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Activated coagulation during open and endovascular abdominal aortic aneurysm repair

Lars Englberger, MD,[a] Hannu Savolainen, MD, PhD,[a] Peter Jandus,[a] Matthias Widmer, MD,[a] Do Dai Do, MD,[b] Andre Haeberli, PhD,[c] Iris Baumgartner, MD,[b] Thierry P. Carrel, MD,[a] and **Juerg Schmidli, MD,[a]** *Berne, Switzerland*

Objective: **The study was conducted to determine activation of coagulation in patients undergoing open and endovascular infrarenal abdominal aortic aneurysm repair (EVAR).**

Methods: **In a prospective, comparative study, 30 consecutive patients undergoing open repair (n = 15) or EVAR (n = 15) were investigated. Blood samples to determine fibrinopeptide A, fibrin monomer, thrombin-antithrombin complex, and D-dimer were taken up to 5 days postoperatively. Routine hematologic and hematochemical parameters as well as clinical data were collected.**

Results: **Both groups showed comparable demographic variables. Operating time was longer in open repair (249 ± 77 minutes vs 186 ± 69 minutes, $P < .05$). Perioperatively elevated markers of coagulation were measured in both groups. Fibrinopeptide A levels did not differ significantly between the groups ($P = .55$). The levels of fibrin monomer and thrombin-antithrombin complex were significantly higher in patients undergoing EVAR ($P < .0001$), reflecting increased thrombin activity and thrombin formation compared with open surgery. The D-dimer level did not differ significantly between the groups. These results were also valid after correction for hemodilution.**

Conclusion: **These data suggest increased procoagulant activity in EVAR compared with open surgery. A procoagulant state may favor possible morbidity derived from micro- and macrovascular thrombosis, such as in myocardial infarction, multiple organ dysfunction, venous thrombosis and thromboembolism, or disseminated intravascular coagulation. (J Vasc Surg 2006;43:1124-9.)**

Possible advantages of endovascular abdominal aortic aneurysm repair (EVAR) over open surgical repair (OAR) have been extensively investigated. Minimally invasive procedures have their own specific side effects that affect recovery as well.[1] Biologic responses to surgical trauma and ischemia–reperfusion injury include complex inflammatory response and activation of coagulation and fibrinolysis. A recent review focusing on the inflammatory response after abdominal aortic aneurysm (AAA) repair found that conventional surgery and EVAR both induce unwanted inflammatory responses. However, overall attenuation of the proinflammatory markers in patients treated with an endovascular technique was demonstrated.[2,3] Additionally, asymptomatic AAA is already associated with increased thrombin generation.[4,5]

OAR of infrarenal AAA induces extensive thrombin generation and activity.[6,7] This procoagulant state may contribute to thrombotic complications that predominately occur in the early postoperative period, including myocardial infarction, lower-extremity and intestinal ischemia, stroke, and venous thrombosis. Consumptive coagulopathy—in an extreme case, disseminated intravascular coagulation—may cause bleeding as well. The aim of the present study was to determine the activation of coagulation in patients undergoing open and endovascular AAA repair.

From the Departments of Cardiovascular Surgery,[a] Angiology,[b] and Clinical Research,[c] Inselspital, University Hospital Berne.

Competition of interest: none.

Reprint requests: Dr Lars Englberger, Department of Cardiovascular Surgery, Inselspital, University Hospital, Freiburgstrasse, 3010 Berne, Switzerland (e-mail: lars.englberger@insel.ch).

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METHODS

Study design and patients. Thirty consecutive patients scheduled for elective infrarenal AAA repair were enrolled in this prospective, nonrandomized, comparative study. The study protocol was approved by the ethical committee on human research of Berne (No. 164/2000). Written informed consent was obtained from all patients. Before being asked for study participation, the patients were allocated to EVAR or conventional OAR according to their aneurysm morphology as determined by computerized tomography and angiography. Exclusion criteria included myocardial infarction ≤6 weeks before surgery, neurologic disorders (eg, cerebrovascular accident), renal failure (serum creatinine >200 μmol/L), liver diseases, active inflammatory disease, malignancy, or preoperative coagulopathies. Patients receiving aspirin were included in the study. Fifteen patients had conventional OAR, and 15 had EVAR.

