CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE
CONTROVERSIES & UPDATES IN VASCULAR SURGERY
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EVAR follow up: answers to uncertainties

Moderators F. Moll, Y. Alimi, M. Bjorck

Inflammatory response after EVAR: causes and clinical implication

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Faculty Disclosure

Christos D. Liapis

I have no financial relationships to disclose

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Introduction

The endovascular treatment of abdominal aortic aneurysms (EVAR) induces a systemic inflammatory response known as **“Post-implantation syndrome”** (PIS).

The **incidence** of the syndrome varies widely between **10% and 60% (underreporting, different criteria?)**

Galle C et al. Early inflammatory response after elective abdominal aneurysm repair: A comparison between endovascular procedure and conventional surgery. J Vasc Surg. 2000

Boyle J et al. Endovascular AAA repair attenuates the inflammatory and renal responses associated with conventional surgery. J Endovasc Ther 2000

The main features of PIS include

- **Fever**
- **Leukocytosis**
- **Elevated C-reactive protein**
- **Coagulation disturbances**

Swartbol P, et al. The inflammatory response and its consequence for the clinical outcome following aortic aneurysm repair. Eur J Vasc Endovasc Surg 21:393-400, 2001

Boyle J et al. Endovascular AAA repair attenuates the inflammatory and renal responses associated with conventional surgery. J Endovasc Ther 2000

Causes of PIS after EVAR

Three main mechanisms

1. **Injury to the vascular endothelium** during endograft implantation.

2. **Manipulation** of the introducer catheters and sheaths **inside the aneurysmal thrombus**

3. **Endograft material and biological response**

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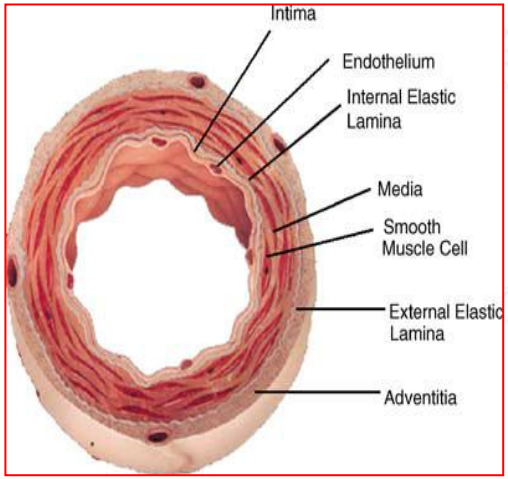
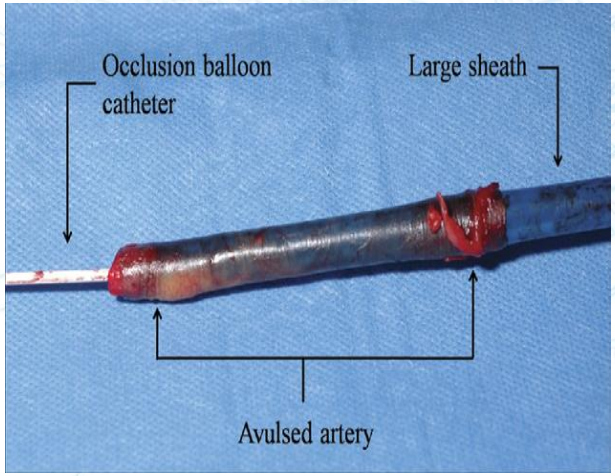
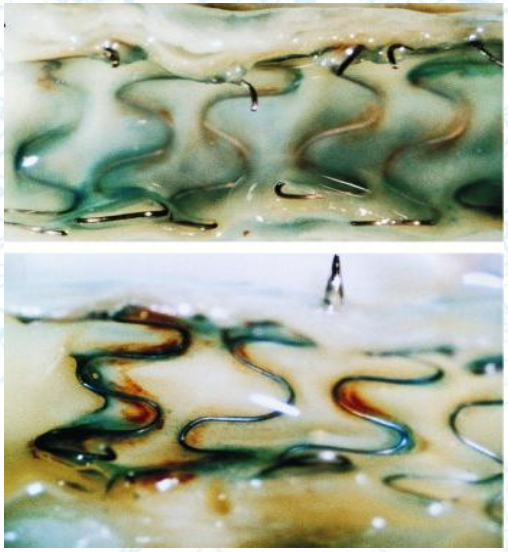
1. Injury to the vascular endothelium during endograft implantation.

<u>5-17%, injury to access vessels</u> during EVAR.

Dissection, plaque rupture, endothelial injury





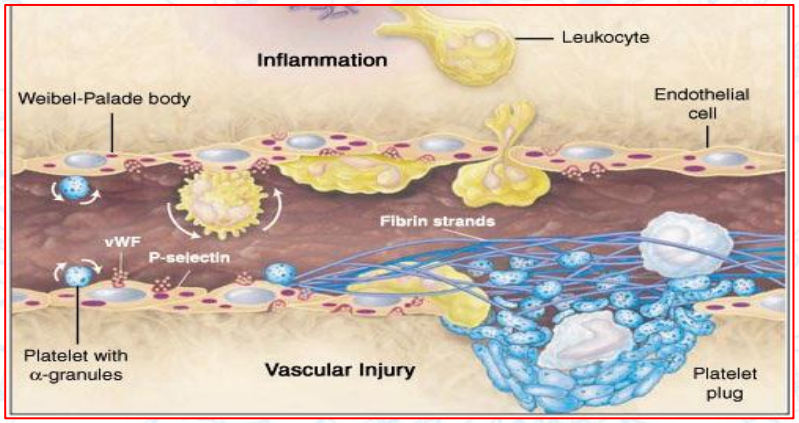


Murray D, et al. Access for endovascular aneurysm repair. J Endovasc Ther. 2006

Injury to the vascular endothelium during endograft implantation.

