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# Abdominal Aortic Aneurysm in Different Races Epidemiologic Features and Morphologic-Clinical Implications Evaluated by CT Aortography

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Additional information is available at the end of the chapter

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## 1. Introduction

By definition AAA is dilatation in diameter of the main arterial vessel in abdomen-abdominal aorta for over 50% compared to expected normal diameter (1). This dilatation is caused by gradual decrease in elasticity and consistence of aortic wall, usually including weakness in middle layer of aortic wall (tunica media), which leads to extension of extern layer (tunica adventitia) and/or inner layer (tunica intima) (2,3). Blood that is pumped through aorta under pressure, gradually stretches this weakened wall and most often creates aneurysmatic dilatation.

The disease is most often found in elderly population (4). In 5% of population older than 65, presence of AAA is confirmed (4,5). It has been noticed that this disease is about 6 times more frequent in males than in female population (6).

Over time, most of AAA (around 80%) increases in diameter (2,6). It is not possible to foresee which aneurysm will increase and which one will remain stable. In most cases, the growth of aneurysm is slow. Aneurysms measuring 5 or more cm in diameter increase for 4-8mm annually (7). Aneurysms with greatest diameter of 4-5 cm grow 3-7mm annually, while those smaller than 4 cm in diameter grow 2-5 mm on average (7,8). This long-term disease presents with nonspecific symptoms and is often unpredictable. The most frequent complication and leading cause of mortality (over 80%) in patients with AAA is rupture.

In many epidemiologic studies it has been noticed that persons with positive family anamnesis for this disease, have significantly higher risk of developing the aneurysm and its rupture. Furthermore, other risk factors for aneurysm have been identified, such as obesity, hypertension, smoking and elevated blood cholesterol level (9-14). The role of diabetes

mellitus, which is a well known risk factor in development of occlusive disease of blood vessels, in terms of aneurysm development remains controversial (15-20).

There are two current therapeutic approaches. The first one is surgery and the other is endovascular (Endovascular Aortic Repair – EVAR). In about half of the patients with intact aneurysm, as well as in those with ruptured one, endovascular approach can be applied. Advantages of endovascular treatment are avoiding general anesthesia, laparotomy and clamping the aorta. The procedure lasts shorter and recovery is fast. However, there are some disadvantages or technical limitations of this procedure. It is not possible to place the graft if proximal neck of the aneurysm is smaller than 15mm and conical in shape (21,22), because origins of renal arteries could be covered. Also, the neck of the aneurysm should be orientated at the angle no smaller than 60° towards the sagittal plane of the aorta, iliac arteries must not be tortuous and must measure at least 9 mm in diameter (23,24). During relatively short period of clinical application and development of EVAR (from 1991) the problem of frequently inadequate commercially available aortic stent-grafts for yellow race and patients with low BMI (21) has arisen. The application of EVAR in yellow race patients showed that only 23-42% grafts, with fabrically defined dimensions, are adequate, in 23-46% they need certain corrections, while in about 30% of patients there is a contraindication for stent placement (25,26,27,28). Contemporary experience in the application of EVAR showed that overall number of complications is relatively high, even up to 30-40%. Also, one of the reasons is a not precise enough preprocedural morphologic evaluation of AAA and early diagnostics of postprocedural complications.

Modern generations of multidetector CT units (generation 16 slice, 2004 to 64 slice detectors-2007), offered a new visualisation quality and possibility to obtain more relevant diagnostic information compared to DSA. MDCT aortography reaffirmed the significance of preprocedural evaluation which ensures obtaining numerous and high quality information in each and every situation, considering the place of graft insertion, graft design and overall indication for EVAR, as well as relevant postprocedural evaluation and early diagnostics of possible complications.

During last 3 years, MDCT units with 10-times lower exponential doses per examination were constructed (29-35). At the same time, routine use of high-resolution ultrasonography as non-ionizing morphologic imaging enabled screening programmes for AAA in elderly and high-risk population, that are conducted and in progress in many countries (36,37,38).

## 2. Body

Main hypotheses of this multicentric study are:

1. Positive family anamnesis for AAA, as well as trauma, personal history of diabetes mellitus and hypertension, smoking, elevated LDL cholesterol, which are risk-factors for AAA
2. There are significant anatomic-morphologic differences in aneurysmatic infrarenal aorta between Caucasian and Asian patients

3. There are precise morphologic parameters based on MDCT aortography which determine indications and contraindications for EVAR, graft dimensions and the place of insertion
4. MDCT aortography enables early diagnostics of EVAR complications
5. The possibility of graft design in individual case is enabled by integrating measurements obtained by MDCT aortography in selective programme

The study was conducted in Clinical center of Serbia - Center for radiology and magnetic resonance and Institute for radiology, University Hospital Saporro (Japan), in period 2009-2011. In this study 31 Asian and 30 Caucasian patients with the infrarenal aortic aneurysm were included, as well as 130 Asian and 126 Caucasian patients with indication for CT aortography (CTA), which confirmed the absence of AAA. Election of patients of both races before referred to CT examination, was performed according to medical history, and definite indication for CT exam was set according to clinical findings and sonographic findings in distal aorta. Exclusion criteria were: rupture of aneurysm, aneurysm that exceeded infrarenal segment, discrete dilatation of aorta and finding of rough intramural and extraluminal calcifications in longer segment.

Data about risk factors for development of AAA (smoking, hypertension, elevated blood cholesterol level) were collected. One of the questions included the presence of diabetes mellitus in personal history. Questionnaire included demographic parameters (sex, age, race, education), antropometric data (body weight, body height, body surface, body mass index), personal history (diabetes, trauma, other) and family medical history (presence of AAA in relatives).

For classifying patients according to the level of nutrition, we used international classification recommended by World Health Organization (WHO) and US Institutes of Health: underweighted-BMI<18,4, normal weighted BMI between 18,5 and 24,9; overweighted BMI 25-29,9 and obese BMI>30. According to body height, all the patients were divided in 4 subgroups: shorter than 160 cm, between 160 cm and 170 cm, between 170-180 cm and taller than 180 cm.

Considering smoking, patients were divided into 3 subgroups according to duration of this habit: 10 years, between 10-20 years and over 20 years. Level of blood cholesterol over 3,4 mmol/l was considered elevated. For calculation of body surface (SA) we used Dubois & Dubois formula:  $SA = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$ . Considering that it is a complex logarithmic formula, we used software (calculator) for SA recommended by US National institutes of health (<http://www.nih.gov>). For the calculation of BMI we used established formula:  $BMI = \text{body weight (kg)} : \text{body surface (m}^2\text{)}$ .

### 3. 64-slice MDCT protocol and measurements used in the study

CTA examination in both centers was performed on the same CT unit of the same generation, type and model of the machine. We performed examinations on 64-slice VCT

Lightspeed unit (GE, Milwaukee, IL, US). In all cases we used non-ionic contrast agent in concentration of 320-370 (1 ml – 370 mg iodine) applied by automatic injector in cubital vein reaching flow rate of 5 ml/sec.

Taking into account heterogeneity of selected population by constitution, sex, race and age, and expected heterogeneity in „delay time“ of the examination start, we used programme mode „SmartPrep“ for defining the appropriate time, by selecting the spot in aorta where appearance of contrast agent triggers the acquisition. Helical mode was used in SmartPrep protocol, 120 kV, 250-700 mAs, rotation speed of the tube 0,35 with slice thickness of 1,25 mm with 64 slice detector in 0.625mm reconstruction.

Postprocessing was performed with the same selected applications in both centers:

Volume Viwer Analysis-CTA Aorta and Advanced Vessel Analysis. Interobserver variability was avoided by the fact that examinations in both centers were performed by a single radiologist.

Number of global selected mathematic variables which define morphology at CTA examination used in this study is 11. Overall number of methodologically defined transverse measurements is 36 (12 for infrarenal aorta and 24 for iliac arteries), overall number of linear measurements is 36 and volumetric measurements 3. All together, these measurements represent methodologic protocol used in the study for defining the morphology of aneurysmatic infrarenal aorta.

Linear, transverse and volumetric measurements were performed according to the protocol defined beforehand, which consisted of following parameters (Figure 1). All linear measurements were performed in 3 characteristic 2D and 3 characteristic 3D reconstructions (AP, PA and semi-oblique) and mean value was used as definite. We used software ruler tool which is a part of every Analysis-CTA Aorta. Proximal point for measuring aneurysmatic neck, linear distances of aorta, angle between AAA and all the other calculations were positioned in the orifice level of main renal artery. We performed following linear measurements:

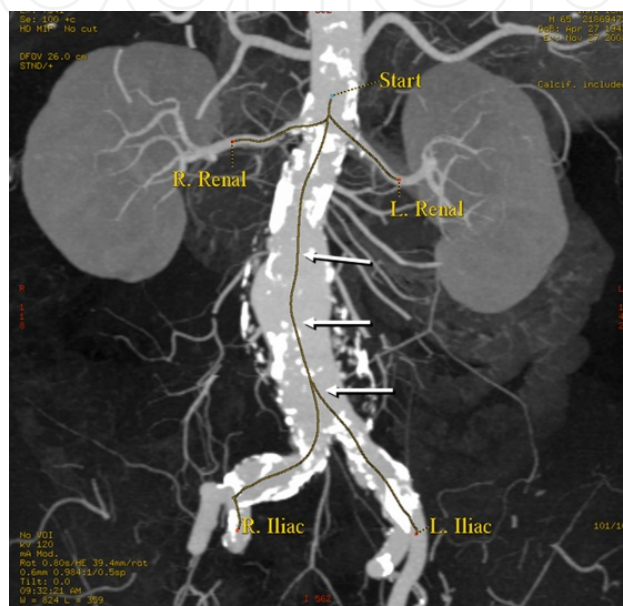
- mean length of abdominal aorta (mm)(Figure 2)
- mean length of the neck of the aneurysm (mm)(Figure 3)
- mean linear distance from renal artery to aortic bifurcation (mm)(Figure 2)
- mean length of common iliac artery (mm)(Figure 4)
- AAA angle (degrees– °)(Figure 2)

Calculations of aortic and iliac arteries volumes represent a part of the basic package of Analysis-CTA Aorta programme. Start and end point are defined (Figure 1). Computer calculates only the lumen of blood vessel that contains contrast agent with no calcium deposits, and without wall structures in cases of thrombosed extraluminal mass; if AAA contains only the dilated vessel wall, the lumen is calculated in total.

