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Cardiovascular Surgery with Cardiopulmonary Bypass in Patients with Preoperative Non-dialysis Dependent Renal Insufficiency

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ABSTRACT

Background: Preoperative renal insufficiency is a predictor of acute renal injury in patients undergoing cardiovascular surgery with cardiopulmonary bypass.

Methods: From January 2010 to September 2012, 121 patients undergoing coronary bypass, valve replacement, or both were included in our retrospective study, using cardiopulmonary bypass. We compared the changes in renal function and clinical outcomes of 66 patients with a baseline serum creatinine level more than 1.5 mg/dL with 55 patients with normal serum creatinine levels. We analyzed the impact of cardiopulmonary bypass in patients with non-dialysis dependent renal insufficiency.

Results: In the group of patients with preoperative renal injury, the need for dialysis was greater, time of mechanical ventilation longer, and daily diuresis lesser compared with the group of patients with normal serum creatinine levels. Other clinical outcomes such as postoperative hemodynamic problems and organ dysfunction were similar. Prolonged time of cardiopulmonary bypass and cross-clamp affected postoperative renal injury. The study also showed intraoperative dopamine infusion at renal dose and ultrafiltration are not effective with protecting renal tubular function. Serum creatinine levels and glomerular filtration rate (GFR) were found to be useful parameters for renal injury.

Conclusion: These results demonstrate the safety and trustworthiness of cardiopulmonary bypass in patients with non-dialysis dependent renal insufficiency.

INTRODUCTION

Preoperative renal dysfunction is an important risk factor for morbidity and mortality in patients undergoing cardiac surgery [Loef 2005]. Acute renal failure (ARF) occurs in up to 30% of these patients [Conlon 1999]. After cardiac surgery, renal vascular resistance increases and renal blood flow and GFR decrease. Also, elaboration of inflammatory mediators leads to additional cellular injury. Acute tubular necrosis is the pathologic lesion in patients with ARF associated with cardiopulmonary bypass (CPB) [Landoni 2007].

The purpose of this retrospective study is to determine preoperative risk factors of renal injury, the effects of CPB in non-dialysis dependent renal insufficiency, and the clinical outcomes of ARF.

MATERIALS AND METHODS

From January 2010 to September 2012, 121 patients undergoing coronary bypass, valve replacement, or both were included in our retrospective study, using CPB. We compared the changes in renal function and clinical outcomes of 66 patients with a baseline serum creatinine level more than 1.5 mg/dL (renal group) with 55 patients with normal serum creatinine levels (control group).

A standard set of perioperative data was collected prospectively for all patients. This included age, sex, weight, diagnosis, type of surgery, history of illness such as diabetes mellitus, hypertension, peripheral vascular disease, anemia, neurological dysfunction, left ventricular ejection fraction (LVEF), prior myocardial infarction, preoperative drug use (NSAI, ACE inhibitors, diuretics, statins), serum creatinine, sodium (NA), potassium (K), blood urea nitrogen (BUN) levels, and GFR measured by using Cockcroft-Gault formula (Table 1).

Patients considered to have radiocontrast-induced nephropathy (RIN) were excluded. Also, both groups were matched on intraoperative data prospectively: type of surgery, urgent and emergent cases, CPB and cross-clamp time, renal dose dopamine infusion, ultrafiltration, diuresis, and blood transfusion (Table 2).

We inscribed the data for time of mechanical ventilation, time of awakening, need of inotropic support and intra-aortic balloon pump (IABP), need of dialysis, daily diuresis, organic failure, and other complications in the postoperative period. Serum creatinine levels and GFRs were measured at the time of hospitalization and postoperatively. Normal serum creatinine levels were evaluated as 0.3-1.2 mg/dL. The highest level of creatinine postoperatively was used to calculate creatinine clearance.

We preoperatively evaluated all patients concerning medical history and clinical examination, including electrocardiogram (ECG) and chest X–ray, complete laboratory investigations, Echo-Doppler evaluation of the heart and valves, and coronary angiography.