Anesthesia and postoperative care. All patients had premedication with benzodiazepines. All patients in the OAR group had combined general and epidural anesthesia. General anesthesia was induced and maintained with midazolam, fentanyl, and inhalants (isoflurane or enflurane). Muscle relaxation was achieved with pancuronium bromide. In the EVAR group, a combined technique or epidural anesthesia alone was performed. For epidural anesthesia, lidocaine, 2% carbon dioxide, and 0.25% bupivacaine were used. Standard monitoring methods included electrocardiography and the

insertion of radial artery, central venous, peripheral venous, and urinary catheters.

Perioperative anticoagulation management. On the evening before surgery, all patients received subcutaneous weight-adjusted low-molecular-weight heparin (LMWH), nadroparinum calcicum (Fraxiparine®, Sanofi-Synthelabo, Geneva, Switzerland) for prophylaxis of thrombosis. Intraoperatively, a single dose of intravenous heparin was administered (70 U/kg of body weight) before clamping of the aorta or the iliac–femoral artery, respectively, to achieve systemic anticoagulation during surgery. Activated clotting time was measured using the ACT II, a kaolin-activated system with an automated coagulation timer (Medtronic HemoTec, Inc, Englewood, NJ).

Protamine reversal after the procedure was not routine, but protamine was given if increased bleeding was clinically observed at the end of reconstruction. A cell-saving device (CATS Continuous Autotransfusion System, Fresenius HemoCare, Bad Homburg, Germany) was available during open repair. Transfusion of packed red blood cells was given if the hematocrit was <23%.

In the intensive care unit or intermediate care unit, the patients were treated according to routine protocol. For 24 hours postoperatively, patients had an intravenous infusion of unfractionated heparin (150 U/kg of body weight every 24 hours); afterwards, thrombosis prophylaxis was maintained during hospitalization with weight-adjusted LMWH. Peroral aspirin (100 mg once daily) was started at the first postoperative day.

Patients with postoperative indication for oral anticoagulation (eg, atrial fibrillation) received intravenous heparin overlapping with institution of oral anticoagulation, which was started during the second postoperative day. The latter was the case in three study patients, all of whom were in the EVAR group. The reasons for oral anticoagulation were pre-existing atrial fibrillation, new intermittent atrial fibrillation postoperatively, and a history of pulmonary embolism and deep vein thrombosis.

Surgical technique. OAR was done through a standard midline laparotomy in 14 patients and via a left lumbar retroperitoneal approach in one patient. Aortic cross-clamping below the renal arteries was suitable in 14 patients, and one patient required suprarenal clamping for technical reasons. Gelsoft Plus Dacron graft material was used in all patients (VASCUTEK, Hamburg, Germany). Patients in the EVAR group were treated with a variety of bifurcated devices, consisting of Talent in 13 (Medtronic, Santa Rosa, Calif), Zenith in one (Cook, Bjaeverskov, Denmark), and Ancure in one (Guidant, Menlo Park, Calif). Delivery was through the common femoral arteries in all patients.

Sample collection and laboratory analyses. Perioperatively, routine hematologic (hemoglobin, hematocrit, white blood cell count, platelet count) and hematochemical parameters such as serum creatinine, C-reactive protein, and international normalized ratio were collected in all patients. All samples were sent to the central hospital laboratory for routine analysis.

Blood samples were also collected from all patients at seven different time points to determine fibrinopeptide A (FPA), fibrin monomer, thrombin-antithrombin complex (TAT), and D-dimer: preoperatively, after induction of anesthesia (T1); after aortic declamping (OAR group) and after final expansion of the stent (EVAR group), respectively (T2); at the end of surgery (T3); 4 hours postoperatively (T4), at the first (POD 1), second (POD 2) and fifth postoperative day (POD 5). T1, T2, T3 were arterial samples, T4 and POD 1 central venous samples, and POD 2 and POD 5 were peripheral venous samples.