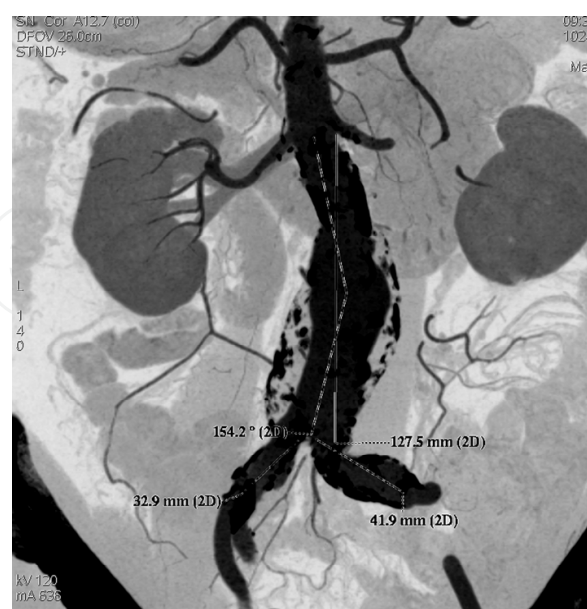
Transverse measurements were performed using Advanced Vessel CT Aorta Analysis programme which enables linear differentiating the lumen of contrast agent that fills the



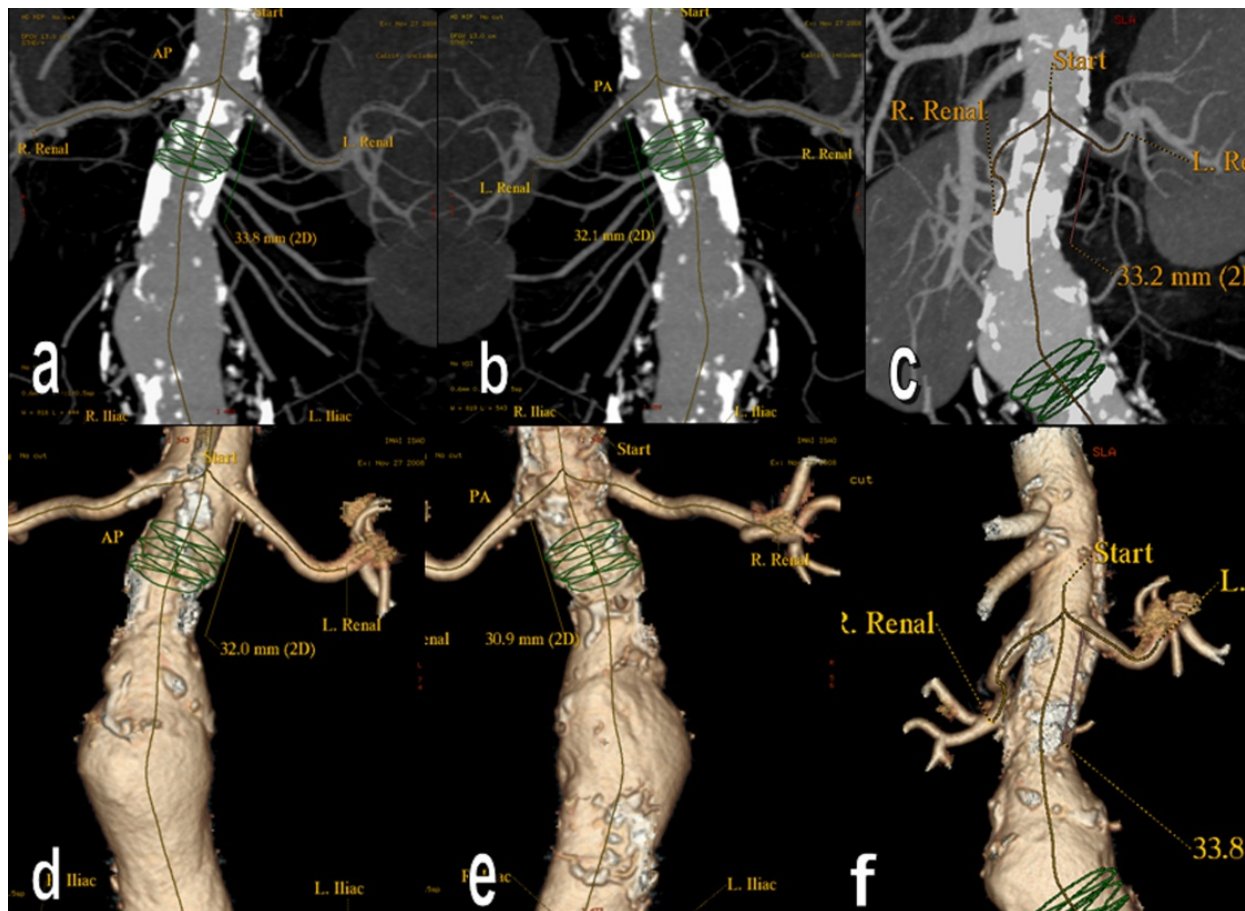
vessel from intramural and endoluminal calcifications, considering the similar attenuation values of calcium and contrast agent which cannot be differentiated visually (there is a possibility of misinterpreting calcified plaque as vessel lumen). We performed 6 typical measurements in the same plane, for the lumen of circulating blood (total of 12 “flow” diameters)(F.d.) and 6 measurements in the same plane for diameters of circulating blood together with thrombosed blood, aneurysm content and thickness of the vessel wall (total of 12 „real”diameters)(R.d)(Figure 5, Figure 7).



**Figure 1.** Characteristic points of interest to mark the CT angiographic analysis in Figure 2D.



**Figure 2.** CT linear measurements of the aorta in the 2D image: mean length of abdominal aorta, mean linear distance from renal artery to aortic bifurcation and AAA angle

