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Inflammation Research

Clinical efficacy of leukofiltration on cardiopulmonary bypass related inflammatory response: *Fact or Foe?*

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Abstract. *Objective:* The powerful precept of preoperative risk assessment has been applied to compare the efficacy of leukofiltration techniques for high-risk cohorts with the documentation of broad indicators of systemic inflammation.
Methods: Forty high risk patients were prospectively assigned to four perfusion protocols; the first group (n=10): Polyethyleneoxide (PEO) based heparin bonded extracorporeal circuits (ECC) + Continuous Leukocyte filtration; the second group (n=10): uncoated ECC + leukofiltration; the third group (n=10): PEO based heparin bonded ECC without leukofiltration; and control (n=10). Blood samples were obtained at the following intervals: Baseline (T1), on cardiopulmonary bypass (CPB) (T2), Cross clamp (T3), off CPB (T4), Intensive care unit-24 h (ICU24) (T5), ICU48 (T6).
Results: Tumor Necrosis Factor-alpha levels were significantly lower in Group 1 at T3, T4 ($p<0.05$) vs. control. Procalcitonin levels were significantly lower in Group 1 at T5, T6 ($p<0.05$) vs. control. Creatinine kinase-MB levels in coronary sinus blood demonstrated well preserved myocardium in filtered+coated (Group1) and coated groups (Group3) ($p<0.05$). Matrix metallopeptidase- 9 and D-Dimer levels in filtered+coated group were significantly lower at T5 and T6 vs. control ($p<0.05$).
Conclusion: Leukocyte filtration on coated surfaces alleviated systemic inflammatory response with a better clinical outcome in high risk patients.

Key Words: Cardiopulmonary bypass – Coated materials-Biocompatible – Leukapheresis – Reperfusion injury – Leukocyte Filtration – Surface Modifying Additives

Introduction

Extracorporeal circulation has experienced many changes in techniques and circuit design since 1953 when Gibbon first demonstrated its successful use (1). Despite many theoretical opportunities and possibilities, the goal of complete attenuation of inflammation and ischemia-reperfusion injury following cardiopulmonary bypass (CPB) remains elusive. Attempts have been made to attenuate the activation of these cascades to reduce the negative effects of CPB.

Activation of leukocytes and their mobilization towards injured tissues are critical steps in inflammation and reperfusion injury. Activated neutrophils may exert damaging effects on tissues of the host, indirectly by releasing inflammatory mediators and directly by damaging endothelial cells with proteolytic enzymes (2,3).

Leukocyte filtration during CPB was initially tested experimentally in the early 1990 s and subsequently used in humans undergoing cardiac surgery. Filters incorporated in series in the CPB circuit have become popular in early 2000 s in clinical application and also been used to deplete the blood cardioplegic solution or even in re-transfused residual blood after CPB (4,5).

The review of leukofiltration in cardiac surgery is a good example of a concept that has not yet been universally adopted for the equivocal results from various small scale studies. Many of them demonstrated that leukocyte

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depletion contributed to early postoperative improvement in heart and lung function but did not influence significantly the overall clinical outcome of patients undergoing elective cardiac surgery (6). This may be due to timing and duration of the filtration procedure and flow and pressure conditions in the filter. One of another concern is the simultaneous removal of platelets which may affect postoperative hemostasis (7).

Risk recognition and risk stratification have received wide acceptance in cardiac surgery over the past decade. Assessment of preoperative risk and risk modeling is an integral part of clinical practice. The EuroSCORE has not only been shown to be a reliable predictor of in-hospital mortality but has also been proven useful for predicting postoperative morbidity and long term mortality (8).

Postoperative infectious complications are rare in patients undergoing open heart surgery (9). However, when infections develop, frequency of morbidity, mortality and cost may increase and hospitalization period may prolong. Infection rate was found to be higher in sicker patients. Nevertheless prospective randomized studies on infection rate linked with CPB is quite a few in the literature. But there are concerns about leukofiltration techniques to interfere with body's defence mechanisms due to captured leukocytes.

