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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Is decreased tissue elasticity more important than histopathological changes in ruptures of ascending aortic aneurysms?

Rüptüre çıkan aort anevrizmalarında azalmış doku elastikiyeti histopatolojik değişikliklerden daha önemli midir?

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ABSTRACT

Background: In this study, we aimed to investigate the natural properties of ascending aortic aneurysms and to compare dilated aortic tissues of patients with ascending aortic aneurysms and the non-pathological aortic tissues of cadavers.

Methods: Between January 2017 and January 2020, a total of 14 patients (12 males, 2 females; mean age: 66.6±8.4 years; range, 54 to 77 years) who underwent elective ascending aortic surgery without genetic disease or family history in the etiology were included in the study. Aortic tissues taken from the patients with ascending aortic aneurysms and cadavers without any aortic pathology were compared histopathologically and biomechanically. An experienced pathologist performed a histological evaluation with appropriate staining and scoring. In the biomechanical examination, stress-strain curves were created with the uniaxial tensile test. The instantaneous elastic modulus was calculated based on the first regions of the curves (Ei) and the slopes of the linear region close to rupturing (Es).

Results: In the pathological examination, there was no statistically significant difference in the parameters of both the patient and control groups (p>0.05). In the biomechanical examination, Ei values were significantly higher in the patients with ascending aortic aneurysms, while Es values were comparable between the groups (p=0.028 and p=0.609, respectively).

Conclusion: Our study results showed that the tissues of the ascending aortic aneurysm were much more rigid, although no significant histopathological changes were detected. These findings are meaningful in understanding the structure of normal and pathological aortic tissue.

Keywords: Aortic aneurysm, biomechanics, elastic modulus, pathology.

ÖZ

Amaç: Bu çalışmada çıkan aort anevrizmalarının doğal özellikleri araştırıldı ve çıkan aort anevrizmalı hastaların dilate aort dokuları ve kadavralardan elde edilen patolojik olmayan aort dokuları karşılaştırıldı.

Çalışma planı: Ocak 2017 - Ocak 2020 tarihleri arasında etiyolojisinde genetik bir hastalığı veya aile öyküsü olmayan ve elektif çıkan aort anevrizma cerrahisi yapılan toplam 14 hasta (12 erkek, 2 kadın; ort. yaş: 66.6±8.4 yıl; dağılım, 54-77 yıl) çalışmaya alındı. Çıkan aort anevrizmalı hastalardan ve herhangi bir aort patolojisi olmayan kadavralardan alınan aort dokuları histopatolojik ve biyomekanik olarak karşılaştırıldı. Histolojik değerlendirme, uygun boyama ve skorlama ile deneyimli bir patoloji uzmanı tarafından yapıldı. Biyomekanik incelemede tek eksenli çekme testi ile stres-gerinim eğrileri oluşturuldu. Elastik modülü, eğrilerin ilk lineer bölgeleri (Ei) ile rüptüre yakın bölgenin eğimlerine (Es) dayalı olarak hesaplandı.

Bulgular: Patolojik incelemede hem hasta hem de kontrol grubu parametreleri açısından istatistiksel olarak anlamlı bir fark bulunmadı (p>0.05). Biyomekanik incelemede ise, Ei değerleri çıkan aort anevrizmalı hastalarda anlamlı düzeyde daha yüksek iken, Es değerleri gruplar arasında benzer idi (sırasıyla p=0.028 ve p=0.609).

Sonuç: Çalışma sonuçlarımız çıkan aort anevrizmalı dokuların çok daha sert olduğunu, ancak anlamlı bir histopatolojik değişikliğe rastlanmadığını gösterdi. Bu bulgular normal ve patolojik aort dokusunun yapısının anlaşılması açısından anlamlıdır.

Anahtar sözcükler: Aort anevrizması, biyomekanik, elastiklik modülü, patoloji.

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Ascending aortic aneurysm (AAA) is still a significant health problem with 5 to 8% mortality rate in elective cases.[1] However, a significant decline in mortality has been achieved with the development of surgical techniques and protection methods for vital organs, particularly the central nervous system.[1-3] The diameter of the ascending aorta reaching between 5.5 and 6 cm is considered the limit for elective surgical repair due to the increased risk of complications, particularly dissection and rupture. The mortality rate increases to 25 to 50% in ruptured AAAs.[1]

Collagen, elastin, and smooth muscle cells are the essential microstructural components of the aortic wall and are extremely important for the tissues to maintain their function. In particular, damage to elastic fibers can cause aortic dilatation and increase the stiffness and stress of the aortic wall. However, dilatation, dissection, or rupture of the ascending aorta is a complex and multifactorial process.