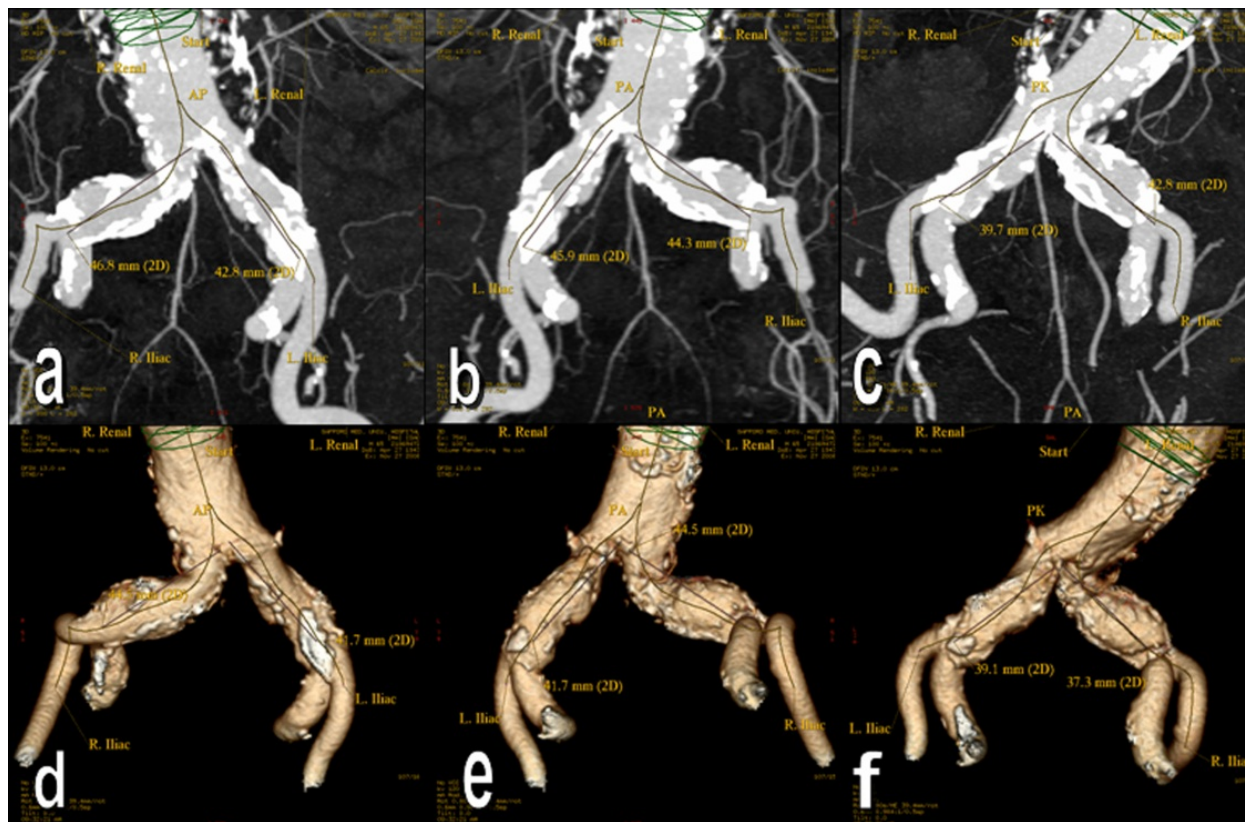


**Figure 3.** AAA neck length in 3 characteristic measurements in 2D (a-c) and 3D image (d-f).

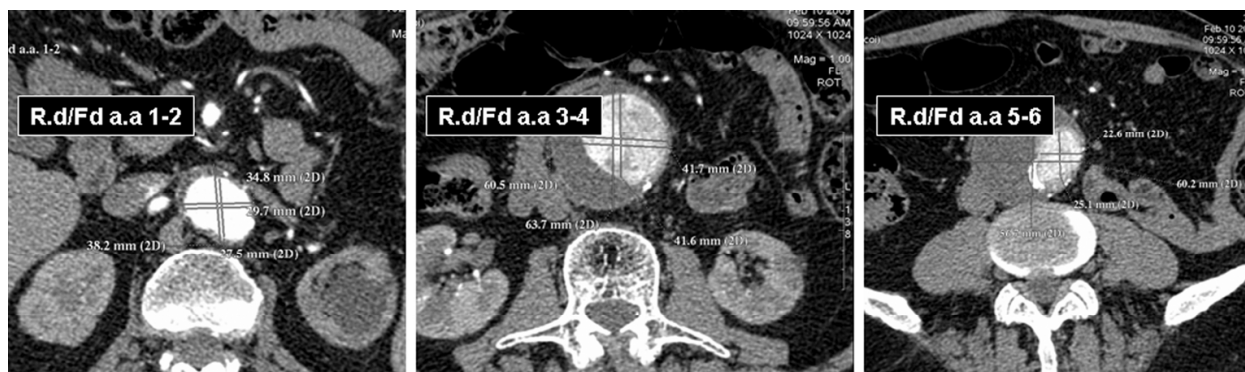
The points of transverse measurements of abdominal aorta (a.a.) and common iliac artery (a.i.c.) performed in this study were following:

- infrarenal, in the level of the neck of the aneurysm, the largest and the smallest F.d. and R.d. (F.d. a.a 1, F.d. a.a 2, R.d. a.a 1 and R.d. a.a 2)
- in the middle part of abdominal aorta, largest and the smallest F.d and R.d diameter (F.d. a.a 3, F.d. a.a 4, R.d. a.a 3 and R.d. a.a 4)
- just above the aortic bifurcation, the largest and the smallest F.d and R.d diameter (F.d. a.a 5, F.d. a.a 6, R.d. a.a 5 and R.d. a.a 6);
- proximal parts of both common iliac arteries distally from aortic bifurcation, the largest and the smallest F.d and R.d diameter (F.d. a.i.c 1, F.d. a.i.c 2, R.d. a.i.c 1 and R.d. a.i.c 2);
- middle parts of both common iliac arteries below aortic bifurcation, the largest and the smallest F.d and R.d diameter (F.d. a.i.c 3, F.d. a.i.c 4, R.d. a.i.c 3 and R.d. a.i.c 4);
- distal parts of both common iliac arteries above their bifurcations, the largest and the smallest F.d and R.d diameter (F.d. a.i.c 5, F.d. a.i.c 6, R.d. a.i.c 5 and R.d. a.i.c 6);

The precise localization of transverse measurements was defined according to the linear reconstruction of aorta and iliac arteries.



**Figure 4.** Measuring the length of the c.i.a in characteristic 3 position (AP, PA and oblique) in 2D (a-c) and 3D image (d-f)

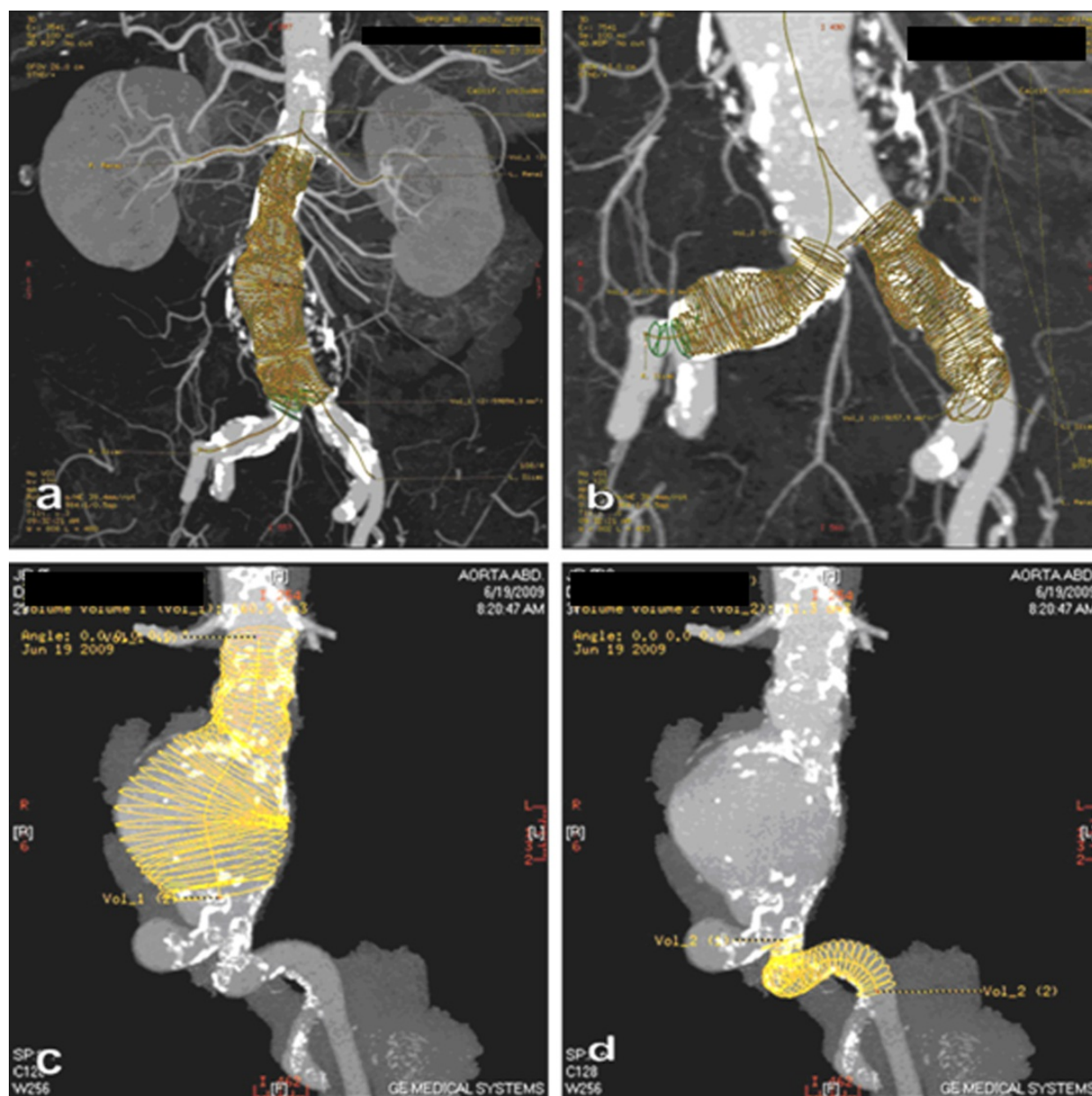


**Figure 5.** Transverse measurement of infrarenal aortic aneurysms (diameters Rd and Fd)

As a variable part of the protocol of morphologic measurements in this study, depending on the individual case, we performed other diagnostic explorations enabled by selected computer application, such as:

