Anesthetic Management in Patients with Renal Transplant Undergoing Coronary Bypass Graft Surgery

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Abstract

Background- By the end of 2000, more than 10,000 patients had received renal transplants in the Islamic Republic of Iran (IRI), and this number is expected to increase yearly. Since the 1-year survival rate for renal transplant recipients is approaching 90% and is continuing to improve annually, an increasing number of patients who have received renal transplants present for coronary artery bypass graft (CABG) surgery. They represent a technically demanding group of patients who require special consideration regarding preserving renal graft function and minimizing possible complications of cardiac surgery. This study was conducted to evaluate the outcome in renal transplant patients undergoing CABG surgery.

Patients and Methods- We prospectively studied seventeen renal transplant patients with approximately normal preoperative renal function (plasma creatinine 1.1-1.5 mg/dL) scheduled for elective coronary artery bypass surgery. Various aspects of anesthesia and the surgical procedures were assessed as regards the function of the transplanted kidney.

Results- Renal blood flow and renal transplant function are influenced before the induction of anesthesia, after sternotomy and before cardiopulmonary bypass (CPB), during hypothermic CPB and normothermic CPB, after sternal closure, and postoperative bleeding.

Conclusion- Protective interventions are very important in renal transplant patients undergoing coronary artery bypass graft surgery to prevent deterioration of renal function. Hemofiltration was performed routinely to prevent volume overload and excessive hemodilution. We used low-dose dopamine infusion (renal dose) throughout the operation and phenylephrine infusion during cardiopulmonary bypass. **(*Iranian Heart Journal.* 2002; 2(4)&3(1): 14-20)**

Key words: renal transplanted patients < coronary bypass graft < immunosuppressive drugs < kidney protection

With advances in anesthetic and surgical management, a larger number of sick patients, including many with renal dysfunction and renal transplants are being referred for cardiac surgery.[1-4] Particularly of importance is the fact that coronary artery disease is the second most common cause of mortality in renal transplant patients, following renal factors such as graft rejection. Preoperative renal dysfunction and renal transplantation are both well - known predictors of

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postoperative renal failure, infection and renal rejection, which remain a serious postoperative complication of surgical procedures, especially those in which cardiopulmonary bypass (CPB) are utilized. Transplant recipients are always under treatment with various regimens of immunosuppressive drug therapy. The immunosuppressive drugs in common use are cyclosporine A, azathioprine, anti-lymphocyte globulin, monoclonal antibodies, and steroids. Newer drugs, such as tacrolimus (FK 506), may replace cyclosporin, and the drug mycophenolate (mofetil) may replace azathioprine in some clinical protocols. [5]

Because cyclosporine or tacrolimus plasma levels must be kept within the indicated therapeutic range, the blood levels of these agents in those renal transplanted patients receiving these drugs should be monitored daily in the perioperative period. Clinically significant reductions of cyclosporine or tacrolimus blood levels can be caused by dilution with massive fluid infusion preoperatively[6] and cardiopulmonary bypass.[7] Extracorporeal circulation may have a negative impact on renal function. Generally however, there is no consensus regarding the etiological factors for this detrimental effect.[12]

Our studies have shown that patients with normally functioning preoperative renal transplants do not suffer detrimental effects from extracorporeal circulation under moderately hypothermic bypass.[3] This study was carried out to evaluate the factors influencing immediate outcome in patients with renal transplants and with an acceptable renal function who undergo coronary artery bypass surgery and hemodilution and moderately hypothermic CPB.

Methods and Materials

This study was performed prospectively on seventeen patients with normally functioning renal transplants, defined as plasma creatinine levels between 1.1-1.5 mg/dL, who were scheduled for elective coronary artery bypass surgery. They ranged from 38 to 61 years of age (mean 50.20 ± 7.10), had no recent myocardial infarctions, and had not been exposed to nephrotoxic drugs; including radiographic contrast media, for at least 3 days. Emergency coronary surgery, unstable anginal pain in the preoperative period, hemodynamic instability, and the use of inotropes or diuretics were considered as exclusion criteria.

Anesthetic/operative technique

The patients all received a continuous infusion of 3mg/kg/min dopamine from the time they arrived in the operating room until they were extubated postoperatively. Invasive monitoring was completed before the induction of anesthesia and included left radial artery cannulation, central venous pressure, arterial blood gases analysis, oropharyngeal and rectal temperatures, pulse oximetry, and a Foley catheter for urinary output measurement. [8]

