Effect of Ultrafiltration on Pulmonary Function and Interleukins in Patients Undergoing Cardiopulmonary Bypass

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Objective: **To evaluate the effect of ultrafiltration on interleukins, TNF-α levels, and pulmonary function in patients undergoing coronary artery bypass grafting (CABG).**

Design: **Prospective, randomized, controlled trial.**

Setting: **University hospital.**

Participants: **Forty patients undergoing CABG were randomized into a group assigned to receive ultrafiltration (UF) during cardiopulmonary bypass (CPB) or into another group (control) that underwent the same procedure but without ultrafiltration.**

Methods: **Interleukins and TNF-α levels, pulmonary gas exchange, and ventilatory mechanics were measured in the preoperative, intraoperative, and postoperative periods. Interleukins and TNF-α also were analyzed in the perfusate of the test group.**

Measurements and Main Results: **There were increases in IL-6 and IL-8 at 30 minutes after CPB and 6, 12, 24, and 36 hours after surgery, along with an increase in TNF-α at 30 minutes after CPB and 24, 36, and 48 hours after surgery in both groups. IL-1 increased at 30 minutes after CPB and 12 hours after surgery, while IL-6 increased 24 and 36 hours after surgery in the UF group. The analysis of the ultrafiltrate showed the presence of TNF-α and traces of IL-1β, IL-6, and IL-8. There were alterations in the oxygen index, alveolar-arterial oxygen difference, deadspace, pulmonary static compliance and airway resistance after anesthesia and sternotomy, as well as in airway resistance at 6 hours after surgery in both groups, with no difference between them.**

Conclusions: **Ultrafiltration increased the serum level of IL-1 and IL-6, while it did not interfere with gas exchange and pulmonary mechanics in CABG.**

KEY WORDS: coronary artery bypass grafts (CABG), inflammatory mediators, lung, ultrafiltration, interleukins

AFTER CPB, various degrees of pulmonary dysfunction take place that are manifested by lower pulmonary compliance, higher pulmonary resistance, and poor alveolar gas exchange.[1–4] Sometimes severe acute pulmonary dysfunction will lead to death. Several factors may contribute to such pulmonary problems. First, hemodilution makes serum albumin concentration and colloid osmotic pressure drop and the effective capillary filtration pressure to increase. That leads to the accumulation of the plasma water in the interstitial space, which in turn will decrease pulmonary compliance and impair air exchange across the respiratory membrane. Additionally, when the aorta and vena cava are cross-clamped, the lung is ischemic, and metabolic products will accumulate in the interstitial fluid of the lung. After the cross-clamp is released, the oxygenated blood will perfuse the lung again and produce oxygen free radicals, which lead to ischemic reperfusion damage of the lung. Furthermore, hypothermia, the contact of blood with the bypass circuit, and the hemodynamic changes all will cause the production and release of inflammatory mediators.[5–14] That, in turn, causes a systemic inflammatory response that can result in further pulmonary damage.[1–14]

With ultrafiltration, most of the excess free water and a part of these mediators may be eliminated, and the inflammatory response to CPB thus may be attenuated.[15–25]

However, conflicting data exist concerning their effectiveness in removing cytokines, and, recently, controversy has mainly focused on filter performance.[15–18]

In the present study, using a randomized controlled trial design, the authors assessed the pulmonary dysfunction and its associated inflammatory modulation through tissue markers of inflammatory activity in adult patients undergoing elective coronary artery bypass grafting (CABG) with CPB with and without ultrafiltration.

METHODS

The study protocol was approved by the ethics committee of the university, and all patients gave informed written consent before inclusion in the study. A total of 40 patients undergoing CABG were selected for the present study. They were alternately prospectively randomized into a UF group (n = 20) with ultrafiltration during bypass or a control group (n = 20) without ultrafiltration. The physicians responsible for postoperative care were blinded in respect to the study group. Exclusion criteria were: emergency cardiac surgery, recent myocardial infarction, mechanical complications after myocardial infarction, indication for mitral repair, or other surgical procedure in addition to the planned CABG, unstable angina, age younger than 18, hyperglycemia (>180 mL/dL), other inflammatory pathologies, pregnancy, renal insufficiency with a creatinine level higher than 2.0 mg/dL, liver insufficiency with a total bilirubin level higher than 2.5 mg/dL, and transaminase or alkaline phosphatase elevation to at least twice above the higher limit of normal values, use of acetylsalicylic acid or oral anticoagulant in a period shorter than seven days, neurologic evaluation with a Glasgow Coma Score lower than 10, and recent bleeding of the digestive system.

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Anesthesia, Cardiopulmonary Bypass and Ultrafiltration

Anesthesia was induced with midazolam (0.1 mg/kg), sufentanil (2-5 μg/kg), and vecuronium (0.1mg/kg) and maintained with sufentanil (5 μg/kg), midazolam (0.1 mg/kg), vecuronium (0.1 mg/kg) and isoflurane (0.5% to 1.25%). Methylprednisolone (30 mg/kg) was administered to all of the patients after induction of anesthesia.

