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On-Pump versus Off-pump Myocardial Revascularization in Patients with Renal Insufficiency: Early and Mid-term Results

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Background: Myocardial revascularization in patients with renal insufficiency is challenging to the cardiac surgeon, irrespective of utilizing extracorporeal circulation. This study aimed to compare the number of bypass grafts and the mid-term results and to evaluate independent survival predictors in patients with renal insufficiency undergoing on-pump or off-pump myocardial revascularization. ***Materials and Methods:*** We retrospectively analyzed the data of 103 patients with renal insufficiency, who had isolated myocardial revascularization between January 1999 and January 2009. The patients were divided into two groups, the on-pump group and the off-pump group. ***Results:*** The off-pump group received a significantly greater number of distal arterial grafts than the on-pump group. However, the mean number of total grafts, the degree of complete revascularization, and survival rate of the patients were not significantly different between the two groups. Multivariate analysis showed the independent predictors for reduced mid-term survival were the number of total grafts and postoperative periodic renal replacement therapy. Off-pump myocardial revascularization does not decrease the number of bypass grafts or influence on the mid-term results for patients with renal insufficiency, compared to on-pump myocardial revascularization. ***Conclusion:*** Myocardial revascularization with a large number of total grafts has a beneficial effect on survival in patients with renal insufficiency, irrespective of utilizing extracorporeal bypass.

Key words: 1. Myocardial revascularization
2. Off-pump
3. On-pump
4. Kidney failure

INTRODUCTION

One of the issues of debate in myocardial revascularization has been that whether utilizing extracorporeal circulation has an effect on the immediate & mid-term results of the patient. As the AHA scientific statement, in spite of merits; namely, less blood loss, less need for transfusion, less myocardial enzyme release for up to 24 hours, less early neurocognitive dysfunction and less renal insufficiency, fewer distal grafts tend to be anastomosed with off-pump myocardial revascularization than with standard on-pump myocardial revascularization [1]. In a retrospective study by the Cleveland Clinic, although there was no difference in the mid-term results, survival, freedom from myocardial infarction, and freedom from

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percutaneous coronary reintervention, the on-pump group received a great number of bypass grafts than the off-pump group (3.5±1.1 versus 2.8±1.0, respectively, $p<0.001$) [2]. In addition, in a prospective randomized trial by Straka et al, fewer distal anastomoses were performed in the off-pump group, compared to the on-pump group (2.7 versus 2.3, respectively, $p<0.001$) [3].

By the way, other studies have addressed the question of whether patients in the off-pump group receive fewer distal anastomoses than on-pump group. Puskas et al. advocated off-pump myocardial revascularization in their study to avoid transfusion requirements, or myocardial injury, and to achieve similar complete revascularization [4]. Nevertheless, other authors are more hesitant, considering complete revascularization with the off-pump method is more laborious to perform because of the difficulty of exposing the circumflex artery or its branches [5].

How about in patients with renal insufficiency? Renal dysfunction or malfunction can lead to fluid over-retention, platelet dysfunction, vascular disease and susceptibility to infections that the cardiac surgeon would want to avoid confronting. In particular, because coronary artery disease is a leading cause of death in patients with renal insufficiency [6], the cardiac surgeons have tried to overcome this combined problem on myocardial revascularization. Myocardial revascularization in patients with renal insufficiency is challenging to the cardiac surgeon, irrespective of utilizing extracorporeal circulation, and off-pump revascularization is suggested as one of the surgical methods to avoid complications. However, several studies have asked the questions on whether off-pump myocardial revascularization would be of advantage to the long-term survival of patients with renal insufficiency [7-9].

The object of this study was to compare the number of bypass grafts, the revascularized territories and early- and mid-term results of patients who received myocardial revascularization either utilizing extracorporeal circulation or the off-pump beating method, and to find the independent survival predictors for patients with renal insufficiency.

