

Impact of Endograft Material on the Inflammatory Response After Elective Endovascular Abdominal Aortic Aneurysm Repair

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The purpose of this paper is to examine the impact of endograft material on the inflammatory response after elective endovascular abdominal aortic aneurysm repair. Consecutive patients (n = 22, all men, 53 to 82 years old) were divided into 2 groups according to the graft material used: In group A (n = 12) the endovascular device was made of polyester and in group B (n = 10) the device was made of expanded polytetrafluoroethylene (ePTFE). All patients received antiinflammatory drugs in the perioperative period. Fever, white blood cells and platelet count, serum concentrations of cytokines (interleukin 6 [IL-6], tumor necrosis factor alpha [TNF- α], interleukin 8 [IL-8], acute-phase proteins high-sensitivity C-reactive protein [hsCRP] and alpha1-antitrypsin [α 1-antitrypsin]), and complement protein (C3a) were measured preoperatively and 1, 3, 6, 24, 48, and 72 hours after aneurysm exclusion. One patient in each group had a systemic inflammatory response syndrome with 2 of the systemic inflammatory response syndrome (SIRS) criteria. No other complication associated with inflammation were present in any patient. Fever was more frequent in group A patients. Increases of white blood cells and serum concentrations of IL-6, TNF- α , hsCRP, α 1-antitrypsin, and C3a and decrease of platelet count were recorded in both groups, but no statistically significant difference between them was recorded. However, serum concentrations of IL-8 were significantly higher in group A patients 24 hours postoperatively (p = 0.01). No significant difference was apparent in the biological response between patients receiving a polyester or an ePTFE stent graft, except for fever and serum concentrations of IL-8.

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Introduction

Endovascular repair (EVAR) is a relatively new approach in treating abdominal aortic aneurysms (AAA). Compared to conventional surgical repair it is considered to be a less invasive procedure, performed under regional or even local anesthesia, and suitable also for patients with severe comorbidities. It is associated with less postoperative pain, faster mobilization, and shorter hospital stay.¹⁻⁵

Several studies have compared the biological responses between open and endovascular AAA repair; most found the endovascular procedure to be less invasive,^{4,6-15} although there are some findings suggesting that the inflammatory responses is greater in the endovascular group.^{5,16} The endovascular treatment of AAA provokes a systemic inflammatory response, which may result in several complications like cardiac events, pulmonary dysfunction, and renal impairment, sometimes leading to acute respiratory distress syndrome or multiple organ failure.⁶ Most of the times it is limited to a milder "postimplantation syndrome" consisting of fever, leukocytosis, and/or coagulation disturbances.⁷⁻¹⁰

Various theories have been proposed to account for this systemic inflammatory reaction. Injuries of the vascular endothelium during the implantation,⁹ manipulation of the introducer catheters and sheaths inside the aneurysmal thrombus,^{9,15-18} or stimulation by the graft material,^{6,7,9,10,15,19} are some of them.

In order to evaluate the contribution of graft material in the inflammatory reaction we compared fever, white blood cell (WBC) and platelet count, plasma concentrations of proinflammatory cytokines (IL-6, IL-8, TNF- α), acute phase proteins (hsCRP, α 1-antitrypsin), and liberation of complement proteins (C3a) between patients receiving a polyester-lined and those receiving a polytetrafluoroethylene (ePTFE)-lined endograft. All patients received antiinflammatory drugs during the perioperative period.

Materials and Methods

Patients

Consecutive patients ($n = 22$) who underwent elective endovascular AAA repair between February and October 2002 were included in this

study (all men, aged 53–82 years). The study was approved by the local ethics committee and all patients gave their informed consent. The demographic characteristics of the patients are shown in Table I. Patients were divided into 2 groups, according to the graft material of the endovascular device used, as follows:

Group A ($n = 12$): A Talent bifurcated stent graft (Medtronic World Medical, Sunrise, FL USA) was inserted. This device is an external nitinol stent inlaid in woven polyester graft material. It has a proximal uncovered stent and its fixation is suprarenal.

Group B ($n = 10$): An Excluder (W. L. Gore and Associates, Flagstaff, AZ, USA) bifurcated stent graft was used. This endovascular device is a nitinol stent covered internally by expanded polytetrafluoroethylene (ePTFE) graft material. It does not have a proximal uncovered stent and its infrarenal fixation is achieved by friction and small hooks.

A computed tomography (CT) scan with IV administration of contrast was used for the preoperative evaluation of the anatomical characteristics and measurement of all the necessary dimensions for the choice of a suitable device. When a complicated morphology of the aorta was suspected (angulation of the proximal neck, tortuosity or kinking of the iliac arteries), a digital subtraction angiography was also performed.