Inflammation plays a critical role in the vascular response to injury.

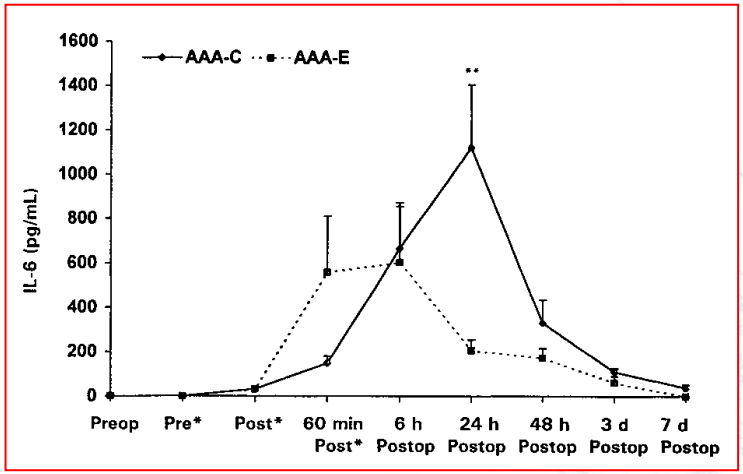
- Mechanical injury using techniques such as **balloon angioplasty and stenting** results in complex inflammatory reactions.



Leukocytes serve as the primary inflammatory cells but **platelets produce a number of important inflammatory mediators**.

Davis C, et al. The role of inflammation in vascular injury and repair. J Thromb Haemost. 2003

2. Manipulation with introducers and catheters inside the aneurysmal thrombus



TNF-α Release in Patients Undergoing Endovascular AAA Repair

Blood Sampling Interval	TNF-α (pg/mL)
Preoperative	0
Before balloon inflation	0
Immediately after balloon deflation	42.0 ± 20.0
60 minutes after balloon deflation	554.0 ± 219.5
6 hours postoperative	81.0 ± 42.8
24 hours postoperative	61.0 ± 6.3
48 hours postoperative	0

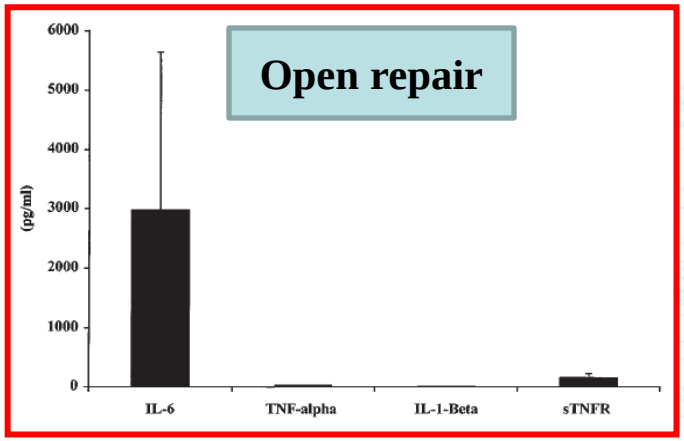
Values are given as mean ± SEM.
No systemically detected TNF-α levels were found in the AAA-C group.

Increased levels of IL-6 in OR - TNF-a release in EVAR only (n=14)

Biological responses in aneurysms with less thrombus were less pronounced or absent !!

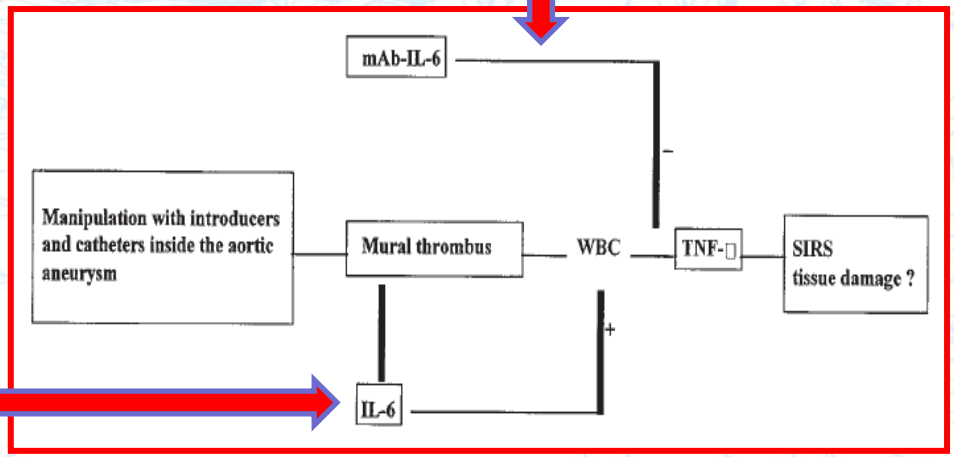
Norgren L, Swartbol P. Biological responses to endovascular treatment of abdominal aortic aneurysms. J Endovasc Surg. 1997

Manipulation with introducers and catheters inside the aneurysmal thrombus



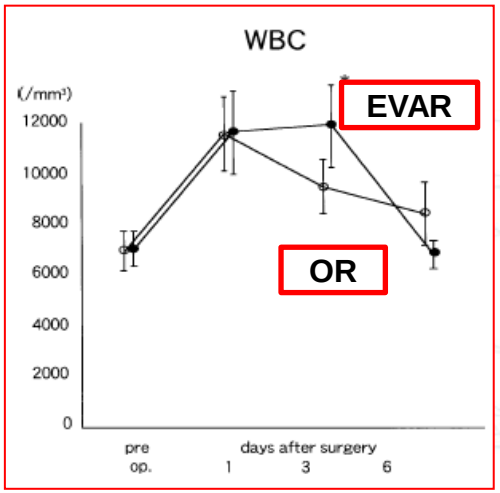
Monoclonal antibodies against IL-6 may prevent such response.

