

Original Article

Investigating the Effects of Two Different Pump Heads (Centrifugal vs. Roller Pump) on Hematological and Immunological Mechanisms

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ABSTRACT

Background and Aim: Technological developments and enhancement of knowledge level enable heart surgery with low mortality rates in most centers. On the other hand, increased systemic inflammatory response against cardiopulmonary bypass (CPB) plays a critical role in the development of postoperative complications. We aimed to compare the effects of centrifugal pump where it is claimed that blood is exposed to minimal trauma and roller pump techniques on inflammatory response and oxidant status during CPB. **Materials and Methods:** A total of 40 patients, who had coronary artery disease and underwent coronary artery bypass graft (CABG) surgery using either roller or centrifugal pump between June 2012 and June 2013 were enrolled in this study. Patients over 40 years old and without any known immunologic, infectious, or inflammatory incidents and hematological problems for the past 6 months were included in the study. Two study groups (Group R: roller pump group and Group C: centrifugal pump group) were created. During CABG surgery tumor necrosis factor (TNF) alpha, interleukin (IL)-6, IL-8, superoxide dismutase (SOD), catalase (CAT), and nitric oxide levels were measured before and after CPB. **Results:** TNF alpha, IL-6, and IL-8 levels measured before and after CPB were found to be similar between groups. SOD, CAT and Nitric oxide levels were also similar between groups. After the CPB period, glutathione peroxidase enzyme activities in Group R measured after CPB were significantly lower than those measured in Group C. The platelet-activating factor (PAF) levels before CPB usage period were same in both groups, where PAF levels after CPB were found to be significantly higher in roller pump group than centrifugal pump group. At inter-group comparisons, the levels of PAF were same at each group before and after CPB. **Conclusion:** The study findings indicate that usage of the centrifugal pump does not have a clear superiority in terms of the effects on inflammatory response and oxidant status during CPB when compared to roller pump. Nevertheless, we believe that our results should be supported by further clinical and experimental studies.

KEYWORDS: *Cardiopulmonary bypass, centrifugal pump, inflammation, oxidant status, roller pump*

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INTRODUCTION

Cardiac surgery is being performed with low mortality rates in many surgical centers. However, postoperative morbidity is commonly seen in relation with various risk factors and complications, mainly based on noncardiac etiology, such as arrhythmia, the ventricular dysfunction that needs inotropic support,

infection, gastrointestinal dysfunction, acute lung injury, and renal failure.^[1,2]

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Increased systemic inflammatory response to cardiopulmonary bypass (CPB) plays an important role during the development of postoperative complications. The inflammatory response may lead different clinical outcomes ranging between mild complications that do not require Intensive Care Unit (ICU) admission, prolonged hospital stay and increased costs and more severe complications such as multiple organ dysfunctions and death.^[1-3]

The aim of CPB pumps is to send gravitational blood pooling in vena cava to the oxygenator and subsequently to the arterial system. While performing this process, the pump maintains a certain pressure and flow velocity. At the present day, there are two commonly used types of pumps; 1 – centrifugal and 2 – roller pumps.^[4]

Pumps that work on volume replacement principle have been used since the beginning of CPB procedures, and roller pumps are the example of this group of pumps nowadays. On the other hand, centrifugal pumps were developed in 1976, and several advantages of these pumps on roller pumps have been reported. These pumps are preferred, especially in heart surgery procedures that expected with increased length of surgery.^[5]

In this study, we aimed to compare the effects of a centrifugal pump and roller pump on immune system functions and hemostatic system during CPB surgery.

MATERIALS AND METHODS

After obtaining ethical committee approval from Clinical Investigations Ethical Committee of Zekai Tahir Burak Women Health and Training Research Hospital and written consent from all patients, we included forty patients undergoing on-pump coronary artery bypass surgery by the same surgical team between June 2012 and June 2013. Patients aged over 40 years, without any immunological, infectious, or inflammatory diseases history in the past 6 months and without any known hematological disease were enrolled in this study.

