

Calcification in Smaller and Larger Infrarenal Aneurysmatic Abdominal Aortas- Differences in Plaque Patterns -

Christina Heilmaier^{1*}, Theodoros Moysidis², Dominik Weishaupt¹ and Knut Kroger²

¹Department for Diagnostic Radiology, Stadtspital Triemli, Zurich, Switzerland

²Clinic for Angiology, HELIOS Klinikum Krefeld, Germany

Abstract

Introduction: Multi-detector computed tomography (MDCT) has established concerning analysis and quantification of vascular calcification in various vessels. We used MDCT for assessment of plaque architecture in smaller (<50 mm) and larger (≥50 mm) infrarenal abdominal aortic aneurysms (AAA).

Material & Methods: Study included 42 patients (<50 mm: n=20; ≥50 mm: n=22), who all underwent MDCT. Two readers performed quantitative and qualitative analysis, including calculation of calcium scores and measurement of plaque size and thickness. Calcium scores were calculated; t-tests were done to look for statistical differences between calcium scores and density ratios (=calcium score/aortic cross-sectional area). Cardiovascular risk factors were compared in patients with smaller and larger aneurysms.

Results: Calcium scores significantly rose with AAA diameter (mean value in smaller aneurysms: 488.8±375.7; in larger aneurysms: 1,687 ± 923; p< 0.001), but no considerable difference was seen in density ratios. Plaque architecture changed: while larger aneurysms mainly contained thin (1 or 2 mm) or intermediate (3 or 4 mm) plaques in circular or mixed grouped-circular arrangement, smaller aneurysms had thicker (≥5 mm) plaques that covered less than half of vessel circumference. On average, subjects had more than 2 cardiovascular risk factors with hypertension being the most frequent one. Number of cardiovascular risk factors present increased with AAA size, in larger aneurysms patients had 3.0 ± 1.2 risk factors compared to a mean of 1.8 ± 1.1 in smaller aneurysms (p=0.001).

Conclusion: Plaque pattern is different in smaller and larger AAA with thicker and more grouped plaques present in smaller AAA, which might have a stabilizing function on vessel wall.

Keywords: Multi-detector computed tomography; Plaque patterns

Introduction

The incidence of abdominal aortic aneurysms (AAAs) has been continuously growing within the last decades [1] with most aneurysms being located below the outflow of the renal arteries (infra renal aneurysms). Per definition an aortic diameter of 30 mm or more constitutes an AAA [2,3], which can be described in terms of its location (suprarenal or infra renal), size (small or large), and morphologic appearance (fusiform or saccular) [1]. AAAs are found considerably more often in men (men:women = 9:1), who usually develop AAAs 10 years earlier than women [4]. In general the prevalence of AAAs increases by approximately 6% per decade [1] and about 1% of men aged 55 to 64 have a clinical relevant AAA (diameter ≥ 40 mm) [5]. Besides male sex a couple of risk factors for AAA formation have been established including smoking, hypertension, age, hyperlipidaemia as well as family history for aneurysms or atherosclerotic disease [6,7]. As demonstrated by several studies subjects with AAAs frequently suffer from comorbidities such as coronary heart disease, stroke and lower limb ischemia [8,9].

Albeit AAA pathogenesis is only partially elucidated yet, mainly three pathophysiologic mechanisms seem to be responsible for development and progression of AAAs: inflammation, proteolysis with matrix degradation and smooth muscle cell apoptosis [1,7]. Due to the fact that atherosclerosis shares similar pathological characteristics and risk factors [10,11], controversy exists whether AAA and atherosclerosis are separate diseases or not [12].

For several vascular beds, including the coronary arteries and the thoracic aorta, a positive relationship of the extent of vessel calcification and the risk of cardiovascular events was proven [13,14]. With regard

to the abdominal aorta plaques have only been assessed in patients suffering from chronic kidney disease, who inherit a high prevalence of vascular calcification [15]. However, detailed evaluation of plaque patterns in subjects with AAA and normal kidney function might improve understanding of processes involved in AAA pathogenesis, which might be useful for development of novel strategies and potential treatments. The aim of our study therefore was to examine the association of the degree and pattern of vascular calcification and infra renal AAA diameter by using Multi-Detector Computed Tomography (MDCT).

