 30%-50%; Hoffman=totally independent of renal function

*drug with active or toxic metabolites dependent on renal excretion; these drugs be avoided or used with caution in CRF patients

&drug with increased unbound fraction in CRF; decrease dosage by 30%-50%

esthetic techniques are used very successfully for this operation. Brachial plexus or axillary block have been very popular for insertion or revision of AVf. Spinal or epidural anesthesia is used for renal transplantation in a number of transplantation centers. Patients with autonomic neuropathy are at an increased risk of hypotension induced by sympathetic blockade. In these cases, treatment by massive fluid administration is the potential danger for acute

pulmonary edema when the local anesthetic effect wears off postoperatively. The sudden loss of sympathetic block causes autotransfusion of blood from the peripheries to the heart and rises the risk of cardiac arrhythmias if epinephrine is added to local anesthetic. The possibility for enhanced systemic effects of local anesthetics due to decreased protein binding appears to be more theoretical than real. *N*-acetyl-procainamide, a metabolite of procainamide, accumulates in persons with CRF and, when used in combination with H_2-blockers, causes prolongation of the QT interval in ECG[44]. A coagulation disorder is a contraindication to spinal or epidural anesthesia or the axillary artery puncture for axillary block.

General anesthesia

Anesthetic induction

In anemic patients, the use of preoxygenation to increase plasma oxygen content assumes great importance[45]. Appropriate fluid loading (250-500 mL) should be given prior to anesthetic induction to prevent acute hypotension in response to anesthetic-induced vasodilatation and venous pooling in anuric patients with normal or even transiently depleted intravascular volume status after last dialysis treatment or after extensive pathologic fluid loss (vomiting, diarrhea, gastric suction, forced diuresis). Reduced protein binding (especially thiopental, methohexital, and diazepam) and uremia-induced alterations in the blood brain barrier may result in the need of lower induction doses of intravenous drugs because in the presence of hypoalbuminemia these drugs have an increased active, unbound fraction. Dosage reduction is also recommended with coinduction techniques, e.g., midazolam+opioides (fentanyl, sufentanil) because of the limited cardiovascular reserve. Ketamine is not affected by renal failure and is a useful agent for emergency anesthetic induction[46]. Hiccups, nausea, and vomiting are common, and gastric emptying is delayed in uremic patients. All patients should be treated as if they have an increased risk of acid aspiration. Although rapid sequence induction may not be appropriate for every patient, cricoid pressure should always considered.

Choice of muscle relaxant

A standard dose of succinylcholine (1 mg/kg) may induce potassium release and elevates serum potassium by 0.5-0.8 mmol/L, could evoke cardiac dysrhythmias and is not reliably prevented by precurarization; however, a single dose of succinylcholine is not absolutely contraindicated in CRF patients if serum potassium is less than 5.5 mmol/L and dialysis has been provided within 24 hours[47]. Pancuronium and pipecuronium should be avoided because of their delayed and unpredictable action after intubation and maintenance doses for general anesthesia, and vecuronium infusions for the accumulation of the active metabolite, 3-deacetylvecuronium, which is dependent on renal elimination. Atracurium and cisatracurium undergo spontaneous Hoffman elimination in the blood and are totally independent of renal function for their clearance. Laudanosine, a metabolite of atracurium and cisatracurium, is dependent on renal function for its prompt clearance[48]. A decreased plasma activity of cholinesterase, an enzyme responsible for breaking down certain anesthetic agents, due to CRF may be associated with prolonged neuromuscular blockade produced by mivacurium and resulting in prolonged respiratory muscle paralysis if neuromuscular blocking agents are used. Recurarization is unlikely, since the elimination of anticholinesterases is also dependent on renal function.

