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Influence of open surgical and endovascular abdominal aortic aneurysm repair on clot quality assessed by ROTEM® test

Uticaj otvorene i endovaskularne rekonstrukcije aneurizme abdominalne aorte na kvalitet koaguluma meren ROTEM® testom

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Abstract

Introduction/Aim. The disturbances in hemostasis are often in open surgical repair (OR) and endovascular repair (EVAR) of an abdominal aortic aneurysm (AAA). These changes may influence the perioperative and early postoperative period inducing serious complications. The aim of this study was to compare the impact of OR and EVAR of AAA on clot quality assessed by rotational thromboelastometry (ROTEM®) tests. **Methods.** The study included 40 patients who underwent elective AAA surgery and were devided into two groups (the OR and the EVAR group – 20 patients in each group). The ROTEM® test was performed in 4 points: point 1 – 10 min before starting anesthesia in both groups; point 2 – 10 min after aortic clapming in the OR group and 10 min after the stent-graft trunk release in the EVAR group; point 3 – 10 min after the releasing of aortic clamp in the OR group and 10 min after stent-graft placement and releasing the femoral clamp in the EVAR group; point 4 – one hour after the procedure in both groups. Three ROTEM® tests were performed as: extrinsically activated assay with tissue factor (EXTEM), intrinsically activated test using kaolin (INTEM), and extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D (FIBTEM). All tests included the assessment of the maximum clot firmness (MCF) and the platelet component of clot strength was presented as maximal clot elasticity (MCE). **Results.** No significant difference in age, gender and diameter of AAA between groups was found. The time required for the procedure was significantly longer and loss of blood was greater in the OR group than in the EVAR group ($p < 0.001$). The significant deviation of MCF values in EXTEM test was found mainly in the point 3 ($p \leq 0.004$) with significant difference between groups ($p < 0.001$). A significant difference of MCF values in INTEM test between groups was found in the points 3 and 4 ($p < 0.001$), which were dose-dependent by heparin sulfate. The MCF values in FIBTEM test were more prominent in the OR group than in the EVAR group without significant difference. The significant changes of MCF values in the FIBTEM test were found during time in both groups ($p < 0.001$). The values of MCE were lower in both groups, but without significant changes and difference between groups ($p = 0.105$). **Conclusion.** The disorders of hemostatic parameters assessed by ROTEM® tests are present in both the OR and the EVAR groups being more prominent in OR of AAA. Vigilant monitoring of hemostatic parameters evaluated by ROTEM® tests could help in administration of the adequate and target therapy in patients who underwent EVAR or OR of AAA.

Key words:
aortic aneurism, abdominal; vascular surgical procedures; blood coagulation; blood loss, surgical; platelet function tests.

Apstrakt

Uvod/Cilj. Poremećaji hemostaze su česti u otvorenoj (OR) i endovaskularnoj rekonstrukciji (EVAR) aneurizme abdominalne aorte (AAA). Ove promene mogu uticati na perioperativni i rani postoperativni period uzrokujući ozbiljne komplikacije. Cilj studije bio je da se uporedi uticaj OR i EVAR AAA na kvalitet koaguluma procenjen testovima rotacione tromboelastometrije (ROTEM®). **Metode.** Studija je obuhvatila 40 bolesnika kod kojih je izvedena elektivna operacija AAA, i koji su bili podeljeni u dve grupe (OR i EVAR grupa – po 20 bolesnika u svakoj grupi). ROTEM® test urađen je u 4 tačke: tačka 1 – 10 min pre uvođenja u anesteziju u obe grupe; tačka 2 – 10 min nakon klemovanja aorte u OR grupi i 10 min nakon otpuštanja trunkusa stent grafta u EVAR grupi; tačka 3 – 10 min nakon otpuštanja kleme sa aorte u OR grupi i 10 min nakon plasiranja stent grafta i otpuštanja klema sa femoralnih arterija u EVAR grupi; tačka 4 – jedan sat nakon operacije u obe grupe. Izvedena su tri ROTEM® testa: spoljašnji aktivacioni esej sa tkivnim faktorom (EXTEM), unutrašnji aktivacioni test

