Journal of Advances in Medicine and Medical Research

24(1): 1-8, 2017; Article no.JAMMR.34684
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Paraoxonase Arylestarase and Oxıdatıve Stress in Coronary Artery Surgery Technıques with Desflurane Anesthesıa

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AOA, YA, EHY, AB, EM, KB and YN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors YA and EHY managed the analyses of the study. Author EHY managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2017/34684
Editor(s):
(1) Murali P. Vettath, Department of Cardiovascular-Thoracic & HeartTransplantation, Director-International Center of Excellence in OPCAB surgery, Malabar Institute of Medical sciences, Govindapuram, Kozhikode, Kerala, India.
Reviewers:
(1) Hani Mufti, Royal Children's Hospital Melbourne, Australia.
(2) Maddury Jyotsna, Deemed University, India.
(3) Takeshi Shirayama, Kyoto Prefectural University of Medicine, Japan.
(4) Gerez Fernandes Martins, State Institute of Cardiology, Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history/21275

Original Research Article

Received 5th June 2017
Accepted 27th September 2017
Published 6th October 2017

ABSTRACT

Background: Cardiovascular disease is the leading cause of morbidity in older people. Coronary artery bypass graft surgery is the most common type of operation performed in the world. Oxidative stress occurs in patients undergoing coronary artery bypass operation. The aim of this study was to investigate the difference in oxidative stress in off-pump versus on-pump coronary artery bypass surgery. We investigated patients undergoing traditional (on-pump) bypass surgery and bypass surgery performed on a beating heart (off-pump) who had been given antioxidant enzymes for

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high-density lipoprotein, as well as measured the levels of paraoxonase-1 (PON1), arylestarase (ARE), total antioxidant capacity (TAS), total oxidative stress (TOS), and oxidative stress index (OSI).

Methods: A total of 40 patients (29 males, 11 females) underwent traditional on-pump bypass, and 30 (24 males, 6 females) underwent off-pump bypass. PON1, ARE, TAS, and TOS levels were measured, and OSI was calculated.

Results: Preoperative and postoperative parameters were compared in the on-pump group, and only high OSI levels ($P = .02$) were found. No significant difference in operative parameters was found in the off-pump group. The serum values of OSI and TOS, were significantly greater in the on-pump group ($P = .007$, $P = .008$). Serum total cholesterol, HDL, low-density lipoprotein (LDL), triglyceride, and OSI levels were significantly higher preoperatively (after anesthesia induction) compared with the levels postoperatively ($P < .001$, $P = .04$, $P = .007$, $P < .001$, and $P = .02$, respectively) in the on-pump group, whereas the difference in the PON1, ARE, TAS, and TOS levels were not statistically significant. No significant difference was found in the other parameters.

Conclusions: On-pump bypass has long been considered the "gold standard" of treatment. However, our study has revealed that the newly developed beating heart off-pump bypass method results in less exposure of the patient to circulatory oxidative stress. Further studies are needed in order to confirm this hypothesis.

Keywords: Paraoxonase; arylesterase; total antioxidant capacity; total oxidant stress; cardiac bypass.

1. INTRODUCTION

Treatment of coronary artery disease includes drug therapy, percutaneous catheter intervention, and coronary artery bypass grafting (CABG). The indication for these treatments depends on the severity of the disease, primarily the number of damaged vessels. Multivessel damage is considered an indication for surgery, and serious coronary artery disease, such as three-vessel disease and damage to the left main coronary artery, is considered as a definite indication for CABG [1,2]. Nevertheless, use of CABG is associated with myocardial ischemia and damage. During the past years, with the introduction of better stabilizing systems, increased attention has been paid to performing CABG on a beating heart. Presently, many studies have compared off-pump and on-pump CABG. The literature documents a more favorable outcome, such as reduced blood transfusion needs and reduction of postoperative morbidity and organ dysfunction rates, in selected high-risk patients undergoing off-pump CABG [3-5]. However, many studies showed that oxidative stress was higher during on-pump CABG [6-8].