We studied the clinical outcome of continuous total leukocyte filtration and heparin coating in a comparative study with high-risk patients.

Patients and Methods

This study was approved by the Medical Ethics Committee of the Institution. Informed consent was obtained from each patient included in the study (No: 06/44).

A- Patients:

During the period from January 2007 until March 2007, 40 high risk patients (Euroscore 6+) undergoing coronary artery bypass grafting were included in the study.

Patients with preoperative immunosuppressive or nonsteroidal therapy, ejection fraction less than 20%, heparin treatment during surgery, disseminated intravascular coagulation, preoperative treatment with steroid, and severe pulmonary, renal, hepatic or cerebrovascular disease, neoplasia or infectious disease were excluded from the study.

Patients were randomly and prospectively assigned to four perfusion protocols:

Group 1 (n=10): Polyethyleneoxide (PEO) based heparin bonded extracorporeal circuits (ECC) (Trillium Affinity ^{NT}, Medtronic, Mn, USA) + Continuous Leukocyte filtration (LG6B and BC2 filters, Pall, NY)

Group 2 (n=10): Uncoated ECC (Affinity ^{NT}, Medtronic, Mn, USA) + leukofiltration

Group 3 (n=10): PEO based heparin bonded ECC without leukofiltration

Group 4 (Control group) (n=10): Uncoated extracorporeal circuit without leukofiltration

The operating room and intensive care unit staff collecting data were blinded to the entire study.

B- Operative Technique:

Anesthesia was induced by fentanyl (35 μg /kg) and muscle relaxation was established with pancronium (0.1 mg/kg). The patients were intubated endotracheally and ventilated with 100% oxygen. A Swan-Ganz catheter was placed via internal jugular vein. All patients were administered 3 mg/kg heparin (Liquemine, Roche, Turkey). The ascending aorta was cannulated for arterial inflow, and the right atrium for venous return. Moderate hypothermia was induced at 30°C. Following cross clamping of aorta, the heart was arrested by using 10–15 mL/kg crystalloid potassium cardioplegia and continued with cold blood cardioplegia at 20 minute intervals. Warm blood cardioplegia was administered before releasing the aortic cross clamp. Left internal mammary artery (LIMA) was used for grafting all left anterior descending artery (LAD) lesions and saphenous vein grafts for all others.

Rewarming was initiated during LIMA grafting. When 36.5°C was reached, CPB was discontinued and heparin was reversed

C- Leukocyte Filtration:

Leukocyte filters were deployed as soon as CPB was on until the end of the procedure. Pump was set up in the usual manner. Using sterile technique, an 18-inch section of the arterial line between the outlet of the oxygenator and arterial line filter was removed and replaced with LG6B filter. A one-way purge line was attached to the luer port of the filter and connected to a three-way stopcock placed on the cardiotomy reservoir. The section of the cardioplegia line of the oxygenator was replaced with the BC2 filter. The $\frac{1}{4}$ inch outflow line from this filter was split with a $\frac{1}{4}$ x $\frac{1}{4}$ x $\frac{1}{4}$ inch connector with one arm incorporating a Robert's clamp prior to its connection to the cardiotomy reservoir. The other arm of the connector was joined to the blood line (also containing a Robert's clamp) of a 4:1 blood cardioplegia circuit. A one-way purge line was attached to the luer port of the filter and connected to a three-way stopcock placed on the cardiotomy reservoir.

The circuit was then primed by 60 ml of mannitol (12 g, 20%) + 300 ml of hydroxyethyl starch and 1000 ml of crystalloid (plasmalyte A, Eczacibasi, Turkey). A clamp was placed on both the arterial line and blood line of 4:1 cardioplegia circuit. All lines including filters were primed and debubbled in a usual fashion.

D- Blood Samples and Assays:

Complete blood count [hemoglobin, hematocrit , erythrocyte , leukocytes (WBC) and platelet counts] was evaluated. Standard blood and urine biochemistry; especially total protein, albumin and globulin fractions were documented.

