

Original Paper

On- versus Off-Pump Coronary Artery Bypass Grafting: No Difference in Early Postoperative Kidney Function Based on TNF- α or C-Reactive Protein

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Key Words

Coronary artery bypass grafting · Renal function · C-reactive protein · Tumor necrosis factor- α · On-pump · Off-pump · Cardiopulmonary bypass · Cardiac surgery

Abstract

Background/Aims: There are controversial data about renal function following off-pump coronary artery bypass grafting (CABG). The present study aimed to evaluate renal function changes 24 h after on- and off-pump CABG, as well as renal function correlated with high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor- α (TNF- α). **Methods:** Ninety patients with coronary artery disease referred to our center for CABG from July 2006 to November 2007 were enrolled in the study. Patients were equally and randomly divided in two groups, on- and off-pump. Serum levels of creatinine (Cr), blood urea nitrogen, creatinine clearance (CrCl), hs-CRP, and TNF- α were determined immediately before and 24 h after surgery. **Results:** Cr and CrCl changes after surgery were not significantly different between the two groups; however, blood urea nitrogen levels after surgery were significantly higher in the on-pump group ($p = 0.035$). No statistically significant difference was noted between the two groups in terms of changes in levels of hs-CRP and TNF- α ($p = 0.350$ and 0.805 , respectively). The changes in CrCl levels had no significant correlation with hs-CRP and TNF- α . **Conclusions:** The early Cr and CrCl levels after surgery are not significantly different in on- and off-pump groups. The early renal function after on- or off-pump CABG is not correlated with the levels of inflammatory markers including hs-CRP and TNF- α .

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Introduction

Coronary artery bypass grafting (CABG) is one of the most frequently performed operations worldwide. Since the incidence of coronary artery disease and, subsequently, the number of CABGs performed continue to rise, any improvement in the safety and efficacy of the procedure would have a major impact on the outcomes [1, 2].

Despite advances in methods and technologies, postoperative acute renal insufficiency continues to be a significant cause of morbidity and mortality after cardiac operations performed through the on-pump method using cardiopulmonary bypass (CPB). The etiology of this condition is multifactorial, including the factors related to conduct and management of CABG such as bypass time, use of vasopressors before CABG, systemic inflammatory response, hypoperfusion, and loss of pulsatile perfusion [3]. As CPB has pathophysiologic sequelae, there has been a revival of interest in performing CABG on a beating heart (off-pump method) [4]. Proponents of off-pump CABG emphasize decreased incidences of postoperative neurological dysfunction, myocardial infarction, bleeding, renal failure, and respiratory failure [5]; however, controversies exist regarding the changes on renal function following off-pump CABG.

Furthermore, it is known that the CPB and pulmonary-myocardial reperfusion during on-pump CABG activate the innate and adaptive immune systems. The extent of this immune reaction has been linked to postoperative complications seen in this type of surgery [6]. Therefore, the avoidance of CPB and subsequent myocardial ischemia reperfusion has been proposed to significantly reduce postoperative complications, one of which is renal dysfunction [7]. It is known that systemic inflammatory response plays a major role in perioperative complications. Interleukin (IL)-1b, IL-6, IL-8, and tumor necrosis factor- α (TNF- α) are produced in the acute phase of the inflammatory response, and high-sensitivity C-reactive protein (hs-CRP) has been shown to correlate with multi-organ failure [8–10]. We aimed to investigate the changes in renal function after on- and off-pump CABG and their association with hs-CRP and TNF- α for the first time.

Materials and Methods

Patients and Study Design

This is a prospective case-control study which was conducted in Shahid Madani Hospital of Tabriz University of Medical Sciences in Tabriz, Iran. Data were collected from July 2008 to July 2009.

Different blinded researchers conducted each part of the study including random assignment of the patients to each group (blocked randomization by varying the size of the blocks from 2 to 8), collecting samples, laboratory evaluations, and data analysis. Ninety patients with coronary artery disease referred to our center for CABG were enrolled in the study. All the patients met the criteria for CABG based on the American College of Cardiology/American Heart Association guideline [11]. Afterwards, patients were divided randomly into the on- and off-pump CABG groups, 45 cases in each group. All the surgeries were conducted by the same surgical team.