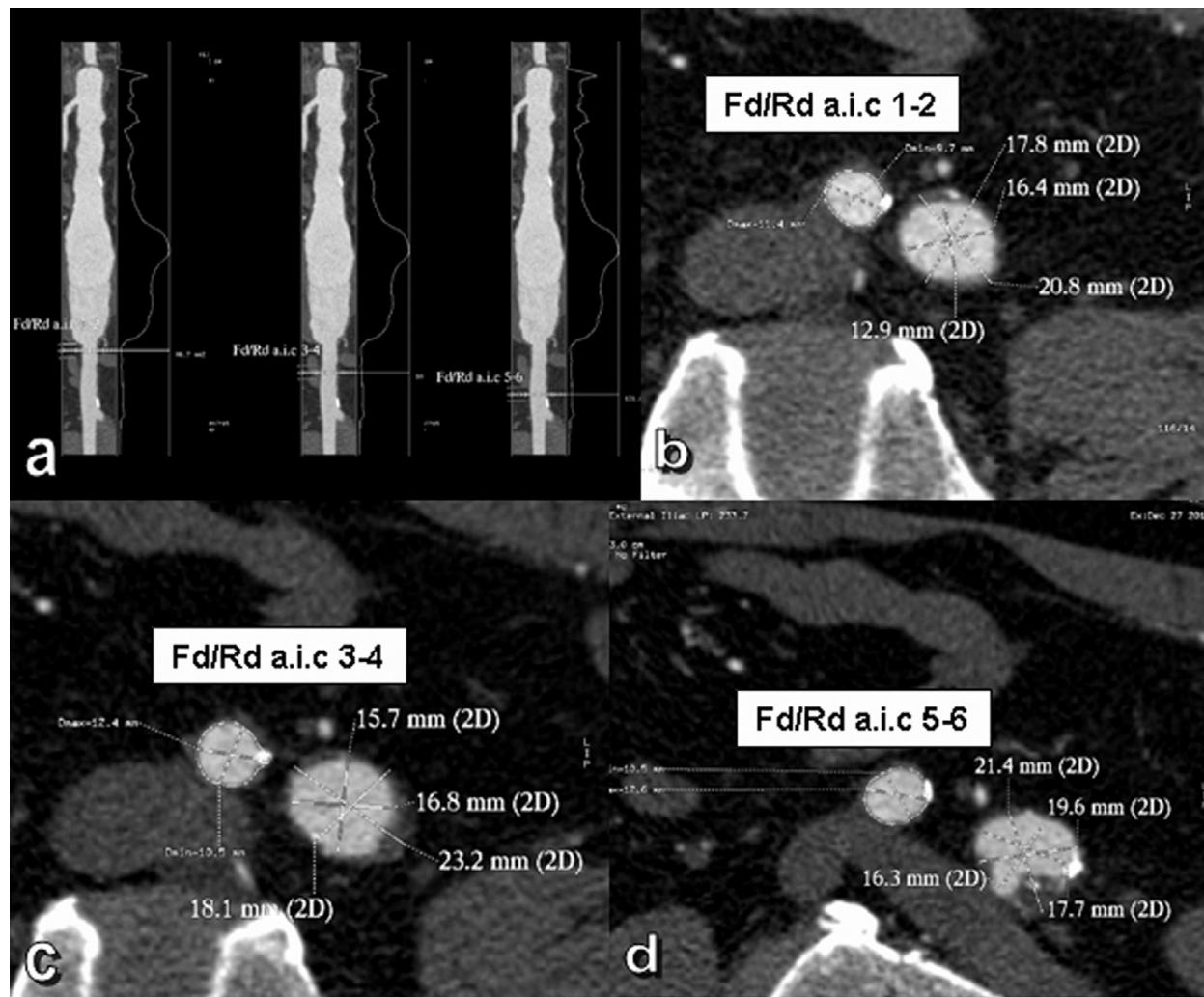
- Defining tissue structure (attenuation) in the region of interest (Figure 8)
- Defining the configuration of the blood vessel (Figure 9)
- Defining calcifications (Figure 10)
- Dynamic analysis of contrast agent flow
- MDCT aortoscopy (Figure 11)
- Coronal or sagittal 3D reconstruction (Figure 12)



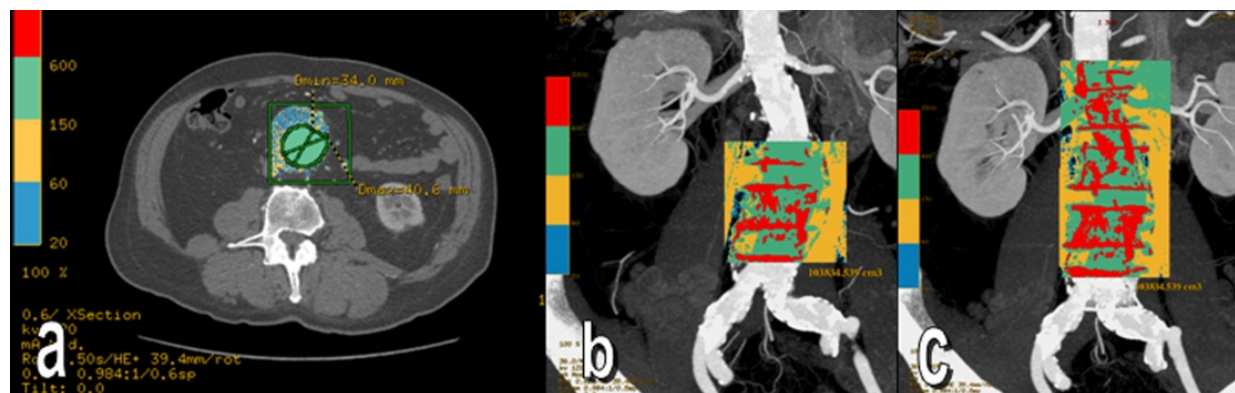


**Figure 6.** MD CT volumetric measurement of infrarenal aorta and aa.iliace comm bill in patients with calcium channel intraluminal nodular induration (a,b) patients with AAA and without calcium induration in the wall (c,d).

a) Defining tissue structure (attenuation) in the region of interest in different planes (most often transverse and sagittal). Using this exploration, known as „color mapping“ it is possible to determine the density of the tissue in ROI or mean tissue density in the wider region. According to the attenuation distribution, it is possible to determine the structure or density of thrombotic aneurysmatic blood as well as differentiate contrast agent from calcified plaques which are pointed intraluminally. Every color represents a range of some interval of tissue density from 20-800 HU. Contrast agent is always represent by color green, low-density strustures (thrombus, blood, fat) by blue, atherosclerotic deposits by yellow and calcified indurations by red.



**Figure 7.** Transverse measurement of infrarenal aortic aneurysms (diameters Rd and Fd)(b-d) compared to the linear angiographic image (a) (a)

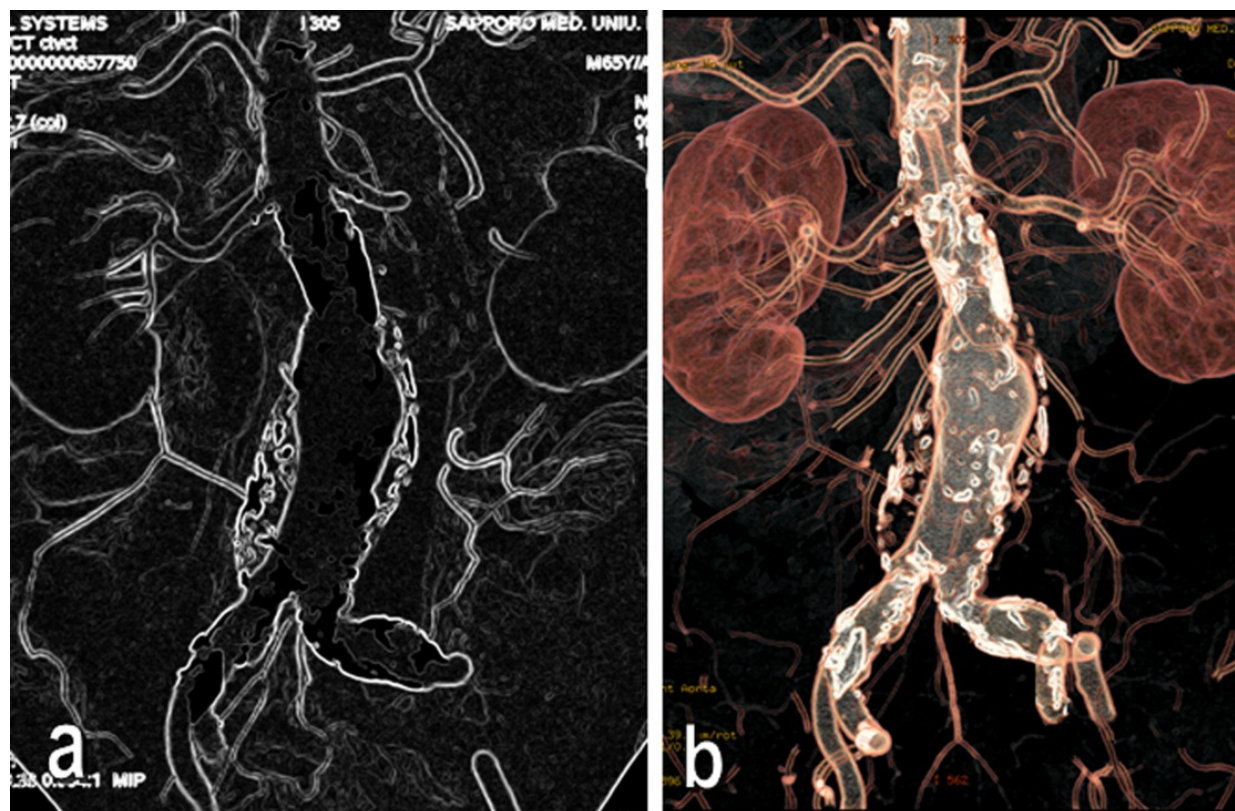


**Figure 8.** Defining tissue structure (attenuation) in the region of interest in the transverse (a) and coronary reconstruction (b,c)

b) Defining the configuration of the blood vessel enables precise visualization in cases of suspected dissection of the vessel wall and enables defining the wall thickness in all planes. Furthermore, it enables clear graphic demarcation of the lesions of aortic wall and



differentiating from the extraluminal lesions. Additional option is definition of calcified indurations inside the „contoured“ picture.

