Paraoxonase 1 low activity and SYNTAX score may predict postoperative complications after coronary artery surgery

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Abstract. – OBJECTIVE: Coronary artery bypass grafting (CABG) seems to present a powerful trigger of oxidative stress (OS) and acute inflammatory response. This study aimed to estimate the effects of off-pump coronary artery bypass (OPCAB) grafting on the OS that is commonly observed in patients undergoing operation under cardiopulmonary bypass (CPB). Additionally, we aimed to examine the relationship between and paraoxonase 1 (PON1) activity and the degree of stenosis, severity and complexity of the atherosclerotic lesions, estimated by SYNTAX score (SS).

PATIENTS AND METHODS: Study group of 107 patients scheduled for CABG were divided into CPB and OPCAB group. Blood samples for OS markers measurement were collected at six-time intervals: before skin incision (t1), immediately after surgery (t2), 6h (t3), 24h (t4), 48h (t5) and 96h after cessation of the operation and surgical trauma (t6). SS was calculated.

RESULTS: A significant decrease in lipid hydroperoxides (LOOH) and advanced oxidation protein products (AOPP) levels after both types of surgeries were observed, whereas PON1 reduction was observed higher in the CPB than in the OPCAB group.

A significant inverse correlation between SS values and PON1 activity, preoperatively and during the early postoperative hours after surgery [in t2, t3 time intervals (p<0.05 for all)] was found. ROC analysis showed that for CPB patients, Model with all OS parameters showed excellent accuracy (AUC=0.957, p<0.001) for prediction postoperative complications.

CONCLUSIONS: Decrease in PON1 activity during the early post-operative phases was related to higher SS. This relationship was more convincing in CPB, compared with OPCAB patients. Moreover, integrated models of OS status parameters have the capability to predict the development of postoperative complications.

Key Words:
Atherosclerosis, Oxidative stress, Paraoxonase 1, SYNTAX score.

Introduction

In cardiac surgery, the cardiopulmonary bypass (CPB) pump has been recognized as the main cause of an oxidative stress (OS) and complex systemic inflammatory response[1]. The OS and inflammatory response to CPB initiate through contact between heparinized blood and non-endothelial cell surfaces of the CPB circuit. Termination of cardioplegic arrest by reperfusion leads to additional OS development, contributing to the complex pathophysiology of ischemia-reperfusion injury[2,3].

Off-pump coronary artery bypass grafting (OPCAB) on the beating heart reduces the OS and acute inflammatory response but does not completely prevent it[4,5]. The avoidance of CPB and myocardial ischemia-reperfusion injury has been proposed to significantly reduce the postoperative

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complications[6,7]. Our previous related study[8] has explicitly confirmed mutual involvement of OS and inflammation in atherosclerosis development, during the entire course of the disease.

The pathological milieu in cardiovascular disease leads not only to increase in OS and inflammatory markers in circulation[9-15], but also leads to reduction of antioxidative defense system[13,16-18].

Serum paraoxonase 1 (PON1) is an enzyme with the capacity to combat against lipid peroxidation in endothelial cells, macrophages and lipoproteins[17]. Namely, PON1 possess numerous atheroprotective properties, which include preserving high density lipoprotein (HDL) function, stimulation of cholesterol efflux, as well as anti-inflammatory and antioxidant activities. PON1 also exhibits anti-adhesive, anti-thrombotic and anti-apoptotic effects[17]. Moreover, PON genetic polymorphisms are regarded as contributors to susceptibility/protection from atherosclerosis-related diseases[19,20]. However, an extensive interest exists recently in disclosing the role of PON1 regarding different human disorders[17,21].

Furthermore, lipid peroxidation and protein oxidation involvement in association with CPB surgery are not fully understood. This is probably related to the assessment of reperfusion injury due to the limitation in available methods for *in vivo* measurement of free radical generation or end products of free radical-catalyzed oxidation of lipids and proteins[22,23]. In line with this, lipid hydroperoxides (LOOH) and advanced oxidation protein products (AOPP) are used to evaluate the effect of reactive oxygen species on lipid and protein structures, respectively[22,23].

The aim of this study was to examine a possible relationship between PON1 activity and the degree of stenosis, severity and complexity of the atherosclerotic lesions of the coronary arteries, estimated by SYNTAX score (SS)[24]. Present project estimated the effects of OPCAB operations on the OS (i.e., LOOH and AOPP) markers and PON1 activity that are commonly affected in patients undergoing operation under CPB. These measurements could be finally proved as potential, beneficial and auxiliary argument for the surgical decision and the final choice of operative technique.