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sa kaolinom (INTEM) i spoljašnji aktivacioni test sa tkivnim faktorom i trombocitnim inhibitorom citohalazinom D (FIBTEM). Svi testovi uključili su procenu maksimalne čvrstine koaguluma (MČK) i trombocitna komponenta jačine koaguluma predstavljena je maksimalnom elastičnošću koaguluma (MEK). **Rezultati.** Nije bilo značajne razlike između grupa u godinama starosti i polu bolesnika i dijametru AAA. Trajanje operacije bilo je značajno duže kao i količina izgubljene krvi u OR nego u EVAR grupi, ($p < 0{,}001$). Nađene su značajne promene u MČF vrednostima u EXTEM-u, naročito u tački 3 ($p \leq 0{,}004$), sa značajnom razlikom između grupa ($p < 0.001$). Nađena je značajna razlika između grupa u vrednostima MČK u INTEM-u u tačkama 3 i 4, što je bilo dozno zavisno od heparina. Vrednosti MČK u FIBTEM-u bile su izraženije u OR grupi nego u EVAR grupi, ali bez značajne razlike između grupa. Značajne promene u MČK vrednostima u FIBTEM-u tokom vremena nađene su u obe grupe ($p < 0{,}001$). Vrednosti MČK bile su niže u obe grupe, ali bez značajnih promena i bez značajne razlike između grupa ($p = 0{,}105$). **Zaključak.** Poremećaji parametara hemostaze procenjenih ROTEM® testovi bili su prisutni u OR i EVAR proceduri, ali su bili izraženiji u OR AAA. Vigilno praćenje parametara hemostaze uz pomoć ROTEM® testova može pomoći u primeni adekvatne i ciljne terapije kod bolesnika podvrgnutih EVAR i OR AAA.

Ključne reči:
aorta, abdominalna, aneurizma; hirurgija, vaskularna, procedure; krv, koagulacija; krv, hirurški gubitak; trombociti, funkcijski testovi.

Introduction

The abdominal aortic aneurysm (AAA) is a common disease in the era of a modern medicine and surgery also and ussualy occurs in patients with different comorbidity states. Those during AAA repair as well as perioperative hemostatic disturbances are common and could deterioate during surgery and in the early postoperative period. In the perioperative period, disturbances of hemostatic parameters such as elevated plasma levels of factor VIII, fibrinogen, disorders of fibrinolysis with elevated level of d-dimer and platelet hyperactivity are reported 1, 2.

The elective open surgical repair (OR) of infrarenal AAA is associated with a perioperative mortality rate of 3% to 10% 3. Perioperative bleeding, general hypothermia, the use of anesthetics, as well as ischemia reperfusion injury result in a systemic inflammatory response with microvascular and macrovascular thrombosis that may cause myocardial infarction, stroke, thromboembolism, and multiple organ failure. Thereby, all of these could increase the operative mortality rate 4, 5.

As compared to OR, endovascular aneurysm repair (EVAR) of an AAA represents a safer alternative in anatomically suitable patients. Thus, the EVAR-1, EVAR-2, and Dutch Randomized Endovascular Aneurysm Management trials reported a 60% reduction in perioperative mortality rate in EVAR compared to OR of AAA, but without difference in a long term mortality rate postoperatively 6, 7.

A systematic inflammatory response is observed in a significant number of patients after EVAR. The intensity of inflammation, assessed mainly by the postoperative high level of C-reactive protein (CRP) values, correlates with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure 8.

The inflammatory response in EVAR could lead to hemostatic disturbances, similar to those seen after OR of AAA, although it is less invasive surgery 9, 10. The explanation for this lies in the use of radiological contrast medium, intra-arterial implants (stent grafts) 11, 12, as well as manipulations with radiological devices such as introducers and cathethers for intra-arterial – endovascular procedures 9, 13. The existence of specific complications in EVAR – endoleak, could also lead to hemostatic disturbances and coagulopathy 14.

The aim of this study was to compare the impact of OR of AAA and EVAR on hemostasis, assessed by quality of blood clot measured by rotational thromboelastometry – ROTEM® (ROTEM® delta, TEM® International GmbH, Munich, Germany) parameters.

Methods

This prospective observational study included 40 patients who underwent elective AAA surgery, and divided into two groups. The first group included 20 patients with OR of AAA (OR group) and the second one included another 20 patients with EVAR of AAA (EVAR group). Written informed consent was obtained from all patients after a detailed description of the procedure.

Inclusion criteria were as follows: asimptomatic AAA of 5.5 cm in diameter and more, confirmed by multi-slice computed tomography (MSCT) scan which was also a parameter for the technical feasibility of performing EVAR procedure. The study excluded patients with any known significant disorder in coagulation, patients on oral antocoagulant and antiplatelet therapy in the last 7 days, patients with chronic renal failure (serum creatinin higher than 200 μmol/L), liver disease, acute and/or active inflammatory states and malignancy. The classification of the American Society of Anesthesiologists (ASA) was used for the assessment of perioperative risk.

The procedure was performed under balanced general anesthesia (propofol, isofluran) in all patients. All patients received a dose of 100 IU/kg of heparin sulfate 15 min before aortic clamping in the OR group and 5000 IU in a single dose 15 min before releasing of stent-graft trunk in the EVAR group (point 2 in both groups). Patients in the OR group received protamine dose of 1 mg/kg for the neutralization of heparin sulfate after the end of aortic clamping (10 min before the point 3). In the EVAR group point 3 was defined as finished endograft placement. Perioperative monitoring was performed in both group. During the operative procedure each patient received crystalloids substitution of 15 mL/kg/h. Blood derivatives and blood substitution therapy were administered according to the results of hemoglobin level perioperatively and amount of intraoperative bleeding.

