

ORIGINAL RESEARCH

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Aortic cross - clamp duration in cardiopulmonary bypass & oxidative stress relationship**Zinet Asuman Arslan Onuk***Antalya Training and Research Hospital, University of Health Science, Department of Anesthesiology, Antalya, Turkey*

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The aim of this study was to determine whether there is a direct correlation between the aortic cross-clamp (ACC) duration and oxidative stress marker levels in systemic blood of patients undergoing CPB (cardiopulmonary bypass). We have evaluated the changes in oxidant-antioxidant balance and its relation to ACC time by measuring PON1, ARE, TOS and TAS. The ACC duration mean of 70 patients (43 males, 27 females) to whom CPB was made was 37 minutes. We divided the patients into two groups since their ACC duration was below and above 37 minutes. The HDL (high-density lipoprotein) and levels of TAS, TOS, PON1 and ARE; the oxidative stress markers, were analyzed by taking blood from the patients in the first hour before the pump and after the pump. The levels of oxidative stress markers, PON1, ARE, TOS and TAS were MEASURED within 1 hour before the pump and after the pump. While the serum TOS levels were 4.59 ± 5.32 as preoperative and 4.01 ± 4.34 as postoperative in Group I (ACC over 37 minutes), they were found 4.28 ± 5.54 as preoperative and 2.02 ± 2.57 as postoperative in Group II and determined as a statistically significant decrease ($p < 0.05$, $p = 0.034$). A significant difference was statistically found in the preoperative and postoperative TAS and TOS values' comparison. A postoperative significant reduction was observed for the TOS values in both Group I and Group II ($p = 0.034$). It is thought that the factors will be able to affect the oxidative stress differently from the ACC duration in the CPB based upon our study's results. Further controlled studies are needed on this topic.

Keywords: Cardiopulmonary bypass, oxidative stress, aortic cross-clamp**Introduction**

The myocardial tissue significantly increases subjected to the oxidative stress in the operations, in which the cardiopulmonary bypass (CPB) was used. The primary resources of oxidative stress occurred in these operations are thought to be ischemia and perfusion of the extracorporeal circulation and myocardial tissue.

Oxidative stress is an oxidant-antioxidant imbalance status, due to oxidants which exceed the antioxidant capacity. CPB is a part of cardiac surgery that has been associated with harmful effects in several organs [1,2]. Numerous studies describing the nature of oxidant and antioxidant status and the time course of their formation during CPB were published [3,4].

During cardiac surgery aorta cross-clamping and cardioplegic cardiac arrest induce global ischaemia, so cardiac surgery can be considered as human model of controlled ischaemia similar to this occurring in myocardial infarction [5,6]. Aortic cross-clamp

(ACC) manipulation is the most attributive resource of oxidative stress secondary to ischemia-reperfusion damage [7]. Increased levels of oxidative stress are associated with inflammatory changes, such as lipid peroxidation, modification of proteins, activation of complement cascades, excessive reactive oxygen radicals, and expression of adhesion molecules [8].

Serum Paraoxonase (PON) E.C.3.1.8.1 is an arylesterase synthesized in the liver and is a HDL associated enzyme which is responsible for the antioxidant properties of HDL [9]. 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 and can reduce oxidative stress [10].

Contribution of the various mechanisms on the oxidant-antioxidant balance during on-pump coronary artery bypass grafting has not been fully evaluated yet [11,12].

The aim of this study was to determine whether there is a direct correlation between the aortic cross clamp duration and oxidative stress marker levels in systemic blood of patients undergoing CPB.

We have evaluated the changes in oxidant-antioxidant balance and

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its relation to ACC time by measuring PON1, ARE, TOS and TAS.

The HDL (high-density lipoprotein) and levels of TAS, TOS, PON1 and ARE; the oxidative stress markers, were measured by taking blood from the patients in the first hour before the pump and after the pump.

We compared the serum TAS (total antioxidative stress), TOS (total oxidative stress), PON1 and ARE levels and researched their changes on the oxidative stress for the groups separated in accordance with aortic cross-clamp durations of the patients, who underwent open-heart surgery by using the cardiopulmonary bypass.

Material and Methods

This study was performed in University of Health Science, Antalya Training and Research Hospital, Department of Anesthesiology.

The ACC duration mean of 70 patients (43 males, 27 females) to whom CPB was made in our hospital was 37 minutes. We divided the patients into two groups since their ACC duration was below and above 37 minutes. The HDL (high-density lipoprotein) and levels of TAS, TOS, PON1 and ARE; the oxidative stress markers, were analyzed by taking blood from the patients in the first hour before the pump and after the pump.

Those having chronic kidney failure, neoplastic disease, autoimmune disease, liver disease, and antioxidant use were not included in the study.

