Clinics in Surgery

Research Article
Published: 12 Jun, 2019

Kidney Protection by Continuous Hemodiafiltration during and Post Cardiopulmonary Bypass

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Abstract

Background: Although continuous hemodiafiltration may protect the kidney by removing inflammatory cytokines released during Cardiopulmonary Bypass (CPB), it remains rather controversial whether renal replacement therapy could also remove end-products of hemolysis that are thought to play a central role in the development of acute kidney injury (AKI) after cardiac surgery with CPB.

Methods: The incidence of AKI has been investigated in two groups of patients undergoing coronary surgery with CPB either with (n=17) or without (n=16) continuous intraoperative and 6 h postoperative hemodiafiltration by perioperatively monitoring plasma free hemoglobin (fHb) and haptoglobin levels, retention parameters and diuresis.

Results: Plasma fHb increased in both groups during CPB ($p<0.05$), whereas urinary fHb was not influenced by hemodiafiltration. Plasma haptoglobin reserve was similarly depleted postoperatively in both groups without reaching a critical level. Filtration significantly improved urine output during CPB (418.07 ± 386.86 *vs*. 224.82 ± 130.7, $p<0.05$), reduced postoperative AKI score ($p<0.05$) and maintained creatinine levels at baseline up to the 10th postoperative day.

Conclusion: Continuous hemodiafiltration during CPB does not remove fHb, but reduces transfusion by increasing acid excretion and urine output thus indirectly diminishing the degree of intravascular hemolysis and the risk for AKI after cardiac surgery.

Keywords: Acute kidney injury; Free hemoglobin; Hemodiafiltration; Cardiopulmonary bypass

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Received Date: *27 Apr 2019*
Accepted Date: *07 Jun 2019*
Published Date: *12 Jun 2019*

Citation:
Friedrich M, Andrasi TB, Kolle J, Awad G, Al-Sabri SMA, Tirilomis T. Kidney Protection by Continuous Hemodiafiltration during and Post Cardiopulmonary Bypass. Clin Surg. 2019; 4: 2470.

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Introduction

Destruction of red blood cells (hemolysis) during cardiac surgery using Cardiopulmonary Bypass (CPB) and sublethal damage caused by factors related to the contact with the extracorporeal circuit are associated with plasma release of free hemoglobin. The underlying mechanisms include mechanical sheer stress, turbulences, microbubbles and air entrapment applied to the red blood cells within the perfusion circuit [1]. After hemolysis, plasma Free Hemoglobin (fHb) exists in a dynamic equilibrium of tetramer and α-ß-subunit heterodimers, with a predominant dimer state at low plasma Hb concentrations [2]. Thus, hemodilution characteristic to CPB further results in an increased dimer concentration. Heterodimers are of relatively small molecular size allowing for protein translocation and access to vulnerable anatomic sites such as the kidney, where it causes oxidative and nitrosative damage [3-5]. Furthermore, hemolysis releases poorly liganded free iron that is nephrotoxic as it forms reactive nitrogen oxide species, such as hydroxyl radicals and superoxide anions, particularly in acidic environments such as the renal tubular urine [6-9]. Both hemodilution and CPB-associated hemolysis reactively increase the need for transfusion that further triggers intravascular hemolysis thus resulting in a vicious cycle that enhances the risks for acute kidney injury in a positive feed-back manner. Conventional ultrafiltration is a technique capable of removing large amount of fluid (isotonic plasma water) while reducing inflammatory mediators complicating CPB procedures [10]. Although hemodiafiltration can be an effective tool to ameliorate the extent of hemodilution and inflammation, it remains unclear whether patients prone to acute kidney injury after cardiac surgery could benefit from the early initiation of renal replacement therapy with hemodiafiltration via a suppression of the hemolysis end-products and their impact on kidney function.