The corpuscular content was immediately separated from the fluid phase by centrifugation at 2,000*g* for 15 minutes at 6°C. Plasma was stored at −80°C before being assayed. To determine parameters of coagulation, plasma treated with CTADPPACK (citrate, theophylline, adenosine, and dipyridamole with D-phenylalanyl-L-propyl-L-arginine chloromethyl ketone) as anticoagulant was used.[8] FPA and TAT were measured using a radioimmunoassay, (IMCO Corporation Ltd AB, Stockholm, Sweden) and enzyme-linked immunoabsorbent assay (ELISA) technique (Enzygnost TAT micro, Behring, Marburg, Germany), respectively. Fibrin monomer was determined by using Enzymun-Test FM (Roche Diagnostics, Rotkreuz, Switzerland), also with ELISA. All samples were assayed in duplicate, and the mean value was retained. D-dimer levels were measured with turbodimetric methods (Sysmex CA-1500 System Analyzer, Dade Behring, Marburg, Germany).

Statistical analysis. Statistical analysis was done by using StatView 5.0.1 software (SAS Institute Inc, Cary, NC). Data in text and tables are presented as mean ± standard deviation (SD), or median and ranges if the SD >50% of the determined mean, which indicates high variability. Fisher's exact test or χ^2 analysis was used for categoric data. Nonparametric evaluation was performed for variables not normally distributed (Mann-Whitney *U* test).

Laboratory results were tested within the groups to detect time interactions (Friedman test). If statistically significant changes were seen, Wilcoxon signed-rank testing was used post hoc to locate the differences. For repeatedly measured variables, global testing by analysis of variance (ANOVA) for both groups was performed. If significant differences were detected, additional two-group nonparametric testing (Mann-Whitney *U*) was performed at single time points to locate the differences. $P < .05$ was considered statistically significant.

Because a different level of hemodilution in both study groups has been anticipated, laboratory results (platelet counts, FPA, fibrin monomer, and TAT) were analyzed by ANOVA, also with correction for hemodilution according to the formula: $[\text{Sample}_{\text{corrected}}]_{TX} = [\text{Sample}]_{TX} \times [\text{hematocrit}]_{T1}/[\text{hematocrit}]_{TX}$. Graphs present laboratory values without correction for hemodilution.

RESULTS

No statistically significant demographic differences were seen between the groups with respect to mean age, gender, history of concomitant disease, cardiovascular risk

Table I. Demographic data

	OAR (n = 15)	*EVAR (n = 15)*	P
Age (year)	69 ± 10	75 ± 8	.11
Gender (male/female)	13/2	14/1	.54
Weight (kg)	80.3 ± 10.9	81.5 ± 5.7	.43
Body mass index	27.1 ± 3.3	26.6 ± 2.9	.35
Ischemic heart disease	7	10	.27
Previous MI	4	2	.65
Peripheral vascular disease	2	3	.99
Cerebrovascular disease	1	3	.6
Pulmonary disease	2	2	.99
Renal impairment	3	7	.26
Smoking	9	8	.99
Hypertension	12	10	.68
Diabetes mellitus	0	2	.48
Dyslipidemia	10	8	.71
Aneurysm diameter (cm)	6.0 ± 0.8	5.7 ± 0.6	.28
Iliac vessel aneurysm	7	4	.45

OAR, Open aneurysm repair; *EVAR*, endovascular aneurysm repair; *MI*, myocardial infarction.
Data are mean ± SD unless otherwise specified.