Patients and Methods

Patients

We carried out a prospective cohort study at the Medical Military Academy, Belgrade (Department for Cardiac Surgery). Biomarkers of oxidative stress were measured at the Faculty of Pharmacy (Department for Medical Biochemistry), University of Belgrade. The Hospital Ethics Committee approved the project protocol. All patients that were included in the study signed fully informed consent.

The present study consisted of 107 patients scheduled for a coronary artery bypass grafting (CABG). The patients encompassed two groups: the CPB group (n=60), where subjects underwent CABG using CPB on the potassium arrested heart, and the OPCAB group (n=47), where subjects underwent CABG on the beating-heart without using CPB.

Patients with acute infections, immunologic or malignant diseases, immunosuppressive medications usage, recent myocardial infarction (in the last three months), chronic renal failure, reoperation, perioperative myocardial infarction, massive mediastinal bleeding after surgical procedure, heart failure, and previous stroke or transient ischemic attack were excluded.

The SYNTAX Score (SS)[24] was preoperatively calculated for all patients.

The SS is a powerful coronary score for prediction events after percutaneous coronary intervention[24]. Accordingly, all patients were divided into 3 subgroups: low (i.e., SS <22), intermediate (i.e., SS between 23 and 30) and high SS (i.e., SS>30).

Anesthesia

All patients underwent standardized anesthetic technique. Etomidate (0.1-0.2 mg/kg), sufentanyl (0.5-1 μg/kg) and rocuronium (1 mg/kg) were induced for each patient. Also, sevoflurane (0.6-1.0%) and sufentanyl (0.5-1 μg/kg/h) were used for maintenance of general anesthesia.

Surgical Procedure

Midline sternotomy and harvesting of left internal mammary artery (a pedicle and saphenous vein grafts) were performed after full exposure of the coronary artery branches for its revascularisation.

CPB group

Ascending aortic cannulation and two-stage venous cannulation in the right atrium were used for CABG using a CPB pump. A roller pump (Stockert-S5, Sorin Group, Munich, Germany) and oxygenator (low-prime) accompanied with an incorporated cardiotomy reservoir (Sorin Inspire 8, Sorin Group, Mirandola, Italy) were used for the CPB circuit. The non-pulsatile pump flow (i.e., at 2.2-2.4 L/min/m^2) and perfusion pressure (i.e., between 50-80 mmHg) during CPB were kept. The homemade cold potassium cardioplegia (i.e., temperature of 4°C) was used to achieve myocardial protection. On the arrested heart all distal anastomoses of the bypass grafts were done.

OPCAB group

The Starfish™ 2 Heart Positioner (Medtronic, Inc., Minneapolis, MN, USA) and the Octopus® IV Tissue Stabilizer were used to maintain the mechanical stability of the coronary arteriotomy area. Myocardial protection was maintained by the soft plastic intraluminal coronary flow-shunt (Medtronic, Clearview®, Medtronic, Inc., Minneapolis, MN, USA). The latter one was passed into the coronary arteriotomy for the whole time aiming to prevent ischemia of myocardium during placing of distal anastomosis. All of the anastomoses were done on the beating heart.

Sample Collection and Analyses

Six-time intervals (t1-t6) were determined for collection of blood samples. The phlebotomy was performed following the protocol (i.e., from the central venous line through jugular internal vein). After centrifugation (i.e., 3000 rpm for 15 minutes) sera were separated and stored at -80°C, until analysis.

Blood collection was performed before the incision of the skin (t1), immediately after the surgery (t2), 6h (t3), 24 h (t4), 48h (t5) and 96 h after termination of the operation and surgical trauma (t6). Sample collection procedure was the same for OPCAB and CPB groups.

Measurement of Oxidative Stress (OS) Status Parameters

LOOH were determined using the method of Gay and Gebicki. The procedure is based on the use the ferric-xylenole-orange method, after precipitation in perchloric acid[25]. The Witko-Sarsat method was applied for AOPP measurement. The method is based on the reaction of glacial acetic acid and potassium iodide[23]. Paraoxon (Chem Service Inc, West Chester, PN, USA) as a substrate was used for kinetic measurement of the serum PON1 activity, following the instructions of the method of Richter and Furlong[26]. The Ellman's method[27] with dinitrodithiobenzoic acid as a reagent in alkaline buffer was applied for the measurement of total SH groups (tSHG). All OS status parameters were measured on an ILAB 650 analyzer (Instrumentation Laboratory, Milan, Italy).

