ELASTIN AND COLLAGEN FIBRES ALTERATIONS FOR ABDOMINAL AORTIC ANEURYSMS POPULATION WITH CONSTANT MAXIMUM DIAMETER SIZE

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Abstract

Development of abdominal aortic aneurysm (AAA) is a dynamic process proceeding as a result of the multi-factor pathological remodelling of elastin and collagen fibres, results an aneurysm expansion. In clinical practice, development of AAA is identified with aneurysm growth. Hence, the aim of this paper is to propose a taxonomy of load-bearing structural components alterations for AAA with relatively constant maximum diameter (average diameter 6.9±0.8 cm). Structural investigations of normal (n=47) and aneurismal (n=46) vessels were carried out on the basis of histological and ultrastructural examinations. The histological preparations were subjected to histometric evaluation; the number of collagen and elastin fibres and additionally the thickness of the particular vascular wall layers. A qualitative analysis of the abdominal aortic wall, mainly estimation of fibres arrangement, based on histological and ultrastructural (SEM) examinations were additionally performed. Using a cluster analysis, three stages of load-bearing fibres alterations for AAA population were distinguished. The clusters were systematized according to NAA results. For AAA population with relatively constant maximum diameter in the first stage of load-bearing fibres remodeling was observed a substantial loss of elastin fibres. The second stage is characterized by an increase in the number of collagen fibres. In the final stage the number of collagen is dramatically reduced. Presented results provide evidence to risk of AAA rupture is not connected with AAA size but a remodelling of extracellular matrix proteins. The remodelling is accompanied by changes in the AAA wall thickness, which should be taken into consideration when evaluating the degree of advancement of this disease.

Keywords: *abdominal aorta, aneurysm, elastin fibres, collagen fibres, maximum diameter size, cluster analysis*

[Engineering of Biomaterials, 102, (2011), 2-6]

Introduction

An abdominal aortic aneurysm (AAA) is a permanent and progressive dilatation of the abdominal aorta. The AAA occurs mainly in the infrarenal part of the abdominal aorta [1,2]. In the second half of the 20th century a dramatic increase (over sevenfold) in abdominal aortic aneurysm incidence occurred [3] and in the last 30 years just in the Eastern hemisphere the incidence has tripled [4]. The current number of persons with the AAA is not precisely known. The prevalence of the AAA in the different parts of the world largely depends on the age structure and the criteria used for classifying pathological changes. Hence AAA incidence may range from 1.2% to 27% [5]. Abdominal aortic aneurysm is a serious and potentially lethal condition. Aneurysm-associated mortality is the 13th most common cause of death in the western world [6,7]. Ruptured abdominal aortic aneurysm is associated with 50% to 90% mortality and most patients die before reaching hospital [8]. The frequency of AAA rupture has not decreased over time [9,10].

An abdominal aortic aneurysm arises as a result of the multifactorial pathologic remodelling of the aorta's connective tissue [11]. Many researches done in recent years indicate that the initiation, development and rupture of the aneurysm are caused by the degradation of the load-bearing structural components of an aortic wall, i.e. elastin and collagen fibres [12-16], induced by proteolytic enzymes from the endopeptidase family, represented mainly by matrix metalloproteinases (MMPs) [1,17]. It has been found a variable degree of reduction in the content of elastic fibres in the walls of abdominal aortic aneurysms [18-22]. The amount of collagen fibres in the AAA wall may increase [20,23], remain unchanged [24] or decrease [1,25]. The variety of the connective tissues fibres content may be justified by different levels of aneurysm development. Thompson and Baxter [17,26] were the first to describe the structural alterations taking place in the abdominal aortic wall in the course of growth of the aneurysm, because the AAA maximum diameter size is used in clinical practice as an indication for aneurysm surgery [9] since it is thought that the probability of rupture of an AAA increases with its diameter [1,27]. However, as research shows, AAA may rupture regardless of the vessel's diameter. The aneurysm may rupture even in the case of vessels with a diameter less than 40 mm in which hypothetically the risk is the lowest [8], while there are cases when aneurysms expand, reaching sizes larger than 80 mm without any signs of rupturing [28]. Hence, the aim of this paper is to propose a classification (taxonomy) of elastin and collagen fibres alterations for abdominal aortic aneurysms with relatively constant maximum diameter due to eliminate grow factor in analysis. We advance a hypothesis that for AAAs with comparable maximum diameter, degree of load-bearing structural components alterations may be significantly different.

