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Early-term results of coronary artery bypass grafting in renal transplant patients

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SOUHRN

Kontext: Kardiovaskulární onemocnění jsou nejčastější příčinou mortality a morbidity u pacientů po transplantaci ledvin. Byla publikována řada kazuistik i popisy malých skupin pacientů a kontrol s koronárním bypassem po transplantaci ledvin. Cílem naší studie bylo zhodnotit stav pacientů, u nichž byl po transplantaci ledvin proveden koronární bypass.
Metody: Mezi 4 330 pacienty, u nichž byl v období od ledna 2012 do prosince 2021 proveden koronární bypass, bylo 11 příjemců renálního štěpu. Sedm z těchto pacientů (64,6 %) byli muži a čtyři (35,4 %) ženy. Medián věku zařazených pacientů byl 52 (42–66) let.
Výsledky: Z uvedeného počtu byl koronární bypass v deseti případech (90,9 %) plánovaný, u jednoho pacienta (9,1 %) se jednalo o urgentní výkon. U pacienta s urgentním výkonem se předoperačně prováděla intraaortální balonková kontrapulsace. Koronární bypass byl proveden s použitím systému pro mimotělní oběh u šesti pacientů, bez tohoto systému u čtyř a koronární bypass bez mimotělního oběhu na bijícím srdci byl proveden při urgentním výkonu. V pooperační době došlo u tří pacientů (27,3 %) k rozvoji fibrilace síní. Délka pobytu na jednotce intenzivní péče byla 3 ± 1,6 dne při hospitalizaci v délce 8 ± 3 dny.
Závěr: Ukázalo se, že transplantace ledviny nijak nezvyšuje riziko z hlediska mortality a morbidity v souvislosti s koronárním bypassem. U pacientů po transplantaci ledviny je nutno provádět imunosupresivní léčbu a jejich ledvinné funkce důsledně monitorovat. U této skupiny pacientů nabývá multidisciplinární přístup ještě více na významu.

Keywords:
Cardiac surgery
Coronary artery bypass surgery
Coronary disease
Kidney transplantation
Renal transplant patients

ABSTRACT

Background: Cardiovascular disease is the most common cause of mortality and morbidity in kidney transplant patients. Many case reports and case series about coronary artery bypass grafting operation after renal transplantation have been presented. In this article, we aim to evaluate the patients undergoing coronary artery bypass surgery after renal transplantation.
Methods: Among the 4330 patients who underwent CABG between January 2012 and December 2021, there were 11 patients who had a previous renal transplant. Seven patients (64.6%) were male and four (35.4%) were female. The median age of the included patients was 52 (42–66).
Results: While ten patients (90.9%) received CABG electively, one patient (9.1%) underwent emergency surgery. Intra-aortic balloon pump was used preoperatively to the urgent patient. On-pump CABG was applied in six patients, off-pump CABG was applied in four patients and beating CABG procedure was applied in one patient who was urgent. Atrial fibrillation developed in three patients (27.3%) in the postoperative period. The length of stay in the intensive care unit was 3±1.6 days , and the length of hospitalization was 8±3 days.
Conclusion: It showed that having a renal transplant does not carry an extra risk in terms of mortality and morbidity when performing CABG. Renal transplant patients should receive immunosuppressive therapy and should be monitored closely in terms of renal function. In these patients, the multidisciplinary approach becomes even more important.

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Background

Cardiovascular disease (CVD) is the most common cause of mortality and morbidity in kidney transplant patients.[1,2] Therefore, cardiac examination is performed prior to all patients who are planned for kidney transplantation. Although these evaluations were done, cardiac pathologies are still more common in renal transplant patients due to the long surveys of renal transplant patients and the chronic use of immunosuppressants.[3] However, most patients after a renal transplant live with multiple comorbidities and chronic immunosuppression that contribute to the development of coronary artery disease. Long-term steroid use is known to accelerate coronary atherosclerosis.[4] Fifty years ago, the first cases of coronary artery bypass grafting (CABG) operation after renal transplantation started to be reported. Subsequently, many case reports and case series have been presented.[4–7] There are publications reporting the results of coronary revascularization studies with a higher number of cases and longer duration in the following years.[8–10] In this article, we aim to evaluate the cardiac risk factors after renal transplantation and the management of CABG cases after 10 years of renal transplantation in our clinic, as well as postoperative mortality and renal function related morbidities.