MATERIALS AND METHODS

Between January 1999 and January 2009, 3,678 patients underwent myocardial revascularization. Of those patients, 138 patients were diagnosed with renal insufficiency, defined as estimated glomerular filtaration rate (GFR) <30 mL/min/1.73 m^2, irrespective of the need for periodic renal replacement therapy. The GFR had been calculated by Modification of Diet in Renal Disease study equation. 28 patients had combined valvular surgery, and follow-up was not complete in the other 7 patients. Consequently, 103 patients who had isolated myocardial revascularization were included in the study. Patients in this study did not underwent redo myocardial revascularization at all. Sixty seven patients had myocardial revascularization utilizing extracorporeal circulation (on-pump group) and off-pump myocardial revascularization was performed for 36 patients (off-pump group). The selection of operative procedures (namely, on-pump or off-pump myocardial revascularization) was based on the followings: Before early 2001, we have performed on-pump myocardial revascularization except for calcific plaque not to avoid manipulating on the ascending aorta. However, we gradually increased the number of off-pump myocardial revascularization from early 2001. With the exception of a stenotic circumflex coronary artery located deep in the myocardium, off-pump myocardial revascularization have performed for all coronary arteries.

We retrospectively reviewed the clinical, operative, echocardiographic and outcome data from medical or surgical records. Mid-term follow-up data were collected from telephone interviews with the patient and family members. Informed consent forms were obtained.

In-hospital mortality was defined as death within 30 days from surgery. Preoperative cerebrovascular accident was defined as focal neurologic deficit demonstrated by computed tomography or magnetic resonance imaging before operation. Preoperative myocardial infarction was defined as state or occurrence of regional hypokinesia or dyskinesia at preoperative echocardiography; ST segment elevation followed by appearance of new Q wave at preoperative electrocardiogram; or increased plasma concentration of creatinine kinase MB fraction greater than 80 IU [10]. Preoperative periodic renal replacement therapy (RRT) was defined as the requirement for dialysis irrespective of mode (specifically, peritoneal dialysis or hemodialysis) before operation. Postoperative transient RRT was defined as the requirement for dialysis only during the in-hospitalization period. Newly developed periodic RRT was defined as new requirement for dialysis after the operation, continuing for whole life. Postoperative RRT was defined as the sum of the number of preoperative patients on periodic RRT and postoperative patients on newly developed periodic RRT. Completeness revascularization was identified by comparing the number of graft performed with the number of diseased coronary systems (specifically, more than 50% stenosis in the left anterior descending coronary artery, circumflex and right coronary artery systems) found on the preoperative coronary angiography [4].

All continuous variables were expressed as mean±S.D and were tested using a Student *t* test. Categorical data were tested using Chi-square statistics. For multivariate analysis, the Cox proportional hazards model was fitted with time to survival. The Kaplan Meier method was used to calculate survival curves, and survival of subgroups was compared by the log rank test. The SPSS software package 14.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. A p value of 0.05 or less was considered statistically significant in all cases.

RESULTS

The demographic and preoperative data are shown in Table 1. Results showed that patients in both groups were similar in terms of age, sex, preoperative serum creatinine level (Cr) and estimated GFR. Myocardial function and history of renal replacement therapy were not different between the two groups. However, a preoperative percutaneous coronary intervention (PCI) history and the presence of hyperlipidemia, which is one of the risk factors for coronary disease, were often found in the off-pump group ($p<0.01$). Other risk factors of atherosclerosis did not significantly differ in the both groups.

Bypass graft information is shown in Table 2. The off-pump group received a significantly greater number of distal targets with arterial grafts than the on-pump group, $p<0.001$. However, distal number of targets with venous grafts are even greater in the on-pump group ($p<0.001$). Therefore, the mean number of total targets with grafts was 3.5±1.2 and 3.1±1.3 for the on-pump and the off-pump group, respectively ($p>0.1$). In almost all patients of both groups, the left internal thoracic artery was used as a graft vessel. Furthermore, between the two groups, there is no difference of statistical results according to the completeness revascularization and the revascularized territories, respectively (Table 2, 3).