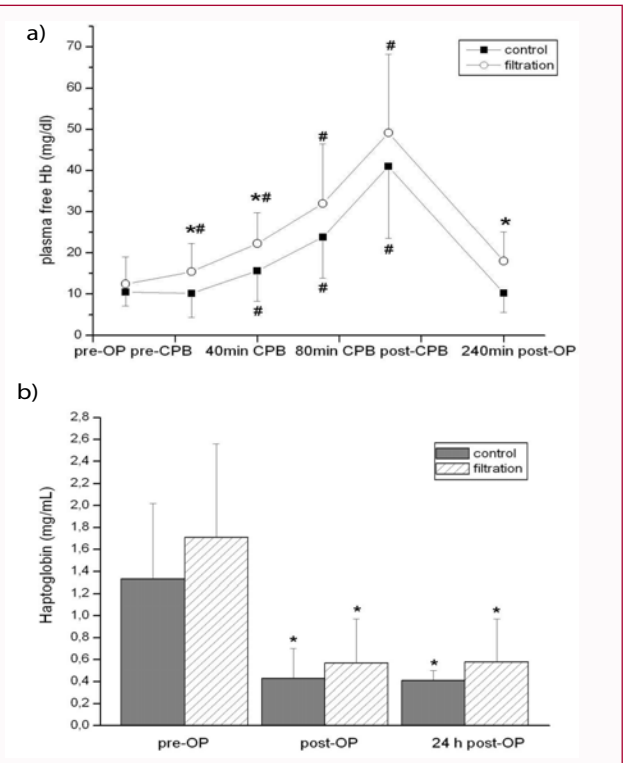

Figure 1: Plasma free hemoglobin and haptoglobin. **a)** Changes in plasma free hemoglobin during the operation. *p<0.05 *vs.* corresponding control group values; #p<0.05 *vs.* **b)** Baseline values of the same group; Perioperative changes of haptoglobin levels *p<0.05 *vs.* preoperative values of the same group, #p<0.05 *vs.* corresponding values of the control group.

Material and Methods

Patient selection and randomization

This prospective interventional randomized study was conducted over a 4 month-period and included 33 adult patients undergoing routine Coronary Artery Bypass Grafting (CABG) at our institution. The study protocol was approved by the Institutional Review Board of the University of Göttingen (No.16-4-10). Written informed consent was obtained before enrollment from the legal guardian of each patient with assent from the patient when appropriate. Exclusion criteria were hematologic disorders, chronic dialysis, and age >80 years old, redo cardiac operation and perioperative hemodynamic instability requiring mechanical circulatory support. The included patients were randomly assigned in advance into two groups: a treated group (hemodiafiltration=filtration) and a control group, with a computerized minimization program (https://www.sealedenvelope.com/simple-randomiser) balanced with respect to age, gender, body mass index, diabetes mellitus and renal dysfunction. Randomization was blinded for surgeon and anesthesiologist, but not for cardiovascular perfusionist and ICU nursing personnel.

Standardized surgical procedure

All procedures were performed electively following a fixed anesthetic protocol. Premedication was achieved with diazepam 10 mg to 15 mg. Peripheral venous and radial arterial cannulae were inserted under local anesthesia. All patients had a standard anesthetic technique: fentanyl (10 to 15 µg/kg) + midazolam 0.05 mg/kg + pancuronium (0.1 mg/kg) for induction, remifentanil infusion (0.05 to 2 µg/kg/min) + propofol infusion (50 to 100 µg/kg/min) + isoflurane (1% to 2%) or sevoflurane (2% to 2.5%) for maintenance of anesthesia. After intubation and institution of mechanical ventilation central venous catheter was introduced into the right internal jugular vein. Cefuroxim 2000 mg was administered intravenously. Sternotomy was performed. Surgical preparation of arterial and venous grafts was similarly performed in all patients. Before cannulation, unfractionated heparin was administered to achieve and maintain an activated clotting time >450 seconds. Cannulation of the aorta and right atrium was done and non-pulsatile CPB in normothermia was performed using a roller pump (Stockert) and membrane oxygenator (Terumo-Vaskutek). The circuit was primed with 1600 ml of solution comprising 500 ml 6% hydroxyethyl starch 130/0.4, 20% mannitol (5 mg/kg), $NaHCO_3$ (40 mEq), 2 g tranexamic acid and acetate Ringer solution. Pump flows of 2.2 to 2.5 l/min/m^2 to achieve a venous saturation of 0.65 to 0.75. Mean arterial pressure between 50 to 70 mmHg were targeted during CPB. Normal systemic vascular resistance was maintained by addition of norepinephrine and nitroglycerine. Myocardial protection was achieved with intermittent cold blood cardioplegia (Buckberg solution). All patients had their CABG performed in a similarly manner. Alpha-Stat regulation of blood pH was similarly used in both groups. Heparin was reversed with protamine at the end of CPB. Packed Red Cells (PRCs) were added whenever necessary to maintain a minimum calculated hematocrit of 25% during the procedure.