Methods

Population of study

This study is a single-center retrospective study. Of all the patients who applied to our clinic between January 2012 and December 2021 and underwent coronary artery bypass surgery (CABG), those who had previous renal transplantation were included in the study. The peroperative (type of surgery, total cardiopulmonary bypass time, operative complications and mortality) and postoperative (intensive care and total hospital stay, renal function and creatinine values) parameters of the patients were evaluated.

Among the 4330 patients who underwent CABG between January 2012 and December 2021, there were 11 patients who had a previous renal transplant. Seven patients (64.6%) were male and four (35.4%) were female. The median age of the included patients was 52 (42–66). The characteristics baseline information of these patients is in Table 1.

Renal transplant was performed for diabetes in four patients (36.4%), polycystic kidney disease in three (27.3%), chronic glomerulonephritis in three (27.3%) patients, and systemic lupus erythematosus in one patient (9.1%). The mean time from renal transplantation to CABG was 7.4±4 years. When we look at the causes of renal transplantation, it was diabetes in 4 patients (36.4%), polycystic kidney disease and chronic glomerulonephritis in three patients (27.3%), and systemic lupus erythematosus in one patient (9.1%). The mean time from renal transplantation to CABG was 7.4±4 years.

Procedure of surgery

Most patients underwent standard CABG procedure with aorta-two stage cannulation technique. Off-pump CABG was applied in patients with appropriate indications. When cardiopulmonary bypass (CPB) was performed, cold blood cardioplegia was preferred and active clotting time was maintained between 400–600 s. Mean pressure was aimed to be 60 mm and above during CPB. Urine volume was closely monitored throughout the surgical procedure. Inotropic support was administered if needed (dopamine, adrenaline, and noradrenaline, respectively). Furosemide or mannitol was administered intravenously when diuresis was not at the desired level.

Postoperative management

During the intensive care unit stay, drainage, blood gas were monitored and muscle strength was examined. Inotropic support was applied when it was needed to provide hemodynamic stability. Prophylactic antibiotics were administered three hours before the operation and 24 hours after. The treatment of patients who received antibiotic therapy for another reason (pneumonia, gastroenteritis, urinary tract infection, etc.) was continued. Postoperative renal function assessment was done by preoperative and postoperative daily serum creatinine levels.

All patients continued to receive oral immunosuppressive therapy until the day of operation. The next first dose was given through an oral or nasogastric tube, depending on the post-operative period. Hydrocortisone (500 mg), prednisolone (5–10 mg) or methylprednisolone (1000 mg) was used when steroid treatment was required during the operations. Continuous intravenous immunosuppressant infusion was also provided using cyclosporine or tacrolimus. During the operation, the intravenous dose of cyclosporine was adjusted to 30–40 mg per day (1/3 of the preoperative oral dose). Again, during the operation, the intravenous dose of tacrolimus was adjusted as 0.5 or 1.0 mg (1/5–1/2 of the oral dose) per day. If cyclosporine is preferred, it was used as 100 mg/daily. If acute renal failure was suspected with decreased urine output or increased serum creatinine level, the dose of immunosuppressive drug was adjusted in consultation with nephrology.

Statistical analysis

Data were expressed as number and percentages, as mean plus standard deviation, or as median with range (minimum, maximum). Continuous variables were compared using the Student t test for independent samples and p values of 0.05 or less were considered significant.

Results

Four patients (36.4%) had a history of PCI due to a previous myocardial infarction, one patient (9.1%) had history of cerebrovascular accident and six patients (54.5%) had chronic peripheral vascular disease. Considering the preoperative comorbidities, five patients (45.5%) had diabetes mellitus, and four of them (36.4%) had insulin-dependent. No patient had hematuria, but three patients (27.3%) had proteinuria. Preoperative laboratory parameters were normal except creatinine values. The creatinine value was 1.1±0.4 (Table 2).