Table 4 shows the postoperative data of the both groups. There was no difference in the ejection fraction (EF) between the two groups during the follow-up period. However, the length of stay and follow-up periods were significantly short-

Table 1. Preoperative data of the patients

Characteristic	Group A (N=67) on-pump	Group B (N=36) off-pump	p-value
Age	62.5±7.4	63.2±8.3	NS
Male	54 (80.6%)	27 (75.0%)	NS
Serum Cr (mg/dL)	5.4±2.6	5.9±5.1	NS
GFR (mL/min/1.73 m^2)			
15～59	23 (34.3%)	12 (33.3%)	NS
<15	44 (65.7%)	24 (66.7%)	NS
RRT history	29 (43.3%)	16 (44.4%)	NS
HD	25 (37.3%)	14 (38.9%)	NS
PD	4 (6.0%)	2 (5.6%)	NS
Myocardial function			
EF (%)	48.7±13.2	50.7±13.6	NS
LVESD (mm)	39.2±8.7	37.6±11.8	NS
LVEDD (mm)	54.8±7.0	53.1±10.1	NS
PCI history	2 (3.0%)	7 (19.4%)	0.008
MI history	11 (16.4%)	4 (11.1%)	NS
CVA history	6 (9.0%)	7 (19.4%)	NS
Risk factor of coronary disease			
DM	26 (38.8%)	21 (58.3%)	0.058
HTN	24 (35.8%)	19 (52.8%)	0.096
Hyperlipidemia	12 (17.9%)	18 (50.0%)	<0.001
Smoking	20 (29.9%)	11 (30.5%)	NS

CVA=Cerebrovascular accident; DM=Diabetes mellitus; EF=Ejection fraction; GFR=Glomerula filtration rate; HTN=Hypertension; HD=Hemodialysis; LVEDD=Left ventricular end diastolic dimension; LVESD=Left ventricular end systolic dimension; MI=Myocardial infarction; PCI=Percutaneous coronary intervention; PD=Peritoneal dialysis; RRT=Renal replacement therapy; NS=$p>0.1$.

Table 2. Bypass graft data of the patients

Variable	Group A (N=67) on-pump	Group B (N=36) off-pump	p-value
No. of total targets with grafts	3.5±1.2	3.1±1.3	0.064
No. of distal targets with arterial grafts	1.5±1.0	2.5±1.3	<0.001
No. of distal targets with venous grafts	2.0±1.3	0.6±0.7	<0.001
LITA usage	62 (92.5%)	36 (100%)	NS
ICOR	1.14±0.05	1.03±0.07	NS

ICOR=Index of completeness of revascularization (number of grafts performed/number of grafts intended); LITA=Left internal thoracic artery; NS=p>0.1.

Table 3. Revascularized territories data of the patients

Variable	Group A (N=67) on-pump	Group B (N=36) off-pump	p-value
No. of LAD territory	1.5±0.5	1.4±0.2	NS
No. of LCx territory	1.2±0.3	1.2±0.5	NS
No. of RCA territory	0.8±0.6	0.5±0.4	0.083

LAD=Left anterior descending coronary artery and branch vessels; LCx=Left circumflex coronary artery and branch vessels; RCA=Right coronary artery and branch vessels; NS=p>0.1.