No statistically significant difference between the 2 groups was observed regarding age, aneurysm diameter, and proximal neck length (all $p > 0.05$) (Tables I, II). In group A the mean aneurysm diameter was 59.8 (± 4.1) mm, and in group B mean the aneurysm diameter was 58.2 (± 6.8) mm. Proximal neck diameter was significantly smaller in group B patients (group A: 25.7 \pm 0.8 mm, group B: 22.7 \pm 0.6 mm; $p = 0.007$).

Procedures

The procedures were carried out in an operating room, equipped with an SIAS SM9-HF C-arm and the possibility to convert to conventional operation in case of failure of the endovascular procedure. Nine of the 12 operations in group A were performed under spinal anesthesia, and 3 under local anesthesia. In 1 patient in group B spinal anesthesia was used and in 9 local anesthesia. The device was inserted via the common femoral arteries, which were exposed bilaterally. The main graft was inserted from 1 side via a 22-24 Fr

Table I. Patient demographics. Age is shown as mean \pm SEM. There was no significant difference between the 2 groups regarding age ($p = 0.346$).

Characteristics and Comorbidities	Group A (n = 12)	Group B (n = 10)
Age, years	71.2 (± 2.1)	67.4 (± 2.5)
Sex, M/F	12/0	10/0
Hypertension (SBP > 150 mm Hg and/or DBP > 90 mm Hg), n (%)	9 (75%)	9 (90%)
Hypercholesterolemia (> 220 mg/dL), n (%)	6 (50%)	4 (40%)
Diabetes mellitus, n (%)	2 (16.7%)	1 (10%)
Current/former smoker, n (%)	9 (75%)	7 (70%)
Ischemic heart disease, n (%)	5 (41.7%)	4 (40%)
Peripheral vascular disease, n (%)	1 (8.3%)	0
Cerebral vascular disease, n (%)	5 (41.7%)	0
Chronic pulmonary disease, n (%)	1 (8.3%)	1 (10%)

Table II. Comparative anatomic and procedural variables. All data are presented as mean \pm SEM. Numbers in bold represent a statistically significant difference

Variable	Group A	Group B	p
Aneurysm diameter, mm	59.8 (± 4.1)	58.2 (± 6.8)	0.418
Proximal neck length, mm	32.9 (± 4.5)	30.8 (± 4.5)	0.771
Proximal neck diameter, mm	25.7 (± 0.8)	22.7 (± 0.6)	0.007
Anesthesia (regional/local)	9/3	1/9	–
Operation time, minutes	86 (± 5)	93 (± 8)	0.628
Occlusion of 1 internal iliac artery, n (%)	2 (16.7%)	1 (10%)	–
Blood transfused (intraoperatively and postoperatively), units	0.67 (± 0.3)	1.10 (± 0.3)	0.254
Fresh frozen plasma transfused (intraoperatively and postoperatively), units	4.75 (± 1.0)	2.50 (± 0.5)	0.123
Hospital stay, days	7.0 (± 0.8)	5.3 (± 0.4)	0.093

introducer sheath for the Talent stent graft, depending on its size, and via an 18 Fr introducer sheath for the Excluder stent graft. The contralateral leg of the bifurcated device was introduced from the opposite common femoral artery via an 18-22 Fr introducer sheath for Talent and a 12 Fr introducer for Excluder.

There was no statistically significant difference regarding blood and fresh frozen plasma transfusion between the 2 groups (Table II).

During the procedure, patients in both groups received 5,000 IU of heparin, 500 mg of hydrocortisone, a dose of an appropriate antibiotic, and 100 mL of mannitol.

Before (at 1 and 12 hours) the operation they received a dose of an antihistamine (cetirizine hydrochloride 10 mg), and postoperatively antibiotics and nonsteroid antiinflammatory drugs (nimesulide 100 mg twice a day) were administered for 72 hours. The oral intake of food and the mobilization started on the first postoperative day.

Blood Collection

Serial peripheral venous blood samples were collected as follows: preoperatively the day before surgery, and at 1, 3, 6, 24, 48, and 72 hours after placement of the endograft. The blood samples were obtained by careful venipuncture. The blood was drawn into tubes and immediately centrifuged. Plasma was frozen and stored for subsequent analysis. Other samples, stored into tubes containing ethylenediaminetetraacetic acid (EDTA), were sent for immediate full blood count.