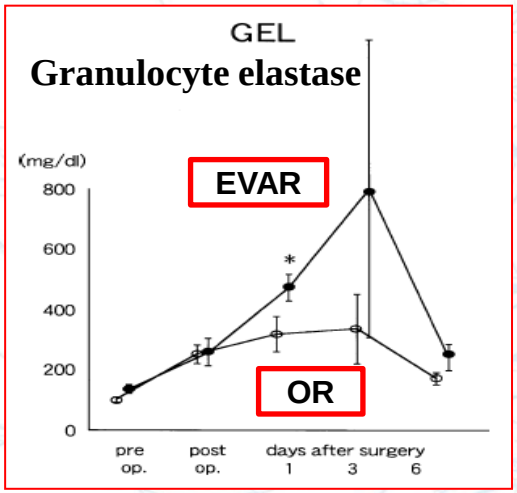
The **intramural thrombus**, which is left in situ after EVAR, **contains high levels of IL-6**.

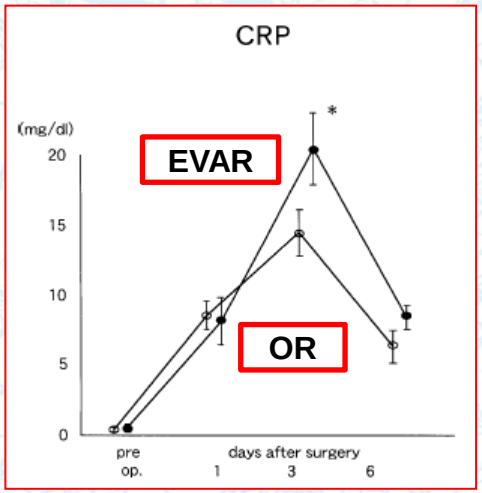


Swartbol P. et al. Adverse reactions during endovascular treatment of aortic aneurysms may be triggered by interleukin 6 release from the thrombotic content. JVS 1998

Manipulation in the aneurysmal thrombus may cause WBC activation and the release of various cytokines







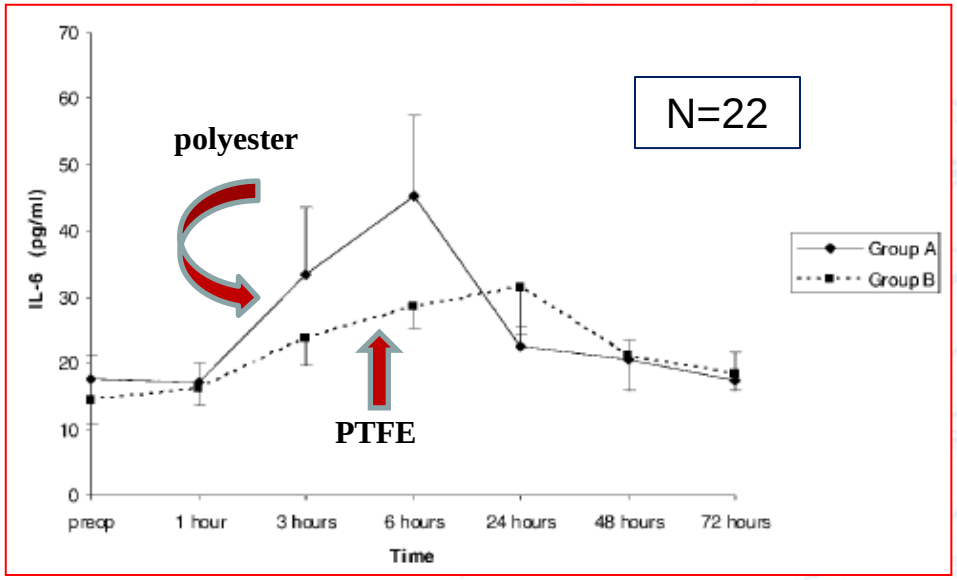
N=14

- **WBC, GEL, CRP and IL-6, were higher in the EVAR Group than in the OR.**
- **<u>These inflammatory responses correlated to the cytokines released from thrombus in AAA.</u>**
- **Manipulation in the aneurysm cause cell activation and release of biochemical products**

Morikage N, et al. Is endovascular treatment of abdominal aortic aneurysms less invasive regarding the biological responses? Surg Today. 2000

3.Endograft material and biological response

Inflammation during AAA repair may be triggered by the extrinsic prosthetic material used.



Plasma Concentrations of IL-6

were higher in the polyester group 6 hours after endograft placement

Significant difference for **fever** and serum concentrations of **IL-6** between patients receiving a polyester vs. an expanded PTFE stent graft.

