Off-Pump Coronary Revascularization Preserves Renal Function in Patients with Preoperative Non-Dialysis Dependent Renal Dysfunction A Prospective, Randomized Study

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The off-pump coronary artery bypass operation (OPCAB) is a relatively new surgical procedure, which avoids the use of cardiopulmonary bypass and is intuitively considered renoprotective in patients with preoperative normal renal function. However, no prospective, randomized study has been done so far to show whether these benefits may also apply to patients with preoperative non-dialysis dependent renal dysfunction. This first ever prospective, randomized, controlled trial was performed in 50 patients (45 men, mean age 51.2±4.8 yrs) with preoperative non-dialysis dependent renal insufficiency, undergoing first-time elective coronary artery bypass grafting. Patients were randomly assigned to conventional revascularization with cardiopulmonary bypass (on-pump) or beating heart revascularization (off-pump). Glomerular and tubular functions were assessed upto 48 hrs postoperatively. There were no deaths, strokes or myocardial infarctions in either group. Glomerular function as assessed by creatinine clearance and the urinary microalbumin/creatinine ratio was significantly worse in the on-pump group (p=0.0003 and p=0.008, respectively). Renal tubular function was also significantly impaired in the on-pump group as assessed by the increased N- acetyl glucosaminidase activity (p=0.021). Six patients in the on-pump group developed acute renal failure requiring renal support compared with one in the off-pump group although statistically the comparison was not significant (p=0.098). This study suggests that off-pump coronary artery bypass surgery reduces the likelihood of acute renal failure in patients with preoperative non-dialysis dependent renal dysfunction and thus shortens postoperative intensive care and length of hospital stay.

Key Words. **Off-pump. On-pump. Coronary revascularization. Non-dialysis dependent. Renal dysfunction.**

The proportion of patients undergoing coronary artery bypass grafting (CABG) with preoperative non-dialysis dependent renal insufficiency is much higher than the proportion of patients undergoing CABG with end-stage renal disease[1]. Mild renal insufficiency increases the risk of surgery[2]. Advances in myocardial protection and improvements in perioperative management have reduced the risk of CABG despite an increasing proportion of high-risk patients[3].

Off-pump coronary artery bypass (OPCAB) surgery has seen resurgence in the last decade or so[4,5,6], with several studies suggesting reduced renal impairment following OPCAB[7,8]. Off-pump coronary revascularization has been shown to offer a superior renal protection when compared with conventional coronary revascularization with cardiopulmonary bypass and cardioplegic arrest in first time coronary bypass patients with normal preoperative renal function[9,10].

There are, however, no data on the effects of beating heart coronary revascularization on renal function from a prospective randomized study of patients with non-dialysis dependent renal dysfunction who had elective surgery. We examine the extent of renal glomerular and tubular damage in this group of patients undergoing either OPCAB or on-pump conventional coronary artery bypass surgery.

Materials and Methods

Patients: After institutional approval and informed consent fifty patients (45 men, mean age 51.2±4.8 years; 5 women, mean age 53.4±4.3 years) with preoperative non-dialysis dependent renal insufficiency (serum creatinine 150 micromol/L) in accordance with the previous work published in literature[11] undergoing first-time elective coronary artery bypass grafting were enrolled in the study. Patients were prospectively randomized on the day before surgery into two groups by card allocation. Patients in the on-pump group had conventional myocardial revascularization with CPB and cardioplegic arrest of the heart, whereas the off-pump group had beating heart revascularization.

Anesthetic Technique: Anesthetic technique was standardized for all patients. Premedication consisted of diazepam, 10 to 15 mg po, 4hr preoperatively. After insertion of peripheral venous and radial arterial cannulae under local analgesia, anesthesia was induced with sufentanil, 2.5 μg/kg, and midazolam, 0.1 mg/kg. Tracheal intubation was achieved with pancuronium, 0.1 mg/kg, and the lungs were ventilated to normocapnia with air and oxygen (45% to 50%) without positive end-expiratory pressure. A triple lumen central venous line was inserted into the right internal jugular vein, and an indwelling bladder catheter was used for urine collection. Anesthesia was maintained with sufentanil, midazolam and pancuronium. After induction, hydroxyethyl starch 6% solution and lactated Ringer's solution were used to obtain a mean arterial pressure of >60 mm Hg to maintain filling pressures and cardiac output. Transfusions of packed cells were administered at a hemoglobin level <5.5mmol/L.

