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Late dialysis rate for coronary artery bypass grafting patients with moderate-to-severe renal impairment: comparison between off-pump and conventional method

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Abstract

Background: Whether off-pump coronary artery bypass grafting has a late renal protective advantage over conventional coronary arterial bypass grafting with cardiopulmonary bypass use is controversial. **Methods:** From 1997 to 2004, 2102 cases of isolated coronary arterial bypass grafting were collected and analyzed, 1116 (53%) in the cardiopulmonary bypass group and 986 (47%) in the off-pump coronary artery bypass grafting group. Cases were stratified by preoperative estimated glomerular filtration rate into three renal groups: 1012 (48%) in group 1, with glomerular filtration rates $\geq$60 ml/h, 864 (41%) in group 2, with glomerular filtration rates of 30—60 ml/h, and 226 (10.8%) in group 3, with glomerular filtration rates <30 ml/h, but without dialysis before surgery. **Results:** The in-hospital mechanical renal replacement therapy rates were 2.0%, 4.6%, and 26.1%, respectively, for the three renal groups that underwent coronary artery bypass grafting with conventional cardiopulmonary bypass, and 1.1%, 3.4%, and 14.0%, respectively for the three renal groups that underwent off-pump coronary artery bypass grafting. After risk adjustment, cardiopulmonary bypass use did not show statistical significance for in-hospital mechanical renal replacement therapy (p = 0.314, 0.524, 0.150, respectively, across renal groups 1—3). At the end of the 4-year follow-up period, 99.1%, 97.2%, and 78.6%, respectively, of patients were free of mechanical renal replacement therapy across the three renal groups (p = 0.0097 between renal groups 1 and 2; $p < 0.001$ between renal groups 2 and 3). Cox regression analysis for renal groups 2 and 3 revealed that cardiopulmonary bypass use was not a risk factor for mid-term mechanical renal replacement therapy (p = 0.452), but preoperative glomerular filtration rate, hypercholesterolemia, insulin-requiring diabetes, young age at surgery, female gender, and in-hospital mechanical renal replacement therapy use were. **Conclusion:** Patient characteristics, rather than operative strategy of using off-pump or conventional coronary artery bypass grafting, influence the mid-term mechanical renal replacement therapy rate for patients with glomerular filtration rates <60 ml/min.

Keywords: Coronary artery disease; Coronary artery bypass grafting; Off-pump coronary artery bypass grafting; Cardiopulmonary bypass; Renal failure

1. Introduction

Pre-existing renal insufficiency is an important risk factor for mortality [1,2] and mechanical renal replacement therapy (MRRT) use [3—5] after coronary artery bypass grafting (CABG). Early studies investigated different pharmacologic interventions, including *N*-acetylcysteine [6], renal-dose dopamine [7], dexamethasone [8], and diuretics [9] to reduce cardiopulmonary bypass-related renal injury. But all those agents failed to show renal protection and some had adverse effects [9,10]. Recently, the focus turned to decide whether off-pump CABG had a renal protective advantage over conventional CABG with cardiopulmonary bypass use, but studies yielded controversial results [11—14]. We investigated the impact of cardiopulmonary bypass use on the MRRT rate immediately after the operation and in the mid-term follow-up after CABG for either preserved or impaired renal function.

2. Material and methods

In order to include a substantial number of CABG cases, we included CABG cases from two hospitals (National Taiwan University Hospital [NTUH], Mackay Memorial Hospital [MKMH]) between 1997 and 2004. Patients with hemodialysis use before surgery, preoperative shock requiring cardiopul-

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monary bypass for temporary support, or CABG associated valvular operations were excluded from the study.

Preoperative estimated glomerular filtration rates (GFR) were calculated using the Cockcroft–Gault formula for all patients [15]. Patients were grouped by GFR into three groups based on the chronic kidney disease (CKD) classification: those with GFR $\geq$ 60 ml/h (CKD 1 or 2) were in GFR group 1; those with GFR of 30–60 ml/h (CKD 3) were in GFR group 2; those with GFR $<$ 30 ml/h and who did not undergo dialysis (CKD 4) were in GFR group 3.

The logistic EuroScore [16] was applied to adjust in-hospital mortality. A renal failure risk stratification system [3], named the 'Renoscore' in the present study, was used to adjust patients' risk of postoperative in-hospital MRRT. Hypercholesterolemia was coded according to STS database version 2.41.