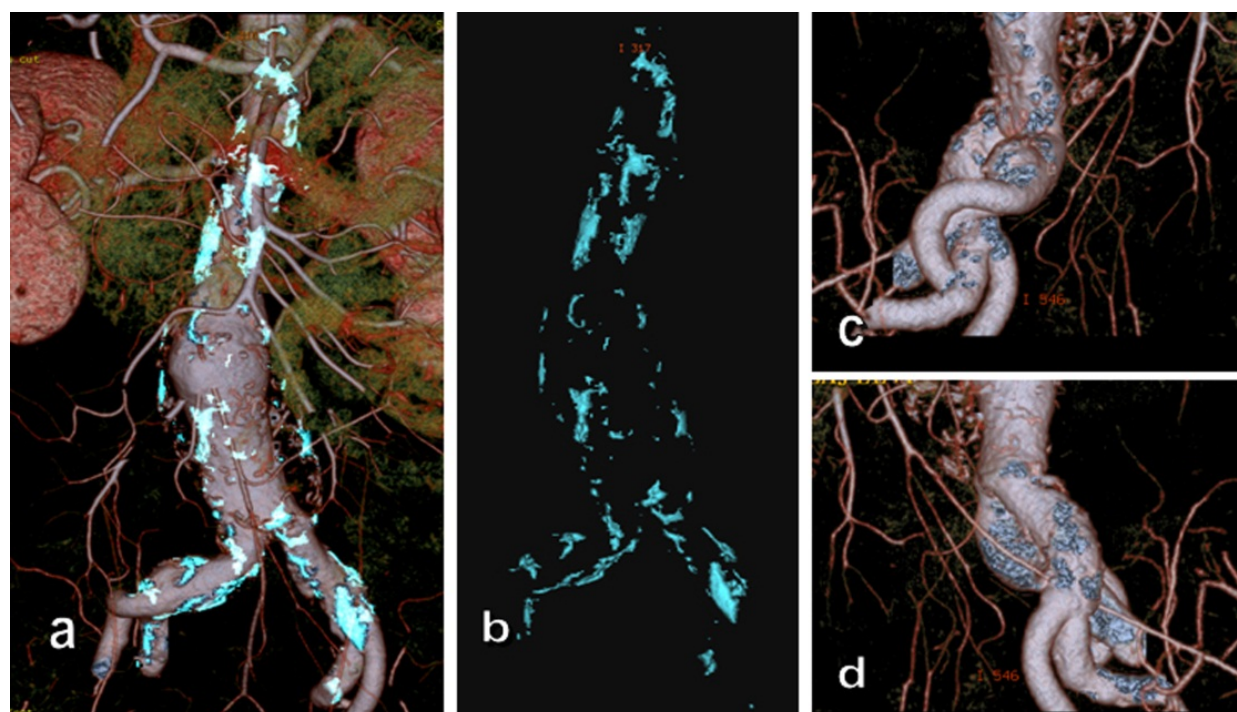


**Figure 9.** Contouring infrarenal aorta: linear (a) and with intramural calcifications (b)

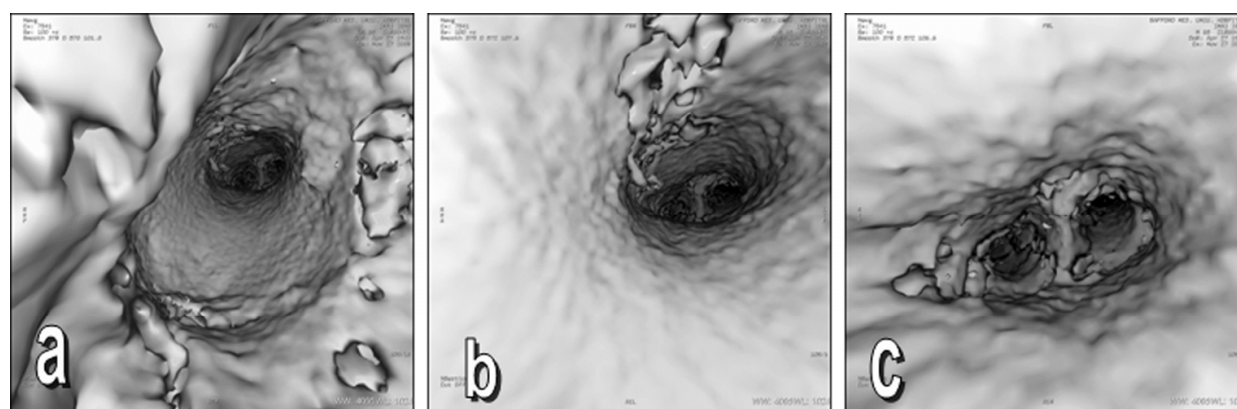
c) Isolated defining extraluminal calcifications (Figure 3.21. a), intramural calcifications and altogether in frontal reconstruction along the aortic segment, in selected planes and positions. This exploration may imply on therapeutic approach in two projections at the level of c.i.a

d) Dynamic analysis of contrast agent flow represents the review of video-recording in selected plane, most often transverse or frontal, where dynamic of the contrast agent flow in aortic lumen can be analysed in real time mode. This exploration has a specific value in postprocedural evaluation and diagnostics of early complications of EVAR, most of all the proximal endoleak as a frequent complication. It is more sensitive than conventional digital aortography video -recording

e) MDCT aortoscopy, known also as „virtual aortography“, is a special visualization option in „advanced“ options of MD CT aortography, which is offered in standard postprocessing units of 16-64 slice MDCT units from the year 2007. It is a relatively simple, but powerful method of endoluminal examination in all planes, that enables optical presentation of the aortic wall inner surface, lesions of the aortic walls, the extent of aneurysmatic dilatation, endoluminal plaques and vessel arborization.



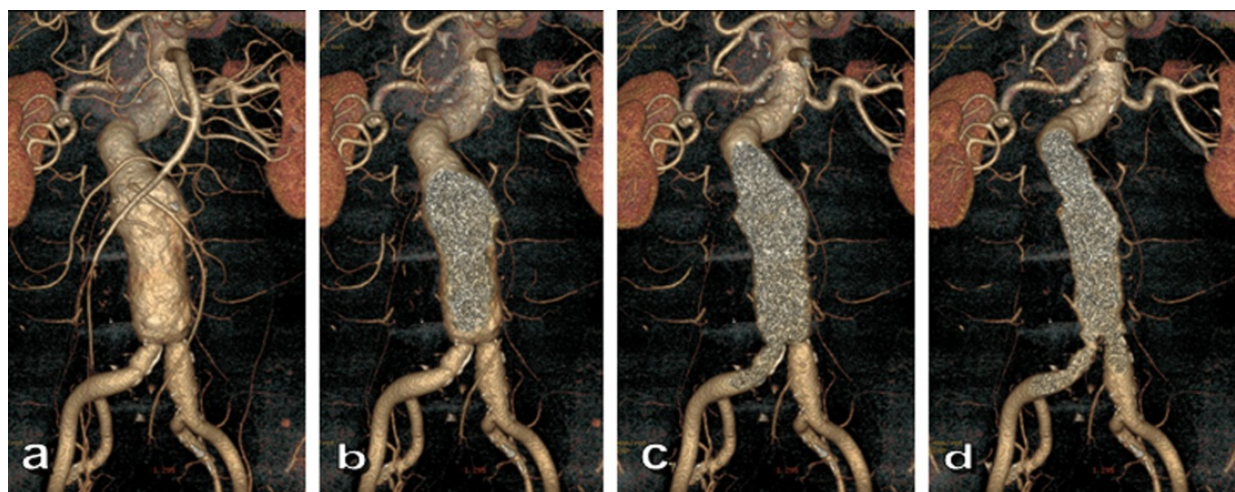
**Figure 10.** Defining calcifications of AAA - the level of the aortic extraluminally (a) and intramural (b)



**Figure 11.** MDCT aortography the level of renal arteries (a), middle third of a.a (b) and before the bifurcation (c)

f) Coronal or sagittal 3D reconstruction (VR 3D cut). It is a postprocessing option from the standard group which is more often used in diagnostics of parenchymatous organs and heart, and represents „listing“ slices at selected distance (0,625 mm at least) in 3D presentation of the organ or lesion. In AAA, it can be used for visualization of thrombotic mass and its structure considering heterogeneity and the presence of calcified indurations. The analysis can be preformed in 6 standard planes: AP – anteroposterior; PA – posteroanterior; L –left lateral, R – right lateral, I – inferior-superior; S – superior-anterior, and additionally in every non-standard plane of rotated 3D image, which defines 4D visualization in terms of movement.





**Figure 12.** VR 3D cut option in coronary reconstruction in the antero-posterior direction (a) in 3 planes (b,c,d)

#### 4. Statistic methodology

Considering the heterogeneity of the population included, as well as the number of analyzed variables, we used several statistical models for data analysis in this study:

Univariant and multivariant statistical methods – for testing statistical significance of difference between parameters for qualitative variables, as well as quantitative variables, univariant methods were used

$\chi^2$  test –for testing the relationship between non-parametric variables.

