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Retrospective evaluation of ultrafiltration during cardiac surgery with cardiopulmonary bypass in adult patients with increased neutrophil to lymphocyte ratio

Erişkin hastalarda kardiyopulmoner baypas ile uygulanan konvansiyonel ultrafiltrasyonun nötrofil / lenfosit oranı ile retrospektif olarak değerlendirilmesi

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Abstract

Aim: The aim of this study was to investigate the efficacy of the ultrafiltration (UF) in adult patients undergoing open-heart surgery with cardiopulmonary bypass (CPB) by evaluating the neutrophil to lymphocyte ratio (NLR).

Methods: A retrospective case-control study was conducted on 288 adult patients who underwent CPB in a University hospital from January 2016 to December 2018. The study groups were composed of a control group (n=116) of patients who underwent surgery without UF and the study group (n=172) of patients who underwent surgery with UF. All perioperative clinical data, including neutrophil, lymphocyte and platelet count, BUN, creatinine, and C-reactive protein (CRP) values were collected. The efficacy of UF and its association with NLR, neutrophil, lymphocyte and platelet count, postoperative bleeding, extubation time, duration of intensive care unit (ICU) stay and in-hospital stay were analyzed.

Results: Neutrophil count, NLR and CRP significantly increased post-operatively compared to pre-operative values ($P<0.05$). The increased post-operative levels of NLR and decreased platelet counts were significantly associated with UF ($P<0.05$). Multivariate linear regression analysis revealed that elevated NLR was significantly and independently associated with UF.

Conclusion: UF followed by CPB in adult patients undergoing cardiac surgery was associated with increased post-operative NLR and low platelet counts, which nonetheless, were not associated with postoperative complications. UF should be chosen only for selective patients with low hematocrit and should not be chosen to attenuate whole body inflammatory response after CPB in adult cardiac surgery patients.

Keywords: Adult patients, Cardiopulmonary bypass, Ultrafiltration, Neutrophil lymphocyte ratio, Platelet, Inflammation

Öz

Amaç: Bu çalışmanın amacı, nötrofil / lenfosit oranını (NLO) değerlendirerek, kardiyopulmoner baypas (CPB) ile açık kalp cerrahisi geçiren yetişkin hastalarda ultrafiltrasyonun (UF) etkinliğini araştırmaktır.

Yöntemler: Ocak 2016'dan Aralık 2018'e kadar bir Üniversite hastanesinde CPB uygulanan 288 yetişkin hasta üzerinde retrospektif bir kohort çalışması yapılmıştır. Nötrofil, lenfosit ve trombosit sayısı, BUN, kreatinin ve C-reaktif protein (CRP) dahil olmak üzere tüm perioperatif klinik veriler geriye dönük olarak toplandı. UF'nin etkinliği ve NLO, nötrofil, lenfosit ve trombosit sayısı, postoperatif kanama, ekstübasyon süresi, yoğun bakım ünitesinde (YBÜ) kalış süresi ve hastanede kalış süresi ile ilişkisi analiz edildi.

Bulgular: Nötrofil sayısı, NLO ve CRP ameliyat öncesi değerlere göre ameliyat sonrası anlamlı olarak arttı ($P<0,05$). Ameliyat sonrası artan NLO seviyeleri ve azalmış trombosit sayıları UF ile anlamlı olarak ilişkili idi ($P<0,05$). Çok değişkenli doğrusal regresyon analizi, yükselmiş NLR'nin UF ile anlamlı ve bağımsız olarak ilişkili olduğunu ortaya çıkarmıştır.

Sonuç: Açık kalp cerrahisi uygulanan yetişkin hastalarda UF uygulamaları, artmış postoperatif NLO ve düşük trombosit sayıları ile ilişkiliydi, ancak yine de postoperatif komplikasyonlarla ilişkili değildi. UF, yalnızca düşük hematokriti olan seçici hastalar için seçilmeli ve yetişkin kalp cerrahisi hastalarında CPB'den sonra tüm vücut enflamatuar yanıtını hafifletmek için seçilmemelidir.

