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# The use of ultrafiltration for inflammatory mediators removal during cardiopulmonary bypass in coronary artery bypass graf surgery

## *Ultrafiltração para remover mediadores inflamatórios durante circulação extracorpórea na revascularização do miocárdio*

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***Abstract***

***Objective:*** **To investigate the efficacy of ultrafiltration in removing inflammatory mediators released by extracorporeal circulation and to correlate ultrafiltration with alterations in organ function according to the Sequential Organ Failure Assessment Score.**

***Methods:*** **Forty patients were included and randomized into two groups: "without ultrafiltration" (n=20; Group I) and "ultrafiltration" (n=20; Group II). Activated complement 3 and 4, interleukins 1beta, 6, 8 and tumor necrosis factor alfa were measured prior to anesthesia induction (Time1), 5 minutes before extracorporeal circulation (Time 2), in the ultrafiltrate fluid (Time 3), 30 minutes (Time 4), and 6 (Time 5), 12 (Time 6), 24 (Time 7), 36 (Time 8) and 48 (Time 9) hours following extracorporeal circulation. Sequential Organ Failure Assessment Score was evaluated at Time 1, 6 and 9. Statistical significance was established at p d" 0,05.**

***Results:*** **In the ultrafiltrate fluid, only tumor necrosis factor alfa levels was detectable. Levels of activated complement 3 at times 5 and 7 and activated complement 4 at times 5 and 6 were significantly higher in the unfiltered group, and levels of interleukin 6 were higher in the filtered group at times 7 and 8. Interleukins 1beta, 8, tumor necrosis factor alfa, and the Sequential Organ Failure Assessment score were not significantly different between groups.**

***Conclusions:*** **Ultrafiltration significantly filtered tumor necrosis factor alfa but did not influence serum levels of this cytokine. Ultrafiltration with the type of filter used in**

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**this study had no effect on organ dysfunction and should be used only for volemic control in patients undergoing extracorporeal circulation.**

***Descriptors:*** **Extracorporeal circulation. Ultrafiltration. Cytokine. Organ disfunction.**

***Resumo***

***Objetivo:*** **Investigar a eficácia da ultrafiltração na remoção de mediadores inflamatórios liberados pela circulação extracorpórea e correlacionar ultrafiltração com alterações da função orgânica de acordo com o "*Sequencial Organ Failure Assessment Score*".**

***Métodos:*** **Quarenta pacientes foram incluídos e randomizados em dois grupos: "sem ultrafiltração" (n=20; Grupo I) e "ultrafiltração" (n=20; Grupo II). Complementos 3 e 4 ativados, interleucina 1beta, 6, 8 e fator de necrose tumoral alfa foram dosados antes da indução anestésica (T1), 5 minutos antes da circulação extracorpórea (T2), no líquido ultrafiltrado (T3), 30 minutos (T4), 6 (T5), 12 (T6), 24 (T7), 36 (T8) e 48 (T9) horas após término da circulação extracorpórea. "*Sequencial Organ Failure Assessment Score*" foi avaliado nos tempos 1, 6 e 9. Significância estatística foi estabelecida com p ≤ 0,05.**

***Resultados:*** **No líquido ultrafiltrado, apenas níveis de fator de necrose tumoral alfa foram detectados. Níveis de complemento 3 ativado, nos tempos 5 e 7, e complemento 4 ativado, nos tempos 5 e 6, foram significativamente elevados no grupo sem ultrafiltração, e níveis de interleucina 6 foram elevados no grupo ultrafiltrado, nos tempos 7 e 8. Interleucina 1beta, 8, fator de necrose tumoral alfa, e "*Sequencial Organ Failure Assessment Score*" não tiveram diferenças significantes entre os grupos.**

***Conclusões:*** **Ultrafiltração filtra significativamente fator de necrose tumoral alfa, mas isto não influencia nos níveis séricos desta citocina. Ultrafiltração com o tipo de filtro usado neste estudo não tem efeito na disfunção orgânica e deverá ser usada apenas para controle volêmico nos pacientes submetidos à circulação extracorpórea.**