Premedication was made with Diazepam 10 mg orally one night before surgery and 5 mg morphine subcutaneously at the operation morning. Following routine monitorization (electrocardiogram, oxygen saturation), peripheral venous cannulation was made. To monitor invasive blood pressure, radial artery cannulation was performed (B-Cat 2 22G, Bıçakçılar Medical Devices Company). Standard anesthesia protocol was carried out. Monitorization of body temperature was made using a nasopharyngeal probe. Venous blood samples were drawn through 18G (Secalon T[®], BD Medical, Singapore) catheter placed in a right internal jugular vein. Exact localization of tip of the catheter was confirmed with X-ray after the operation.

Following skin antiseptis, surgical site was covered with sterile drapes. After making skin and subcutaneous incisions, median sternotomy was performed, and pericardium was opened. After preparing vascular grafts, anticoagulation was made with heparin at a dose of 4 mg/kg. Priming fluid was prepared using 1 gr cefazolin plus 50 mg heparin added into 1500 ml of lactated ringer. ACT levels were maintained above 400 s to achieve proper anticoagulation. After performing standard aorta-atrial cannulation, CPB was started. In Group R, a roller pump (Stöckert SIII, Sorin Group Deutschland GMBH, München) was used where a centrifugal pump was used in Group C. Furthermore, a 25 µm arterial filter (Jostra, Anaheim, CA), an adult membrane oxygenator (Jostra, Anaheim, CA) and a hard-shell venous cardiomy reservoir (Jostra, Anaheim, CA) were used.

Total pump blood flow was adjusted at 2.4 L/m²/min and hemodilution was achieved by decreasing hematocrit levels to 26%. The pressure of pump stream was adjusted at 60–70 mmHg during CPB. Until withdrawing the cannulas, ACT (Hemochron[®] Jr Signature Plus Whole Blood Microcoagulation System, Tx, USA) measurement was done with 30 min intervals. Additional heparin administration was used when needed.

Cardioplegia solution was prepared using 40 mEq of KCl, 20 mEq of NaHCO₃, and 0.5 ml of Ca Gluconate (0.9%) in 500 ml isotonic saline. Following aortic cross-clamping antegrade hypothermic (+8°C) blood cardioplegia solution (15 ml/kg) was infused. Cardioplegia infusion was repeated at 5 ml/kg dose at every 20 min intervals. Minimal body temperature measured through nasopharyngeal probe was 30 C.

After performing distal anastomosis, cross-clamp was removed, and heart has started beating. Proximal anastomosis was made during aortic partial clamping. After achieving sufficient blood pressure and heart rate, CPB was discontinued. Following decannulation and bleeding control, thoracic and mediastinal drains were inserted, and sternum and skin incisions were closed, and the patients were transferred to the ICU.

Patients were followed in ICU at least 1 night, after weaning and extubation patients were transferred to ward. Patients with a stable hemodynamic status, sufficient mobilization, and completely improved consciousness level were discharged from the hospital. Mean length of hospital stay was 6–7 days.

Serum samples and biochemical tests

Blood samples (10 ml) were drawn through jugular venous catheter before and after CPB. Superoxide dismutase (SOD) (Cayman Chemical [USA, LotNo: 0439125], Catalase [CAT]) (Cayman Chemical [USA,

Lot no: 0438590), nitric oxide (NO) (Cayman Chemical [USA, Lot No: 0442044]), tumor necrosis factor (TNF)-alpha (Diasource, Belgium, Lot No: 121902/A), interleukin (IL)-6 ([Diasource, Belgium, LotNo: 124802]), IL-8 ([Diasource, Belgium, Lot NO: 124501/A]), platelet activating factor (PAF) (Eastbiopharm, Chinese, Lot No: 20130319) (TNF-alfa, IL-6, IL-8 levels were measured using ELISA) and glutathione peroxidase (GPx) (Cayman Chemical [USA, Lot No: 0442309]) levels were measured in blood samples.