Material and methods

Experimental material

The experimental material was obtained at surgical infrarenal abdominal aorta aneurysm walls (AAA) resection and normal abdominal aortas (NAA) autopsy. The AAAs walls were intraoperatively harvested from 46 patients (34 male, 12 female, average age: 68±9 years). Average diameter of AAA were relatively constant and amounted to 6.9±0.8 cm. Due to restrictions of surgical AAA resection and to avoid the differences between parts of the aneurysm, vascular walls samples were taken from the anterior region of the AAAs only. The NAA walls were taken during autopsies from 47 age-matched donors (39 male, 8 female, average age: 66±11 years, average diameter: 2.4±0.5 cm).

Histological and ultrastructural examinations

For the purpose of histological analysis, vascular wall segments 10 mm^2 in area were fixed in a 4% buffered formalin solution for 48 hours, washed under running water, dehydrated through ascending grades of alcohol, cleared in methyl benzoate and xylene, consecutively, and then embedded in paraffin wax, according to routine techniques. The paraffin-embedded tissues were sectioned into 5 μm thickness. The slides were stained routinely with hematoxylin and eosin according to Delafield, Verhoff's and van Gieson method. The sections stained with Verhoff's and Van Gieson's method were subjected to histometric analysis. The collagen and elastin fibres were counted. A single slide was divided into 10 sections along which all the fibres that the drawn lines intersected were counted. Measurements of the overall wall thickness of the investigated vessels and the thickness of the layers (the intima, the media and the adventitia) were performed. The results of the histometric calculations were averaged for each investigated preparation. The stained preparations were viewed with a light microscope (*AxioImager M1m, Zeiss)*.

Aortic wall fragments 10 mm^2 in area constituted the material for ultrastructural examinations. The experimental material was fixed in a 2.5% phosphate-buffered glutaraldehyde, dehydrated in an acetone series, then dried and stuck onto microscope stages, using carbon glue. For the purpose of ultrastructural analysis the previously dried material had to be sprayed with gold. The preparations were viewed under a scanning electron microscope (*Leo 435 VP, Zeiss*) and the image was recorded in high vacuum.

Statistical analysis

The histometric results were subjected to statistical analysis (*Statistica 8.0, StatSoft*). The results were presented in the form of averages with standard deviations (X ± SD). The statistical analysis of the data was based on Student's t-test for independent samples. The statistical tests were carried out to a significance level (p) of 0.05.

Cluster analysis

The cluster analysis (*Statistica 8.0, StatSoft*) was used to group into sets the histometric measurements for taxonomic purposes. This method enables to group the results into sets (clusters) comprising data with the highest degree of similarity and maximally different from one to another. Number of sets for the AAA population were adopted as 3 likewise like Thompson and Baxter findings [17,26].

Results

Histological examinations

No significant pathological changes were found in the histological images of the healthy abdominal aortic walls. No atrophy or significant structural disorders were observed in them. Numerous elastin fibres (E) were present within the aortic media of the NAA walls (FIG. 1a,b).

TABLE 1. Average number of elastin and collagen fibres in walls of normal abdominal aortas (NAA) and abdominal aortic aneurysms (AAA).

		Average	SD
NAA	Elastin fibres (E)	54.2	9.8
	Collagen fibres (K)	83.8	10.9
AAA	Elastin fibres (E)	9.1	6.2
	Collagen fibres (K)	45.8	38.4

The collagen fibres (K) observed in both the aortic media and the adventitia were morphologically normal (wavy). Their number varied between the preparations, but the differences were not considerable (TABLE 1).