Anahtar kelimeler: Erişkin hasta, Kardiyo-pulmoner baypas, Ultrafiltrasyon, Nötrofil lenfosit oranı, Trombosit, Enflamasyon

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Introduction

Previous studies have demonstrated that material dependent factors, such as exposure of blood to artificial surfaces, and condition, patient, and prevalent disease-dependent factors, such as surgical trauma, ischemia-reperfusion to the organs, changes in body temperature, and release of endotoxins inevitably affect the outcomes of cardiopulmonary bypass (CPB). The activation of a complex inflammatory response, including complement activation, release of cytokines, leukocyte activation along with the expression of adhesion molecules, and the production of oxygen-free radicals, arachidonic acid metabolites, platelet-activating factor, nitric oxide, and endothelin have been well demonstrated [1-3]. These inflammatory reactions, which are invoked at the beginning of the surgery, may contribute to the development of postoperative complications including respiratory failure, renal dysfunction, bleeding disorders, neurological dysfunction, altered liver function and ultimately, multiple organ failure [2,4].

Several studies have demonstrated a relationship between over-production of inflammatory mediators, fluid accumulation to the third space of the body and/or vital organs and postoperative complications in adult patients after on-pump cardiac surgery [1-4].

The theory of ultrafiltration (UF) involves the retention of solutes of high molecular weight when the excess fluid and low molecular weight solutes such as inflammatory mediators in the blood stream are forced under hydraulic pressure through a membrane of a very fine pore size, typically between 0.001 and 0.1 µm [5-6]. Although several studies have indicated a high rate of favorable outcomes when UF was performed during CPB in cardiac surgery, some studies suggested that the long duration needed to carry out UF and UF related technical and material causes may augment the adverse effects of CPB [1-4].

Systemic inflammation during CPB is triggered by neutrophil activation, which can be monitored by a novel biomarker, the neutrophil to lymphocyte ratio (NLR) [7]. A high NLR has been associated with poor prognosis in many cardiovascular diseases [8]. Besides, recent studies suggest that increased perioperative NLR is related to poor outcomes in adult cardiac surgery patients [9]. However, NLR has not been studied well exclusively in adult patients undergoing on-pump cardiac surgery along with UF. Therefore, the objective of the present study was to examine the association of NLR levels with clinical outcomes in adult patients undergoing on-pump cardiac surgery with UF.

Materials and methods

Study design, population, and patients

288 adult patients undergoing cardiac surgery requiring CPB from January 2016 to December 2018 were included in this retrospective study (Van Yuzuncu Yil University Medical Faculty, Ethical committee approval reference number: 2020/03-31, 22/05/2020). The inclusion criteria of this study were as follows: Being between 18 and 72 years of age and undergoing cardiac surgery requiring CPB. Exclusion criteria of this study included pediatric cardiac surgery, age greater than 80 years, emergency surgery, previously diagnosed chronic renal or hepatic insufficiency, malignancy, systemic inflammatory disease, a history of cardiac surgery and failure to obtain patient data necessary for the study. The study groups were composed of a control group (n=116) of patients who underwent surgery without UF and the study group (n=172) of patients who underwent surgery with UF.

Anesthesia and management of CPB

Anesthesia and management of CPB were performed using standard techniques. Briefly, anesthesia and endotracheal intubation was performed after an intravenous injection of fentanyl (5 µg/kg), cisatracurium (0.15 mg/kg), propofol (3 mg/kg), and midazolam (0.05 mg/kg). For continuation of anesthesia, propofol (8 mg/kg/h), cisatracurium (2 µg/kg/min), and sevoflurane (1–3%) were used. Methylprednisolone (1 mg/kg) and cefazolin sodium (1000 mg) were used before skin incision as a routine surgery technique. None of the patients received intraoperative steroids.