Understanding the natural structure and behavior of the ascending aorta may help to revise follow-up and treatment options in such a high-mortality case. In the literature, there is a limited number of studies examining AAA simultaneously with normal ascending aortic tissues in terms of histopathological and wall tensions.

In the present study, we, therefore, aimed to investigate the natural properties of AAAs and to histopathologically and biomechanically compare dilated aortic tissues of patients with AAA and the non-pathological aortic tissues of cadavers.

PATIENTS AND METHODS

This single-center, retrospective, experimental study was conducted at Kocaeli University, School of Medicine, Department of Cardiovascular Surgery between January 2017 and January 2020. The preoperative data of all patients who were electively operated for AAA were analyzed. Of these patients, 14 (12 males, 2 females; mean age: 66.6±8.4 years; range, 54 to 77 years) who underwent elective ascending aortic surgery with no genetic disease or family history in the etiology were included in the study. The ascending aortic tissue samples of the control group were taken from six cadavers without any aortic pathology or a disease predisposing to aortic pathologies. A total of 75 ascending aortic tissue samples, 42 from greater curvatures, 33 from lesser curvatures, and 37 longitudinal, 38 circumflex oriented, were examined. While examining the histopathological differences of the ascending aortic samples, the biomechanical responses of the samples against stress-strain were also assessed.

Sample collection and specimen preparation

In all of the patients with AAA, the ascending aortic wall segments were excised, preserving their integrity. Surgical specimens were taken tubularly over the sinus of Valsalva, with proximal-distal orientation at the discretion of the surgeon. Adventitial adipose tissue was removed from the samples. The ascending aorta samples were circular to preserve the ring integrity of the ascending aorta for histopathological examination and as 4 cm strips with a thickness of 1 cm at the distal ends and 0.5 cm in the middle for the biomechanical examination. The thickness of the ascending aortic strips was measured with a caliper, and the average thickness was 1.94 mm in the patient group and 1.85 mm in the control group. Samples taken from the ascending aorta were classified according to the aortic regions where the strips were taken (grater-lesser curvature) and to the orientation of the aortic tissue from which it was taken (circumflex-longitudinal).

The most suitable ascending aortic tissue sample that can be used in studies for comparison are obtained from cadaveric tissue; therefore, to make a healthy comparison, the tissue samples were preserved under the same conditions. All ascending aortic tissue samples were kept in 10% formalin to be approximately five times their volume to be suitable for pathological examination. The storage durations varied. The first cross-linking between 10% formalin and collagen is complete 24 h to 48 h after penetration, while the formation of the second stable covalent cross-links can take approximately 30 days.[4,5] The minimum and maximum waiting time of our samples in 10% formalin was six months and three years, respectively.

Histopathological examination

Slices of circular samples obtained from ascending aortic wall segments of each patient were stained with hematoxylin and eosin, PAS-AB (Periodic acid-Schiff - Alcian blue), elastic von Gieson, and Masson-Trichrome. Histological evaluation was performed by an experienced pathologist using an Olympus BX50 microscope (Olympus Inc., Tokyo, Japan). Common terminology was used for the findings for each sample to optimize the histological diagnosis. A single expert pathologist's opinion determined the score evaluation for the numerical scoring.

Mechanical experiment

A portable universal tensile device was used for the uniaxial tensile test with a 500 N ± 0.01 N load cell and 250 mm ± 0.02 displacement accuracy. The uniaxial

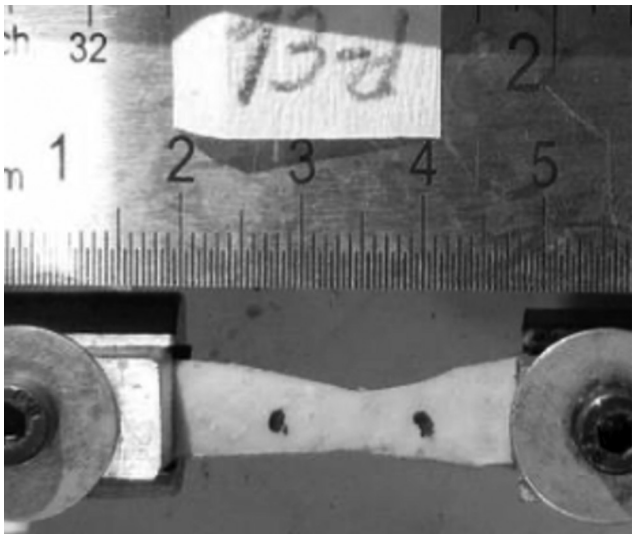

Figure 1. Application of uniaxial tensile test to ascending aortic samples taken as strips.