In the histological images of the abdominal aortic aneurysm walls numerous pathological changes were discovered (FIG. 1). All the abdominal aortic aneurysm walls were characterized by a considerable reduction in the number of elastin fibres (E) in the media (TABLE 1). Extremely variable amount of elastin fibres (E) randomly occurred in the full histological picture of the aneurysm walls (FIG. 1c). In a few cases, elastin fibres fragmentation was observed (FIG. 1d). The measurements of elastin fibres number were not performed for these cases. The number of collagen fibres (K) in the adnominal aortic aneurysm walls was found to be reduced, but the size of the reduction varied between individual cases. The arrangement of collagen fibres in the media of the AAA walls was disordered.

On average, the reduction in the number of elastin and collagen fibres in the AAA walls, in comparison with the results obtained for the normal abdominal aortas, was statistically significant with significance levels p=0.000001 and p=0.0059, respectively.

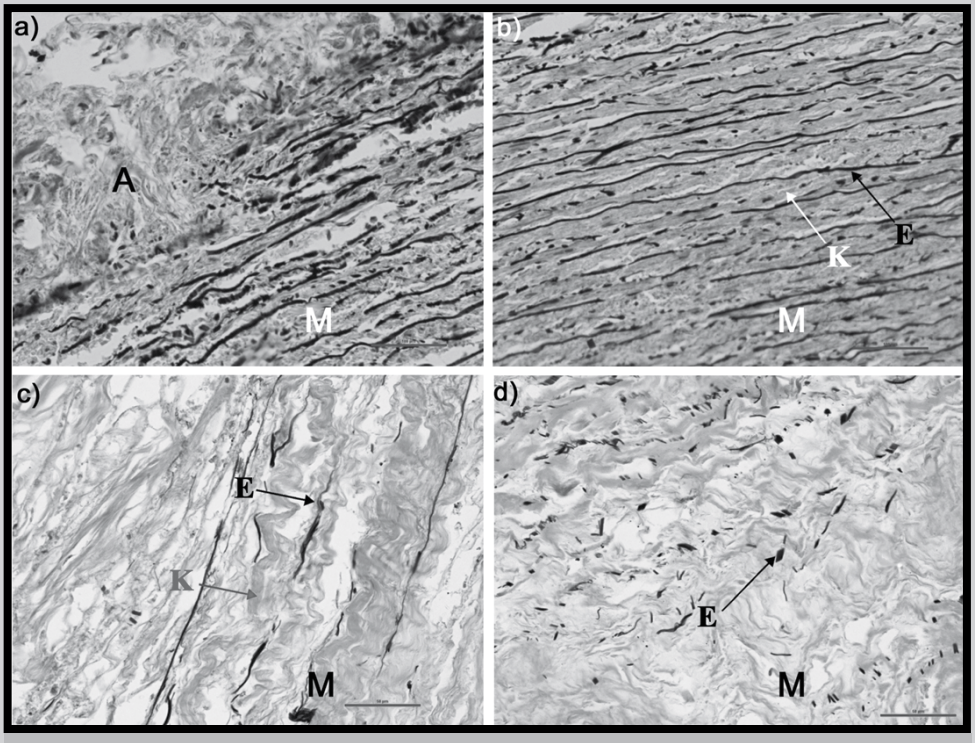

FIG. 1. Histological images of normal abdominal aortic walls (NAA) and abdominal aortic aneurysm walls (AAA): a) NAA wall (A – adventitia, M – media) according Verhoff's stain, b) elastin (E) and collagen (K) fibres in histological image of NAA wall media (Verhoff's stain), c) single elastin fibre (E) in AAA wall (Van Gieson's stain), d) fragmentation of elastin fibres (E) in AAA wall media (Van Gieson's stain). Reprinted with permission from [29].

TABLE 2. Wall thickness of normal abdominal aortas (NAA) and abdominal aortic aneurysms (AAA) and that of their individual constitutive layers.

