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Analysis of factors for abdominal aortic aneurysm growth after endovascular repair

SUMMARY OF DOCTORAL DISSERTATION

Medicine and Health Sciences,
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Academic supervisor: Prof. Dr. Germanas Marinskis (Vilnius University, Medicine and Health Sciences, Medicine – M 001)

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Chairman – Prof. Dr. Janina Tutkuvienė (Vilnius University, Medicine and Health Sciences, Medicine – M 001).

Members:

Prof. Habil. Dr. Aleksandras Antuševas (Lithuanian University of Health Sciences, Medicine and Health Sciences, Medicine – M 001);

Assoc. Prof. Dr. Jūratė Dementavičienė (Vilnius University, Medicine and Health Sciences, Medicine – M 001);

Assoc. Prof. Dr. Saulius Mikalauskas (Medical University of Graz, Austria, Medicine and Health Sciences, Medicine – M 001);

Prof. Dr. Pranas Šerpytis (Vilnius University, Medicine and Health Sciences, Medicine – M 001).

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Address: Santariškių str. 2, LT-08661 Vilnius, Lithuania.

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Veiksnių, lemiančių pilvinės aortos aneurizmos didėjimą po endovaskulinės operacijos, analizė

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Disertacija ginama viešame disertacijos Gynimo tarybos posėdyje

Pirmininkė – prof. dr. Janina Tutkuvienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Nariai:

prof. habil. dr. Aleksandras Antuševas (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina – M 001);

doc. dr. Jūratė Dementavičienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001);

doc. dr. Saulius Mikalauskas (Graco medicinos universitetas, Austrija, medicinos ir sveikatos mokslai, medicina – M 001);

prof. dr. Pranas Šerpytis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

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ABBREVIATIONS

AAA	–	abdominal aortic aneurysm
ABP	–	arterial blood pressure
COPD	–	chronic obstructive pulmonary disease
CRP	–	C reactive protein
CTA	–	computed tomography angiography
DM	–	diabetes mellitus
ECG	–	electrocardiogram
EVAR	–	endovascular aneurysm repair
HU	–	Hounsfield Unit
IQR	–	interquartile range
MAAAD	–	maximum abdominal aortic aneurysm diameter
MMPs	–	matrix metalloproteinases
MRI	–	magnetitic resonance imaging
p	–	value in statistical significance
PAH	–	primary arterial hypertension
PIS	–	post implantation syndrome
RAWD	–	relative aortic/aneurysm wall density
ROS	–	reactive oxygen species
SPCMS	–	synthetic polymer-coated metal stent
t-PA	–	tissue-type plasminogen activator

1 INTRODUCTION

1.1 Research problem and relevance of the study

Abdominal aortic aneurysm (AAA) – is a localized dilatation of all the layers of abdominal aortic wall with a diagnosis of 3 cm and greater (or 50% larger than normal) aortic diameter[1]. This pathology is common in older, smoking men. Especially in men, the prevalence of AAA is increasing with better diagnostic options and higher life expectancy, reaching 4 to 8% of the population[2,3]. The risk of asymptomatic AAA rupture is significantly increased when the aneurysm reaches 5.5 cm in men and 5.0 cm in women, exceeding the risk of surgery and reaching 11% per year [4]. Timely diagnosis and scheduled operative treatment are recommended to avoid rupture. The aim of the operation is to either replace the weakened and dilated aortic wall with an artificial vessel (open repair), or to reduce the direct arterial blood pressure (ABP) on the aneurysm wall by introducing a stent graft, or synthetic polymer-coated metal stent (SPCMS) (endovascular aneurysm repair (EVAR)). Currently, endovascular repair accounts for up to 70% of all AAA repairs. Endovascular repair is a minimally invasive treatment and therefore operative and early postoperative mortality is lower (0.5 – 2%) compared to open repair (3 – 5%)[5,6]. There is no significant difference in long-term survival after open and endovascular repair[7]; however, the rate of repeated interventions after EVAR is 3 to 4 times higher than after an open surgery[8]. The aneurysm sac remains after introducing the stent graft into the lumen of AAA. So, there is a possibility that it will expand even after a successful repair. Therefore, more frequent monitoring and screening of patients are required.

Computed tomography angiography (CTA) is the most widely used diagnostic technique for screening patients after EVAR[9,10]. This method is highly sensitive and specific in diagnosing complications associated with stent graft and its' implantation, though there are no unanimous recommendations on screening frequency. Frequent repetition of CTA increases the likelihood of early detection of complications but also increases the overall dose of medical radiation

received during the screening. Rarely performed CTA increases the risk of unsuccessful or late complication detection and thus prevents to avoid aneurysm growth and rupture. The European and American Societies of Vascular Surgery recommend to perform CTA after 1- and 12-months following EVAR and repeat it every 5 years if there are no complications detected. If radiological evidence of endoleak is found in the AAA sac in the first month, it is recommended to perform the following CTA after 6 months[4,11]. Thus, patient follow-up after successful endovascular surgery is highly personalized.

Challenges in the follow-up after EVAR occur when there is no radiological evidence of endoleak and other stent graft-related complications on CTA, but AAA diameter is still increasing. This is so called type V endoleak (endotension). Other imaging techniques which record very slow blood flow such as magnetic resonance imaging (MRI) often do not find any signs of endoleak either. Although the etiology of type V endoleak is still unclear, this type of complication occurs in up to 2.3 – 3.1% of cases after EVAR and may be the cause of rupture as the aneurysm grows[12,13].

In routine daily practice the maximum diameter of AAA (MAAAD) is computed when evaluating follow-up CTA's after EVAR for possible aneurysm enlargement and is compared with previous results. Enlargement of ≥5 mm of maximum diameter is considered to be clinically significant and requires additional intervention[4]. However, the most common is ECG-non-synchronized CTA imaging, therefore an error up to 2 mm is possible due to aortic pulse wave during cardiac systole and diastole[14]. Since aortic aneurysm wall is remodeling after stent graft implantation, the pressure vectors of the internal aneurysm sac change, so greater blood force may be applied to the different location other than MAAAD. AAA can also expand in the longitudinal dimension. The shape of the aortic aneurysm may change, thus increasing the volume of the aneurysm and leaving the MAAAD unchanged. Special expensive software is required in order to calculate AAA volumes and the process takes longer than measuring MAAAD. As the incidence of AAA increases, so does the number

of EVAR's as well as the number of patients being followed. Thus, routinely performed measurements of aortic aneurism volumes would require additional work power and would cause an economic burden on the country's medical system. Therefore, definite recommendations are required for the inclusion criteria of the patients.