The study was approved by the Institutional Review Board of Tabriz University of Medical Sciences and was in compliance of the Helsinki Declaration. All patients gave informed consent for participation in the study.

Inclusion criteria included age between 45 and 65 years; no history of neoplastic diseases including benign and malignant tumors; no recent history of steroid or non-steroidal anti-inflammatory drug therapy in the last 2 weeks before surgery; no history of respiratory failure including asthma, adult respiratory distress syndrome, prolonged mechanical ventilation, and acute lung injury; no history of rheumatologic diseases including gout, lupus, dermatomyositis, polymyositis, sclerodermia, rheumatoid arthritis, and osteoarthritis; no history of autoimmune neurologic diseases including myasthenia gravis and multiple sclerosis; no history of chronic hematologic and oncologic disorders including hemolytic anemia and idiopathic and thrombotic thrombocytopenic purpura; no insulin-dependent diabetes; no

acute/chronic renal failure, determined by creatinine clearance (CrCl) using Cockcroft-Gault equation [12] ≤ 50 ml/min, and no recent active infectious diseases. Presence of any major complications during 24 h after surgery including cardiac arrest and inability to obtain serum samples were considered as exclusion criteria.

Surgical Management

On-Pump CABG Method

Cefazoline (Kefzol; 1 g) was given for preoperative antibiotic prophylaxis. Anesthesia was induced with etomidate (Amidate; 200–300 mg/kg) and fentanyl (Sublimaze; 20–30 mg/kg). After muscle relaxation with cisatrocium (Nimbex; 0.15 mg/kg) and endotracheal intubation, anesthesia was maintained using fentanyl (Sublimaze), midazolam (Versed; <http://en.wikipedia.org/wiki/Midazolam>) and isoflurane (0.4–1.5%).

The CPB equipment included nonpulsatile roller pumps (Stoekert, Munich, Germany) and membrane oxygenators (Affinity, AVEC Cardiovascular, Plymouth, Mass., USA). The pump was primed with a standard electrolyte solution containing 5,000 IU heparin, 1,000 ml Ringer's lactate, 500 ml NaCl 0.9%, and 250 ml of a 15% mannitol solution (Osmofundin 15% N; Braun Melsungen, Melsungen, Germany). Heparin (300 IU/kg) was administered immediately before vascular cannulation. After the institution of CPB at a flow rate of 2.4–3 l/m²/min, the aorta was cross clamped and a bloody cardioplegic solution was injected. After CPB, protamine sulfate was infused.

Off-Pump CABG Method

The same perioperative management steps described for the on-pump CABG method were applied here; this includes induction of anesthesia, endotracheal intubation, and the maintenance of anesthesia.

Once the pericardium was opened, an initial heparin dose of 2 mg/kg was administered. Intravenous heparin was then used to maintain an activated clotting time of >350 s until the anastomoses were created. An Octopus stabilizer system (Medtronic Inc., Minneapolis, Minn., USA) was used during the operation. After incision of the coronary artery, an intracoronary shunt was inserted and an anastomosis was performed.

Following revascularization, the heparin effect was reversed with protamine sulfate (at a ratio of 1.5:1).

Blood Sampling

Venous blood samples were taken immediately before operation and 24 h after operation. Samples were collected in sterile tubes, centrifuged at 3,000 r.p.m. for 10 min at 4°C, and then stored at –79°C until assayed.

General Parameters

General parameters studied included age; sex; weight; history of disease including hypertension, diabetes, and hyperlipidemia; history of smoking and drug history; family history; the number of involved coronary arteries; graft type, and ejection fraction.

Biochemical Parameters

Serum levels of creatinine (Cr) and blood urea nitrogen (BUN) were measured using an automated chemical analyzer (Abbott analyzer, Abbott laboratories, Abbott Park, North Chicago, Ill., USA) with commercial reagents obtained from Pars Azmoon Laboratories Ltd. (Tehran, Iran). CrCl was determined by using the standard formula – Cockcroft-Gault equation [12].

Inflammatory Parameters

Levels of hs-CRP and TNF- α were measured by the ELISA method using commercial kits (hs-CRP by Monobind Inc., Calif., USA, Lot No. EIA-1K2L7, and TNF- α by Human TNF- α ELISA, Bender Med-Systems, Vienna, Austria, Lot No. 41881009).