In the on-pump group, heparin was given at a dose of 300IU/kg to achieve a target activated clotting time of 480 seconds or above before the commencement of CPB. The activated clotting time was monitored during the bypass period (every 15 minutes) and an additional 3000 IU of heparin were administered if required. In the off-pump group, heparin 100 IU/kg was administered before the start of the first anastomosis. The target activated clotting time in this group was 250 to 350 seconds. Protamine was used at the end of the operation to reverse the effect of heparin and return the activated clotting time to preoperative levels.

Surgical Technique - Cardiopulmonary Bypass: Non-pulsatile CPB was performed with a roller pump and flat sheet membrane oxygenator (Cobe Excel; Cobe Laboratories; Lakewood, CO). The extracorporeal circuit was primed with 500mL of hydroxyethyl starch 6% and 1000mL of lactated Ringer's solution. Flow during CPB was maintained at 2.2 L/min/m^2 during moderate hypothermia (32°C) with α-stat regulation of blood pH. Cold St. Thomas solution was infused into the aortic root to maintain cardioplegia during aortic cross-clamping. During CPB the mean arterial pressure (MAP) was allowed to vary between 60mmHg and 90mmHg. Deviations beyond this range were corrected with phenylepherine or nitroglycerine administration. Myocardial protection was achieved by using intermittent antegrade cold crystalloid cardioplegia. Once all distal anastomoses were completed, the aortic cross-clamp was removed and the proximal anstomoses performed with partial clamping. One surgeon completed all procedures.

Off-Pump: The Octopus-3 stabilization system (Medtronic Inc; Minneapolis, USA) was used for exposure and stabilization during off-pump coronary artery bypass grafting. The target vessel was exposed and snared above the chosen point for anastomosis by using a 4-0 Prolene (Ethicon, Somerville, NJ) suture with a soft plastic snugger to prevent coronary injury. The coronary artery was then opened and anastomosis performed. Visualization was enhanced using the surgical blower-humidifier (model SSVW-002; Surgical Site Visualization Wand, Research Medical Inc, Midvale, UT) with ¼-inch polyvinylchloride gas line and fluid administration set connected to a regulated gas source of medical air. An intracoronary shunt (Anastoflo Intravascular Shunt; Research Medical Inc, Midvale, UT) was used only in cases of relative electrocardiographic or hemodynamic instability and excessive bleeding during anastomosis. In the off-pump group, mean arterial pressure of 60mmHg or higher was maintained with increments of metaraminol 0.5 to 1.0 mg and volume as dictated by the hemodynamic condition, in combination with esmolol to maintain a heart rate less than 70 beats per minute.

Biochemical Markers: A selection of noninvasive markers was used to examine both glomerular and tubular function. Creatinine clearance is a well-established indicator of glomerular filtration rate[12]. The Cockroft-Gault equation[13] was selected as the most consistently favored algorithm to calculate pre- and postoperative creatinine clearance.

For men: Creatinine clearance=([140-age]x weight/serum Creatinine x 72)

For women: Creatinine clearance=([{140-age}x weight]/serum Creatininex72) x 0.85

Units are weight (kgs), age (yrs), serum creatinine (mg/dL; 88.4 μmol/L=1mg/dL).

Function alterations were evaluated further by assessing the urinary levels of microalbumin-to-creatinine ratio as an index of glomerular damage. Increased N-acetyl-β-glucosaminidase (NAG) activity in urine was used as a marker of renal tubular damage[14].

Laboratory Methods: A blood sample was taken at the beginning of each period for serum creatinine measurement. Furthermore, 10mL aliquots of urine were collected at the same stages to assay NAG activity. Blood was allowed to clot and centrifuged at 2,000 x g for 15 minutes; the serum was separated immediately, and analysis was performed on fresh serum. Serum creatinine values were determined with a commercial reagent kit (HiCo Creatinine; Boehringer Mannheim GmbH Diagnostica, Lewes, UK). Serum creatinine level at the start of each period was used to determine the creatinine clearance during that period. Urine microalbumin levels (mg/L) were determined by immunoturbidometry on the Cobas Mira (Koni Inst, Sweden) calibrated for albumin, an assay designed to quantify concentrations of urinary albumin less than 100 mg/L. N-acetyl-β-glucosaminidase activity was measured as reported by Horak and associates[15].