EVAR procedure: after surgically exposing both femoral arteries for EVAR the angiography was performed in all patients. The endoprosthesis was inserted and released into the aorta using extra stiff 300 cm long 0.035 inch guidewire (Lunderquist Extra Stiff Guide Wire, Cook medical, USA), controlled by angiography. The exclusion of the aneurysm sac was confirmed by angiography immediately following the procedure. Primary success criteria were intraoperative survival rate, the absence of an open surgical conversion, the exclusion of aneurysmal sac, the absence of type I or III endoleaks. We used one or more GORE® EXCLUDER® AAA Endoprosthesis (W. L. Gore & Associates, Inc. Arizona, USA) for all patients. A bifurcated prosthesis was implanted in all patients.

OR technique: through medial laparotomy and transperitoneal approach the AAA and iliac blood vessels were exposed in all patients. The femoral blood vessels were exposed through inguinal approach on the both sides if the aortobifemoral reconstruction was necessary. After heparin sulfate administration a proximal and distal aortic clamping was performed. After aortotomy the aortic reconstruction was done in a typical way. Proximal anastomosis was created endoaneurysmatically end-to-end sided with tubular graft. In cases with aneurysm in iliac artery (one or both), or in cases with occlusive iliac disease a distal anastomosis was created end-to-end or end-to-side between bifurcated graft and iliac/femoral arteries. After finished reconstruction, all patients without extensive bleeding received protamine. The aneurysmatic sac was sutured over the graft.

The ROTEM® tests were performed several times in all patients: before intervention, perioperatively and postoperatively.

Three ROTEM® tests were performed: extrinsically activated assay with tissue factor (EXTEM), intrinsically activated test using kaolin (INTEM), and extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D (FIBTEM) (Figure 1). Reference ranges for the tests' parameters have been previously determined in a multi-centre investigation 15. The ROTEM® test was performed: 10 min before starting anesthesia in both groups – point 1; 10 min after aortic clamping in the OR group and 10 min after of stent-graft trunk release in the EVAR group – point 2; 10 min after releasing the aortic clamp in OR group and 10 min after finished stent-graft placement and releasing the femoral clamp in the EVAR group – point 3; and one hour after the operation in both groups – point 4.

Blood samples for ROTEM® analysis were collected in a standard coagulation tube syringe containing a 0.106 M citrate solution, with blood/citrate ratio of 9 : 1.

ROTEM® tests were performed according to the manufacturer's recommendations, and the analyses were performed within 5 min of blood sampling. The EXTEM, INTEM and FIBTEM analyses included the assessment of the maximum clot firmness (MCF). The platelet component of clot strength was calculated as follows: MCE (platelet) = MCE (EXTEM) – MCE (FIBTEM). Maximum clot elasticity (MCE) was calculated by formula (MCFx100)/(100-MCF).

All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL). The data were presented in number (%), median (range) and mean ± standard deviation. The comparison between groups including demographic and clinical characteristic of the patients was assessed with $\chi 2$ test ant t-test. Multiple comparisons between measured variables in different points were assessed with Bonfferoni test method. The comparison between each variable was performed using logistic regression and ANOVA test. P value less than 0.05 was considered as significant.

Results

The demographic and clinical characteristics of patients are presented in Table 1.

There was no in-hospital mortality in both groups of patients. No significant difference in age, gender and diameter of

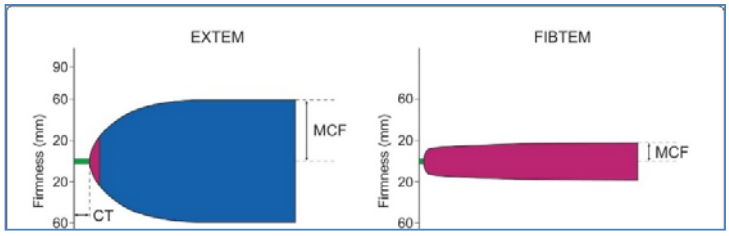

Fig. 1 – The ROTEM® analyses.

EXTEM® test (extrinsically activated test) and FIBTEM® test (fibrin clot obtained by platelet inhibition with cytochalasin D); CT – clot time. The maximum clot firmness (MCF, mm) represents the total amplitude of the clot.

Table 1

The demographic and clinical characteristics of operated on patients

Patients	OR (n = 20)	EVAR (n = 20)	*p*
Age (years), $\bar{x}$ ± SD	66.2 ± 7.4	68.8 ± 11.01	0.253
Sex M/F, n (%)	27/3 (11.1%)	29/1 (3.48%)	0.630
Aneurysm diameter (cm), $\bar{x}$ ± SD	6.6 ± 2.02	7.03 ± 1.23	0.093
Duration of operation (min), $\bar{x}$ ± SD	167.0 ± 58.1	102.9 ± 34.8	< 0.001
Bleeding volume (mL), $\bar{x}$ ± SD	1058.21 ± 722.9	389.6 ± 161.6	< 0.001
ASA class III or IV, (%)	56.5	93.1	< 0.001

Abbreviation: OR – open surgical repair; EVAR – endovascular aortic repair; AAA – aortic abdominal aneurysm; ASA - American Society of Anesthesiologists.