Statistical Analyses

Statistical analyses were performed using the SPSS statistical package version 13.0 (SPSS Inc., Chicago, Ill., USA). The quantitative data are presented as means \pm SD, and the qualitative data are expressed as numbers and percentages. The Kolmogorov-Smirnov test was used to assess the normality. Independen-

Table 1. Demographic characteristics of studied population and comparison between the groups

	Type of CABG surgery		p
	off-pump (n = 45)	on-pump (n = 45)	
Age, years	58.08 \pm 5.10	59.24 \pm 4.24	0.267
Weight, kg	77.54 \pm 8.74	73.17 \pm 8.98	0.087
Ejection fraction, %	43.85 \pm 9.32	45.45 \pm 8.27	0.423
Smoking	28 (62.22)	27 (60)	0.470
Uncontrolled hypertension	11 (24.44)	15 (33.34)	0.144
Diabetes mellitus	9 (20)	9 (20)	1
Hyperlipidemia	10 (22.22)	15 (33.34)	0.391
Number of grafts one/two/three vessels	2/15/28	0/14/31	0.201
Type of graft LIMA/SVG/both	10/3/32	6/0/39	0.125
Surgery duration, min	352.66 \pm 37.94	331.85 \pm 20.11	0.176

Values are means \pm SD or numbers with percentages in parentheses unless otherwise indicated.
LIMA = Left internal mammary artery; SVG = saphenous vein graft.

dent sample/paired t tests, and Mann-Whitney U and Wilcoxon signed rank tests were used to assess the differences between stages when applied. Comparison of qualitative data was also performed by χ^2 test and correlation assessed using Pearson's correlation test. Also, multivariable analysis using a multiple regression test was carried out to assess effects of the type of surgery and of the changes in levels of hs-CRP and TNF- α on the CrCl changes. A p value <0.05 was considered significant.

Results

The demographic characteristics of patients are shown in table 1. There was no significant difference between the two groups in terms of age, weight, history of smoking, uncontrolled hypertension, diabetes mellitus, hyperlipidemia, left ventricular ejection fraction, number of bypassed arteries, type of graft, and blood/Rho groups. Also, as shown in table 2, there were no significant differences between the two groups in terms of the medications they were on before surgery.

As demonstrated in table 3 and figures 1, 2, and 3, preoperative levels of serum Cr, BUN, and CrCl were not significantly different between off- and on-pump groups. Postoperative levels of Cr and CrCl between the two groups were not significantly different either; however, postoperative BUN levels were significantly higher in the on-pump group compared to the off-pump group (p = 0.035). Intragroup comparison of the off-pump group showed no significant changes in levels of Cr, BUN, and CrCl before and after surgery (p = 0.537, 0.497, and 0.932, respectively). In the on-pump group, although Cr and CrCl levels were not significantly changed (p = 0.934 and 0.480, respectively), BUN levels were significantly increased after surgery compared to before surgery (p = 0.020).

In both off- and on-pump groups, hs-CRP levels after CABG surgery were significantly increased (p < 0.001 for both); however, the amount of increase (Δ hs-CRP = postsurgical hs-CRP – presurgical hs-CRP) was not significantly different in the off-pump group compared to the on-pump group (table 4). Postsurgical levels of TNF- α did not differ significantly in either group compared to the presurgical levels (p = 0.171 and 0.710, respectively); the amount of change in TNF- α level (Δ TNF- α = postsurgical TNF- α – presurgical TNF- α) was not significantly different comparing the two groups either (table 4).