Continuous hemodiafiltration technique

Zero balance continuous hemodiafiltration was performed in the treated group with a dialysate flow of 3000 ml/h and a blood flow to 300 ml/min (Multifiltrate; filter: Ultraflux EMiC2, polysulfone membrane 1.8 m^2; solution: multiBic 2 mmol/L potassium, Fresenius Medical Care, Homburg, Germany). Continuous veno-veno hemodialysis system was connected to the extracorporeal circuit before the venous reservoir. Hemodiafiltration performed during the entire CPB period. After completion of the CPB, the hemodiafiltration was continued for additional 6 h via a temporary dialysis catheter inserted preoperatively into the femoral vein.

Data collection

Hemodynamic monitoring, arterial blood sampling and urine output measurements were performed at 20 min intervals during the operation and at 4 h postoperatively. Venous blood samples for laboratory and special measurements were taken before the operation, immediately after the operation, and thereafter at 24 h intervals for first 10 postoperative days.

Assessed parameters

Operative features including total operation time CPB and cardiac arrest time, fluid input, transfusion of blood products, laboratory parameters and urine output as well as postoperative intensive care stay and total hospital stay periods were included in the current analysis. The level of Free Hemoglobin (fHb), a biomarker of intravascular hemolysis, was determined in both blood and urine. Plasma levels of the fHb-scavenger haptoglobin (Hp) were determined pre- and postoperatively. Postoperative acute kidney injury was diagnosed by Acute Kidney Injury Network (AKIN) criteria within 10 days after the operation [11]. Requirement for renal replacement therapy and further PRCs transfusion were registered.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (mean ± SD) and compared by a two-tailed Student t-test or Wilcoxon rank sum test in non-parametric responses. Changes in parameter

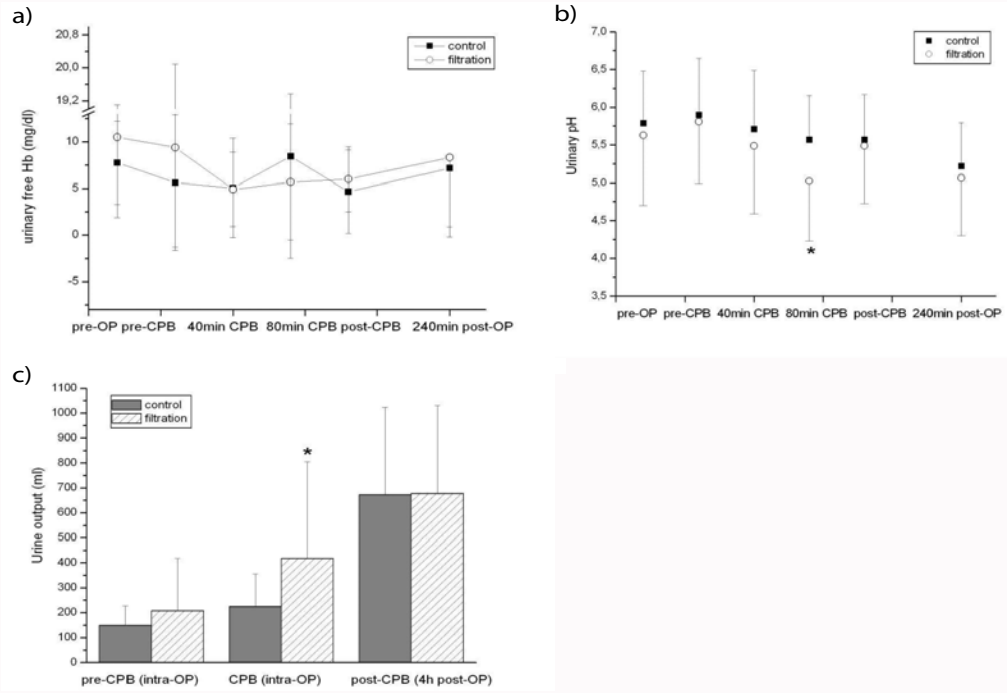

Figure 2: Urinary parameters during the early postoperative period. **a)** Free hemoglobin **b)** Urinary pH **c)** Urine output *p<0.05 *vs.* corresponding value of the control group.

over the time and comparison of multiple mean values were tested using repeated measures Analysis of Variance (ANOVA) followed by paired Student t-test. Categorical distributions were expressed as percentages and analyzed using Pearson's chi square test or Fisher's exact test. The statistical analysis was done using OriginPro and SPSS version 10.0 software (SPSS Inc., Chicago, IL). Statistical significance was defined at the level of $p<0.05$.