		Average [μm]	SD [μm]
NAA	Intima (I)	272	81
	Media (M)	722	202
	Adventitia (A)	202	52
	Overall wall thickness	**1196**	**335**
AAA	Intima (I)	63	23
	Media (M)	674	347
	Adventitia (A)	194	105
	Overall wall thickness	**931**	**475**

All the layers of the abdominal aortic aneurysm walls were normally formed. The boundaries between the layers were distinct whereby the thickness of the latter could be precisely determined (TABLE 2). In most cases, the boundaries between the AAA wall layers had become blurred. Disorders in the laminar structure were observed. The thickness of the particular layers in the abdominal aortic aneurysm walls was difficult to measure. It could be measured only in the cases when their boundaries were discernible in the histological images (TABLE 2).

The statistical analysis showed that the wall thickness of the aneurysms becomes reduced relative to that of the normal abdominal aortas (p=0.02). The largest reduction (about 80% as regards average values) occurs in the case of the tunica intima (p=0.0015).

Ultrastructural examinations

The characteristic morphologically normal arrangement of fibres (forming a three-dimensional network) was observed in SEM images of the normal abdominal aortic walls (FIG. 2a). SEM images of the abdominal aortic aneurysm walls showed that the shape of collagen fibres in the adventitia was disordered and in most of the examined cases it was almost straight-linear (FIG. 2b).

Load-bearing fibres alterations for AAAs with relatively constant diameter

AAAs population with relatively constant diameter had to be grouped into sets on the basis of the histometric measurements by used the cluster analysis. The sets were systematized and normalized to NAA results. Three main stages of load-bearing fibres remodeling for abdominal aortic aneurysm population with relatively constant diameter were distinguished by different structural parameters (FIG. 3). No differences were observed between AAA diameter in particular sets.

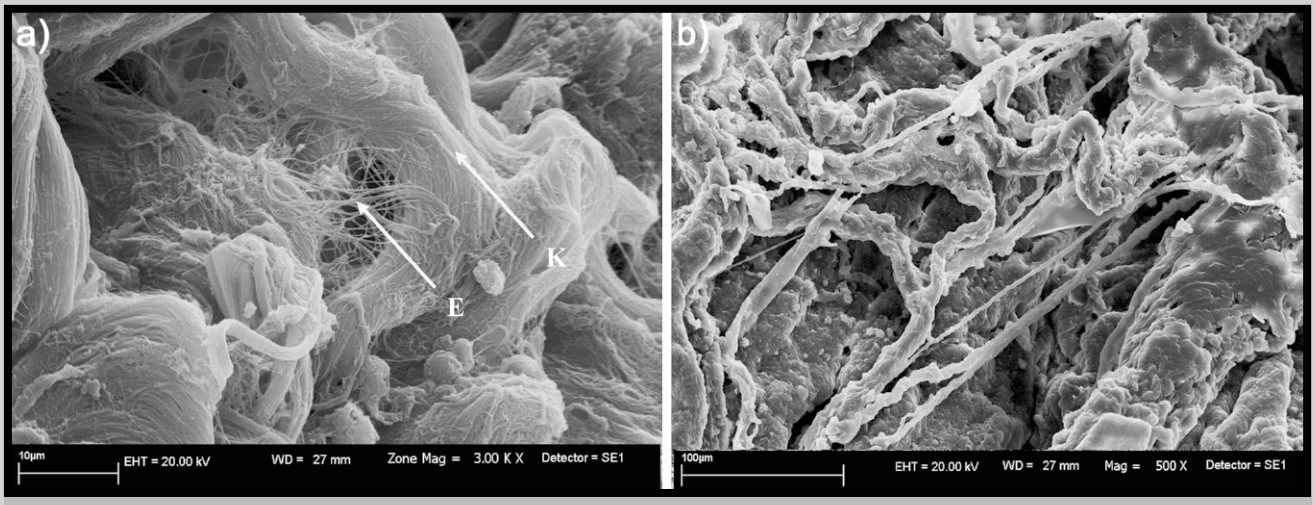

FIG. 2. SEM images of walls of normal abdominal aortas (NAA) and abdominal aortic aneurysms (AAA): a) elastin (E) and collagen (K) fibres in NAA wall media; b) straight-linear shape of collagen fibres in adventitia of AAA. Reprinted with permission from [29].