Maintenance of anesthesia

If chronic metabolic acidosis is present (i.e. preoperative electrolyte panel reveals total CO_2 less than 20 mmol/L), minute ventilation should be increased above normal to continue respiratory compensation during anesthesia. Compared with intravenous drugs, the potent volatile anesthetics may have some advantages in renal failure patients. Elimination of volatile anesthetic agents is independent of renal function; however, anemia decreases the blood-gas partition coefficeint for these gases so that the rate of induction and emergence is increased. Fluoride-induced nephrotoxicity is a theoretical possibility with enflurane or sevoflurane anesthesia. However, evidence suggest that CRF is not worsened by these agents[49]. There is no evidence that fluoride produced by the metabolism of enflurane or sevoflurane exacerbates chronic renal disease. After sevoflurane anesthesia, CRF patients had similar serum fluoride levels, rates of fluoride elimination, and areas under the curve for serum fluoride compared with patients with normal renal function; however, CRF patients had significanly lower urinary fluoride levels, suggesting some alteration in sevoflurane pharmacokinetics. Elevated inorganic fluoride concentrations have been associated with nephrotoxicity following methoxyflurane anesthesia[50]. Isofurane, desflurane, and halothane produce negligible levels of inorganic fluoride, which may make them preferable in patients undergoing renal transplantation. About 10% of morphine is conjugated to morphine-

6-glucuronide, which has 40 times the sedative potency of the parent compound, is dependent on renal elimination, and after a single dose may accumulate up to 15 –fold normal concentration in CRF patients. The accumulation of morphine glucuronides may account for the prolonged depression of ventilation observed in some patients with renal failure[51]. This complication should be less likely with low doses of fentanyl. Morphine and meperidine both undergo demethylation to normorphine and normeperidine, respectively. These metabolites are eliminated by the renal route and are potentially nephrotoxic. For these reasons these agents are better avoided in CRF. Furthermore, enzymes responsible for drug metabolism exist in many tissues outside the liver perhaps accounting for prolonged or enhanced effects of drugs such as morphine in patients with renal failure. Neither fentanyl nor sufentanil has active metabolites, although the elimination of fentanyl may be significantly prolonged in patients with severe uremia. Remifentanil undergoes rapid inactivation (elimination half-life, 5 minutes) by nonspecific esterases in the blood independently of renal function. The excretion of its principal metabolite (GR90291) is delayed in patients with ESRD but does not produce significant opioid effects[52]. Hepatic clearance of propofol is unchanged in CRF patients. Although glucuronide conjugates of propofol do accumulate, they lack activity and propofol pharmacodynamics is also unchanged. Total intravenous anesthesia, with a combination of propofol, remifentanil, and cisatracurium, is an attractive combination to use in CRF patients because their pharmacology is virtually unaltered in renal failure[53].

Anesthetic emergence

Delayed emergence, pulmonary edema, respiratory depression, vomiting and aspiration, and hypertension are potential problems that should be anticipated. Persistent neuromuscular blockade caused by hypermagnesemia may be partially antagonized by calcium[54]. The elimination of anticholinesterases is delayed more than anticholinergic agents, and excessive muscarinic effects (bradyarrhythmia, salivation, and bronchospasm) may manifest in the recovery room. Patients should not be extubated until they are fully awake, preferably in the right lateral position to reduce the risk of aspiration. If in doubt, a short period of postoperative mechanical ventilation may allow for controlled emergence, avoid the unnecessary use of reversal agents, and facilitate proper evaluation of neurologic and ventilatory function prior to tracheal extubation.

Intraoperative Management

Vital sign monitroing

- ECG may provide early detection of hyperkalemia and cardiac dysrrhytmias.
- Pulse oximetry is especially useful because of the increased risk of tissue hypoxia, should the SaO_2 decrease.

Preservation of vascular access

- Great attention should be paid to preservation of AVf.
- Do not position intravenous or radial arterial catheters or blood pressure cuffs at AVf site.
- Ensure that the AVf site is protected during surgery.
- Verify AVf site patency intraoperatively.
- Note that a patient with AVf will have lower diastolic pressure and higher cardiac output; also note that mixed venous O_2 saturation is affected, since it contains arterial blood flow through AVf.

Fluid management

- Central venous pressure monitoring in any procedure where large fluid shifts are anticipated.
- Pulmonary artery catheterization in patients with sepsis or cardiopulmonary insufficiency.
- Monitoring of urine output is recommended in nonanuric CRF patients. Urinary catheter should not be placed in anuric or oliguric patients to prevent ascending urinary infection.

