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A Propensity Score Analysis of Renal Dysfunction in Patients after On-Pump and Off-Pump Coronary Artery Bypass Surgery

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ABSTRACT

Introduction: Cardiovascular disease has emerged as a major health burden worldwide with coronary artery disease (CAD) causing highest mortality and morbidity. Coronary surgery has revolutionized CAD management and has been one of the most studied procedures worldwide. Based on the application of cardiopulmonary bypass (CPB), coronary artery bypass grafting (CABG) can be on-pump or off-pump. The CPB is known to have multifactorial effects on all end-organ functions due to nonpulsatile flow and inflammation response. Renal function alteration is one of the multiple deleterious effects. There have been reports on better renal function using off-pump CABG. The present study aimed to investigate and compare the prevalence of renal dysfunction in the two techniques (i.e., on-pump and off-pump CABG).

Materials and Methods: This was a single-center retrospective study conducted with the data from 199 patients categorized into two groups of off-pump [n=106] and on-pump [n=93]. Renal parameters were monitored at days 0, 1, 3, and 5 after the operation using glomerular filtration rate and creatinine clearance of patients with diabetes, hypertension, as well as both diabetes and hypertension. In addition, normal patients were analyzed in the present study.

Results: Among 199 subjects who underwent the surgery, renal functions were compared between the two groups. Accordingly, no significant difference was observed in renal function derangement between the off-pump and on-pump groups.

Conclusion: It was concluded that CPB does not have any additional role as the culprit in renal dysfunction. Both groups shared an almost similar change of trends in renal functions.

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Introduction

Coronary revascularization is one of the procedures with the highest impact on the history of medicine. No other operation has led to more prolonged lives and been better characterized with respect to its short- and long-term outcomes (1).

The CABG has improved the morbidity and mortality in conditions, such as triple-vessel disease, double-vessel coronary artery disease (CAD), and angina refractory to medical intervention. There are two basic ways of performing CABG, namely on-pump CABG and off-pump CABG. The major difference between on-pump and off-pump CABG is the use of cardiopulmonary bypass (CPB) in which a machine maintains the body's blood supply in case of on-pump CABG. Off-pump CABG is a relatively newer approach with no need for cardiopulmonary bypass (CPB) machine (2).

Traditionally, on-pump CABG is the preferred choice; however, the use of CPB leads to inflammatory effects responsible for multiple organ dysfunction affecting the kidneys, liver, lungs, brain, and heart (3).

Off-Pump CABG has recently gained popularity because it negates the ill effects of CPB; nonetheless, it requires more technical expertise.

Postoperative renal dysfunction following CPB is relatively common (8%) with acute renal failure (ARF) developing in 1.2-13% of patients depending on their preoperative glomerular filtration rate (GFR). Among the cases who developed postoperative renal dysfunction, 18% of them required dialysis. Overall mortality among patients who develop postoperative renal dysfunction is reported as 19% (4, 5). Predictors of renal dysfunction

Include advanced age, history of congestive heart failure, prior bypass surgery, type 1 diabetes, and prior renal disease (6). Patients with advanced preoperative renal dysfunction (preoperative creatinine level≥2.5 mg/dL) who undergo CABG have an extraordinarily high risk of postoperative dialysis, and 40-50% of the cases require hemodialysis (7). Intraoperative renal risk factors include low normal cardiac output, decreased effective arterial blood volume, prolonged CPB time longer than 130 to 180 min, development of a systemic inflammatory response syndrome (SIRS), inappropriate hemodilution, and embolic phenomenon. Acute renal injury (AKI) has been reported following cardiac surgery; however, emergency surgery, chronic kidney disease, and female gender are among the most prominent risk factors (8).

During CPB, despite wide fluctuations in mean arterial pressure (MAP), only minute changes arise in GFR due to renal autoregulation. The renal blood flow begins to decline at MAPs lower than 50 mm Hg, and the autoregulation of GFR occurs at higher pressures (70-80 mm Hg). This concept becomes clinically relevant during CPB when perfusion pressure is decreased below the autoregulatory threshold for GFR resulting in diminished urine output. Increasing perfusion pressure is often considered when managing intraoperative oliguria to theoretically prevent ARF (9, 10).

During CPB factors affecting GFR and consequently urine formation may be diminished for several reasons, including decrease in kidney function due to exposure to nephrotoxins or decrease in glomerular capillary pressure due to hypoperfusion and increase in intratubular pressure from intratubular

obstruction due to cellular debris or increase in glomerular concentration from the concentration of proteins due to dehydration.