Results

Demographic and procedural data

No significant differences in preexisting comorbidities were observed in the two groups (Table 1). The patients in the filtration-group had a lower LV-EF compared to the patients in the control group. However, LV-EF was not a predictor for any of the biomarkers tested. All 33 patients included survived the hospital stay (Table 2). None of the patients required postoperative kidney replacement therapy. Transfusion was required less often in the filtration group (2 patients) than in the control group (7 patients without reaching the level of significance (p=0.216). When transfusion was needed, RCPs units were comparable in the control and filtration groups (3.4 ± 2.6 units vs. 3.8 ± 3.2 units, respectively, p=0.459).

Biomarkers of intravascular hemolysis

Plasma fHb increased significantly in both groups during CPB ($p<0.05$) and returned to baseline values 4 h postoperatively (Figure 1a). These changes were joined by a significant and similar depletion in the plasma haptoglobin reserve after the operation ($p<0.05$) that also persisted 24 h later in both groups (Figure 1b), without dropping below the minimal normal reference value of 0.3 mg/ml. Interestingly, plasma fHb levels increased more in the filtration group than in the control group during CPB and remain slightly higher at 4 h after the operation (Figure 1a). In contrast, urinary fHb (Figure 2a) remained similar and unchanged in both groups during and after the operation, whereas urinary pH (Figure 2b) was slightly decreased by filtration during CPB, achieving the level of significance at 80 min CPB (p=0.044) and returning to baseline levels after the end of CPB.

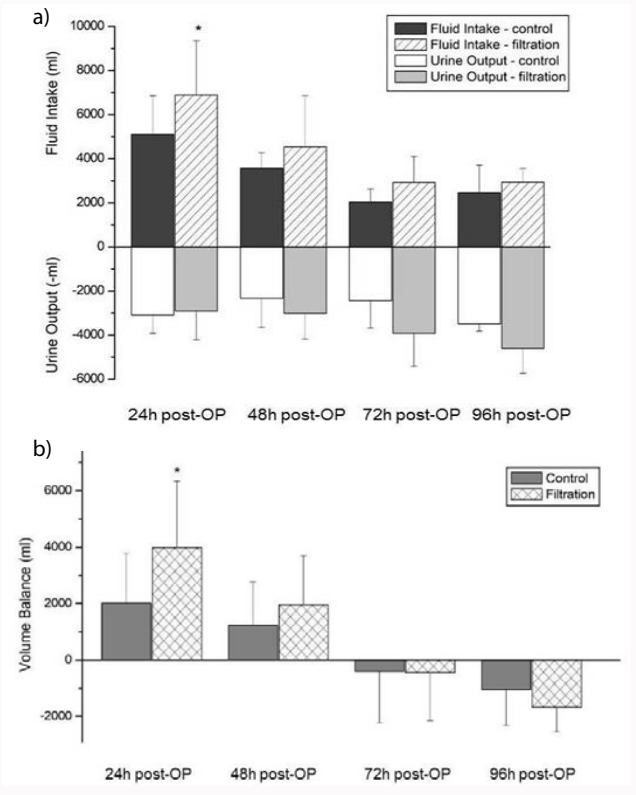

Figure 3: Postoperative fluid balance. **a)** Daily fluid intake and urine output. **b)** Overall fluid balance during the postoperative period. *p<0.05 *vs.* corresponding value of the control group.

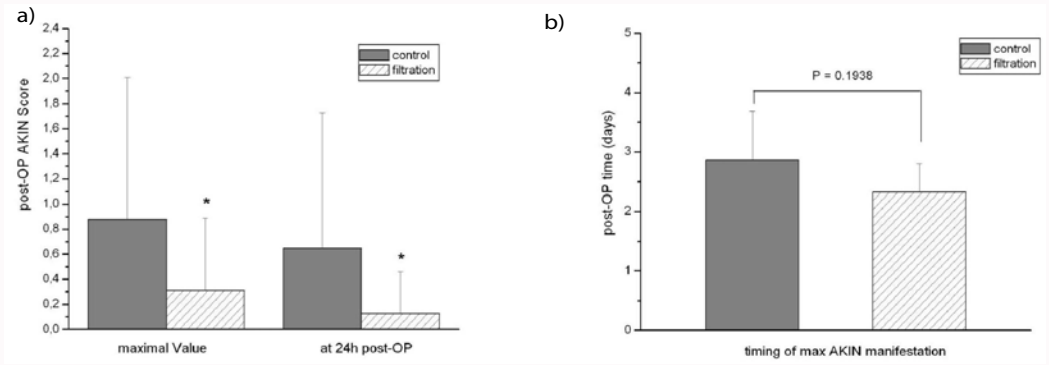

Figure 4: The AKIN score. **a)** Maximal values and 24 h values. **b)** Appearance time of the maximal AKIN score is depicted. *p<0.05 *vs.* the control group.