Table II. Operative characteristics

	OAR (n = 15)	*EVAR (n = 15)*	P
Operating time (minutes)	249 ± 77	186 ± 69	< .05
Tube / bifurcated graft	5/10	0/15	—
Contrast media infused (mL)	—	231 ± 103	—
Anesthesia (combined*/only peridural)	15/0	7/8	—

OAR, Open aneurysm repair; *EVAR*, endovascular aneurysm repair.
Data are mean ± SD unless otherwise specified.
*General and epidural anesthesia.

profile, aneurysm diameter, or involvement of the iliac vessels (Table I). Intraoperative characteristics differed according to the type of surgery. Operating time in EVAR was significantly shorter than in OAR (Table II). All patients in the EVAR group received a bifurcated prosthesis, and four patients had distal extension of one of the iliac limbs. A tube graft was implanted in five patients in the OAR group. One patient had additional femoral thrombectomy at the end of OAR. In the EVAR group, implantation was performed under epidural anesthesia in eight of the 15 patients (Table II).

Hematologic and chemical blood data did not differ significantly between the groups, except for white blood cell count, which was both significantly lower at the end of surgery and significantly higher in the EVAR group on the first postoperative day (Table III). A significant fall in platelet count during surgery was noted in both groups, with the lowest values at the end of surgery. The decrease was more pronounced in the OAR group (Table III). The decrease remained through the postoperative period, and values comparable with the baseline were restored at the fifth postoperative day in both groups.

Table III. Perioperative hematologic and chemical blood data

	OAR (n = 15)	*EVAR (n = 15)*	P
Hemoglobin (g/L)			
Preoperative	14.5 ± 1.3	13.9 ± 1.5	.33
End of surgery	10.2 ± 1.5	10.8 ± 1.5	.26
1. POD	10.9 ± 1.3	11.3 ± 1.5	.48
5. POD	11.3 ± 1.7	11.1 ± 1.5	.98
WBC count (10^9/L)			
Preoperative	7.7 ± 2.3	6.8 ± 1.5	.28
End of surgery	9.3 ± 3.6	6.7 ± 1.9	.05
1. POD	8.5 ± 2.1	11.0 ± 2.7	<.05
5. POD	7.7 ± 2.8	7.2 ± 1.4	.77
Platelet count (10^9/L)			
Preoperative	232 ± 52	226 ± 46	.82
End of surgery	127 ± 44	168 ± 48	<.05
1. POD	143 ± 52	165 ± 56	.41
5. POD	229 ± 75	229 ± 74	.98
Serum creatinine (mmol/L)			
Preoperative	103 ± 21	112 ± 37	.79
1. POD	115 ± 42	113 ± 32	.95
5. POD	101 ± 43	120 ± 52	.2
C-reactive protein (mg/L)			
Preoperative	9 ± 9	10 ± 12	.73
1. POD	75 ± 24	73 ± 33	.89
2. POD	198 ± 51	191 ± 47	.66
5. POD	113 ± 50	120 ± 49	.54

OAR, Open aneurysm repair; *EVAR*, endovascular aneurysm repair; *POD*, postoperative day; *WBC*, white blood cell.
Data are mean ± SD unless otherwise indicated.

Table IV describes perioperative anticoagulation, postoperative blood loss, and transfusion requirements. The main difference was a significantly higher blood loss in the OAR group. Even though six patients (40%) in the OAR group received packed red blood cells compared with only two patients (14%) in the EVAR group, the difference was not statistically significant in the samples.

Early clinical outcome was similar in both groups, with no mortality. Hospitalization times are presented in Table V. The incidence of adverse events during hospitalization was low in both groups. One perioperative myocardial infarction occurred in the EVAR group, none in the OAR group.

Fibrinopeptide A. Levels of FPA did not differ significantly between the groups (ANOVA between groups, $P = .07$; for values corrected for hemodilution, $P = .55$) (Fig 1). Compared with baseline (T1) FPA, a significant increase was seen in both groups, with maximal mean values during stent implantation (T2) in the EVAR group ($P < .01$) and at the end of surgery (T3) in the OAR group ($P < .01$). In both groups, FPA values returned to baseline by POD 2.

