# Normovolemic modified ultrafiltration is associated with better preserved platelet function and less postoperative blood loss in patients undergoing complex cardiac surgery: A randomized and controlled study

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**Objective:** The purpose of the investigation was to study the impact of normovolemic modified ultrafiltration (N-MUF) on hemostasis and perioperative blood loss.

**Methods:** Fifty patients scheduled for elective complex cardiac surgery were enrolled in this prospective, randomized, and controlled study. Patients were randomized into a control group (n = 25) or an N-MUF group (n = 25). N-MUF was performed using a BC140plus Filter (Maquet Cardiopulmonary AG, Hirrlingen, Germany) in the N-MUF group. Blood samples were taken before (T1) and 30 minutes after (T2) N-MUF in the N-MUF group and at corresponding time points in the control group. Platelet function analyses (TRAPtest, ASPItest, ADPtest) using multiple electrode aggregometry (Multiplate, Dynabyte, Munich, Germany), thrombelastometry (ROTEM, Pentapharm GmbH, Munich, Germany), and conventional laboratory coagulation analyses were performed at each time point. Intraoperative and postoperative transfusion requirements, hemostatic therapy, and blood loss were recorded.

**Results:** There were no significant group differences in demographic or surgical data. At T1, platelet aggregation revealed no significant group differences in the TRAPtest, ASPItest, or ADPtest. Platelet aggregation at T2 was significantly higher in the N-MUF group compared with the control group in the TRAPtest (65 [50/87] U vs 44 [28/51]; $P < .001$), the ASPItest (52 [36/69] U vs 22 [8/47] U; $P = .001$), or the ADPtest (39 [28/51] U vs 28 [19/39] U; $P = .009$). The postoperative chest tube blood loss was significantly lower in the N-MUF at 24 hours (890 [500/1100] mL vs 1075 [800/1413] mL in the N-MUF group vs the control group; $P = .039$) and 48 hours (900 [550/1350] mL vs 1400 [900/1750] mL; $P = .026$) postoperatively. Conventional laboratory coagulation analyses and thrombelastometric parameters did not differ within the groups at T1 or T2.

**Conclusions:** N-MUF improved general platelet aggregation and reduced postoperative blood loss in a significant manner. However, performing N-MUF did not result in less postoperative transfusion requirements. (J Thorac Cardiovasc Surg 2011;141:1298-304)

Perioperative hemorrhage in patients undergoing cardiac surgery is related to a marked deterioration in prognosis because it is associated with a variety of negative outcomes, such as renal failure, sepsis, atrial arrhythmias, prolonged requirement for mechanical ventilatory support, prolonged hospitalization, and increased mortality.[1] In particular, patients undergoing complex cardiac surgery procedures with cardiopulmonary bypass (CPB) are at increased risk for severe intraoperative and postoperative coagulopathy. In addition to dilution, consumption, and activation of coagulation factors, an imbalance between the coagulation and fibrinolytic system, especially a CPB-induced complex platelet dysfunction, has been shown to be the most important hemostatic abnormality in this setting.[2]

Since the 1970s, several blood filtration techniques have been proposed to prevent or attenuate the adverse effects of CPB on hemostasis. In particular, in pediatric patients undergoing cardiac surgery, the so-called modified ultrafiltration (MUF) method was adopted as standard practice in 75% of pediatric centers in North America to mitigate the distinctive hemodilution caused by CPB.[3] When performing hemoconcentration, this technique removes free water excess after terminating CPB. In this context, MUF

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The work was performed at the Clinic for Anesthesiology, Intensive Care Medicine and Pain Therapy, J.-W. Goethe University Hospital Frankfurt, Frankfurt am Main, Germany.

Funding: The study was funded by the University of Frankfurt and performed without any industrial support.

Disclosures: C.F.W. and C.J. received speaking honoraria from Pentapharm and Dynabyte. C.J. received financial research support from Dynabyte.

Received for publication May 19, 2010; revisions received Aug 30, 2010; accepted for publication Sept 12, 2010; available ahead of print Dec 6, 2010.

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0022-5223/$36.00



doi:10.1016/j.jtcvs.2010.09.057



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**Abbreviations and Acronyms**

aPTT = activated partial thromboplastin time
CPB = cardiopulmonary bypass
INR = international normalized ratio
MEA = multiple electrode aggregometry
N-MUF = normovolemic ultrafiltration

is known to be associated with clinical benefits, such as increased hematocrit and platelet count,[4,5] improved pulmonary performance after reperfusion of the lungs,[6] improved cardiovascular function,[7] and reduced postoperative chest tube blood loss in pediatric patients.[8]

In contrast with pediatric patients, blood filtration during or after CPB is not a part of the standard procedure in adult patients. Its influence on the coagulation system, perioperative blood loss, and the clinical outcome in general remains controversial.[9-11] The aim of the present study was to determine the influence of normovolemic MUF (N-MUF) on perioperative hemostasis, with special regard on platelet function.

## MATERIALS AND METHODS

This prospective, randomized, and controlled monocenter study complies with the Declaration of Helsinki and was approved by the local scientific and ethic review board. All patients gave written informed consent. Before collecting the data, the study was registered online at ClinicalTrials.gov (Identifier: NCT00998647).

### Study Design

Patients were eligible for study inclusion if they underwent elective complex cardiac surgery. Complex cardiac surgery was defined as combined procedures, double-valve surgery, aortic surgery, and reoperations. Further inclusion criteria were defined as age more than 65 years, euroSCORE more than 5, and expected duration of extracorporeal circulation more than 120 minutes. The exclusion criterion was patients' failure to obtain consent. A total of 50 consecutive patients at the Department of Thoracic and Cardiovascular Surgery of J.-W. Goethe University Hospital Frankfurt, Germany, were enrolled in this study between April 2009 and February 2010. Patients were preoperatively assigned to a control group (n = 25) or an N-MUF group (n = 25) by block-wise randomization.