Blood samples were centrifuged at 3500/min for 10 min and were stored at - 80°C until study day. After collecting samples from all patients, measurements were performed on the same study day. Repeated cycles of freezing and melting were avoided. All measurements were performed at Central Biochemical Laboratory in Gazi University Faculty of Medicine.

Statistical analysis

SPSS version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were expressed as the mean ± standard deviation. A value of $P < 0.05$ was considered as statistically significant.

Kolmogorov–Smirnov test was used to determine normal distribution of data. Between-group differences in normally distributed variables Student’s *t*-test were used.

Data regarding two different time points (before and after CPB) within the groups were evaluated using paired *t*-test.

Variables such as gender and concomitant disease status of patients were evaluated using Chi-square or Fisher’s exact Chi-square tests.

RESULTS

Demographical data of patients – except for patients’ weight – were similar in two study groups [Table 1].

Duration of CPB and cross-clamping and number of grafts were found to be similar in two groups [Table 2].

Before and after CPB serum NO and CAT enzyme activities were similar between the groups [Table 3]. However, in both groups, serum NO and CAT enzyme activities measured at after CPB were significantly higher than those measured before CPB in comparisons within the groups [Table 3].

Serum SOD enzyme activities before and after CPB were similar in the groups [Table 3]. However, serum SOD enzyme activities in two study groups measured after CPB were significantly lower than those measured before CPB [Table 3].

Serum GPx enzyme activities measured before CPB were found to be similar between the groups; however,

Table 1: Demographical data of patients in study groups (mean±standard deviation, n)

	Group R (n=20)	Group C (n=20)	P
Age (year)	61.70±9.65	61.40±9.15	0.920
Weight (kg)	73.20±9.18	83.20±12.20*	0.006
Height (cm)	166.75±5.07	171.10±8.99	0.069
Gender (male/female)	16/4	16/4	-

* $P < 0.05$ (compared with Group R)

Table 2: Duration of pump, cross clamp, and number of vessels bypassed (mean±standard deviation, n)

	Group R (n=20)	Group C (n=20)	P
Duration of pump (min)	92.55±30.73	95.70±33.36	0.758
Duration of cross clamp (min)	52.75±15.27	54.00±19.82	0.824
Number of vessels bypassed (n)	2.95±1.05	2.95±1.05	1.000

Table 3: Parameters referring oxidant status of patients in groups (mean±standard deviation)

	Group R (n=20)	Group C (n=20)	P
CAT (nmol/min/ml)			
Pb	21.43±21.90	26.17±16.86	0.448
Pa	78.08±5.96 ⁺	76.89±9.11 ⁺	0.626
NO (U/m)			
Pb	12.86±8.40	12.32±6.43	0.819
Pa	25.25±13.30 ⁺	22.76±11.64 ⁺	0.532
SOD (U/ml)			
Pb	7.20±2.66	7.11±3.28	0.920
Pa	5.82±1.87 ⁺	5.30±2.53 ⁺	0.465
PAF (ng/ml)			
Pb	16.99±14.88	10.37±6.89	0.082
Pa	15.59±10.93	8.95±4.46*	0.019
GPX (nmol/min/ml)			
Pb	46.23±14.99	54.60±20.07	0.149
Pa	42.38±15.69 ⁺	54.57±21.65*	0.049

* $P < 0.05$ (when compared to Group R); ⁺ $P < 0.05$ (when compared to data achieved Pb). Pb=Before pump; Pa=After pump; SOD=Superoxide dismutase; CAT=Catalase; NO=Nitric oxide; PAF=Platelet-activating factor; GPX=Glutathione peroxidase

GPx enzyme activities in Group R measured after CPB were significantly lower than those measured in Group C [Table 3]. When within-group comparisons were performed, in Group R, GPx enzyme activities before CPB was significantly lower than those measured after CPB [Table 3].