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Table 1. Preoperative Clinical Characteristics

	Renal (N = 66)		Control (N = 55)		*P*
	N	%	N	%	
Type of operation					
Coronary bypass	49	74.2%	39	70.9%	.432
Valve replacement	7	10.6%	10	18.2%	
Valve replacement + coronary bypass	10	15.2%	6	10.9%	
EF					
30% (low)	8	12.1%	1	1.8%	.034*
30-50%	26	39.4%	17	30.9%	
50% (normal)	32	48.5%	37	67.3%	
DM					
-	37	56.1%	32	58.2%	.814
+	29	43.9%	23	41.8%	
Anemia					
-	54	81.8%	48	87.3%	.412
+	12	18.2%	7	12.7%	
HT					
-	24	36.4%	18	32.7%	.676
+	42	63.6%	37	67.3%	
MI					
-	39	59.1%	37	67.3%	.354
+	27	40.9%	18	32.7%	
PAD					
-	65	98.5%	53	96.4%	.455
+	1	1.5%	2	3.6%	
CAD					
-	56	84.8%	50	90.9%	.314
+	10	15.2%	5	9.1%	
COD					
-	64	97.0%	53	96.4%	.853
+	2	3.0%	2	3.6%	
COPD					
-	50	75.8%	42	76.4%	.938
+	16	24.2%	13	23.6%	
State of operation					
Elective	6	9.1%	2	3.6%	.305
Prior	12	18.2%	7	12.7%	
Urgent		48	72.7%	46	83.6%
Drug usage					
-	36	54.5%	28	50.9%	.690
+	30	45.5%	27	49.1%	

Data is mean. *$P < .05$. **$P < .01$. Key: EF, ejection fraction; DM, diabetes mellitus; HT, hypertension; MI, myocardial infarction; PAD, peripheral arterial disease; CAD, carotid artery disease; CVO, cerebrovascular occlusive disease; COPD, chronic obstructive pulmonary disease

Table 2. Perioperative Variables

	Renal (N = 66)		Control (N = 55)		MW	*P*
	Mean	SD	Mean	SD		
CPB Time	124.58	40.09	117.11	48.27	1507	.109
CC Time	93.62	33.52	85.55	41.79	1467	.070
Diuresis	1227.58	560.39	1240.18	394.81	1720	.617
		Mean	SD	Mean	SD	
UF						
-		47	71.2%	54	98.2%	.000**
+		19	28.8%	1	1.8%	
Dopamine						
-		37	56.1%	55	100%	.000**
+		29	43.9%	0	0%	

Key: CC, cross-clamp; UF, ultrafiltration

STATISTICAL ANALYSIS

Data was collected and managed in Microsoft Access. We used the Kolmogorov-Smirnov test to analyze statistical methods and normal distribution. Pearson's chi-squared test was used for non-parametric variables; Mann-Whitney U test was used for parametric variables. Wilcoxon signed-rank test was used to compare the parameters in the groups, and Spearman's rank correlation coefficient was used to compare the qualified data. All continuous variables were expressed as mean ±SD, and statistical significance was assumed if $P < 0.05$. $P < 0.01$ means higher significance.

OPERATIVE TECHNIQUE

The management of the operation was similar with all patients. Heart rate and rhythm were monitored on ECG monitor, during all procedures. Pulse oximetry was used for O2 saturation measurements. A urinary catheter evaluated urine output, and nasopharyngeal temperature continuously was monitored.

Following median sternotomy and heparinization, CPB was established with an ascending aortic cannula and two caval cannulae in mitral valve replacement operations and two staged venous cannulae in CPB operations and aortic valve operations. Blood cardioplegic solution was used in all patients. During bypass, the hematocrit levels were maintained between 20% and 25% and mean arterial pressure above 50 mmHg. Ultrafiltration and/or renal dose dopamine perfusion was used in some of the patients with preoperative renal dysfunction and whose intraoperative urinary output was low.

Patients with hemodynamic instability received inotropic medication. An IABP was percutaneously inserted in patients with difficulty weaning from CPB or those with inadequate cardiac performance developed in the intensive care unit.

Whole blood or packed red blood cells were transfused in patients with a hematocrit value less than 24%. Some patients postoperatively received furosemide perfusion because of low urine output. Serum creatinine, BUN, NA, K levels, and GFRs were measured at the time of hospitalization and postoperatively on Days 1, 3, and 5. Renal insufficiency was defined according to guidelines from the National Kidney Foundation. Acute renal dysfunction was classified on the basis of risk, injury, failure, loss of kidney function (RIFLE) criteria.