Gerasimidis T, et al. Impact of endograft material on the inflammatory response after elective endovascular abdominal aortic aneurysm repair. Angiology. 2005

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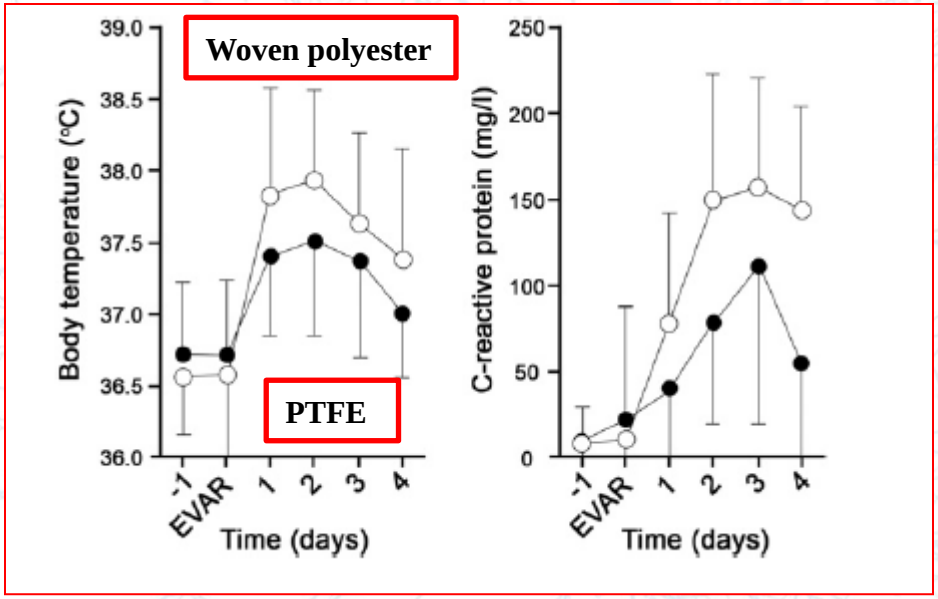
Endograft material and biological response

149 patients

Implantation of stent grafts based on **woven polyester** was independently associated with a **stronger inflammatory response**.



Voûte MT, et al. Stent graft composition plays a material role in the postimplantation syndrome. J Vasc Surg 2012;56:1503-9

Clinical implication of PIS after EVAR

- Fever and lumbar back pain

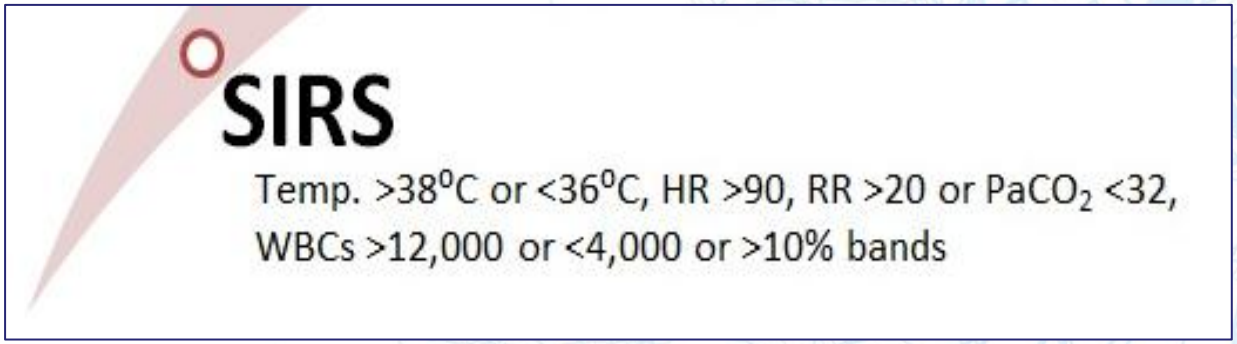
- The biological response following EVAR is not always spontaneously attenuated and **could lead to the development of systemic inflammatory response syndrome (SIRS)** even several days post-op.

- SIRS may result in severe complications (**cardiac, renal, pulmonary)**, **sometimes leading to acute respiratory distress syndrome (ARDS) or multiple organ failure.**

1. **Galle C,et al. Early inflammatory response after elective abdominal aneurysm repair: A comparison between endovascular procedure and conventional surgery. J Vasc Surg. 2000**

2. **Arnaoutoglou E, et al. Post-implantation syndrome after endovascular repair of aortic aneurysms: need for postdischarge surveillance. Interact Cardiovasc Thorac Surg. 2010**

Incidence of Systemic Inflammatory Response Syndrome (SIRS) after EVAR



- **Retrospective** analysis of 66 pts.
- **60% of pts** met the SIRS criteria within the first 5 postoperative days

	SIRS Group	Non SIRS Group	P
Reintervention	(11) 28%	4 (15%)	Non significant
30-day Mortality	3%	0%	Non significant

De La Motte L, et al. Incidence of systemic inflammatory response syndrome after endovascular aortic repair. J Cardiovasc Surg (Torino). 2011 52(1):73-9

Readmission due to protracted inflammatory response after EVAR

Among 162 patients who underwent EVAR, PIS was recorded in 49 patients.