Serum interleukin 10 (IL-10), human tumor necrosis factor alpha (TNF-alpha) and procalcitonin levels were measured by ELISA (Biosource Internatonal Inc, Camarillo, CA, USA). Matrix metallopeptidase 9 (MMP 9) and D-Dimer (Triage Stroke Panel, Biosite Ltd., Belfast, UK) were evaluated by Triage system. Creatine kinase MB (CKMB) levels were measured in the samples obtained from retrograde cardioplegia catheter (coronary sinus blood) before start and after cessation of CPB.

Blood samples were obtained via radial artery catheter in potassium-EDTA tubes at the following intervals:

T1: Baseline: Following induction of anesthesia (before administration of heparin)

T2: On CPB: 5 min. following initiation of CPB

T3. X-Clamp: 5 min. following cross clamping of aorta

T4: Off CPB: 5 min. following cessation of CPB

T5: ICU24: First postoperative day in intensive care unit at 8:00 a.m.

T6. ICU48: Second postoperative day in intensive care unit at 8:00 a.m.

Additional samples were obtained via lines before and after the leukocyte filters in potassium-EDTA tubes at every 15 min. for documentation of percentage reduction rate of leukocytes, neutrophils and platelets.

E-Thromboelastography (TEG):

Platelet function was evaluated by TEG (ROTEG® , Pentapharm, GmbH, Germany) during the operation. Coagulation time, clot formation time, α-angle, mean clot firmness and amplitude 5 mm. point (A5) on graph were measured in samples T1 up to T4.

F- Perioperative Follow-up:

Hemodynamic parameters, perfusion and cross clamp duration, intubation period, postoperative hemorrhage, the use of blood and plasma, incidence of arrhythmia (atrial fibrillation-AF), use of inotropic support, rate of infection, complications, the duration of intensive care unit and hospital stay, perioperative mortality, New York Heart Association Classification, and doppler echocardiography were evaluated before discharge and documented. Comparison between the groups was performed retrospectively.

Patients were observed closely for infectious disease symptoms (fever, surgical site infection, respiratory and urinary tract infection, bacteriemia) and labortatory findings (leukocytosis, high levels in acute phase reactants, radiographic findings, urinary analysis, culture for microorganisms) by a specialist in infectious disease.

G- Statistical Analysis:

Data was expressed as mean ± standard error of mean. Two-way ANOVA was used to analyze differences over time in each group (Repeated measures ANOVA) and for differences between groups. A p value less than 0.05 was considered significant. Data was analyzed using SPSS 15.0 program. Evaluations were done with respect to control group.

Results

WBC counts (leukocyte in peripheral blood) in Group 1 (filtered+coated) group demonstrated significant difference at T4 (Fig 1) ($p<0.05$, vs. control). There was not any significant difference between Group 1 and 3. WBC and platelet counts decreased due to circuit priming for deairing and hemodilution before the start of the procedure as expected. There was a significant difference in platelet counts at T3 and T4 in Group 3 vs. control ($p<0.05$ vs. control) but a slight difference versus Group 1 ($p=0.046$) (Fig2). Serum IL-10 levels were not significantly different in study groups vs. control (data not shown). TNF-alpha levels were significantly lower in Group 1 at T3, T4 ($p<0.05$, vs. control). Group 1 had significantly lower levels versus Group 3 at T3 (Fig 3). Procalcitonin levels were significantly lower in Group 1 at T5, T6 ($p<0.05$, vs. Group 3 and control) (Fig 4).

CKMB levels in coronary sinus blood demonstrated well preserved myocardium in filtered+coated (Group 1) and coated groups (Group 3) ($p<0.05$, vs. control) (Fig 5). Group 2 did not show any significant difference. There was not any difference between Group 1 and 3, postoperatively.

MMP 9 and D-Dimer levels in filtered+coated group (Group 1) were significantly lower at T5 and T6 ($p<0.05$, vs. control). MMP9 levels in Group 1 were significantly lower than Group 3 at T5 ($p<0.05$) and no difference in between Group 1 and Group 3 was detected for D-Dimer. (Fig 6&7).