Factors which would allow to evaluate the possible risk for postoperative complications and additional interventions before the surgery are being sought. For example, an intraluminal thrombus of AAA is still a controversial factor. It was previously thought to be a protective factor against aneurysm rupture as it strengthens the enlarged wall by its volume. However, subsequent studies have revealed some conflicting data. The intraluminal AAA thrombus has been shown to be biochemically and biomechanically active. Histological and immunohistochemical studies have revealed that the thrombus contains active inflammatory cells that secrete both pro-inflammatory factors as well as protein-degrading enzymes[15,16]. The most important are matrix metalloproteinases (MMPs) which directly degrade the protein structure of the aortic wall thereby weakening the wall structure and allowing further expansion of the aorta[17]. Clinical data is still limited on the impact of newly developed postoperative intraluminal thrombus on the subsequent changes in the AAA.

Another factor – oxygen deficiency (hypoxia) in the aortic wall is one of the essential conditions which determine the occurrence and progression of AAA. Oxygenation of the aortic wall tissue occurs by diffusion from the bloodstream of the aortic lumen and through the vessels (*vasa vasorum* in Latin) in the outer aortic wall layer (adventitia)[18]. The vessel network of vasa vasorum is sparser in the infrarenal part of the aorta than suprarenal and thoracic parts. Hypoxia increases compensatory aortic wall neovascularization, reactive oxygen species' (ROS) formation and inflammatory response[19,20]. This results in the disruption of the normal histological structure of aortic wall. So far, no data is available on the changes in oxygenation of the aneurysm wall after EVAR.

1.2 Hypotheses of the study

1. Measurement of the AAA volume is useful for a certain group of patients after successful EVAR as an additional method to measuring the maximum aortic aneurysm diameter.
2. Intraluminal thrombus of the aortic aneurysm is associated with alteration in size of the aneurysm after EVAR.
3. The postoperative immune response to the implanted stent graft is associated with subsequent size changes of AAA.
4. Following a successful endovascular repair, the circulation of aortic aneurysm wall is impaired in growing aneurysms.

1.3 Aims of the study

1. To evaluate AAA changes in size after EVAR and to analyze the determinants of that.

1.4 Tasks of the study

1.1 To measure the MAAAD and AAA volume in patients by evaluating CTA performed after 3- and 24-months following EVAR.

1.2 To measure changes in MAAADs and volumes over an average of 24 months and to evaluate the relation between these differences.

2.1 To select a group of patients to whom despite MAAAD increase after EVAR being not clinically relevant, the aortic aneurysm volume measurement would be beneficial.

3.1 To measure the volume of the intraluminal AAA thrombus on CTA before and after the repair as well as volume changes.

3.2 To evaluate the relation between the changes in volume of the intraluminal AAA thrombus and the changes of AAA size following EVAR.

4.1 To evaluate the relation between leucocyte and C reactive protein (CRP) concentrations in the postoperative 12-hour period and the changes in AAA size during the postoperative follow-up.

5.1 To measure and compare aortic wall density (in Hounsfield Units) at the level of the diaphragm and MAAAD in patients following

the EVAR and at the level of the diaphragm and infrarenal aorta in the control group.

1.5 Statements to be defended

1. For eligible patients considering a possible aneurysm enlargement after endovascular repair repeated follow-up CTA imaging should be performed by measuring the volume of the aneurysm.
2. The intraluminal AAA thrombus is a biochemically active material thus contributing to the further enlargement of the aneurysm after endovascular repair.
3. Aa active immune response to an implanted stent graft affects the subsequent enlargement of the aneurysm following endovascular repair.
4. The reduced accumulation of contrast material in the AAA wall on CTA imaging is associated with further enlargement of the aneurysm after EVAR.

1.6 The scientific novelty of the study

Currently, MAAAD is measured in daily clinical practice to screen patient following EVAR. Studies have shown conflicting results regarding the benefits of measuring aortic aneurysm volumes. However, isolated clinical cases where the measurement of aortic aneurysm volume in the absence of clinically significant MAAAD could be valuable as an additional radiological indicator have not yet been investigated.

The importance of the intraluminal AAA thrombus in progression of the aneurysm has been demonstrated but its influence on postoperative aneurysm behavior is still unclear[17].

Aortic wall ischemia is important for the occurrence and progression of AAA. However, there are still no clinical studies evaluating the possible postoperative aortic aneurysm wall ischemia and its importance in progression of the aneurysm following a successful endovascular repair.

Although the first EVAR was performed in 2006 in Lithuania, the outcome of this treatment modality has not been evaluated yet.

2 METHODOLOGY

This is a prospective and retrospective cohort observational clinical trial conducted in the department of vascular and endovascular surgery at Vilnius University Hospital Santaros Klinikos (VUH SK). Approval of the Vilnius Regional Bioethics Committee (Nr. 158200-16-877-386) was obtained. The inclusion criteria involved patients who were at least 50 years old and underwent EVAR between 11th of January 2007 and 30th of September 2017 and had been followed for at least 24 months by performing repeated CTA after the treatment. All participants signed an informed consent form, except patients whose data was collected retrospectively and the consent was not available (e.g. deceased patients/no available contact information). A control patient group was also included in the study. It was a randomized group of patients who were at least 50 years old. All of the patients signed an informed consent form and went through CTA imaging of abdominal aorta between the 1st of January, 2015 and 31st of December, 2017 at VUH SK, but no signs of aortic pathology (significant atherosclerosis, occlusion, thrombosis, aneurysm, infection) were observed. The study respected ethical principles in medical research involving human subjects provided in the Declaration of Helsinki[21].

Out of 107 patients a total of 39 (36.5%) were involved in the treatment group. 44 (41.1%) patients were excluded from the study because the follow-up after EVAR was completely unsuccessful due to unavailable contacting information. Other exclusion criteria: in 14 (13.1%) patients endoleak (other than type V) was found on CTA imaging, 10 (9.3%) patients also had other stent graft-related complications (total or partial occlusion or thrombosis). Over a three-year period, 1847 patients underwent abdominal CTA in VUH SK with no evidence of aortic pathology. A total of 39 patients were randomly involved in the control group.

Patients who were enrolled in the study had their data anonymized and recorded in a specially designed database. Epidemiologic data (age, gender, history of smoking, primary arterial hypertension (PAH), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM)), CTA data (maximum abdominal aortic aneurysm diameter,

volume of the abdominal aneurysm, volumes of the preoperative and postoperative intraluminal thrombus of the aneurysm, aortic wall density at the level of the diaphragm and infrarenal aorta, aortic wall and lumen density) and laboratory test data (white blood cell count and CRP concentration within the first 12 hours after the surgery) were collected. Other risk factors of atherosclerosis (cholesterol level, obesity, physical activity) as a factor in the development of AAA could not be collected and evaluated due to lack of data.