AAA between groups was found. The time required for the procedure was significantly longer in the OR group than in the EVAR group. Blood loss during the procedure was present in both groups, and significant difference between groups was found. As it was expected, blood loss during surgery was greater in the OR group ($p < 0.001$). Only one patient in the EVAR group required blood transfusion of erythrocyte concentrate. There were more patients with ASA class III or IV in OR group with significant difference between groups ($p < 0.001$).

The values of MCF in EXTEM test in each point of measurement are presented in Table 2 and analysis of values comparison is presented in Table 3. The dynamic of MCF values change in EXTEM test in both groups and in all points of assessment (dynamics in clot quality in each point of measurement) is shown in Table 2. There were no significant deviations in MCF values in EXTEM in the EVAR group and these values were in the normal ranges mainly. Significant changes were in MCF value in EXTEM test in the OR group during procedure with maximum noted deviation in the point 3 ($p \leq 0.004$) (Table 3), with significant difference between groups ($p < 0.001$). The values of MCF in EXTEM test in the OR group after the point 3 gradually returned in the normal ranges in the point 4 (one hour after procedure).

The values of MCF in INTEM test in each point of measurement are presented in Table 4 and analysis of values comparison is presented in Table 5. The dynamic of MCF

Table 2

The values of MCF in EXTEM test in each time point of measurement in both groups

Group	Time point	Mean	SD	Median	Range
EVAR (n = 20)	1	66.93	5.982	67.0	56–79
	2	63.81	9.108	65.5	35–76
	3	58.50	16.403	61.5	7–74
	4	58.71	17.709	63.0	7–78
OR (n = 20)	1	64.54	10.819	67.0	12–76
	2	62.56	7.048	61.0	48–78
	3	41.77	12.313	43.0	6–59
	4	53.77	9.201	54.0	18–73

OR – open surgical repair; EVAR – endovascular aortic repair; EXTEM – extrinsilally activated assay with tissue factor; MCF – maximum clot firmness (normal range 49–71 mm).
Time points: 1 – 10 min before starting anesthesia in both group; 2 – 10 min after aortic clamping in the OR group and 10 min after of stent-graft trunk release in the EVAR group; 3 – 10 min after releasing the aortic clamp in OR group and 10 min after finished stent-graft placement and releasing the femoral clamp in the EVAR group; 4 – one hour after the operation in both groups.

Table 3

Bonferroni test for multiple comparison (MCF values in EXTEM)

Group	Time point	Time point			
		1	2	3	4
		Sig.	Sig.	Sig.	Sig.
EVAR	1		1.000	0.691	0.397
	2	1.000		1.000	0.647
	3	0.691	1.000		1.000
	4	0.397	0.647	1.000	
OR	1		1.000	0.000	0.116
	2	1.000		0.000	0.061
	3	0.000	0.000		0.004
	4	0.116	0.061	0.004	

Based on estimated marginal means; Dependent variable: tExtem MCF; Adjustment for multiple comparisons: Bonferroni statistical significance;
For abbreviations and explanations see Table 2.

Table 4

The values of INTEM MCF in each time point of measurement in both groups

Group	Time point	Mean	SD	Median	Range
EVAR (n = 20)	1	66.25	5.183	65.50	56–78
	2	62.31	9.112	64.50	42–80
	3	56.81	8.998	59.50	40–67
	4	51.88	15.064	52.00	15–72
OR (n = 20)	1	64.87	6.400	66.00	47–76
	2	41.05	20.109	45.00	6–72
	3	55.63	11.504	57.50	8–70
	4	62.49	6.104	63.00	47–73

INTEM – intrinsically activated test using kaolin; MCF – maximum clot firmness (normal range 52–72 mm).
For abbrevations and explanations see Table 2.

values change in INTEM test in both groups and in all points of assessment (dynamics in clot quality in each point of measurement) is shown in Table 4.

Analysis of MCF values in INTEM test showed different dynamics of clot quality due to influence of heparin sulfate on hemostasis and coagulation status as well. After administration of heparin sulfate (point 2) in the EVAR group there was an evident slow decrease in MCF values which continued to decline in the point 3 and 4 (patients in the EVAR group did not received protamine for the neutralization of heparin sulfate). After a decrease in MCF values in the point 2 in the OR group, a normalisation of MCF values in the point 3 and 4 was evident, which were in normal ranges in the point 4 (protamine administration).

Analysis of MCF values in FIBTEM test showed impact of fibrinogen on the clot firmness during OR and EVAR of AAA. It was evident that the value of MCF in FIBTEM test declined slowly in EVAR group with normalisation after one hour postoperatively (point 4). However, normal ranges were in each point. The changes in MCF values in FIBTEM test were more prominent in the OR group, mainly in the point 3. The dynamics of MCF values in FIBTEM test in both groups and in all points of assessment (dynamics in clot quality in each point of measurement) are shown is Table 6.