2.1. Surgical procedure

Procedure selection, where it was decided whether patients underwent conventional CABG with cardiopulmonary bypass (CPB group) or off-pump CABG (OPCAB group) remained at the discretion of the attending surgeons. The surgical procedure was performed via a full median sternotomy for both groups. For the CPB group, the core body temperature was kept about 28–32 °C during surgery. The nadir hematocrit was maintained at 25%. Myocardial protection was achieved by intermittent antegrade/retrograde cold blood cardioplegia. Solumedrol (1000 mg) was injected into cardiopulmonary bypass circuit before starting cardiopulmonary bypass. For the OPCAB group, stabilization of the target vessels was accomplished with either an Octopus Stabilizer (Medtronic, Inc., Minneapolis, MN) or a Cardiothoracic Systems (CTS) stabilizer (CardioThoracic Systems, Inc., Cupertino, CA). Heparin was administered at a dose of 200 IU/kg to achieve an activated clotting time of greater than 300 s for the OPCAB group, and 300 IU/kg to achieve activated clotting time of greater than 450 s for the CPB group. Coronary anastomoses were performed as routine.

Postoperatively, the decision to use MRRT was made by the ICU medical doctors, mainly based on oliguria refractory to strong diuretics, clinical evidence of fluid overload, or electrolyte imbalance. Continuous veno–veno hemofiltration (CVVH) was usually used for MRRT in the immediate postoperative period, and then was gradually shifted to regular hemodialysis or peritoneal dialysis once the patient showed hemodynamic stability.

2.2. Follow-up

The 48-month follow-up data were completed by chart review and clinical investigation for all participating patients. Mortality of all causes was counted. Chronic dialysis for greater than 3 months was counted as an event of follow-up MRRT.

2.3. Statistics

Data were expressed as means $\pm$ standard deviations (SDs). Frequencies of simple morbid events were reported as simple percentages. Statistical comparisons between groups were computed using Student's *t*-test or the Chi-square test, according to the data type. Non-Gaussian distributed numerical variables with marked right screw (including ventilator use hours and ICU days) were presented as medians, 25th, 75th inter-quartile range, and compared using the Mann–Whitney *U*-test. Follow-up events of death and MRRT were plotted according to actuarial life tables and compared using Cox regression tests. For all statistical evaluations, differences in data with *p*-values of less than 0.05 were considered significantly different. All statistical work was performed using SPSS for Windows (SPSS Inc., Chicago, Illinois.)

3. Results

A total of 2102 cases were included in the study, 1116 (53%) were included in the CPB group, and 986 (47%) were in the OPCAB group. In the analysis of demographic data (Table 1), variables were comparable between both groups, except for the percentage of urgent operations and the percentage of New York Heart Association (NYHA) class 3–4, which were higher in the CPB group than in the OPCAB group (urgency, 9.1% vs 5.5%, respectively, $p = 0.001$; NYHA class 3–4, 29.4% vs 24.3%, respectively, $p = 0.01$). The predicted mortality and predicted postoperative renal failure rates were comparable between the groups (logistic EuroScore was

Table 1
Characteristics of patients who underwent coronary artery bypass grafting (CABG) with conventional cardiopulmonary bypass (CPB group) and those who underwent off-pump CABG (OPCAB group)

	CPB (n = 1116)	OPCAB (n = 986)	p
Age (years)	64.4 $\pm$ 10.3	65.1 $\pm$ 10.8	0.125
Male	75.9%	74.1%	0.352
Diabetes, all	47.7%	47.6%	0.962
Diabetes, insulin therapy	6.1%	4.6%	0.122
PAOD	11.9%	9.9%	0.162
COPD	7.1%	8.1%	0.409
Old CVA	10.7%	11.6%	0.531
AMI <30 day	16.9%	18.0%	0.565
Urgency	9.1%	5.5%	0.001 *
NYHA groups 3 and 4	29.4%	24.3%	0.01 *
LVEF	56 $\pm$ 14%	55 $\pm$ 14%	0.307
Hypercholesterolemia	36.7%	46.7%	0.062
Predicted mortality rate with logistic EuroScore	5.4 $\pm$ 8.5%	5.2 $\pm$ 7.6%	0.615
Renoscore	2.2 $\pm$ 2.1	2.0 $\pm$ 1.9	0.086

5.4% ± 8.5% in the CPB group and 5.2% ± 7.6% in the OPCAB group, $p = 0.615$; the Renoscore was 2.2 ± 2.1 in CPB group and 2.0 ± 1.9 in the OPCAB group, $p = 0.086$.)