Pressure drop through leukofilters was never over critical security level (<60 mmHg) in both study groups. Perioperative hemodynamic follow-up was summarized in Table 1A and infection outcome in Table 1B.

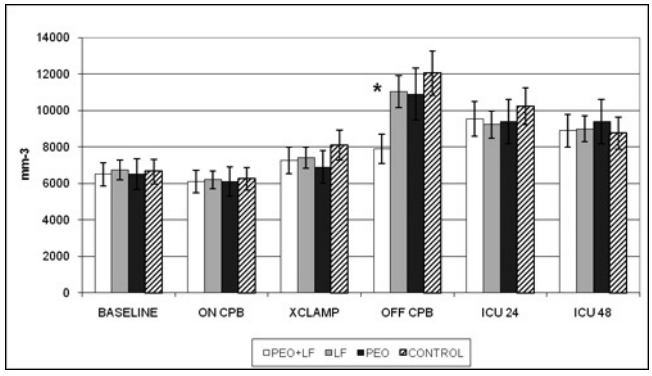

Fig. 1: White blood cell count in peripheral blood (/mm^3) throughout the procedure in patient groups. *N= 10 for each group. Abscissa: Blood sampling points Ordinate: White blood cell count/mm^3 PEO: Polyethyelenoxide coating LF: leukocyte filtration CPB: Cardiopulmonary bypass Xclamp: Aortic cross clamp ICU: Intensive care unit* Mean±SEM *: $p<0.05$ vs. control

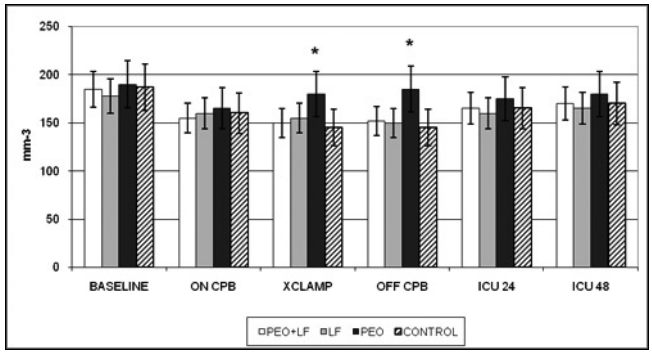

Fig. 2: Platelet count (/mm^3) throughout the procedure in patient groups *N= 10 for each group. Abscissa: Blood sampling points Ordinate: Platelet count/mm^3* Mean±SEM *: $p<0.05$ vs. control

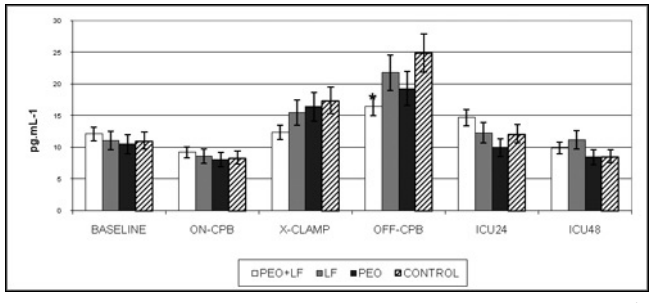

Fig. 3: Tumor necrosis factor alpha (TNF-alpha) levels (pg.mL^{-1}) throughout the procedure in patient groups *N= 10 for each group. Abscissa: Blood sampling points Ordinate:TNF-alpha levels* Mean±SEM *: $p<0.05$ vs. control δ: $p<0.05$ (Group 1 vs. Group3)

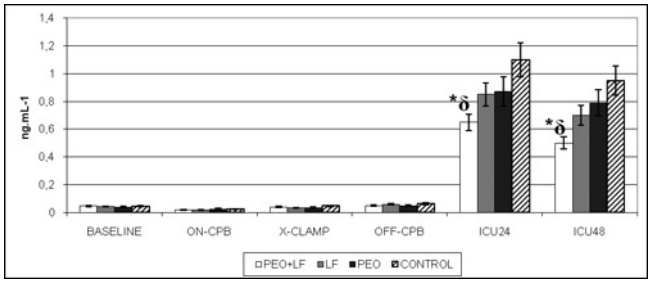

Fig. 4: Procalcitonin levels (ng.mL^{-1}) throughout the procedure in patient groups *N= 10 for each group. Abscissa: Blood sampling points Ordinate: Procalcitonin levels* Mean±SEM *: p<0.05 vs. control δ: p<0.05 (Group 1 vs. Group3)