The protocol for this study for inclusion criteria and patient monitoring was developed by the academic supervisor Prof. Germanas Marinskis and doctoral student Arminas Skrebūnas. Patient selection for this study as well as data collection and analysis were executed by the doctoral student.

2.1 Evaluation and parameter measurement of computed tomography angiography images

All CTA images (MAAAD, volume of the abdominal aneurysm, volumes of the preoperative and postoperative intraluminal thrombus of the aneurysm, aortic wall density at the level of the diaphragm and infrarenal aorta, aortic wall and lumen density) were evaluated by 2 independent radiologists. Their measurements were compared using Bland-Altman analysis and no statistically significant difference was found: median (IQR) difference in MAAAD measurement was 0.3 mm (0.2–0.42), median (IQR) volume measurement difference was 2.1 ml (1.4–2.7), median (IQR) density measurement difference was 9.7 HU (8.9–10.7), $p > 0.05$.

2.2 Measurements of the maximum diameter, volume and volume of the intraluminal thrombus of the abdominal aortic aneurysm

MAAAD was measured in the first and last postoperative CTA images. After manual correction of the apparent central aneurysm line, the maximum perpendicular distance in mm between the outer parts of the aneurysm wall was measured (Fig. 1). The MAAAD was rounded to the nearest tenth of a millimeter.

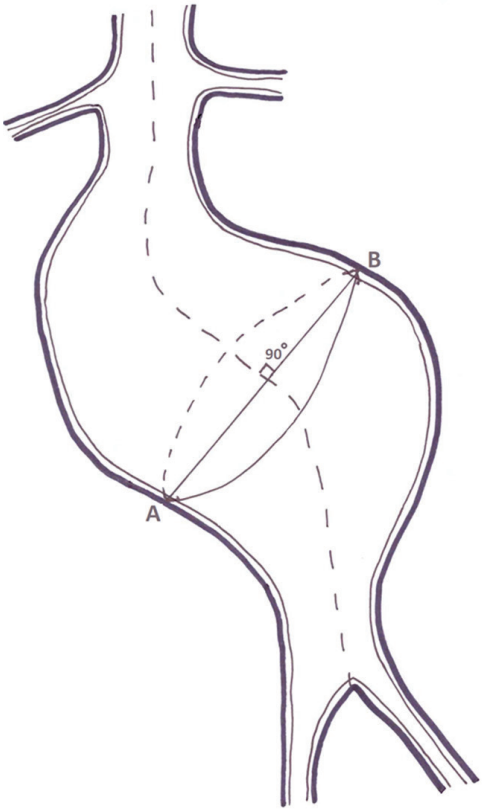

Figure 1. Three-dimensional reconstruction of CTA: AB – diameter of the aneurysm measured perpendicularly to the apparent central axis (C) of the aorta.

Volume measurements (in ml) of the AAA and intraluminal thrombus were performed by software using automatic 3D segmentation and manual correction of external and internal lumen outlines of the aneurysm as well as intraluminal thrombus, aorta and stent graft. Volume of the aneurysm was measured in the aortic and iliac artery segment covered by stent graft. The volumes were rounded to the nearest tenth of a milliliter. After making the measurements, relative changes (%) in volumes were calculated, MAAAD and relative volume changes were compared and their relation during the follow-up period was evaluated. 5 mm and more increase in aneurysm diameter and 5% and more increase in aneurysm volume were considered clinically significant[4,22]. A group of patients with clinically significant increase in AAA volume, albeit the increase in MAAAD was not relevant, was selected.

Depending on changes in AAA volume after the surgery, the treatment group was divided into 2 subgroups: growing aneurysm subgroup and shrinking or stable aneurysm subgroup.

Volumes of the intraluminal aneurysm thrombus were measured in the preoperative and the first postoperative CTA images. After measuring the absolute volumes of the intraluminal thrombus and AAA the relative proportions (%) of the intraluminal thrombus volume inside the aneurysm were calculated. Only following derived quantities were used in the further analysis. The relation between relative volumes of preoperative and postoperative intraluminal thrombus and aneurysm behavior following EVAR was evaluated.

2.3 Density measurements of the abdominal aortic aneurysm wall and lumen

Densities were measured in the last postoperative CTA images of the treatment group and the control group. Using 3D Slicer 4.9 software, manual aortic segmentation was performed at two levels: at the diaphragm and at the MAAAD in the treatment group or at the infrarenal aorta in the control group (Figure 2). Density values of the aortic and aortic aneurysm wall as well as the lumen of the aorta and stent graft were measured in HU. Atherosclerotic plaques or artefacts were not included in the measurements.

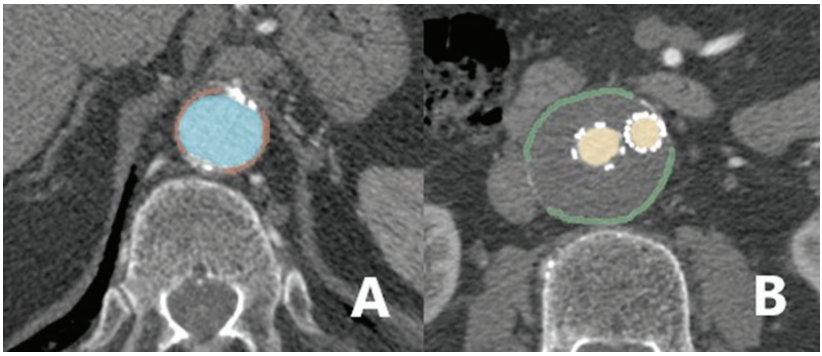

Figure 2. Segmentation of the abdominal aorta at the level of the diaphragm (A) and maximum aortic aneurism diameter (B) in the treatment group: aortic wall segment (red), aneurysm wall segment (green), aortic lumen (blue) and implanted stent lumen (yellow).

Densities of the aortic segments are highly sensitive to the patient's cardiovascular status, the amount of intravenous contrast used in the CTA and the scan time after injection[23]. Therefore, the absolute values of the measurements vary greatly. In order to unify them, the radio of aortic or aortic aneurysm wall density to aortic or stent graft lumen density – relative aortic/aneurysm wall density (RAWD) – was calculated for further analysis.

The following comparisons were performed:

- Relative aortic wall densities at the level of the diaphragm in the treatment and control groups (Fig. 3A, B);
- Relative aortic wall densities at the level of the diaphragm and infrarenal aorta in the control group (Fig. 3B, D);
- Relative aortic wall densities at the level of the diaphragm and MAAAD in the treatment group (Fig. 3A, C);
- Relative aortic wall densities at the level of MAAAD in the treatemtn group and relative aortic wall densities in the infrarenal aorta in the control group (Fig. 3C, D).