er in the off-pump group (p<0.01). Complications other than renal problems developed more often in the on-pump group but there was no significant difference (p>0.1). The main complications in the on-pump group were bleeding (N=4), low cardiac output syndrome (N=3), wound infection (N=3), CVA (N=3), pneumonia (N=1), sepsis (N=1) and tamponade (N=1). Usually one patient had more than one complication. In the off-pump group, however, there were 2 wound infections and 1 case of pneumonia occurring in 2 patients. The deteriorations of renal function developed in 21 patients in the on-pump group and 6 patients in the off-pump group, who did not need RRT preoperatively. Postoperatively, they needed periodic permanent hemodialysis but there was no significant difference (p>0.1). At discharge, 74.6% of patients (N=50) in the on-pump group and 61.1% of patients (N=22) in the off-pump group were dependent on periodic renal replacement therapy. Death of 6 patients occurred in the on-pump group during the hospitalization period, resulting in a hospital mortality rate of 5.8% (6 of 103). 3 patients died of low cardiac output syndrome with newly developed atrial fibrillation; the cause of death for the remaining 3 patients was cerebrovascular accident, respiratory failure with pneumonia and sepsis. The mean follow-up periods of the 97 hospital survivors was 36.69 months (range, 0.9 to 116.8 months). During follow-up, 1 patient in the on-pump group and 1 patient in the off-pump group underwent renal transplantation and are still surviving. In the on-pump group, ten of the 23 late deaths were from cardiac causes, 2 patients from cerebrovascular disease, and the other patients from causes unrelated to the vascular system. Meanwhile, three of the five late deaths in the off-pump group were from the cardiovascular disease (Table 5).

Table 4. Postoperative data of the patients

Variable	Group A (N=67) on-pump	Group B (N=36) off-pump	p-value
Length of stay	14.5±11.7	9.3±3.7	<0.001
Last echocardiographic EF (%)	50.5±13.0	53.4±10.8	NS
Early mortality	6 (9%)	0 (0%)	0.064
Postop complication (excluding renal problem)	10 (14.9%)	2 (5.6%)	NS
Preop periodic RRT	29 (43.3%)	16 (44.4%)	NS
Postop periodic RRT	50 (74.6%)	22 (61.1%)	NS
Newly developed periodic RRT	21 (31.3%)	6 (16.7%)	NS
Postop temporally RRT	9 (13.4%)	2 (5.5%)	NS
Follow-up (month)	40.5±31.5	23.5±20.2	<0.001

EF=Ejection fraction; RRT=Renal replacement therapy; NS=p>0.1.

To identify factors influencing the survival rate, several variables were analyzed using the Cox regression model. Univariate analysis showed that only the number of total grafts acted as a determinant of the postoperative survival rate. Postoperative periodic RRT trended toward being an independent factor for survival (Table 6).

However, at multivariate analysis using the Cox proportional hazards modeling on variables after exclusion of perioperative deaths, the independent predictors for reduced sur-

Table 5. The causes of deaths of the 97 hospital survivors

Causes	Group A (N=61) on-pump	Group B (N=36) off-pump
Cardiac		
Congestive heart failure	5	1
Sudden sustained arrythmia	2	1
New ischemic insult to myocardium	3	1
Non-cardiac		
Cerebrovascular hemorrahge	2	1
Bowel ischemia	1	
Sepsis	1	
Cholecystitis with hepaticrenal encephalopathy	1	
Peritonitis	1	
Pneumonia	1	
GI bleeding	2	1
Hepatic failure related with HBV	2	
Cancer	1	
Unknown	1	
Total	23	5

GI=Gastrointestinal; HBV=Hepatitis B virus.

Table 6. Univariate analysis of risk factors for survival

Variable	Hazard ratio	95% CI	p-value
Preop EF (%)	0.98	0.92～1.04	NS
Preop LVESD (mm)	1.01	0.93～1.09	NS
No. of total grafts	0.70	0.48～0.99	0.046
No. of distal arterial grafts	0.93	0.62～1.40	NS
No. of RCA territory	0.89	0.90～1.03	NS
Preop periodic RRT	1.37	0.55～3.41	NS
Postop periodic RRT	3.34	0.90～12.31	0.071

CI=Confidence interval; EF=Ejection fraction; LVESD=Left ventricular end systolic dimension; RCA=Right coronary artery and branch vessels; RRT=Renal replacement therapy; NS=p＞0.1.