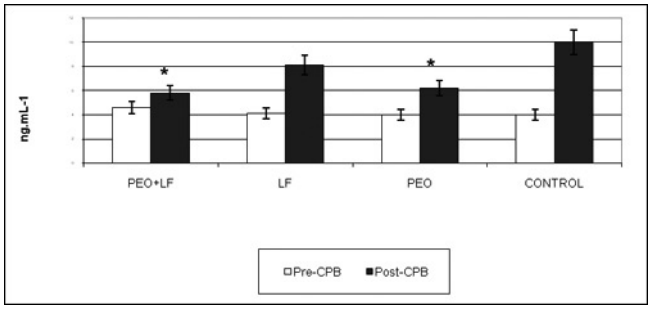

Fig. 5: Creatinine kinase-MB (CK-MB) levels (ng.mL^{-1}) before and at the end of CPB *N= 10 for each group. Abscissa: Blood sampling points Ordinate: CKMB levels* Mean±SEM *: p<0.05 vs. control

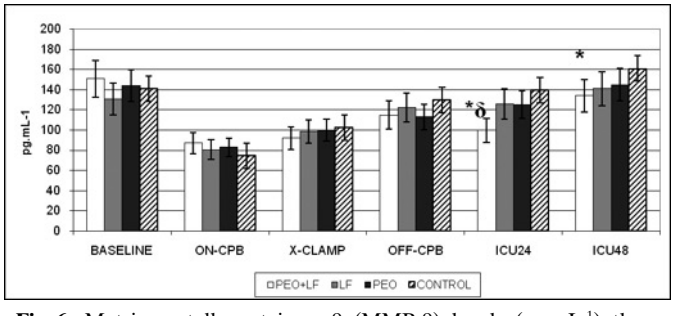

Fig. 6: Matrix metalloproteinase-9 (MMP-9) levels (pg.mL^{-1}) throughout the procedure in patient groups *N= 10 for each group. Abscissa: Blood sampling points Ordinate: MMP-9 levels* Mean±SEM *: p<0.05 vs. control δ: p<0.05 (Group 1 vs. Group3)

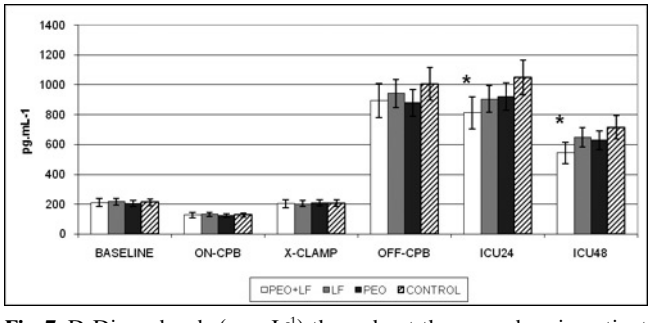

Fig. 7: D-Dimer levels (pg.mL^{-1}) throughout the procedure in patient groups *N= 10 for each group. Abscissa: Blood sampling points Ordinate: D-dimer levels* Mean±SEM *: p<0.05 vs. control

Discussion

Multi-factorial reasons mediate adverse consequences of ECCs; activation and damage of cellular components of the blood, dysfunction of cellular immunity, engage to one another through various feedback mechanisms, intrinsic and extrinsic coagulation, fibrinolysis and complement cascade. In addition, cell and tissue damaging release products, like free oxygen radicals, proteinases, nitric oxide, cytokines, endotoxins act a part in this process (10,11,12,13).