The extracorporeal circuit included a membrane oxygenator (Affinity Fusion® oxygenator, Medtronic Inc., Minneapolis MN) and a roller pump system (Sorin C5, Sorin Group, München, Germany) equipped with a heat exchanger (Stockert®, Sorin Group, München, Germany). The circuit was primed with 500 ml of crystalloid solution (Laktatlı Ringer Solüsyonu®, Polifarma Ilac San.ve Tic. A.Ş. Ankara, Turkey), 500 ml of colloid solution (Voluven®, Fresenius Medical Care AG, Bad Homburg, Germany) and 250 ml of 20% mannitol (20% Mannitol®, Polifarma Ilac San.ve Tic. A.Ş. Ankara, Turkey) according to institutional standards. Heparin (Nevparin®, Mustafa Nevzat Ilac Sanayii A.S. Gayrettepe, Istanbul, Turkey) was administered repetitively to maintain an activated clotting time (ACT) of greater than 400 s. During CPB, non–pulsatile flow was maintained at 2.6-3 l/min/m² and the mean arterial blood pressure was maintained at 50–70 mmHg by the addition of norepinephrine (Arterenol®, Sanofi-Aventis GmbH, Hoechst, Germany). Myocardial protection was achieved with cold blood cardioplegia (4-8°C).

The prime used in the CPB circuit consisted of Ringer's acetate solution, 20% mannitol, 5% sodium bicarbonate and heparin. Blood HCT was diluted to 24–28% during CPB. The body was cooled to a target esophageal temperature of 18 to 37°C, considered moderate / mild / deep hypothermia. Once the surgery was completed, the patients were warmed and weaned from CPB. To reverse the anticoagulant effects of heparin, protamine sulfate (Promin, VEM Ilac San.ve Tic. A.Ş. Cankaya, Ankara, Turkey) was administered, guided by the ACT.

Indicators for UF were hypervolemia, hyperpotassemia, dilution of hematocrit levels and lowering the inflammatory mediators after a long duration of CPB. UF (Adult Hemofiltration Package, Sasan Ilac San.ve Tic. A.Ş. Ankara, Turkey) was initiated while the patient was being warmed using a filtration pressure of 150 - 250 mmHg at a filtration rate of 10 to 15 mL/min. The filtration membrane pressure was increased to 350 - 450 mm Hg by the end of CPB and during residual blood UF with a filtration rate of 40 to 75 mL/min. The duration of UF was maintained for at least 20- 30 minutes, unless mean blood pressure decreased to 50-60 mm Hg.

Data collection

The hospital patient database system was used to obtain pre-operative and post-operative levels of neutrophils, lymphocytes and platelet counts, urea, creatinine and CRP. NLR was calculated based on the data collated. Clinical observation data were obtained from medical and nursing records of the patient.

Statistical analysis

Categorical and numerical data are expressed as n (%) and mean (SD), respectively. Post-operative neutrophil and lymphocytes counts, NLR and CRP were compared with the pre-operative counts using the repeated measures test and between group analysis were compared with ANOVA. Spearman rank correlation coefficients were used to assess the association between neutrophil counts, NLR, CRP and continuous clinical outcomes. Multivariate linear regression was used to further examine the relationship between post-operative neutrophil counts, NLR and CRP and clinical outcome variables, including extubation time, postoperative bleeding, the duration of the ICU stay, and length of hospital stay. The significance level was defined as a $P<0.05$. All statistical analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL).

Results

During the study period (January 2016 to December 2018), 288 patients who underwent CPB (Ultrafiltration n= 172, 44.8% female, control n= 116, 36.2% female) were included in the final analysis. The procedures that 288 study participants underwent comprised of coronary artery bypass surgery (CABG, UF =41.9%, control= 73.3%), mitral valve replacement (MVR, UF =25.6%, control= 13.8%), aortic valve replacement (AVR, UF =7.6%, control= 1.7%), atrial septal defect (ASD, UF =2.9%, control= 5.2%), ventricular septal defect (VSD, UF =0.6%, control= 0.9%), aorta aneurism (UF =3.5%, control= 0.9%), aorta dissection (UF =8.7%, control= 0.9%), multiple valve replacement (UF =4.7%, control= 2.6%), and CABG with valve replacement (UF =4.8%, control= 0.9%) (Table 1).