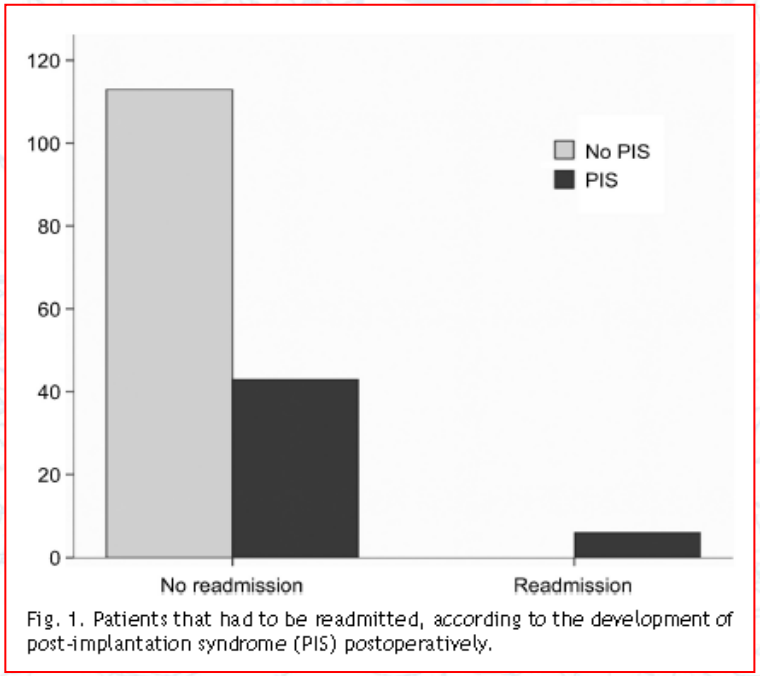


Fig. 1. Patients that had to be readmitted, according to the development of post-implantation syndrome (PIS) postoperatively.

<u>6 (3%) developed SIRS</u> postdischarge which led to **<u>readmission within the first 30 postoperative days</u>**.

Arnaoutoglou E, et al. Post-implantation syndrome after endovascular repair of aortic aneurysms: need for postdischarge surveillance. Interact Cardiovasc Thorac Surg. 2010

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Our Experience

The impact of endograft type on inflammatory response after endovascular treatment of abdominal aortic aneurysm

Konstantinos G. Moulakakis, MD,[a] Maria Alepaki,[b] George S. Sfyroeras,[a] Constantine N. Antonopoulos, MD,[a] Triantafillos G. Giannakopoulos,[a] John Kakisis,[a] Petros Karakitsos,[b] and Christos D. Liapis,[a] *Athens, Greece*

Objective: To evaluate the impact of endograft type on the inflammatory response after elective endovascular repair of abdominal aortic aneurysms.

Methods: From January 2011 to November 2011, we included 100 consecutive patients who underwent elective abdominal aortic aneurysm endovascular repair. Thirteen patients were excluded from the analysis: four with cancer, three with autoimmune disease, two because of recent infection, two who were receiving long-term anti-inflammatory medication, and two because of recent surgery. Temperature, white blood cell count, platelet count, and serum concentrations of cytokines (interleukin [IL]-6, IL-8, and IL-10) were measured preoperatively, 24 hours postoperatively, and 48 hours postoperatively. The study sample was divided into four groups with respect to the type of endograft used: group A, n = 28 (Anaconda; Sulzer Vascutek, Bad Soden, Germany); group B, n = 26 (Zenith; Cook Inc, Bloomington, Ind); group C, n = 23 (Excluder; W. L. Gore and Assoc, Flagstaff, Ariz); and group D, n = 10 (Endurant; Medtronic, Minneapolis, Minn). Endograft configurations included bifurcated grafts only.

Results: Epidemiologic characteristics, atherosclerotic risk factors, type of anesthesia, mean blood loss during surgery, and baseline serum levels of cytokines did not differ among the four groups. Mean elevated temperature was more pronounced postoperatively in group A. Serum levels of IL-6 and IL-10 were significantly higher 24 hours and 48 hours postoperatively compared with preoperative levels in all groups. Patients in group C showed the smallest increase in levels of serum IL-6 and IL-10 at 24 hours and 48 hours postoperatively. Mean difference in cytokine levels after aneurysm exclusion was greater for group A vs group C ($P < .01$) compared with group A vs B ($P < .05$). No differences in the mortality and morbidity rates were observed among the four groups.

Conclusions: Endograft type appears to influence the inflammatory response after endovascular aortic repair. The postimplantation syndrome was apparent during the first 24 hours and decreased afterward. Anaconda and Zenith endografts induced a more intense inflammatory response. A "milder" inflammatory activation was observed in patients with an Excluder endograft. The postimplantation syndrome was not associated with perioperative adverse clinical events showing a benign course. The possible long-term sequelae of postimplantation syndrome require further investigation. (J Vasc Surg 2012;■:1-10.)

Moulakakis KG, Liapis CD. The impact of endograft type on inflammatory response after endovascular treatment of abdominal aortic aneurysm. **Journal of Vascular Surgery. In Press Feb 2013**

Methods

From January 2011 to November 2011

- We included 100 consecutive patients with elective EVAR.

- **Fever, WBC**, **PLT**, serum concentrations of **IL- 6, IL- 8** and **IL-10** were measured **preoperatively, 24 and 48 hours postoperatively**.

- Serum concentrations of cytokines were determined with the Luminex 200^{TM} platform (Luminex Corporation).

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Exclusion criteria

13% of patients were excluded

- **Recent infection** **(2 pts)**
- Surgical **operation or trauma** during the **last 2 months** **(2 pts)**
- History of **autoimmune or systemic inflammatory** disorder receiving **anti-inflammatory or immunedepressant** drugs **(5 pts)**
- History of **malignant disease** **(4 pts)**

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Groups of patients

Patients were divided into 4 groups according to the endograft type

- Group A n = 28 Polyester (Anaconda, Sulzer Vascutek)
- Group B n = 26 Polyester (Zenith, Cook Inc.)
- Group C n = 23 PTFE (Excluder, W.L.Gore)
- Group D n = 10 Polyester (Endurant, Medtronic, Inc.)