The beneficial effects of leukocyte filtration on the outcome of cardiac surgery with CPB is probably due to the limitation of pathogenesis mediated by over-stimulated neutrophils (14). An ideal filter theoretically would have the capacity of removing only activated granulocytes

without affecting the whole population in blood and bone marrow, of the normal granulocytes necessary in the body's postoperative defence against infections (15). This concept has been used for the explanation of the lack of effect of leukocyte filters in possible exacerbation of infection following procedures. However many studies have demonstrated that the filter positioned in the arterial line failed to limit neutrophil stimulation but rather augmented polymorphonuclear elastase (PMNE) levels. Augmented PMNE or myeloperoxidase levels were speculated to stem mainly from neutrophils that were captured within the mesh of the filter (16). Our study showed that WBC counts were maintained within lower levels during the whole procedure in filtered groups. Also proinflammatory markers confirmed better response to SIRS post-CPB in study groups. We believe that proinflammatory markers were secreted from activated leukocytes but also to a great extent from activated endothelial cells.

One of the most underestimated points in previous studies was the platelet preservation issue. Our previous studies indicated that leukocyte filters on uncoated circuits caused a pressure difference and platelet destruction (5,17,18). The uncoated surface induced an activation of platelets and complemented the inflammatory process. Therefore we have chosen to compare coated and uncoated circuits simultaneously with filters to investigate this problem. In our study, the highest mean platelet count was found in coated group. The platelet counts in Group 3 were significantly higher than that of the control group. Certainly, uncoated circuit caused reduction of the platelet counts, as seen in Groups 2 and 4. The filtratrion apparatus may cause reduction of the platelet counts, despite usage of the coated ECC. This may be the reason why the platelet counts in Group 4 (PEO+LF) were reduced.

The amount of postoperative hemorrhage was also less in all groups with respect to control group but difference was marked statistically in Groups 1 and 3 (Table 1). We suggest to use leukocyte filtration on coated surfaces.

Tab. 1. (A) Perioperative hemodynamic follow-up (A) and infection outcome (B) of patient population *t-intub: Intubation (respiratory support) duration* Mean±SEM *: p<0.05 vs. control

	GROUP 1(N=10) (PEO+LF)	**GROUP 2(N=10) (LF)**	**GROUP 3 (N=10) (PEO)**	**CONTROL (N=10)**	**P (vs.control)**
Duration of CPB (min)	121±7	129±7	142±7	134±8	NS
t-intub (h)	11±2*	13±2*	15.2.2±1	16.9±2	<0.05
Postoperative hemorrhage (mL)	675±50*	805±50	610±50*	858±50	<0.05
Arrhythmia (%)	20*	20*	40	60	<0.05
Blood transfusion (Unit)	2.2±0.5	2.0±0.5	2.1±0.5	2.6±0.5	NS
Inotropic support (%)	20%*	40%	40%	60%	<0.05
Hospital stay (day)	8.5±2*	9.4±2	9.1±2	12.4±2	<0.05
Mortality rate (%)	10%	20%	20%	30%	NS

Tab. 1. (B)

(N)	GROUP 1 (PEO+LF)	GROUP 2 (LF)	GROUP 3 (PEO)	CONTROL	P
Fever	4	4	3	3	NS
Culture(+)	1	1	-	2	NS
Surgical Site infection	2	3	3	1	NS
Urinary Tract Infction	2	4	4	2	NS
Respiratory Infection	3	5	4	6	NS
Catheter Infection	1	-	-	-	NS
Systemic Infection	-	-	1	-	NS

Mean±SEM *: p<0.05 vs. control

We demonstrated better platelet preservation and less postoperative hemorrhage in coated+filtered group. Also filtration efficiency and duration was much better with additional coating. In our previous studies, we have compared leukocyte filtration on coated and uncoated circuits and concluded that leukofiltration on uncoated circuits did not have any additional advantage, even interfered platelet preservation (17, 18).

Considering the comparison between coated+filtered group versus only coated group, we observed anti-inflammatory outcome clearly in combined group (TNF-alpha, procalcitonin and MMP levels) but slightly better platelet preservation in only coated group.