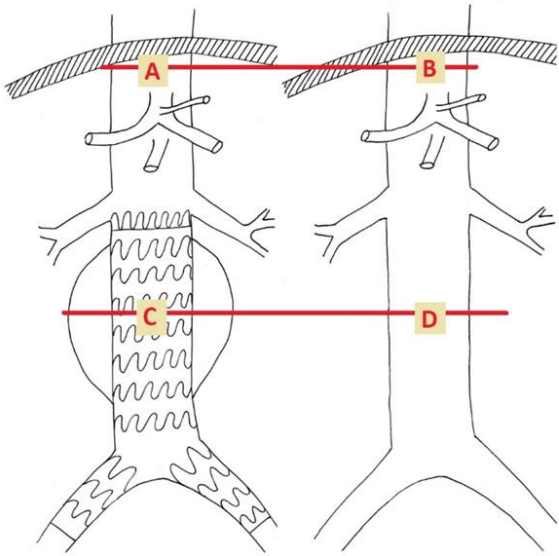

Figure 3. Relative aortic wall densities (RAWD): at the level of the diaphragm (A) and MAAAD (C) in the treatment group, and at the level of the diaphragm (B) and infrarenal aorta (D) in the control group.

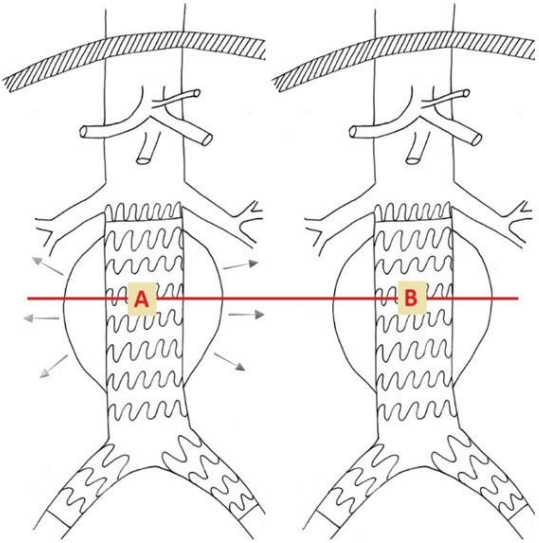

Figure 4. Aortic wall densities at the level of MAAAD in the growing aneurysm (A) and stable or shrinking aneurysm (B) subgroups.

Relation between relative aortic wall density at the level of MAAAD and aneurysm behavior after EVAR was evaluated (Fig. 4A, B). Relative differences in RAWD between the groups and subgroups at different aortic levels were calculated.

2.4 Statistical data analysis

The normal distribution of variables in the sample was examined using the Shapiro-Wilk test. Quantitative variables which do not satisfy the condition of normal distribution are presented as the median of the variables with interquartile range (IQR; Q1 – Q3) and the qualitative variables as the absolute score (n) and the percentage of the analyzed sample (%). The non-parametric Mann-Whitney U test was used to compare the means of two independent groups and the Wilcoxon test was used for dependent samples. Chi-square test of independence or Fisher's exact test were used to compare the qualitative variables. A linear regression model was used to determine the relation between MAAAD and aneurysm volume changes after endovascular repair.

p value of <0,05 was considered statistically significant. Statistical analysis of the study was performed using Microsoft Office suite program Excel 2016 and SPSS 26.0 (SPSS, Chicago, IL, USA).

3 RESULTS

3.1 Changes of MAAAD and AAA volume after EVAR

3.1.1 Baseline characteristics of the treatment and control groups

A total of 78 patients were enrolled in the research: 39 (50%) in the treatment group and 39 (50%) in the control group. There were 35 (89.7%) male and 4 (10.3%) female patients in the treatment group and 31 (79.5%) male and 8 (20.5%) female patients in the control group. There was no statistically significant difference between the distribution of genders in the groups ($p = 0.347$). Medians (IQR) of age in groups were 71 years (63–76) and 73 years (64–81.5), $p = 0.215$, respectively. Patients' smoking habits, incidence of primary arterial hypertension, COPD and diabetes mellitus are presented in Table 2.

Table 2. Smoking habits, incidence of primary arterial hypertension, COPD and diabetes mellitus in the treatment and control patient groups

	Treatment Group n = 39	**Control Group n = 39**	***p***
Smoking, n (%)	9 (23.1)	10 (25.6)	0.968
PAH, n (%)	34 (87.2)	31 (79.5)	0.309
COPD, n (%)	6 (15.4)	5 (12.8)	0.368
DM, n (%)	4 (10.3)	8 (20.5)	0.334

PAH - primary arterial hypertension; COPD - chronic obstructive pulmonary disease; DM - diabetes mellitus; *p* - value in statistical significance.

There was no statistically significant difference between the groups considering all patient characteristics.

3.1.2 Results of the MAAAD and volume measurements after endovascular repair

The change in MAAAD was calculated by comparing the first and last CTA images performed during the postoperative follow-up period. The median (IQR) decrease in MAAAD was 3.3 mm (-1.35–8.7).

28 (71.8%) patients had a decrease in AAA after EVAR and for 11 (28.2%) patients the AAA has enlarged. The median (IQR) decrease in MAAAD was 7.35 mm (3.2–11.85) and the median (IQR) increase was 2.5 mm (1.6–3.45).

By comparing the first and last CTA images the change in relative AAA volume after EVAR was also calculated. The median (IQR) relative volume decrease was 16.1% (-0.7–27.1). In 27 (69.2%) patients the AAA has shrunk after endovascular repair and for 12 (30.8%) patients it has increased. The median (IQR) relative reduction in aneurysm volume was 22.3% (16.0–30.2) and the median (IQR) relative increase in volume was 7.5% (1.0–23.3).

Using a linear regression model, a strong linear relation between MAAAD and aneurysm volume measurements following endovascular repair was found (r = 0.7725). This association is depicted in Figure 5.