A significant difference in MCF values changes in FIBTEM test in all patients was found ($F = 50.402$; $p < 0.001$), with no significant difference between groups ($F = 0.179$; $p = 0.674$). However, there was a significant impact of operative procedures (OR and EVAR) on MCF values changes in FIBTEM test in time ($F = 4.986$; $p < 0.001$).

Using the above mentioned formula in Methods, the platelet component of clot strength and MCE were calculated. Tables 7 and 8 represent the dynamics of clot elasticity and the platelet component of clot with its influence on clot quality in each point of measurement in both groups.

The significant influence of operative procedures on MCE value changes during the time was not found ($F = 1.853$; $p = 0.105$). The amount of platelet and other factors in the clot and their influence on clot elasticity was without significant changes in both groups, and with no difference between groups ($p = 0.105$).

Table 5

Bonferroni test for multiple comparison (MCF values in INTEM)

Group	Time point	Time point			
		1	2	3	4
		Sig.	Sig.	Sig.	Sig.
EVAR	1		1.000	0.013	0.000
	2	1.000		1.000	0.183
	3	0.013	1.000		0.840
	4	0.000	0.183	0.840	
OR	1		0.000	0.000	0.782
	2	0.000		0.000	0.000
	3	0.000	0.000		0.012
	4	0.782	0.000	0.012	

Based on estimated marginal means; Dependent variable: Intem MCF; Adjustment for multiple comparisons: Bonferroni.
For abbrevation see and explantations Tables 2 and 4.

Table 6

The dinamycs of MCF values (mm) in FIBTEM test in both groups

Group	Time point			
	1	2	3	4
OR	20.53	16.53	13	17.89
EVAR	21.89	18.5	18.31	18.37

FIBTEM – fibrin clot obtained by platelet inhibition with cytochalasin D; MCF – maximum clot firmness (normal range 9–25 mm).
For abbrevations and explanations see Table 2.

Table 7

Maximum clot elesticity (MCE) in each time point of measarement in the EVAR group

MCE	Time point			
	1	2	3	4
Extem	202.38	177.23	140.96	142.18
Fibtem	27.89	22.69	22.41	22.5
Platelet	174.49	153.54	118.55	119.68

For abbrevation and explantations see Tables 2 and 6.

Table 8

Maximum clot elasticity (MCE) in each time point of measurement in OR group

MCE	Time point			
	1	2	3	4
Extem	198.86	167.09	71.73	116.3
Fibtem	25.83	19.66	14.94	21.78
Platelet	173.03	147.43	56.84	94.52

For abbrevation and explantations see Tables 2 and 7.

Discussion

AAA is almost always associated with disorders of hemostasis. It was reported that a lot of patients with AAA had elevated serum levels of d-dimer, fibrinogen, as well as altered platelet functions. Also, a relationship between diameter of AAA, thrombus volume and serum level of d-dimer was found [16]. Aging may affect the changes in hemostasis also [17]. All those disorders can lead to disturbances in hemostasis during the surgical procedure and/or after the procedure with dangerous consequences (bleeding, thromboembolism, etc). Generally, OR of AAA is accompanied with greater trauma of the body as compared to EVAR. Also, the implantation of prosthetic material in both OR and EVAR techniques has an impact on hemostasis. General hypothermia during surgical procedure has influence on hemostasis and can lead to hemostatic disturbances and coagulopathy [18]. Bleeding and blood substitution therapy lead to changes in hemostatic parameters *per se* [19]. The immune system is affected also with altered immunologic parameters. A high concentration of IL-1, IL-6 and TNF in AAA, and elevated serum level of CRP were shown [20, 21].

In comparison to OR of AAA, EVAR technique is less traumatic with lower incidence of serious perioperative and early postoperative complications [22]. However, the usage of radiographic contrast medium could change the homeostasis of hemostasis and platelet functioning [23]. Manipulation into arterial blood vessels and endoprothesis implantation lead to the activation of immune system as well as disturbances in hemostasis with development of well known post-implantation syndrome [23, 24]. In contrast to OR of AAA whereas the thrombus is removing with all active substances, in EVAR technique it remains *in situ* and represents a source of inflammatory mediators with all their systemic effects. The existence of specific complications in EVAR (endoleaks), especially the endoleak type 2, could lead to a leakage of cytokines into systemic circulations. This is one of the reasons for the hemostasis disturbances occurrence, and in some cases the appearance of coagulopathy [25]. All mentioned suggests that the changes in hemostasis during and after EVAR are similar or slightly less than those during OR of AAA.