Anesthetic management was uniform in all the patients. Premedication consisted of 0.1mg/kg morphine IM and 1mg/kg promethazine orally 30 min. preoperatively and 10mg diazepam orally the night before the operation. The induction of anesthesia was done with 20mg/kg sodium pentobarbital within one minute, midazolam 5mg, pancuronium bromide 0.12mg/kg and after 3 minutes of pre-oxygenation with pure oxygen via face mask, oro-tracheal intubation was performed with a suitable endotracheal tube. The maintenance of anesthesia was achieved with the infusion of midazolam, pancuronium bromide and fentanil, without any volatile anesthetic agents or nitrous oxide. A nitroglycerine infusion of 1.5mg/kg/min was given to all the patients. After induction, 10-15mg/kg of Ringer's solution was infused to maintain filling pressures near the baseline and a cardiac index above 2.2 L/min/m^2. The urinary

output was measured and if it was less than 1 ml/kg/h before CPB, an additional 5 ml/kg Ringer's solution was given. If the urinary output was below 2 ml/kg/h during CPB or less than 1 ml/kg/h after CPB, 10 mg furosemide was administered intravenously. Two patients had hypotension and tachycardia and received 3-µg/kg/min epinephrine, and dopaminergic doses of dopamine, and their blood pressure and heart rate returned to the acceptable range.

Non-pulsatile extracorporeal circulation was performed with a roller pump and a microporous hollow fiber membrane oxygenator, primed with 1.5 L of Ringer's solution and 0.5-1g/kg of mannitol. The pump flow was at an average of 2.2 $L/min/m^2$.

Moderate hypothermia (28-32º C) was used in all the patients. The hematocrit level was not allowed to descend below 25%. A hollow fiber hemofilter was utilized throughout the period the patients were on cardiopulmonary bypass.

Blood samples were obtained and analyzed at the following times: 1) pre-anesthetic measurement before the induction, 2) after the induction and at the beginning of mechanical ventilation, 3) during early hypothermic extracorporeal circulation, 4)during normothermic bypass, 5) during sternal closure, 6) 1 hour into the postoperative period. During the perioperative period, urine was collected in plastic graduated bottles.

The surgical procedure was carried out as routine for CABG surgery, paying particular attention to meticulous skin prep and total asepsis, and considering the immunosuppressed state of the patients due to chronic immunosuppressive therapy.

Results

From the 17 patients who underwent coronary bypass surgery in this study, 16 patients recovered without any complication after surgery and were discharged from hospital within 2 weeks after the operation. One patient with severe left ventricular dysfunction (preoperative ejection fraction 20%) died a few hours after surgery because of intractable cardiac failure. The revascularization was technically difficult in these patients because of advanced coronary and peripheral atherosclerosis.

The renal function values of these patients during their stay in hospital were within the normal range, and no instances of increased blood urea and nitrogen levels or creatinine levels were seen (Table I).

Table I. Patient demographics

Patient no.	Sex	Age (yr)	CAD	Years post-transplant	EF	Creatinine	MAP (mm Hg)	Urinary Output (ml/kg/min)	Patient no.	Sex	Age (yr)
						Pre CPB	*Post CPB*	*Pre CPB*	*During CPB*	*Post CPB*	*During CPB*
1	M	46	3VD	10	50	1.2	1.2	108	55	103	2.3
2	M	37	2VD	8	55	0.9	1.1	82	54	79	2.5
3	M	47	3VD	9	40	1.2	1.4	105	60	99	1.8
4	M	55	3VD	8	50	0.8	1.5	77	52	82	3.2
5	M	59	3VD	4	35	1.1	1.3	110	55	98	4.1
6	F	58	2VD	6	50	1.2	1.5	85	62	90	3.8
7	M	39	3VD	7	55	1.3	1.4	95	63	88	2.5
8	M	41	3VD	9	45	1.1	1.3	94	49	99	3.2
9	M	53	2VD	10	35	0.9	1.5	91	57	95	3.3
10	M	56	3VD	10	50	0.8	1.3	90	52	88	2.3
11	M	61	3VD	8	20	1.5	1.2	97	53	95	4.1
12	M	38	3VD	9	55	1.1	1.4	89	59	82	3.2
13	M	43	SVD	7	45	1.3	1.1	92	64	85	3.3
14	M	54	3VD	8	35	1.2	1.2	93	63	90	3.4
15	M	57	3VD	6	40	1.1	1.3	94	67	85	2.3
16	M	59	2VD	5	55	1	1.5	80	55	79	3.2
17	M	51	3VD	6	50	1.1	1.1	84	62	78	3.3

EF indicates ejection fraction; MAP, mean arterial pressure; CPB, cardiopulmonary bypass; M, male; F, female; VD, Vesele disease; CAD, coronary artery disease

Discussion

Renal transplantation is growing rapidly in the Islamic Republic of Iran. Therefore, complications of renal transplantation and chronic immunosuppressive therapy as well as natural phenomena continue. As we know, certain human arteries are more prone to develop atherosclerosis than others. For example, the coronary, renal, and internal carotid arteries, as well as some areas of the aorta, are known to be common sites for lesion formation. Furthermore, chronic steroid use for immunosuppression accelerates atherosclerosis. Consequently, revascularization in patients with renal transplants must be performed with great care because of advanced atherosclerosis, and the fact that perioperative myocardial infarction or graft compromise is probable. The success of renal transplantation, especially in diabetic and elderly patients, is associated with an increase in the incidence of cardiovascular disease, especially coronary artery disease in this population. [8,9] Recipients with adequately functioning kidneys grafts usually have creatinine levels within the normal range. However, the glomerular filtration rate and effective plasma flow are likely to be significantly lower than those of healthy subjects, and the activity of drugs excreted by way of the kidney may be prolonged.[10] Azotemia, proteinuria, and hypertension may indicate chronic rejection of the graft.[11]

Because variable renal function parameters are likely to be abnormal in kidney transplant recipients, it seems prudent to choose anesthetic drugs that do not rely on the kidney for excretion (e.g. atracurium).[13,14] Obviously, nephrotoxic drugs should be avoided.