In current study, there was no significant difference among study groups (coated and leukofiltrated) and control with respect to the evaluation of infectious process. This may be due to the limited amount of patient population. Reduction of platelet activation may have implemented the less postoperative blood loss with heparin-coated CPB. We used procalcitonin which has the greatest sensitivity (85%) and specificity (91%) for differentiating patients with SIRS from those with infection, when compared with IL-2, IL-6, IL-8, CRP and TNF-alpha (19). Results on the early postoperative period were higher but never as high as to confirm severe infection. Immunosuppression that engendered with homologous blood transfusion was demonstrated by clinical data (20). Bacterial infection rate (wound, pulmonary, urinary, etc) is significantly related with transfused blood volume when controlling for other variables. Pulmonary infection ratio was 1.6% in patients with non-transfused, whereas this infection rate was 13.7% of those who transfused blood greater than 6 units (21). Coating of the device may ameliorate early and late phase systemic inflammatory response because of its efficacious biocompatibility. This improvement may probably lead to improving multiple organ function. Also, lesser activation of cells may help the prevention of postoperative infection. In the meantime, this practice regularizes the perioperative clinical course and embarrasses the infections probably by reducing leukocyte consumption. Although inflammation was depleted with the employment of heparin-coated groups, the differences were not demonstrated in infection rate.

Hamada et al. presented the combined use of a heparin-coated circuit and a leukocyte depleting arterial line filter and found decreased inflammatory responses and improved pulmonary function in routine patients (22). We studied high-risk patients with a different technique of total leukocyte filtration (arterial+cardioplegia) on heparin-coated circuits to observe whether improvement will be increased or not. Benefit was not contributory and below our expectance.

The high standard of current CPB systems has made it increasingly difficult to test technical improvements in clinical studies involving relatively small patient groups. In most cases, the statistical power of such studies will not suffice to show a significant clinical benefit associated with changes in the CPB circuit (23). We believe performing such evaluations in high risk patients to get a clear picture. When we combined the anti-inflammatory effects of coating and leukocyte filtration, we could get some statistical significance in blood assays. Leukocyte filtration and coating showed synergistic efficacy.

Benchmark of cardiac damage, CKMB, was statistically lower in coated groups (group 1 and 3). Postoperative atrial fibrillation was evolved in fewer patients in all groups compared with control. These consequences are demonstrated that coating of circuit enhanced the leukofiltration in decrementing the cardiac injury and complications.

IL-10 levels, as an anti-inflammatory cytokine, increases after elevated pro-inflammatory cytokine levels for representing an endogenous response for limiting the inflammatory response (24). In our study, IL-10 concentration was not significantly better in study groups compared with control.

Consequently, leukocyte filtration worked well to overcome SIRS in the early post-CPB period. We think this method should be performed on coated circuits to be more efficient causing less platelet damage and hemorrhage. Although we had a small patient population, considering the number of high risk cases, we concluded that leukocyte filtration did not have any negative effect on increasing infection rate postoperatively.

As an overview of leukofiltration during CPB, it must be underlined that the inflammatory response is multifactorial and combined therapies may be more efficient than a single intervention to improve outcome (25). Both pharmacologic interventions and modification of techniques or mechanical devices may have clinical implications.

References

[1] Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. Minn Med 1954; 37:171–185

[2] Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 2003; 75:S715-S720

[3] Asimakopoulos G, Taylor KM. Effects of cardiopulmonary bypass on leukocyte and endothelial adhesion molecues. Ann Thorac Surg 1998; 66:2135–2144.

[4] Samankatiwat P, Samartzis I, Lertsithichai P, Stefanou D, Punjabi PP, Taylor KM, et al. Leucocyte depletion in cardiopulmonary bypass: a comparison of four strategies. Perfusion 2003; 18(2): 95–105.