The median age and body mass index of the UF and control groups were 57 (15) vs 57 (13) years (P=0.926) and 27.1 (2.94) vs 27.53 (3.85) kg/m^2 (P=0.483), respectively. The mean duration of cross clamp and CPB in UF vs control groups were 72.67 (33.48) vs 57.54 (25.71) (P< 0.001) and 112.37 (45.48) vs 90.72 (31.55) (P<0.001) minutes, respectively. The mean filtrate volume was 880 (800) ml (ranging from 50 to 2800 ml). The study demographics, preoperative characteristics and operative features of the entire study are presented in Table 1.

The data showed that post-operative neutrophil counts and NLR were significantly higher compared to their respective pre-operative levels in the UF group (Table 2, P<0.001 and P<0.001, respectively) and also were significantly higher compared to the control group (Figure 1A and 1C, P<0.001). Inversely, post-operative lymphocyte and platelet counts were significantly lower compared to their respective pre-operative levels in the UF group (Table 2, P<0.001 for all comparisons) and also were significantly lower compared to the control group (Figure 1B, 2D, P<0.001 for all comparisons). The post-operative platelet counts remained low after the 5th postoperative day in the UF group, while the same was raised to preoperative levels in the control group at postoperative 5th day (Table 2).

Table 1: Demographic and preoperative features of patients with UF (n=172) and controls (n=116) participating in the study

		Ultrafiltration (n=172)	Controls (n=116)	*P*-value
Age (year) (SD)		57 (15)	57 (13)	0.926
Gender, Woman (%)		44.8	36.2	0.180
Body mass index (kg/m^2) (SD)		27.1 (2.94)	27.53 (3.85)	0.483
Procedure (%)	CABG	41.9	73.3	none
	MVR	25.6	13.8	
	AVR	7.6	1.7	
	VSD Closure	0.6	0.9	
	ASD Closure	2.9	5.2	
	Aorta aneurism	3.5	0.9	
	Aorta dissection	8.7	0.9	
	Multiple valve surgery	4.7	2.6	
	Valve and bypass surgery	4.8	0.9	
Operation temperature classification (C°)	Deep	8.7	0.9	<0.001
	Cold	34.3	16.4	
	Moderate	57.0	82.8	
	Warm	0	0	
Cross clamp duration (minutes) (SD)		72.67 (33.48)	57.54 (25.71)	<0.001
CPB duration (minutes) (SD)		112.37 (45.48)	90.72 (31.55)	<0.001
Ringer lactate volume in prime (ml) (SD)		485 (60)	484 (54)	0.872
Mannitol volume in prime (ml) (SD)		103 (25)	102 (10)	0.765
Colloidal fluid volume in prime (ml) (SD)		433 (109)	426 (99)	0.625
FFP suspension usage in prime (%)		11	0	<0.001
Erythrocyte suspension usage in prime (%)		49.4	24.1	<0.001
Total filtrate volume (ml) (SD)		880 (800)	0	none
Rest of the prime after operation (ml) (SD)		111 (112)	70 (95)	0.002
Postoperative drainage volume (ml) (SD)		716 (386)	725 (438)	0.854

Data are expressed as mean [Standard Deviation (SD)] or %. The Wilcoxon rank-sum test was used for continuous variables, and the Fisher exact test was used for categorical variables in univariate analysis. P<0.05 was considered as significant. ASD: Atrial Septal Defect, AVR: Aorta Valve Replacement, CABG: Coronary Artery Bypass Grafting, FFP: Fresh Frozen Plasma, MVR: Mitral Valve Replacement, VSD: Ventricular Septal Defect