Table 1 – Characteristics of 11 patients undergoing coronary artery bypass surgery after renal transplantation

Patients No	Age (years)	Sex	Reason for transplantation	Duration of transplantation	Serum creatinin (mg/dL)	Steroid	Immunosuppression	Procedure	Vessels of CABG
1	42	M	Polycystic kidney disease	13 years	0.6	Hydrocortisone 500 mg	Cyclosporine 50 mg daily	CABG	4
2	54	M	Chronic glomerulonephritis	5 years	0.7	Methylprednisolone 1000 mg	Tacrolimus 1 mg daily	CABG	4
3	52	F	Systemic lupus erythema-todes	14 years	0.9	Prednisolone 10 mg	Cyclosporine 50 mg daily	Off-pump CABG	3
4	63	M	Diabetes	4 years	1	Methylprednisolone 1000 mg	Tacrolimus 1 mg daily	Off-pump CABG	3
5	47	F	Polycystic kidney disease	11 years	0.9	Hydrocortisone 500 mg	Tacrolimus 0.5 mg daily	CABG	2
6	51	F	Chronic glomerulonephritis	2 years	0.9	Prednisolone 5 mg	Cyclosporine 50 mg daily	Off-pump CABG	2
7	64	M	Diabetes	6 years	1.1	Methylprednisolone 1000 mg	Tacrolimus 0.5 mg daily	On-pump beating CABG	2
8	49	M	Chronic glomerulonephritis	7 years	1.6	Prednisolone 5 mg	Cyclosporine 50 mg daily	CABG	5
9	55	F	Diabetes	10 years	1.8	Prednisolone 10 mg	Cyclosporine 100 mg daily	Off-pump CABG	3
10	52	M	Polycystic kidney disease	7 years	1.4	Methylprednisolone 500 mg	Tacrolimus 2 mg daily	Off-pump CABG	3
11	66	M	Diabetes	4 years	0.8	Hydrocortisone 500 mg	Cyclosporine 100 mg daily	Off-pump CABG	3

Table 2 – Preoperative patients' variables

Patients	Mean±SD	n (%)
Age (years)		54±7.5
Male		7 (63.6)
Hypertension		4 (36.4)
Diabetes mellitus		5 (45.5)
Insulin-treated diabetes		4 (36.4)
Smoking		3 (27.3)
Hyperlipidemia		2 (11.2)
Renal insufficiency		1 (9.1)
Prior MI		4 (36.4)
Prior CVE		1 (9.1)
Prior PCI		4 (36.4)
PVD		6 (54.5)
COPD		2 (11.2)
LVEF	52±10	
Hematuria		0
Proteinuria		3 (27.3)
Laboratory value		
Hematocrit	38.5±4.0	
Platelets	228.39±67.4	
ALT	28.71±29.9	
AST	26.46±19.8	
BUN	21.1±5.4	
Kreatinin	1.1±0.4	

While ten patients (90.9%) received CABG electively, one patient (9.1%) underwent emergency surgery. Intra-aortic balloon pump was used preoperatively to the urgent patient. On-pump CABG was applied in six patients, off-pump CABG was applied in four patients and beating CABG procedure was applied in one patient who was urgent. An average of 3±0.9 bypasses were applied. The aortic cross clamp duration was 66±40.5 min. Six patients (54.5%) needed inotropic support. As an inotropic support, dopamine was preferred in the first step, if hemodynamics could not be achieved, noradrenaline was applied afterwards. No patient required revision due to bleeding (Table 3).

Mechanical respiratory support lasted longer than 24 hours in two patients, and these two patients were known to have chronic obstructive pulmonary disease. Atrial fibrillation developed in three patients (27.3%) in the postoperative period. Cardioversion was applied at the 4th postoperative hour because of unstable hemodynamics. In the other 2 patients, electrolyte imbalance was detected and electrolyte replacement was applied. In one of these patients, there was no change despite appropriate electrolyte replacement, so amiodarone (2 gr) perfusion was administered for 2 days. Wound revision was performed due to discharge from the incisions on a patient's sternum and on other patients. It was determined that the skin flora grew in the wound samples taken from

