

The Effect of Cardiopulmonary Bypass in Coronary Artery Bypass Surgeries (On-Pump versus Off-Pump) on Erectile Function and Endothelium-Derived Nitric Oxide Levels

Onder Canguven, Selami Albayrak, Ahmet Selimoglu, Muhsin Balaban, Ahmet Sasmazel, Ayse Baysal

Clinic of Urology II (OC, SA, AS, MB), Kartal Teaching and Research Hospital; Department of Cardiac Surgery (AS) and Anesthesiology (AB), Kartal Kosuyolu Heart and Research Center, Istanbul, Turkey

ABSTRACT

Purpose: To investigate the effects of on-pump and off-pump coronary artery bypass grafting (CABG) on the erectile function and endothelium-derived nitric oxide (eNO) levels.

Materials and Methods: Twenty-eight consecutive patients were randomized into two groups depending on use of cardiopulmonary bypass in CABG surgery. The erectile function was evaluated by using the IIEF-5 questionnaire. The plasma eNO levels were determined at baseline and after reactive hyperemia before and after surgery. Blood was collected in one minute after cuff deflation from the radial artery on the same side.

Results: After CABG surgery the mean IIEF-5 score increased insignificantly over baseline from 14.8 to 15.8 ($p = 0.29$) and 12.4 to 14.3 ($p = 0.11$) after on-pump and off-pump CABG surgeries, respectively. The baseline plasma NO levels before surgery were 18.16 ± 7.63 nmol/L in on-pump and 21.76 ± 11.08 nmol/L in off-pump CABG. After reactive hyperemia the plasma NO levels were 22.14 ± 10.52 nmol/L in on-pump and 21.49 ± 9.13 nmol/L in off-pump CABG before the surgery. The difference in the plasma NO levels before surgery was not significant ($p = 0.51$). Two hours after surgery, the difference of the plasma NO levels at baseline (24.44 ± 12.31 on-pump and 20.58 ± 6.74 nmol/L off-pump CABG) and after reactive hyperemia (35.55 ± 23.54 nmol/L on-pump and 23.00 ± 15.40 nmol/L off-pump CABG) were not significantly different from each other ($p = 0.11$).

Conclusions: Patients who had on-pump or off-pump CABG surgeries had higher IIEF-5 scores. Nevertheless, the improvement was insignificant in both groups. Meanwhile, on-pump or off-pump CABG surgeries did not have significant effect on plasma eNO levels.

Key words: coronary artery bypass; Blood Vessel Prosthesis; Erectile Dysfunction
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INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED is a vascular disorder and all men with ED should be considered at risk of cardiovascular disease until proven otherwise (1). Endothelial dysfunction is a key variable in the pathogenesis of atherosclerosis and its complica-

tions, including ED. Coronary artery bypass grafting (CABG) is mainly performed for patients who cannot be treated medically or by stent placement. In the last decade, off-pump choice is successfully performed by cardiac surgeons. CABG surgery with cardiopulmonary bypass (CPB) may have adverse effects on endothelial functions. CPB reduces the ability of endothelium to synthesize and release of plasma nitric oxide (NO) and this leads to increased

risk of the postoperative complications (2). Quality of life and clinical morbidity after off-pump versus on-pump CABG were investigated in assorted articles (3-5). However, there are limited number of studies published the effect of different CABG types on erectile function.

Aims

The aim of this study is to compare the effects of CPB on erectile function and the endothelium-derived NO (eNO) levels in on-pump and off-pump CABG surgeries.

Methods

Study Protocol

Twenty-eight male patients with coronary artery disease (CAD) from September 2008 to October 2009 were prospectively enrolled in the study depending on the use of CPB in CABG or not. The inclusion criteria included all patients between 45 to 75 years of age, NYHA Class I-II, and CAD confirmed by angiographic study. The exclusion criteria included diabetes mellitus, renal or hepatic impairment (blood creatinine > 1.5 mg/dL, blood aspartate aminotransferase (AST), blood alanine aminotransferase (ALT) levels higher than two fold of normal values) congestive heart failure, active inflammatory diseases, or a history of myocardial infarction in the past 6 months. The reasons for exclusion criteria are mainly related to the other comorbidities that are associated with endothelial dysfunctions. The comorbidities have been documented to be associated with impaired response to flow mediated dilatation (FMD). These include elevated sympathetic activation (congestive heart failure), diabetes mellitus, and patients with renal or hepatic dysfunctions (6). Pre- and post-operative uses of all medications were recorded.