Total : 87

Moulakakis KG, Liapis CD. The impact of endograft type on inflammatory response after endovascular treatment of abdominal aortic aneurysm. **Journal of Vascular Surgery. In Press Feb 2013**

Preoperative-Baseline characteristics

	Group A (n=28)	Group B (n=26)	Group C (n=23)	Group D (n=10)	p value
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Age (years)	73.11(0.86)	73.08 (1.06)	70.87 (1.34)	74.17 (1.55)	0.30
Aneurysm size (cm)	5.49 (0.04)	5.59 (0.16)	5.31 (0.06)	5.35 (0.18)	0.31
	%	%	%	%	
▪ Males	92.6	96.2	95.7	83.3	0.49
▪ CAD	25.9	34.6	39.1	33.3	0.79
▪ Hypertention	40.7	61.5	60.9	66.7	0.30
▪ COPD	18.5	19.2	13.0	33.3	0.55
▪ Dyslipidemia	33.3	15.4	30.4	33.3	0.44
▪ DM	11.1	15.4	8.7	33.3	0.24
▪ Smoking	37.0	38.5	34.8	50.0	0.84
Statin (On Admission)	25.9	26.9	26.1	33.3	0.97
Antiplatelet	35.7	26.9	39.1	30.0	0.92
β-blockers	14.3	19.2	13.0	20.0	0.94
Anti-hypertensive	60.7	57.7	56.5	60.0	0.98

No significant differences were observed regarding demographics, atherosclerotic risk factors, drugs, aneurysm size and thrombus

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Perioperative details for the 4 groups

	Group A (n=28)	Group B (n=26)	Group C (n=23)	Group D (n=10)	p value
General Anesthesia	50%	46.2%	65.2%	40%	0.31
Epidural anesthesia	50%	53.8%	34.8%	60%	0.34
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	p value
Blood Loss (ml)	266.2(16.21)	258.2(21.35)	313.91(60.89)	300(16.28)	0.64
Contrast Media Volume (ml)	176.6 (7.84)	194.2(15.56)	157.39 (8.39)	192.2(12.21)	0.12

- There were **no deaths, no open conversions**, and **no major perioperative complications**.
- No difference in blood loss and contrast media

Moulakakis KG, Liapis CD. The impact of endograft type on inflammatory response after endovascular treatment of abdominal aortic aneurysm. **Journal of Vascular Surgery. In Press Feb 2013**

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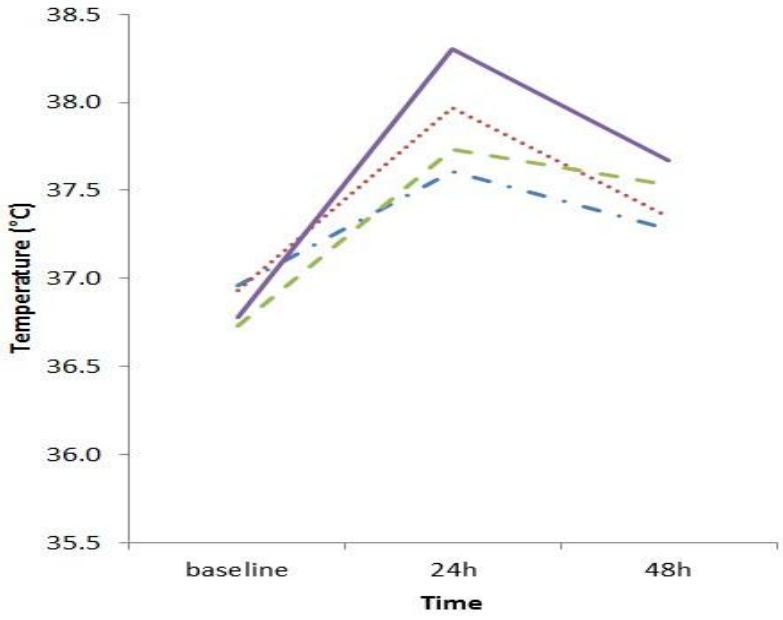
Results

Temperature (°C)



A	Anaconda
B	Zenith
C	Excluder
D	Endurant

repeated measures ANOVA

- In **<u>24h and 48h</u>** postoperatively, **Group A pts.** presented statistically higher mean values compared to **Group B, C and D**.

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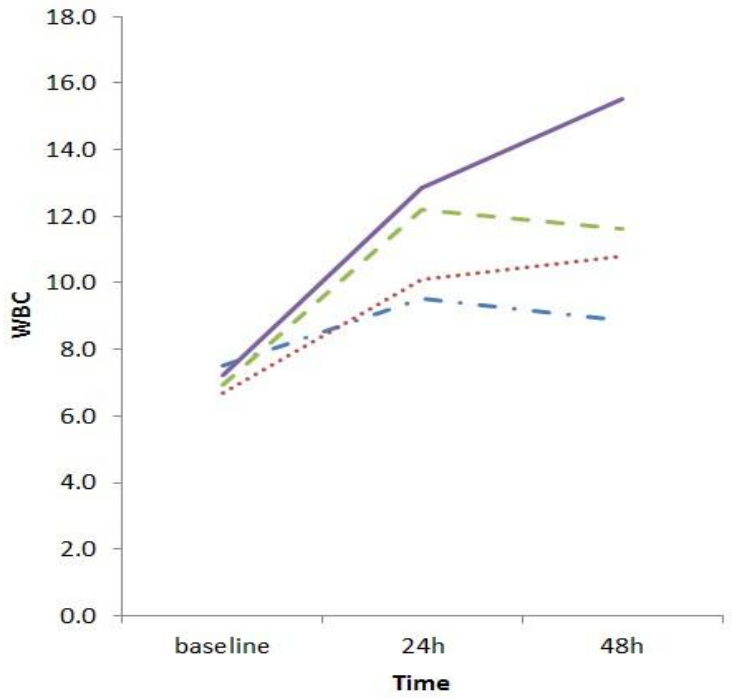
White blood cells (WBC)