Table 2: Within group analysis of the study groups [UF (n=172) and controls (n=116)]

		Preoperative (T1)	Postoperative 24th Hours (T2)	Postoperative 5th Days (T3)	*P*-value
Neutrophil count (10^9/l)	Ultrafiltration	6.29 (3.419	10.75 (4.21)*	7.97 (4.31)	<0.001
	Control	5.73 (2.81)	9.26 (2.78)*	5.91 (2.13)	<0.001
Lymphocyte count (10^9/l)	Ultrafiltration	1.96 (0.89)	1.04 (0.97)*	1.39 (0.74)**	<0.001
	Control	2.08 (0.93)	1.01 (1.33)*	1.70 (0.71)	<0.001
Neutrophile / lymphocyte ratio	Ultrafiltration	3.99 (3.43)	15.27 (10.47)*	7.6 (5.96)**	<0.001
	Control	3.41 (2.4)	13.85 (7.84)*	4.20 (3.26)	<0.001
Urea (mg/dl)	Ultrafiltration	42.95 (20.42)	44.56 (20.24)	45.38 (23.23)	0.597
	Control	42.98 (20.01)	46.08 (20.71)	42.91 (18.53)	0.004
Creatinine (mg/dl)	Ultrafiltration	0.97 (0.64)	1.02 (0.79)	0.98 (0.72)	0.008
	Control	1.06 (0.88)	1.15 (0.99)	0.98 (0.96)	<0.001
C-reactive protein (mg/dl)	Ultrafiltration	3.96 (1.21)	-	41.27 (26.73)**	<0.001
	Control	3.96 (1.22)	-	41.11 (24.84)**	<0.001
Platelet Count (10^9/L)	Ultrafiltration	231.54 (71.84)	183.67 (68.68)*	193.29 (82.49)**	<0.001
	Control	248.67 (79.42)	191.20 (59.12)*	253.42 (88.89)	<0.001

Data are expressed as mean [Standard Deviation (SD)]. The Repeated Measures Friedman test was used for within group analysis and test results indicated as *P*-value which <0.05 was considered as significant.

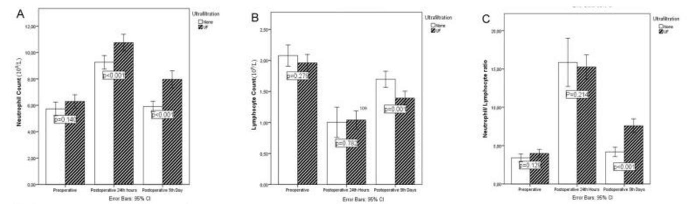

Figure 1: Graph representing the mean level of preoperative, postoperative 24th hours and postoperative 5th days of the neutrophil counts (A), lymphocyte counts (B), and neutrophil / lymphocyte ratio (NLR) (C) of the patients undergoing ultrafiltration during cardiopulmonary bypass in cardiac surgery. Post-operative neutrophil, lymphocytes counts and NLR were analyzed by using the ANOVA. *P*-value of <0.05 was considered to be statistically significant.

The data showed that post-operative urea, creatinine and CRP levels were similar in the UF and control groups (Figure 2A-C) but were significantly higher compared to their respective pre-operative levels in both groups. The exception was the urea level, which was similar to the pre-operative level in the UF group (Table 3, P<0.001).

The statistically significant changes in serum lymphocyte, neutrophil and platelet counts, and neutrophil / lymphocyte ratio may be biased due to the prolonged duration of CPB. Therefore, to account for this factor, we also analyzed a subgroup of patients in whom the CPB lasted longer than 120 minutes (Figure 3). The results showed that serum lymphocyte, neutrophil and platelet counts, and neutrophil / lymphocyte ratio were similar when CPB lasted longer than 120 minutes in both UF and control groups (Figure 3).