Evaluation of Erectile Function

The erectile function was evaluated using the IIEF-5 questionnaire (7) by one examiner who was blinded to treatment groups. Patients were stratified by baseline (preoperative) and six months after surgery, the erectile function was reevaluated according to the same preoperative measures. IIEF-5 scores were measured ED severity using IIEF-5 scores of 22-25 (no ED) and ≤ 21 (mild to severe ED) (7).

Evaluation of plasma NO

Blood samples for plasma NO were drawn a total of four times and in the following sequence: in the surgical room before start of the surgery prior to the reactive hyperemia procedure (basal level), after the reactive hyperemia procedure two hours after operation, and before and after reactive hyperemia procedures. The measurement of plasma NO level was based on the method introduced for reactive hyperemia (8,9). A pressure cuff was placed at the brachial artery and inflated up to 250 mmHg for 5 minutes, and it was subsequently deflated. This maneuver causes an increase in shear stress exerted by the flow of blood over the surface of the endothelium in the brachial artery in the forearm circulation (10,11). The arterial blood sample was withdrawn from the radial artery catheter on the same side in 1 minute after the deflation of the cuff for the measurement of the eNO. NO-derived end products (NO₂, NO₃) were measured by triiodine/ozone-based chemiluminescence assay, described elsewhere (12).

Operative procedure

Both groups underwent sternotomy procedure. In the off-pump group, all patients underwent CABG without CPB. In this group patients were kept normothermic, heparin at a dose 300 U/kg was given intravenously and was reversed with protamine at a dose of 0.5 mg/300 units. In on-pump group, CABG with CPB was performed under hypothermia. Heparin was administered at a dose of 300 U/kg and it was reversed with protamine of 1 mg/300 units of heparin. Induction and maintenance of anesthesia were similar for all patients and it includes administration of intravenous weight-related doses of fentanyl, midazolam, and pancuronium bromide. Central venous catheterization and radial artery cannula insertion were completed before induction of anesthesia.

Statistical analysis

Statistical analysis SPSS (Chicago, IL, USA) for Windows 15.0 statistics package program was used for statistical analysis of the data. A Student's *t*-test for paired samples was used for variables with normal distribution. Independent sample *t* test, χ^2 test, Pearson correlation, and linear regression tests were

done. The data were expressed as mean ± standard deviation and the categorical variables as percentages. P < 0.05 was considered statistically significant.

The present clinical study was carried out in an academic institution and was approved by the Institutional Ethical Review Board. All subjects volunteered to participate in this study and gave informed consent after the objectives and method of the study had been explained. All patients had to anticipate having the same female sexual partner (vaginal intercourse was a required study activity) throughout the study for consistency in recording responses to efficacy questionnaires.

Main Outcome Measures

IIEF-5 scores were used for assessment of erectile function of the CAD patients before and after CABG surgeries. The measurement of plasma NO level was used in order to assess change in endothelial function.

RESULTS

Demographic characteristics of on-pump and off-pump groups were shown in Table-1. Based on the IIEF-5 scores, ED was present in 24 of the

total 28 patients selected for the study. The degree of ED was determined as mild, mild to medium, medium and severe in 21.4, 35.7, 14.3 and 14.3% of patients, respectively. In four (14.3%) patients, there was no ED. The mean IIEF-5 score increased insignificantly over baseline from 14.9 to 15.8 (p = 0.29) and 12.4 to 14.3 (p = 0.11) after on-pump and off-pump CABG surgeries, respectively. Change in IIEF-5 scores was also statistically insignificant between two groups (p = 0.46). Comparison of IIEF-5 between on-pump and off-pump patients after surgery was shown in Table-2.