repeated measures ANOVA

<u>Group A</u> presented the higher and **<u>Group C</u>** **the lower mean values 24h and 48h postoperatively**

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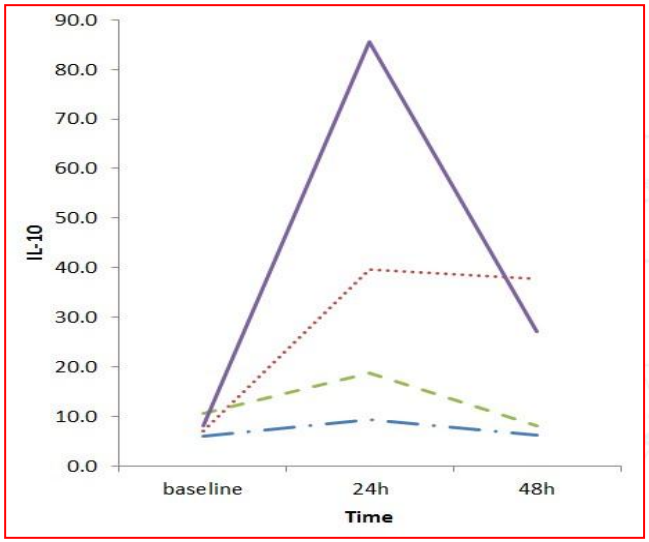
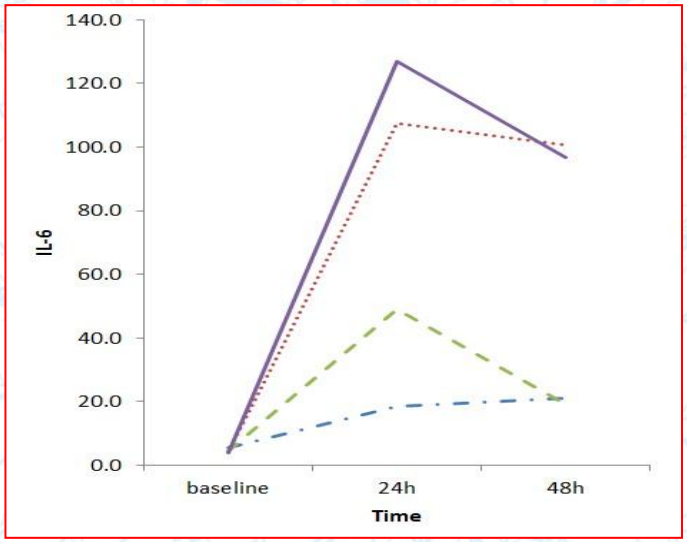
IL-10 (pg/ml)



A Anaconda
B Zenith
C Excluder
D Endurant

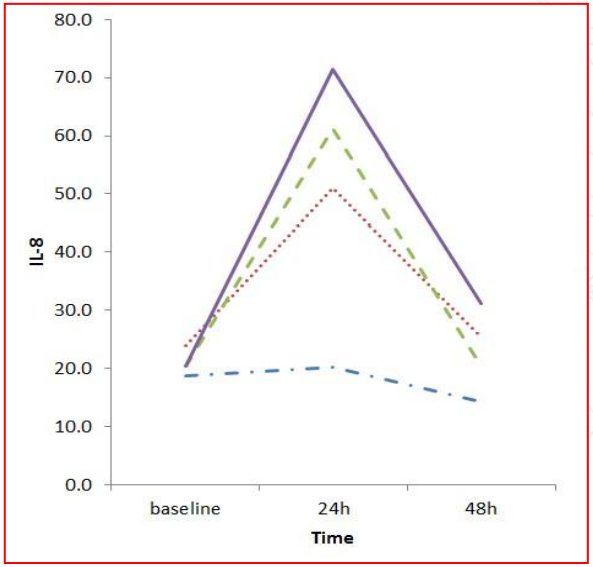
repeated measures ANOVA

IL-6 (pg/ml)



- **Group A presented the higher mean values of IL-6 and 10 at 24h.**
- **Group C presented the lower mean values at 24h and 48h postoperatively**