Although the decline in GFR results in the reduction of urine output, the contrary is not necessarily true that is a decrease in urine volume does not always mean a decline in GFR. In addition, it does not imply the diagnosis of ARF (11). Despite the observations that CPB duration is independently associated with ARF, the benefits of off-pump cardiac bypass surgery for renal function remain controversial in many retrospective studies.

Pathophysiology of cardiac surgery-associated AKI (CS-AKI) is complex and is believed to be multifactorial. Occurrence of CS-AKI may be explained by different mechanisms acting synergistically, including endogenous and exogenous toxins, metabolic mechanisms, neurohormonal activation, ischemia-reperfusion, oxidative stress, and inflammation (12).

Materials and Methods

This retrospective study was carried out on a cohort of patients with CAD admitted in Kasturba Hospital in Manipal, India, who underwent similar surgical intervention during 2014 and 2017. Only the subjects with stable angina (not in heart failure) who underwent elective isolated CABG were included in the present study. Patients operated on an emergency basis with previous renal dysfunction and the cases who had undergone CABG with valve surgery and redo cardiac surgery were excluded from the study. Medical records of the patients were analyzed for obtaining the necessary data after acquiring the approval from the Medical Records Department of Kasturba Hospital. A total of 199 patients were included in this study and divided into two groups based on the CABG technique. In all cases, the treatment was based on a prior review of coronary angiograms of the respective patient, and the procedures were performed through midline sternotomy incision. Used grafts were left internal mammary artery and/or saphenous vein graft/left radial artery. During off-pump surgery, median sternotomy was performed by simultaneous harvesting of radial artery/saphenous vein and left internal mammary artery. In off-pump CABG, activated clotting time was maintained over > 300-350 sec. The heart was stabilized using an Octopus tissue stabilizer. During distal grafting, MAP was maintained above 70 mm Hg.

For on-pump surgery, median sternotomy was performed using simultaneous harvesting of radial artery/saphenous vein and left internal mammary artery. Standard bypass techniques were employed in on-pump surgery. After systemic heparinization (400 units/kg heparin), CPB was instituted, and the patients were cooled at 28°C. The CPB was set up using two-stage right atrial cannulation with an arterial return to the ascending aorta. The aorta was cross-clamped, and cold blood cardioplegic arrest was achieved. However, in CPB, MAP was maintained between 60-80 mmHg. In both procedures, heparin was neutralized with protamine after the grafting procedure, and hemostasis was attained. Sternotomy was repaired by steel wires after placing one-mediastinal and left-pleural drains.

In both groups, during the postoperative period, urine output was maintained higher than 1ml/kg/h, and diuretics were used as necessary. Hemodynamic parameters, such as heart rate, MAP, and central venous pressure, were monitored and recorded intraoperatively and postoperatively. Renal parameters were monitored on the days 0, 1, 3, 5 after the

operation using GFR and calculated by the abbreviated modification of diet in renal disease (aMDRD) equation as follows:

$186 \times (\text{plasma creatinine})^{-1.154} \times (\text{age})^{-0.203}$ [0.742 if the patient is female]

Renal function is graded from I to IV according to the classification proposed by the Kidney Disease Outcome Quality Initiative as follows:

I (GFR>89 mL/min/1.73 m^2)
II (GFR 60-89 mL/min/1.73 m^2)
III (GFR 30-59 mL/min/1.73 m^2)
IV (GFR 15-29 mL/min/1.73 m^2)

Statistical analysis was conducted by collecting preoperative clinical features, operative data and postoperative data expressed as percentages, as well as mean and standard deviations, wherever applicable.

Statistical Methods

Propensity Score Matching

Propensity score (PS) matching is a method used to balance observed covariates in two treatment groups. In the present study, PS was the conditional probability of receiving on-pump or off-pump treatment as a binary dependent variable under a set of measurements. These measurements included the clinical risk factors, such as age, gender, hypertension, diabetes mellitus, previous stroke, history of myocardial infarction, peripheral vascular disease, extent of CAD, and baseline renal parameters. All these potential confounders were added into a nonparsimonious multiple logistic regression model to predict the chance of using on-pump or off-pump CABG. The predicted probability derived from the logistic equation was used as PS for each individual.