Table 7. Multivariate analysis of risk factor for survival with the Cox proportional hazards model

Variable	Hazard ratio	95% CI	p-value
Preop EF (%)	0.98	0.95～1.01	NS
Preop LVESD (mm)	1.03	0.99～1.07	NS
No. of total grafts	0.64	0.46～0.90	0.008
No. of distal arterial grafts	0.82	0.59～1.14	NS
No. of RCA territory	0.96	0.96～1.01	NS
Preop periodic RRT	1.86	0.87～3.96	NS
Postop periodic RRT	4.06	1.22～13.53	0.022

CI=Confidence interval; EF=Ejection fraction; LVESD=Left ventricular end systolic dimension; RCA=Right coronary artery and branch vessels; RRT=Renal replacement therapy; NS=p＞0.1.

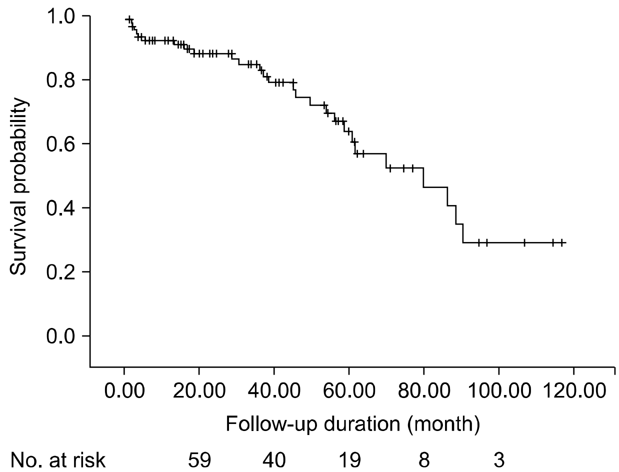

Fig. 1. Kaplan-Meier survival curve of all patients.

vival after hospital discharge were the number of total grafts and postoperative periodic renal replacement therapy (Table 7).

The survival rates of all discharged patients at 1, 3 and 5 years were 92.6%, 85.0% and 64.1% respectively (Fig. 1).

Survival rates of the on-pump group declined more rapidly than those of the off-pump group during the immediate postoperative period due to higher in-hospital mortality, but the on-pump group showed a similar survival rate to the off-pump group after the perioperative period (Fig. 2). The survival rates of discharged patients at 1, 3 and 5 years were 90.0%, 86.1% and 62.7% in the on-pump group, and 97.1%, 79.0% and 69.1% in the off-pump group, respectively. In spite of the differences in mortality during the perioperative period, there was no significant difference in the 5 year survival rate between the both groups by log rank statistic (p=0.57). Freedom from cardiac related death at 3 and 5 years were 95.7% and 77.7% in the on-pump group, and 81.3% and 71.2% in the off-pump group (p＞0.1 by log rank statistic) (Fig. 3).

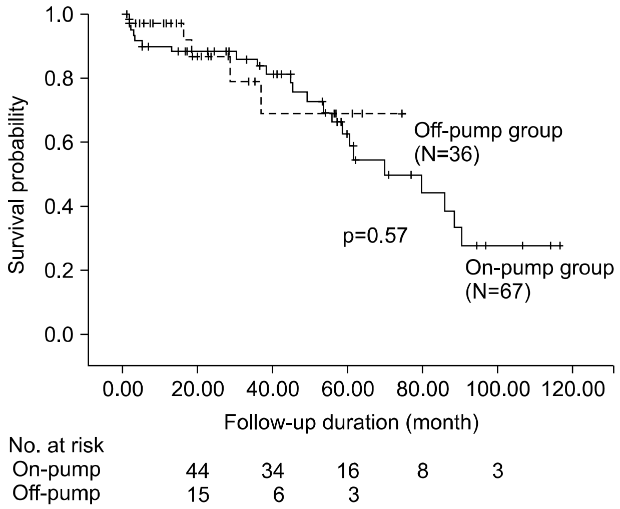

Fig. 2. Kaplan-Meier survival curve of both groups.