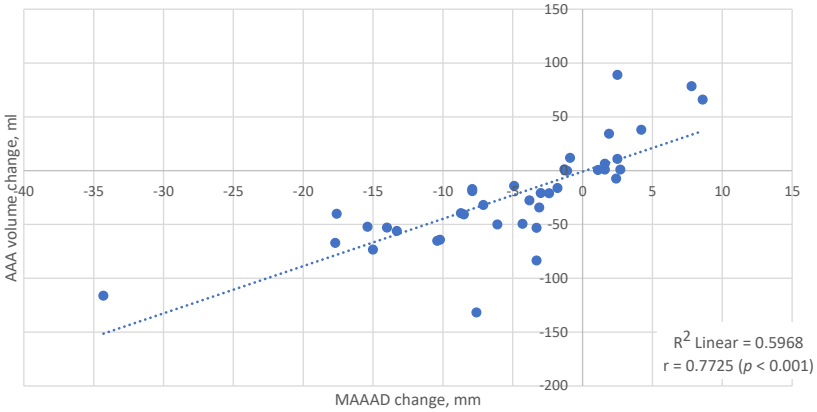

Figure 5. Association between MAAAD and aneurysm volume measurements following endovascular repair.

3.2 Selection of the patients with clinically relevant increase of AAA after endovascular repair

Although there was a statistically significant association between increased aneurysm volume and increased MAAAD and vice versa, yet in 4 (36.4%) out of 11 patients the diameter increase was clinically irrelevant (less than 5 mm), with a median (IQR) increase in MAAAD

of 2.5 mm (2.5–2.5), excluding the potential ECG-non-synchronized CTA errors. For the same 4 patients the median (IQR) relative aneurysm volume increase was 7.6% (1.4–28.6). All the four were male patients with PAH and median (IQR) age of 64.5 years (62–75.5).

3.3 Relation between AAA thrombus and change of aneurysm size after EVAR

3.3.1 Baseline characteristics in the subgroups of patients with growing, stable or shrinking aneurysm

The treatment group was subdivided into subgroups based on changes in aneurysm volume following EVAR. A subgroup of growing aneurysms included 12 (30.8%) patients and 27 (69.2%) in stable or shrinking aneurysm subgroup.

The growing aneurysm subgroup included 12 (100%) male and 0 (0%) female patients, there were 23 (85.2%) male and 4 (14.8%) female patients in the stable or shrinking aneurysm subgroup. Subgroups were similar in terms of gender distribution ($p = 0.292$). The medians (IQR) of age in the subgroups were 72 years (63– 80) and 70 years (62–74) respectively, $p = 0.552$. Patients' smoking habits, incidence of primary arterial hypertension, COPD and diabetes mellitus are presented in Table 3.

Table 3. Smoking habits, incidence of primary arterial hypertension, COPD and diabetes mellitus in the subgroups

	Growing AAA sac subgroup n = 12	**Stable or shrinking AAA sac subgroup n = 27**	***p***
Smoking, n (%)	2 (16.7)	7 (25.9)	0.681
PAH, n (%)	11 (91.7)	23 (85.2)	0.540
COPD, n (%)	1 (8.3)	5 (18.5)	0.646
DM, n (%)	1 (8.3)	3 (11.1)	0.439

PAH - primary arterial hypertension; COPD - chronic obstructive pulmonary disease; DM - diabetes mellitus; *p* - value in statistical significance.

There was no statistically significant difference between the growing AAA and stable or shrinking AAA subgroups when considering all patient characteristics.

3.3.2 Results of preoperative intraluminal thrombus measurements

All the 39 patients had CTA performed before the surgery. The median (IQR) volume of preoperative intraluminal thrombus was 97.5 ml (54–173). The median (IQR) relative volume of thrombus was 59.2% (48.4–66.0). The relation between AAA and intraluminal thrombus volumes before the surgery is presented in Figure 6.

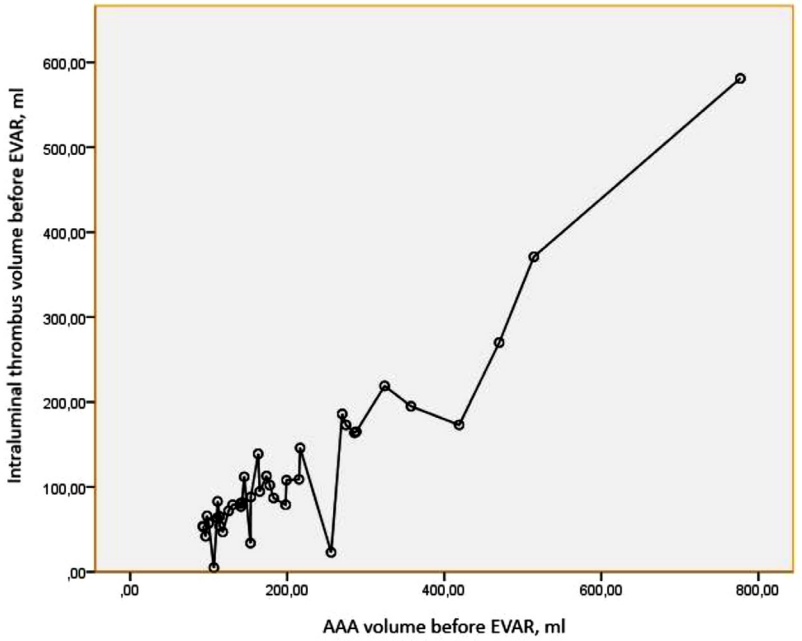

Figure 6. The relation between AAA and intraluminal thrombus volumes before the surgery

In the subgroups of growing and stable or shrinking aneurysm the median (IQR) volumes of preoperative AAA thrombus were 65.6% (48.0–69.8) and 57.6% (48.9–63.1%) respectively. No statistically

significant difference was found comparing relative volumes of preoperative intraluminal thrombus in the subgroups ($p = 0.231$).

3.3.3 Results of postoperative AAA thrombus measurements

The volume of postoperative AAA thrombus was evaluated in 39 patients in the first and last postoperative CTA images. In the first postoperative CTA image the median (IQR) relative volume of thrombus was 80.5% (73.8−84.2). In the last postoperative CTA image, the median (IQR) relative volume of thrombus was 70.4% (65.8−81). The median (IQR) reduction in relative volume of thrombus in the postoperative follow-up was 7.4% (0.5−10.6).

In the subgroup of growing AAA, the median (IQR) reduction in relative volume of thrombus was 0.2% (-2.6−0.8). In the subgroup of stable or shrinking AAA the median (IQR) decrease in relative volume of thrombus was 8.2% (7.4−13.4). In 4 (33.3%) of the 12 patients in the subgroup of growing AAA an increase in relative volume of thrombus was observed with a median (IQR) increase of 2.9% (1.5−3.3). In the postoperative period, the relative volume of thrombus decreased more significantly in the subgroup of stable or shrinking AAA than in the subgroup of growing aneurysm $p = 0.000037$ (Fig. 7).