Serum PAF enzyme activities measured before CPB were found to be similar in both groups. However, PAF enzyme levels after CPB in Group R were significantly higher than those measured in Group C [Table 3]. When within-group comparisons were performed, no significant differences were found in serum PAF enzyme levels before and after CPB in both of study groups [Table 3].

Table 4: Serum tumor necrosis factor-alpha, interleukin-6, and interleukin-8 levels of patients (mean±standard deviation)

	Group R (n=20)	Group C (n=20)	P
TNF-alpha (pg/ml)			
Pb	3.62±3.62	6.42±7.48	0.140
Pa	126.32±132.83 ⁺	86.35±115.68 ⁺	0.317
IL-6 (pg/ml)			
Pb	89.65±164.14	57.30±55.09	0.409
Pa	1481.30±1083.27 ⁺	1557.10±1294.00 ⁺	0.842
IL-8 (pg/ml)			
Pb	83.95±200.44	20.90±12.65	0.176
Pa	1323.70±1196.84 ⁺	937.45±1010.78 ⁺	0.277

⁺P<0.05 (when compared to results achieved in samples drawn Pb). Pb=Before pump; Pa=After pump; TNF=Tumor necrosis factor; IL=Interleukin

Serum TNF alpha, IL-6 and IL-8 levels before and after CPB were similar in both groups [Table 4]. However when comparisons were performed within the groups, serum TNF alpha, IL-6 and IL-8 levels measured after CPB were significantly higher than those measured before CPB in both groups [Table 4].

DISCUSSION

CPB is the essential element of open heart surgery; however, it is also a well-known cause of unwanted inflammatory response.^[6] This unwanted cascade of inflammatory response either results from used materials (contact of blood to nonphysiological surfaces) or other factors independent from used materials (surgical trauma, ischemic injury of organs, changes in body temperature, endotoxin release, etc.). There are various mechanisms that trigger inflammatory response during CPB. These mechanisms are a complement and leukocyte activation, cytokine release, production of free oxygen radicals, arachidonic acid metabolites, platelet activating factor, nitric oxide, and endothelin overexpression.^[7]

In this study, we aimed to investigate whether centrifugal pump technique is superior than roller pump technique in terms of oxidant status and preventing an inflammatory response. Our results indicate that there is no significant difference between TNF-alpha, IL-6, IL-8, SOD, CAT, and NO levels of patients in two study groups before and after CPB. However, we found that PAF and GPx levels measured after CPB were significantly different between the groups.

An inflammatory response cascade similar to that seen after ischemia may be established secondary to CPB. Kirklin and Kirklin *et al.*^[6] stated that the inflammatory response that arises secondary to contact of blood with abnormal surfaces is a result of several factors including activation of coagulation cascade, kallikrein, fibrinolysis,

and complement system. Complement activation is the most remarkable and fastest response that evidenced by promptly increased C5a and C3a levels.^[8] Cytokine release is another characteristic feature of the process and begins soon after starting of coronary artery bypass grafting, and the production of IL-6, TNF alpha, IL-1, IL-8 rapidly increases.^[9]

Wei *et al.*^[10] showed increased TNF-alpha, IL-6, IL-8, IL-10 levels after coronary artery bypass graft (CABG) when compared with measured cytokine levels at preanesthesia induction, 5 min after reperfusion, 1st, 4th, and 20th h at postoperatively. Authors concluded that increased systemic pro-inflammatory cytokine levels are closely related to postoperative myocardial dysfunction. In another study, Karube *et al.*^[11] indicated a positive correlation between IL-8 and TNF-alpha release and myocardial ischemia.

Parolari *et al.*^[12] compared TNF-alpha levels of patients undergoing CABG using CPB with roller pump or off-pump coronary artery surgery. They found significant increases in TNF-alpha levels in patients in both groups after protamine administration. Furthermore, TNF-alpha levels were significantly higher in roller pump group than those in the off-pump group.

Recently, Zhao *et al.*^[13] found 10-fold increase in TNF-alpha levels after CPB with roller pump when compared with levels before CPB (15.6 ± 5.7, 157.7 ± 35.0 pg/ml).