The two groups of on-pump and off-pump were combined and classified according to PS; accordingly, the subjects were matched based on PS in the two groups. The patients were selected by 1:1 matching without replacement using the nearest neighbor method. If an appropriate PS match could not be found for the subjects within the two groups, they were excluded from the study. Descriptive statistics were utilized to summarize the data.

As the two surgery groups were matched, the appropriate analysis methods for matched groups, namely paired t-test and repeated measures analysis of variance, were used for statistical analysis. All the analyses were performed using STATA statistical software (version 13.1). P-value less than 0.05 was considered statistically significant in this study.

Results

A total of 199 (153 males and 46 females) patients were included in the present study. Preoperative patient demographics are detailed in (Table 1). There was no significant difference, in terms of demographics, between the two groups.

All the patients who had undergone the surgery were categorized into two groups, including off-pump and on-pump, among whom 106 (53.3%) and 93 subjects (46.7%) belonged to the off-pump and on-pump group, respectively.

During the conduction of CPB on the on-pump patients in the present study, the mean values of aortic cross-clamp time and total CPB time were 84.70±33.98 and 148.86±47.95 min, respectively.

After adjustment of baseline covariates according to propensity score matching, the renal function parameters were analyzed for the postoperative period in (Table 2).

In the comparison of postoperative creatinine levels between the off-pump and on-pump groups, there was a significant difference between the two groups [P=0.008].

However, there were significant changes in the urea levels between the two groups. In both groups, the urea

levels showed a rising trend on postoperative day 3 in comparison to postoperative day 1 that further declined on postoperative day 5. In this regard, there was a significant difference between the two groups [P=0.001].

Similarly, creatinine clearance (CrCl) data were also analyzed in both groups. The off-pump and on-pump patients showed a mild downward trend in CrCl levels mostly noted between the postoperative days 3 and 5 with no gross derangement. P-value for CrCl was reported as 0.04 in the present study.

Table 1. Preoperative characteristics according to surgical strategy

Covariates	Off-Pump n=106 (%)	On-Pump n=93 (%)
Gender		
Male	85 (80.2)	68 (73.2)
Female	21 (19.8)	25 (26.8)
Comorbidities		
Diabetes	29 (27.3)	31 (33.3)
Hypertension	46 (43.3)	40 (43)
Peripheral vascular disease	1 (0.94)	0
Stroke	9 (8.4)	2 (2.1)
Recent myocardial infarction	1 (0.94)	0
Ejection fraction		
> 50%	63 (59.4)	40 (43)
35-49%	28 (26.4)	24 (25.8)
20-34 %	10 (9.4)	19 (20.4)
< 20%	6 (5.6)	9 (9.6)
Extent of coronary artery disease		
LMCA +/- other vessels	14 (13.2)	8 (8.6)
Single Vessel Disease (SVD)	2 (1.8)	0
Double Vessel Disease (DVD)	12 (11.3)	4 (4.3)
Triple Vessel Disease (TVD)	78 (73.5)	72 (77.4)
Multiple-Vessel Disease (MVD)	52 (49)	26 (27.9)

In the comparison of postoperative creatinine levels between the off-pump and on-pump groups, there was a significant difference between the two groups [P=0.008]. However, there were significant changes in the urea levels between the two groups. In both groups, the urea levels showed a rising trend on postoperative day 3 in comparison to postoperative day 1 that further declined

on postoperative day 5. In this regard, there was a significant difference between the two groups [P=0.001].

Similarly, creatinine clearance (CrCl) data were also analyzed in both groups. The off-pump and on-pump patients showed a mild downward trend in CrCl levels mostly noted between the postoperative days 3 and 5 with no gross derangement. P-value for CrCl was reported as 0.04 in the present study. The creatinine and CrCl levels were analyzed in the two groups among patients with diabetes, hypertension, both diabetes and hypertension, as well as normal individuals, preoperatively

Table 2. Comparison of postoperative urea, creatinine, and creatinine clearance in study groups

Renal parameters	Type of surgery	Preoperative	Postoperative day 0	Postoperative day 1	Postoperative day 3	Postoperative day 5	P-value
Urea	Off-Pump	21.18±6.75	24.25±10.61	27.08±8.41	35.39±15.33	33.27±15.11	
	On-Pump	21.15±6.33	24.02±9.65	27.58±8.79	33.46±10.43	31.79±10.63	0.001
Creatinine	Off-Pump	0.95±0.19	0.97±0.26	1.07±0.31	1.06±0.40	1.03±0.38	
	On-Pump	0.92±0.20	0.98±0.35	1.08±0.39	1.05±0.41	0.99±0.35	0.008
CrCl	Off-Pump	85.13±22.37	86.17±28.26	83.51±31.97	81.46±29.86	81.46±29.86	
	On-Pump	87.58±24.1	86.14±31.12	83.90±37.36	82.89±34.90	82.89±34.90	0.04

CrCl: Creatinine clearance. Paired t-test was performed considering pre and postoperative measurements.