Table 2. Medication history of participants

Drug type	Drug subgroup	Type of CABG surgery		p
		off-pump (n = 45)	on-pump (n = 45)	
ACE-I/ARBs	Captopril (Capoten)/enalapril (Vasotec) Losartan (Cozaar)	15 (33.34) 3 (6.66)	18 (40) 5 (11.11)	0.207
β -Blocker		36 (80)	39 (86.66)	0.248
Ca channel blocker	Dihydropyridin Non-dihydropyridin	6 (13.33) 2 (4.44)	9 (20) 2 (4.44)	0.729
Digoxin (Lanoxin)		2 (4.44)	4 (8.88)	0.691
Anticoagulant	Aspirin (USAN) Enoxaparin (Xaparin)	30 (66.66) 1 (2.22)	32 (71.11) 1 (2.22)	0.874
Diuretic	Thyazids Furosemide (Lasix) Spironolactone (Aldactone)	0 0 1 (2.22)	1 (2.22) 2 (4.44) 1 (2.22)	0.486
Statins		38 (84.44)	30 (66.66)	0.099
Nitrates	Nitrocontin Nitroglycerin	25 (55.55) 26 (57.77)	2 (4.44) 3 (6.66)	0.798

Values are numbers with percentages in parentheses.
ACE-I = Angiotensin-converting enzyme inhibitor; Ca = calcium.

Table 3. Comparison of renal function parameters between on-pump and off-pump methods, and before and after operation

		Type of CABG surgery		p
		off-pump (n = 45)	on-pump (n = 45)	
Cr, mg/dl	Before	1.03 \pm 0.28	1.03 \pm 0.17	0.918
	After	1.01 \pm 0.19	1.04 \pm 0.18	0.772
Δ Cr, mg/dl		-0.02 \pm 0.18	0.00 \pm 0.19	0.631
CrCl, ml/min	Before	103.98 \pm 28.80	102.13 \pm 16.37	0.536
	After	103.15 \pm 21.12	99.49 \pm 12.80	0.351
Δ CrCl, ml/min		-0.35 \pm 18.66	-3.69 \pm 19.74	0.608
BUN, mg/dl	Before	16.08 \pm 6.69	16.28 \pm 4.41	0.609
	After	16.86 \pm 5.74	20.31 \pm 6.45	0.035
Δ BUN, mg/dl		1.00 \pm 0.15	3.45 \pm 8.33	0.136

Values are means \pm SD.
 Δ Cr = Cr level after surgery - Cr level before surgery; Δ CrCl = CrCl level after surgery - CrCl level before surgery; Δ BUN = BUN level after surgery - BUN level before surgery.

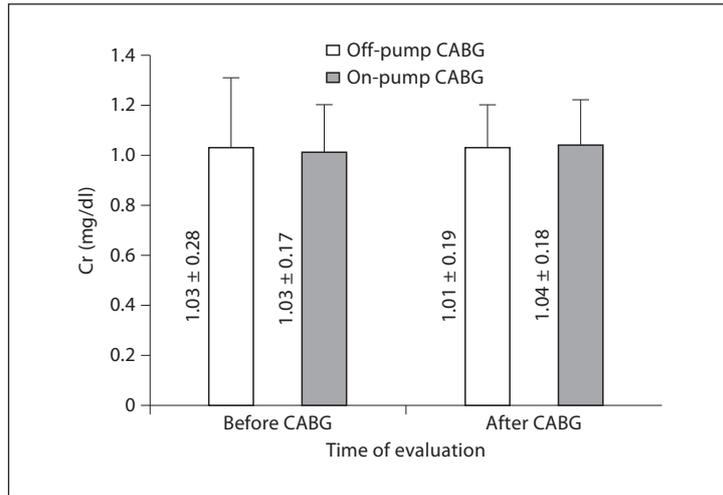


Fig. 1. Cr levels following CABG.

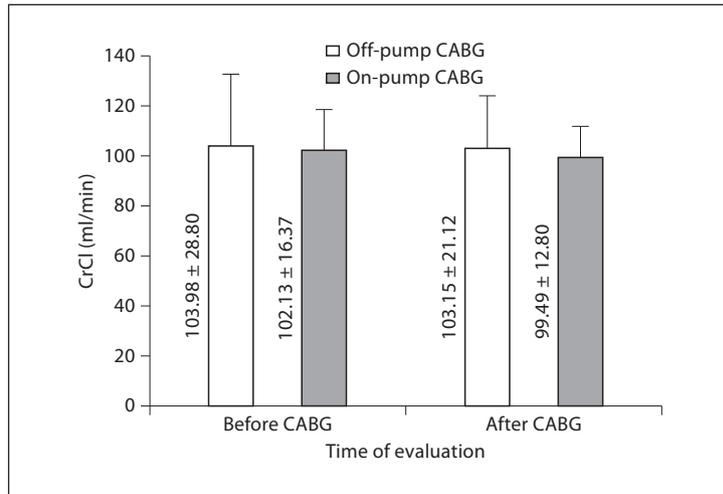


Fig. 2. CrCl levels following CABG.