Statistical Analysis

Statistical analysis was performed using SPSS statistical package (version 18.0 for Windows, SPSS Inc., Chicago, IL, USA). Data are presented as mean±standard deviation (SD), median (interquartile range), or counts and percentages (%). Differences between groups were evaluated with ANOVA repeated measures as the non-parametric Friedman test, followed by the Wilcoxon signed-rank test, Kruskal-Wallis non-parametric analysis of variance, followed with the Mann-Whitney U test. Chi-square test was used to analyze the differences between categorical data. A correlation analysis with Spearman's (ρ) correlation coefficient was used to determine the relationships between variables. Multiple linear regression (MLR) analysis was performed to estimate clinical and general factors that could influence PON1 activity. The starting model of parameters consisted of the following variables: SYNTAX score, hypertension status, diabetes, peripheral arterial disease, smoking status, family history of coronary artery disease, acute myocardial infarction, hyperlipidemia, BMI, gender and age. Receiver Operating Characteristic (ROC) curve analysis was used to test the discriminatory potential of OS status parameters in predicting postoperative complications. In all analyses, a p-value < 0.05 was considered as statistically significant.

Results

Table I shows basic characteristics of the coronary artery disease patients, immediately before them underwent the surgical procedure. The study group consisted mainly of males. Among patients undergoing elective CABG surgery the highest percent was those of overweight (50.5%) and obese (29.0%) patients. The majority of patients were also hypertensive (87.9%), hyperlipidemic (66.4%) with a positive family history of coronary artery disease (74.8%). A minor percentage had diabetes mellitus type 2 (31.8%). Additionally, a high percent of patients were smokers (71.0%). Data on their long-term medication are also presented in Table I.

This project assessed up to four oxidative status parameters (i.e., LOOH, AOPP, PON1, and tSHG) in order to get a more precise insight into the redox balance before and its changes after

Table I. General and clinical characteristics of the study population.

Variable	Study group
Age, (years)	64.1±9.6
Gender (m/f), n (%)	81/26 (75.7/24.3)
BMI (kg/m²)*	27.6 (25.3-30.7)
Clinical data	
Obesity- lean/overweight/obese, n (%)	22/54/31 (20.6/50.5/29.0)
Hypertension, n (%)	94 (87.9)
Diabetes mellitus type 2, n (%)	34 (31.8)
Hyperlipidemia, n (%)	71 (66.4)
Chronic obstructive pulmonary disease, n (%)	12 (11.2)
Chronic Renal Failure, n (%)	6 (5.6)
Acute myocardial infarction, n (%)	62 (57.9)
Peripheral arterial disease, n (%)	47 (43.9)
Smoking, n (%)	76 (71.0)
Family history of coronary artery disease, n (%)	80 (74.8)
Left ventricular ejection fraction, %*	50.0 (45.0-55.0)
SYNTAX Score (points)	27.1±10.3
Therapy	
β-blockers, n (%)	102 (95.3)
ACE inhibitors, n (%)	94 (87.9)
Calcium-antagonists, n (%)	36 (33.6)
Nitrates, n (%)	95 (88.8)
Statins, n (%)	76 (71.0)
Oral antidiabetics, n (%)	22 (20.6)
Diuretics, n (%)	36 (33.6)

*parameters with non-normal distribution; Data shown as means (SD), median (25th -75th percentile), or numbers (%)

CABG surgery. Moreover, we estimated possible differences between the two distinct surgical procedures, CPB and OPCAB, regarding OS development. In this acute situation non-parametric ANOVA repeated measures (Friedman's test followed by Wilcoxon's signed rank test as post-hoc test) enabled us to compare OS parameters at different time intervals, as well as between surgical modalities at the same time. Results are presented in Figure 1.

A significant decrease in LOOH and AOPP concentrations after both types of surgeries was observed.