Table 1: Demographic Data.

Pat. Nr.	Control	Filtration	P-value
	17	16	
Age (Mean ± SD)	67.5 ± 8.4	62.1 ± 10.4	0.0622
BMI (Mean ± SD)	29.9 ± 4.0	29.1 ± 4.0	0.306
Male Gender	14	13	1
Diabetes mellitus	1	3	0.3326
Renal Dysfunction	3	3	1
COPD	2	2	1
LV-EF <35%	1	3	0.3326
Nr. of Bypasses	3.0 ± 0.7	3.7 ± 0.7	0.0895

BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; LV-EF: Left Ventricular Ejection Fraction

Markers of kidney function

Urine output was significantly improved in the filtration group during CPB (Figure 2c), despite comparable fluid administration during the operation (1844 ± 651 ml in the filtration group vs. 1688 ± 629 ml in the control group, p=0.2476). However, this positive effect did not persist longer than 24 h postoperatively and resulted in similar fluid supply, urine output, and volume balance in both groups (Figure 3a and 3b). Moreover, filtration significantly reduced the maximal postoperatively determined AKIN score (p=0.0412) as well as the AKIN score determined at 24 h after the operation (p=0.0453, Figure 4a). The timing of maximal AKIN score manifestation did not differ between the groups (Figure 4b). Finally, filtration maintained the plasma creatinine levels at baseline values during the entire postoperative period, whereas a significant increase in creatinine levels (p<0.001) was assessed between the 2nd and the 9th postoperative days in the control group (Figure 5).

Table 2: Intra- and postoperative Times.

Patient Nr.	Control	Filtration	P-value
	17	16	
Operation (min)	230.3 ± 57.7	247.4 ± 44.6	0.2413
CPB (min)	111.2 ± 28.7	124.9 ± 34.2	0.1282
Cardiac Arrest (min)	68.8 ± 19.6	77.9 ± 26.7	0.1896
ICU Stay (days)	3.0 ± 2.7	2.4 ± 1.5	0.4183
Hospital Stay (days)	13.2 ± 11.9	12.3 ± 4.3	0.3709

CPB: Cardiopulmonary Bypass; ICU: Intensive Care Unit

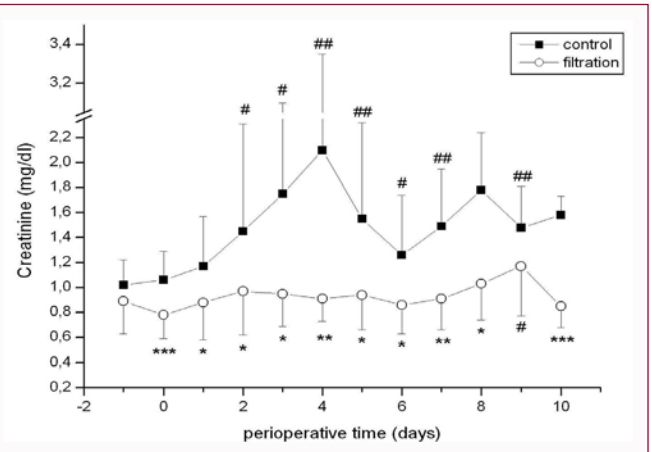

Figure 5: Perioperative changes of plasma creatinine. *p<0.05, **p<0.01 and ***p<0.001 *vs.* corresponding values of the control group #p<0.05; ##p<0.001 *vs.* the baseline values of the same group.