Diuretics should not be given without a careful evaluation of the patients' volume

status. Renal hypoperfusion from inadequate intravascular volume and during cardiopulmonary bypass should be prevented. [15]

Because of the high incidence of hypertension in this population, it is common for renal transplant recipients to receive oral anti-hypertensive therapy. [16]

Patients with renal graft dysfunction who have recently been hemodialyzed may have hypovolemia and/or hypokalemia. Hypovolemia leads to hemodynamic instability and hypokalemia causes cardiac arrhythmias and increased susceptibility to muscle relaxants.[17]

The preoperative assessment of renal transplant recipients undergoing coronary artery bypass surgery should focus on graft function, any history of rejection, presence of infection, and the function of other organs, particularly those that may be compromised due to either immuno-suppressive therapy or dysfunction of the transplanted kidney.[18]

Rejection results in a progressive deterioration in renal function tests, and is the main cause of late mortality in renal transplant recipients [18,] and should be suspected if function tests of the transplanted kidney are abnormal. The presence of rejection should always be ruled out preoperatively. There is some evidence that patients undergoing coronary artery bypass surgery during a period of rejection have higher mortality. [19]

The presence of an infection should also always be ruled out preoperatively. Infection is a significant cause of morbidity and mortality after transplantation.[10] Immuno-suppressed patients are at significantly increased risk of infection, be it bacterial, viral, fungal, or protozoan. [20] However, reducing the doses of immunosuppressive drugs in the perioperative period may increase the risk of rejection, especially when coronary artery surgery is done with cardiopulmonary bypass. It is imperative to realize that immunosuppressed patients do not present with the typical signs, and symptoms of infection are often absent. A high index of suspicion is required in view of reports citing a 4%-20% incidence of abdominal complications requiring surgery.[21] In therapeutic doses, cyclosporine and tacrolimus may cause a dose-related decrease in renal blood flow and glomerular filtration rate, especially when the patient is on cardiopulmonary bypass circulation and the mean blood pressure is lower than normal. Both increased thromboxane $A_{2,}$ and perhaps endothelin production are responsible for many of these renal hemodynamic effects, especially in renal transplanted patients.[22]

Complications such as upper gastrointestinal bleeding may be secondary to peptic ulcer disease, gastritis, or gastroenteritis in these patients.[17]

Hepatobiliary and pancreatic disease are relatively common after transplantation. [23]

Kidney transplantation has many complications, which can accelerate coronary artery disease. The most important of these is hypertension, which may be caused by native kidney disease, rejection activity in the transplant, renal artery stenosis, if an end-to-end anastomosis is constructed with an iliac artery branch, and renal cyclosporin toxicity. [24] The latter may improve with a reduction in cyclosporine doses. Whereas angiotensin-converting enzyme inhibiters may be useful, calcium channel blockers are frequently more effective in cyclosporin-treated patients. [25]

Cyclosporin and tacrolimus are metabolized in the liver through the cyclosporine P-450 cytochrome oxidase system. Therefore, many drugs administered during anesthesia or preoperatively may effect cylcosporine and tacrolimus blood levels.[18] All immunosuppressive drugs now in use have significant side effects that may have a direct impact on the anesthetic and perioperative management. Steroids are used for the prevention of rejection and for

the treatment of acute rejection episodes. Despite intense efforts to eliminate or replace them, steroids are still a mainstay of the post-transplant immunosuppression protocol, and their long-term use may result in steroid-related side effects and accelerated atherosclerosis. [26,27]

Conclusion

In conclusion, renal transplant recipients have considerable medical, physiological, and pharmacological problems; therefore, a clear understanding of the physiology of the transplanted kidney, the pharmacology of the immunosuppressive drugs, such as cyclosporin A, azathioprine, anti-lymphocyte globulin, monoclonal antibodies, and steroids is mandatory. These drugs have many serious side effects and their avoidance is essential for these patients to safely undergo anesthesia and surgery, especially when surgery is associated with extracorporeal circulation. General anesthesia can be safely delivered to renal transplant recipients, and a successful anesthetic and perioperative management can be provided. Many of the perioperative problems in the renal transplant population have not been specially studied, because organ transplantation is a relatively new procedure, and it will take more time for complications to appear in these patients. For these reasons, there are no formal recommendations for their management. A registry for the perioperative problems of renal transplanted patients requiring elective or emergency coronary artery surgery is needed to formulate appropriate management and follow-up guidelines.

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