White cell (WBC), platelet count, serum concentrations of interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor alpha (TNF- α), high-sensitivity C-reactive protein (hsCRP), alpha1-antitrypsin (α 1-antitrypsin), and complement protein C3a were determined.

Laboratory Techniques

The cytokines TNF- α , IL-6, and IL-8 were quantified by using commercially available enzyme-linked immunosorbent assays (Accucyte Human IL-6, Cytimmune Sciences, Inc, CytElisa™, Maryland). The methodology relies on the capture or "trapping" of the cytokine by a mouse antihuman monoclonal antibody, followed by the detection of this captured cytokine by the addition of a rabbit antihuman polyclonal antibody. The presence of the rabbit antihuman polyclonal

antibody is determined by goat antirabbit polyclonal antibody conjugated to alkaline phosphatase. With use of a patented color amplification system, the amount of cytokine present in the sample is linearly related to the amount of color generated; the more cytokine in the standard/unknown, the higher the optical density (OD) of the solution. The ODs were spectrophotometrically determined at 490 nm (reference filter 620 nm). Each sample was tested twice. The specifications of the assays were as follows: (1) for IL-6: sensitivity 3.4 pg/mL, range of detection: 8.0 to 500 pg/mL, intraassay variation: \pm 8.1%, interassay variation: \pm 10.4%; (2) for TNF- α , sensitivity: 4.8 pg/mL, range of detection: 15.6 to 1,000 pg/mL, intraassay variation: \pm 8.3%, interassay variation: \pm 10.8%; and (3) for IL-8, sensitivity 9.2 pg/mL, range of detection: 15.6 to 1,000 pg/mL, intraassay variation: \pm 7.4%, interassay variation: \pm 10.9%.

The acute-phase proteins hsCRP and α 1-antitrypsin were measured by rate nephelometry (Image Array 360 System, Image Immunochemistry Systems, Beckman Coulter). The analytical sensitivities for hsCRP, and α 1-antitrypsin determination were 0.02 mg/dL and 10 mg/dL, respectively. Normal values are 0.02–0.06 and 88.0–174, respectively.

C3a were quantified through use of commercially available enzyme-linked immunosorbent assay (Quidel C3a Enzyme Immunoassay, Quidel, San Diego, CA). The ODs were spectrophotometrically determined at 450 nm (reference filter 620 nm). Each sample was tested in duplicate (range of detection: 123 to 2,228 ng/mL, mean: 450 ng/mL).

Statistical Analysis

Data are expressed as mean \pm SEM. Comparisons were made using the Wilcoxon rank sum test for unpaired data and the Wilcoxon signed rank test for matched pairs. A p value less than 0.05 was considered significant

Results

The procedures were technically successful in all 22 patients. There were no deaths or any other major complications in either group. A unilateral intended occlusion of the internal iliac artery was performed in 2 patients in group A (16.7%)

and in 1 patient in group B (10%). Hospital stay lasted 4–14 days for the patients in group A (mean 7.0 ± 0.8) and 4–7 days for the patients in group B (mean 5.3 ± 0.4) ($p = 0.093$). A patient in group A, hospitalized for 14 days, was operated on day 11 of his hospital stay, for technical reasons. A temperature above 38°C was recorded postoperatively in 3 patients in group A (25%) and in 1 patient in group B (10%), representing a statistically significant difference ($p < 0.05$). The systemic inflammatory response syndrome (SIRS) criteria²⁰ were present in 1 patient in each group.

The white blood cell (WBC) count showed an increasing tendency in both groups starting immediately after the operation. It began to be statistically significant, compared to the preoperative values in group A patients, 3 hours postoperatively ($p = 0.05$), continued at 6 hours ($p = 0.034$) and 24 hours ($p = 0.008$), and returned to a nonsignificant difference 48 and 72 hours postoperatively ($p = 0.091$ and $p = 0.735$, respectively). Patients in group B presented a more prolonged statistically significant increase of WBC: It started at 3 hours ($p = 0.05$) and lasted until 72 hours postoperatively ($p = 0.013$, 0.005 , 0.011 , and 0.043 at 6, 24, 48, and 72 hours, respectively). Peak mean values were recorded at 24 hours for both groups ($12,568 \pm 1,239/\text{mm}^3$ and $14,710 \pm 1,790/\text{mm}^3$, respectively). In comparing the WBC counts between the 2 groups there was no statistically significant difference at any time ($p = 0.203$, 0.833 , 1.000 , 0.959 , 0.799 , 0.401 , 0.102 at preoperative, 1, 3, 6, 24, 48, and 72 hours, respectively) (Figure 1).