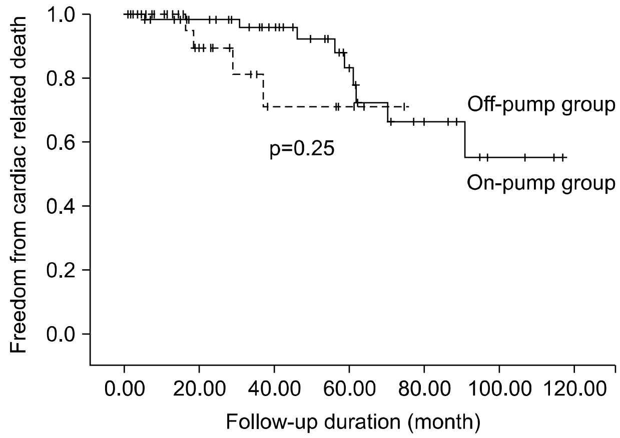

Fig. 3. Freedom from cardiac related death of the 97 hospital survivors.

DISCUSSION

Whether complete myocardial revascularization or the use of extracorporeal circulation is more beneficial in patients with renal insufficiency is a question of great importance for the cardiac surgeon. Patients with renal dysfunction have several obstacles that prevent optimal revascularization and contribute to an unfavorable postoperative outcome. Pressure overload as a result of stiffness of large capacity arteries like the aorta, and volume overload as a result of chronic fluid retention lead to left ventricular hypertrophy and increased left ventricular end diastolic diameter, which makes patients with renal dysfunction susceptible to ischemic insult and left ventricular dysfunction [11,12]. Probably, these pathophysiologic changes in myocardium render off-pump myocardial revascularization difficult. In addition, a significantly greater incidence of plaques has been reported in the common carotid artery, rendering patients more prone to perioperative ischemic cerebral insult [9]. High level exposure to traditional risk factors such as smoking and dyslipidemia, and also endothelial dysfunction, commonly characterized by reduced production of the vasodilator nitric oxide (NO), are thought to be a factors leading to a worse postoperative outcome [13,14].

An overview of the available literature summarizing the perioperative mortality rate for isolated myocardial revascularization for patients with renal insufficiency shows a rate of 8.9%, with increased but acceptable perioperative mortality. This mortality ratio is lower than that of isolated cardiac valve surgery and a combined procedure (19.3 and 39.5% respectively) [15]. Therefore, cardiac procedures, especially myocardial revascularization, to relieve ischemic insult is the best treatment for patients with renal insufficiency having ischemic heart disease. In particular, when comparing myocardial revascularization with PCI in patients receiving RRT, there may be better long-term survival and freedom from angina with myocardial revascularization, compared with balloon angioplasty [16].

However, the inherent side effects of conventional myocardial revascularization utilizing extracorporeal circulation may impose more serious problems on patients with renal insufficiency, especially such as bleeding tendency due to platelet malfunction, fluid overloading, systemic inflammatory reactions and compromise of renal function. A prospective randomized study, by Ascione et al. shows that off-pump myocardial revascularization offers superior renal protection when compared with the on-pump, namely conventional myocardial revascularization in first time coronary revascularied patients. Furthermore, glomerular filtration was assessed by creatinine clearance and the urinary microalbumin/creatinine ratio, which was significantly worse in the on-pump group. In addition, compared to the off-pump group, renal tubular function was also impaired in the on-pump group as assessed by an increased N-acetyl glucosaminidase activity [17].

Also, Osaka et al. suggest that off-pump myocardial revascularization has several advantages compared to on-pump myocardial revascularization for patients with renal insufficiency, in that there is less bleeding, the systemic inflammatory response syndrome can be avoided and electrolyte imbalance can be prevented [18]. In the case of calcified and narrow native stenotic coronary arteries, distal anastomosis may be difficult to perform, so emphasis is placed upon precise preoperative angiographic evaluation of native coronary arteries. However, the authors concluded that graft anastomosis problems in difficult cases may be improved dramatically as experience with off-pump revascularization increases.