Human serum paraoxonase (PON1) and arylesterase (ARE) are lipophilic antioxidant enzymes. Serum PON1 binds to high-density lipoprotein (HDL) and contributes to the elimination of organophosphorus compounds and free radicals. PON1 is one of the endogenous free-radical scavenging systems in humans [9]. Serum PON1 and ARE have been demonstrated to function as a single enzyme [10]. Human serum PON1 shows neither age-related change in activity nor sex differences. Reduced PON1 enzyme activities have been shown in several groups of patients with hypercholesterolemia, diabetes mellitus, and cardiovascular disease who are under increased oxidative stress [11-13].

Serum levels of different oxidant species can be determined in laboratories. However, these measurements are time-consuming, expensive to perform, and require complicated equipment. Recently, lipid peroxidation concentrations were observed by determining total oxidant status (TOS) [14]. Total antioxidant status (TAS) also is helpful to determine the activity of antioxidants in a medium [15]. Therefore, measurements of TAS and TOS can provide information on an individual's overall serum oxidative stress index (OSI), which may include antioxidants and oxidants that are not yet known or easily measured [16].

We compared the activity of serum PON1 and ARE in patients undergoing on-pump and off-pump CABG, and investigated the possible changes with regard to oxidative stress.

2. MATERIALS AND METHODS

2.1 Patients

We included 70 patients (53 males and 17 females; mean age, 64.6±1.2 years) in this study who were randomly assigned to undergo off-pump (30 patients; 24 males and 6 females; mean age, 64.8±11 years) or on-pump (40 patients; 29 males and 11 females; mean age, 61.2±10 years) CABG. Patients who used antioxidants were excluded from the study, as were those who received a blood transfusion or blood products during the operation since the antioxidant properties of such products are not as yet established. No patient was taking vitamins or dietary supplements with established antioxidant properties before the study. The study was approved by the Antalya Education and Research Hospital Medical Ethics Committee, and written informed consent was obtained from all participants.

2.2 Anesthetic Technique

The anesthetic technique was standardized for all patients and consisted of balanced anesthesia. All patients were premedicated with diazepam 5 mg the night before surgery and with midazolam 0.03 mg/kg intravenously (IV) 10 minutes preoperatively. Anesthesia was induced with thiopental (5 mg/kg) and fentanyl (4 μg/kg). Vecuronium was used as a muscle relaxant (0.1–0.15 mg/kg). After tracheal intubation, anesthesia was maintained with a 50% air/oxygen mixture with desflurane at a concentration of 4% to 5%. Additional fentanyl and propofol were administered whenever necessary.

2.3 Surgical Procedure

Off-pump CABG was performed through a median sternotomy. After harvesting the bypass conduits, heparin was given at a dose of 100 IU/kg to achieve a target activated clotting time of 250 to 300 seconds. No myocardial stabilization device was used except for cotton sutures. During the anastomosis, coronary flow was occluded by bulldog clamps. The proximal anastomosis was performed using a site clamp on the aorta or the internal mammary artery. All grafts were arterial (internal mammary or radial artery).

On-pump CABG was performed through a median sternotomy. After harvesting the bypass conduits, heparin was given at a dose of 400 IU/kg to achieve a target activated clotting time of 450 seconds or above. Cardiopulmonary bypass was instituted using ascending aortic cannulation and two-stage venous cannulation in the right atrium. The extracorporeal circuit consisted of a membrane oxygenator and a roller pump primed with crystalloid solution. Myocardial protection was achieved with cold potassium cardioplegia (Plegisol; Abbot Laboratories, Inc., Chicago, IL, USA) and warm blood cardioplegia before removing the aortic cross-clamp. Cardioplegia was given retrogradely except for the first two-thirds of crystalloid cold cardioplegia, which was given anterogradely. All distal and proximal anastomoses were completed before the aortic cross-clamp was removed. At the end of CABG, heparin was neutralized by administration of protamine chloride until the activated clotting time was less than 180 seconds. Hematocrit was maintained at more than 20% during the cardiopulmonary bypass in the on-pump group and at more than 25% in the off-pump group.