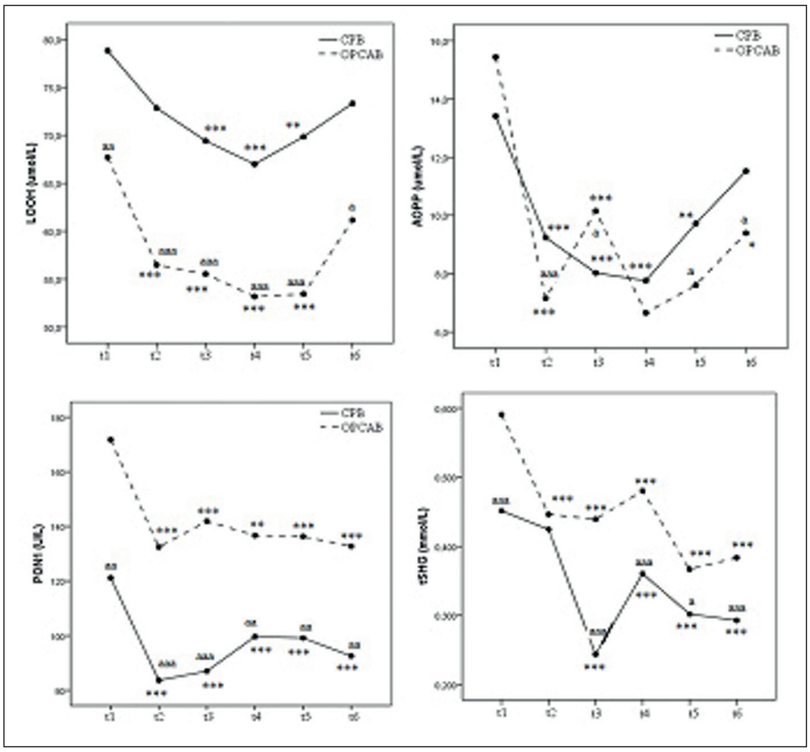
These experiments showed also a significant decrease of both antioxidative parameters, PON1 activity and tSHG concentration as representatives of enzymatic and non-enzymatic parts of the endogene antioxidative defence system. PON1 reduction was observed higher in the CPB than in the OPCAB group. Thus, we performed further analysis to find a possible explanation for above discrepancy.

To assess the mutual involvement of coronary vessel occlusion reflected through the preoperative SS value and surgery type on PON1 activity in distinct pre- and postoperative points, we performed a non-parametric Kruskal-Wallis ANOVA test, followed by the Mann-Whitney U test for inter-groups comparison, in sub-groups according to surgical modality and SS cut-off values of 22 and 30 points. More precisely, we compared a CPB subjects with a OPCAB subjects having the same level of coronary vessel occlusion, i.e., sub-groups with low SS – below 22, intermediate SS level (23-30 points) and high SS – above 30 points, as determined by tertile value boundaries for this current group of patients. The results are presented in Figure 2.

Obtained results showed a significantly higher PON1 activity in the OPCAB group with an intermediate SS level compared with the CPB group with the same level of plaque severity, and this was true for the t2-t5 study points (Figure 2).

More important was the slight but, relatively constant increase in PON1 activity in subjects with the highest level of coronary artery stenosis.

Figure 1. Changes in oxidative stress parameters during CABG surgery, for two surgical procedures until 96h post-operatively: t1-before skin incision, t2-after protamine-sulfate administration, t3- 6h, t4-24h, t5-48h, t6-96h after operations.*,**,***p<0.05, <0.01, <0.001 *vs.* basal value (before surgery – t1), a, aa,aaa – p<0.05, <0.01, <0.001 CPB *vs.* OPCAB at the same time point.