Moreover, it is well known that off-pump myocardial revascularization reduces postoperative complications and early mortality in patients with renal insufficiency [19-21]. In our study, although there is no difference in the complications other than a renal problem in the both groups ($p > 0.1$), early mortality showed a trend of being lower in the off-pump group, $p < 0.064$. Furthermore, Yokoyama et al. concluded that off-pump myocardial revascularization had a consistent trend of reducing morbidity and early mortality overall, including all high-risk subsets (80 years of age or older, EF < 0.25, concurrent chronic obstructive pulmonary disease, prior renal failure, prior neurologic event and reoperation) [22].

But what about the mid- or long-term results of the off-pump myocardial revascularization in patients with renal dysfunction?

In an analysis of current trends that divided the study period into 4 periods of time, Bechtel et al. demonstrated that improvement in perioperative survival after cardiac surgery in dialysis dependent patients in recent years does not continuously improve the long-term prognosis [8]. They also noticed that overall survival was significantly dependent on the type of surgery and was better for patients receiving isolated myocardial revascularization than isolated valve surgery and myocardial revascularization with concomitant valve surgery. Although we didn't analyze the trend over time in our study, 5 patients among in-hospital death of a total of 6 patients of on-pump group received surgery before the year 2004 (5 deaths out of a total of 69 patients who were operated on in 1999～2003, and 1 death out of a total of 34 patients who were operated on in 2004～2009).

Dewey et al. studied patients with end-stage renal disease undergoing myocardial revascularization, comparing the results of on-pump group to off-pump group [7]. Although there were early mortality benefits, the long-term survival rate was significantly worse in patients revascularized using off-pump method ($p=0.03$). The authors suggest the significantly fewer number of grafts performed in the off-pump group may be related to the cause of lower mid- or long-term survival.

However in our study, there is no difference in the mid-term survival of patient with renal insufficiency between the on-pump group and off-pump group ($p=0.57$). Particularly, both groups have a similar total number of targets with grafts, and distal number of targets with arterial grafts are even greater in the off-pump group ($p < 0.001$). In addition, the revascularized territories were not different between the two groups. Perhaps increased experience and new devices for the stabilization of the heart make it possible for surgeons to adeptly perform complete myocardial revascularization with off-pump methods. Because postoperative angiography was not performed in all patients, we cannot guarantee the patency of the bypass grafts; however off-pump myocardial revascularization is not a difficult surgery for multiple or complete revascularization.

Graft patency is no less important than the number of grafts. Although not a study dealing exclusively with patients with renal insufficiency, Puskas et al. reported that graft patency was not different between the off-pump group and the on-pump group at 1 month postoperative data [23]. However, in another study by Khan et al, the authors found better patency of the graft was shown in the on-pump group than the off-pump group (98% versus 88% respectively, $p=0.002$). The interesting finding of this study is that graft patency in both groups show different statistical results according to the revascularized territories and the kind of grafts that was used [24]. In considering the susceptibility to development of atherosclerosis in the coronary arteries of patients with renal insufficiency, graft patency may be one of the other key independent determinants that affect mid- or long-term results in these patients.

This study has several limitations. First, we didn't always assess graft patency postoperatively at regular intervals due to the concern of renal toxicity of radiologic contrast, which could affect the survival rate. Some patients refused to undergo follow-up angiography because they had no symptoms. Second, information on the duration of preoperative dialysis was not obtained from medical records. Generally, the longer the history of preoperative hemodialysis, the lower the survival rate. Third, the current study is not a prospective randomized study, but retrospective observation study. Finally, a relatively short term follow-up duration, a small sample size and a selection bias for the choice of utilization of extracorporeal circulation may affect the results of survival analysis.

CONCLUSION

In conclusion, off-pump myocardial revascularization does not affect the number of bypass grafts and does not affect mid-term survival for patients with renal insufficiency, in spite of having the benefit of early mortality, compared to on-pump myocardial revascularization. Especially, for patients who are likely to take periodic renal replacement therapy postoperatively, regardless of the use of arterial or venous grafts, myocardial revascularization with a large number of total grafts has a beneficial effect of increasing mid-term survival, irrespective of utilizing extracorporeal bypass.

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