After comparing creatinine values in the diabetic group, P-values were reported as 0.007 and 0.06 in the off- and on-pump CABG, respectively, which were significant; however, there was no statistical significance in CrCl group. In hypertensive off-pump group, both creatinine (P=0.001) and CrCl (P=0.08) were statistically significant. In hypertensive on-pump group, only creatinine (P=0.01) was significant. Furthermore, there were no major statistical changes observed in both diabetes and hypertensive groups. In normal patients, off-pump and on-pump groups showed statistically significant creatinine values (P=0.001 and P=0.003); nonetheless, no significance was noted in CrCl. (Table 5) tabulates the comparison of exclusive postoperative renal function in diabetes, hypertension, as well as both diabetes and hypertension, between the two study groups. It was ascertained that there was no statistically significant change in the CrCl and creatinine levels after the surgery. Overall, renal function grading was performed on all patients postoperatively in both the off-pump and on-pump groups summarized in (Table 6). Later, these patients were observed for the changes of renal function grading to detect whether there was an improvement or they remained unchanged or deteriorated postoperatively

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Table 3. Comparing preoperative and postoperative Creatinine and creatinine clearance [CrCl] of patients with diabetes, hypertension, both diabetes and hypertension, and normal patients in off-pump group

Comorbidities	Renal parameters	Pre-operation	Postoperative day 0	Postoperative day 1	Postoperative day 3	Postoperative day 5	P-value
Diabetes [n=29]	Creatinine	0.95±0.18	1.01±0.27	1.14±0.33	1.14±0.50	1.06±0.47	0.007
	CrCl	85.82±24.63	82.71±29.32	77.64±26.34	77.77±30.04	77.77±30.04	0.143
Hypertension [n=46]	Creatinine	0.94±0.21	1.00±0.27	1.11±0.28	1.04±0.36	1.03±0.32	0.001
	CrCl	86.21±24.75	85.00±31.23	78.22±25.33	81.24±27.10	81.24±27.10	0.08
Diabetes and hypertension [n=11]	Creatinine	0.91±0.21	1.09±0.20	1.21±0.29	1.11±0.30	1.06±0.33	0.102
	CrCl	91.29±31.80	74.58±17.88	68.68±17.84	75.38±24.72	75.38±24.72	0.491
Normal patients [n=41]	Creatinine	0.95±0.19	0.96±0.26	1.06±0.31	1.06±0.42	1.02±0.38	0.001
	CrCl	84.41±21.13	87.52±28.99	85.22±32.85	82.17±30.44	82.17±30.44	0.389

*Repeated measures analysis of variance test for independent covariates

Table 4. Comparing preoperative and postoperative Creatinine and creatinine clearance [CrCl] of patients with diabetes, hypertension, both diabetes and hypertension, and normal patients in on-pump group

Comorbidities	Renal parameters	Pre-operation	Postoperative day 0	Postoperative day 1	Postoperative day 3	Postoperative day 5	P-value
Diabetes [n=31]	Creatinine	0.86±0.22	0.97±0.40	1.10±0.40	1.05±0.37	0.98±0.36	0.06
	CrCl	93.51±29.56	89.29±29.74	82.64±32.05	84.90±35.58	84.90±35.58	0.328
Hypertension [n=40]	Creatinine	0.92±0.20	1.02±0.35	1.13±0.31	1.01±0.32	0.95±0.31	0.01
	CrCl	86.95±21.26	81.87±24.14	76.57±23.51	84.62±31.21	84.62±31.21	0.239
Diabetes and hypertension [n=18]	Creatinine	0.84±0.20	1.01±0.46	1.08±0.39	1.01±0.36	0.98±0.40	0.108

Table 5. Comparison of postoperative significance of renal functions in diabetes, hypertension, as well as both diabetes and hypertension between two study groups