Baseline NO levels in on-pump were 18.16 ± 7.63 nmol/L, and in off-pump they were 21.76 ± 11.08 nmol/L (p = 0.64). Pre-operatively, after reactive hyperemia, the plasma NO levels were 22.14 ± 10.52 nmol/L in on-pump and 21.49 ± 9.13 in off-pump (p = 0.96). Two hours after the CPB, in both groups, baseline NO levels were 24.44 ± 12.31 in on-pump and 20.58 ± 6.74 nmol/L in off-pump (p = 0.66). The difference in the plasma NO levels in on-pump (3.98 ± 12.29) and off-pump (-1.62 ± 16.40) groups before surgery was not significant (p = 0.51).

Baseline NO level in patients without ED (n = 4) was 15.45 ± 1.46 nmol/L. Pre-operatively, after reactive hyperemia, the plasma NO levels was 19.46

Table 1 - Demographic characteristics of on-pump and off-pump CABG.

	On-pump (mean ± SD) (n = 12)	Off-pump (mean ± SD) (n = 16)	p*
Age (years)	57.35 ± 7.65	59.30 ± 6.72	0.43
Ca-channel blocker (n,%)	3(25)	1(6.3)	0.19
Nitroglycerine (n,%)	10(83.3)	8(50)	0.19
ACE-inhibitor (n,%)	9(75)	4 (25)	0.06
Beta-blocker use (n,%)	12 (100)	7(43.8)	0.01*
Myocardial infarction (n,%)	7(58.3)	8 (50)	0.53
Hypertension (n,%)	8(66.6)	10 (62.5)	0.65
Lipid-lowering statin use (n,%)	12 (100)	16 (100)	0.73
Smoker (n,%)	10(83.3)	7(43.8)	0.08
Total cholesterol (mg/dL)	194.4 ± 28.2	157.7 ± 31.2	0.35
HDL cholesterol (mg/dL)	36.2 ± 11.5	39.7 ± 16.3	0.27

*: p < 0.05 statistically significant.

SD: Standard deviation

Table 2 - Comparison between on-pump and off-pump patients.

	On-pump patients (n = 12)	Off-pump patients (n = 16)	All patients (n = 28)
IIEF-5 results before surgery			
Normal	2 (16.6%)	2 (12.5%)	4 (14.3%)
Mild ED (17-21)	1 (8.3%)	1 (6.3%)	2 (7.1%)
Mild-moderate ED (12-16)	2 (16.6%)	3 (18.8%)	5 (17.9%)
Moderate ED (8-11)	6 (50.0%)	7 (43.8%)	13 (46.4%)
Severe ED (5-7)	1 (8.3%)	3 (18.8%)	4 (14.3%)
IIEF-5 mean \pm SD	14.9 \pm 6.9	12.4 \pm 7.1	
IIEF-5 results and change after surgery			
IIEF-5 mean \pm SD	15.8 \pm 5.3	14.3 \pm 8.4	
No IIEF-5 change	7 (58.3%)	8 (50.0%)	15 (53.6%)
Increased IIEF-5	5 (41.6%)	7 (43.8%)	12 (42.9%)
Decreased IIEF-5	-	1 (6.3%)	1 (3.6%)

\pm 1.31 nmol/L. Two hours after the CPB baseline NO levels was 13.66 ± 6.15 nmol/L.

After reactive hyperemia, the NO levels were found as 35.55 ± 23.54 and 23.00 ± 15.40 nmol/L in on-pump and off-pump, respectively. Two hours after surgery, the difference of the plasma NO levels in on-pump (11.11 ± 22.02) and off-pump (2.42 ± 18.20) groups were not significantly different from each other ($p = 0.11$).

Pearson correlation analysis of change in preoperative and postoperative plasma NO levels and IIEF-5 scores of ED patients before and 3 months after the surgery were also not significant ($r = -0.07$; $p = 0.84$). Pearson correlation analysis of preoperative and postoperative plasma NO levels and parameters that include; preoperative beta-blocker use, calcium channel blocker use, angiotensin converting enzyme inhibitors, operation time, use of CPB were done and the only relation was found with preoperative nitroglycerine use ($r = 0.51$, $p = 0.001$).