2.4 Sample Collection and Analyses

Samples were obtained preoperatively (before anesthesia induction) and within 1 hour postoperatively for each surgery technique. Serum samples then were separated from cells by centrifugation at 3000 revolutions per minute (rpm) for 10 minutes. Lipid parameters and other routine parameters were measured immediately. Remaining serum portions were stored at −80°C and used to analyze PON1, ARE, TOS, and TAS.

2.5 Measurement of Serum PON1 and ARE Activities

PON1 and ARE enzyme activities were measured using commercially available kits (Rel Assay Diagnostics, Gaziantep, Turkey). The fully automated PON1 activity measurement method consists of application of two different sequential reagents. The first reagent is an appropriate Tris buffer that also contains calcium ion, which is a cofactor of PON1 enzyme [17]. Phenylacetate was used as a substrate to measure the ARE activity [18].

2.6 Measurement of Serum TOS and TAS

The TOS and TAS of the plasma were measured using novel automated colorimetric measurement methods developed by Erel [14,15]. The results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H2O2 Equiv./L) for TOS and micromolar trolox equivalent per liter (μmol trolox Equiv./L) for TAS.

2.7 OSI Measurement

The percentage ratio of TOS to TAS levels was accepted as the OSI [16]. For calculation, the resulting micromolar unit of TAS was changed to millimoles per liter, and the OSI value was calculated according to the following formula: OSI (arbitrary unit) = TOS (μmol H2O2 Equiv./L)/TAS (μmol trolox Equiv./L).

2.8 Statistical Analysis

Continuous variables were summarized as means and standard deviation for various groups. The statistical analysis was done with MedCalc statistical software version 11.5.1.0 (MedCalc Software, Mariakerke, Belgium). The values at regular intervals were compared with the baseline values using Student's t-test in the on-pump and off-pump groups. Intergroup comparison was carried out using the unpaired t-test. A value of $P < .05$ was taken as significant.

3. RESULTS

No patient received inotropic backing during the surgical procedure, and none suffered any significant complication (i.e., arrhythmia, pulmonary insufficiency, infection, or excessive bleeding) over 24 hours of investigation. During the study, there was no mortality among the patients. Demographic data and general characteristics for the on-pump and off-pump groups are summarized in Table 1.

Serum total cholesterol, HDL, low-density lipoprotein (LDL), triglyceride, and OSI levels were significantly higher preoperatively (after anesthesia induction) compared with the levels postoperatively ($P < .001$, $P = .04$, $P = .007$, $P < .001$, and $P = .02$, respectively) in the on-pump group, whereas the difference in the PON1, ARE, TAS, and TOS levels were not statistically significant. Similarly, there was no statistically significant difference in the preoperative versus postoperative PON1, ARE, TAS, TOS, and OSI levels in the off-pump group. However, serum total cholesterol, LDL, and triglyceride levels were significantly higher preoperatively compared with the levels postoperatively ($P < .001$, $P = .001$, and $P = .007$ respectively; Table 2) in the off-pump group.

Serum TOS and OSI levels were significantly higher preoperatively in the on-pump group compared with that in the off-pump group ($P = .02$, and $P = .03$, respectively), whereas the difference in the PON1, ARE, TAS, and lipid levels were not statistically significant. There was no statistically significant difference in the postoperative PON1, ARE, and TAS levels between the two groups. However, HDL levels were significantly lower and TOS and OSI levels were significantly higher postoperatively in the on-pump group compared with that in the off-pump group ($P = .005$, $P = .007$, and $P = .008$, respectively; Table 3).

4. DISCUSSION

On-pump cardiac arrest long has been the gold standard for CABG. However, off-pump CABG

Table 1. Clinical and demographic features of patients undergoing on-pump and off-pump CABG were similar except for operation time, anesthesia time, and coronary artery bypass number