In group A patients the platelet count significantly decreased compared to the preoperative value by 3 hours postoperatively and this lasted until 72 hours ($p = 0.062$, 0.023 , 0.003 , 0.034 , 0.003 , and 0.018 at 1, 3, 6, 24, 48, and 72 hours, respectively). The significant decrease in platelet count for patients of group B started earlier, 1 hour postoperatively ($p = 0.008$) and also lasted until 72 hours ($p = 0.012$, 0.007 , 0.014 , 0.008 , and 0.042 at 3, 6, 24, 48, and 72 hours). The lowest mean value was recorded 48 hours postoperatively in group A patients and 72 hours postoperatively in group B patients. The lowest mean value was less than the lowest normal limit ($150,000/\text{mm}^3$) only in group A ($142,420 \pm 16,389/\text{mm}^3$) while in group B it remained in the normal range ($172,400 \pm 14,400/\text{mm}^3$). Comparing the values between the 2 groups there was no significant difference at any time (all $p > 0.05$) (Figure 2).

Cytokines

Serum concentrations of IL-6 increased after endograft placement in both groups. Only group A patients had a statistically significant difference, compared with preoperative values, 6 hours postoperatively ($p = 0.012$) when the peak mean value was recorded ($45.2 \pm 12.2 \text{ pg/mL}$). Serum concentrations of IL-6 of group B patients had a peak mean value at 24 hours ($31.5 \pm 7 \text{ pg/mL}$), but no statistically significant difference was recorded, compared to preoperative values ($p = 0.41$, 0.18 , 0.10 , 0.18 , 0.59 , and 0.32 at 1, 3, 6, 24, 48, and 72 hours, respectively). Between

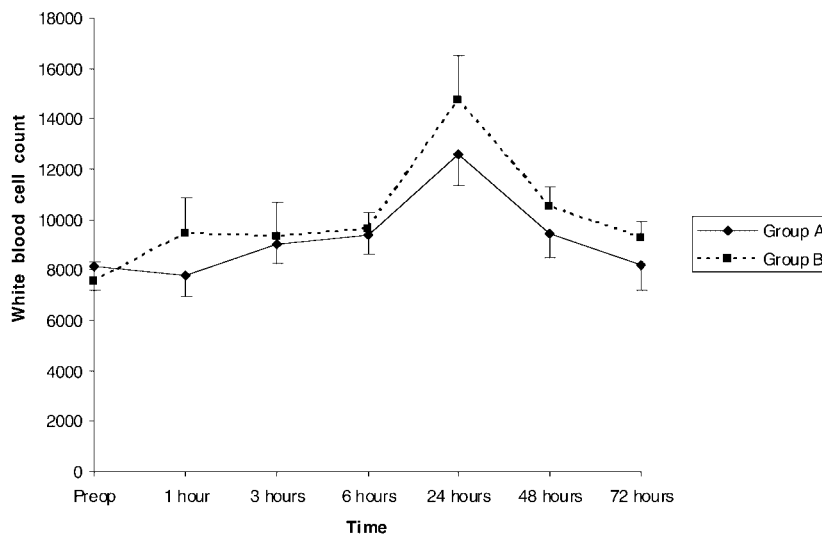


Figure 1.
White blood cell count.
Peak mean value was recorded 24 hours postoperatively for both groups.

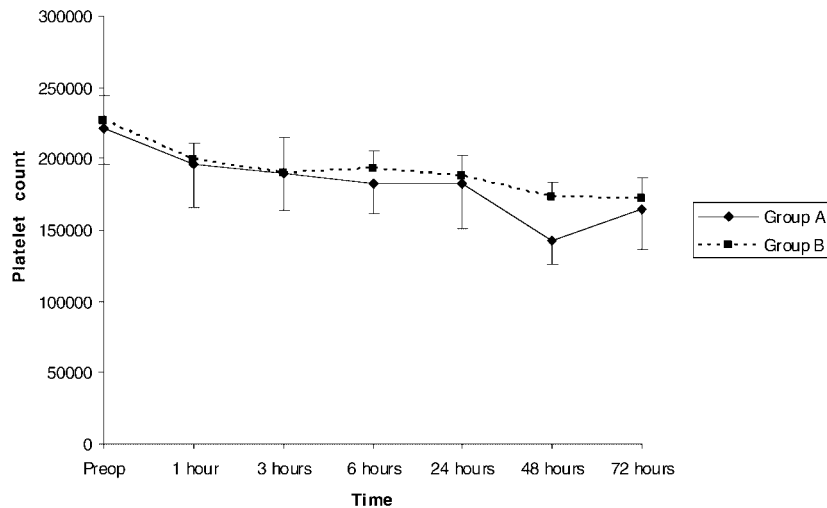


Figure 2. Platelet count. The lowest mean value was recorded 48 hours after endograft placement in group A and 72 hours postoperatively in group B patients.