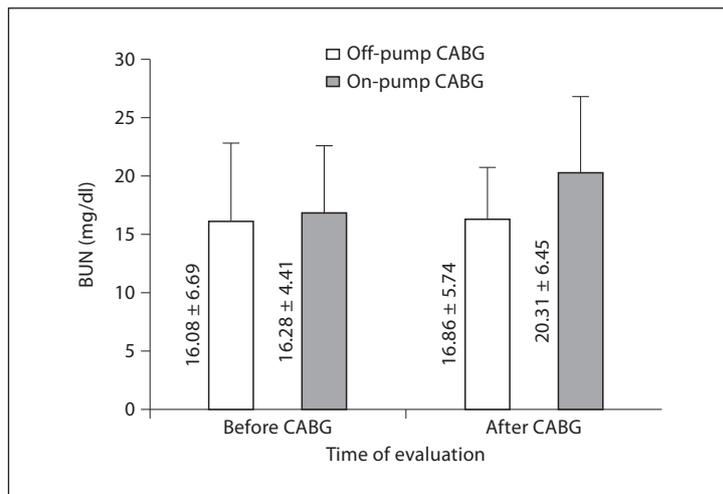


Fig. 3. BUN levels following CABG.

Table 4. Comparison of hs-CRP and TNF- α levels between on-pump and off-pump groups

	Type of CABG surgery		p
	off-pump (n = 45)	on-pump (n = 45)	
hs-CRP before surgery, mg/dl	10.91 \pm 14.92	10.77 \pm 14.77	0.967
hs-CRP after surgery, mg/dl	136.06 \pm 88.76	116.07 \pm 92.97	0.338
TNF- α before surgery, pg/ml	12.63 \pm 12.11	12.69 \pm 11.77	0.790
TNF- α after surgery, pg/ml	14.50 \pm 12.50	14.25 \pm 11.33	0.953
Δ hs-CRP, mg/dl	105.15 \pm 95.58	125.28 \pm 91.92	0.350
Δ TNF- α , pg/ml	0.86 \pm 5.24	1.55 \pm 6.58	0.805

Values are means \pm SD.

Also, there was no significant correlation between the level of Cr, BUN, and CrCl changes and Δ hs-CRP (p = 0.910, 0.335, and 0.947, respectively) or Δ TNF- α (p = 0.193, 0.450, and 0.081, respectively) in either group.

Hierarchical multiple regression was used to assess the effect of the type of surgery and the amount of change in hs-CRP and TNF- α levels on CrCl after controlling for the influence of demographic characters and lipid profiles. After entry of the type of surgery and changes of hs-CRP and TNF- α levels, the total variance explained by the model as a whole was 51.5% [F (10, 25) = 2.653, p = 0.023]. These factors explained an additional 10.45 of the variance in CrCl changes after controlling for demographic characters and lipid profiles [R² change = 0.104, F change (3, 25) = 1.789, p = 0.175]. In the final model, only the two control variables significantly affected CrCl changes, with the hypertension history recoding a higher β value (β = -0.545, p = 0.001) than the weight of patients (β = -0.383, p = 0.017).

Discussion

Results of the present study demonstrated that renal function – measured by Cr and CrCl – following CABG was not significantly different in patients undergoing on-pump or off-pump methods. The changes in renal function following both methods were related neither to the levels of hs-CRP nor TNF- α . We were able to successfully control for major confounding factors which could potentially affect the postsurgical renal function including demographic characteristics, concomitant diseases, number of bypassed arteries, duration of surgery, medication history, and preoperative renal function. Furthermore, none of the patients had CrCl <50 ml/min before or after surgery.