***Descritores:*** **Circulação extracorpórea. Ultrafiltração. Citocinas. Falência de múltiplos órgãos/etiologia.**

## INTRODUCTION

Patients who undergo cardiac surgery with the use of extracorporeal circulation (ECC) suffer a systemic inflammatory reaction, previously referred to as post-perfusion syndrome [1], and now called systemic inflammatory response syndrome (SIRS). The most common causes of SIRS include: surgical trauma, contact of the blood with non-endothelial surfaces, cardiac reperfusion and lung injury from ventilation during anesthesia. These causes activate of a variety of biological systems, such as the complement cascade, coagulation, fibrinolysis, and the cellular and humoral immune system. Clinically, this post-ECC SIRS affects pulmonary, renal, cerebral and cardiac functions. SIRS manifests with fever, tachycardia, arterial hypotension, leukocytosis, coagulopathy, susceptibility to infections, and changes in vascular permeability leading to the accumulation of interstitial fluid, vasoconstriction and hemolysis [2]. In addition, 1-2% of all cases are linked to multiple organ dysfunction syndrome [3].

Tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin 6 (IL-6) and interleukin 8 (IL-8) are the cytokines most involved in post-ECC SIRS. These cytokines are released by activation of the complement system following contact of the blood with the artificial surface of the extracorporeal circuit or through the action of endotoxins. The cytokine release causes significant pathophysiological changes in the organism [4,5]. Ultrafiltration in ECC has been proposed as a means of removing inflammatory mediators.

## METHODS

A prospective, randomized, observational study was carried out in 40 patients who had cardiac artery bypass graft (CABG) surgery, They were assigned to one of two groups according to an alternating designation: no ultrafiltration (n=20) or ultrafiltration (n=20) during ECC (Table 1). The protocol was approved by the Internal Review Board of the institution and each patient gave his/her signed informed consent prior to admission.

Table 1. Clinical characteristics of the 40 patients who underwent cardiac artery bypass graft (CABG) surgery.

| Characteristics | Group I | Group II | p |
|---|---|---|---|
| Gender | 16 M; 4 F | 15 M; 5 F | ns |
| Age (years) | 59.85 ± 9.9 | 59.25 ± 9.7 | ns |
| Body surface area(m²) | 1.77 ± 0.24 m² | 1.86 ± 0.14 m² | ns |
| EuroSCORE logistic(%) | 2.16 ± 1.56 % | 1.89 ± 1.50 % | ns |
| Duration of ECC (minutes) | 74.85 ± 17.6 | 72.40 ± 18.9 | ns |
| Duration of aortic clipping (minutes) | 49 ± 11.6 | 45.50 ± 10.9 | ns |
| Duration of myocardial ischemia (minutes) | 22.35 ± 9.4 | 24.45 ± 7.0 | ns |
| Number of grafts | 2.9 ± 1.0 | 3.1 ± 0.8 | ns |

*M = male; F = female; ns = not statistically significant; Group I - no ultrafiltration, Group II - with ultrafiltration*

Exclusion criteria were: emergency surgery, acute myocardial infarction (AMI) less than three months previously, unstable angina, uncontrolled diabetes mellitus, inflammatory diseases, cardiac ejection fraction < 30%, creatinine level > 2.0 mg/dL, total bilirubin level > 2.5 mg/dL, use of acetylsalicylic acid, corticosteroids or any kind of non-hormonal anti-inflammatory medication less than 7 days prior to surgery, Glasgow Coma Scale < 10, ileus or recent bleeding from the upper digestive tract.

The following demographic information was collected on the patients: gender, age, body surface area, surgical logistic risk score (EuroSCORE) [6], duration of ECC, duration of aortic clamping, duration of myocardial ischemia, and number of coronary grafts received. Standard techniques were used for anesthesia and ECC. Methylprednisolone at the dose of 30 mg/kg was administered shortly after induction of anesthesia in all patients. In the group in which ultrafiltration was to be carried out, a polyacrylonitrile (PAN) synthetic membrane filter (650 SF 1.3 - Laboratórios B. Braun S.A., Rio de Janeiro, Brazil) was installed in the recirculation line between the venous reservoir and the oxygenator. The rate of utrafiltration was controlled at 1000 mL/hr and done during the entire period of ECC.