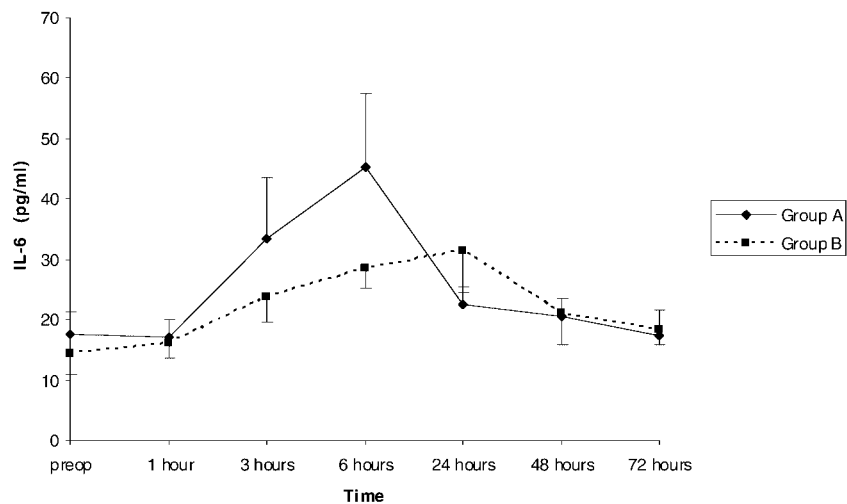


Figure 3. Plasma concentrations of IL-6. Concentrations were higher in group A with a peak 6 hours after endograft placement.

the 2 groups no significant difference was seen at any time ($p = 0.92, 0.86, 0.83, 0.37, 0.21, 0.94,$ and 0.41 at preoperative, 1, 3, 6, 24, 48, and 72 hours, respectively), although group A had a tendency for a greater increase (Figure 3).

Tumor necrosis factor alpha levels increased early postoperatively and fell rapidly thereafter. A statistically significant increase was recorded in group A at 1 hour ($p = 0.03$) and in group B at 6 hours ($p = 0.02$), compared to preoperative levels. Peak mean levels were recorded earlier in group A patients, 3 hours postoperatively, (94.1 ± 21.1 pg/mL) than in group B patients in whom peak mean values occurred 6 hours postoperatively (95 ± 14.7 pg/mL). No statistically significant difference between the 2 groups was seen at

any time ($p = 0.46, 0.70, 1.00, 0.72, 0.80, 0.67,$ and 0.50 at 1, 3, 6, 24, 48, and 72 hours postoperatively) (Figure 4).

Group A levels of IL-8 were significantly increased in all measurements compared to the preoperative values ($p = 0.01, 0.02, 0.01, 0.008, 0.02,$ and 0.01 at 1, 3, 6, 24, 48, and 72 hours, respectively) with a peak at 24 hours (29.1 ± 5.4 pg/mL). Group B levels showed a statistically significant increase 1 and 3 hours after endograft placement ($p = 0.04$ and 0.01 , respectively). The peak mean value occurred 3 hours postoperatively in group B patients (28.5 ± 4.7 pg/mL). A significant difference in serum values of IL-8 between the 2 groups was recorded at 24 hours (higher mean value in group A, $p = 0.01$) (Figure 5).