Lehmann *et al.*^[14] compared TNF-alpha levels at pre-CPB, during CPB and after CPB time intervals in pigs undergoing CPB either with roller or centrifugal pumps or off-pump technique. They found significant increases in TNF-alpha levels in roller pump groups 1 h after reperfusion when compared with the off-pump group. On the other hand, only mild increases were noted in the centrifugal pump and heparin-coated circuit groups.

Jensen *et al.*^[15] compared TNF-alpha, IL-6, and IL-8 levels in pediatric patients who underwent CPB either with roller pump or centrifugal pump techniques. Even though, authors expected lower cytokine levels in patients treated with heparin-coated centrifugal pump, they found no significant difference between groups in terms of TNF-alpha, IL-6, and IL-8 levels.

Lindholm *et al.*^[16] compared TNF-alpha, IL-6, and IL-8 levels in elderly patients who underwent CPB with either roller or heparin-coated centrifugal pump techniques and reported similar cytokine levels in both study groups.

In this study, we found similar TNF-alpha levels in study groups with two studies cited above. Furthermore, we

noted significant increases in TNF-alpha levels after CPB in both groups.

Parolari *et al.*^[12] showed significant postoperative inflammatory activation independent from used revascularization technique (on-pump or off-pump) and they concluded that the inflammatory response might encounter treatment processes of patients undergoing CPB.

We suppose that similar increases in TNF-alpha levels in both study groups indicate independence of inflammatory pathways from the type of used pump technique in conjunction with Parolari *et al.*^[12]

Hennein *et al.*^[17] showed a positive correlation between high IL-6, IL-8 levels, and local wall contractile dysfunctions. They accepted high postoperative cytokine levels as a risk factor independent from aortic cross-clamping duration.

Morgan *et al.*^[18] compared IL-6 and IL-8 levels in newborn and pediatric patients who underwent CPB through either roller or centrifugal pump techniques. They found higher IL-6 levels in roller pump group only at 2 h after CPB. Cytokine levels were found identical at other time points. They suggested that cytokine release is a multifactorial process and several factors such as surgical trauma and tissue ischemia may be strong stimulants for the process.

Ashraf *et al.*^[19] found increases in IL-6 and IL-8 levels both roller and centrifugal pump groups; however, they could not find any statistically significant differences between these groups. Similar to previous studies we could not find any significant difference in terms of IL-6, IL-8 levels measured before and after CPB. IL-6 and IL-8 levels measured after CPB were significantly higher than those measured before CPB.

Despite many advances in cardiac surgery, various evidence related with myocardial injury during perioperative period including unexpected myocardial damage and cell death, edema, microvascular injury, arrhythmias have been shown. Formation of reactive oxygen species at an early phase of reperfusion may underlie myocardial injury. Reactive oxygen species related to cellular membrane and protein changes are accepted as primary factors for ischemia-reperfusion (I/R) injury.^[20]

Ferreira *et al.*^[21] showed a significant decrease in myocardial antioxidant capacity during first 10 min of myocardial reperfusion period of CABG procedure. Furthermore, they reported a significant decrease in myocardial glutathione load 5–20 min after removal of aortic cross-clamping. The inflammatory response in

CPB is thought to be related to the interaction between blood components and artificial surfaces. Furthermore, I/R injury, endotoxemia, and operative trauma are other suspected factors.^[22,23]

Inal *et al.*^[24,25] reported increased activity of SOD and GSH-Px and decreased CAT activity during CPB. Furthermore, they found unchanged glutathione and GSH-Px levels. These findings were accepted as important signs of oxidative injury.

Islekel *et al.*^[26] reported decreased GPx and glutathione reductase activities and increased SOD activity starting at ischemia period during CPB. Akila *et al.*^[27] compared GPx levels during off-pump and CPB with roller pump techniques. They reported significant decreases in GPx levels in both study groups when compared with preoperative levels however decreases in GPx levels in the roller pump group were more significant.