Statistical Analysis: Data are presented as mean ± standard deviation. Comparisons between preoperative variables were made using Fisher's exact test. Repeated measures analysis of variance was used to assess differences over time between groups, and the Bonferroni test was used to assess differences within a group. Analyses were performed using SPSS version 10.0 (SPSS Inc; Chicago, IL, USA).

Results

The randomization sequence was strictly adhered to, and no patients allocated to off-pump group were crossed over to the on-pump group. The preoperative clinical and intraoperative data are shown in Tables 1 and 2 respectively. The groups were similar with respect to demographic and surgical data. There were no instances of stroke, myocardial infarction, or death in either group.

Table1. Preoperative Clinical Data (n=25)

Variable	On-pump	Off-pump	*p* value
Male	23	22	>0.999
Age (y)*	53.8±5.7	49.4 ± 9.5	0.065
Weight (kg)*	84.8±18.5	84.6 ± 18.2	>0.999
Diabetes mellitus	17	18	>0.999
Hypertension	8	7	>0.999
Angina Class	-	-	0.773
I	-	4	2
II	-	11	12
III	-	8	9
IV	-	2	2
Ejection fraction	-	-	>0.999
Good (>50%)	-	17	18
Moderate (30-49%)	-	4	3
Poor (<30%)	-	4	4
Parsonnet Score*	5.8±4.5	4.4±3.6	0.280
Preoperative serum creatinine (μmol/L)	-	-	0.886
150-174	-	2	4
175-199	-	5	7
200-224	-	7	8
225-249	-	4	2
250-274	-	5	2
>275	2	2	2

* Data are presented as mean ± standard deviation.

For creatinine clearance over time, the use of cardiopulmonary bypass had a significant effect (p=0.0003). Creatinine clearance deteriorated significantly in the on-pump group compared with the off-pump group from a mean of 89.4±26.3 ml/minute preoperatively to 72.2±44.4ml/minute during the operative period (p=0.0001). It then deteriorated even further during the first postoperative 24 to 48 hours period to 70.8 ± 23.4 ml/minute and 62.7±23.1 ml/minute, respectively, which was significantly worse than the off-pump group (p<0.0001).

Cardiopulmonary bypass also had a significant overall effect with respect to urinary microalbumin-to-creatinine ratios (p=0.008). Perioperatively the ratio increased significantly in the on-pump group (1.04 ±1.8 to 5.7 ± 6.48) compared with the off-pump group (1.01±0.6 to 2.6±3.2) (p<0.0001), decreasing to levels similar to those of the off-pump group over the next 24 to 48 hours.

Table 2. Intraoperative Data (n=25)

Variable	On-pump	Off-pump	*p* value
Bypass grafts	-	-	0.773
1	-	2	4
2	-	13	10
3	-	8	9
>3	-	2	2
Bypass time (min)*	75.7±35.4	-	-
Cross-clamp time (min)*	40.5±18.1	-	-
Fluid balance at 24hr (mL)*	1,230±290	1100±310	0.21

*Data are presented as mean ± standard deviation.

Urinary N-acetyl-β-glucosaminidase activity (NAG) was comparable in both groups preoperatively. It increased significantly from 5.00±3.5 mcg/mL preoperatively to 13.41±8.71 mcg/mL at the end of operation in the on-pump group and from 4.45±2.76 mcg/mL to 9.18±5.08 mcg/mL in the off-pump group (p<0.0001). The urinary NAG activity values remained significantly higher in the postoperative 24 to 48 hours period in the on-pump group compared with the off-pump group (p=0.021). Mean and standard deviations for all groups are shown in Table 3.

Table 3. Changes in Markers of Renal Damage

Variable	Pre-operative	Operative	Postop Day 1	Postop Day 2
Creatinine clearance (mL/min)				
Off-pump	91.5± 23.5	77.9± 26.8	87.1± 24.4	91.2± 32.5
On-pump	89.4± 26.3	72.2± 44.4*	70.8± 23.4^{τ}	62.7± 23.1^{δ}
Urine Microalbumin-to-creatinine Ratio				
Off-pump	1.01± 0.6	2.6± 3.2	2.6± 1.7	2.1± 1.8
On-pump	1.04± 1.8	5.7± 6.48*	2.7± 3.5^{α}	2.9± 3.0
N-acetyl-β-glucosaminidase level (mcg/ml)				
Off-pump	4.45± 2.76	9.18± 5.08	10.95± 5.74	10.68± 6.49
On-pump	5.00± 3.5	13.41± 8.71*	14.84± 11.45	16.47± 12.4

*p<0.0001 between operative and preoperative levels with on-pump.
τ p<0.0001 between day 1 and operative levels with on-pump.
α p=0.02 between day 1 and operative levels with on-pump.
δ p<0.0001 between day 1 and operative levels with on-pump.
Data are presented as mean ± standard deviation.