The premedication was made by 0.1 mg/kg midazolam to each group before the anesthesia induction. The radial artery cannulation was made for the hemodynamic follow-up. All cases were had breathed by 100% O₂ during the anesthesia induction and intubated by 5-7 mg/kg thiopental, 5 mcg/kg fentanyl and 0.6 mg/kg rocuronium bromide. In the maintenance, 5-6% desflurane, 50% O₂ + 50% dry air, and rocuronium bromide and fentanyl were used. The rectal body temperature and urination were followed up during the surgery by applying 3-lumen central catheter from the right internal jugular vein.

After systemic administration of heparin (300 UI/kg body weight), CPB was initiated in a standard manner with cannulas placed in the ascending aorta and right atrium. Moderate hypothermia was used (32–33°C), and local hypothermia for myocardial protection was achieved by antegrade infusion of a cool cardioplegic solution (Cardi-Braun), administered intermittently (every 25–30 minutes average) during clamping. After removing the cross clamp, protamine was given for heparin reversal.

The ACC duration was above 37 minutes in 30 patients in Group I and 11 of the patients were coronary artery patients (3 grafts to 8 patients, 4 grafts to 3 patients), 15 of them were valve patients (mitral valve to 8 patients, aorta valve to 7 patients) and 4 of them were valve+coronary artery patients. The ACC duration was below 37 minutes in Group II and there were 40 patients. 27 of the patients in this group were coronary artery patients (4 grafts to 3 patients, 3 grafts to 18 patients and 2 grafts to 6 patients) and 13 of them were patients to whom valve replacement was made (10 mitral valves; 3 aortic valves) (Table 1).

The patients' body mass index (BMI), left ventricular ejection fraction (LVEF), pump duration, surgery, and anesthesia durations were recorded. The patients' smoking habits and associated diseases were also recorded.

The blood samples were taken just before and after the cardiopulmonary by-pass. Samples were separated from the cells for 10 minutes by a centrifuge running at 3000 rounds per minute (rpm), then kept at -80 °C and used to analyze the TOS, TAS, PON1 and ARE.

The statistical analysis was performed at the statistics department of Akdeniz University, Wilcoxon paired test was used to compare mean values at each stage of the experiment. The Mann Whitney test was used to compare the differences of TAS, TOS, PON1 and ARE activity between groups according to the clinical features. P values less than 0.05 were considered significant.

Results

In our study, we researched the cross-clamp duration length's influence on the oxidative stress for the patients underwent open-heart surgery and analyzed the oxidative stress indicators' levels including serum TAS, TOS, PON1 and ARE.

The male/female ratio of 30 patients included in the study in Group I was 16/14 (53% of them were female, 46% of them male), male/female ratio of 40 patients included in the study in Group II was 27/13 (67% of them were female, 32% of them male) and age means of the patients found in Group I and Group II were found as 59.10±14.25 and 59.10±14.2, respectively (p=0.42).

The diabetes mellitus, one of the associated diseases, was found in 7 patients in Group I (n=30) and in 12 patients in Group II (n=40) and hypertension was found in 21 patients in Group I and in 27 patients in Group II. While there was a smoking history in 10 of 30 patients in Group I, there was in 14 of 40 patients in Group II. While the LVEF values were 57.27±9.12 in Group I, it was 58.60±8.07 in Group II. There was not statistically any significant difference between the intergroup LVEFs (p=0.52). There was a statistically significant difference when both groups' pump durations were compared (p=0.001). The pump durations were found as 74.83±15.51 in Group I and as 54.45±16.60 in Group II, respectively (Table 1).

When the preoperative serum PON1 levels (128.70±60.19 in Group I and 114.30±85.24 in Group II) in each group were compared by the postoperative serum PON1 levels (118.55±44.33 in Group I and 109.65±61.48 in Group II) they were not statistically significant (p>0.05, p=0.18, p=0.50, Table2).

When the preoperative serum ARE levels (229.25±71.69 in Group I and 218.07±66.87 in Group II) in the groups were compared by the postoperative serum ARE levels (222.80±44.05 in Group I and 207.71±49.1 in Group II) they were not statistically significant (p>0.05, p= 0.42, p=0.20, Table 2).

While the serum TAS levels decreased to 2.01±0.27 preoperatively and 1.97±0.22 postoperatively in Group I (ACC over 37 minutes) and were at the value of 2.01±0.25 preoperatively in Group II, they were postoperatively found as 2.12±0.35 and statistically

evaluated as significant ($p<0.05$, $p=0.042$, Table 2, Figure 2).