ANOVA - one-sample analysis of variance- univariant analysis of the effect of one selected factor on dependent variable. Comparing mean values, standard deviations in development of aneurysm between races and in the same race compared to control subjects, was performed using this method.

Median Test, Kolmogorov-Smirnov Z-test analysis of the mutual influence (of the selected variable among the groups), testing the compatibility of controls and patients in terms of developing the aneurysm, between races, and in the same race compared to the controls.

We determined the correlation coefficient (Pearson correlation) related to groups, smoking habit, and smoking history of all the subjects included, subjects according to sex (in males and females separately).

According to univariant logistic regression analysis (ULRA) we tested the influence of selected variable (risk factors) and their correlation on the aneurysm development at the probability level  $p \leq 0,01$ .

Regression analysis (logistic model) In the model of MLRA we included all variables (risk factors) that were confirmed by univariant logistic regression analysis (ULRA) to be connected to the aneurysm development at the level of  $p \leq 0,01$ , so we determined the independent risk factors for development of aneurysm in all the subjects, and then separately for male and female groups. All the variables were additionally tested in terms of age.

Odds Ratio (OR) or (expB) with confidence interval of 95%- chance ratio, or the possibility of the selected happening, the assessment of the correlation of risk factors (happening) and disease occurrence (development of aneurysm).

Statistic significance was determined at the level of probability of the null hypothesis  $p \leq 0.05$  to  $p < 0.0001$ . Statistical analysis was performed using SPSS ver.20, while graphs and tables were edited using MICROSOFT OFFICE (EXCEL and WORD).

## 5. Study results

Distribution of patients according to the site of aneurysm, mean values  $\pm$  SD in demographic and anthropological criteria and CT measurements between two races of the respondents suffering from AAA is shown in Table 1. The other criteria did not find statistically significant differences in relation to race in patients with AAA.

Demographic / Anthropological variables, MD CT measurements	AP with AAA	EP with AAA	ANOVA, F	p
	Mean $\pm$ Std.Dev.	Mean $\pm$ Std.Dev.		
age	75,60 $\pm$ 6,13	61,13 $\pm$ 10,97	39,75	0,001***
hight (cm)	159,90 $\pm$ 8,85	176,63 $\pm$ 8,20	57,70	0,001***
body weight (kg)	56,46 $\pm$ 11,55	80,00 $\pm$ 11,99	59,94	0,001***
surface area (m2)	1,58 $\pm$ 0,18	1,97 $\pm$ ,189	70,50	0,001***
BMI (kg/m2)	22,04 $\pm$ 3,77	25,38 $\pm$ 3,19	13,64	0,001***
aneurysm neck length	22,73 $\pm$ 6,9	38,72 $\pm$ 11,92	3,176	0,013**
aver.c.i.a.length	47,41 $\pm$ 12,99	59,68 $\pm$ 15,25	11,25	0,001***
aver.distance a.a.	84,39 $\pm$ 31,58	63,27 $\pm$ 50,76	3,65	0,05*
Fd-a.a1	19,05 $\pm$ 3,95	22,87 $\pm$ 6,44	7,65	0,01**
Fd-a.a2	22,08 $\pm$ 4,13	26,88 $\pm$ 7,62	9,22	0,001***
Rd-a.a1	24,06 $\pm$ 4,98	29,39 $\pm$ 9,28	7,67	0,01**
Rd-a.a2	26,18 $\pm$ 5,79	31,57 $\pm$ 10,98	5,66	0,02*
Rd-a.a3	32,53 $\pm$ 12,37	43,42 $\pm$ 20,74	6,11	0,02*
Rd-a.a4	34,46 $\pm$ 12,75	48,07 $\pm$ 22,35	8,39	0,01**
Rd-a.a6	28,91 $\pm$ 10,90	36,61 $\pm$ 17,29	4,25	0,04*
volume c.i.a.	6405,86 $\pm$ 2819,07	8560,63 $\pm$ 5145,87	4,05	0,05*

**Table 1.** Distribution of patients according to the site of aneurysm, mean values  $\pm$  SD of age, height, body weight, surface area, BMI index, aneurysm neck length, aver.c.i.a.length, aver.distance a.a., Fd-a.a1, Fd-a.a2, Rd-a.a1, Rd-a.a2, Rd-a.a3, Rd-a.a4, Rd-a.a6 and volume c.i.a. - where the parameters are found statistical differences (\*,\*\*) and the difference is highly statistically differences (\*\*\*).

Distribution of respondents to the AP and EP aneurysm and control groups the same race by age, gender, BMI and body height is shown in Table 2.

Age / Gender BMI, Body height		patients with aneurysm				patients without aneurysm			
		AP		EP		AP		EP	
		No	%	No	%	No	%	No	%
Age	≤ 74	13	41,90	26	86,60	62	47,69	114	90,47
	≥74	18	58,10	4	13,40	68	52,31	12	9,53
Gender	Male	25	83,3	24	77,4	58	46,03	90	83,3
	Female	5	16,7	7	22,6	68	53,97	40	16,7
BMI (kg/m <sup>2</sup> )	< 18,4	0	0,00	3	9,68	3	2,38	7	5,38
	18,5 -24,9	12	40,00	22	70,97	96	76,19	113	86,92
	25-29,9	15	50,00	6	19,35	24	19,05	7	5,38
	> 30	3	10,00	0	0,00	3	2,38	3	2,31
Body height (cm)	< 160	14	45,20	0	0,00	73	56,15	0	0,00
	160-170	12	38,70	7	23,3	50	38,46	24	19,05
	≥171	5	16,10	14	46,70	7	5,38	73	57,94
Total		31	100	30	100	126	100	130	100

Age  $\chi^2=13,322$ ;  $p=0,0001$

Gender  $\chi^2=0,337$ ;  $p=0,561$

BMI  $\chi^2=12,785$ ;  $p<0,005$

Body height  $\chi^2=28,57$ ;  $p<0,0001$

**Table 2.** Distribution of respondents to the AP and EP aneurysm and control groups the same race by age, gender, BMI and body height.

The presence of factors in patients and control subjects as well as univariant regression analysis (ULRA) for assessment risk-factors among patients and controls in AP and EP groups of patients is shown in Table 3a. The presence of risk-factors in patients and control subjects as well as multinivariant regression analysis (MLRA) for assessment risk-factors among patients and controls in AP and group of patients is shown in Table 3b and the presence of risk-factors in patients and control subjects as well as multinivariant regression analysis (MLRA) for assessment risk-factors among patients and controls in EP group of patients is shown in Table 3c.

PREDICTORS	AP patients with aneurysm		EP patients with aneurysm	
	Unst.B	*p	Unst.B	*p
(Constant)	9,549	0,000	27,901	0,000
Age (up to and over 75 years)	-0,096	0,848	0,912	0,591
Height (< 160, 160- 170, ≥171 cm)	-0,050	0,896	0,657	0,382
BMI (< 18,4, 18,5-24,9, 25-29,9, > 30)	0,466	0,351	-3,386	0,000
Smoking (yes/no)	3,254	0,000	1,348	0,496
Smoking (to10,10-20, over 20 years)	-2,284	0,000	-2,969	0,001
BP (>140/90) (yes/no)	-1,695	0,003	-2,725	0,009
LDL- cholesterol (>3,4 mmol/l) (yes/no)	-4,677	0,000	-4,545	0,000
Diabetes Melitus (yes/no)	3,238	0,000	3,121	0,011
Tab 3a				
* p value according to the results ULRA (p ≤ 0,01)				
PREDICTORS		OR	95% confidence interval	*p
Smoking	no	0,069	0,005-0,874	0,003
	yes			
Length of smoking (years)	to 10	7,608	2,836-20,408	0,0001
	10-20			
	over 20			
Hypertension (> 140/90)	no	3,831	1,079-10,911	0,037
	yes			
LDL- cholesterol (>3,4 mmol/l)	no	11,817	3,734-37,396	0,0001
	yes			
Tab 3b				
* p value according to the results of MLRA				
PREDICTORS		OR	95% confidence interval	*p
BMI	< 18,4	4,923	1,873-12,941	0,001
	18,5-24,9			
	25-29,9			
	> 30			
Length of smoking (years)	to 10	2,784	1,743-4,446	0,0001
	10-20			
	over 20			
Hypertension (> 140/90)	no	3,421	1,089-10,767	0,036
	yes			
LDL- cholesterol (>3,4 mmol/l)	no	6,696	2,092-21,430	0,001
	yes			
Tab 3c				
* p value according to the results of MLRA				

**Table 3.** The presence of risk-factors in patients and control subjects as well as multinivariant regression analysis (MLRA) for assessment risk-factors among patients and controls in EP group of patients.