Stratified by their preoperative estimated GFR, there were 1012 (48%), 864 (41%), and 226 (10.8%) cases in GFR groups 1, 2, and 3, respectively (Table 2). The predicted mortality rates, calculated by logistic EuroScore, were comparable between the CPB and OPCAB groups across all GFR groups. The Renoscore was comparable between the CPB and OPCAB groups for GFR groups 1 and 2. But for GFR group 3, the Renoscore was higher in the CPB group than in the OPCAB group (5.8 ± 2.2 vs 5.1 ± 1.8, $p = 0.013$), which attributed to greater urgency of surgery and greater clinical congestive heart failure within the NYHA 3–4 subgroup of the CPB group.

3.1. Postoperative events

Postoperative ventilator time, ICU stay (days), and in-hospital mortality rate increased progressively from GFR groups 1–3 (Table 3). The mortality rates were significantly lower in the OPCAB group than in the CPB group across all GFR groups, indicating a generally superior outcome in the OPCAB group compared to the CPB group.

3.2. In-hospital MRRT

The postoperative MRRT rate was significantly higher for the CPB than the OPCAB group for GFR group 3 (Table 3), but was not statistically significant for the other two GFR groups. For GFR groups 1 and 2, both the crude and Renoscore-adjusted odds ratios were not significant for postoperative MRRT (Table 4). For renal group 3, the crude odds ratio for conventional CPB use was statistically significant, but Renoscore-adjusted odds ratio was not (Table 4).

Table 2
Patients within the CPB and OPCAB groups (abbreviations as in Table 1 were further categorized into another three groups by estimated glomerular filtration rate (GFR)

	GFR group 1	GFR group 2	GFR group 3
Patients (*n*)			
CPB	539	458	119
OPCAB	473	406	107
Creatinine (mg/dl)			
CPB	0.97 ± 0.20	1.27 ± 0.30	2.85 ± 1.78
OPCAB	0.97 ± 0.20	1.27 ± 0.33	3.04 ± 1.74
p	0.970	0.748	0.409
GFR (ml/min)			
CPB	82.8 ± 20.0	46.6 ± 8.1	21.3 ± 6.3
OPCAB	82.3 ± 19.8	46.8 ± 8.2	20.7 ± 7.2
p	0.644	0.701	0.492
Hypercholesterolemia			
CPB	36.7%	25.3%	27.7%
OPCAB	42.5%	33.5%	25.2%
p	0.062	0.009	0.763
Predicted mortality**			
CPB	3.1 ± 4.0%	6.1 ± 8.4%	13.3 ± 15.5%
OPCAB	3.0 ± 4.0%	6.3 ± 8.5%	10.8 ± 11.3%
p	0.975	0.729	0.152
Renoscore			
CPB	1.1 ± 1.5	2.4 ± 1.7	5.8 ± 2.2
OPCAB	1.0 ± 1.3	2.4 ± 1.5	5.1 ± 1.8
p	0.231	0.3 6 1	0.013

*GFR group 1: GFR ≥ 60 ml/min, GFR group 2: GFR 30–60 ml/min, GFR group 3: GFR < 30 ml/h, but without dialysis before surgery.
**Predicted mortality rate was calculated with the logistic EuroScore.

Table 3
Postoperative events categorized by GFR groups

	GFR group 1	GFR group 2	GFR group 3
Ventilator time (h)			
CPB	19 (12–33)	20 (13–48)	38 (14–116)
OPCAB	11 (4–19)	15 (7–22)	18 (11–38)
p	<0.001	<0.001	<0.001
Postoperative ICU days median (25–75th percentile)			
CPB	3 (2–4)	3 (2–6)	5 (3–11)
OPCAB	2 (2–3)	2 (2–4)	3 (2–5)
p	<0.001	<0.001	<0.001
Hospital mortality			
CPB	1.9%	5.9%	16.8%
OPCAB	0.6%	2.7%	6.5%
p	0.099	0.030	0.023
MRRT			
CPB	2.0%	4.6%	26.1%
OPCAB	1.1%	3.4%	14.0%
p	0.313	0.490	0.031

ICU, intensive care unit; MRRT, mechanical renal replacement therapy. Other abbreviations as in Table 1.

3.3. Follow-up mortality

Only patients discharged from the hospital (2024 out of 2102, 96.3%) were included in the following analysis. The follow-up period ranged from 0 to 48 months, with a total of 6671 patient-months and a mean of 26.4 ± 22.4 months of follow-up. There were significant survival differences between three GFR groups (Fig. 1), of which freedom from all-cause death were 91.4%, 83.9%, and 62.9% in GFR groups 1, 2, and 3, respectively ($p < 0.001$ between groups 1 and 2; $p < 0.001$ between groups 2 and 3.) The survival rates did not differ between the CPB and OPCAB groups across all renal groups.