Patients received heparin prior to ECC using a dose of 400 IU/kg and additional doses were administered as necessary to maintain the activated coagulation time (ACT) > 500 seconds. ECC was initiated with a flow of 2.4 - 2.6 l/min/$m^2$, and mild systemic hypothermia (32-33ºC) was induced in all patients and monitored through a nasopharyngeal sensor. Following aortic clamping, cardiac arrest was achieved using antegrade warm blood cardioplegia. Distal anastomoses were created the aortic clamp was removed, and the proximal anastomoses in the aorta were completed during the re-warming period. ECC was terminated during rewarming when the nasopharyngeal temperature reached 37ºC, and heparin was neutralized using protamine sulphate.

**Parameters analyzed**

The Sequential Organ Failure Assessment (SOFA) score [7] used in this study evaluates six organs and systems based on the following measures: the respiratory system (the ratio of arterial oxygen tension to fractional inspired oxygen concentration - $PaO_2/FiO_2$), the central nervous system (Glasgow Coma Scale), the liver (bilirubin level), coagulation (number of platelets), the kidneys (concentration of creatinine) and the cardiovascular system (level of hypotension). Calculation of the SOFA score was made according to the parameters below and the final result was the sum of the points obtained for each organ or system evaluated:

1. $PaO_2/FiO_2$: above 401: 0 points; 400 - 301: 1 point; 300 - 201: 2 points; 200 - 101 with respiratory support: 3 points; below 100 with respiratory support: 4 points.
2. Platelets (x $10^3/mm^3$): above 150: 0 points; 149 - 101: 1 point; 100 - 51: 2 points, 50 - 21: 3 points; below 20: 4 points.
3. Bilirubin (mg/dL): below 1.2: 0 points; 1.2-1.9: 1 point; 2.0-5.9: 2 points; 6.0-11.9: 3 points; above 12: 4 points.
4. Hypotension: no hypotension: 0 points; mean arterial pressure (MAP) < 70 mmHg: 1 point; dopamine < 5 μg/kg/min or dobutamine (any dose): 2 points; dopamine 5 - 14 μg/kg/min or noradrenalin d" 0.1 μg/kg/min: 3 points; dopamine > 15 μg/kg/min or noradrenalin > 0.1 μg/kg/min: 4 points.
5. Glasgow Coma Scale: 15: 0 points; 13-14: 1 point; 10-12: 2 points; 6-9: 3 points; < 6: 4 points.
6. Creatinine: (mg/dL): below 1.2: 0 points; 1.2-1.9: 1 point; 2.0-3.4: 2 points; 3.5-4.9 or urinary volume 21 - 500 mL/day: 3 points; > 5.0 or urinary volume below 20 mL/day: 4 points.

**Laboratory parameters**

Serial samples of arterial blood were collected from a radial artery, punctured to monitor mean arterial pressure. Arterial blood was analyzed to measure cytokines, complement, platelets, bilirubin and creatinine prior to induction of anesthesia (T1), 5 minutes before the start of ECC (T2), 30 minutes (T4), and 6 (T5), 12 (T6), 24 (T7), 36 (T8) and 48 (T9) hours after the end of ECC. Measurement of plasma levels of cytokines (TNF-α, IL-6 and IL-8) was carried out using an enzyme-linked immunosorbent assay (ELISA; Duoset Kit, R&D Systems, Inc., Minneapolis, MN, USA). IL-1β was assessed using an ultra-sensitive kit (sensitivity 0.1 pg/mL), (R&D Systems, Inc., Minneapolis, MN, USA). C3a and C4a were measured by immunonephelometry (BN Prospec, Dade Behring) in serum samples and the results were expressed as g/L. The normal reference values applied for serum were C3a: 0.9 -1.8 g/L and C4a: 0,1- 0,4 g/L. Gasometry was performed using an ABL3 apparatus (Radiometer, Copenhagen, Denmark). A sample of the ultrafiltered fluid was collected (T3) to measure the levels of TNF-α, IL-1β, IL-6, IL-8, C3a and C4a from the patients whose serum had undergone ultrafiltration. Creatinine and bilirubin were measured at T1, T6, T7, T8 and T9. Platelet count was carried out at all time-points except T3.

**Statistical analysis**

The two groups were evaluated using parametric tests: analysis of variance, Student's t-test and chi-squared test for unpaired samples. For the evaluation of interleukins and activated complement, the Mann-Whitney test was applied. Differences were considered significant when $p<0.05$. The GraphPad Prism software package, version 3.00

for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com) was used in the analysis.

RESULTS

The results obtained with serum measurements of C3a and C4a, IL-1β, IL-6, IL-8 and TNF-α are shown in Figures 1 to 6.