RESULTS

The study included 121 patients. Out of the total, 85 patients were male (71.2%). The patient mean age was 62.3 years in the renal group and 58.6 years in the control group. Ejection fraction (EF) was lower in the renal group. Other preoperative variables were not statistically significant between the two groups.

Cross-clamp and CPB times also were similar. As expected, intraoperative ultrafiltration and dopamine infusion were used more in the renal group. Prolonged time of CPB and cross-clamp effected postoperative renal injury. In the group of patients with preoperative renal injury, the need for dialysis was greater, time of mechanical ventilation longer, and daily diuresis less compared with the group of patients with normal serum creatinine levels. Other clinical outcomes like postoperative hemodynamic problems, organ dysfunction, time of awakening, need of inotropic support and IABP, and need of reoperation for bleeding were similar. In the renal group, the amount of intraoperative and postoperative transfusion significantly was higher than the control group.

The study also showed that intraoperative dopamine infusion at renal dose and ultrafiltration don't have any effect

Table 3. Postoperative Variables

	Renal (N = 66)		Control (N = 55)		*P*
	N	%	N	%	
Postoperative dialysis					
-	44	66.7%	52	94.5%	.000**
+	22	33.3%	3	5.5%	
Hemodynamic problems					
-	41	62.1%	40	72.7%	.217
+	25	37.9%	15	27.3%	
Postoperative organic dysfunction					
-	51	77.3%	49	89.1%	.087
+	15	22.7%	6	10.9%	
IABP need					
-	52	78.8%	52	94.5%	.013*
+	14	21.2%	3	5.5%	
Inotropic support					
-	29	43.9%	24	43.6%	.973
+	37	56.1%	31	56.4%	
Need for reoperation					
-	51	77.3%	47	85.5%	.253
+	15	22.7%	8	14.5%	
Postop CVO					
-	63	95.5%	54	98.2%	.403
+	3	4.5%	1	1.8%	
+	30	45.5%	27	49.1%	
A/EX					
Alive	61	92.4%	54	98.2%	.146
Mortality	5	7.6%	1	1.8%	
Need for dialysis					
-	58	95.1%	53	98.1%	.370
+	3	4.9%	1	1.9%	
	Ort Ss	Ort	Ss		
Bleeding	941.67	425.22	950.91	478.18	.744
Postoperative awakening	11.69	10.89	9.58	8.27	.120
Mechanical ventilation time	23.92	38.37	15.19	17.35	.004**
Daily diuresis	2173.79	1020.68	2969.09	921.73	.000**

protecting renal tubular function. The preoperative serum creatinine and BUN levels were 1.89 mg/dL ± 0.57 mg/dL and 35.62 mg/dL ± 12.45 mg/dL, respectively in the renal group. The postoperative serum creatinine and BUN levels were measured as 2.26 mg/dL ± 0.95 mg/dL and 40.95 mg/dL ± 12.37 mg/dL.

In the control group, the preoperative serum creatinine and BUN levels were 0.84 mg/dL ± 0.16 mg/dL and 16.30 mg/dL ± 4.14 mg/dL, respectively. In the renal group, the postoperative serum creatinine and BUN levels were measured as 1.14 mg/dL ± 0.92 mg/dL and 23.43 mg/dL ± 15.98 mg/dL.

Preoperative GFR values were 44.34 ± 13.04, and postoperative GFR values were 39.47 ± 15.82 in the renal group. In the control group, preoperative GFR values were 100.54 ± 31.83, postoperative GFR values were 94.37 ± 43.65.

Serum creatinine, BUN levels, and GFR were found to be useful parameters for renal injury. In this study, the change of GFR, serum creatinine and BUN levels were not significant according to the presence of DM and EF. The type of operation and state of operation (whether it is urgent or not) did not affect the change. Permanent dialysis was needed in three patients (4.9%) in the renal group and one patient in the control group. One death was observed in the control group in the postoperative period (mortality 1.8%) and five deaths were observed in the renal group (mortality 7.6%) (Table 3).