Methods

Study group

The study was conducted in accordance with the Helsinki Declaration and informed consent was obtained from all subjects. The focus of this study was evaluation of plaque pattern in AAAs by using Multi-Detector Computed Tomography (MDCT). Exclusion criteria were suprarenal AAAs, prior open surgery or intervention with

***Corresponding author:** Christina Heilmaier, Department for Diagnostic Radiology, Stadtspital Triemli, 8063 Zurich, Switzerland, Tel: 0041-44-4661452; E-mail: christina.heilmaier@uni-due.de

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insertion of stent or vessel prosthesis, or chronic kidney disease. To identify corresponding patients we cross-referenced our institutional imaging with the hospital's report database and found 185 subjects (118 men, 67 women), who underwent MDCT of the abdominal aorta between January 2010 and July 2011 for different clinical indication. Of these 185 patients only 42 (23%) met all aforementioned criteria, therefore, the focus population included 42 patients (29 men, 13 women) with a mean age of 72.7 ± 8.5 (range, 54-85 years).

Of the 42 subjects 20 had an AAA with a diameter smaller than 50 mm. This subgroup consisted of 14 men and 6 women with a mean age of 72.3 ± 8.1 years (range, 54-83). The other subgroup included all patients with an aneurysm diameter exceeding 50 mm and was composed of 15 men and 7 women with a mean age of 73.0 ± 9.0 years (range, 57-85).

Cardiovascular risk factors are known to have an influence on aneurysm formation and therefore were assessed by using standardized questionnaires and/or medical data available in the hospital's database.

Definition of cardiovascular risk factors was as follows:

Hypertension: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg and/or current use of anti-hypertensive medication.

Diabetes mellitus: fasting plasma glucose > 126 mg/dl or current use of hypoglycemic medication.

Hyperlipidemia: total to HDL cholesterol ratio > 5 or current use of cholesterol level lowering drugs.

Adiposity: Body Mass Index (BMI) (weight in kilograms/height in meters squared) > 25 .

Smoker: current smoker or history of nicotine abuse (> 10 pack years).

Distribution of cardiovascular risk factors in the patient collective is summarized in Table 1.

MDCT Imaging

All MDCT examinations were performed on a 256-detector row CT scanner (Brilliance iCT, Philips, Hamburg, Germany). Subjects underwent either single-phase (27/42; 64%) or dual-phase (15/42; 36%) MDCT scans of the abdomen timed to capture the arterial and (in dual-phase scans) the portal venous phase of the contrast medium. As a consequence of known non-life-threatening contrast reactions to iodine contrast media prophylactic medication was given in 3/42 patients (7%) before the scan was begun.

During preparation of MDCT examination a 20-22 gauge catheter was placed in an antecubital vein and connected with an automatic injector (Medrad Stellant, Pittsburgh, PA, USA). The flow rate was set at 4 ml/s and a total of 120 ml of nonionic contrast medium (Imeron, Bracco Imaging, Konstanz, Germany; 350 mg iodine per mL) was administered, followed by a 20 ml flush of saline. The bolus-tracking technique was used to assess time delay required after application of the contrast medium to achieve optimal intraluminal contrast in the

arterial phase; the portal venous scan was started 60 s after injection of the contrast medium.

Scanner settings were kept identical in all patients and included a X-ray tube voltage of 120 kV, a mean tube current of 150 mA, and a pitch of 1.2. Image reconstructions were performed in the transverse section with a nominal slice thickness of 4.5 mm, an interval of 3.4 mm and a matrix size of 512 x 512.

Image Analysis

An interactive PACS workstation (OsiriX, Version 4.1.2, 64-bit) was used for quantitative and qualitative assessment of imaging datasets, which was done in a consensus panel by two readers (C.H., K.K.). If considered useful, readers were allowed to change window centers and level setting to their own preferences. Both readers were blinded to all clinical data and analysis took place in random order.

The first step was to determine the expansion of the aneurysm and to measure the cross-sectional area of the aneurysmatic aorta at each slice level. Afterwards quantitative evaluation of atherosclerotic plaques within the aneurysm was performed, which involved all plaques $\geq 1\text{mm}^2$ with a density of ≥ 130 Hounsfield Units (HU). Analysis included measurement of the plaque's (maximum) thickness and size, which was recorded by using the following subsegmentation: thickness, 1 or 2 mm, 3 or 4 mm, or > 5 mm; size, 1-20 mm^2 , 21-50 mm^2 , 51-100 mm^2 or > 100 mm^2 .

Thereafter readers were asked to qualitatively assess plaque pattern by describing the most apparent arrangement of the plaques. For that purpose, 3 different categories were provided: (1) circular (= plaques envelop (almost) the whole vessel circumference), (2) grouped (= plaques conglomerate at certain points of vessel wall and involve less than half of the vessel circumference), and (3) mixture of both (= some slices show circular pattern, while others have mainly grouped plaques).

Length of AAA was approximated by determining slice position of the beginning and end of aneurysm multiplied with slice thickness.