Intraoperative dialysis

- Massive amount of infusion during surgery.
- Massive amount of blood transfusion during surgery.
- Massive tissue conquassation during surgery.
- Long duration of operation.

Prevention of hypothermia

- Increased ambient temperature, use of a heater-humidifer to warm and moisten inspired gases, blood warmer for all infused fluids, and use of a forced-air convection blanket.

Prevention of bone fracture

- Careful positioning and manipulation in patients with renal osteodystrophy.
- Prevention of pressure-related injuries of skin due to severe sensory neuropathy.

Postoperative Monitoring

The initial assessment on admission to the recovery room or intensive care unit (ICU) must include evaluation of airway reflexes, volume status, residual neuromuscular blockade, and opioid effect. Acid aspiration continuses to be a risk in the early postoperative period. The sensory level should be carefully evaluated if spinal or epidural anesthesia has been used. If regional anesthesia wears off abruptly, the resolution of sympathetic block and increased systemic vascular resistance could precipitate acute pulmonary edema in patients with compromised cardiac function. Acute pulmonary edema may also occur later when the sequestered extravascular fluid is mobilized back into the intravascular space. Delayed or incomplete reversal of neuromuscular blockade may occur, particularly if pancuronium has been used or respiratory acidosis develops. In CRF patients, the presence of chronic metabolic acidosis limits the reserve to buffer opioid-induced CO_2 retention. Even the modest degrees of hypercarbia commonly encountered during emergence (e.g., $PaCO_2$ 45 mm Hg) may rapidly result in low pH and an increased risk of acute hyperkalemia. Rhabdomyolysis is a rare complication of major surgery in patients with ESRD, and the important clinical indicator of "red urine" and positive urine myoglobin may be missed because of the established anuria or oliguria. Myoglobin may cause additional impairment of residual renal function in CRF patients. Severe hypocalcemia, hyperphosphatemia, and elevated creatinine phosphokinase (CPK) are present, and the treatment is dialysis[55]. No preoperative cardiac assessment is indicated for emergency surgery; however, postoperative cardiac assessment must be performed and continued for 3-5 days with daily ECGs and screening of cardiac enzyme levels to detect and treat the possible perioperative MI. Perioperative MI occurs mostly within the first 72 hours; however, most occurrences are silent. The incidence rate of perioperative MI is approximately 1% but carries a high mortality rate of almost 50%[56]. Be aware of discordant blood test results of total creatine kinase (CK), myocardial band enzymes of CK (CK-MB), and troponin T. Total CK levels are elevated in CRF patients but CK-MB levels are not; thus, elevation in the CK-MB levels is due to myocardial injury. Elevation of troponin T levels without a corresponding elevation in total CK levels has been shown to reflect enzyme elimination kinetics due to renal failure or cross-reactivity of the troponin I assay with noncardiac antigens[57]. Therefore, any enzyme elevations are not diagnostic in and of themselves. The diagnosis of postoperative MI should be made based on a combination of clinical, laboratory, and ECG evidence. In anuric CRF patients, maintenance fluid must be restricted; however, ongoing sequestration or overt losses should be replaced with crystalloid, colloid, or blood products. If not, hypovolemia and hypotension will result. Dialysis can be repeated in the immediate postoperative period if intraoperative fluid requirements increase intravascular fluid volume to an excessive level. Postoperative early HD may be useful in patients with inadequate urine output and a high potassium level. Dialysis was instituted whenever a serum creatinine increase to 3221 mmol/L was observed or the patient exhibited inadequate urine output (<400 mL in 24 hours) despite correction of hemodynamic status and diuretic therapy, especially if fluid overload, hyperkalemia, or metabolic acidosis were also present. If early postoperative dialysis is required but the patient is hemodynamically unstable, consideration should be given to continuous renal replacement therapy: continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF), or continuous venovenous hemofiltration (CVVH)[58].