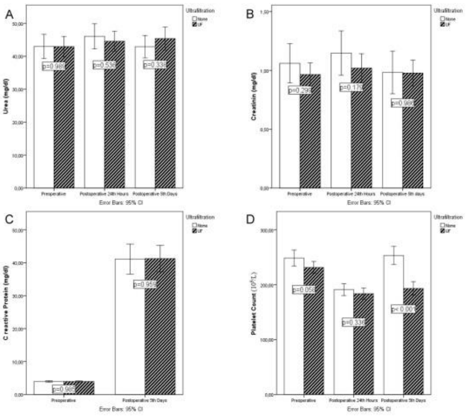

Figure 2: Graph representing the mean level of preoperative, postoperative 24th hours and postoperative 5th days of the urea (A), creatinine (B), C reactive protein (C) and platelet counts (D) of the patients undergoing ultrafiltration during cardiopulmonary bypass in cardiac surgery. Variables were analyzed by using the ANOVA. *P*-value of <0.05 was considered to be statistically significant.

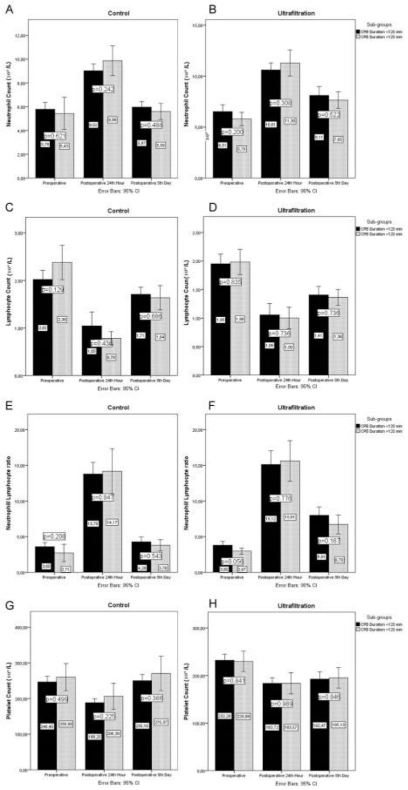

Figure 3: Graphs representing the mean levels of neutrophil counts (A and B), lymphocyte counts (C and D), neutrophil / lymphocyte ratio (NLR) (E and F), and platelet counts (G and H) of UF patients and control groups divided into subgroups according the cardiopulmonary bypass duration (< 120 minutes and > 120 minutes). Variables were analyzed by using the ANOVA. A *P*-value of <0.05 was considered to be statistically significant.

Using a univariate analysis of clinical outcomes (Table 4), we observed that on the 5th postoperative day, the NLR and platelet counts were significantly associated with UF ($P<0.05$). However, pre-operative NLR was significantly associated with the duration of cross clamping and cardiopulmonary bypass time ($P<0.05$). An additional regression analysis to determine the association between post-operative 5th day NLR and platelet counts (Table 5) indicated a significant association with UF.

Table 3: Postoperative complications of patients with UF and controls participating in the study

	Ultrafiltration (n=172)	Controls (n=116)	*P*-value
Pneumothorax (%)	0.6	0.9	0.469
Delirium (%)	4.7	2.6	
Atrial fibrillation (%)	5.2	6	
Temporary ventricular arrythmia (%)	1.2	6	
Long duration of intubation (%)	4.7	5.2	
Acute renal insufficiency (%)	3.5	2.6	
Exitus (%)	3.1	3.4	

Table 4: Spearman rank correlation coefficients of neutrophil / lymphocyte ratio (NLR) after operation with clinical outcome