The results of our study showed the active changes in the coagulation system throughout both EVAR and OR of AAA. We analyzed the firmness of clot in several points in EVAR and OR of AAA assessed with ROTEM® tests. This is the first study which assessed the clot firmness in all EXTEM, INTEM and FIBTEM tests in both EVAR and OR of AAA. MCF values by ROTEM® were evaluated and reported in the study with cardiac surgery patients but not in all tests [26, 27]. These studies suggested that ROTEM® may be used to manage anticoagulation and transfusion therapy for bleeding. The tests we used for MCF assessment were EXTEM, INTEM and FIBTEM, and we calculated the MCE with mathematic model, as well as compound of platelet in clot elasticity – MCE platelet. Generally, we found that both techniques, EVAR and OR, for AAA solving changed the whole system of hemostasis, evaluated by ROTEM® tests. Also, we found a change in the blood clot composition in term of clot quality reduction. The reduction in clot quality (MCF) was found in all tests in both groups. It was reported an active fibrinolysis, platelet and coagulation factors consumption in patients with aortic pathologies who were treated by EVAR technique [28]. We found a coagulation disturbances not only in the EVAR but in the OR group, too.

The equivalent of MCF value in ROTEM® tests is a value of maximum amplitude (MA) in thrombelastography (TEG®) test. The changes in these parameters in patients who underwent AAA reconstruction were reported by Franks et al. [29]. They found a reduced clot quality during OR of AAA, whereas clot quality has been improving two hours after EVAR technique. Our findings are similar but not identical. In the OR groups Franks et al. [29] showed continuous reduction of clot quality in EXTEM test during surgical procedure and two hours after. We found a similar trend of MCF, however clot quality had started improving one hour after the procedure with subsequent upward trend. This could be explained by active substitution of blood and blood derivates in our patients during and after the surgery. The intraoperative changes in MCF values in EXTEM test were more prominent in the OR group than in the EVAR group, whereas clot quality and elasticity were decreasing until the end of the procedure. If the blood loss is greater during surgery, the clot quality and elasticity will be more changed. That was the conlusion of Plotkin et al. [30] also, who sugessted that clot quality could be possible predictor of bleeding and blood transfusion. Our results correspond to these findings. In the Medline database we could not find a study that analyzed MCF parameters in INTEM test during EVAR nor during OR of AAA. However, Mittermayr et al. [31] assessed influence of heparin sulfate on INTEM parameters (ROTEM®) and reported dose dependence of parameters. In our study we found significant difference in MCF values in INTEM test in both groups and between groups. Also, MCF values in INTEM test were influenced by heparin sulfate. Both groups received heparin sulfate in the point 2 when the MCF values dropped. The declining in MCF values in the EVAR group was linear until the end of procedure. After finished EVAR, MCF values did not normalized due to the absence of heparin sulfate neutralization by protamine. These findings were similar with dynamics of clot time (CT) values in INTEM test reported by Mittermayr et al. [31]. In the OR group the values of MCF started normalizing after the point 3 (administration of protamine) and were in normal ranges one hour after the end of the procedure. Parameters in INTEM test were dose dependent by heparin sulfate, so INTEM test can be used for monitoring of heparin sulfate and protamine administration.

The influence of fibrinogen on coagulation could be assessed by FIBTEM parameters, as well as concentration and amount of fibrinogen and platelet in clot, and clot elasticity and quality. Besides analyses of the clot quality and elasticity it is important to determine the influence of other coagulation factors on coagulation. The assessment of ethiopathogenesis of the quality changes in hemostasis should includes factor XIII [32], usage of antiplatelet drugs, fluid resuscitation [33], body temperature during surgery, duration of the procedure, bleeding, blood substitution therapy, radiological contrast medium in EVAR [19, 22], etc, in addition to ROTEM® and TEG®

analyses. Schochl et al. [34] reported significantly decreased values of MCF in FIBTEM test (less than 6 mm) in patients with trauma and massive bleeding. These values of MCF should correspond values of fibrinogen less than 1 g/L. We found that MCF values in FIBTEM test were more prominent in the OR group than in the EVAR group without significant difference between groups. However, there were significant changes of MCF values in FIBTEM test during the time in both groups of patients ($p < 0.001$), and significant impact of group on MCF values in FIBTEM test ($p < 0.001$). The greatest decline in MCF values in FIBTEM test was noted in the point 3, mainly in the OR group, when the largest amount of bleeding was recorded.

Shenkman et al. [35] recorded that the clot quality may be improved by administration of factor XIII in cases with low level of platelet, but improving of clot quality was limited. In such cases where the level of platelets was extremely low, clot quality could not be improved. Our results showed that clot quality declined during intervention, and that was more significant in the OR than in the EVAR group due to higher blood loss in the OR group of patients. The amount of platelet and other factors in the clot and their influence on clot elasticity were without significant changes in both groups without difference between groups. The ROTEM® test during EVAR and OR can indicate a disturbances in hemostasis and may predict possible conversion of EVAR in OR of AAA. Vigilant and timely monitoring of hemostatic parameters with the adequate and target substitution of blood and blood products therapy in patients who underwent EVAR and OR of AAA can reduce disturbances in hemostasis and subsequent lower incidence of complications.