## 6. Evaluation of the methodology of imaging studies

Generation of spiral CT units enabled the examination of large blood vessels for the first time as a substitute for the invasive conventional angiography, most importantly for aorta, extracranial arteries of the neck and skull base, main trunks of visceral arteries of thorax and abdomen and ilio-popliteal vessels. There have been numerous attempts to affirm spiral angiography for the exploration of 2<sup>nd</sup> and 3<sup>rd</sup> order arteries of parenchymatous organs, but diagnostic sensitivity was disappointing (33,39). Development of CT technology from the year 2000, enabled the start of new epoch with multidetector CT units, that brought amazing possibilities of image acquisition and spatial to temporal resolution ratio (30,31). In the same terms, a new postprocessing editing of transverse CT images was developed, offering faster, more detailed and accurate reconstruction possibilities in all planes. Definitely, MDCT examination established itself as diagnostically most sensitive in postprocedural evaluation of AAA and became method of choice in this field. In year 2007, exponential dose for the examination of infrarenal aorta using standard protocol at 64-slice unit, was approximately 6-8 mSv for both sexes. In obese patients it was somewhat higher (29). During the following 3 years, introducing new pulse generators and faster rotating tubes in clinical practice, exponential dose for CT exam of infrarenal aorta was lowered for 8-10 times, remaining the preoccupation of inovators until now.

## 7. Evaluation of demographic, antropologic and epidemiologic results of the study

In the discussion of the results of this study, we used every available data base, but most of all US National Library of Medicine National Institutes of Health ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)), as well as other browsers for medical papers in MEDLINE and other indexed publications. Browsing bibliographic data was performed using relevant key words (races, aorta, CT, aortography, MDCT, aneurysm etc. )

Sex distribution in both groups of patients and controls in this study showed three basic features: there is no statistically significant difference in terms of sex in patients, that in control Caucasian subjects predominant group consisted of females and that in analyzed groups of patients predomination of males was statistically significant. Compared to the most cited epidemiologic studies considering the sex of patients, showing 4-6 times more frequent development of aneurysms in men, in this study we showed slight predominance of male patients in Caucasian group (around 72%), while in Asian group the number of male patients was smaller (around 50%). According to available data on the frequency of AAA in different races, it is generally accepted that the disease is most frequent in Caucasian population (12,14). In USA, for example, the incidence of AAA is significantly higher in white males than Afro-americans, while in female population, there is no statistically significant difference in the occurrence of the disease. Asian population (yellow race) is the least frequently affected by AAA (10,12). In Africa, aneurysm of thoracic aorta is more frequent, as well as in Carribean population. African males are three times less affected than Europeans (40). Interesting epidemiologic fact might be that in Britain, the

morbidity ratio of Asian population is insignificantly lower than Caucasians, which is not applicable for non-emigrants (9). In China, AAA is a rare disease, as well as in population of Indonesia (9).

It remains unclear why AAA predominantly affects male population. Almost all the studies that tackle this question, insist on the fact that male population has higher incidence of etiopathogenetic risk factors: arteriosclerosis, smoking, hypertension and elevated blood cholesterol level. Generally speaking, the cause of this fact remains unclear, and as predisposing factors arise hormones, genetic disposition, disposition to atherosclerosis, more frequent risk factors or the combination of aforementioned factors. Singh K and Bønaa KH from famous University Hospital of Tromsø, Norway, in their study including 6.386 subject of both sexes, established the diagnosis of AAA using sonographic screening, in 263 (8.9%) males and 74 (2.2%) females (9,20). Bearing in mind that subjects ranged in age (from 24-85 years), they compared the diameter of infrarenal aorta in terms of age and concluded that in male population there was a progressive growth in diameter of infrarenal aorta during the process of ageing. The effect of elevated plasma fibrinogen level in male population also remained unclear (8,11,44).

In terms of age distribution, Caucasian patients are statistically significantly younger than Asian patients (for 15 years). Compared to other studies, European patients are shown to be significantly younger than in other Caucasian populations (21,40). This data becomes interesting if we analyze distribution by age subgroups, where dominant incidence in white race population is found in the subgroup of patients younger than 64 (66%), while almost half of these patients are even younger than 54. The same distribution is shown in the control group of this population. On the other hand, in the Asian group of patients, AAA occurs in much older population- dominant incidence was found in the subgroup of older than 75 (54,8%). In the light of these results, we can analyze AAA as a primary disease (in white race) or in the setting of generalized atherosclerotic pathologic changes in the process of ageing (yellow race). Special attention must be paid to EVAR procedure in the group of elderly population, patients with cardiopulmonary and cerebrovascular insufficiency.

Definite conclusion is that the incidence of AAA increases with age, which is explained by prolonged impact of risk factors, long period between latency of risk factors and aneurysm development, and increased sensitivity of aorta to risk factors in the process of ageing. Hypothetically, changes in elastin structure cause increased mechanic stress on collagen which forms a strong fiber network. Experiment models of aneurysmatic blood vessels showed that isolated destruction of elastin led to dilatation of the vessel for 25-65%; also, following dilatation and possible rupture occur due to the alteration of collagen (6). Half-life of elastin is considered to be 75 years, and aorta of adult does not have the ability to produce functional elastin (6,7,42).

In terms of correlation patient height in study population and control groups, we obtained expected results. There is a statistically significant difference in the average height (Caucasian population is 17 cm taller than Asian population, dominant group in Asian

population are patients shorter than 160 cm, while in Caucasians dominant group consists of patients over 171 cm )(17,29).

Further, there is statistically significant difference in body weight in study populations-European patients weigh 25.6 kg more than the Asian population, on average. This might be explained by obesity as a modern social-medicine phenomenon in developed countries where there is an increase in AAA incidence. Body weight in this study arised as statistically significant risk factor for the development of AAA.

Considering the level of nutrition, in the yellow race the dominant group consisted of normal weighted (70,97%), while there was no obese subjects (with BMI over 30) in this population. On the other hand, in the white race population over 50% patients were overweighted and obese. BMI can be observed as a universal parameter nondependent of the race, and obtain valid results with the use of simple statistical models (21). This parameter excludes race constitutional features and heterogeneity of the subjects in terms of body weight and body height, since last two parameters in 20% of observed patients and control subjects showed no statistically significant difference. If we use BMI value of 23 (approximate height of 170cm and weight of 58kg-mean BMI value in both groups of patients BMI=22,04±3,77 for Asian group and BMI=25,38±3,19 for Caucasian group) as observation criterion, instead of race, and divide all the subjects in two subgroups, BMI-1 (BMI<23) and BMI-2 (BMI>23), a correlation of antropologic and morphologic parameters calculated by MDCT aortography can be obtained (21).

In this study, there was no statistically significant difference in the presence of risk factors in subjects of both groups. In the Asian population, only 3,2% showed no risk factors present, while in the Caucasian population this percentage was 3,3%. Since patients with no risk factors present represent statistically insignificant subgroup in both populations, we can consider the presence of risk factors as a leading impact factor on the pathogenesis of the development of AAA. Considering the number of present risk factors, in Caucasian population the dominant group consists of patient with 3 or 4 risk factors (40% + 30% = 70%), while in Asian population dominant group consists of patients with 2 or 3 risk facotrs present (45,2% + 19,4% = 64,6%). In terms of the presence and number of RF in patients of both races, there is statistically significant difference in development of the disease. In Asian population, AAA occurs most frequently in patients with 2 RF (with 1 or 2 RF: 64,6%) while in white race this percentage is almost 3 times lower, only 23,3%. As a conclusion, Asian population seems to be more prone to the development of this disease.

The number of associated risk factors in patients of Asian population is statistically significantly higher than in control subjects of the same population. Over 40% (41,54%) control subjects in this population showed no risk factors present, while 25,3% showed only 1 RF present. Number of subjects with 3 associated RF is insignificant (2,3%), while there were no subjects with all 4 RF present. In total, there was statistically significant difference in the presence of risk factors in the patients and controls of the Asian population. In the same term, there is a positive correlation in the presence of risk factors in the patients and controls in European population also, while it is especially applicable for the presence of 3 or 4 associated risk factors.

The analysis of the results considering smoking as risk factor in all the study subjects independently of race and smoking history, there was statistically significant number of smokers in both subgroups of patients compared to controls. The analysis of the results considering male and female populations showed that in patients of both populations smoking represents an extremely significant risk factor for the development of AAA. The results of multivariate logistic regression analysis were concordant.

On the contrary, hypertension as a risk factor in this study was proven to be controversial. In both races, the number of patients with hypertension was not significantly different than the number of normotensive patients. Epidemiologically significant finding was that in Asian population the number of normotensive patients was for 17% higher than hypertensive, while in European population there was 20% more hypertensive than normotensive patients. Generally speaking, in patients of both populations, hypertension is more commonly found than in control subjects, especially in the European population.

One of the referring studies considering pathogenesis of peripheral vascular diseases (McConathy, Oklahoma Medical Research Foundation) showed that in AAA, the level of cholesterol in plasma is lower than in patients with stenotic-occlusive arterial diseases, as well as VLDL level and apolipoprotein B, C-III and E. Total cholesterol is shown to be a statistically significant factor in the study of Reed et al. performed in integrated clinical-autopsy study in the 20-year period on 8000 men living in Hawaii (9). This study predominantly addressed the question of atherosclerosis as a risk factor in the development of AAA. The results concordant to this study were obtained in the Whitehall study of Strachan, published in British Journal of Surgery in 2005 considering younger population. Integrated epidemiologic study included 18,403 men, aged 40-64, working as accountants, in the period of 18 years. There were 99 lethal cases of ruptured AAA, and smoking and elevated systolic pressure were isolated. Considering type of cholesterol, LDL and less importantly VLDL, are considered the dominant risk factor by many previous studies on this subject.