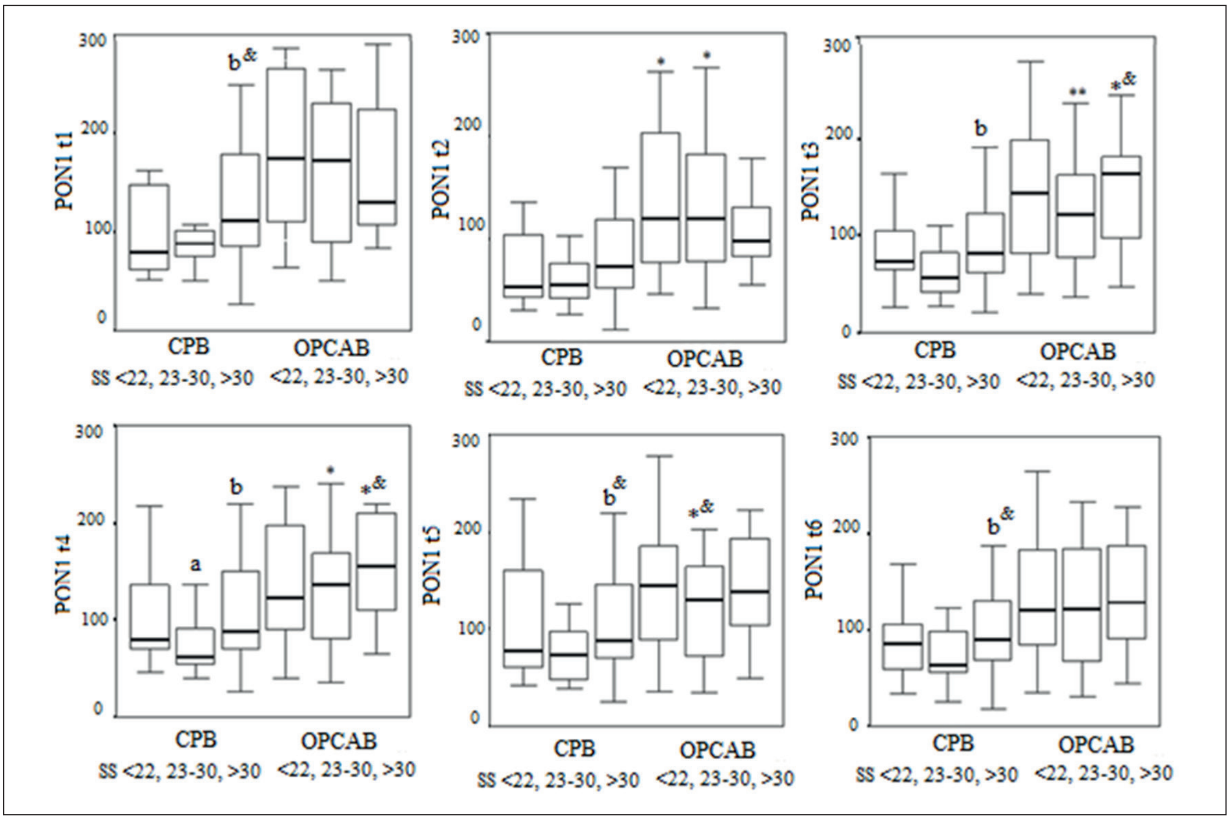


Figure 2. PON1 (U/L) activity in different time points before and after CPB and OPCAB surgery according to SYNTAX Score tertile value subgroups (low SS ≤ 22, intermediate SS 23-30 and high SS ≥30); a-p <0.05 vs. low SS group, b-p <0.05 vs. intermediate SS group; *, **p<0.05, <0.01 OPCAB *vs.* CPB in the same SYNTAX score subgroup, Kruskall-Wallis test and subsequent Mann-Whitney U test - *&-borderline significance (0.05< p <0.100).

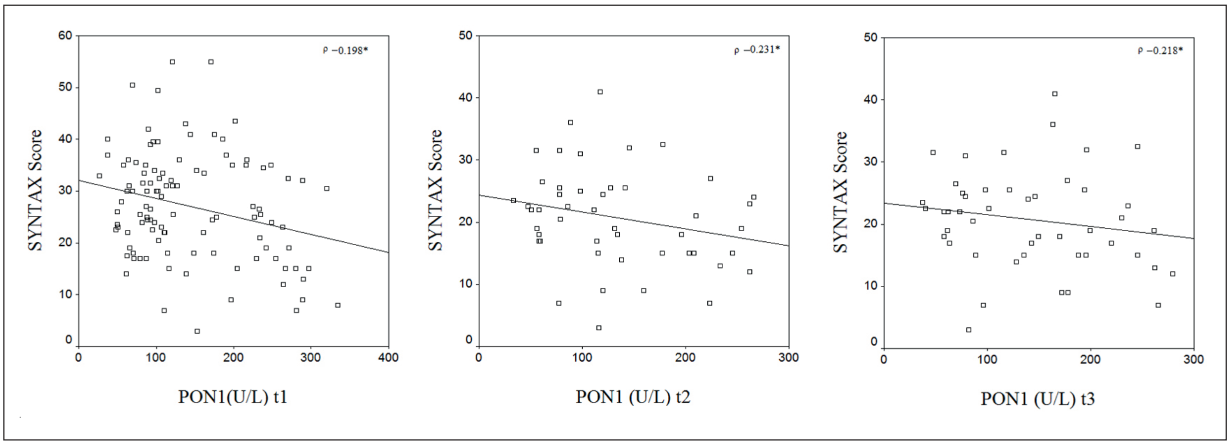


Figure 3. Correlation between PON1 activities at different time points during CABG surgery and preoperative SYNTAX Score values. Spearman's (ρ) and *p* values are shown on the graphs (*$p<0.05$).

This was more evident, and from the first study point in the CPB group (Figure 2).

In order to confirm the possible influence of coronary vessel wall stenosis level on systemic PON1 activity we conducted Spearman's non-parametric correlation analysis. The results are presented in Figure 3.