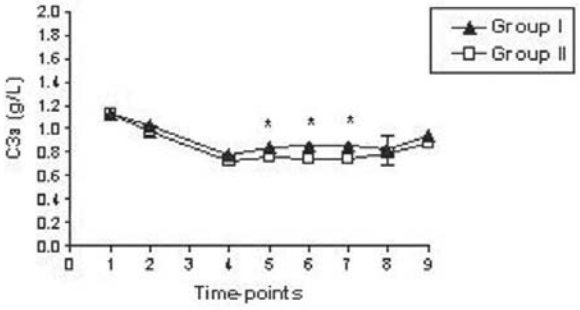


*Fig. 1 - C3a over time. Group 1 - no ultrafiltration; Group II - with ultrafiltration. * statistically significant*

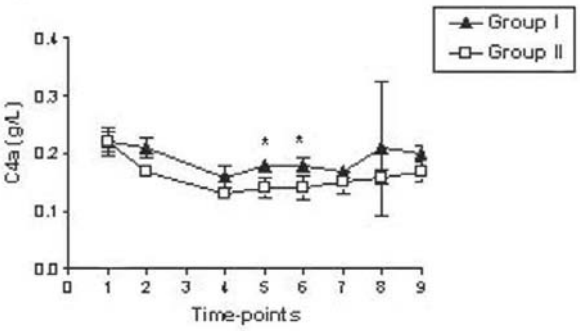


*Fig. 2 - C4a values over time. Group 1 - no ultrafiltration; Group II - with ultrafiltration. * statistically significant*

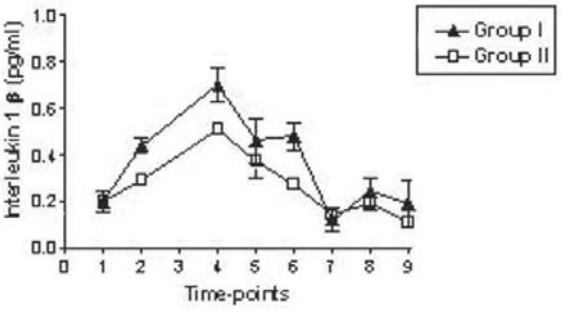


*Fig. 3 - Interleukin 1-â values over time. Group 1 - no ultrafiltration; Group II - with ultrafiltration. * statistically significant*

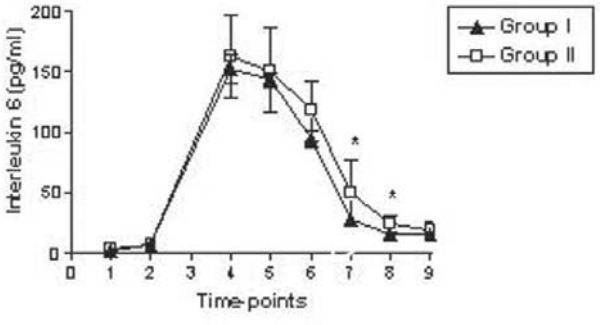


*Fig. 4 - Interleukin 6 values over time. Group 1 - no ultrafiltration; Group II - with ultrafiltration. * statistically significant*

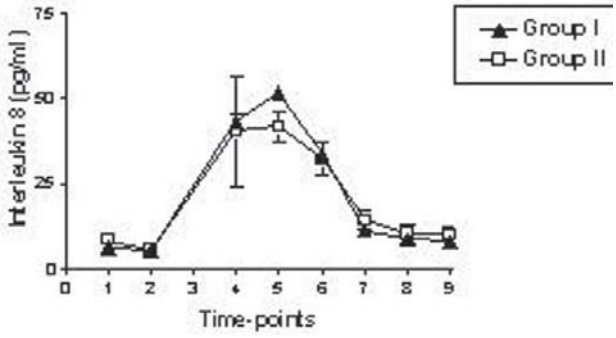


*Fig.5 - Interleukin 8 values over time. Group 1 - no ultrafiltration; Group II - with ultrafiltration. * statistically significant*