Discussion

The present study reveals that the homeostatic imbalance caused by CPB-induced hemolysis promotes renal dysfunction during the early postoperative period in CABG patients. Although hemodiafiltration proves unable to directly remove fHb from plasma or urine, it may protect renal function by improving hemoconcentration and reducing the need for transfusion. Previous studies showed that fHb is released to the plasma after the institution of CPB, and it reaches its nephrotoxic heterodimer form proportionally with CPB-associated hemodilution [2,10]. Our data confirm higher free plasma fHb levels found after induction of anesthesia and at 20 min CPB in the filtration group (Figure 1a). This finding could be a consequence of higher hemodilution assessed at these particular time-points due to the priming solution and cristalloid cardioplegia volumes During intravascular hemolysis, haptoglobin - a plasma scavenger protein - accomplishes a certain clearance and detoxification of extracellular fHb and hemin [12,13]. According to a previous study intravascular sequestration is the most effective way by which Hp prevents the Hb-induced renal damage. Our present results further demonstrate that hemodiafiltration does not influence the physiologic scavenger activity of Hp that remains potent during the entire operation [14]. This appropriate activity results in constant urinary fHb levels in both groups during and after the operation (Figure 4a). Under regular uncomplicated surgical conditions, in patients with normal coagulator function -such as in our study the plasma Hp reserves were significantly depleted during and after the operation in both groups (Figure 1b); however, without being entirely consumed, and remaining in the normal range of 30 to 200 mg/dl [15]. Since fHb: Hp complexes are entirely metabolized in the liver or by intravascular

macrophages, plasma Hp takes longer than Hb to normalize after recovery, possible remaining decreased even in the presence of normal Hb levels [16]. Whereas Hp supplementation was shown to have a beneficial effect and protect hemolysis-induced kidney injury in CABG patients suffering from extensive acute intravascular hemolysis, the question arises whether Hp supplementation would be required and beneficial under normal operative circumstances [17]. In as much as the primary clinical criteria for Hp administration and dosing in this study was the appearance of hemoglobinuria, our results reveal that patients not suffering from hemolytic disorders or not being under anticoagulation therapy do not develop accentuated hemoglobinuria during CPB (Figure 2a) and therefore might neither require nor profit from Hp supplementation. We incline to believe that the stable hemoglobinuria assessed during the entire operation in our study might reflect the relatively short and uncomplicated elective operations performed on hemodynamically and cardiopulmonary stable patients. Interestingly, a slight drop of urinary pH was observed parallel to the duration of filtration and this drop became significant at 80 min CPB (Figure 2b). Urine pH generally mirrors the degree of acidification of the urine that normally varies with systemic acid-base balance and reflects a low acid retention. In patients with metabolic acidosis, the appropriate protective physiologic response is the increase of urinary acid excretion, with the urine pH falling below 5.3 and often below 5.0 [18]. Previous studies already demonstrated that acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone [19]. Accordingly, our results reveal that acidic urine in the filtration group during CPB is accompanied by improved urine output. Moreover, ultrafiltration significantly reduced the CPB-related postoperative AKIN score in our study and maintained creatinine levels almost unchanged during the first 10 postoperative days (Figure 4); and these findings are in consent with Song et al. [20], who recently demonstrated an association between the amount of CPB urine output and the incidence of postoperative acute kidney injury. Increase of urinary pH after ending CPB reflects the sufficient hydration performed in the filtration group (Figure 3a). A persistently low urine pH after the operation could indicate inadequate volume repletion [21]. Whereas Magruder clearly demonstrated that volume-neutral zero balance ultrafiltration protects against post-CPB kidney injury, Paugh and colleagues found that overzealous volume removal resulted in higher postoperative AKIN scores [22,23]. Nonetheless, filtration significantly improved urinary output during CPB in our study and prevented the increase of creatinine levels as assessed in the control group during the first 10 postoperative days (Figure 5). The degree of hemodilution during CPB has been shown to be an independent risk factor for acute renal failure requiring dialysis [24]. By reducing hemodilution, filtration also reduces the need for postoperative transfusion, indirectly decreasing further development of transfusion-associated intravascular hemolysis [25-27]. Our results show that filtration during CPB does not influence the requirements for intraoperative transfusion, however it may reduce the need for transfusion in the postoperative period and, thus, additionally protect against kidney dysfunction. On the other side, filtration reduces hemodilution that is a known to trigger intravascular hemolysis and, therefore, diminishes the need for postoperative transfusion [10].

Conclusion

Continuous hemodiafiltration during CPB does not remove fHb, but may reduce hemodilution and need for transfusion, thus diminishing the degree of intravascular hemolysis and the risk for acute kidney injury after cardiac surgery.

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