Parameters	On-pump (n = 40)	Off-pump (n = 30)	pP
Age	61.2 ± 10	64.8 ± 11	0.17
Male	29 (72.5%)	24 (80%)	0.13
Female	11 (27.5%)	6 (20%)	
Smoking	21 (52.5%)	18 (60%)	0.24
BMI kg/m2	28.4 ± 4.08	28.1 ± 4.2	0.78
DM	16 (40%)	16 (53.3%)	0.07
HT	28 (70%)	19 (63.3%)	0.24
LVEF (%)	55.3 ± 9	55.1 ± 10	0.91
Operation time (min)	179.8 ± 32	113 ± 32	<0.001
Anesthesia time (min)	214 ± 35	143 ± 31	<0.001
Aortic cross-clamp time (min)	33.8 ± 11		
Pomp time	66.4 ± 17.5		
Coronary artery bypass (*n*)	2.9 ± 0.6	1.5 ± 0.5	<0.001

BMI, body mass index; CABG, coronary artery bypass grafting; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction

Table 2. Preoperative and postoperative comparisons in the on-pump group

Parameters (mean ± SD)	Preop. on-pump CABG	Postop. on-pump CABG	P
PON1 (U/L)	103.7 ± 79	125.5 ± 51	0.66
ARE (kU/L)	216 ± 61.3	208 ± 40.8	0.39
TAS (nmol Trolox/L)	2.03 ± 0.28	2.1 ± 0.33	0.19
TOS (μmol H2O2 Equiv./L)	4.52 ± 5.2	2.78 ± 3.32	0.08
OSI	0.22 ± 0.24	0.14 ± 0.15	0.02*
TC (mg/dL)	190 ± 49	138 ± 38.4	<0.001*
HDL-C (mg/dL)	35.7 ± 10.5	32.7 ± 8.36	0.04*
LDL-C (mg/dL)	126 ± 62	83 ± 29	0.007*
TG (mg/dL)	189 ± 103	126 ± 77	<0.001*
PON1 (U/L)	141 ± 83.7	119 ± 63	0.12
ARE (kU/L)	236 ± 47	220 ± 48	0.11
TAS (nmol Trolox/L)	2.05 ± 0.24	2.02 ± 0.44	0.77
TOS (μmol H2O2 Equiv./L)	2.02 ± 3.63	0.86 ± 2.17	0.12
OSI	0.1 ± 0.19	0.04 ± 0.09	0.10
TC (mg/dL)	188 ± 37	149 ± 27	<0.001*
HDL-C (mg/dL)	40.9 ± 9.8	41.3 ± 9.6	0.84
LDL-C (mg/dL)	114 ± 38	84 ± 18	0.001*
TG (mg/dL)	182 ± 123	122 ± 66	0.007*

** Statistically significant, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol LDL-C: low-density lipoprotein cholesterol, TG: triglyceride*

Table 3. Comparison of the two techniques in preoperative parameters (between groups)

Parameters	Preop.on-pump CABG	Preop. off-pump CABG	P
PON1 (U/L)	129 ± 79	141,5 ± 83	0.52
ARE (kU/L)	216 ± 61	236 ± 47	0.15
TAS (nmol Trolox/L)	2.03 ± 0.2	2.05 ± 0.2	0.75
TOS (μmol H2O2 Equiv./L)	4.52 ± 5.2	2.02 ± 3.6	0.02*
OSI	0.22 ± 0.24	0.10 ± 0.19	0.03*
TC (mg/dL)	190 ± 49	188 ± 37	0.89
HDL (mg/dL)	35.7 ± 10	41 ± 9.8	0.06
LDL (mg/dL)	126 ± 62	114 ± 38	0.40
TG (mg/dL)	189 ± 103	182 ± 123	0.82
PON1 (U/L)	125 ± 53	119 ± 63	0.19
ARE (kU/L)	208 ± 40	220 ± 48	0.17
TAS (nmol Trolox/L)	2.1 ± 0.3	2.02 ± 0.44	0.33
TOS (μmol H2O2 Equiv./L)	2.7 ± 3.3	0.86 ± 2.17	0.007*
OSI	0.14 ± 0.17	0.04 ± 0.09	0.008*
TC (mg/dL)	139 ± 38	149 ± 27	0.22
HDL (mg/dL)	33 ± 8.3	41 ± 9.2	0.005*
LDL (mg/dL)	84 ± 30	84 ± 21	0.98
TG (mg/dL)	120 ± 75	117 ± 62	0.86

** Statistically significant, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol LDL-C: low-density lipoprotein cholesterol, TG: triglyceride*

has been developed to avoid detrimental effects of extracorporeal circulation [19]. This relatively new surgical procedure markedly reduces oxidative stress and systemic inflammation [20]. Therefore, we have evaluated some biochemical parameters of oxidative stress and antioxidant capacity in patients undergoing CABG, performed either with on-pump or off-pump techniques. The most remarkable findings were increased TOS and OSI levels in the on-pump group preoperatively and postoperatively compared with that in the off-pump group (Table 3).