3.4. Follow-up MRRT

At hospital discharge, 100%, 99%, and 91.5% of patients were free from MRRT in GFR groups 1, 2, and 3, respectively. At the end of 4 years of follow-up (Fig. 2A), the freedom from MRRT rate was much lower for GFR group 3 compared to GFR groups 1 and 2 (99.1%, 97.2%, and 78.6% for renal groups 1, 2, and 3, respectively. $p = 0.0097$ between group 1 and 2; $p < 0.001$ between group 2 and 3). The MRRT rates did not

Table 4
Logistic regression of cardiopulmonary bypass use for in-hospital mechanical renal replacement therapy (MRRT) by glomerular filtration rate (GFR group)

	GFR group 1	GFR group 2	GFR group 3
Crude odds ratio (OR)	1.95	1.35	2.16
(95% confidence interval, CI)	(0.67–5.65)	(0.68–2.68)	(1.09–4.27)
p	0.219	0.399	0.027
Renoscore-adjusted OR*	1.74	1.26	1.69
(95% CI)	(0.59–5.12)	(0.62–2.53)	(0.83–3.48)
p	0.314	0.524	0.150

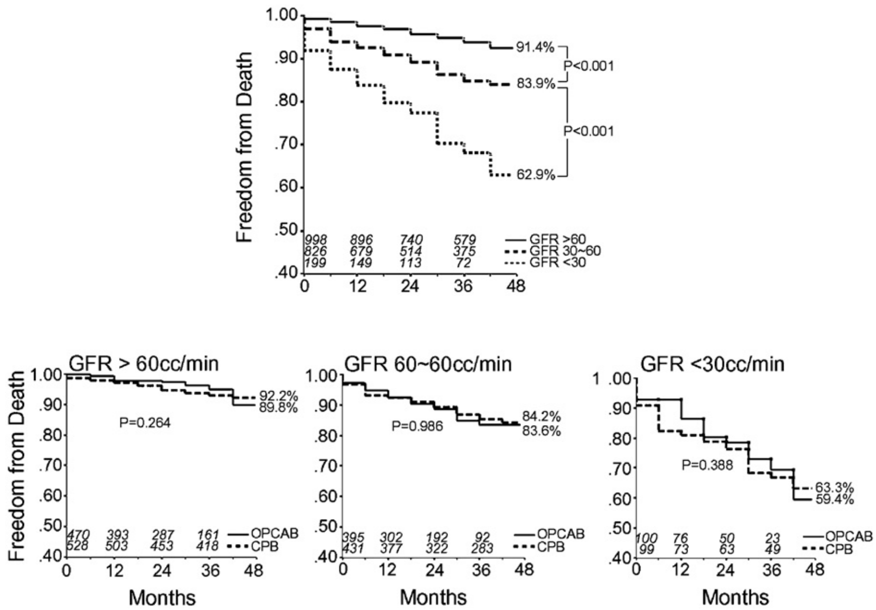

Fig. 1. Follow-up mortality, grouped by preoperative glomerular filtration rate (GFR) and cardiopulmonary bypass (CPB) use or not.

differ between the CPB and OPCAB groups across all three GFR groups at the mid-term follow-up (Fig. 2B) (for GFR group 1, 99.7% of the CPB group and 99.7% of the OPCAB group were free from MRRT, $p = 0.872$; for GFR group 2, 96.6% of the CPB group and 98.7% of the OPCAB group were free from MRRT, $p = 0.710$; for GFR group 3, 82.1% of the CPB group and 73.3% of the OPCAB group were free from MRRT, $p = 0.472$.

3.5. Cox regression analysis for mid-term MRRT

Only patients in GFR groups 2 and 3 were included in the following risk analysis for the potential risk factors of mid-term MRRT because the incidence of MRRT for GFR group 1 was very low (Table 5). By univariate analysis, several risk factors were significant, including preoperative GFR, hypercholesterolemia, insulin-requiring diabetes, young age at surgery, female gender, and in-hospital MRRT (Table 5). PAOD tended to be an indicator for late MRRT, but did not reach statistical significance. Noteworthily, cardiopulmonary bypass use was not a statistically significant risk factor for late MRRT (Table 5). In the multivariate analysis, preoperative GFR, hypercholesterolemia, insulin-requiring diabetes, age at surgery, and in-hospital MRRT were significant risk factors for late MRRT (Table 5).