The analysis of results considering diabetes mellitus (DM) as a risk factor in this study showed some unexpected results. The first „paradoxal“ finding was extremely low number of patients in both groups with DM (3 patients in each group), with no significant difference between groups. In control groups of both populations, the incidence of DM is lower than 30%, with no statistically significant difference between controls and patients in both populations. The unexpected result is that higher incidence of DM is found not in patient, but in control group of both populations. The most stunning result is the correlation of the presence of DM in patients and controls of the white race, where disease is significantly more frequent in the control subjects. These results raise the question: Does DM have etiopathogenetic correlation with the development of AAA, or closer to the results of this study- is DM some kind of protective factor in the AAA development? Meta analysis of 11 relevant studies considering correlation of DM and etiopathogenesis of AAA shed light to this „paradox“. Out of 11, 4 studies were excluded for no existing or inadequate control group. The rest of the studies showed that there is a small possibility of associated DM in



patients with AAA (OR=0.65, 0.60-0.70,  $p<0.001$ )(30). 3 referring studies found decreased prevalence of DM in patients with AAA (17,18,20).

## 8. Evaluation of morphologic measurements

European population showed statistically significantly longer neck of the aneurysm. With the premise that the length of the neck of 15 mm is the minimal infrarenal distance needed for graft insertion, this study showed that 31,7% patients in the Asian populaion had contraindication for EVAR, e. g. length of the neck of the AAA shorter than 15 mm. Furthermore, the mean length of the anuerysmatic neck in this population is 18,49 mm. Analyzing the subgroup of the Asian population with the neck length  $< 15$  mm, we found that in 8 of 11 patients this length was  $< 10$  mm, 9 mm on average.

The neck of AAA is the place of the proximal insertion of the graft, and in most cases there is a small distance between the normal and pathologic structures of aortic wall. The largest number of EVAR complications, of endoleak type, occur in this proximal part of graft insertion (43). CT aortography (CT fluoroscopy), as a dynamic analysis, enables monitoring of contrast agent flow along the aorta, or the region of interest established in examination protocol. More accurately, due to small slice thickness (0,625 mm), high spatial and temporal resolution, possibility of retroreconstruction in postprocessing at the distance of 0,2 mm and other technical features of this exam, it is possible to analyze CT exam as continuous video-recording in various visualization extensions. Also, „film“ can be stoppped and paused in every moment to analyze the segment in 3D and 4D projections, in all planes and projections.

Valuable advantage of these possibilities is that aorta, AAA and graft can be evaluated in all morphologic features, from the lateral aspects and also as ortogonally isolated transverse projections, a feature which cannot be performed using conventional aortography. These visualization possibilities favour MDCT over conventional aortography or catheter aortography. Beside the fact that it is a non-invasive procedure, additional advantage is that more diagnostic information on the early complications, such as proximal endoleak, can be obtained. Exceptional software features in standard postprocessing allow measuring of the contrast flow rate above the insertion place, inside the graft and distally, as well as different features of AAA before theraputic procedure. Critical moment for the development of proximal endoleak is physical contact of the contrast (blood) with graft contours. As it advances in cranio-caudal direction, contrast flow rate changes as a function of age, constitutional and hemodynamic cardiovascular parameters (stroke volume, width of aorta, degree of sclerotic changes, tortuosity, dilatation, etc.), but usually varies in range of 20-40 cm/sec. If the length of AAA neck is at the critical value (10-20 cm) this contact occurs in the place where vessel wall is already weakened, and its contractility, elasticity and histology are changed. Proximal endoleak can occur anywhere in the upper circumference of the graft, can be minimal, discrete and without clinical manifestations. Also, it can remain minimal in a long period of time, but usually there is a certain degree of progression, dilatation and degradation of the graft function.

Due to physical contact and strike of contrast flow onto the upper edge of the graft, the speed with which blood continues to flow, decreases gradually. Presumption is that the velocity gradient directly influences the possibility of proximal endoleak occurrence. Developing this hypothesis, in the sense of possible clinical implications and technical advances, study offered the idea that the first contact of contrast and graft occurs suprarenally, e. g. 2-3 cm cranially of the insertion place. As a consequence, in last 10 years, fenestrated grafts with suprarenal insertions have become commercially available (44,45). In this study, a new design of graft for AAA treatment is proposed, for patients with short aneurysmatic neck. Innovation is the annular extension of existing graft that is continuous with the basic graft on the back side, while it is opened on the front and lateral sides, where is also the orifice of renal arteries. If the force of contrast stroke at MDCT exam is marked as F1 in the common concept of insertion place, and as F2 in the proposed graft design with suprarenal insertion, we could say that  $F2 > F1$  and that blood, distally from the suprarenal insertion flows continuously with lower speed (29).

The angle between aneurysm and sagittal plane of aorta in Asian population was significantly larger than in Caucasian. Also, in Asian population there were no patients with contraindication for EVAR (considering mean angle and standard deviation), while in Caucasian population, this number was not statistically significant.

On the contrary to the length of infrarenal aorta, a.i.c. in control group of Caucasian population was statistically significantly longer than in Asian. The mean length of both femoral arteries in white race population was about 14 mm higher than in yellow race, which was statistically significant. There was no significant difference in the length of infrarenal aorta between Asian and Caucasian population, but the linear distance between lower renal artery and bifurcation was significantly higher in European patient group (mean value was about 20 mm longer). This result can be explained by variations in the angle of AAA. Compared to the Hong Kong authors, this study found that linear distance in the white race patients was twice longer (40).

Transverse CT measurements considering flow diameter were performed in advanced CT aortography postprocessing programme, after transverse visualizations in graphic tool „X-section“. This software tool enables contouring flow diameter along complete length and is used for differentiating contrast agent from intraluminal and intramural calcifications, while it enables continuity and accuracy in measuring in each segment.

There was significant difference between the study populations at the level of largest and smallest flow diameter below main trunks of renal arteries (F.d. a.a. 1-2) as well as total diameter of aneurysm with the vessel wall structures at the level of maximum width of aneurysm (R.d. a.a. 3-4). Especially significant was the difference between diameters R.d. a.a. 3-4. To the best of our knowledge, there are no similar results published in literature, nor have these measurements been performed in populations of different races. CT aortographic measurements performed in this study were inspired by problems that doctors who perform EVAR encountered due to incompatibility of the commercially available grafts for the patients of yellow race.

Infrarenal segment of aorta in patients with AAA is a nondilated part. However, the fact that infrarenal segment of aorta in all the subject of Asian population was significantly wider than transverse diameter of control subjects, and additionally, that it is related to the neck which is not dilated in transverse diameter, leads to conclusion that AAA patients in general have wider aneurysmatic neck than infrarenal segment of control subjects (with discrete aortic dilatation or normal findings). Furthermore, the width of this segment may be disposing factor for the development of AAA or/and vice versa, that the development of AAA leads to dilatation of the aneurysmatic neck.

Most of the studies showed that the diameter of abdominal aorta aneurysm grows for 0,08 cm annually, so the most accurate conclusions could be obtained by comparing subjects of the same age (29,40).

Asian population with the presence of aneurysm had significantly higher following diameters F.d. a.i.c. 2-6 i R-d. a.i.c. 1-6. compared to controls, while in F.d. a.i.c 1 there was no significant difference. The most prominent result was found in the transverse diameters F.d. a.c.i 1 of patients and controls. This was the only parameter where there was no difference in patients and controls of the Asian population, while in Caucasian there was a border-line difference. The exact place is just above the bifurcation, where depending on the bifurcation angle, there is a different flow gradient that correlates with the angle of bifurcation, which is lower in the population of yellow race. Additionally, there is a subtle difference between the blood flow velocity of the aorta and proximal parts of iliac arteries. The changes in the vessel wall, as well as propagation of the aneurysm from aorta to iliac arteries, have no direct impact on Fd diameter.

## **9. Possibilities of computer integration in postprocedural evaluation of AAA**

In the preprocedural evaluation of EVAR method, nowadays the use of separate workstation is common. It is often used by vascular surgeons in order to obtain 3D visualization and measuring in individual case, for precise planning and choice of suitable type and dimensions of the graft. Actually, they use specially developed software applications on Windows platform, which are suitable for personal computers; widely spread are „3Mensio surgery“, „TeraRecon“ and „OsiriX“.

This study showed that there is clearly defined user's need to upgrade MDCT aortography postprocessing and integrate it with softwares allowing typization and individualization of stent grafts in each case, as a definite preprocedural finding, similar to stenting procedures in non-vascular interventional radiology.

## **10. Conclusion**

This study showed that modern imaging techniques, particularly high-resolution MDCT diagnostics, discovered fresh and unexpected possibilities to obtain new knowledge on anatomy and morphology of the human body, as well as numerous clinical implications,

applicable to all organs, organic systems, pathologic and pathophysiologic features, and studies in the field of anatomy.

The use of modern low-dose MDCT diagnostics will allow the development of screening programmes for many diseases of enormous diagnostic significance, related to blood vessels, such as coronary disease, cerebrovascular insufficiency, arteriosclerosis etc. In conclusion, the possibilities of correlating anatomy and morphology of different races in the context of a particular disease or planned study are limitless with use of CT diagnostics.

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