Fibrin monomer. Levels of fibrin monomer were significantly lower in the OAR group (ANOVA between groups with and without correction for hemodilution, $P < .0001$) (Fig 2). Compared with baseline (T1) fibrin monomer, values were significantly elevated at T2 to POD 1 in the EVAR group ($P < .05$ for each correlation); whereas

Table IV. Anticoagulation, postoperative blood loss, and transfusions

	OAR (n = 15)	*EVAR (n = 15)*	P
Activated clotting time (sec.)			
After heparin	233 ± 90	198 ± 23	0.56
End of surgery	153 ± 59	149 ± 26	0.68
Protamine given	5	4	0.69
Cell saver used	13	—	—
Retransfused volume (mL)	1483 ± 1753		
	811 (170-5826)	—	—
Intraop. blood loss (mL)	3967 ± 4249	507 ± 440	<.0001
	2500 (800-14000)	325 (50-1500)	
PRBC received	6 (40%)	2 (14%)	0.21
FFP received	4 (26%)	1 (6%)	0.33
Platelet concentrates	1	0	—
Bleeding (re-exploration)	1	1	—

OAR, Open aneurysm repair; *PRBC*, packed red blood cells; *FFP*, fresh-frozen plasma.
Data are numbers of patients, mean ± SD, or median (range).

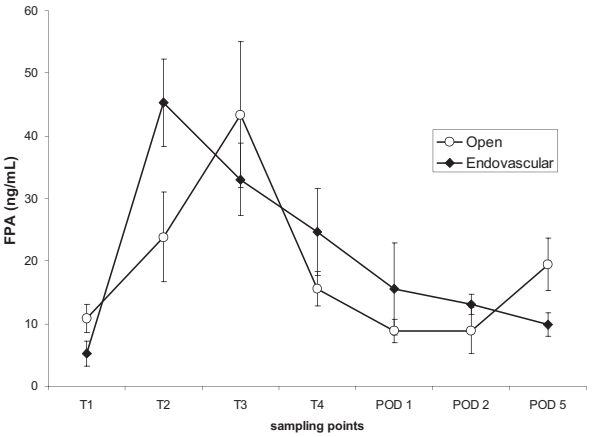

Fig 1. Fibrinopeptide A *(FPA)*. Analysis of variance testing, $P = .07$. *T1*, baseline; *T2*, during operation; *T3*, end of operation; *T4*, 4 hours postoperatively; *POD*, postoperative day. Data are presented as mean ± SEM.

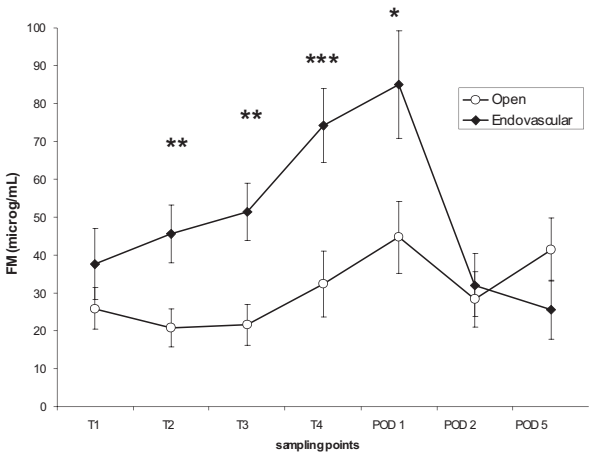

Fig 2. Fibrin monomer *(FM)*. Analysis of variance testing, $P < .0001$. *T1*, baseline; *T2*, during operation; *T3*, end of operation; *T4*, 4 hours postoperatively; *POD*, postoperative day. Data are presented as mean ± SEM. Significant intergroup differences: $*P < .05$; $**P < .01$; $***P < .001$.

only a trend toward increased values was detected in the OAR group, with a maximal mean fibrin monomer value at POD 1 ($P = .07$). Fibrin monomer values returned to baseline in both groups on POD 2.

Thrombin-antithrombin complex. Levels of TAT were significantly lower in the OAR group (ANOVA between groups with and without correction for hemodilution $P < .0001$) (Fig 3). Compared with baseline (T1) TAT, values were significantly elevated in both groups at T2 to POD 1 ($P < .05$ for each correlation) and returned to values near baseline at POD 5.