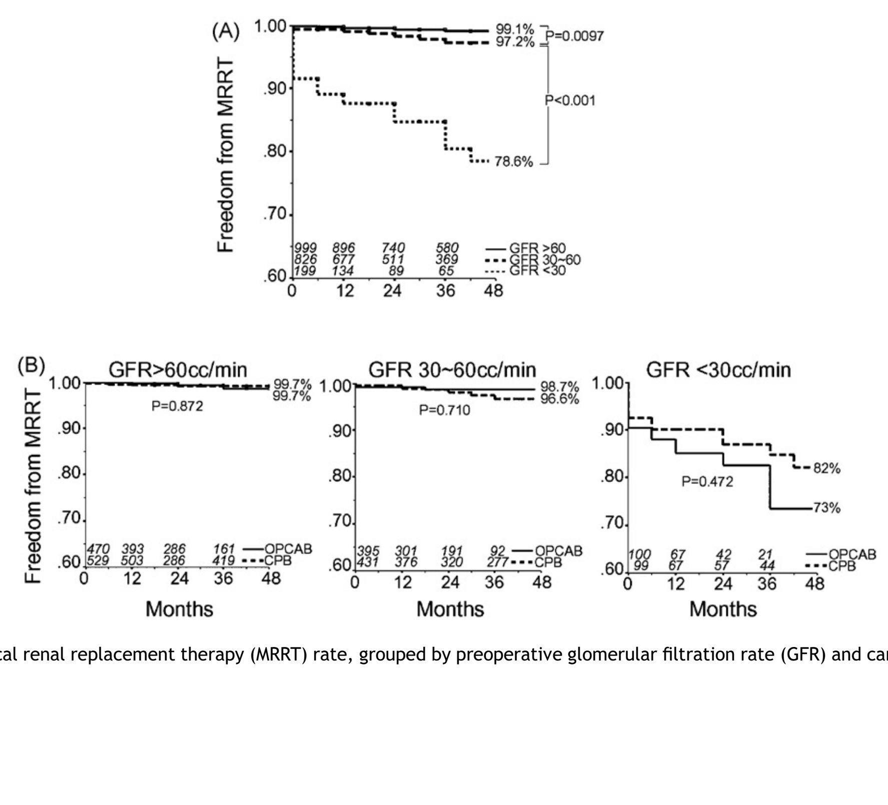

Fig. 2. Follow-up mechanical renal replacement therapy (MRRT) rate, grouped by preoperative glomerular filtration rate (GFR) and cardiopulmonary bypass (CPB) use or not.

Table 5
Cox regression for mid-term mechanical renal replacement therapy (MRRT) rate for patients with moderate-to-severe renal impairment (glomerular filtration rate, GFR, groups 2 and 3)

	GFR groups 2 and 3			
	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Patient factors				
Preoperative GFR (+1 ml/min)	0.90 (0.89–0.92)	<0.001	0.91 (0.89–0.93)	<0.001
Hypercholesterolemia	2.45 (1.41–4.26)	0.002	2.54 (1.40–4.58)	0.002
DM-insulin	4.39 (2.24–8.59)	<0.001	2.66 (1.33–5.31)	0.006
Age at surgery (per +1 year)	0.97 (0.93–0.99)	0.036	0.96 (0.93–0.99)	0.003
Preoperative NYHA 3 or 4	1.61 (0.91–2.85)	0.105	–	0.325
Preoperative LVEF	1.00 (0.98–1.01)	0.695	–	–
COPD	0.23 (0.03–1.64)	0.141	–	–
PAOD	1.82 (0.93–3.55)	0.081	1.86 (0.9–3.7)	0.077
Female gender	3.23 (1.85–5.88)	<0.001	–	0.154
Operative and postoperative factors				
In-hospital MRRT use	12.4 (6.7–23.2)	<0.001	2.91 (1.4–5.9)	0.003
Postoperative IABP use	0.43 (0.13–1.37)	0.152	–	–
CPB use	0.80 (0.44–1.44)	0.452	–	–

(1) Only the patients that survived to hospital discharge in GFR groups 2 and 3 were included in the analysis because the incidence of mid-term MRRT was low (1%) for GFR group 1. (2) Only risk factors with $p < 0.10$ in univariate analyses were included in the multivariate analysis. HR, hazard ratio; MRRT, mechanical renal replacement therapy.