DISCUSSION

The present study demonstrates that the patients, who were performed on-pump or off-pump CABG surgery, had similar change in IIEF-5 scores.

ED which was based on IIEF-5 scores was found in 24 (85.7%) study group patients. Fifty percent (12/24) of the patients with ED had an insignificant increase in IIEF-5 scores. Although the number of our ED patients was higher than in the previous studies which investigated cardiac patients (13,14), it was found similar in patients who were candidate for CABG (15).

Outcomes of on-pump versus off-pump CABG surgery were examined in various studies on different topics (3,4,16). To assess midterm quality of life after off-pump CABG with that after on-pump CABG procedure, Immer et al. compared an age- and sex-matched standard population (3). Immer et al. demonstrated that the use of CPB allows CABG surgery to be performed with excellent results without impairment in neurocognitive outcome and quality of life in low-risk patients (3). Van Dijk et al. have recently published a randomized trial referring to the data of 281 patients looking at cognitive outcome and cardiac outcomes 5 years after on- or off-pump CABG surgery (16). They found that the avoiding the use of CPB had no effect on five-year cognitive or cardiac outcomes (16). In a meta-analysis study, Marasco et al. evaluated eight prospective randomized controlled trials to assess neurocognitive out-

comes after off-pump versus on-pump CABG (17). Marasco et al. concluded that there is no clinically relevant difference between two groups either early or late after surgery (17). According to the studies evaluating neurocognitive outcome, there was also no difference between on- or off-pump CABG surgery groups (3,16,17). In a large series during the 10-year follow-up, Puskas et al. found that on-pump and off-pump of CABG result in similar survival, regardless of gender (18).

Penile erection is a neurologically driven hemodynamic action. Erection is initiated by NO, a potent vasodilator, released from the nerve endings. Further production of NO depends on increased blood flow which is also known as shear stress (19). In most vascular beds, the NO is released by a stimulus that increases the shear stress over the endothelium. Shear stress over the brachial artery has been reported to induce activation of eNOS in the endothelium. Rassaf and his colleagues showed that up to 72 to 90% of circulating plasma NO is derived from eNOS activity (11).

Although it is well established that cardiovascular risk factors are associated with ED, once it is present there is mixed information on whether treating the risk factors will treat the ED (13). Recently, Mohamed et al. investigated the difference between the on pump and off-pump CABG surgery on the sexual function (15). The study design included subjective (IIEF-5 score) and objective (penile duplex ultrasonography) findings related to erectile function (15). The number of patients who reported post-operative improvement of their IIEF-5 score was found significantly higher in off-pump group. Nevertheless, there was no significant change in the duplex ultrasound data (peak systolic, end-diastolic velocities, and resistance index) after surgery between both groups (15). Although Mohammed et al. concluded that type of surgery can be considered a predictive factor of sexual function following CAB surgery, it was not clearly explained how it affects penile tissue without any change in vascular bed. Besides, previous studies demonstrated that NO-mediated erectile function fundamentally involves both nNOS and eNOS locally, whereby the former initiates the erectile response and the latter facilitates full erection (19).

In our study, we investigated whether CPB-induced transient pulmonary endothelial dysfunction result in decreased NO release that contributes to post-operative change in erectile function. Although twelve patients had improved IIEF-5 scores, this increase was found insignificant. We also demonstrated that there was no significant relation between postoperative plasma NO levels after reactive hyperemia following on and off-pump CABG. The current study implied that pre-operative nitroglycerine use was associated with increased plasma levels of NO after the on or off-pump CABG.

Limitations of our study are the relatively small number of patients, the lack of long-term follow-up data. A better study design for simultaneous evaluation of FMD and plasma NO levels is warranted for further studies.

CONCLUSIONS

This study demonstrates that in on- and off-pump CABG surgeries the IIEF-5 score and plasma NO levels did not reveal any significant difference in the early postoperative period.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Onder Canguven
Sakacı sokak 34/5 Yildiz apt.
Kozyatagi, Kadikoy, 34738 Istanbul, Turkey
Fax: + 90 216 352 0083
E-mail: ocanguven@yahoo.com