Cardiac Surgery in CRF Patients

In recent years, the number of CRF patients who will have CAD amenable to surgical revascularization is likely to increase. Patients receiving long-term HD are at a high risk of both morbidity and mortality also after cardiac surgery. Performing cardiac surgery in these patients can be challenging. In the literature, the morbidity in different series ranged from 17% to 77%, and mortality from 8% to 31%[59]. Despite this increased risk, long-term studies have demonstrated a benefit of surgical revascularization over percutaneous transluminal coronary angioplasty in both overall survival and angina-free survival. The restenosis rate is higher in patients undergoing dialysis than in the general population undergoing coronary angioplasty[60,61]. ESRD has been viewed as an important preoperative predictor of surgical outcome. However, the impact of renal impairment on the results of heart surgery has been somewhat ill defined. There is considerably less information in the literature about operative morbidity and mortality in CRF patients who are not undergoing dialysis. A limited number of series show that morbidity ranged from 32% to 80% and mortality from 5% to 19%[62-65]. CRF patients with relatively mild renal dysfunction remain at a risk of poor outcome. In patients with creatinine levels 3221 mmol/L, there is a strong likelihood of postoperative dialysis besides the increased risks of mortality and morbidity. It is important to

carefully identify patients at a high risk of perioperative renal failure because renal ischemia is generally silent, unlike ischemia of the coronary, cerebral, and peripheral vascular beds, which are usually overt, manifested by angina pectoris, neurologic sequels, and claudication, respectively. After cardiac surgery, in CRF patients with mild impairment of renal function, correct evaluation of the necessity of dialysis and proper timing to start it are the major concerns for diminution of postoperative morbidity and mortality.

Cardiopulmonary bypass in CRF patients

For most cardiac operations, the cardiothoracic surgeon requires a bloodless, motionless field in which to work. To achieve this, the motion of the heart and lungs must be stopped. For this to occur, there needs to be a means for blood to circulate throughout the body, delivering the nutrients and oxygen necessary for life while the heart and lungs are not functioning. This is made possible through a process known as cardiopulmonary bypass (CPB) or "the heart-lung machine". CPB also plays an important role in the occurrence of postoperative organ dysfunctions by two principal means. It induces a profound hemodilution, which impairs oxygen transport through tissues. This phenomen becomes obvious in the postoperative period by the existence of increased transpulmonary O_2 gradients, extravascular lung water volume, and subsequent impairments of O_2 transport[66]. CPB is deleterious by triggering an important systemic inflammatory reaction. This reaction is largely related to the duration of exposure to CPB and to the ratio of the circuit area to the patient's body surface area, and is therefore maximal in children. It has been widely demonstrated that the very early paths of this reaction imply several humoral factors including kinins, coagulation factor XII and complement fragments (C3a, C5a). The activation of these factors is self-amplified and triggers both expression and release of numerous mediators by endothelial cells and leukocytes. Finally, these mediators are responsible for the well described "post-bypass syndrome," which is, from the clinical viewpoint, very close to hyperkinetic septic shock[67]. Several methods have been proposed to reduce the deleterious effects of both cardiac surgery and CPB: hypothermia, heparin-coated components of extracorporeal circuit and hemofiltration. Because of its very high tolerance in patients with compromised circulatory status these techniques have already been used in the intraoperative and early postoperative period to treat CRF patients with additional postoperative impairment of residual renal function or in patients already on dialysis. With a reduced renal capacity, the tolerance to CPB is worsened. The outcome of the operation depends in part on the ability of the kidneys to deal with high fluid shifts during CPB hemodilution. CRF patients who are unable to manage perioperative electrolyte levels, excess water, and uremic toxins may benefit from intraoperative dialysis. Ultrafiltration is valuable in removing excess plasma water during CPB. Modified ultrafiltration studies suggest that ultrafiltration post-CPB can improve postoperative patient outcomes and that the mechanism for these improvements involve more than excess water removal. Initially hemofiltration was intended to correct the accumulation of extravascular water and hemoconcentration during or immediately following the surgical procedure. Nevertheless, several of its side effects appeared to be useful, such as the reduction of postoperative blood loss and immediate improvement in hemodynamics[68]. Since there are no contraindications for ultrafiltration or dialysis during CPB, the decision to use these techniques depends on the perceived potential benefits and the cost of adding a component to the CPB circuit (Fig. 1). Several studies attempted to point out the mechanism of action of hemofiltration and, although removal of inflammatory mediator occurs, there is currently no proof that this removal is only one of the actual mechanisms by which this technique acts[69]. The most important electrolyte imbalance in CPB operations in CRF patients is that of potassium, because elevated and reduced levels are associated with life-threatening cardiac arrhythmia, especially after myocardial ischemia. Hypothermic and hyperkalemic solutions administered selectively to the myocardium result in diastolic electromechanical dissociation and myocardial arrest, thereby greatly lowering the metabolic rate of the heart. Mechanical arrest (potassium-induced) will reduce oxygen consumption by 80%, and hypothermia will reduce consumption by another 10%-15%. Aerobic metabolism can be maintainted with oxygenated cardioplegia. There are numerous cardioplegia custom solutions available to the surgeon. Some are premanufactured, many are mixed in the pharmacy. The cardioplegia consists of a potassium concentration four times the normal concentration found in the blood (15-17 mmol/L). The cardioplegia solution is used for cardiac asystole and myocardial preservation. It is used with a 4:1 blood to crystalloid cardioplegia delivery system. Some solutions use a blood/crystalloid ratio of 1:1, 1:2 or 1:4 using a specially designed administration set with an integrated cooling coil[70]. The solution is composed of the following: high-potassium (10 mmol/L) and low-potassium (5 mmol/L). Cardioplegia is typically administered at an