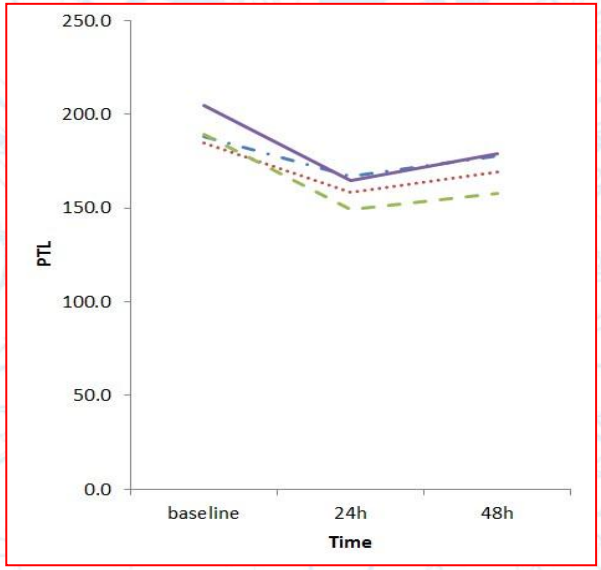
IL-8 (pg/ml)



A — Anaconda
B — Zenith
C — Excluder
D — Endurant

repeated measures ANOVA

Platelets (PLT)



Group C presented the lower mean values in 24h and 48h postoperatively

No significant differences were observed concerning **PTL values** in 24h and 48h

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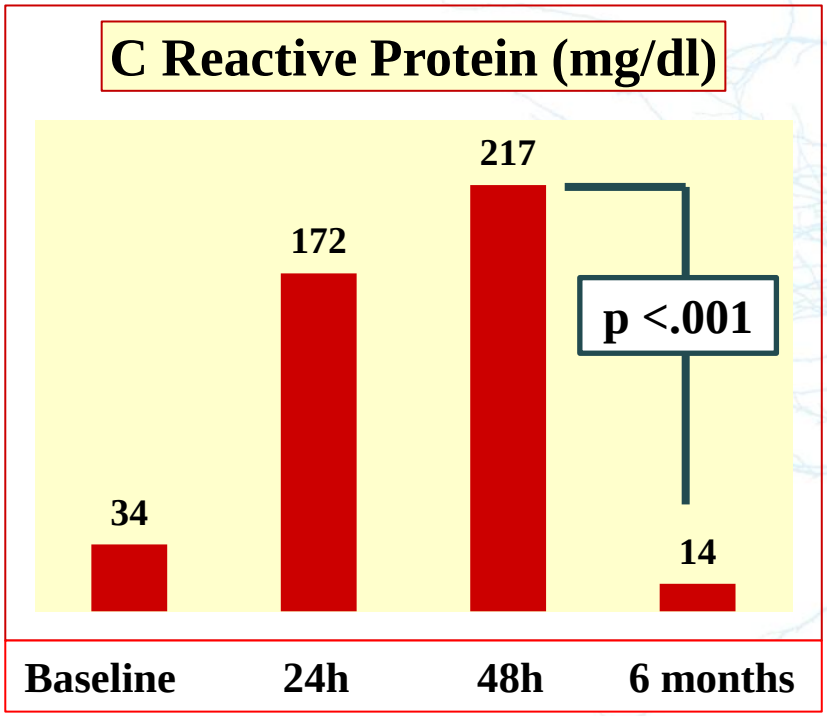
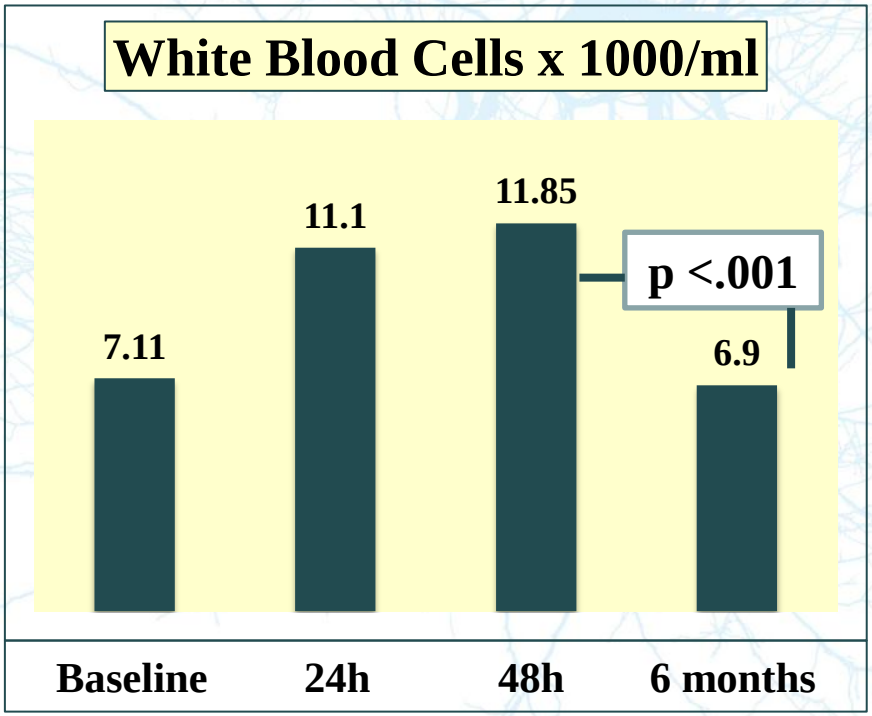
C Reactive Protein and WBC at 6 months (mean values)





CRP and WBC returned to normal values

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Conclusions

- **The PIS in our study** was **transient** during the early postoperative phase and **was not associated with adverse clinical events and increased mortality**
- **Endograft type** appears to **influence the immediate inflammatory response** following EVAR.
- **Polyester** endografts induce a more intense inflammatory response. Manufacturing differences could explain variation of results between them.
- The **"milder" postimplantation syndrome** was observed in the **PTFE** endograft.
- Long-term studies are required to determine possible late sequelae

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