In our study, GPx levels measured in samples drawn during CPB with roller pump were lower than those measured before CPB. In centrifugal pump group, GPx levels were similar with pre-CPB levels. Lower GPx levels in roller pump group may be a consequence of increased GPx depletion against more reactive oxygen species formation in roller pump technique.

Akila *et al.*^[27] investigated CAT activities in off-pump and roller pump CPB surgery and they found increased CAT activities compared with preanesthesia levels however increases in the roller pump group were significantly higher than those in off-pump group. In addition, they reported that maximum levels of increase in CAT levels were at the 1st h after reperfusion period. The authors concluded that increased CAT levels indicate an activated antioxidant level against free radicals.

Ege *et al.*^[28] compared CAT enzyme activities in patients who underwent CABG using CPB with left internal mammary artery (LIMA) graft or without LIMA graft. In all cases, CPB procedures were performed using roller pump technique. They found decreased CAT enzyme activities in both groups; however, there were no significant differences between the two groups.

We found increased CAT activities in both groups as found in the study conducted by Akila *et al.*^[27] when compared to pre-CPB levels. We suggest that increased CAT enzyme activities after reperfusion phase indicate the activation of antioxidant defense systems to protect cells from free radical-induced injury.

NO is another important mediator of oxidative stress-related to myocardial injury. At low levels, NO exerts cytoprotective features; however, high levels of NO is potentially toxic for the tissues.^[29]

Viaro *et al.*^[30] compared NO levels during roller pump used vs centrifugal pump used CPB procedures and reported similar NO levels at every time points during the study. According to their findings, authors concluded that inflammatory response during CPB surgery may not be related to NO production. In contrast, Schulze *et al.*^[31] compared NO levels during off-pump and conventional CPB methods. They reported lower NO levels in the off-pump group when compared to the on-pump group. A limited number of studies investigating NO levels during CPB procedures and methodological limitations regarding NO measurement and bioavailability may lead conflicting results in the literature.

In this study, we found increased NO activities in both groups as found in the study conducted by Viaro *et al.*^[30] compared with levels measured before anesthesia induction. Furthermore, no significant difference was found between groups in terms of NO measurements at all-time points.

PAF is a phospholipid structured intracellular transporter and has anti-inflammatory and neurotoxic effects.^[32,33] PAF increases intracellular calcium concentration, induces changes in blood-brain barrier, decreases cerebral blood flow and stimulates leukocyte activation in damaged neuronal tissue, and consequently, cerebral damage occurs.^[34,35]

Various studies showed increased PAF and PAF metabolites after CPB.^[36,37] Møller and Steinbrüchel^[38] reported significant increases in PAF-mediated thrombocyte aggregation after off-pump surgery.

In our study, we found similar PAF levels before CPB in two study groups, however, PAF levels measured after CPB were significantly different from each other. PAF levels measured before and after CPB were similar when within-group comparisons were performed.

CONCLUSION

We found similar TNF alpha, IL-6, and IL-8 levels between the roller and centrifugal pump groups after CPB. We suggest that two techniques have identical effects on inflammatory cascades. When we investigate effects of these techniques on oxidative stress, we found similar results in terms of SOD, CAT, and NO. However, GPx activity after CPB was significantly lower in roller pump group and this result may indicate increased consumption of GPx against increased reactive oxygen radical formation during roller pump technique. PAF levels before CPB were similar between groups, however, in roller pump group, we found higher PAF levels after CPB.

In conclusion, centrifugal pump technique may have several advantages over roller pump technique; however

in general review, we could not find any significant difference between the effects of two pump techniques on inflammatory responses and oxidative status during CPB surgery. Relatively shorter mean CPB duration recorded in our study (100 min) may lead such similar results. However, centrifugal pump technique may be superior over roller pump in longer CPB procedures. We suggest that findings of this study have to be supported by future larger-scaled clinical and experimental studies.

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Conflicts of interest

There are no conflicts of interest.

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