A membrane oxygenator, roller pump, adult membrane oxygenator, cardiotomy reservoir, arterial line filter, cardioplegia reservoir, 2-stage arterial and venous cannulae, and polyvinylchloride tubes (Braile Biomédica Ind. Come Representações S.A) were used in the extracorporeal circuit for both groups. No cardiopulmonary bypass circuits had heparin coating. The ultrafiltration system was installed with a recirculation arterial line between the venous reservoir and oxygenation chamber by the insertion of a "Y" connector and using a synthetic polyacrylonitrile membrane filter (PAN) 650 SF 1.3 (Laboratórios B. Braun S.A. Rio de Janeiro, Brazil). In the UF group, ultrafiltration was carried out during the entire CPB time, and it was estimated that 1000 mL/h of ultrafiltrate were withdrawn.

Before CPB, heparinization was begun with 400 UI/kg, and additional doses were administered when necessary to maintain an activated coagulation time (ACT) of more than 500 seconds. The pump flow of CPB was 2.4-2.6 L/min/m^2 body surface area and light systemic hypothermia (32-33°C) was maintained throughout CPB. After aortic clamping, cardiac arrest was obtained with anterograde normothermic blood microcardioplegia infusion. Distal anastomoses were carried out, aortic clamping was removed, and proximal aorta anastomoses were completed during the reheating period. Heparin was neutralized with protamine chloride (100 IU/100 IU heparin). All operations were performed by the same surgeon. Thus, neither the surgeon performing the operation nor the anesthesiologist in charge was blinded to the nature of the intervention.

Measurements and Laboratory Examinations

Blood samples were analyzed before induction of anesthesia (T1); 5 minutes before the start of CPB (T2); 30 minutes after CPB (T3); and 6 hours (T4), 12 hours (T5), 24 hours (T6), 36 hours (T7) and 48 hours (T8) after the surgery. Interleukin 1β, interleukin 6, interleukin 8, tumor necrosis factor TNF-α and arterial blood gases were measured. At the same time that blood was sampled, pulmonary variables were calculated, including alveolar-arterial oxygen differences (A-aDO_2) and oxygenation index (PaO_2/F_IO_2).

Concomitant measurements of physiologic deadspace (VD/VT), pulmonary static compliance (Cst), and airway resistance (Raw) were carried out before anesthesia (T1), 5 minutes after the start of CPB (T2), 30 minutes after CPB (T3), and before extubation (T4).

Measurement of Inflammatory Mediators

The serum levels of IL-1β, IL-6, IL-8, and TNF-α were measured at all protocol times. In addition, during ultrafiltration in the UF group, ultrafiltrate samples were obtained. Blood samples were collected in sterile vacuum tubes and were centrifuged at 3,000 rpm at 4°C for 10 minutes to obtain aliquot plasma, which was stored at −80°C until the assays were performed. The measurements of the interleukins were done as samples in duplicate. The IL-6, IL-8, and TNF-α levels were measured with commercially available ELISA test kits (DuoSet Kit, R&D Systems, Inc, Minneapolis, MN). The IL-1β level was measured with an ultrasensitive kit (0.1 pg/mL sensitivity) from R&D Systems, Inc. (Minneapolis, MN).

Pulmonary Variables

During surgery, patients were ventilated with volume-controlled mode, tidal volume 8-10 mL/kg, respiratory frequency 8-12 per minute, fraction of inspired oxygen (F_IO_2) 100% and positive end-expiratory pressure of 5 cmH_2O. In the ICU, patients were ventilated with pressure-controlled ventilation, tidal volume 6 mL/kg, frequency 12 to 16 per minute, inspiratory/expiratory relation 1:2, F_IO_2 40% to 60% and positive end-expiratory pressure of 5-to-10 cm H_2O.

Oxygenation index (PaO_2/F_IO_2) and alveolar-arterial oxygen differences were calculated (A-aDO_2). The assessment of ventilatory mechanics (Cst and Raw) and capnography (VD/VT) were measured with a respiratory profile monitor DX-8100 (CO_2SMO *PLUS*®) Dixtal/Novametrix in the operating room and the ICU. The arterial blood gas tests were performed with Radiometer ABL-700 series, Copenhagen (ABL-735®), Denmark.

Study Outcomes

Primary outcomes were evaluated to determine if ultrafiltration had influence on pulmonary dysfunction after surgery, mechanical ventilation time, and ICU hours. Secondary outcome was inflammatory response, which was assessed by serum levels of IL-1β, IL-6, IL-8, and TNF-α.

Statistical Analysis

To describe the sample profile according to the study variables, frequency analyses were made of the categorical variables and descriptive statistics of the continuous variables with mean and standard deviation values.

To compare the categorical variables between groups, chi-square test and Fisher's exact test (in the presence of expected values lower than 5) were used. To compare continuous variables between groups at baseline, the authors used the Mann-Whitney test. To analyze the influence of using ultrafiltration on pulmonary function variables and in the inflammatory process, an analysis of variance was used for repeated measurements for 2 factors (2-way ANOVA for repeated measures), followed by Tukey's multiple comparison test to compare the groups at any time and profile test for contrasts to analyze the evolution between assessments in each group. The variables were transformed into points (ranks) in the absence of normal distribution. A p value of less than 0.05 was considered significant (The SAS System for Windows, Statistical Analysis System, version 9.4.SAS Institute Inc, 2002-2012, Cary, NC).