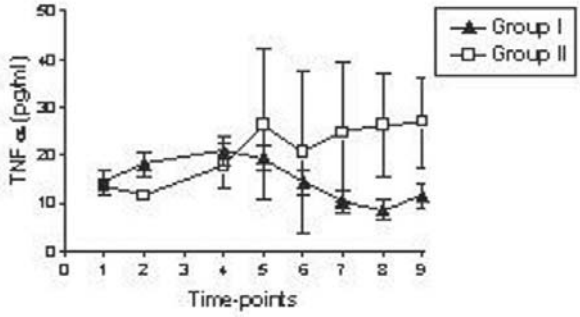


*Fig. 6 - TNF-á values over time. Group 1 - no ultrafiltration; Group II - with ultrafiltration. * statistically significant*

**C3a over time:** Baseline values did not differ significantly between the two groups. Values were slightly decreased prior to extracorporeal circulation (ECC), remained stable during ECC, and were lowest after ECC. At T5, T6 and T7 (6, 12 and 24 hours after ECC respectively), C3a values were significantly higher in the group without ultrafiltration than in the group with ultrafiltration.

**C4a values over time:** Baseline values did not differ significantly between the two groups. At T5 and T6 (6 and 12 hours following the end of ECC, respectively), C4a values were significantly higher in the group without ultrafiltration than in the group with ultrafiltration. C4a values did not differ between the two groups at any other time-points.

**Interleukin 1-β values over time:** Interleukin-1-β levels did not vary significantly before or after extracorporeal circulation (ECC). The group without ultrafiltration had slightly higher values than the group with ultrafiltration, but the difference was not statistically significant.

**Interleukin 6 values over time:** Baseline values did not differ between the two groups. At T4 (30 minutes following extracorporeal circulation [ECC]), interleukin-6 increased markedly with respect to baseline but did not differ between the two groups. The levels gradually decreased, and at T7 and T8 (24 and 36 hours after ECC respectively) the group with ultrafiltration had significantly higher values than the group without ultrafiltration.

**Interleukin 8 values over time:** At baseline the IL-8 levels did not differ, but increased markedly in both groups at T4, after extracorporeal circulation (ECC). Note the gradual decrease in levels after T5 (6 hours after ECC). IL-8 levels did not differ significantly between the two groups.

**TNF-α values over time:** At baseline TNF-α levels did not differ- significantly between the two groups. Starting at T5 (6 hrs after extracorporeal circulation), TNF-α increased in the group with ultrafiltration and decreased in the group without ultrafiltration; however, the groups did not have any statistically significant differences.

With respect to the variables analyzed in the ultrafiltered fluid, significant filtration was only achieved in the case of TNF-α (34.540 ± 21.840 pg/mL). This value was higher in the ultrafiltrate collected at T3 than in the serum collected at T1 in both groups. No statistically significant difference was found in the SOFA scores at T1, T6 and T9 (Table 2).

Table 2. SOFA score in the two groups.

| Time | T1 | T6 | T9 |
|---|---|---|---|
| Group I | 0.525 ± 0.289 | 1.220 ± 0.095 | 1.050 ± 0.352 |
| Group II | 0.600 ± 0.250 | 1.210 ± 0.196 | 1.260 ± 0.193 |
| p-value | 0.8926 | 0.9893 | 0.8208 |

*Group I - no ultrafiltration, Group II - with ultrafiltration*

## DISCUSSION

Ultrafiltration has been used frequently in ECC, principally in patients with compromised renal and/or cardiac function in whom volemic control is difficult. The use of ultrafiltration in these cases is highly effective, improving the hydro-electrolytic balance, reducing swelling and balancing hemodynamics. It has been used principally in pediatric surgery in low-weight children undergoing ECC, when the volume of priming is generally greater than the body volume. Ungerleider [8] reported that modified ultrafiltration in pediatric ECC reduces total body fluid and serum levels of inflammatory mediators, resulting in elevation of hematocrit without transfusion and an improvement in pulmonary compliance in the immediate postoperative period.

The technique of ultrafiltration has been shown to be effective in improving postoperative hemodynamics [8-10] and restoring myocardial [1], cerebral [11], respiratory [4] and hemostatic [9] function following pediatric cardiac surgery. These benefits are principally attributed to the capacity of ultrafiltration to remove excess free-water from plasma [9].