Variables	NLR preoperative		NLR postoperative 24th hours		NLR postoperative 5th Days		Platelet count postopreative 5th days	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Duration of Cross Clamping	-0.141	0.071	0.056	0.342	0.083	0.159	-0.068	0.252
Duration of Cardiopulmonary bypass	-0.127	0.322	0.051	0.392	0.094	0.113	-0.071	0.228
Total Filtrate volume	0.025	0.742	0.011	0.888	-0.133	0.081	0.103	0.178
Length of Intubation	-0.094	0.112	-0.043	0.467	0.026	0.655	0.025	0.674
Length of Intensive Care Unite Stay	-0.059	0.321	0.043	0.467	-0.004	0.940	0.059	0.321
Postoperative drainage volume	-0.086	0.145	0.032	0.591	-0.042	0.477	-0.029	0.624
In-hospital Stay	-0.053	0.369	0.071	0.229	0.089	0.133	-0.062	0.292
Ultrafiltration	0.017	0.778	0.073	0.214	0.315	<0.001	-0.334	<0.001

r: Spearman Correlation Coefficient

Table 5: Relationship between the ultrafiltration and postoperative neutrophil / lymphocyte ratio (NLR) and platelet count variables. (Multiple linear regression analysis)

Variables at postoperative 5th Days	B	Standard Error	β	*P*-value
NLR	0.020	0.006	0.218	<0.001
Platelet Count	-0.001	0.0003	-0.241	<0.001
	Adjusted R Square = 0.142 F(2,285)= 24.683 n=288 *P*<0.001			

Discussion

The main findings of this study were that neutrophil count and NLR were significantly increased, and platelet and lymphocyte counts were significantly decreased post-operatively compared to their pre-operative levels in adult patients undergoing UF during CPB. In addition, the post-operative increase of NLR and decrease of platelet count were significantly correlated with UF. However, none of the other perioperative or post-operative patient features was associated with the studied variables. Our data suggest that UF may be implicated in post-operative inflammation, especially in adult patients who have undergone CPB.

Recently, several studies have demonstrated that extracorporeal circulation during CPB triggered a systemic inflammatory response, which was a major cause of postoperative complications after cardiac surgery [1,2,4,10]. Neutrophils, which are central in the mediation of systemic inflammatory responses to CPB and are activated by the complement system and kallikrein, arrive rapidly at sites of acute inflammation where they are responsible for phagocytosis and killing of invading pathogens by releasing proteolytic and cytotoxic enzymes (including elastase, myeloperoxidase and lactoferrin), chemokines, cytokines and arachidonate metabolites [7]. Over-activation of neutrophils, on one hand, is involved in the collateral destruction of tissues and cell together with injury from oxygen free radicals. On the other hand, activation of inflammatory cascades by the 'non-self' foreign surfaces of the CPB circuit result in cellular damage, endothelial cell and leukocyte activation, histamine release, increased vascular permeability and generalized inflammatory responses [11].

Miniaturizing the CPB and related extracorporeal circulation (ECC) units [12], improving the inner surface of the ECC that has direct contact with blood [13] or working on the beating heart without CPB [14] may attenuate the negative outcomes of CPB by diminishing the inflammatory response during cardiac surgery. New generation CPB devices are manufactured with simple and miniaturized ECC units [15]. Similarly, reducing the duration of CPB during surgery was suggested as a method to attenuate the inflammatory response of CPB [16]. Mongero et al. [10] have demonstrated a positive correlation between postoperative complications with the duration of CPB in a review of 73,506 cardiac procedures from a national registry (SCOPE). In the current study, subgroup analysis of extended CPB duration (longer than 120 minutes) did not reveal any association with postoperative complications.

UF during CPB (just before the cessation of CPB) is also a favored technique to attenuate inflammation attributed to prolonged CPB by filtering the circulating mediators and to hemoconcentrate the blood in low HCT patients by removing excess water that may accumulate by priming CPB and intravenously administered fluids [10]. Hemoconcentration of the blood during UF is an imperfect technique resulting in confusing and opposing data on the evaluation of UF and the generation of inflammatory mediators [17,18]. Torina et al. [17] reported an increased inflammatory response despite the use of modified UF in adults undergoing coronary bypass grafting. Soliman et al. [18] reported an increase in serum lactate levels after UF during CPB. NLR can be easily calculated using complete blood count and is a simple and cost-effective test to provide valuable data about systemic inflammatory responses [19]. In the current study, NLR was used to evaluate the inflammatory status of adult patients who underwent UF during CPB. We have shown for the first time that NLR was increased at the 5th postoperative day in adult patients with CPB undergoing UF compared to CPB patients who did not undergo UF.