As Figure 3 shows, the SS level was significantly and inversely correlated with PON1 activity before surgery and the first two times after the surgery t2 and t3; after 24h this correlation was not observed. The other oxidative status parameters also showed correlations with SS level, as follows: LOOH (t2, t4, t5) and AOPP (t2) showed significant positive correlation with SS, whereas tSHG was negatively correlated with SS (t1, t3, t4).

MLR (backward selection) enabled us to get the best model of parameters which could explain the diminishing PON1 activity in coronary artery disease patients in general, and upon surgical conditions (Table II).

When we analyzed the whole group of patients, irrespective of the surgery modality, MLR revealed SS and BMI to be the main determinants of PON1 activity. Considering the significant negative correlation between SS value and PON1 activity, it is reasonable to suppose that atherosclerotic plaque aggravation causes a reduction in PON1 activity. This was the true for each of the six time points. The same analysis within the CPB group detected mainly BMI as a significant PON1 activity predictor. In OPCAB group we found peripheral arterial disease as a main factor for the variability in PON1 activity before surgical procedure, so as after that.

Furthermore, we performed ROC analysis for all CABG patients combined and separately for the CPB group to test the clinical accuracy of oxidative status parameters in predicting postoperative complications (Figure 4). Twelve postoperative complications were noted in the CPB group, and three in the OPCAB group. The three Models were constructed consisting of pro-oxidant parameters (i.e. LOOH and AOPP-Model 1), antioxidative parameters (i.e. PON1 and tSHG-Model 2) and all four OS parameters (Model 3). Logistic regression analysis showed that the Model 2 ROC curve had very good discriminatory capability (AUC=0.828, $p<0.001$)[28]. Model 3 had the best clinical accuracy in the CPB group-all OS parameters integrated by logistic regression analysis (excellent accuracy, i.e., AUC=0.957, $p<0.001$).

Discussion

Our current study revealed several important findings. Generally, we reported the post-operative reduction in concentrations of LOOH and AOPP in patients with coronary artery disease (Figure 1). We also found higher LOOH and AOPP levels in the CPB, as compared with OPCAB group during the post-operative period, showing that OS was greater in the CPB group which could be explained by more severe conditions of the CPB patients or their decreased capability to respond to the OS challenge.

Several research groups[29,30] detected that lipid peroxides are generated during CABG surgery undergoing the β-scission reaction[31]. This process

Table II. Multiple linear regression analysis of clinical factors' influence on PON1 activity.

	The best model Adjusted R^2	The best model Variables	Unstandardized Coefficients Beta (SE)	95% Confidence Interval for β	*p*
All patients PON1					
t1	0.221	Syntax Score	–3.30 (0.86)	-5.0– -1.6	<0,001
		BMI	7.00 (2.30)	2.3 – 11.6	0.004
t2	0.188	Syntax Score	-3.00 (0.76)	- 4.5 – -1.5	<0.001
		BMI	4.10 (2.10)	0.03-8.25	0.049
t3	0.162	Syntax Score	-2.62 (0.70)	-4.0 – 1.2	<0.001
		BMI	3.40 (1.50)	-0.38 –7.30	0.076
t4	0.110	Syntax Score	-1.88 (0.68)	-3.23 – 0.56	0.007
		BMI	3.71 (1.85)	0.013 –7.40	0.049
t5	0.158	Syntax Score	-2.52 (0.69)	-3.91 – -1.12	0.001
		BMI	3.62 (1.91)	-0.178 –7.42	0.062
t6	0.116	Syntax Score	-2.06 (0.69)	-3.43 –0.68	0.004
		BMI	3.39 (1.88)	-0.35 – 7.14	0.075
CPB group PON1					
t1	0.202	BMI	9.44 (2.83)	3.72-15.16	0.002
t2	0.266	BMI	7.13 (2.21)	2.66-11.61	0.003
		Age	-1.86 (0.95)	-3.78 –0.062	0.057
t3	0.153	BMI	4.97 (1.73)	1.47-8.46	0.007
t4	0.252	BMI	7.55 (1.99)	3.54 – 11.57	<0.001
t5	0.283	BMI	8.03 (1.93)	4.07-11.99	<0.001
t6	0.288	BMI	6.74 (1.68)	3.34-10.15	<0.001
		Hyperlipidemia	-23.5 (13.7)	-51.2 – -4.34	0.095
OPCAB group PON1					
t1	0.277	Hypertension	-58.8 (31.6)	-123.2–5.61	0.072
		Peripheral arterial disease	-67.6 (23.7)	-116.0– -19.3	0.008
		Smoking	-55.5 (25.1)	-106.6– -4.3	0.034
t2	0.136	Peripheral arterial disease	-57.3 (22.8)	-103.6– -11.0	0.017
t3	0.292	Peripheral arterial disease	-48.5 (20.4)	-90.2– -6.8	0.024
		Age	-3.11 (1.1)	-5.3– -0.897	0.007
t4	0.027	Peripheral arterial disease	-28.5 (20.4)	-70.0-13.1	0.172
t5	0.131	Peripheral arterial disease	-48.7 (21.6)	-92.6– -4.7	0.031
		Hypertension	-49.5 (28.6)	-107.8 – -8.8	0.093
t6	0.035	Peripheral arterial disease	-34.8 (23.3)	-82.2 – 12.5	0.144