4. Discussion

Our study demonstrated comparable mid-term MRRT rates between the CPB and OPCAB groups for CABG patients with moderate-to-severe renal impairment before surgery. In earlier studies, only data from the immediate postoperative period were investigated [13,17], so it was unclear whether cardiopulmonary bypass had any late impact on renal insufficiency, especially for those with already impaired renal function before CABG surgery. Because of the nation-wide health insurance database in Taiwan, follow-up events including death and long-term dialysis use can be collected and studied in a reliable way.

The potential hazard of cardiopulmonary bypass to renal damage is multifactorial and includes decreased renal blood flow during hypothermia, non-pulsatile perfusion [18], hemodilution during cardiopulmonary bypass [19], inflammation and activation of the complement system [20,21], and atheroembolism [22]. Data from the present study revealed a significant impact on the postoperative mortality rates with use of cardiopulmonary bypass in advanced renal impaired cases (Tables 2 and 3). Though the estimated mortality rate by EuroScore was comparable between OPCAB and CPB groups in the GFR groups 2 and 3, the observed mortality rate was higher for CPB group as compared to the OPCAB group (5.9% vs 2.7%, $p = 0.030$ for GFR group 2; 16.8% vs 6.5%, $p = 0.023$ for GFR group 3.) These differences in the mortality rate can suggest the primary selection of OPCAB procedure in patients with impaired renal function to surgeons. We believe cardiopulmonary bypass carries a transient renal damage, and, theoretically, patients with preserved renal function can tolerate this transient renal damage [12,23] and withstand the cardiopulmonary bypass procedure safely, without additional increase in the chance of postoperative MRRT compared to those without cardiopulmonary bypass use. But for cases with moderate and severe renal insufficiency before surgery, whether this degree of transient insult has a detrimental effect on renal function is not currently clearly understood. The results of our study demonstrate that cardiopulmonary bypass use is not associated with increased in-hospital and mid-term MRRT rates for CABG patients with either preserved or impaired renal function.

Another interesting finding of our study is that hypercholesterolemia was associated with increased follow-up MRRT rates for patients with moderate and severe renal insufficiency. Previous animal studies proved that hypercholesterolemia induces renal injury by multiple mechanisms including accumulation of cholesterol and lipoprotein in the renal tubular system [24] and consequential inflammation, or excessive oxidative stress induced by hypercholesterolemia [25]. Our finding might provoke study interest for lipid-lowering therapy in preventing renal insufficiency for coronary artery disease patients with moderate-to-severe renal insufficiency. Whether this finding can be applied to other relatively low-risk populations needs further investigation.

5. Study limitations

The present study was not a randomized prospective one. The proportion of patients with urgent operation and NYHA III–IV were higher in the CPB group compared to the OPCAB group. These differences of patients' characteristics may have an important impact on the immediate postoperative results including the hospital mortality, ventilator time and ICU stay. As learned from EuroScore calculator, urgency/emergency operation carries about twice the operative risk when compared with elective operations. The percentage of urgency operation was higher in CPB group (9.1%) than in OPCAB group (5.5%) in the present study, and a total of 62 cases (10.7%) in GFR group 2 or 3 for CPB group received operation in urgency setting, and 17 of them (27%) died immediately after the operation. On the other hand, 32 cases (6.2%) in GFR group 2 or 3 for CPCAB group received an urgency operation, and 5 cases (15%) died immediate postoperatively. It remains unanswered whether or not the high early mortality for CPB group with advanced renal impairment may mask the late MRRT rate. But since to stabilize hemodynamic status by using cardiopulmonary bypass support for the critical patients is always a priority over late renal protection, we believe this uncertainty is ethically tolerable.

The endpoint for renal outcome evaluation in the present study is MRRT use, which is a standardized criterion but may not be a sensitive one. Further study on the serial change of biochemical markers representing glomerular or tubular function or injury [14,23] is necessary to confirm the effect of the risk factors reported in the present study.

Regarding hypercholesterolemia, it is undetermined what specific type of lipoprotein is the culprit for the accelerated deterioration of renal function. Besides, the potential effect of lipid-lowering medication and other anti-hypertensive medication on renal insufficiency is not studied in the present study.

6. Conclusion

In conclusion, the present study demonstrated that the operative strategy of using either off-pump technique or conventional CABG with cardiopulmonary bypass is not associated with different mid-term MRRT rate for patients with impaired renal function. Patients' preoperative characteristics including preoperative GFR, insulin-requiring diabetes, hypercholesterolemia, female gender, and younger operative age were significant for mid-term MRRT rate.

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