[5] Gunaydin S, McCusker K, Vijay V, Sari T, Sargon MF, et al. Clinical evaluation strategic leukofiltration with surface modification: Enhanced preservation or fantasy. Filtration 2005; 1(1):57–67

[6] Sheppard SV, Gibbs RV, Smith DC. Does leucocyte depletion during cardiopulmonary bypass improve oxygenation indices in patients with mild lung dysfunction? Br J Anaesth 2004; 93(6):789–792.

[7] Ortolano GA, Aldea GS, Lilly K, O'Gara P, Alkon JD, Mader F, et al. A review of leukofiltration in cardiac surgery: the time course of reperfusion injury may facilitate study design of anti-inflammatory effects. Perfusion 2002; 17: S53-S62.

[8] Toumpoulis IK, Anagnostopoulos CE, Swistel DG, DeRose JJ Jr. Does EuroSCORE predict length of stay and specific postoperative complications after cardiac surgery? Eur J Cardiothorac Surg. 2005; 27(1):128–133.

[9] Tayama E, Hayashida N, Akasu , Kosuga T, Fukunaga S, Akashi H, et al. Biocompatibility of heparin coated extracorporeal bypass circuits: New heparin bonded bioline system. Artificial Organs 2000; 24(8): 618–623.

[10] Colman RW. Hemostatic complications of cardiopulmonary bypass. Am J Hematol. 1995; 48(4):267–272.

[11] Taylor KM. SIRS–the systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 1996; 61(6): 1607–1608.

[12] Asimakopoulos G. The inflammatory response to CPB: the role of leukocyte filtration. Perfusion 2002; 17 Suppl: 7–10.

[13] Falagas ME, Rosmarakis ES, Rellos K, Michalopoulos A, Samonis G, Prapas SN. Microbiologically documented nosocomial infections after coronary artery bypass surgery without cardiopulmonary bypass. J Thorac Cardiovasc Surg 2006; 132(3): 481–490.

[14] Repo H, Jansson SE, Leirisalo-Repo M. Flow cytometric determination of CD11b upregulation in vivo. J Immunol Methods 1993; 164:193–202

[15] Kozik JD, Tweddell JS. Characterizing theinflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2006; 81:S2347-S2354

[16] Baksaas ST, Flom-Halvorsen HI, Ovrum E, et al. Leucocyte filtration during cardiopulmonary reperfusion in coronary artery bypass surgery. Perfusion 1999; 14: 107–117

[17] Gunaydin S, McCusker K, Vijay V. Strategic leukofiltration in cardiac surgery. Curr Med Chem-Cardiovascular & Hematologic Agents 2005; 3:173–179

[18] Gunaydin S, McCusker K, Vijay V et al. Clinical significance of strategic leukocyte filtration in different risk cohorts undergoing cardiac surgery. Filtration 2005, 1(2):95–106.

[19] Balci C, Sungurtekin H, Gurses E, Sungurtekin U, Kaptanoglu B. Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. Crit Care 2003;7(1):85–90.

[20] Mahoney CB. Heparin-bonded circuits: clinical outcomes and costs. Perfusion 1998; 13(3): 192–204.

[21] Zimmermann AK, Aebert H, Reiz A, Freitag M, Husseini M, Ziemer G, Wendel HP. Hemocompatibility of PMEA coated oxygenators used for extracorporeal circulation procedures. ASAIO J 2004; 50(3): 193–199.

[22] Hamada Y, Kawachi K, Nakata T, Kohtani T, Takano S, Tsunooka N. Antiinflammatory effect of heparin-coated circuits with leukocyte-depleting filters in coronary bypass surgery. Artif Organs 2001; 25:1004–1008.

[23] Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999; 16:9–13

[24] de Vroege R, van Oeveren W, van Klarenbosch J, Stooker W, Huybregts MA, Hack CE, et al. The impact of heparin-coated cardiopulmonary bypass circuits on pulmonary function and the release of inflammatory mediators. Anesth Analg 2004; 98(6): 1586–1594.

[25] Gunaydin S, Ayrancioglu K, Dikmen E et al. Clinical effects of leukofiltration and surface modification on post-cardiopulmonary bypass atrial fibrillation in different risk cohorts. Perfusion 2007, 22(4):279–88