Giakoumidakis et al. reported an association between increased NLR and increased mortality and morbidity in patients undergoing cardiac surgery [20]. However, in that study, postoperative complications were not associated with increased NLR whereas in the current study, the use of UF during CPB was significantly associated with high NLR. In a study that evaluated adult patients undergoing CABG with MUF after CPB, it was observed that UF patients had higher SVR, cardiac output and PVR at the end of the surgery, which were decreased to baseline levels after 48 hours [21]. We hypothesize that an increased systemic inflammatory response resulted in a rollback in cardiovascular improvement 48 hours after cardiac surgery in the UF group. Future investigations are needed to establish this hypothesis.

In addition, to account for any bias in data interpretation due to the long duration of CPB in patients undergoing UF, a subgroup analysis was carried out with patients classified according to the duration (<120 minutes and > 120 minutes) of the CPB. The increase in the NLR was similar between the groups, which suggests that UF led to the increase in NLR, and not the duration of CPB (Figure 3). In addition, there was a significant and positive correlation between the UF and serum NLR in adult patients after cardiac surgery with UF during CPB. These findings suggest that monitoring of the NLR has the potential to make simple predictions about the status of inflammation in adult patients undergoing cardiac surgery with CPB.

Data from the current study demonstrated that UF was associated with a significant decrease in platelet levels even though postoperative blood loss was not significantly different between the groups. In a review article, Weerasinghe et al. [22] reported that upon exposure to CPB and artificial surfaces, platelet counts are decreased but platelet cell functions are increased due to structural changes such as expression of a range of surface molecules that mediate their hemostatic and inflammatory functions and biochemical changes such as secretion of the α-granules that contains a trimeric glycoprotein named thrombospondin [22]. In subgroup analyses in the current study, CPB lasting for two hours showed significantly decreased platelet counts; moreover, CPB accompanied by UF decreased the platelet counts even more (please see Table 5 for the regression analysis). Of note, the postoperative blood loss in both groups was similar suggesting that the activation of platelets may compensate for impaired platelet counts and lead to lower postoperative risk of bleeding and/or need for transfusion. Kiziltepe et al. [23] reported that UF resulted in low platelet levels but also less bleeding related complications. The current study supports this observation. An analysis of previously published data and results of the current study demonstrates the need for careful platelet focused management of unavoidable bleeding during surgery in patients with complaints such as complicated aneurism or dissection repair.

Limitations

The first limitation of the present study was the low number of patients in one hospital. Therefore, a multicenter study with a large number of patients needs to be carried out in order to further confirm our findings. Secondly, although it has been carefully studied, collected prospectively and analyzed independently, the retrospective design of our study may potentially be susceptible to systematic error and bias. The third limitation was lacking the measurement of inflammation specific parameters or acute phase reactants to support the study results. Finally, the patient groups belonging to different preoperative diagnoses were not balanced because of ethical rules while conducting and the inclusion of the patients in the study. Again, for the same reason, patients had different volumes of ultrafiltration. Future studies are needed to further develop and confirm these initial findings by classifying the procedures for each type of heart disease.

Conclusion

The use of UF during CPB was associated with increased post-operative NLR and decreased platelet count in adult patients after CPB surgery. Although this association was statistically significant, none of the other postoperative complications were significantly associated with the use of UF. In the light of the study results, it is recommended that the UF procedure is chosen solely for those patients with low hematocrit because of volume overload. It should not be chosen for reducing circulating mediators for the attenuation of whole body inflammatory response by after CPB in adult cardiac surgery patients.

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