DISCUSSION

The reasons of renal injury in patients undergoing cardiovascular surgery with CPB are multifactorial. Inefficient perfusion is the main factor for renal ischemia. Behind this nonpulsatile flow, the effects of different kinds of mediators, micro and macro emboli also cause renal dysfunction. These events lead to dramatic hemodynamic effects as well as activation of immune responses that can extend renal injury.

Renal insufficiency is a predictor for mortality and morbidity in cardiac surgery [Loef 2005]. In many studies, preoperative renal dysfunction is found to be the main reason for renal failure [Fukushima 2004].

For those with a baseline serum creatinine level between 2.0 mg/dL - 4.0 mg/dL, the risk of ARF is 10% to 20% [Weerasinghe 2005].

Off-pump coronary artery bypass (OPCAB) grafting, has been reported to be associated with a lower incidence of AKI [Weerasinghe 2005; Hix 2006]. This issue still is controversial, as other studies did not confirm this finding [Chukwuemeka 2005; Schwann 2004].

In their study, Landoni and colleagues [Landoni 2007] expressed the opinion that rather than the CPB's elimination, regulation of hydration in the preoperative period, elimination of drugs to avoid renal side effects, use of inotropic or vasodilator agents for the stabilization of hemodynamic status, and correction of acid-base balance are required to prevent renal dysfunction. Most of the studies are limited because the definitions of AKI widely varied.

RIFLE criteria recently were used for the classification of AKI. In the RIFLE criteria, AKI was based on a 50% increase in serum creatinine levels occurring over one to seven days or the presence of oliguria for more than six hours. The Acute Kidney Injury Network (AKIN) criteria added an absolute increase in serum creatinine level of 0.3 mg/dL and reduced the timeframe for the increase in serum creatinine level to 48 hours [Mehta 2007].

CPB creates an inflammatory process with a number of cytokines, complement system and free oxygen radicals. Gas and particulate material and microembolism as a result of platelet aggregation are one of the causes of renal damage [Hashimoto 1993]. In many studies, CPB is evaluated as an independent and modifiable risk factor for ARF. Levine et al randomized 20 patients undergoing CPB with pulsatile and nonpulsatile flow and reported that in patients perfused with a pulsatile flow the increase in vasopressin, thromboxane A2 and prostacyclin levels are less and in patients undergoing CPB with non-pulsatile flow there is an increase in angiotensin II levels [Ashraf 1997].

There is a wide spectrum of renal injury after CPB from subclinical damage to renal failure requiring dialysis. Loef and colleagues [Loef 2005] examined in a study hospital and long-term mortality of the patients with ARF associated with cardiac surgery. This study shows that ARF is one of the high risk complications of morbidity and mortality in cardiac surgery. In our study, the need for dialysis requirement in the postoperative period was in 22 patients (33.3%) of the renal group compared with only in three patients (5.5%) of the control group. Permanent dialysis was needed in three patients (4.9%) in the renal group and one patient in the control group.

Many studies have tried to determine preoperative and intraoperative risk factors for the development of severe ARF after cardiac surgery, though failed to reveal any specific variables. In an important study, ARF risk assessment is carried out in 33,217 patients, who had undergone open heart surgery at the Cleveland Clinic Corporation (1993 to 2002). Serum creatinine level greater than 1.2 mg/dL, history of diabetes, chronic obstructive pulmonary disease, having previously undergone cardiac surgery and to have cardiovascular disease markers, and to be female found out to be the high risk factors [Thakar 2005]. Cardiomegaly, advanced age, cerebral vascular disease, digoxin use, use of diuretics, peripheral vascular disease, intravenous nitroglycerin use, the left main coronary artery stenosis, myocardial infarction history in the last seven days, low LVEF, use of preoperative IABP, a history of prior heart surgery, resting angina with ST-segment depression are reported to be associated with ARF after cardiac surgery [Chertow 1997].

In our study, diabetes mellitus and impaired EF were not found to be independent risk factors. Also, the type of operation and emergent cases are not seen as risk factors for postoperative renal damage.