Legend: Unstandardized β coefficients (SE), 95% Confidence Interval and P values for the parameters in the best-fit model for the association of several parameters with PON1 activity, backward selection. PON1, paraoxonase 1; SYNTAX Score, synergy between percutaneous coronary intervention with taxus and cardiac surgery score; BMI, body mass index; CPB, cardiopulmonary bypass; OPCAB, off-pump coronary artery bypass.

results in the formation of gaseous carbon-hydrogen species, which as volatile substances are exhaled almost immediately upon formation. Cristescu et al[32] showed that CPB conditions led to higher increases in exhaled gas than with the OPCAB procedure, but within a shorter period of time, according to procedural specificity. CPB caused more peaks in ethylene evolution than OPCAB, i.e., more aspects of the CPB procedures can lead to lipid peroxidation compared with procedures in OPCAB surgery[32]. Thus, our results are in line with those presented in their study[32] regarding higher OS and reduced antioxidative protection seen in CPB patients.

AOPP is a measure of oxidized proteins, mainly albumin[33]. Albumin concentration was found to decrease[34] as the acute phase reaction develops, knowing that it is a negative acute response reac-

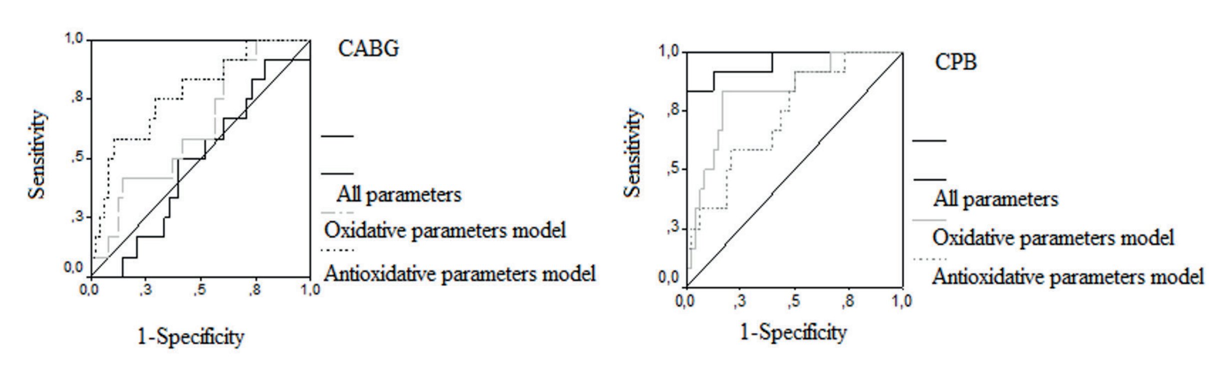


Figure 4. ROC curves of the discriminatory ability of selected parameters regarding postoperative complications in all CABG patients, and in the CPB group.

tant. This could explain the AOPP decrease after the CABG surgery in our study.

As previously reported, it has been established that low PON1 activity is connected with a possible coronary artery disease development[35,36], and we have shown that this is certainly the case for the Serbian population[18].

Results regarding plaque complexity (i.e., through SS value) and surgery modality (i.e., CPB *vs.* OPCAB) revealed the mutual involvement of these two specificities of this current study. Thus, in the present study we demonstrated decreased PON1 activity in CPB patients with advanced stenosis (i.e., intermediate level – 22-30 SS values) compared with OPCAB subjects with the same level of stenosis. These findings are convincing data, since these two-time intervals were the earliest times after the surgery termination (up to 6h). Therefore, we could suppose that these must be most closely connected with each of the two surgery specificities. A similar relationship between PON1 activity and angiographic severity of coronary artery disease was found by Granér et al[37].

Our results indicated also a decrease in PON1 activity together with increase in vessel wall plaque complexity comparing low with moderate SS, and especially and consistently in the CPB group.