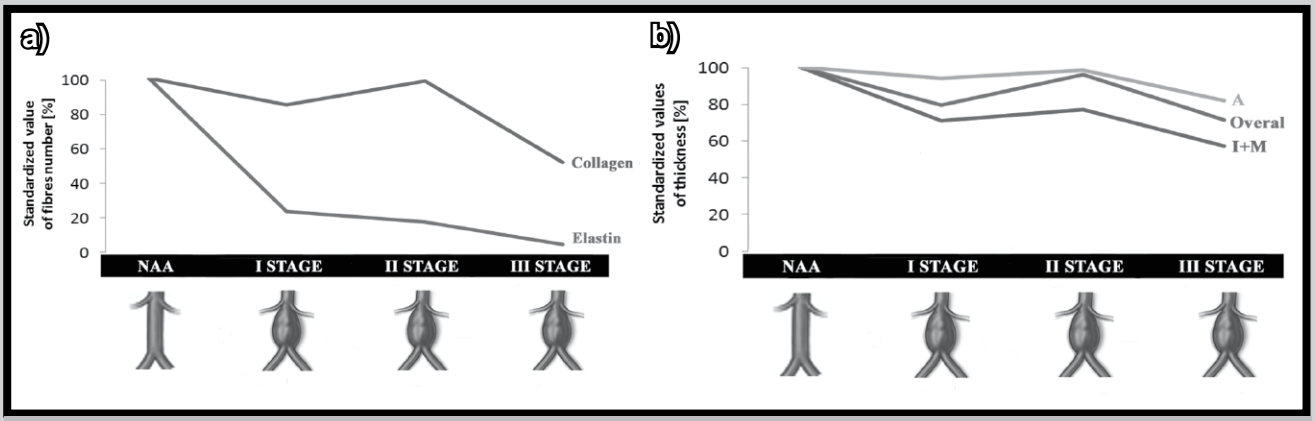

FIG. 3. Structural parameters alterations for AAAs population with relatively constant diameter: a) load-bearing fibres and b) thickness of adventitia (A), media (M) and overall aortic wall (Overall).

The walls of the abdominal aortic aneurysms in the first stage are characterized by a considerable reduction in the number of elastin fibres relative to their number in the walls of the normal aortas. No significant reduction in the number of collagen fibres was observed. No distinct anomalies were found in the walls of the aneurysms. The thickness of all the aneurysm wall layers underwent insignificant reduction (the intima was still discernible). The second stage is characterized by inflammatory infiltrations and numerous newly formed vasa vasorum (neovascularization) were commonly observed in the histological and SEM images of the walls of the aneurysms. An increase in the number of collagen fibres relative to their number in the preceding stage was observed. As the activity of the collagen fibres and their production intensify, the thickness of the AAA wall increases (mainly in adventitia and media part). However, no intima was found in the histological images of the aneurysm walls. In the final stage the number of collagen is dramatically reduced. In most of the analyzed cases, the spaces between collagen fibres were filled with thrombuses. The wall thickness was much reduced in comparison with the preceding stage.