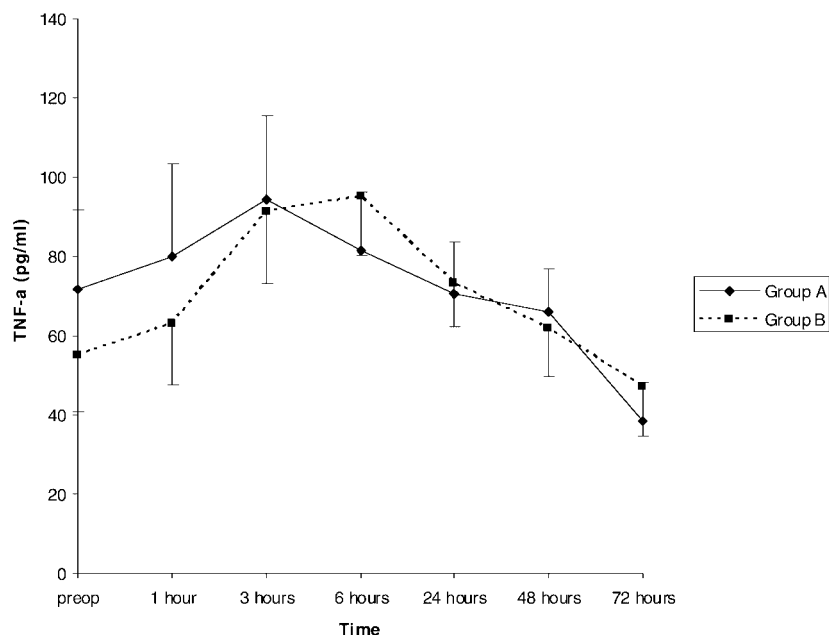


Figure 4. Plasma concentrations of TNF- α . There was an earlier but not a higher peak in group A patients.

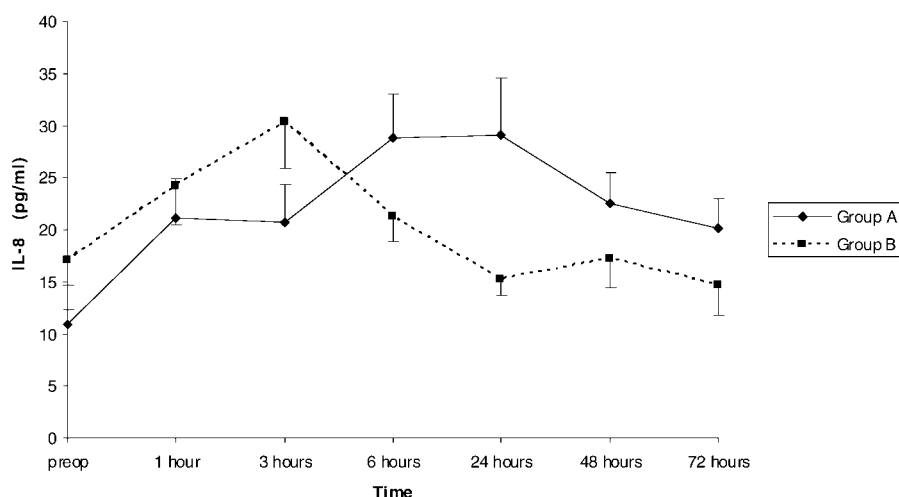


Figure 5. Plasma concentration of IL-8 remains elevated longer in group A. A statistically significant difference was recorded 24 hours postoperatively between the 2 groups ($p = 0.01$).

Acute-Phase Proteins

Levels of hsCRP started to increase 6 hours postoperatively, with the highest level 48 hours after the procedure in group A (8.81 ± 2.32 mg/dL) and at 72 hours in group B (5.55 ± 2.34 mg/dL). The peak mean value in group B remained in the normal range, but in group A it exceeded the highest limit. A statistically significant increase compared to the preoperative values was recorded in group A at 6, 24, 48, and 72 hours ($p = 0.01, 0.008, 0.008, 0.01$, respectively) and in group B at 24, 48, and 72 hours ($p = 0.01, 0.01, 0.03$, respectively). No statistically significant difference between the 2 groups was recorded at any time (all $p > 0.05$) (Figure 6).

The serum concentrations of α 1-antitrypsin reached the highest levels 72 hours postoperatively for both groups (group A: 208.00 ± 18.70 mg/dL, group B: 227.71 ± 15.83 mg/dL). The peak level in group B patients was slightly different but not significantly higher ($p = 0.68$). There was no significant difference between the 2 groups (Figure 7).

Complement

Compared to preoperative values, C3a was significantly elevated 1, 6, 24, and 48 hours postoperatively in group A patients ($p = 0.03, 0.04, 0.09, 0.06$, respectively) and only at 3 hours in group B patients ($p = 0.03$). The peak mean