D-dimer. Levels of D-dimer did not differ significantly between the groups (for ANOVA between groups, $P = .21$; for values corrected for hemodilution, $P = .16$) (Fig 4). Compared with baseline (T1), a significant increase was seen in both groups, with maximal mean values at POD 1. D-dimer values returned to baseline at POD 5 in both groups.

DISCUSSION

Patients with AAA are increasingly being managed with endovascular techniques, but despite promising initial clinical results, the long-term outcome is still under investigation. Additionally, at present, the physiologic response triggered by EVAR is not completely understood. Complications such as myocardial ischemia, peripheral thrombosis and occlusion, bleeding, renal failure, and deep vein thrombosis that are observed in OAR also occur in patients treated with endovascular techniques, although morbidity seems to be lower after EVAR.[9-11] The inflammatory response to surgery, as well as activation of the hemostatic process, may play a role in hemorrhagic and thromboembolic events after both OAR and EVAR. Since in EVAR not only the surgical injury is minimized, but other factors are also different compared with OAR (eg, endovascular manipulation with catheters, contrast infusion), one may as-

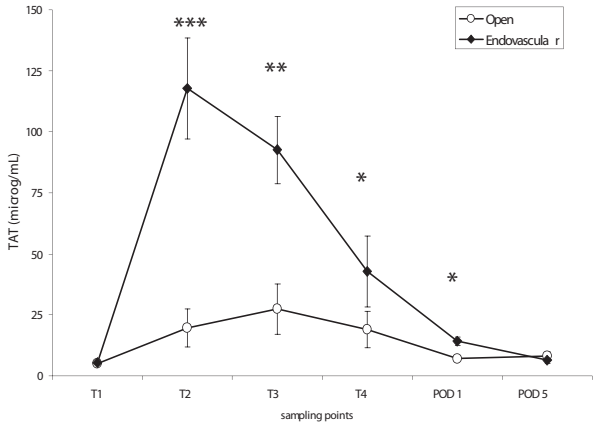

Fig 3. Thrombin-antithrombin complex *(TAT)*. Analysis of variance testing $P < .0001$. *T1*, baseline; *T2*, during operation; *T3*, end of operation; *T4*, 4 hours postoperatively; *POD*, postoperative day. Data are presented as mean ± SEM. Significant intergroup differences: $*P < .01$; $**P < .001$; $***P < .0001$.

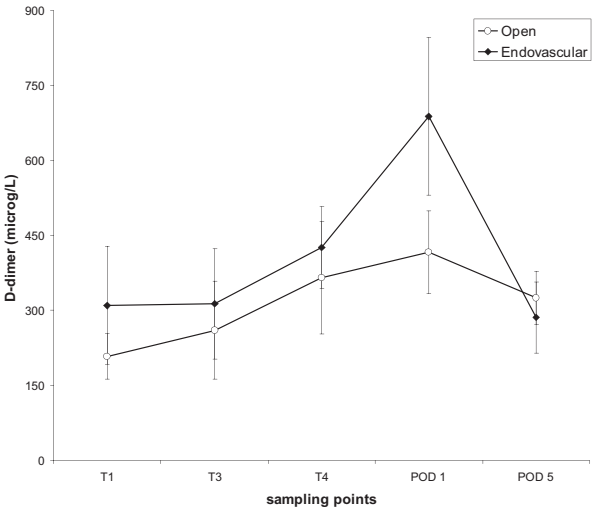

Fig 4. D-dimer. Analysis of variance testing, $P = .21$. *T1*, baseline; *T3*, end of operation; *T4*, 4 hours postoperatively; *POD*, postoperative day. Data are presented as mean ± SEM.

sume that activation of coagulation and inflammation are different between these treatment modalities.