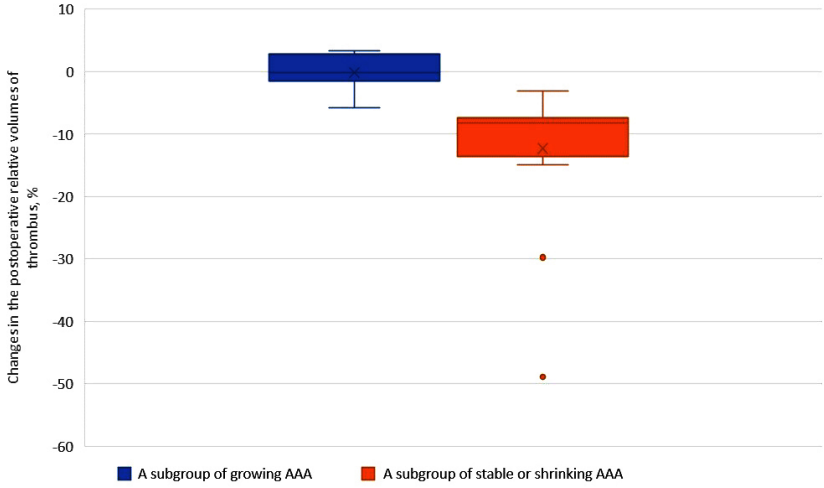

Figure 7. Changes in relative volumes of the thrombus in the subgroups during the postoperative follow-up period

3.4 Results of the postoperative measurements of inflammation markers

3.4.1 Results of the measurements of inflammation markers in the treatment patient group

The median (IQR) WBC count and CRP concentration in the treatment group were calculated. They were 8.9 $\times 10^9$/l (8.3−10.3) and 37.1 mg/l (22.5−70.3), respectively. Three patients (7.7%) had both leukocytosis and elevated CRP level.

3.4.2 Comparison of measurements of inflammation markers between the subgroups

In both subgroups, the systemic inflammatory response indicators were compared. The median (IQR) WBC count was 10.8 $\times 10^9$/l (8.6−12.5) and 8.5 $\times 10^9$/l (7.8−9.2), respectively, $p = 0.081$. The median (IQR) CRP was 63.5 mg/l (49.6−74.5) and 25 mg/l (18.9−51.5), respectively, $p = 0.157$. Although the median WBC count and CRP level were higher in the growing AAA subgroup, there was no statistically significant difference between the subgroups.

3.5 Results of aortic/aneurysm wall and lumen density measurements

3.5.1 Comparison of the measurements of relative aortic/aneurysm wall density between the groups

The most recent 39 CTA images conducted during follow-up in the treatment group and 39 CTA images in the control group were evaluated. In the treatment group the median (IQR) RAWD was lower at the level of MAAAD than at the level of diaphragm – 0.10 (0.07−0.12) and 0.15 (0.11−0.18), respectively, $p < 0.0001$. In the control group the median (IQR) RAWD at the level of the diaphragm was 0.16 (0.11−0.18), and 0.17 (0.12−0.23) in the infrarenal aorta. There was no statistically significant difference in the median RAWD between the aortic segments in that group ($p = 0.3030$).

The median (IQR) RAWDs measured at the level of the diaphragm in both groups were 0.15 (0.11−0.18) and 0.16 (0.11−0.18), respectively, and no statistically significant difference was found (p = 0.5378). In the treatment group, the median (IQR) RAWD at the level of MAAAD was 0.10 (0.07−0.12). In the control group, the median (IQR) RAWD measured at the level of infrarenal aorta was 0.17 (0.12−0.23). There was a statistically significant difference (p < 0.0001) comparing above-mentioned measurements. The median (IQR) RAWD at the level of MAAAD was 26.2% (-4.6−56.4) lower than at the level of diaphragm and the median (IQR) RAWD at the level of infrarenal aorta was 24.5% (-15.9−51.8) higher than at the level of the diaphragm in the control group. When comparing both medians, a statistically significant difference was obtained (p = 0.0003).

3.5.2 Comparison of the measurements of relative aortic/aneurysm wall density between the subgroups

In both subgroups the median (IQR) RAWDs at the level of the diaphragm were 0.16 (0.11−0.20) and 0.14 (0.10−0.17), respectively, and did not differ significantly (p = 0.1592). The median (IQR) RAWDs and MAAADs in both subgroups were 0.09 (0.06−0.10) and 0.11 (0.09−0.13), respectively. When comparing median RAWDs in both subgroups a statistically significant difference was obtained (p = 0.0096). In the subgroups the median (IQR) RAWD was 57.2% (12.4−66.6) and 16.4% (-11.1−36.9) lower at the level of MAAAD than at the level of the diaphragm, respectively (p = 0.0678).

A summary of comparison between groups and subgroups measurements of relative aortic/aneurysm wall density is presented in Table 4.

Table 4. Comparison of aortic and aortic aneurysm wall density measurements between groups and subgroups

RAWD	Treatment Group n = 39		Control Group n = 39	*p*
	A subgroup of growing AAA n = 12	A subgroup of stable or shrinking AAA n = 27		
at the level of the diaphragm	0.15 (IQR: 0.11−0.18)		0.16 (IQR: 0.11−0.18)	0.5378
	0.16 (IQR: 0.11−0.20)	0.14 (IQR: 0.10−0.17)		0.1592
at the level of MAAAD or infrarenal aorta	0.10 (IQR: 0.07−0.12)		0.17 (IQR: 0.12−0.23)	<0.0001
	0.09 (IQR: 0.06−0.10)	0.11 (IQR: 0.09−0.13)		0.0096
lower at the level of MAAAD, %	26.2 (IQR: -4.55−56.4)		-24.45 (IQR: -51.81−15.9)	0.0003
	57.18 (IQR: 12.43−66.57)	16.38 (IQR: -11.12−36.87)		0.0678

RAWD, relative aortic/aneurysm wall density; MAAAD, maximum aortic aneurysm diameter; IQR, interquartile range; *p*, value in statistical significance.

4 DISCUSSION

4.1 Changes of MAAAD and AAA volume after endovascular repair

Medical technology advances in software which allows to measure AAA volumes quickly and reliably without the help of a physician[24]. Nonetheless, many studies indicate that more complex aneurysm volume measurements in repetitive CTA's are not required for routine follow-up of patients following EVAR, as faster MAAAD measurements are sufficiently accurate to assess postoperative changes in AAA[25–28]. In addition, a strong association between MAAAD and aneurysm volume measurements is also found in many studies[29]. We also found a strong linear relation between MAAAD and aneurysm volume measurements following EVAR. A greater than 99.99% probability that an increased or decreased AAA diameter would change the aneurysm volume accordingly was obtained.