initial dose of 10-30 ml/kg at 7-10 °C with subsequent doses every 15-20 minutes if desired. Whatever solutions are used the main ingredient responsible for asystole or paralysis of the heart is the potassium concentration. Myocardial protection is dependent on maintaining asystole and relatively low myocardial temperatures of less than 15 °C[71].

Potassium-rich cardioplegia has advantages over other cardioplegic solutions in preserving the myocardium during CPB, but it is avoided in CRF patients because of hyperkalemia[72]. Intraoperative HD can effectively and safely remove potassium administered during potassium-rich cardioplegia during CPB in CRF patients and prevent postoperative hyperkalemia in the majority of patients. Overall mortality in CRF patients undergoing cardiac surgery is high irrespective of the potassium balance control in these patients.

Pharmacologic alterations during CPB

CPB results in profound changes that have important consequences for the pharmacokinetics (changes in distribution and clearance) and pharmacodynamics (changes in drug effect) of most anesthetic drugs[73]. Changes in blood flow, hemodilution and a decrease in plasma proteins can affect drug disposition. At the onset of bypass the priming fluid is mixed with the patient's blood, with an increase in plasma volume by 40%-50%. This results in considerable dilution of plasma proteins and acute falls in the total concentrations of circulating drugs. The hemodilution at the start of CPB produces a reduction in plasma protein concentration of 40%-50% for adults and can be larger in pediatric patients[74]. Another effect on protein binding occurs when bypass causes denaturation of proteins. This was most marked when bubble oxygenators were used, but can occur during contact with any of the walls of the tubing or oxygenator. The suckers used during surgery probably contribute more to this effect than the oxygenator. A fall in plasma drug concentration does not automatically result in a comparable change in the drug's pharmacologic effects. The decrease in plasma proteins alters drug protein binding, with an increase in the free drug fraction by as much as 30%. It is the free concentration that is responsible for the pharmacologic effect of a drug. However, because the unbound drug is freely diffusible, any increase tends to be offset by redistribution into the tissues, so that the overall unbound drug plasma concentration may change little during CPB. CPB is also associated with marked changes in the regional distribution of blood flow, and decreases in hepatic and renal perfusion can have significant effects on the elimination of many drugs. Liver blood flow is often decreased during CPB, and this will result in a decrease in the clearance of drugs dependent on hepatic metabolism. Hepatic clearance will also be further reduced by hypothermia due to a reduction in hepatic enzyme activity. Hypothermia also causes a 20% reduction in the clearance of remifentanil, an ultra-short acting opioid metabolized by nonspecific cholinesterases in the blood and tissues[75]. Renal blood flow is also decreased during bypass so that the renal excretion of drugs and their metabolites will be reduced. The anesthetic drugs most likely to be affected are the nondepolarizing muscle relaxants, many of which are predominantly excreted by the kidneys (renal excretion of pancuronium is 90% and of vecuronium 30%). During CPB there may also be marked changes in acid-base balance, resulting in changes in ionized and nonionized drug concentrations. This affects not only the protein binding of a drug but also its pharmacodynamics since it is only the nonionized fraction that can cross cell membranes and produce the pharmacologic effect. The magnitude of these changes depends on the nature of the drug (base or acid) and its dissociation constant. Many anesthetic drugs, e.g., benzodiazepines, opioids, are bases and their nonionized fraction will decrease with acidosis. The opposite occurs with acidic drugs such as propofol[76]. Sequestration of drugs to the CPB apparatus may have a significant influence on their plasma concentrations, with a decline greater than predicted on the basis of hemodilution alone. This effect has been most studied for the opioids[77]. The circuit component with the greatest potential for binding is the oxygenator because of the large surface area to which the blood is exposed[78]. Drug sequestration is most marked with silicon-based circuits and much less with polypropylene circuits, which make up the majority of those currently used. However, polypropylene-based circuits are not immune to these changes. For example, polypropylene-based systems primed with 625 ml crystalloid and colloid and 50 μg fentanyl *per* 100 ml prime should produce a fentanyl concentration of 480 ng/mL, yet the measured concentration was only 87 ng/mL[79].