Discussion

The development of the abdominal aortic aneurysm leading to the rupture of its wall can be considered as a classical case of material failure due to excessive loading, the insufficient strength of the material or the two factors combined [30]. The underlying process is the remodelling of the structural elements which bear mechanical loads, i.e. elastin and collagen fibres [14-16]. It has been found that the concentration of elastic fibres in the walls of abdominal aortic aneurysms undergoes considerable reduction [18-22]. Roughly about 63-92% of the elastin fibres are lost [31]. The amounts of collagen fibres in the AAA wall may increase [20,23], remain unchanged [24] or decrease [1,25]. The discrepancies between the results obtained by the cited authors are justified since remodelling which takes place in the abdominal aortic aneurysm wall is considered as a dynamic process. According to the best of our knowledge the unique AAA development identification model were proposed by Thompson and Baxter [17,26]. They proposed three-stage taxonomy of characteristic structural changes in relation to the aneurysm's maximum diameter. We propose a new classification of load-bearing elements alteration based on histometric measurements carried out for a large group of asymptomatic abdominal aneurysm with a constant maximum diameter (average diameter 6.9±0.8 cm). We no longer take into account the maximum aneurysm diameter as the main aneurysm development parameter, but degree of elastin and collagen remodeling. First elastin fibres undergo fragmentation and their concentration in the aortic wall media decreases. As a result of the degradation of the elastin fibres in the media the vessel's capacity to carry tensile stresses decreases and collagen production is triggered. In the second stage, for the sake of progressive elastin fibres degradations collagen fibres behave compensatory and the taking over of the elastin fibres' load bearing function by them. The third stage is characterized by decreases of the collagen fibres content in the vascular wall so does the latter's tensile strength, which is the main cause of rupture of the aneurysm. This corroborates the thesis proposed earlier that the loss of elastin fibres in the AAA wall is connected mainly with the development of the aneurysm while the breaking of AAA wall continuity is linked with the degradation of collagen fibres [25,32,33]. Presented results provide evidence to risk of AAA rupture is not connected with AAA size but a remodelling of extracellular matrix proteins.

The presented results indicate that the thickness of the aneurysm wall and that of its individual layers change with the changes taking place in the wall structure. Measurements of intima – media thickness is existing in clinical practise as predictor of arteriosclerosis diagnosis and development [34]. In clinical conditions vascular wall thickness can be measured (similarly as the AAA diameter) using non-invasive diagnostic techniques (e.g. ultrasonography or computer tomography). The use of the new parameter (AAA wall thickness) for evaluating the degree of advancement of an aneurysm requires further research, although, as indicated by using cluster analysis, it is theoretically possible to correlate AAA wall thickness with the number of fibres and the condition of the vessel's tissue.

This study has some limitations. Firstly, due to restrictions associated with open surgical procedures, the current results were derived from AAA wall samples from the anterior region of the AAA only. Hence, samples should be obtained from the anterior, posterior, and both lateral regions of AAA due to most AAAs are asymmetric as a result of the local support provided by lumbar vertebrates. Furthermore, abdominal aortic aneurysm rupture is observed to occur at a greater rate at the posterior wall than the anteriorly [35]. Recent reports on the variability in AAA wall strength as a function of location [36] suggest this may be one of a few factors to consider whenever using in presented classification. Secondly, number of elastin and collagen fibers only were considered. Evaluation of fibers arrangement influences on AAA development were not discussed. One can expect that the arrangement is significant as the fibers number [37]. Three-dimensional fibers arrangement was analyzed only in scanning electron microscopy, although we did not obtain quantitative results by this method. Some limitation of our study is fact that semi-quantifications of elastin and collagen were done through histology, which permits only histometric measurements of elastin and collagen content in 2D imaging. Biochemical assay could improve the knowledge about total quantity of elastin and collagen fibres in tissue volume. However, the results of biochemical assays are in general agreement with our results [25,31-33]. Additionally, histological examinations provide more information about associate phenomenon, like inflammatory or neovascularization processes, which could be connected with the degradation of elastin and collagen fibres [38-40]. Our histological examinations of the walls of aneurysms revealed extensive inflammatory infiltrations in most of the cases (presented in [29]). The inflammatory infiltrations are composed mainly of B lymphocytes, T cells and macrophages [6,41]. The inflammatory cells in the media and in the adventitia come directly from the blood which is supplied to the wall by the newly forming (as a result of intensified neovascularization characteristic of this pathology) vessels of the vessels (*vasa vasorum*) [1]. In the histological images of the abdominal aortic aneurysm walls all of them were discovered (presented in [29]).

Acknowledgements

This publication is part of project „Wrovasc – Integrated Cardiovascular Centre", co-financed by the European Regional Development Fund, within Innovative Economy Operational Program, 2007-2013.

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