There are controversies regarding the efficacy of ultrafiltration in removing inflammatory mediators (cytokines and complements) and improving the inflammatory response triggered by ECC [1] and postoperative morbidity in neonates and children [9]. The conflicting results from the various studies in the literature [3,12] are partially explained by the different methods of ultrafiltration and the different types of filters with various physical and functional properties. In this study, we chose a synthetic membrane filter capable of supporting high flow rates, with a porosity that allows the passage of particles of up to 30 kDa. Nevertheless, the transport of inflammatory mediators by convection does not depend exclusively on their molecular weight. Other physical factors interfere with the passage of these solutes, making efficacy based only on molecular size unpredictable. Other variables that interfere with transport are: spacial conformation of the molecule, electrical charge, hydrophilia and hydrophobia, ligation to acute phase reactive proteins, and ligation to receptors [13,14]. Current evidence suggests that the most promising option for cytokine clearance is through the mechanism of adsorption in certain types of membrane (polyacrylonitrile, polymethylmethacrylate) during ultrafiltration, along with convective transport of other molecules that have not been detected in ultrafiltration [9]. Tetta et al. [9] suggest that some polymer derived membranes behave as sponge layer, therefore, during the convection, the force at the interior of the membrane expands its pores and the area exposed for adsorption of bigger molecules increases. We chose polyacrylonitrile filter because of its largest available pores (30 kD x 20 kD polysulfone filter) which allowed us to study the molecules in question. We didn't think of internal washing of the hemofilter for detection of the cytokines retained by adsorption during the elaboration of the study. That procedure could help us understand better the filtering process that took place.

The diversity of the studied population was one of the

reasons for difficulties in comparing the obtained data. In this study, comparing gender, age, body surface, surgical risk score (Euroscore), CEC time, aortic clamping time, myocardial ischemic time and number of coronary artery grafts received, there were no differences between the two groups, as shown in Table 1.

The IL-1β and TNF-α stimulate the systemic liberation of IL-6 e IL-8, increasing, in this way, the inflammatory response [15]. The IL-8 is a protein of low molecular weight, belongs to a family of cytokines. It is a potent quimiotaxic agent and activator of neutrofils, capable of increasing the inflammatory response through induction of liberation for free radicals and proteolytic enzymes.

Circulating levels of TNF-α, IL-6, and IL-8 are not present in normal healthy subjects [16]. Tumoral necrosis factor alpha and IL-8 were present in pre-operatory period (T1) in plasma of most of the subjects in our research. The TNF-α has been detected previously in circulation of patients with chronic heart failure, and we suggest that this finding reflect the severity of the cases.

IL-6 is the key mediator in the acute phase response to tissue injury or infection, inducing hepatic synthesis of acute-phase proteins [17]. Elevated plasma levels of IL-6 occur following both cardiac surgery with ECC [18] and non-cardiac surgery [19]. In the present study IL-6 release was high in both patient groups (with and without ultrafiltration), peaking 30 minutes after termination of ECC. Higher measurements were found in the ultrafiltration group at all time-points; however, the difference was statistically significant only at 24 and 36 hours following the end of ECC. This implies a greater acute phase response and suggests a greater degree of tissue damage with the use of ultrafiltration.

The role of neutrophil activation in lung and myocardial injury following ECC has been well-documented [20]. This led us to measure IL-8, a potent neutrophil chemotactic and activating factor [21]. Unlike IL-6, there was no statistically significant difference between the group with ultrafiltration and the group without ultrafiltration. A possible interpretation for this disparity in the release of these two cytokines is that IL-8 release occurs principally in situations of ischemic-reperfusion injury [22], whereas IL-6 release reflects organ response to any kind of acute insult.

Brasil et al [23] studied patients who underwent myocardial revascularization with or without the use of ECC, and detected the presence of TNF-α only in the group in which ECC was used. In our study TNF-α had a different pattern than that of other interleukins. In the group in which ultrafiltration was not carried out, TNF- α levels were relatively consistent over time. The levels of TNF-α increased slightly, but insignificantly, following ECC, and later decreased to slightly below the levels found in the collected 12 hours after the end of ECC. In the group in which ultrafiltration was carried out, there was a gradual but statistically insignificant increase at all time-points and measurements remained high for up to 36 hours following ECC. When we analyzed the ultrafiltered fluid, we observed significant filtration of only TNF-α (34.540 ± 21.840 pg/mL), this value being higher than that in the first serum sample (T1) in both groups (Group I, 14.42 ± 12.16 pg/mL and Group II 13.59 ± 1.98 pg/mL). However, serum levels of TNF-α were not significantly different between the two groups. These findings suggest that although a great quantity of this mediator was filtered by the ultrafiltrator membrane, this procedure seems to have a simultaneous stimulating effect on the production of this cytokine.