Statistics

Statistical analysis was done by employing commercially available software (SPSS, release 20.0; SPSS, Chicago, IL, USA). In each subject plaque sizes were summed up to determine the calcium score, which was given as mean $\pm$ standard deviations. Moreover, plaque density, which is the ratio of calcium score and aneurysm cross-sectional area, was calculated for each patient. To check for significant differences between calcium scores, plaque density and the number of plaques in patients with smaller (< 50 mm) and larger (≥ 50 mm) aneurysms the t-test was applied. Moreover, the t-test was used to evaluate differences in the distribution of cardiovascular risk factors in small (< 50 mm) and large aneurysms (≥ 50 mm). A p-value < 0.05 was considered to represent statistical significance.

Results

Clinical and MDCT data of all patients was completely available and of adequate quality; therefore, analysis encompassed 42 subjects. Two subjects suffered from a minor contrast reaction (rash) after

Gender	Diabetes	Hypertension	Smoking	Hyperlipidemia	Adiposity
Women (n= 13)	4 (31%)	11 (85%)	5 (38%)	5 (38%)	7 (54%)
Men (n= 29)	4 (14%)	28 (97%)	12 (41%)	13 (45%)	10 (34%)
Total	8 (19%)	39 (93%)	17 (40%)	18 (43%)	17 (40%)

Table 1: Distribution of cardiovascular risk factors in the patient cohort, separated for women and men.

Plaque thickness	1 or 2 mm				3 or 4 mm				≥ 5 mm			
Plaque size in mm ²	1-20	21- 50	51-100	> 100	1-20	21-50	51-100	> 100	1-20	21-50	51-100	> 100
AAA < 50 mm	3.8	2.9	1.3	1.6	1.2	1.2	1.4	0.4	0.1	0.6	0.6	0.2
AAA ≥ 50 mm	7.8	8.2	3.3	1.5	2.1	3.6	1.2	0.04	0	0.2	0.2	0.04
Mean	5.9	5.7	2.3	1.5	1.7	2.5	1.3	0.2	0.04	0.4	0.4	0.1

Table 2. Plaque characteristics change with increasing aneurysm diameter: the first row displays plaque thickness (1 or 2 mm, 3 or 4 mm, > 5 mm); in the second row plaques are further separated due to their size (1-20 mm², 21-50 mm², 51-100 mm², > 100 mm²). In the third row the mean number of certain plaques patterns per patient is given as present in smaller AAA (>50 mm): e.g. each patient had on average 3.8 plaques with a thickness of 1 or 2 mm and a size of 1- 20 mm². The forth row provides this data for patients with larger aneurysms and the last row shows mean data of the whole study group.

AAA = abdominal aortic aneurysm

Diameter	Diabetes	Hypertension	Smoking	Hyperlipidemia	Adiposity
< 50 mm (n= 20)	3 (15%)	18 (90%)	5 (25%)	4 (20%)	5 (25%)
≥ 50 mm (n= 22)	7 (25%)	21 (95%)	12 (55%)	14 (64%)*	12 (55%)

Table 3. Distribution of cardiovascular risk factors in small (< 50 mm) and large (≥ 50 mm) abdominal aortic aneurysms.

* indicates a statistical significant difference regarding both groups (< 50 mm versus ≥ 50 mm)

MDCT scanning, which quickly resolved after application of anti-allergic medication.

Abdominal Aortic Aneurysm (AAA) diameter ranged from 32 mm to 80 mm with a mean diameter of 55 ± 15 mm. On average the AAA had a cranio-caudal length of 73 mm with a minimum of 18 mm and a maximum of 106 mm and involved the aortic bifurcation in 9/42 subjects (21%). All patients showed AAA calcifications. Mean calcium score measured within the AAA was $1,117 \pm 932$, varying between 70 and 3,357. Calcium score significantly rose with AAA diameter ($p < 0.001$): patients with a diameter less than 50 mm mainly had calcium scores < 1,000 (mean value, 488.8 ± 375.7), while in those with diameter ≥ 50 mm a mean score of $1,687 \pm 923$ was found (Figure 1) ($p < 0.001$).

In addition to that plaque pattern changed with increasing AAA diameter (Table 2): in AAA ≥ 50 mm significantly more thin plaques (thickness 1 or 2 mm) with a size < 100 mm² were demonstrated when compared to subjects with smaller aneurysms ($p < 0.001$). Moreover, larger AAA showed more plaques of intermediate thickness and small size (3 or 4 mm, < 50 mm²) ($p < 0.001$), whereas thick plaques (≥ 5 mm) of all sizes (1 - > 100 mm²) were predominantly noticed in small aneurysms; however, the latter did not reach statistical significance ($p = 0.12-0.27$).