The postoperative clinical data are given in Table 4. There was no significant difference between the two groups with respect to complications, such as chest infection, low output syndrome, or acute renal failure requiring renal support although six patients in the on-pump group ended up having acute renal failure compared with just one in the off-pump group. Blood loss and transfusion requirements were significantly greater in the on-pump group (p=0.003 and p=0.0009, respectively). Intensive care unit and hospital length of stay were significantly longer in the on-pump group (p=0.03).

Table 4. Postoperative Data (n=25)

Variable	On-pump	Off-pump	*p* value
Acute renal failure	6	1	0.098
Chest infection	2	0	0.489
Low output syndrome	3	0	0.234
Total blood loss (mL)*	1030±536	644±268	0.003
Transfusion requirement (units)*	1.20±1.4	0.20±0.6	0.0009
ITU stay (days)*	1.8±1	1±0.2	0.03
Hospital stay (days)*	7.30±3	5.64±1.7	0.03

* Data are presented as mean ± standard deviation.

Discussion

Perioperative renal dysfunction occurs in 7-13% of patients with 1-1.5% requiring some form of dialytic therapy[16,17]. Renal insufficiency following cardiac surgery increases ICU and hospital stay and greatly increases mortality (27%*vs*0.9%)[17]. The pathogenesis of this complication is usually multi factorial. General risk factors associated with postoperative renal dysfunction are pre-existing renal disease, advanced age, and postoperative low cardiac output state[17, 18]. Cardiopulmonary bypass is widely regarded as an important contributor to renal failure[19]. The injurious action of CPB on renal function is caused by several mechanisms, including nonpulsatile perfusion and increased levels of circulating catecholamines, cytokines and free hemoglobin[20].

In recent years there has been an upsurge of interest in beating-heart coronary surgery in an attempt to avoid the deleterious effects of CPB. With rapid improvements in surgical techniques and the development of cardiac stabilizing retractors, off-pump coronary artery bypass grafting (OPCAB) has become an established procedure. Studies on patients with normal renal function have shown that OPCAB offers superior renal protection to conventional CPB[12,13,21]. However, no prospective, randomized study so far has been done to assess the effect of OPCAB on patients with preoperative non-dialysis dependent renal dysfunction. To the best of our knowledge, the present study is the first prospective, randomized study to investigate the effect of beating heart revascularization on renal function in patients with pre-existing non-dialysis dependent renal dysfunction undergoing first-time, elective coronary artery bypass grafting.

This study in cardiac surgical patients with preoperative non-dialysis dependent renal dysfunction shows that CPB aggravates renal injury, as evidenced by a decrease in creatinine clearance and increased levels of markers of glomerular and tubular damage. Changes in these parameters were markedly abnormal in the intraoperative and early postoperative period and remained persistently elevated upto 48 hours.

In contrast, these parameters were not significantly abnormal in the off-pump patients. Baseline measurements of parameters of glomerular and tubular damage were the same in both groups, indicating that CPB results in significant renal damage.

The progressive deterioration in creatinine clearance accompanied by the marked increases in urinary microalbimin-to-creatinine ratio and NAG activity levels in the current study confirm the potential deleterious effects of the CPB on renal function. Furthermore, changes in these markers appeared to be significantly lower in the off-pump group, suggesting better functional preservation. The current study also showed a significantly higher blood loss and transfusion requirements in the on-pump group most likely due to the activation of complement cascade[22] and cytokine-mediated impairment of platelet function[23]. Acute renal failure requiring renal support was defined as a sudden rise in serum creatinine by more than 2.3 mg/dl (177 μmol/L) above the baseline value. Although six patients in the on-pump group needed some form of renal replacement therapy compared with one in the off-pump group, the difference was not statistically significant ($p=0.098$). The reduced length of ICU stay and postoperative hospital stay for OPCAB patients compared with CPB patients in this study were in agreement with previous reports[24,25].

In conclusion, this study in patients with preexisting non-dialysis dependent renal dysfunction shows that on-pump coronary surgery exacerbates renal damage both at the glomerular and tubular levels, whereas off-pump coronary revascularization prevents worsening of renal function and thus shortens postoperative recovery and length of hospital stay.

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