Activation of the complement cascade occurs during ECC, predominantly by the alternative route [17]. The longer the duration of ECC, the greater the activation of this system, as expressed by the plasma concentration of C3, C3a and C4 [24]. Additional activation of the complement cascade by the heparin-protamine complex led to an increase in the levels of C3a and C4a following protamine infusion. Contrary to findings in the literature, in the present study C3a and C4a concentrations were lower than control values. C3a levels were significantly different between the two groups at 6, 12 and 24 hours after ECC, and C4a levels were significantly different at 6 and 12 hours after ECC, with higher values in the group without ultrafiltration.

Patients who develop SIRS after ECC suffer changes in organ function and in 1-2% of all cases this is related to multiple organ dysfunction syndrome [3]. No statistically significant differences were found in the SOFA scores between groups.

The SOFA score was used because it is currently considered one of the best methods for monitoring organ dysfunction, since it monitors and grades the function of 6 systems (with points ranging from 1 to 4 in accordance with the degree of dysfunction) rather than signs and symptoms. In this way the SOFA score differs from the APACHE score.

In this work all patients have received 30 mg/kg of methilprednisolone, it is standard to perform bypass at our institution. The corticosteroid administration has been effective action on minimize systemic inflammatory response during and after bypass [25,26].

In the late 1970s and early 1980s, some papers has showed better outcome with methilprednisolone administration in low cardiac output syndrome after bypass with cardiac index increase, coronary blood flow improvement, and lower periphery vascular resistance [27,28]. Fey et al. [29] have showed protective effect by corticosteroid administration with less myocardium depression after ischemia and reperfusion. The corticosteroids have properties on lysossomal stabilization membrane, as consequence less cellular death and improve on viable myocardial cells.

Fosse et al. [30] have showed effects on leukocyte periphery blood, less leucocytes in broncoalveolar washed, improvement on pulmonary function, in patients underwent cardiac surgery with bypass and methilprednisolone administration.

Brasil et al. [31] have showed similar results with corticosteroid administration with less proinflammatory cytokines release in patients underwent bypass. The TNFα has evident release decrease and less adverse systemic effects resulting from inflammatory response after bypass. We believe that corticosteroid administration and short period times of bypass and aortic cross clamp could interfere in cytokine expression. The TNFα, IL-6, IL-8, protein C has diminished release, and IL-10 (anti-inflammatory cytokine) have improvement with corticosteroid administration. The corticosteroid administration has been showed better cardiac index and diminished troponin T release in the postoperative time [32-34].

Although these evidences, there is not consensus about corticosteroid administration and its effect on systemic inflammatory response. The patients underwent bypass and corticosteroid administration still have inflammatory response.

Our aim in this work was showed the additional effects of ultrafiltration in patients underwent to cardiac surgeries with bypass, even with corticosteroid administration.

Short extracorporeal circulation time and aortic clipping time could contribute to diminish cytokines expression. De Vriese et al. [35] showed that venovenous continue hemoconcentration using polyacrylonitrile filter method is the most efficient for withdrawal of inflammatory mediators in septic patients, when compared to other filtering techniques.

The present study is limited by the low number of patients and it may be interesting to perform one another study with more patients. The levels of various substances were analyzed by a point-to-point comparison, rather than a comparison of the area under the curve. The point-to-point comparison offers the advantage of identifying the times at which significant differences are present. Similar studies have routinely used point-to-point comparison and this technique has been shown to be sufficiently precise. Since this is a longitudinal study, there is an add-on effect with respect to the sample size at various time-points. This effect increases the precision of the calculations. The fact that the variances are homogeneous throughout the study also adds greater precision to the calculations. In addition, methodologically similar studies have used sample sizes similar to those used in the present study for the reasons pointed out above.

## CONCLUSION

Ultrafiltration significantly filters TNF-α but ultimately has no effect on serum levels of this cytokine. Ultrafiltration did not remove other mediators of inflammatory response (IL-1β, IL-6, IL-8, C3a and C4a).

The use of ultrafiltration in our study had no effect on organ dysfunction during the postoperative period and should be used only for volemic control in patients who undergo extracorporeal circulation.

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