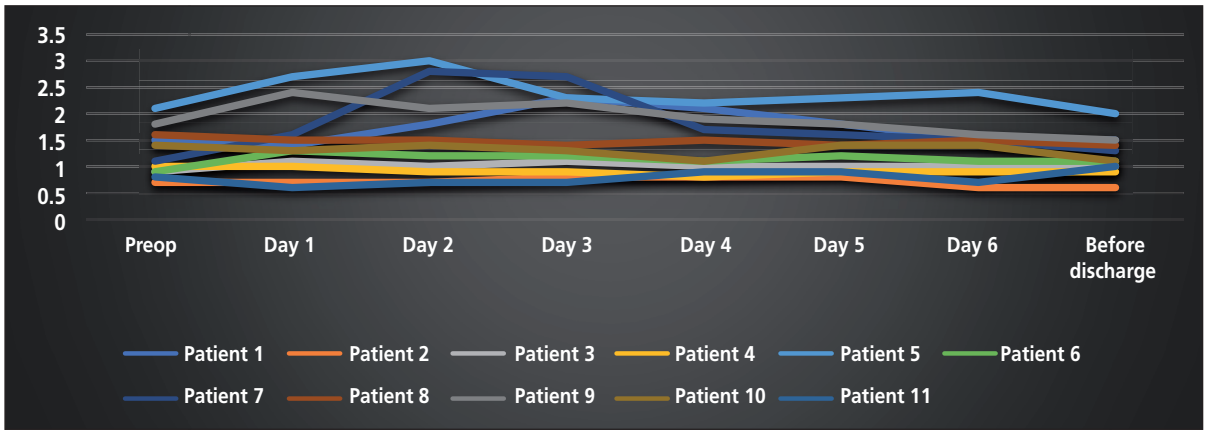

Fig. 1 – Changes in serum creatinine after coronary artery bypass surgery.

Table 3 – Per- or postoperative patients' variables

Patients	Mean±SD	n (%)
Elective operation		10
Urgent/emergency surgery		1
Procedure		
Conventional CABG		4 (36.4)
Off-pump CABG		6 (54.5)
On-pump beating CABG		1 (9.1)
Vessels of CABG	3±0.9	
Aortic clamping time	66±40.5	
Cardiopulmonary bypass time	105±32.4	
Need for inotropes		6 (54.5)
Need for IABP		1 (9.1)
Reexploration for bleeding		0
Mechanical ventilation support for >24 h		2 (11.2)
Perioperative MI		0
Postoperative atrial fibrillation		3 (27.3)
Postoperative cerebrovascular event		1 (9.1)
Need for hemofiltration		1 (9.1)
Need for hemodialysis		0
Local infection		2 (11.2)
Stay in ICU (days)	3±1.6	
Stay in hospital (days)	8±3	
Mortality		0

these two patients. No treatment changes were needed as they were sensitive to routine antibiotic therapy. The length of stay in the intensive care unit was 3±1.6, and the length of hospitalization was 8±3 days (Table 3). Hospitalization, early period, and creatinine results before discharge of the patients were shown in Fig. 1.

Discussion

In patients with end-stage renal disease, we encounter an increase in the number of patients treated with renal transplantation, so an increase is observed in the number of patients who have undergone CABG operation after renal transplantation.[4,8–10] We know the negative effect of CABG process on renal functions.[11–13] Therefore, the treatment approach, CABG method selection, and follow-up during the intensive care unit become more important, especially in renal transplant patients, who are a risky group in terms of renal function. In this study, we examined the results of patients with CABG after renal transplant in our clinic.

Early deaths after CABG are generally higher in dialysis patients than in patients not receiving dialysis treatment.[14–16] Considering the poor prognosis and higher renal damage in renal transplant patients with ischemic heart disease, we think that CABG can be performed with an increased but acceptable early mortality. It is important that patients receive the correct immunosuppression therapy in the preoperative period. Variables such as whether the operation is on-pump or off-pump in the peroperative process, and if it is on-pump, the cross-clamp time should be carefully evaluated. In addition, hemodynamic parameters and medication should be closely monitored in the intensive care unit.