Comorbidities	Renal parameters	P-value
Diabetes	Creatinine	0.775
	Creatinine clearance	0.927
Hypertension	Creatinine	0.149
	Creatinine clearance	0.307
Diabetes and hypertension	Creatinine	0.775

Table 6. Postoperative renal function grading

	On-Pump		Off-Pump	
	[n=93] 46.7%		[n=106] 53.3%	
Renal Function grading	n [%]		n [%]	
I [GFR>89 mL/min/1.73 m2]	39	[41.9%]	36	[33.9%]
II [GFR: 60-89 mL/min/1.73 m2]	52	[55.9%]	68	[64.1%]
III [GFR: 30-59 mL/min/1.73 m2]	2	[2.1%]	2	[1.8%]
IV [GFR: 15-29 mL/min/1.73 m2]	0	[0%]	0	[0%]

In the present study, the majority of the patients were observed with no changes in renal function grading and they remained unchanged throughout the hospital stay. The cases with unchanged renal functions in the off-pump and on-pump groups were reported as 60.4% and 60.2%, respectively. In addition, improvement in renal function grading was observed in 16% and 17.2% of the patients, respectively. Moreover, 23.6% and 22.6% of the subjects in the off-pump and on-pump groups had deterioration in renal function grading, respectively. Overall, no significant difference was noted regarding postoperative renal function grading between the off-pump and on-pump groups when GFR was correlated [P=0.969].

Discussion:

Multiple studies have been conducted to evaluate postoperative renal dysfunction between off-pump and on-pump CABG. However, there are very few studies addressing the Propensity score analysis of renal dysfunction between the two groups.

Numerous observational studies and randomized controlled trials compared the potential benefit of preserving RFT in the off-pump patients over the on-pump CABG subjects, which has been settled in short-term and long-term follow-up. The

findings of previously published studies comparing the effect of renal dysfunction between the two groups revealed both mixed and conflicting results. Few studies demonstrated no extra benefit of postoperative renal impairment in the two groups. However, the results of most studies show off-pump surgeries have better renal protection intraoperatively and postoperatively.

Abu-Omar et al, analyzed the effect of on-pump vs. off-pump CABG on renal function using multiple regression analysis (13). They concluded that on-pump group had significantly lower postoperative creatinine clearance in comparison to the off-pump group and there was a decline in postoperative renal injury. Ogawa et al likewise reported Off-pump CABG provides better renal protection than on-pump CABG [13]. Schwann et al. [14] conducted a prospective observational trial, which determined whether off-pump coronary artery bypass was associated with lower postoperative renal dysfunctions, compared to coronary bypass surgery with CPB. They suggested that the choice of operative technique is not associated with reduced renal morbidity.

Sajja et al. [15] measured MDRD GFR and serum creatinine levels in 116 consecutive patients with preoperative non-dialysis-dependent renal insufficiency undergoing primary CABG were randomized to on-pump and off-pump groups and divided them further into diabetes, hypertension, as well as both hypertension and diabetes. The results suggested that on-pump CABG is more deleterious to renal function in diabetic patients with non-dialysis-dependent renal insufficiency in comparison to off-pump CABG. Reents et al. [16] reported that AKI was common in elderly patients undergoing CABG; nevertheless, the worsening of renal function requiring renal replacement therapy was unlikely. Furthermore, off-pump CABG was not linked with the lower rates or reduced severity of AKI in elderly subjects.

According to the evidence, more deleterious effects on renal function in on-pump CABG were due to diabetes and an important confounding factor. We aimed to compare similar renal dysfunction between different covariates, such as diabetes, hypertension, as well as both diabetes and hypertension, in both the off-pump and on-pump groups and determine which one had the most deleterious effect on renal function.in our study comparing pre and postoperative renal function in individual diabetic and hypertensive group we noticed there was slight renal alteration in renal function compared to pre-operative period. But overall postoperatively GFR was not affected in any of the groups. We did not observe extra benefit in renal dysfunction in patients belonging to the off-pump group in comparison to those in the on-pump group.

The limitations of our study include its retrospective, descriptive nature and small cohort size. More prospective long-term studies must be designed to explore and to validate our current findings.

Conclusion:

We concluded that deterioration of renal function in patients with normal preoperative renal parameters is dependent on hemodynamics, cardiac output, and mean pressures. The CPB does not have any additional role as the culprit in renal dysfunction. The reduction of renal dysfunction should not be considered as a reason to argue for the off-pump CABG over on-pump CABG.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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