Previous studies have compared the degree of renal injury after on- and off-pump procedures. Some of these studies have emphasized biochemical markers of renal injury while others have primarily focused on clinical parameters. In one randomized trial, it was shown that CrCl was significantly higher in the on-pump group intraoperatively, but it deteriorated during the first 48 h postoperatively compared to off-pump patients. In the same study, urinary N-acetyl-b-glucosaminidase (NAG), a marker for renal tubular damage, remained significantly lower in the off-pump group, both during and after surgery [13]. Another study reported increased signs of oxidative stress – as measured by urinary concentrations of hypoxanthine, xanthine, and malondialdehyde – in the on-pump group, while only minimal changes were reported in the off-pump group [4]. A randomized study found that off-pump

CABG induced fewer biochemical markers of renal injury including microalbuminuria, free water clearance, NAG levels, and free hemoglobin [14]; however, these parameters were not found to be different between on- and off-pump groups in a different randomized study [15]. Another case-controlled trial found that serum Cr levels were significantly lower and CrCl was significantly higher in the off-pump group compared to the on-pump group [16]. Karthik et al. [17] constructed a propensity score for risk-adjusted comparison of patients undergoing nonelective on- and off-pump CABG. The incidence of renal impairment, as assessed by an increase in Cr level >1.5 mg/ml, was significantly higher in the on-pump group. In a similar analysis of propensity-matched pairs of patients, the rate of renal failure requiring dialysis was 1.5% in the on-pump group versus none in the off-pump group [7]. The incidence of postoperative dialysis in a large cohort of diabetic patients undergoing off-pump CABG was 0.87 versus 2.75% in the on-pump group, while the rate of renal failure not requiring dialysis was similar between the two groups [18]. In a recent meta-analysis, the rate of renal failure was lower in off-pump patients [19]. A recent meta-analysis of randomized and observational studies carried out by Nigwekar et al. [1] showed that patients undergoing off-pump CABG surgery were prone to renal injury and failure despite the different acute kidney injury definitions used in the enrolled studies. As it is evident, the literature reflects controversial evidence regarding renal impairment following on-pump and off-pump surgeries. The results of our study showed no difference in Cr and CrCl levels following on-pump and off-pump techniques; however, BUN levels were higher in the on-pump group, which was associated with using CPB.

It is well recognized that CABG may lead to major organ dysfunction including, but not limited to, renal injury. However, the role of an extracorporeal circulation device in the development of renal injury is not entirely clear. CPB is associated with the development of systemic inflammatory response, endothelial damage, and subsequent tissue edema and organ dysfunction. Interestingly, systemic inflammation is also observed in patients undergoing off-CPB cardiac surgery, albeit on a smaller scale [20]. Although hs-CRP and TNF- α levels were increased after both on- and off-pump surgery in our study, it was statistically significant only in terms of hs-CRP level. More importantly, we found that renal function was related neither to hs-CRP nor TNF- α .

The results of the present study did not show a consistent association between the inflammatory biomarkers and renal function, while prior cross-sectional studies have shown such association. Some studies found associations between renal function and CRP [21], while others revealed a direct relationship between cystatin C and CRP, IL-6, and TNF- α and its two soluble receptors [22]. Considering a significant increase in CRP levels following on-pump CABG, some consequences could be expected including activation of coagulation, down-regulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis [23, 24], all of which predispose CABG patients to major organ dysfunction such as renal injury. However, during the last decade, the practice of the CPB has benefited from major refinements and improvements in the field of biocompatibility, such as the introduction of warm heart surgery, coated circuits, anti-fibrinolytic drugs, and the elimination of cardiomy suckers. Warm cardioplegia seems to reduce the oxidative stress [25–27] and inflammatory response [28, 29].

We acknowledge the limitations inherent in our study including single-sex patient population, small sample size, and short duration of follow-up. We continue to gather data from a larger group of patients for our future studies. Additionally, better renal function biomarkers (e.g. cystatin C) have since been introduced which were not available at the time we conducted our study.

In conclusion, none of our patients in either group developed renal failure, and renal function, determined by early postoperative Cr and CrCl levels, was not different between

the on- and off-pump groups. Also, on-pump CABG patients developed mild decrease in renal dysfunction, although within a normal range, and the use of CPB did not result in postoperative CrCl of <50 ml/min after on-pump CABG. These insignificant changes in renal function were independent of inflammatory markers.

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Disclosure Statement

The authors have no proprietary interest in any aspect of this study.

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