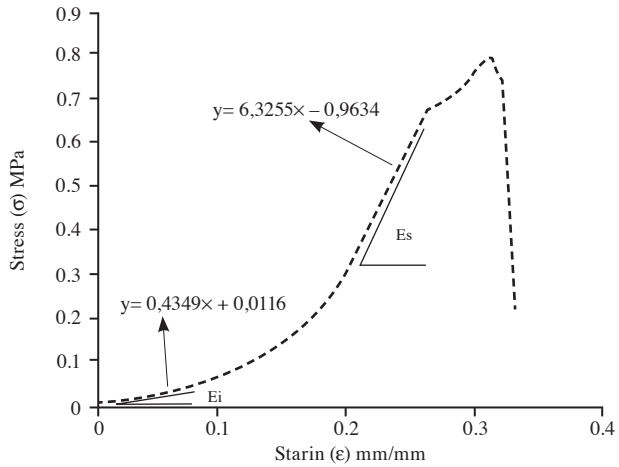

Figure 2. A sample curve of ascending aortic aneurysm in uniaxial test.

test clamps were designed to hold samples without damage. During the experiment, sandpaper was used to carry out the test without slipping between the clamps of the specimens (Figure 1). Tissue was removed from 10% formalin solution immediately before mechanical testing. Samples were subjected to static uniaxial tensile testing at a maximum of 10 mm/min until failure. Time-dependent force and displacement data from the data logger connected to a portable universal tensile device were recorded in a spreadsheet file.

The stress-strain diagram was plotted by deriving the load and displacement graph used to determine the biomechanical properties from the data obtained. The elastic modulus was calculated by taking the derivative of the equation of the initial and near-rupture linear regions of the stress and strain curves, and its unit

Table 1. Demographic and clinical data of the patients with ascending aortic aneurysm (n=14)

	n	%	Mean±SD	Min-Max
Age (year)			66.6±8.4	54-75
Sex				
Male	12	85.7		
Hypertension	6	42.9		
Diabetes mellitus	3	21.4		
Annuloaortic ectasia	10	71.42		
Diagnosis of aortic valve disease	9	64.28		
Advanced aortic stenosis	2	14.3		
Advanced aortic insufficiency	6	42.9		
Bicuspid aortic valve	7	50		
Infective endocarditis	1	7.1		
EuroSCORE value			6.7±2.2	3-11
Ascending aorta diameter (cm)			52.3±3.7	45-57
Sinus Valsalva diameter (cm)			42.6±4.7	34-50
Sinotubular junction diameter (cm)			35.8±7.4	25-53

SD: Standard deviation; EuroSCORE: European System for Cardiac Operative Risk Evaluation.