Plaque density, which refers to the ratio of calcium score and aneurysm size (cross-sectional area) was comparable in patients with different AAA diameter (< 50 mm, 0.03; ≥ 50 mm, 0.04) ($p = 0.465$).

Qualitative analysis of plaque pattern revealed that the majority of subjects with AAA < 50 mm had grouped plaques, which covered less than half of the aortic circumference (18/20 patients; 90%) (Figure 2). Contrary to that in 7/22 (32%) patients with AAA ≥ 50 mm plaques were circularly arranged, enveloping the whole vessel circumference with only small distances between the plaques (Figure 3). A mixture of both patterns was present in 13/22 (59%) subjects with AAA ≥ 50 mm.

On average, each patient displayed 2.4 ± 1.3 risk factors. The number of risk factors was significantly different in patients with smaller (< 50 mm) aneurysms (1.8 ± 1.1) compared to subjects with larger (≥ 50 mm) aneurysms (3.0 ± 1.2) ($p = 0.001$) (Table 3). Hypertension was present in 39/42 patients (93%) and was found considerably more often when compared to the other cardiovascular risk factors (for all, $p < 0.001$). Within the whole patient group there

was no statistical significant difference between the frequency of adiposity, diabetes, hyperlipidaemia, and smoking ($p = 0.07-0.83$). However, analysis of risk factor distribution in subjects with small (< 50 mm) and large aneurysms (≥ 50 mm) revealed higher prevalence of hyperlipidemia, adiposity, diabetes, and smoking in the large aneurysm group, but results only reached statistical significance with regard to hyperlipidemia ($p = 0.004$).

Discussion

Especially in older men Abdominal Aortic Aneurysms (AAAs) have a high prevalence and remain one of the leading causes of death in developed countries, even though technical improvements in diagnostic and therapeutic procedures as well as in the peri-operative care have been evolved within the last years. Due to the fact that atherosclerosis is strongly associated with AAA formation and progression, we aimed to qualitatively and quantitatively analyze plaque patterns as present in 42 subjects with infra renal AAAs. The main findings of our study were:

Calcium score significantly increases with AAA diameter, but plaque density is basically unchanged.

Larger aneurysms (≥ 50 mm) predominantly contain thin (1 or 2 mm) or intermediate (3 or 4 mm) plaques, mainly arranged in a circular or a mixed grouped-circular pattern.

Thick (≥ 5 mm) plaques of all sizes covering less than half of the vessel circumference were more often found in small aneurysms (< 50 mm) when compared to larger aneurysms.

On average, each subject had more than 2 cardiovascular risk factors with hypertension being the most frequent one.

Significantly more risk factors were found in subjects with large aneurysms (≥ 50 mm) when compared to those with smaller aneurysms (< 50 mm).

Even though already in the 19th century Rokitsky and Virchow figured out that some mechanisms involved in plaque development are similar to that of bone formation [16], pathogenesis of AAA formation and progression is only partially elucidated yet. Atherosclerosis and AAA are strongly associated and there is controversy as to this association is causal or results from shared environmental and genetic risk factors. Based on the premise of a causative role of atherosclerosis in AAA formation arterial remodelling appears to be the central

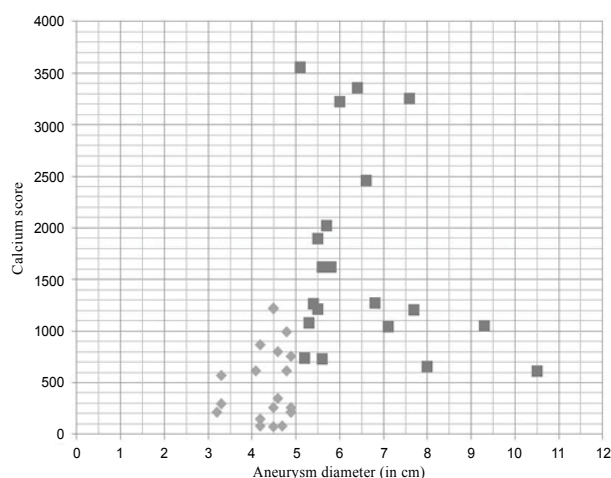


Figure 1: Relationship of aneurysm diameter and calcium score: most subjects with large aneurysms (≥ 50 mm) have calcium scores $> 1,000$.



Figure 2: In larger aneurysms (≥ 50 mm) plaques often show a circular pattern and cover almost the whole vessel circumference.