It has been demonstrated previously that reactive oxygen species are generated during

CABG leading to lipid peroxidation, and pretreatment with antioxidants before CABG minimizes lipid peroxidation [21,22]. Paradies et al. [23] found a significant increase in malondialdehyde (MDA) production during ischemia and reperfusion times. Gonenc et al. [21] demonstrated a significant increase in plasma MDA levels in a CABG group during the ischemic period compared with that preoperatively and during anesthesia induction. Serum concentrations of different oxidant species can be measured separately in laboratories; however, in our study, we used the measurements of TAS and TOS, so that we could provide information on an individual's overall OSI. OSI may include those antioxidants and oxidants not yet recognized or easily measured [24]. Even though there were increases in TOS and OSI levels in the on-pump group, demonstrating the increase in oxidative stress in these patients, we could not observe any difference in TAS values (Table 3).

Pechan et al. [25] found that the antioxidant capacity in patients in both the operated groups decreased, but this decline was already present preoperatively and did not change during the whole postoperative period. The design of our study allowed us to compare patients only before and after surgery, so we had no chance to compare the TAS values with a control group. However, our results showed a pattern similar to that of Pechan et al. [25], since no difference was observed in TAS values postoperatively in both groups.

An interesting observation in our study was that HDL levels were lower postoperatively in the on-pump group compared with that in the off-pump group (P = .005; Table 3). HDL perform various functions, including several immunological activities. The atheroprotective functions of HDL that more recently have attracted attention among other actions include its antiapoptotic, antithrombotic, and anti-infectious functions [26]. Generally, cardiac surgery on the beating heart (off-pump technique) is considered to be less demanding for patients and is associated with a decrease in systemic inflammatory response compared with the on-pump technique [27]. HDL can directly inhibit oxidation of LDL or other targets containing phospholipids. In addition, inhibition of oxidative events and oxidative stress in vivo may be achieved indirectly via other functions of HDL, such as induction of cholesterol efflux and, in general, via “anti-inflammatory” functions of HDL [26]. The antioxidative activities of HDL might equally become impaired in the presence of inflammation due to the altered enzymatic activities. Normal functional HDL has high levels of antioxidants and active antioxidant proteins and enzymes with high antioxidant potential, and it has anti-inflammatory activity. As part of the acute-phase response, activities of HDL-associated enzymes, including PON1, can be compromised and/or made dysfunctional [26]. In accordance with this background, the antioxidant enzyme activities of PON1 and ARE were not significantly different in our two patient groups (Table 3). Indeed, antioxidative deficiency of HDL relative to LDL oxidation in the artery wall cells is observed in the acute phase, concomitant with decreases in the activity of PON1 [26]. Inflammation converts HDL to a particle that not only is ineffective as an anti-inflammatory and antioxidant, but is proinflammatory and pro-oxidant, promoting LDL oxidation. The search is continuing to find the best approaches for prevention of the loss or restoration of the antioxidant and anti-inflammatory potential of HDL [26]. We suggest that the decrease in HDL levels in the on-pump group postoperatively could be related to the increased oxidant stress and decreased systemic inflammatory response in these patients.

5. CONCLUSIONS

Our results indicate that patients undergoing on-pump CABG were under a heavier oxidative stress preoperatively and postoperatively compared with those undergoing off-pump CABG. However, we observed no significant differences in the TAS or the antioxidant enzymatic activities of PON1 and ARE, suggesting that the antioxidant status is not related to the CABG technique.

CONSENT AND ETHICAL APPROVAL

The study was approved by the antalya education and research hospital medical ethics committee, and written informed consent was obtained from all participants.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/21275