4.2 The benefit of measuring the volume of the abdominal aortic aneurysm

Balm et al. were the first to evaluate the benefits of AAA volume measurement in patients following successful EVAR[30]. Implantation of a stent graft results in remodeling of the aortic aneurysm. Changing aortic aneurysm configuration may affect AAA volume without alteration of MAAAD. According to a study by Kauffmann et al. the measurement of aneurysm volume is a more sensitive method than MAAAD alone to determine the growth of AAA[24]. This is also confirmed by other studies which have examined the behavior of aneurysm following EVAR[31,32]. However, despite these results there is still a lack of knowledge on the clinical significance of aneurysm volume change. Following EVAR, a 10% or greater decrease in aneurysm volume within the first 6 months is associated with a lower incidence of late complications[33,34]. Data from another study indicates that a postoperative change in AAA volume of 0.3% and less is an independent factor in the occurrence of late endoleaks[35].

A clinically significant change of AAA volume after EVAR is still debated. Increase in aneurysm volume greater than or equal to 5% is considered relevant[22]. The threshold reported by Bley et al. is 2% and greater increase in aneurysm volume[36]. Meanwhile, a study by Quan et al. showed that a clinically significant (greater than or equal to 5 mm) increase in MAAAD is equated to a 12% or greater increase in aneurysm volume[37].

To our knowledge, there are still no studies evaluating whether aneurysm volume measurement additionally to diameter measurement following EVAR is more valuable than diameter measurement alone. According to our results, a significant increase in aneurysm volume was observed in those patients who did not have a clinically significant increase in MAAAD after the repair. Because of a very small sample size we are unable to make statistically significant conclusions. However, the following trends can be drawn. Although there was no clinically significant increase in MAAAD in our study, the AAA volume increased significantly in men with PAH and median age of 64.5 years. These are significantly younger patients compared to the median age of the entire sample. Although smoking is the main risk factor for aneurysm progression, but we did not find this relation because of a very small sample[38–41]. Association between COPD as another risk factor for aneurysm progression and aneurysm enlargement also was not confirmed[42,43]. DM is considered to prevent further aneurysm enlargement, but we have not established such relation[38,39].

4.3 The importance of the intraluminal thrombus in further disease progression after endovascular repair

The theory about intraluminal thrombus as a protective factor which prevailed for several decades has been denied[44]. On a contrary, the intraluminal thrombus has been shown to be an important factor for the progression of AAA. The mechanism which has not yet been fully elucidated is associated with increased levels of protein-degrading enzymes in the aortic aneurysm wall[19,45–47]. This results in a reduction in rigidity of the wall, enlargement of the aneurysm and an increased risk of rupture[48].

The influence of preoperative intraluminal AAA thrombus on postoperative aneurysm behavior is not fully understood. The higher volume of preoperative thrombus is associated with a lower risk of type II endoleaks following EVAR, as the thrombus could be dislocated and close aortic branches while implanting stent graft[49–51]. On the other hand, if the intraluminal thrombus lies on the landing zones of stent graft (AAA neck, iliac arteries) it could result in a greater number of detectable endoleaks in the late postoperative period[52]. It is believed that over time the structure of the intraluminal thrombus is changing and complete adhesion of the implanted stent graft to the abdominal aorta or iliac artery is lost.

In our study we found that the volume of preoperative thrombus was higher in the subgroup of patients with growing aneurysm than in the subgroup of stable or shrinking aneurysms. Our findings as well as those of Kim et al. contradict the results of other authors who observed an association between a larger preoperative AAA thrombus and shrinking aneurysm after EVAR[53]. Only Müller-Wille et al. also estimated the relative volume of preoperative intraluminal thrombus[54]. Sadek and Yeung measured the relative area of the intraluminal thrombus in AAA cross section[51,52], therefore comparing our study results with the latter is debatable.

While following patients after EVAR and without any signs of endoleak (except type V), we found out that aneurysm thrombus tends to decrease. However, in the subgroup of growing aneurysms, it decreased very slightly compared to the subgroup of stable or shrinking aneurysms or even increased by one third. When comparing the changes in postoperative aneurysm thrombus volume between the subgroups, there was a statistically significant difference suggesting that stable or growing thrombus volume is associated with the subsequent enlargement of the AAA. To our knowledge, the influence of postoperative aneurysm thrombus volume on aneurysm behavior has not yet been investigated in the literature. The formation of the thrombus inside the implanted stent is described and analyzed in most of the studies[55,56].

As it was previously mentioned, the aneurysm thrombus is a biochemically active substance. The most active part of the thrombus is the one which is in contact with the blood flow. It is believed that all major biochemical processes occur within the first centimeter of the thrombus towards the aneurysm wall[15]. Neutrophils that migrate from the blood to the thrombus release not only interleukins that support the cellular immune response, but also enzymes (MMP's, tissue-type plasminogen activator (t – PA), urokinase, plasmin and neutrophil elastase) that break down proteins. Gradually the intraluminal thrombus rearranges. Mesenchymal cells which support the subsequent cellular and humoral immune response grow into the thrombus and collagen fibers are deposited[57,58]. The part of the thrombus which is directly contacting with AAA wall is a compressed gelatinous mass filled with disrupted fibrin fibers[59,60]. Although there are no active immune response cells in the above-mentioned part of the thrombus, proinflammatory factors and enzymes are secreted into this part. The latter contribute to the degradation of elastin fibers in the aneurysm wall and the inflammatory cellular response[61,62]. The role of intraluminal thrombus in aneurysm progression is determined in histological and immunohistochemical studies. According to our study, we can assume that the decrease in aneurysm thrombus volume after EVAR is related to decreased biochemical activity in it. This leads to a reduction of the aneurysm. However, aneurysm continues to grow in some patients after endovascular repair. Consequently, the thrombus may remain biochemically active while its volume is almost unchanged or even increased. Further studies are required to confirm these claims.