While the serum TOS levels decreased to 4.59 ± 5.32 preoperatively and 4.01 ± 4.34 postoperatively in Group I (ACC over 37 minutes)

and were at the value of 4.28 ± 5.54 preoperatively in Group II, they were postoperatively found as 2.02 ± 2.57 and statistically evaluated as significant ($p<0.05$, $p=0.034$, Table 2, Figure 1).

Table 1. Demographic data and perioperative variables of groups

Characteristics	Group I(n=30) (ACC over 37 minutes)	Group II(n=40) (ACC under 37 minutes)	p
Age (years)	59.10 $\pm$ 14.25	59.58 $\pm$ 11.96	0.42
Sex (M/F)	16/14	27/13	-
BMI (kg/m ²)	26.87 $\pm$ 4.15	27.75 $\pm$ 4.99	0.44
Diabetes mellitus (n)	7	12	
Hypertension (n)	21	27	
Cigarette smoking (n)	10	14	
LVEF(%)	57.27 $\pm$ 9.12	58.60 $\pm$ 8.07	0.52
Pump duration	74.83 $\pm$ 15.51	54.45 $\pm$ 16.60	0.001*
Anesthesia time	201.00 $\pm$ 41.18	194.25 $\pm$ 41.15	0.49
Surgery time	174.17 $\pm$ 37.49	164.50 $\pm$ 34.93	0.36
Aortic valve replacement (n)	7	3	
Mitral valve replacement (n)	8	10	
Valve replacement with coronary graft	4	-	
CABG (n)	11	27	
Number of grafts per patients			
2 graft	-	6	
3 graft	8	18	
4 graft	3	3	

ACC: Aortic Crossclamp, BMI: Body Mass Index, LVEF: Left ventricular ejection fraction, CABG: Coronary Artery Bypass Graft * $P<0.05$ significantly

Table 2. PON1, HDL, ARE, TAS and TOS values of groups.

		GROUP 1	GROUP 2	p
PON1	preoperative	128.70 $\pm$ 60.19	114.30 $\pm$ 85.24	0.18
	postoperative	118.55 $\pm$ 44.33	109.65 $\pm$ 61.48	0.50
HDL	preoperative	35.77 $\pm$ 10.61	35.56 $\pm$ 11.35	0.93
	postoperative	34.20 $\pm$ 8.91	36.46 $\pm$ 10.08	0.32
ARE	preoperative	229.25 $\pm$ 71.69	218.07 $\pm$ 66.87	0.42
	postoperative	222.80 $\pm$ 44.05	207.71 $\pm$ 49.1	0.20
TAS	preoperative	2.01 $\pm$ 0.27	2.01 $\pm$ 0.25	0.51
	postoperative	1.97 $\pm$ 0.22	2.12 $\pm$ 0.35	0.042*
TOS	preoperative	4.59 $\pm$ 5.32	4.28 $\pm$ 5.54	0.46
	postoperative	4.01 $\pm$ 4.34	2.02 $\pm$ 2.57	0.034*

Values expressed as mean $\pm$ SD.

PON1: Paraoxonase 1, HDL: High density lipoprotein, ARE: Arylesterase

TAS: Total Antioxidative Stress, TOS: Total Oxidative Stress

* $P<0.05$ significantly

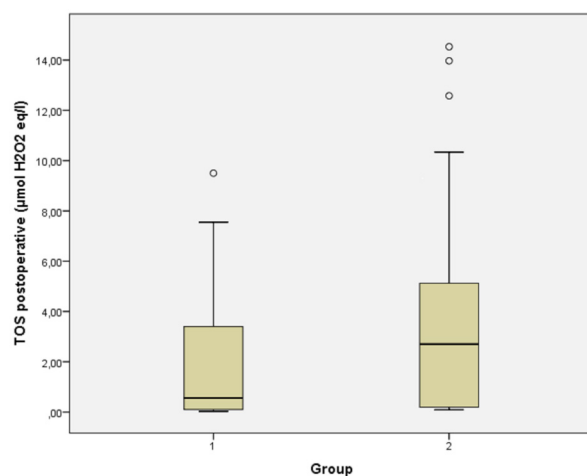


Figure 1. Postoperative TOS levels in in group I (n=30)and group II (n=40)
* $p<0.05$, $p=0.034$

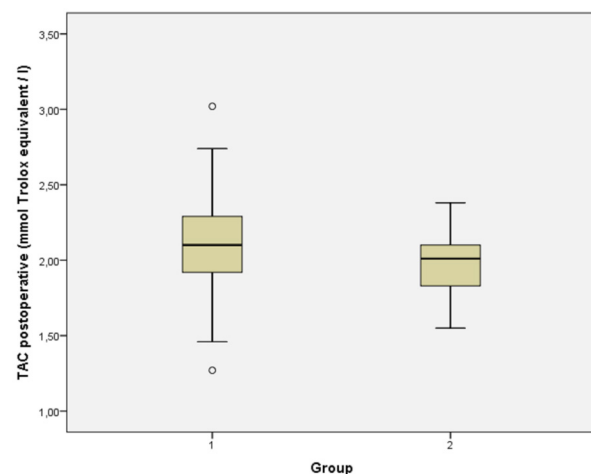


Figure 2. Postoperative TAS levels in in group I (n=30)and group II (n=40)
* $p<0.05$, $p=0.042$

Discussion

The free radicals are controlled by antioxidants levels and excessive free radical formation and insufficient removal by antioxidants leads to oxidative stress on heart [13].