To date, there are many case reports and patient outcomes of cardiac surgery after kidney transplant.[4,8–10] When these studies are examined, we see that mortality and morbidity have decreased over the years. We think that these results can be explained by technological developments and current changes in the treatment approaches. In a study with 57 patients, which can be considered as a large study, mortality was reported as 5.3%.[4] In our study, however, no intraoperative and postoperative mortality was observed. This difference in mortality rates can be explained by the fact that one of the patients in the mentioned study had emergency type 1 aortic dissection and the other two patients had an EF of 20%. In our study, only patients with isolated CABG were included and there were patients with an EF of 30% and above.

While deciding on the CABG method to be applied to the patients, the hemodynamic status and the experience of the surgeon should be carefully considered. Conventional CABG, on-pump beating heart CABG and off-pump CABG (OPCAB), and especially in recent years, minimally invasive CABG and robotic CABG are frequently applied

surgical techniques.[17–20] Although there are studies showing that the OPCAB technique is safer in terms of renal functions and has rarer adverse effects because CPB is not used,[21,22] when the results of long-term studies are examined, it is seen that the effect on renal functions or end-organ damage is not very different.[23–25] In our study, six (54.5%) off-pump CABG, four (36.4%) conventional CABG, one (9.1%) on-pump beating heart CABG operations were performed. Since only one of these patients had postoperative anuria, hemofiltration was needed for two days, and this patient was the only patient who underwent on-pump beating CABG. It is very important to achieve complete revascularization in the off-pump CABG operation performed after renal transplant. If there is any doubt that complete revascularization cannot be achieved, the on-pump CABG technique will not cause any different results in terms of mortality and morbidity, contrary to what is aimed at the first place. In addition, it has been proven that failure to perform complete revascularization due to insistence on the off-pump CABG technique will result in negative results in long-term mortality.[20,26] Considering these in our study, we prioritized the hemodynamic status and provided full revascularization in terms of which technique to perform. If we can meet the aforementioned conditions, just then we preferred the off-pump CABG technique. Our results showed that this approach did not cause any mortality.

In addition, the duration of CPB was found to be associated with morbidity after CABG. The normal pulsatile flow that cannot be achieved as the time lengthens and the higher cytokine release due to CPB during this period adversely affect the possibility of morbidity.[27,28] In our study, conventional CABG was applied to four patients. On-pump beating heart CABG was performed in one patient. CVE (cerebrovascular event) was seen in one of these patients. It was observed that this patient had a low EF and underwent on-pump beating. It was thought that the reason for this situation was not directly related to the CABG technique. Due to the small number of patients in our study, a clear conclusion could not be reached on this issue.

In many studies comparing on-pump and off-pump CABG, off-pump CABG was found to be superior in terms of renal protection.[22,29] On the contrary, there are studies reporting that there is no difference between the two techniques in terms of renal functions.[30,31] In our study, renal failure developed in 1 patient (9.1%), despite being a high-risk group. This patient was operated with the on-pump beating heart technique under emergency conditions. Hemofiltration was performed on the 1st postoperative day, since this patient had elevated creatinine and anuria. It is thought that the reason for this may be a renal failure due to low cardiac output resulting from low EF and hemodynamic instability rather than the CABG technique.

Most renal transplant patients receive immunosuppressive therapy. The aim of this treatment is to prevent early graft rejection and to ensure longer graft survival.[32] On the other hand, it is known that immunosuppressive treatment predisposes to infection.[33,34] In the study of Zhang et al., loss of kidney graft was found in 8 patients (14%) and postoperative infection was found in 10 (18%) patients.[4] Dosage adjustment of immunosuppressive therapy is important in terms of complications that may develop after cardiac surgery and also renal graft health. Since its oral bioavailability is lower than intravenous, we used intravenously during the operation avoids the feared complications.[35,36] All patients in our study receive immunosuppressive therapy (tacrolimus or cyclosproine etc.). None of the patients experienced renal graft rejection. Mediastinitis, one of the most feared complications of cardiac surgery, did not develop in any of the patients postoperatively. Local infection developed in 2 patients (11.2%). Wound revision was performed due to discharge from the incisions on a patient's sternum and on other patients. It was determined that the skin flora grew in the wound samples taken from these two patients. No treatment changes were needed as they were sensitive to routine antibiotic therapy. The reason for these local infections is that both patients suffer from DM and high BMI rather than immunosuppressive therapy.