4.4 Immune response to an implanted stent graft

Following stent graft implantation, the intraluminal thrombus loses direct contact with the blood flow and a fresh thrombus is formed[63]. Not only the thrombus itself but also manipulations near the aneurysm thrombus during implantation has an impact on post implantation syndrome (PIS)[64]. It is described as body's inflammatory response to an

implanted stent which is found in up to 60% of the cases[65]. The syndrome is characterized by fever greater than 38º C and increased WBC count (>10 ×10^9/l) as well as elevated CRP levels without any clear evidence of infection[66–68]. The newly formed thrombus is biochemically active and secretes factors involved in the systemic inflammatory response. On the other hand, the outer layer of the intraluminal thrombus has the highest concentration of inflammatory factors therefore manipulation in the aneurysm sac during the operation is thought to release them into the bloodstream[69,70]. This is likely to initiate the PIS. In our study, body temperature measurements were not included in the patient monitoring protocol. Complete data of immune response factors was not available for the subjects. Leukocytosis and elevated CRP levels were identified in only 7.7% of all cases. When analyzing the overall inflammatory response rates in the subgroups, we found that subgroup of growing AAA had both leukocytosis and a significant increase in CRP levels compared with the subgroup of stable or shrinking AAA. However, no statistical significance was obtained because of a small sample size. We were not able to perform post hoc analysis to confirm or rule out significant differences between the later measurements in the general population because we used median rather than average values in our analysis. The relation between leukocytosis and elevated CRP levels and progression of AAA is widely debated, but no consensus on this topic has yet been released[71,72]. It is also unclear whether leukocytosis and elevated levels of CRP (a non-specific marker of PIS) in the first 12 hours after surgery effect the behavior of the aneurysm in the late postoperative period.

4.5 Relation between AAA wall density and aneurysm size change after EVAR

Aortic wall degeneration, especially in media, is the main key of AAA formation, development and progression after endovascular repair. We analyzed and measured the density (in HU) of aortic and aneurysm wall on CTA images. Tissue density depends on the amount of contrast material diffusing from the arterial bloodstream[73]. Higher than normal aortic wall density may occur due to increased vascularization,

atherosclerotic plaques, hematoma or ongoing inflammatory process as well as lower density may occur due to decreased vascularization after developing ischemia[74]. To our knowledge, there are no published clinical studies examining the relation between AAA wall density and aneurysm behavior following EVAR.

We compared the density of the aorta at the level of the diaphragm in patients without established aortic pathology (the control group) and the density of aorta at the same level in patients following EVAR. Aorta was not dilated at the level of diaphragm in both groups. We did not find a statistically significant difference between the measurements in the groups. Therefore, we can conclude that aortic wall vascularization and inflammatory response in aneurysmatically unchanged AAA are not disturbed. Comparing aortic wall density at the level of the diaphragm and at the level of MAAAD in the treatment group the latter was statistically significantly lower. It was also lower comparing it with aortic wall density of infrarenal aorta in the control group. In contrast to the treatment group, the wall density of the infrarenal aorta was higher than at the level of the diaphragm in the control group. There are no evidence-based studies which indicate that decreased aortic wall density on CTA images is due to wall ischemia. However, based on Varga-Szemes et al. assessment of myocardial density on CTA images the assumption of ischemia could be made[75]. Our findings contradict with those of other researchers who suggest that oxygen deficiency induces neoangiogenesis and formation of new vessels causing an increase of aneurysm wall density[76–78]. Several experimental studies have also shown the effectiveness of antiangiogenic therapy in inhibiting the development of AAA[79–81]. On the other hand, newly formed vessels are immature and may not yet participate in active circulation or accumulation of contrast material during CTA.

We evaluated the density of the aorta and aortic aneurysm wall by dividing our patients into two subgroups of growing AAA and stable or shrinking AAA. No statistically significant difference was found comparing aortic wall density at the level of the diaphragm. However, the wall density of the aneurysm at the level of MAAAD

was statistically significantly lower in the subgroup of growing aneurysm than in the subgroup of stable or shrinking aneurysm. This suggests that lower aneurysm wall density may affect AAA progression after EVAR. However, the factors of decreased wall density after endovascular repair remain unclear. As it was mentioned before, blood circulation in the aortic wall occurs directly from the aortic lumen and through vasa vasorum. A decrease in density is associated with tissue ischemia[18,74]. A histological examination in swine conducted by Scheumann et al. discovered the thinning and necrosis of aortic tunica media after 5 days following stent implantation into the uninjured descending thoracic aorta[82]. We could state that stent graft disrupts the circulation of the aneurysm wall and causes ischemia, but the aneurysm does not change or even shrinks after successful EVAR in most cases. Therefore, further studies are required to assess the impact of the implanted stent and its eccentric force on the circulation of the aortic wall. In previous histologic examinations after open AAA repair some samples contained atherosclerotic lesions in vasa vasorum[18,83]. These lesions may become significant and lead to aortic aneurysm wall ischemia because of the additional effect of eccentric force after stent graft implantation.

5 CONCLUSIONS

1. Following EVAR, as MAAAD increases, so does the volume of the aneurysm and vice versa.
2. In the absence of MAAAD decrease after EVAR, additional measurement of the aneurysm volume may be valuable in detecting AAA growth, especially in men with PAH and with a median age of 64.5.
3. No effect of intraluminal AAA thrombus volume on aneurysm size after EVAR was observed. However, stable or growing volume of the intraluminal thrombus after the repair is associated with further increase in AAA.
4. An increased aneurysm growth was observed following endovascular repair in patients with leukocytosis and CRP levels greater than 50 mg/l.
5. A lower density of aortic aneurysm wall in AAA patients is associated with aneurysm growth after successful EVAR.

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7 LIST OF PUBLICATIONS

- **Skrebūnas, A.**; Lengvenis, G.; Builytė, I.U.; Žulpaitė, R.; Bliūdžius, R.; Baltrūnas, T.; Misonis, N.; Marinskis, G. The Aortic Sac Enlargement after EVAR: Volume-related Changes and the Impact of Intraluminal Thrombus. *Pol J Radiol.* 2019 Aug 30;84: e335-e339. https://doi: 10.5114/pjr.2019.88064
- **Skrebūnas, A.**; Lengvenis, G.; Builytė, I.U.; Žulpaitė, R.; Bliūdžius, R.; Purlys, P.; Baltrūnas, T.; Misonis, N.; Matačiūnas, M.; Marinskis, G.; Vajauskas, D. Is Abdominal Aortic Aneurysm Behavior after Endovascular Repair Associated with Aneurysm Wall Density on Computed Tomography Angiography? *Medicina* 2019, 55, 406. https://doi.org/10.3390/medicina55080406

8 BRIEF INFORMATION ABOUT THE DOCTORAL STUDENT

Education and training in the last five years:

- Medical doctor, Master in Health Sciences (7/7/2010; Vilnius University, Faculty of Medicine);
- Professional qualification in Vascular Surgery (23/6/2015; Vilnius University, Faculty of Medicine);
- Internship at Uppsala University Hospital, Sweden (24-30/1/2016)

Work experience:

- Assistant physician (3/2012 – 12/2014, Vilnius City Clinical Hospital);
- Assistant physician (10/2014 – 6/2015, Vilnius University Hospital Santaros Klinikos);
- Vascular surgeon (7/2015 – present, Vilnius University Hospital Santaros Klinikos);
- Vascular surgeon (1/2016 – present, Vilnius City Clinical Hospital).

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