Sociodemographic data, including preoperative antiplatelet therapy, were recorded. Surgical data, perioperative blood loss, and hemostatic therapy, including transfused blood products and coagulation factor concentrates up to 48 hours postoperatively, were assessed. Hematologic analyses were performed 30 minutes before and after N-MUF (or at corresponding time points in the control group) and included routine conventional laboratory, thrombelastometric, and platelet function analyses. No hemostatic therapy was performed during and up to 30 minutes after N-MUF (T2). The primary end point was the arachidonic acid induced ex vivo platelet aggregation in multiple electrode aggregometry (MEA, ASPItest). Secondary end points were the results of conventional laboratory, thrombelastometric, and remaining platelet function analyses and the perioperative blood loss.

### Anesthetic Management

Anesthetic, operative, CPB, and coagulation management were standardized. No changes in surgical, anesthetic, or perfusion techniques were made for the purpose of the study. On the day before the surgery, the patients were treated with 20 mg dikaliumclorazepat (Tranxilium, Sanofi-Aventis GmbH, Hoechst, Germany) for premedication. General anesthesia was induced with 0.3 to 1 $\mu$g/kg sufentanil (Sufenta, Janssen-Cilag GmbH, Neuss, Germany), 1 to 2.5 mg/kg propofol (Disoprivan, AstraZeneca GmbH, Wedel, Germany), and 0.6 mg/kg rocuronium (Esmeron, Essex GmbH, Munich, Germany). The maintenance of general anesthesia was achieved using 1 to 2 Vol% sevoflurane (Sevoran, Abbott, Wiesbaden, Germany) and intermittent boli of sufentanil until the transfer to an intensive care unit. All patients were orally intubated and mechanically ventilated using a LeonPlus anesthesia machine (Heinen & Loewenstein, Bad Ems, Germany). Packed red blood cell concentrates were transfused to maintain a hematocrit greater than 18% during and 25% after CPB.

### Management of Extracorporeal Circulation and Normovolemic Modified Ultrafiltration

The extracorporeal circuit included a membrane oxygenator (Quadrox oxygenator, Maquet Cardiopulmonary AG, Hirrlingen, Germany) and a roller pump system (HL20, Maquet Cardiopulmonary AG) equipped with a heat exchanger (Plegiox, Maquet Cardiopulmonary AG). The circuit was primed anterogradely with 500 mL crystalloid solution (Sterofundin, B.Braun Melsungen AG, Melsungen, Germany), 500 mL colloid solution (6% HES 130/0.4, Voluven, Fresenius Medical Care AG, Bad Homburg, Germany), and 250 mL 20% Mannitol (Mannitol Baxter, Baxter, Unterschleissheim, Germany) according to institutional standards. Heparin (Heparin-Natrium Braun, B.Braun Melsungen AG) was administered repetitively to maintain an activated clotting time of more than 400 seconds after an initial bolus of 400 IE/kg. During CPB, a nonpulsatile flow was maintained at 2.6 to 3 L/min/m$^2$, and the mean arterial blood pressure was targeted at 50 to 70 mm Hg by the addition of norepinephrine (Arterenol, Sanofi-Aventis GmbH), if needed. Myocardial protection was achieved with cold blood cardioplegia (20°C). An antifibrinolytic therapy consisted of the application of 2 g tranexamic acid (Cyclocapron, MEDA Pharma GmbH & Co KG, Bad Homburg, Germany) after induction of anesthesia, and another 2 g was added into the priming volume of the heart-lung machine and during CPB, respectively. Extracorporeal circulation was performed in mild hypothermia. When surgery was completed, patients were rewarmed to 36°C and weaned from CPB. To reverse the anticoagulant effects of heparin, protamine sulfate (Protaminsulfat, Novo Nordisk Pharma GmbH, Vienna, Austria) was administered guided by activated clotting time.

N-MUF was started after the protamine infusion. A hemofilter (BC 140 plus; Maquet Cardiopulmonary AG) with a surface area of 1.35 m$^2$, a priming volume of 98 mL, a maximal transmembranous gradient of 600 mm Hg, a luminal diameter of 215 $\mu$m, and a membrane thickness of 50 $\mu$m was used. The hemofilter was placed in the CPB circuit with blood coming in from the arterial site and returning to the venous site. Accelerated by the roller pump, the blood flow through the filter was 500 mL/min, and the ultrafiltration rate was 150 mL/min. To maintain normovolemia, a simultaneous infusion of 150 mL/min crystalloid solution (Multibic Kaliumfrei, Fresenius Medical Care AG) was administered to the patient using a second roller pump. N-MUF was stopped after a filtration volume of 3000 mL.

### Blood Sampling

Blood samples were taken before (T1) and 30 minutes after (T2) N-MUF in the N-MUF group and at corresponding time points in the control group, respectively, from a preoperatively placed central venous line. The first 10 mL of blood was discarded. For conventional laboratory coagulation and ROTEM analyses, blood was collected into 3-mL tubes containing sodium citrate as anticoagulant (Sarstedt AG, Nürnbrecht, Germany) and a 4.7-mL EDTA tube (Sarstedt AG). For MEA (Multiplate) analyses, the blood was collected into 2-mL heparin-anticoagulated and calcium-balanced tubes (Bloodgas-Monovette, Sarstedt AG).

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