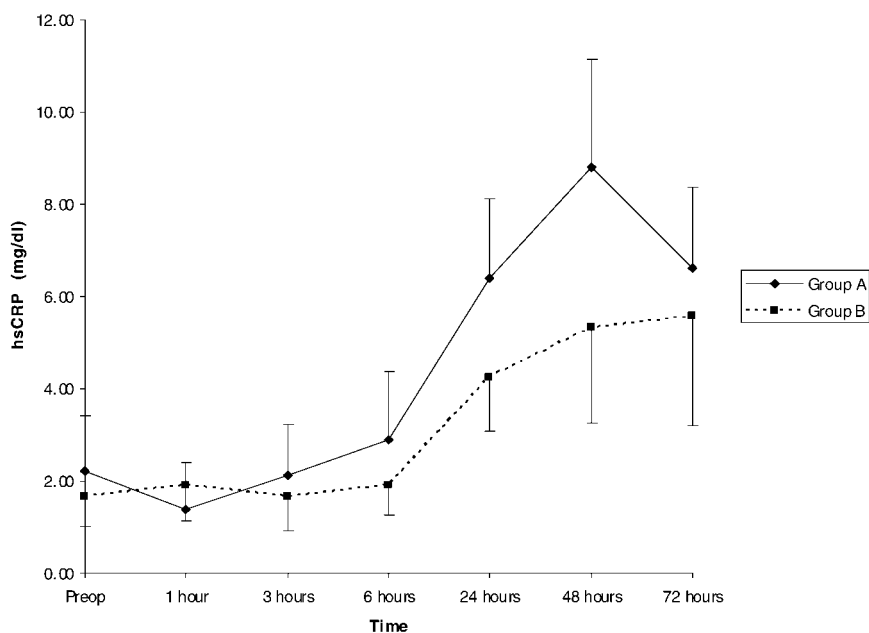


Figure 6. Plasma hsCRP concentrations had a tendency for greater increases in group A patients, although there was no significant difference.

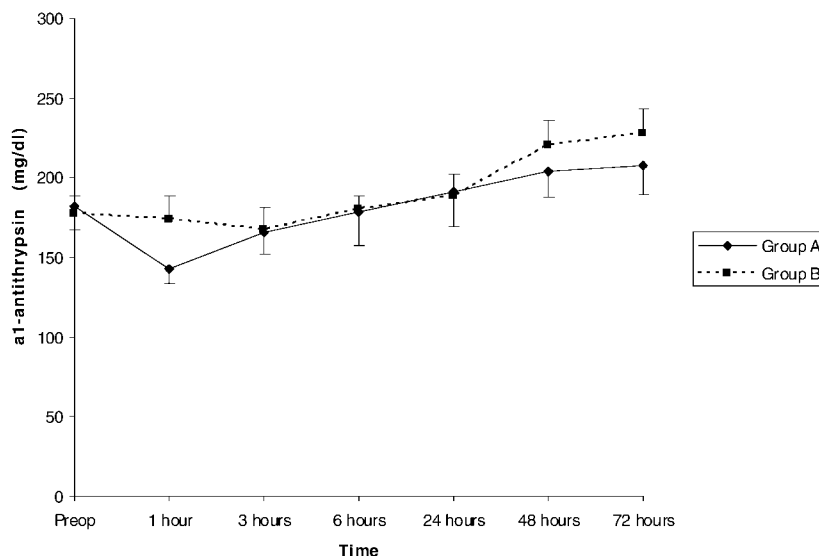


Figure 7. Serum concentrations of alpha1-antitrypsin. There was no significant difference between the groups.

value occurred 6 hours postoperatively in group A (87.75 ± 8.74 ng/mL) and 3 hours postoperatively in group B patients (70.00 ± 11.89 ng/mL). There was no significant difference between the 2 groups (Figure 8) at any time (all $p > 0.05$).

Discussion

The systemic inflammatory reaction after endovascular aneurysm repair is caused by activated leukocytes (mainly neutrophils) modulated by proinflammatory mediators (cytokines) and chemotactic factors (chemokines and comple-

ment proteins).⁶ IL-6 is released during intraoperative manipulations and after aneurysm sac exclusion.¹⁷ It is also released by the vascular endothelium during the implantation process.⁹ IL-6 induces the production of CRP²¹⁻²³ and stimulates blood white cells to produce TNF- α .¹⁷

Tumor necrosis factor alpha is a mediator of the systemic inflammatory response syndrome (SIRS).²⁴ Endovascular aortic aneurysm repair induces an inflammatory response mainly involving TNF- α .^{12,15,17,18} Plasma concentrations of TNF- α peaked and declined rapidly following the provoking stimulus. Peak levels were recorded during surgery or up to 6 hours postoperatively.¹⁵ IL-6 and TNF- α are endogenous pyrogens and they induce acute-phase protein synthesis.¹⁶