Ischemic period associated with oxidative stress in open heart surgery patients. Authors (Garcis-de-la-Asuncion et al.) reported that ACC time was positive correlated with total peroxide, 8-isoprostane and nitrites/nitrates levels in patients undergoing open heart surgery patients [14,15]. As a reference, they took the median value of the aortic cross-clamp duration (50 minutes) from all patients (n = 30). However, they could not find an intergroup difference in 30 patients who were separated into two groups (coronary surgery and valve surgery).

The groups were classified as those being shorter and being longer than 37 minutes since the ACC duration was meanly observed as 37 minutes in our study (Group I, n=30; Group II, n=40). We could not find a positive correlation between the ACC durations and TOS, TAS, PON1 and ARE levels in the patients who underwent cardiopulmonary bypass surgery.

Some studies have measured other oxidative stress markers, such as TBARS, malondialdehyde, oxidized glutathione, protein carbonyls [16,17]. We measured the oxidative stress markers such as PON1, ARE, TAS and TOS in the blood before and after the pump within this study.

Ferrari et al. reported a significant and sustained increase in OS in 10 patients undergoing ONCABG with a mean ACC duration of 55.2 minutes, while a mild and temporary increase in oxidative stress in 10 patients undergoing ONCABG (on-pump coronary artery bypass graft) with a mean ACC duration of 25.2 minutes [18].

Nowicki et al. also reported the absence of a significant oxidative damage in the myocardial biopsy specimens of 8 patients undergoing ONCABG with a mean ACC duration of 29.5 minutes [19].

In our study, while the ACC duration was 27.48 ± 5.96 in 30 patients to whom CPB was made in Group I, it was found as 50.20 ± 13.31 in 40 patients in Group II.

The Diabetes Mellitus, hypertension and smoking history also affect oxidative stress. There was diabetes mellitus, one of the associated diseases, in 7 patients in Group I (n=30) and in 12 patients in Group II (n=40) for the patients that we included in our study. The hypertension was found in 21 patients in Group I and in 27 patients in Group II. While there was smoking history in 10 of 30 patients in Group I, there were 14 of 40 patients in Group II. There was not statistically any significance between the groups.

Previous studies in patients have demonstrated that cardiac surgery with CPB is associated with ischemia-reperfusion consecutive to cross-clamping [22-25].

In our study, our patients were the patients, whose on-pump CPB was applied due to the CABG, valve (mitral and aortic) and valve replacement with coronary graft operations. The pump times were found as 74.83 ± 15.51 (Group I) and 54.45 ± 16.60 (Group II), respectively. This difference was statistically found significant (p: 0.001, Table 1) We think that the differences seen in TAS and TOS values do have a relationship with the pump.

These patients may suffer systemic oxidative stress with an increase of multiple oxidative stress markers and a decrease in antioxidant reserves that can result in increased postoperative morbidity and prolonged hospital stay [26,27].

The TAS, TOS, PON1 and ARE levels were also evaluated in our study in order to determine the cardiopulmonary bypass application's relationship with the oxidative stress. A significant difference was statistically found in the preoperative and postoperative TAS and TOS values' comparison. A postoperative significant reduction was observed in the TOS values in both

Group I and Group II (p=0.034, Table 2, Figure 1). A postoperative reduction also revealed similarly in the PON1 and ARE, however, the difference is not significant. On the other hand, not any significant difference was statistically found in the intergroup oxidative stress markers.

Conclusion

In conclusion, we believe that the results of this study contribute to a better understanding of the pathophysiology of reperfusion of the human heart. This study suggests that considerable oxidative stress occurs early during conventional cardiac surgery with CPB. The degree of oxidative stress in the myocardium and in other tissues depends on the duration of the ischemic period.

It is thought that the factors will be able to affect the oxidative stress differently from the ACC duration in the CPB based upon our study's results. Further studies, in which the different parameters are evaluated, are needed on this topic.

New strategies need to be proven to reduce the systemic oxidative stress and to improve patient outcomes after CPB, which will require large-multicenter studies

Financial Disclosure

All authors declare no financial support.

Ethical approval

The study was approved by Ethics Committee of Antalya Education and Research Hospital.

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