Low PON1 activities reported in our research could suggest a more exhausted antioxidative capability in our patients and a possible threat for the development of post-operative complications over a prolonged period, and post-operative complications that were noted during the subsequent patients' stay in hospital. This implies a need for more thorough monitoring of patients with the lowest PON1 activities (e.g., the lower tertile value for our CPB group was 52 U/L and 85 U/L for the OPCAB group at sampling time t2, when the lowest activities were found). These lower tertile values suggest that a huge impairment in this protective enzyme activity occurred. In our previous study we have observed this order of magnitude of low

Table III. Area under the curve, 95% Confidence Interval and Standard error for the selected Models' discriminatory ability regarding postoperative complications presence in CABG group and CPB, respectively.

	AUC (SE)	p	95% Confidence Interval
CABG group			
Model LOOH/AOPP	0.704 (0.066)	0.012	0.574-0.833
Model PON1/tSHG	0.828 (0.050)	<0.001	0.730-0.926
Model All OS parameters	0.599 (0.066)	0.222	0.469-0.728
CPB group			
Model LOOH/AOPP	0.733 (0.077)	0.013	0.582-0.883
Model PON1/tSHG	0.832 (0.065)	0.000	0.703-0.960
Model All OS parameters	0.957 (0.034)	0.000	0.890-1.023

Legend: AUC, area under the curve; CABG, coronary artery bypass grafting; LOOH, lipid hydroperoxides; AOPP, advanced oxidatiom protein product; PON1, paraoxonase 1; tSHG, total sulfhydril group; OS, oxidative stress.

PON1 values in a group of acute ischemic stroke patients, immediately after hospital admission[38].

The SS value was also significantly and inversely correlated with PON1 activity at the beginning, as well as during the early postoperative hours after surgery. This correlation was present 24 h post-operation (t4) but was not present later, probably because of the activation of other homeostatic factors which could influence PON1 activity and/or its polymorphisms. Moreover, a relationship between SS and other OS parameters at some sampling occasions (i.e., positive correlations with LOOH and AOPP and negative with tSHG) was shown. The direct correlation between OS markers (i.e., AOPP and LOOH) with preoperative SS values and inverse correlation of PON1 and tSHG with the same measure of blood vessel stenosis could clearly imply a general connection between atherosclerotic plaque severity and redox disbalance.

Although the frequency of postoperative complications in cardiac surgery have been substantially reduced during the past decade, the deleterious clinical status of patients, reflected as surgery-related disturbances, is still remained the main problem in this area, and the general cause of mortality in coronary artery disease patients[39]. Out of 107 CABG patients, 15 developed postoperative complications (i.e., 12 in the CPB group and 3 in the OPCAB group) and the most important complications were: pleural effusion, leg wound infection, shallow sternal wound infection and pulmonary thromboembolism.

Finally, ROC analysis enabled us to estimate the clinical reliability of OS status markers in predicting the development of postoperative complications. Construction of logistic regression models showed that for all CABG patients, the Model 2 ROC curve, integrating both antioxidative parameters and all their sampling occasions, had very good discriminatory capability (AUC=0.828, $p<0.001$)[28]. In the CPB group alone, the model with the best clinical accuracy was Model 3, with all OS parameters included (excellent accuracy, i.e., AUC=0.957, $p<0.001$).

Several limitations[17,40] of this investigation needs to be acknowledged. We were not able to provide data for HDL particles which are carriers for PON1. HDL particles differ in size, density, structure, and metabolic function. Namely, chronic inflammatory state such as coronary artery disease may induce major changes in HDL function and structure. This condition may further compromise HDL's atheroprotective role, which can be, at least in part, related to changes in PON1 and loss of its antioxidant capability and might affect the results of the current study[17]. Additionally, this was a single-center study, and a relatively small number of patients were included. Thus, multicentric studies with larger number of patients are needed to confirm our results.

Conclusions

The significant decrease in PON1 during the early post-operative phases were related to the atherosclerosis status of patients estimated through the SS as a quantitative measure of coronary artery stenosis severity and complexity. This relationship was more convincing in CPB, compared with OPCAB patients, having on the one hand higher SS levels, and more complicated surgery conditions on the other. Integrated models of OS status parameters have the capability to predict the development of postoperative complications, which suggests an extra need for further development and implementation of OS biomarkers in different fields of clinical practice. This could be the case for cardiac surgery area that at the end of the day could substantially influence patients' post-surgery outcome.

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Conflict of Interests

All Authors declare no conflicts of interest.

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