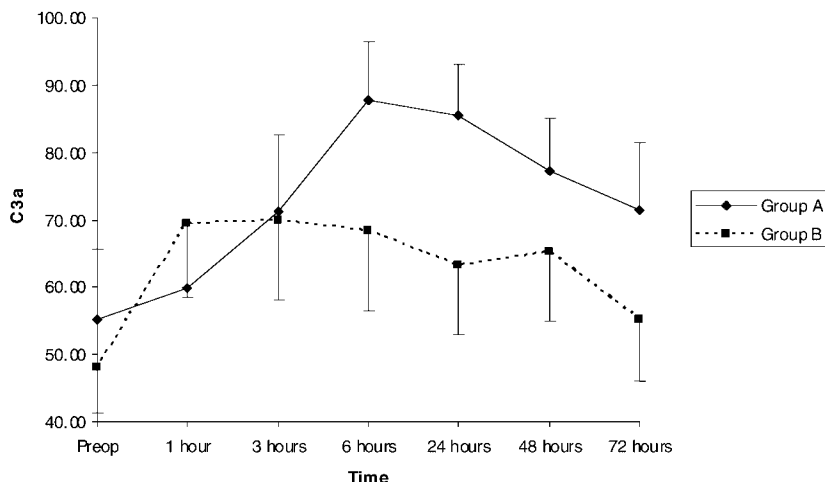


Figure 8. Serum C3a concentrations. C3a was more elevated in group A patients but no statistically significant difference was recorded.

A prolonged or enhanced IL-6 or TNF response in the postoperative period is not a good prognostic sign^{23,24} and is associated with serious complications.²⁴ IL-8 is a member of the CXC subfamily of chemokines (CXCL8) and is released from several cell types, including activated endothelial cells, monocytes, and T cells. It appears to be a powerful chemoattractant and activator of polymorphonuclear leukocytes, which are key mediators of inflammatory injury.²⁵ C-reactive protein is an acknowledged marker of inflammation involved in abdominal aortic surgery.^{4,6,7,16} Alpha1-antitrypsin has also been recognized as a regulator of proteinase activity and as a signaling molecule for the expression of proinflammatory molecules.²⁶

C3a is a potent anaphylatoxin and is generated during activation of the complement system via the classical or the alternative pathway. C3a exerts several effects including leukocyte chemotaxis, aggregation of neutrophils and platelets, increased capillary permeability and smooth muscle contraction resulting in bronchospasm, the release of histamine, the generation of leukotrienes, and the increased release of IL-1 and IL-6.²⁷

Inflammation during endovascular AAA repair may be partly triggered by the biomaterial itself.^{6,10} Variations in graft material may explain different early biological responses, mainly involving TNF- α , between open and endovascular aneurysm repair.⁶ Up to now there is no study comparing the inflammatory response after endovascular AAA repair using different graft materials. In the present study there was a significant difference only for IL-8 at 24 hours but not for cytokines, acute-phase proteins, and complement

proteins, although there were some differences in the time course patterns. In group A the IL-6 release was more significant during the early postoperative period with a peak plasma level at 6 hours. IL-6 was associated with a greater and more prolonged production of hsCRP. The peak value of IL-6 in group B patients was observed later (24 hours postoperatively). This fact may explain the more prolonged white blood cell increase in group B, which lasted until 72 hours postoperatively since IL-6 is an activator of leukocytes.²⁴ Plasma concentrations of IL-8 were significantly higher 24 hours postoperatively in group A patients.

The higher percentage of fever in group A patients, despite the administration of anti-inflammatory drugs, could perhaps be explained by the difference in cytokine release, mainly IL-6. Although several cytokines may induce fever, IL-6 produced in the brain stem is required for the final steps leading to fever.²⁸

Platelet activation following elective AAA repair occurs as the aneurysm sac is thrombosed, and by direct stimulation by the graft material.¹⁰ Some coagulation disturbances observed early postoperatively after endovascular aneurysm repair, characterized sometimes as part of the "postimplantation syndrome"⁷ can be associated with this procedure. The platelet count is an indirect index of platelet activation and consumption. In our study both groups had a significant decrease in the platelet count. The count in group A patients fell beyond the lowest normal value, whereas in group B it remained within the normal range. No significant postoperative hemorrhage or groin hematomas were observed.

The endovascular repair of AAA, a minimally invasive alternative to the open surgery, allows faster mobilization and a shorter hospital stay. The postoperative complications are often associated with the inflammation provoked by endograft emplacement, which stimulates the inflammatory cascade. Limiting the extent of the inflammatory response is crucial, for it can lead to even lower morbidity and mortality rates. In this context, the perioperative administration of anti-inflammatory drugs could be beneficial, although further studies, mainly direct comparisons, are needed. Other drugs like statins, fibrates, antiplatelet agents clopidogrel and aspirin, and beta-blockers have been reported to lower the inflammatory markers²⁹⁻³³ and decrease perioperative mortality and nonfatal myocardial infarction in patients undergoing AAA surgery.³⁴ Their role in endovascular AAA repair should also be examined. Stent graft material appears to play a limited role in influencing the inflammatory response following this procedure.

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