In CRF patients treated with CPB various dialytic techniques are used in the management of fluid overload, hyperkalemia and to avoid systemic inflammatory response (HD, CVVHF, CVVHD, CVVHDF). These various techniques have a great potential for removal of large quantities of ultrafiltrable anesthetic drugs contained in cardioplegic solution and blood. Unfortunately, no *in vivo* studies of pharmacologic alterations during CPB and dialysis have been published. In the future, pharmacokinetic stud-

ies in these patients under these complex conditions can be challenging.

"Off-pump" technique for coronary artery bypass grafting in CRF patients

For coronary artery bypass grafting (CABG), the "off-pump" technique ("the beating heart") has been recently revived, because CPB appears to worsen the multiple organ dysfunction after conventional CABG. Patients must be selected for "off-pump" CABG only when complete revascularization has been technically feasible. It involves multi-vessel coronary artery bypass grafting of two to five vessels. Complete sternotomy is used but the patient remains off the heart-lung machine while the heart remains beating. Not all patients may be candidates for this procedure[80,81]. The "off-pump" CABG is as safe and effective as conventional CABG in selected dialysis patients. It might even be beneficial because it is associated with less Hb drop and blood product use, a lower catabolic rate, and fewer dialysis requirements after surgery. Technical advantages to the "off-pump" procedures include avoidance of aortic manipulation. Ascending aorta multiple cross-clamping during conventional CPB may cause atherosclerotic microemboli formation and liberation. These may cause embolization of renal artery branches and impairment of renal function[82]. Disadvantages of the "off-pump" procedure also include the difficulty in accessing vessels on the posterior and lateral heart walls. During complete revascularization, the heart will be rotated, elevated and posiblly transposed. The perfusion pressure in aorta and renal arteries significantly drop. These manipulations lead to low cardiac output and ischemia of the kidney, and may cause additional impairment of renal function. However, the impact of "off-pump" technique on the long-term clinical outcome and resource utilization in CRF patients requires further investigation[83,84].