In our study, in the renal group, longer cross-clamp and CPB time significantly increased the level of creatinine postoperatively and the increased amount of urine output during surgery significantly reduced the BUN and creatinine level. Longer cross-clamp time reduced postoperative GFR and the increased amount of urine removed was found to increase postoperative GFR. However, there was not a significant relationship between the duration of CPB and GFR. In the control group, longer cross clamp and CPB time caused postoperative creatinine elevation, but there was not a significant relationship with GFR. Also, in the control group, there was not a significant relationship between the amount of urine output and postoperative GFR and creatinine levels.

Monitoring the increase in the level of serum creatinine in the diagnosis of ARF is a better marker for monitoring the increase in the level of BUN [Lameire 2005]. But GFR is a more reliable marker than creatinine. Off-pump or on-pump bypass were performed in 14,000 patients with low preoperative GFR (<90ml/min) and it was claimed that low GFR causes postoperative hemodynamic complications and decreases longtime survival [Boulton 2011]. In our study, postoperative increase in BUN, creatinine values, and the decrease in GFR were indicators of renal damage; postoperative NA and K values were considered to vary depending on

ICU interventions. In several studies in patients with ARF, delay of nephrology consultation has been shown to cause increased mortality and morbidity. Two recent studies demonstrated that hemodilution (down to hematocrit levels < 25%) is associated with an increased risk for renal injury as measured by changes in serum creatinine [Swaminathan 2003; Karkouti 2005]. In addition, it's important to stop using all nephrotoxic drugs such as angiotensin-converting enzyme inhibitors, nephrotoxic antibiotics, radiocontrast agents, and nonsteroidal, anti-inflammatory drugs before the operation. To avoid developing ABY after cardiac surgery, many drugs were used to increase renal blood flow or increase natriuresis and inhibit inflammation. Dopamine, fenoldopam, and theophylline can be considered the drugs to increase renal blood flow. Using low doses of dopamine stimulates dopamine receptors (DA-1 and DA-2) and causes the inhibition of sodium absorption in the proximal tubule and increases renal blood flow. However, studies have shown that the use of dopamine hasn't got any protective effects for developing ARF after cardiac surgery [Tang 1999; Australian and New Zealand Intensive Care Society Clinical Trials Group 2000]. Also as a drug to increase natriuresis, furosemide treatment was found not to be protective [Lassnigg 2000; Lombardi 2003]. The potential role of Mannitol and atrial natriuretic peptide (ANP) remains unclear. Our study also showed that intraoperative dopamine infusion at renal dose and ultrafiltration don't have a significant effect to protect renal tubular function. Randomized and controlled trials are needed to show the efficacy of inflammation-blocking drugs such as Pentoxifylline, Pexelizumab, Dexamethasone, and N-Acetyl Cysteine. Early dialysis in the postoperative period is recommended to reduce mortality.

Wolf et al [Wolf 2010] have seen serum creatinine levels and creatinine clearance are still the gold standard, in terms of monitoring renal function. Markers that rise prior to ARF in the urine and plasma are a recent development. Kidney-specific proteins (as a marker to detect early changes in renal function) are new candidates. These include neutrophil gelatinase-associated lipocalin (NGAL), Cystatin C, Kidney Injury Molecule-1 (KIM-1), Interleukin-18, α1-Microglobulin, Fetuin, and Groα [Zhou 2006]. These markers are expected to make a major contribution for the future diagnosis and treatment of ARF. Further studies have to be made for these markers said to provide early diagnosis of ARF.

Treatment of congestive heart failure and fluid replacement must be done prior to the operation, if necessary to increase the cardiac output and renal perfusion. For patients at risk for renal injury, minimizing the cross-clamp and CPB time can be effective. In the operating room and ICU, close follow up for ventricular function, hematocrit and serum glucose levels, and keeping average blood pressure should help maintain the optimal level of renal perfusion. Severe hemodilution during CPB should be avoided.

CONCLUSION

On-pump cardiac surgery can be safely done with renal dysfunction patients, who are not taking hemodialysis. It is clear that classifying risk factors and stages of renal failure is necessary for doctors to take precautions for patient mortality and morbidity. Clinical studies like this one may identify high-risk patients for ARF. These high-risk patients can then be targeted for renal protective strategies.

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