POAF is common after cardiac surgery and is significantly associated with increased hospital stays, as well as both short- and long-term stroke and mortality rates.[37] While the risk of mortality and morbidity in renal transplant patients is already high, the development of POAF will increase this risk many times over. That is why it is important to avoid POAF. It is known that POAF is often caused by hypoxia and electrolyte imbalance. It is of great importance to meticulously perform the electrolyte balance in the renal transplant patients since one of the major causes of electrolyte imbalance is the renal dysfunction itself. It is important to closely monitor the patients' measurable values such as potassium and sodium, as well as to regularly replace the electrolytes that cannot be measured as daily routine. During postoperative period, blood gas should be evaluated more frequently than usual to keep electrolytes at the desired value. There were three (27.3%) patients with POAF in our study. Electrolyte imbalance was detected in two patients and appropriate replacement was applied. The other patient had AF despite the correction of the electrolyte imbalance therefore amiodarone (2 gr) was administered as perfusion for two days.

Even in the absence of severe renal dysfunction, the renal graft becomes susceptible to ischemia-reperfusion injury and systemic inflammatory reaction caused by surgical cardiopulmonary bypass. There are studies showing that cardiac surgery have a significant effects on serum creatinine levels and renal function within 5 days postoperatively.[4] While this effect was transient in most patients, 1 of the renal transplant patients suffered permanent damage. In the light of this information, we applied hemofiltration from the first day to prevent kidney damage that affects other organs and mortality rates. In the ongoing process, after the hemofiltration was applied for 48 hours, the patient started to urinate spontaneously, and the hemofiltration was gradually terminated. It is important to ensure that there is an adequate renal perfusion and urine output and also to adjust immunosuppression perioperatively to prevent allograft injury in this patient group. Therefore, teamwork should be done with the nephrology clinic definitely in the whole process. Much more care should be taken if a sustained

increase in serum creatinine is detected after the third postoperative day.[4] However, the results of our study are not sufficient to make this interpretation. In addition, if renal dysfunction is observed and this situation affects hemodynamics, hemofiltration or hemodialysis should be applied with a quick decision. In this process, in order to be able to make the right decision, patients' pH and electrolytes and the amount of urine should be carefully evaluated.

Considering the 25-year single center study, CABG was applied to 31 patients after renal transplant. The 5-year survival time was seen as 85%. Three of these patients were followed up again as hemodialysis patients.[38] In our study, short-term follow-up was also performed and no mortality was observed. None of them had permanent hemodialysis patients. When we look at these results, it has a mortality rate that can be considered normal.

Cardiac screening prior to transplant is important. Patients who are found to be at cardiac risk at the time of cardiac screening after kidney transplant have a higher cardiac risk afterwards. The excess of risk factors during preoperative evaluation is a condition that increases the risk of coronary artery disease after transplantation. Therefore, pre-transplant screening is predictive for CAD. When we look at the current studies, 770 kidney transplant patients were found to be suspicious in the pre-transplant evaluation. Coronary artery disease was detected in 11 patients after coronary angiography. CABG was applied in one of them. When evaluated preoperatively, the presence of known CAD, PAH, and more than three risk factors is a serious predictive condition.[39] When we looked at our results, we saw that there were risk factors for CAD before transplantation.

One of the limitations of our study is the small number of patients. All of these patients should be followed up prospectively. In addition, only patients who underwent CABG were included in the study. Other cardiac surgeries may also be included in the study. The patients in the study were followed up only during their hospital stays. It is obvious that there is a need for information to be obtained by following a larger number of patients for a longer period of time.

Conclusion

In conclusion, our study showed that having a renal transplant does not carry an extra risk in terms of mortality and morbidity when performing CABG. Making a quick decision on the treatment in order to prevent mortality and morbidity in this patient group will help prevent major and minor complications. Renal transplant patients should receive immunosuppressive therapy and should be monitored closely in terms of renal function. In these patients, the multidisciplinary approach becomes even more important.

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Ethical statement
Ethics committee approval was received.

Informed consent
Informed consent was obtained from the participants.

Authors' contribution
All authors read and approved the final version of the manuscript.

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