Figure 3: In small aneurysms (< 50 mm) plaques are often grouped and cover less than half of the vessel circumference.

process as proven by a large body of data [12,17]. In response to shear stress alterations in arterial luminal stenosis compensatory processes such as extracellular matrix remodelling take place in the media. By expansion of the artery lumen diameter as well as shear stresses should be normalised [17]. To gain further insight in these processes recent trials have used advanced Computational Fluid Dynamics (CFD) techniques in order to simulate hemodynamic pathophysiology in different vascular disorders including AAA [18-20]. They found out that the maximum wall shear stress at the site of highest enlargement in chronic type B aortic dissections was considerably lower than in normal aortas, which initiated an up-regulation of endothelial cell genes with progression of atherosclerosis consequently [21], coming along with aortic wall weakening, aneurysm growth and increasing the chance of aneurysm rupture [22]. It therefore will be the task of future studies to combine information from qualitative and quantitative analysis of plaque patterns as performed in our study with results from CFD techniques to further elucidate pathophysiologic processes taking place in aneurysm formation possible finding warning signs indicating disease progression.

Irrespective of the underlying pathophysiological process vessel calcification is an important feature in AAAs and at least one plaque was found in each patient of our study group. We analyzed the amount and distribution of calcifications within AAAs in subjects with normal kidney function, which as far as we know has never been done before. Based on our findings that calcium scores considerably rose with aneurysm diameter but plaque ratio was almost unchanged in small (< 50 mm) and large aneurysms (≥ 50 mm), argues for the hypothesis that plaques break apart during aneurysm development. The thin and on the whole smaller-sized plaques in larger aneurysms and their often circular arrangement compared to thick and grouped plaques in small aneurysms support this hypothesis because they may be the result from thicker plaques in smaller aneurysms that had been broken apart coming along with further vessel enlargement. In addition to that the observation of thicker and larger plaques in the infrarenal segment of normal aortas, indicating a protective role of plaques with respect to aneurysm formation [23,24], further suggests plaque rupture and dispersion, when disease begins.

The strong association of atherosclerosis and AAA development is also stressed by the high prevalence of cardiovascular risk factors and their positive relationship with aneurysm diameter (on average each patient with an aneurysm ≥ 50 mm displayed 3 risk factors). Most subjects in our study were treated with antihypertensive drugs or had pathological diastolic or systolic blood values during examination, leading to a considerable higher prevalence of hypertension than described in other studies [25]. Prevalence of hyperlipidemia was 43 % in our study, which is comparable to data published elsewhere [26]. Interestingly, hyperlipidemia was the only risk factor, which positively correlated with aneurysm diameter. Given that smoking is known to be the strongest independent risk factor for AAA development with a prevalence of 90% in other studies [6], it was surprising that only 40% of our subjects had current or previous nicotine abuse. Contrary to that the low rate of diabetes mellitus is in line with studies, which reported on a negative association of AAA and diabetes [12].

We are aware of the following limitations: first, we performed the present study with a relatively small patient group, thus, results might not be representative, especially with regard to the distribution of risk factors. Here, further studies are required. Second, measurement of aortic diameter was done in the axial plane, although recent data showed overestimation of aneurysm size when measured on axial

MDCT slices, recommending application of the more reproducible orthogonal method [27]. For the same reason measurements of aneurysm length might not have been optimal and might have led to underestimation; however, we did not encounter significant vessel kinking, so that our approach appeared to be the most practical way. Third, we did not consider subject's size, albeit it was proven that arterial size measured as a diameter related to patient's size was larger in men [28]. Forth, definition of hyperlipidemia might not be optimal, given that only low levels of high-density lipoprotein seem to play a role in AAA formation, while concentrations of low-density lipoprotein and triglycerides are not associated with the presence of AAA [26]. Fifth, random errors in computed tomography measurements of plaque thickness and size as well as missing of small plaques might have happened, although we tried to minimize these errors by performing a consensus reading of two experienced readers. However, especially with regard to the overlooking of small plaques it seems unlikely that such errors considerably influence our results. Moreover, our study compared plaque patterns in smaller and larger aneurysms, but we did not consider their morphology (e.g. fusiform or saccular), which might have also influenced plaque patterns. Finally, detailed statistics such as multiple logistic regression models or adjustment e.g. for age or sex, were not done albeit a strong predilection for men is well known. However, our study design was mainly descriptive.

In conclusion, our study was the first to assess amount, pattern, and distribution of plaques in AAAs, showing differences between smaller (< 50 mm) and larger aneurysm (≥ 50 mm). To gain deeper insight in pathophysiological processes and in the influence of cardiovascular risk factors in AAA formation further studies are required, ideally combined with newer techniques such as advanced computational fluid dynamics.

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