Conclusion

The results of our study show active changes in the coagulation parameters during both EVAR and OR of AAA evaluated by ROTEM® analysis. In the OR group a significant deviation of MCF values was found with maximum deviation noted in the point 3. The reduction in clot quality (MCF) was present in all tests in both groups. A significant difference of MCF values in INTEM test between the EVAR and the OR group was found. The MCF values in INTEM test were dose dependent by heparin sulfate, so INTEM test can be used for monitoring of heparin sulfate and protamine administration. The MCF values in FIBTEM test were more prominent in the OR group than in the EVAR group but without significant difference. The significant changes of MCF values in FIBTEM test during time were found in both groups. A decline in MCF values in FIBTEM test was noted in the OR group patients when the largest amount of bleeding was recorded. The clot quality declined during intervention in both groups, mainly in the OR group due to higher blood loss. The values of MCE were lower in both groups, but without significant changes and without difference between the groups. Vigilant and timely monitoring of hemostatic parameters by ROTEM® tests could help in administration of the adequate therapy with subsequent reduction of disturbances in hemostasis and incidence of complications.

REFERENCES

1. *Takagi H, Manabe H, Kawai N, Goto S, Umemoto T.* Plasma fibrinogen and D-dimer concentrations are associated with the presence of abdominal aortic aneurysm: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2009; 38(3): 273−7.
2. *Golledge J, Muller R, Clancy P, McCann M, Norman PE.* Evaluation of the diagnostic and prognostic value of plasma D-dimer for abdominal aortic aneurysm. Eur Heart J 2011; 32(3): 354−64.
3. *Dueck AD, Kucey DS, Johnston WK, Alter D, Laupacis A.* Long-term survival and temporal trends in patient and surgeon factors after elective and ruptured abdominal aortic aneurysm surgery. J Vasc Surg 2004; 39(6): 1261−7.
4. *Van Poucke S, Stevens K, Marcus AE, Lancé M.* Hypothermia: effects on platelet function and hemostasis. Thromb J 2014;12(1):31.
5. *Galle C, de Maertelaer V, Motte S, Zhou L, Stordeur P, Delville JP*, et al. Early inflammatory response after elective abdominal aortic aneurysm repair: a comparison between endovascular procedure and conventional surgery. J Vasc Surg 2000; 32(2): 234−46.
6. *EVAR trial participants.* Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005; 365(9478): 2179−86.
7. *EVAR trial participants.* Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005; 365(9478): 2187−92.
8. *Arnaoutoglou E, Kouvelos G, Papa N, Kallinteri A, Milionis H, Koulouras V*, et al. Prospective evaluation of post-implantation inflammatory response after EVAR for AAA: influence on patients' 30 day outcome. Eur J Vasc Endovasc Surg 2015; 49(2): 175−83.
9. *Englberger L, Savolainen H, Jandus P, Widmer M, Do DD, Haeberli A,* et al. Activated coagulation during open and endovascular abdominal aortic aneurysm repair. J Vasc Surg 2006; 43(6): 1124−9.
10. *Swartbol P, Norgren L, Albrechtsson U, Cwikiel W, Jahr J, Jonung T,* et al. Biological responses differ considerably between endovascular and conventional aortic aneurysm surgery. Eur J Vasc Endovasc Surg 1996; 12(1): 18−25.
11. *Polanowska R, Wilczyńska M, Sławiński W, Goch JH, Augustyniak W, Cierniewski CS.* Changes in platelet activity and tissue plasminogen activator during arteriography in patients with chronic limb ischaemia. Thromb Res 1992; 65(4−5): 663−5.
12. *Zhang H, Holt CM, Malik N, Shepherd L, Morcos SK.* Effects of radiographic contrast media on proliferation and apoptosis of human vascular endothelial cells. Br J Radiol 2000; 73(874): 1034−41.
13. *Swartbol P, Truedsson L, Norgren* L. Adverse reactions during endovascular treatment of aortic aneurysms may be triggered by interleukin 6 release from the thrombotic content. J Vasc Surg 1998; 28(4): 664−8.
14. *Nienaber JJ, Duncan AA, Oderich GS, Pruthi RK, Nichols WL.* Operative and nonoperative management of chronic disseminated intravascular coagulation due to persistent aortic endoleak. J Vasc Surg 2014; 59(5): 1426−9.
15. *Lang T, Bauters A, Braun SL, Pötzsch B, von Pape K, Kolde H,* et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 2005; 16(4): 301−10.
16. *Adolph R, Vorp DA, Steed DL, Webster MW, Kameneva MV, Watkins SC.* Cellular content and permeability of intraluminal