In this prospective, comparative study, we focused on markers of thrombin activity (FPA, fibrin monomer), thrombin formation (TAT), and fibrinolysis (D-dimer). We demonstrated increased markers of activated coagulation and fibrinolysis in both groups. Furthermore, the principal finding is a significantly higher magnitude of thrombin activity and thrombin formation in the EVAR group compared with OAR, reflecting a procoagulant state. Since intergroup differences were found in levels of fibrin monomer but not in FPA generation (both markers of thrombin activation), one explanation may be the different kinetics of these markers. FPA, with a short half-life of 3 to 5 minutes, reflects acute thrombin activity, whereas elevated fibrin monomer suggests ongoing coagulation, or reflects the sum of the coagulation process by accumulated molecules due to a long half-life, or both.

Thrombin is a strong physiologic activator of fibrinolysis, and elevated D-dimer levels were therefore present in both groups. In addition, higher levels were observed in EVAR patients, but the intergroup difference did not reach statistical significance. This may be due to the number of patients investigated. However, the patient who had a perioperative myocardial infarction had some of the highest levels of markers of activated coagulation (FPA, fibrin monomer, and TAT).

Asymptomatic AAA in itself is associated with increased thrombin generation.[4,6] It may be caused by the mural thrombus within the aneurysm sac triggering chronic consumptive coagulopathy, by concomitant peripheral occlusive vascular disease, or by other risk factors for atherosclerotic disease. Additionally, marked activation of coagulation during and after OAR has been previously described.[6,7,12] This biologic response seems to be triggered the same way as activation of inflammatory cascades by ischemia–reperfusion injury and the surgical insult itself.

Although this is well described in OAR, one could expect an attenuated biologic response in connection with less invasive surgical techniques such as EVAR. In contrast, we found increased activation of coagulation in the EVAR group. Contributing factors may include (1) prolonged and repeated passage of endovascular tools, which may disturb the endothelium and stimulate coagulation, (2) release of prothrombotic substances from the aneurysmatic thrombus (present in all our patients) as a result of mechanical manipulation during stent-graft deployment, (3) contrast media, depending on type and volume, which may have an effect on hemostasis,[13] and (4) blood contact with the foreign materials such as sheaths, guidewires, and the stent-graft itself.

These factors are not present in OAR. After aortic clamping, the thrombus is no longer in contact with the blood stream and can be manually removed. On the other hand, OAR through a midline laparotomy is associated with prolonged ischemia during aortic cross-clamping followed by the ischemia–reperfusion phenomena. More blood loss and transfusions may count for increased hemostatic derangement, which may be a confounding factor in our study in that a cell-saving device was used in 13 of the 15 OAR patients.

One may argue that markers of thrombin activation could be washed out during the processing of saved blood before it has been transfused back. However, assessing the intravascular activation in the EVAR group, the use of a cell saver in the OAR group seems not to conflict with our findings, as blood that is sucked from an open abdomen likely has a high extravasal activation of coagulation present.

Blood loss was significantly higher perioperatively in the OAR group. Thus, the lower postoperative platetet counts in the OAR group may be explained by consumption of platetelets, hemodilution, and more transfusions. In

contrast, a different pattern is present in connection with leukocytes: lower white blood cell counts observed in the EVAR group at the end of implantation were followed by higher levels on postprocedure days 1 and 2. Thus, EVAR activates the cellular inflammatory system as well.[14]

CONCLUSION

Thrombin activation is more pronounced in EVAR compared with conventional open surgery perioperatively. The clinical impact of this pathophysiologic finding has yet to be determined. However, endovascular manipulation, a possible factor in triggering thrombin activation, should be kept at a minimum.

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AUTHOR CONTRIBUTIONS

Conception and design: LE, HS, JS, TPC
Analysis and interpretation: LE, HS, PJ, DDD, JS, IB, AH
Data collection: PJ, LE, MW, HS, JS, DDD
Writing the article: LE, HS, PJ, TPC
Critical revision of the article: IB, HS, LE, JS, TPC, PJ, MW
Final approval of the article: LE, HS, PJ, MW, DDD, AH, IB, TPC, JS
Statistical analysis: LE, PJ, AH
Obtained funding: JS, TPC
Overall responsibility: LE

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