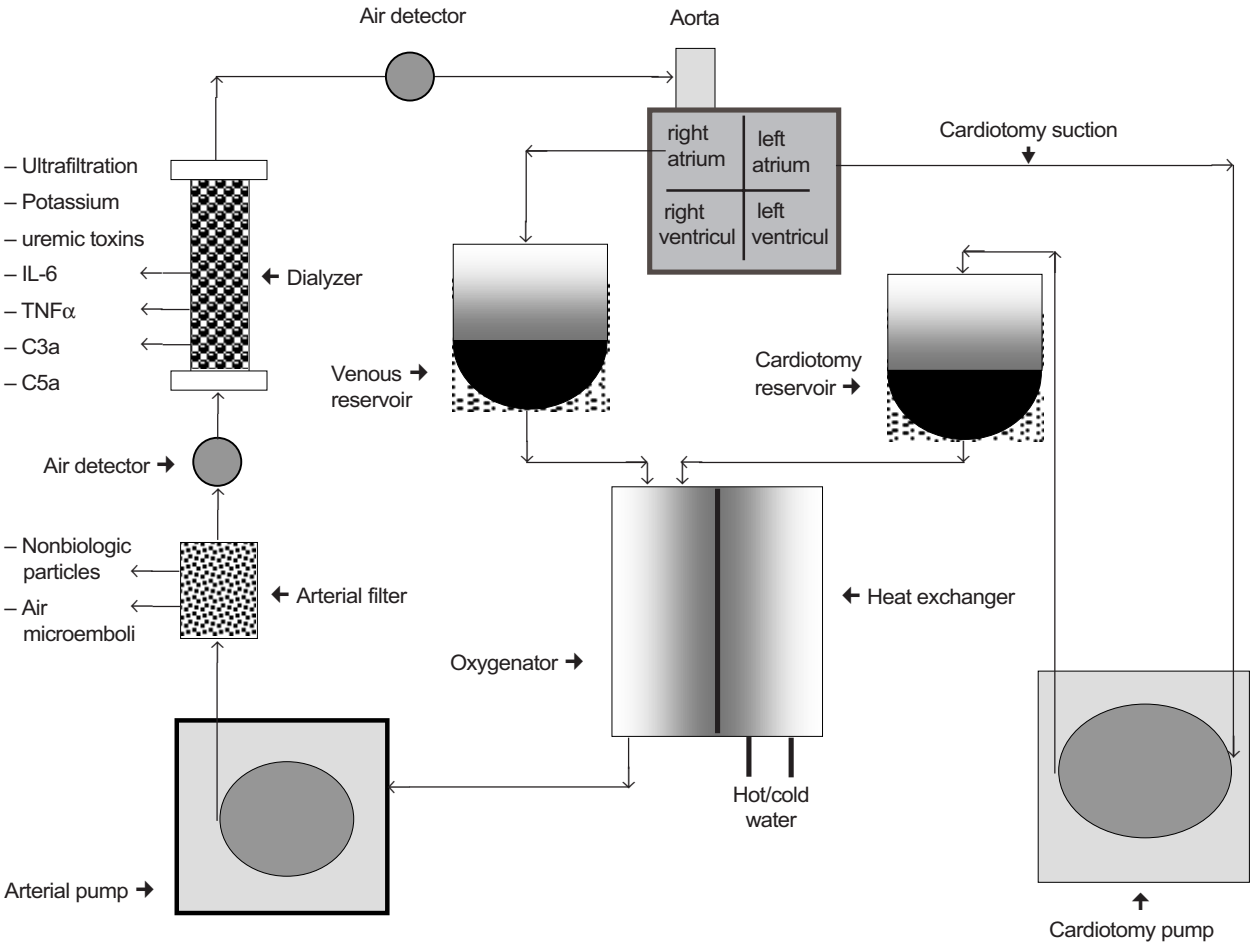

Figure 1. Components of cardiopulmonary bypass circuit modified with addition of dialyzer.

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Sažetak

Perioperacijsko zbrinjavanje bolesnika s kroničnim bubrežnim zatajenjem

S. Šefer, V. Juranko, P. Kes i V. Degoricija

Svaki kirurški postupak, od relativno jednostavnih (u ovih bolesnika najčešći su operacijsko stvaranje arteriovenske fistule i postavljanje katetera za peritonejsku dijalizu) do operacije na otvorenom srcu, može se u bolesnika s kroničnim bubrežnim zatajenjem koji se liječe konzervativno ili dijalizom učiniti bez značajnog porasta pobola i smrtnosti u odnosu na bolesnike bez bubrežne bolesti. Kako bi se mogli provesti planirani kirurški zahvati uz smanjenje srčanog i bubrežnog rizika za ove bolesnike neophodna je multidisciplinska suradnja nefrologa, anesteziologa, kardiologa, kirurga, liječnika opće medicine i sestrinskog tima za njegu bolesnika.

Ključne riječi: *Bubrežno zatajenje, kronično – kirurgija; Bubrežno zatajenje, kronično – anestezija; Prijeoperacijska skrb; Intraoperacijska skrb; Prethodni lijekovi*