thrombus in abdominal aortic aneurysm. J Vasc Surg 1997; 25(5): 916−26.
17. *Hashimoto Y, Kobayashi A, Yamazaki N, Sugawara Y, Takada Y, Takada A.* Relationship between age and plasma t-PA, PA-inhibitor, and PA activity. Thromb Res 1987; 46(5): 625−33.
18. *Lier H, Krep H, Schroeder S, Stuber F.* Preconditions of hemostasis in trauma: a review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. J Trauma 2008; 65(4): 951−60.
19. *Johansson PI, Stensballe J, Oliveri R, Wade CE, Ostrowski SR, Holcomb JB.* How I treat patients with massive hemorrhage. Blood 2014; 124(20): 3052−8.
20. *Marjanović I, Jevtić M, Misović S, Vojvodić D, Zoranović U, Rusović S*, et al. Early inflammatory response following elective abdominal aortic aneurysm repair: a comparison between endovascular procedure and conventional, open surgery. Vojnosanit Pregl 2011; 68(11): 948−55.
21. *Nessvi OS, Gottsäter A, Acosta S, Palmqvist B, Lindblad B.* Inflammatory mediators after endovascular aortic aneurysm repair. Cytokine 2014; 70(2): 151−5.
22. *Pickard R, Lam T, Maclennan G, Starr K, Kilonzo M, McPherson G,* et al. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy. Health Technol Assess 2012; 16(9): 1−197.
23. *Lukasiewicz A, Lebkowska U, Galar M.* Effect of iodinated low-osmolar contrast media on the hemostatic system after intraarterial and intravenous contrast administration. Adv Med Sci 2012; 57(2): 341−7.
24. *Kakisis JD, Moulakakis KG, Antonopoulos CN, Mylonas SN, Giannakopoulos TG, Sfyroeras GS*, et al. Volume of new-onset thrombus is associated with the development of postimplantation syndrome after endovascular aneurysm repair. J Vasc Surg 2014; 60(5): 1140−5.
25. *Nienaber JJ, Duncan AA, Oderich GS, Pruthi RK, Nichols WL.* Operative and nonoperative management of chronic disseminated intravascular coagulation due to persistent aortic endoleak. J Vasc Surg 2014; 59(5): 1426−9.
26. *Venema L, de Vries H.* Comparison of TEG® and RoTEM® Thromboelastographic Variables with Routine Laboratory Measurements during Cardiac Surgery. Meeting abstract A4253. Netherlands, Groningen; 2014 October 14. Available from: http://www.asaabstracts.com/strands/asaabstracts/searchArticle.htm;jsessionid=D68CB1840E3D7F48D865C872D83B2A7A?index=2&highlight=true&highlightcolor=0&bold=true&italic=false
27. *Hlaing M, Hincker A, Feit J, Sladen R, Wagener G.* Evaluation of Hypercoagulability Via ROTEM Thromboelastography After Ventricular Assist Device Implantation. 2013. Meeting abstract A1029. New York; 2013 October 12. Available from: http://www.asaabstracts.com/strands/asaabstracts/searchArticle.htm;jsessionid=8DFFD7B970777BD2CD4950749B6665C1?idex=7&highlight=true&highlightcolor=0&bold=true&italic=false
28. *Monaco M, di Tommaso L, Stassano P, Smimmo R, de Amicis V, Pantaleo A,* et al. Impact of blood coagulation and fibrinolytic system changes on early and mid term clinical outcome in patients undergoing stent endografting surgery. Interact Cardiovasc Thorac Surg 2006; 5(6): 724−8.
29. *Franks S, Lloyd G, Fishwick G, Bown M, Sayers R.* Endovascular treatment of ruptured and symptomatic abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2006; 31(4): 345−50.
30. *Plotkin AJ, Wade CE, Jenkins DH, Smith KA, Noe JC, Park MS,* et al. A Reduction in Clot Formation Rate and Strength Assessed by Thrombelastography Is Indicative of Transfusion Requirements in Patients With Penetrating Injuries. J Trauma 2008; 64(2 Suppl): S64−8.
31. *Mittermayr M, Margreiter J, Velik-Salchner C, Klingler A, Streif W, Fries D,* et al. Effects of protamine and heparin can be detected and easily differentiated by modified thrombelastography (Rotem): an in vitro study. Br J Anaesth 2005; 95(3): 310−6.
32. *Siebenlist KR, Meh DA, Mosesson MW.* Protransglutaminase (factor XIII) mediated crosslinking of fibrinogen and fibrin. Thromb Haemost 2001; 86(5): 1221−8.
33. *Reyher C, Bingold TM, Menzel S, Zacharowski K, Müller M, Pape A*, et al. Einfluss der akuten normovolämischen Hämodilution auf die primäre Hämostase. Der Anaesthesist 2014; 63(6): 496−502.
34. *Schochl H, Cotton B, Inaba K, Nienaber U, Fischer H, Voelckel W,* et al. FIBTEM provides early prediction of massive transfusion in trauma. Critical Care 2011; 15(6): R265.
35. *Shenkman B, Einav Y, Livnat T, Budnik I, Martinowitz U.* In vitro evaluation of clot quality and stability in a model of severe thrombocytopenia: effect of fibrinogen, factor XIII and thrombin-activatable fibrinolysis inhibitor. Blood Transfus 2014; 12(1): 78−84.

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