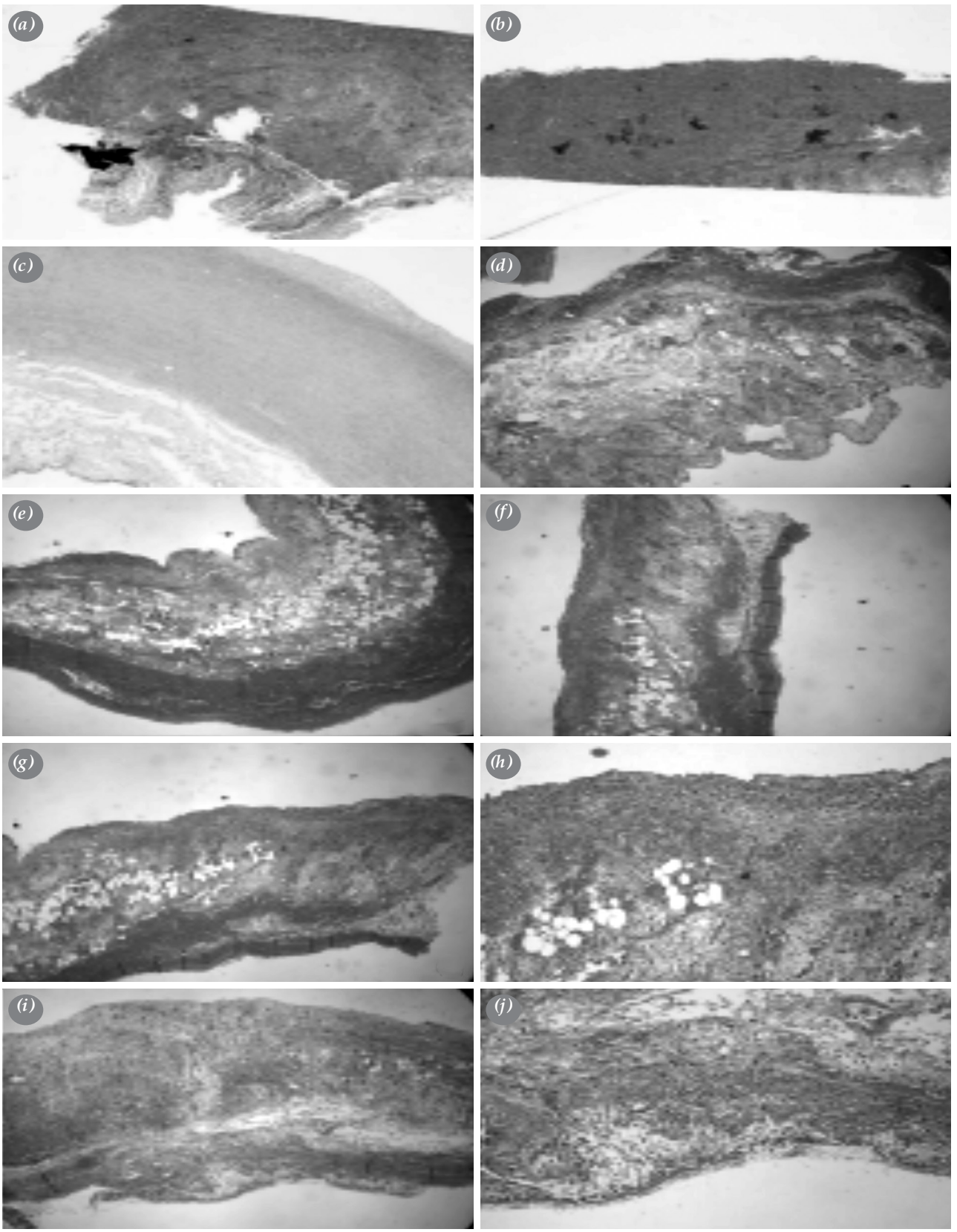

Figure 3. Histopathological sections of ascending aortic samples. **(a-c)** Histopathological image samples of normal cadaveric ascending aortas (H&E, ×10). **(d-j)** Histopathological image samples of aneurysmatic ascending aortas (d-g, i: H&E, ×100; h,j: H&E, ×200).

Table 2. Pathological findings and statistical analysis of the patients with ascending aortic aneurysm and control group (cadaver)

	Patient group (n=14)				Control group (n=6)				
	n	%	Mean	Min-Max	n	%	Mean	Min-Max	*p*
Decrease in smooth muscle cells			2.50	1-3			2.00	1-3	0.841
Fibrosis			2.50	1-3			2.00	1-3	0.841
Mucin accumulation			1.50	0-3			0.00	0-1	-
Elastic fiber content			1.00	1-3			1.50	1-3	0.718
Medial degeneration			2.00	1-3			2.00	1-2	0.444
Atherosclerosis	6	42.9			4	4			0.628
Inflammation	1	7.1			0	0			-

was megapascal (MPa). Basically, the increase in the elastic modulus refers to an increase in the rigidity and to a decrease in the elasticity of the examined system. The curves in the graph were also non-linear, since the biological tissues used for the test samples were hyperelastic materials. The most optimal way to describe the elastic modulus of non-linear biological tissues was to calculate the slope at a given point. In this study, the instantaneous elastic modulus was determined at two points. The first elastic modulus was calculated based on the first regions of the curves (Ei), and the second elastic modulus was based on the slopes of the linear region close to rupturing (Es) (Figure 2). The line function was calculated by taking the derivative of the second-order curve function at a certain point, and the coefficient of X was taken as the slope value. Data processing was performed using the Excel 2019 (Microsoft Corp., WA, USA).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The conformity of the data to the normal distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables were presented in mean ± standard deviation (SD) or median and interquartile range (IQR, 25th to 75th), while categorical variables were presented in number and frequency. The difference between the groups was analyzed using the Mann-Whitney U test for numerical variables that did not have a normal distribution. The Fisher exact chi-square test was used for categorical variables. A two-sided *p* value of <0.05 was considered statistically significant.

RESULTS

The demographic data of the patients with AAA are shown in Table 1. Six (42.9%) patients had hypertension and three (21.4%) had diabetes mellitus. The mean diameter of the ascending aorta of the patients with AAA was 52.3±3.7 mm. The mean aortic diameter at the sinus of Valsalva level was 42.6±4.7 cm, and the mean diameter at the level of the sinotubular junction was 35.8±7.4 cm. Ten (71.4%) patients had annuloaortic ectasia. Seven (50%) patients had bicuspid aortic valve and 10 (71.4%) patients had associated aortic valve disease (Table 1).

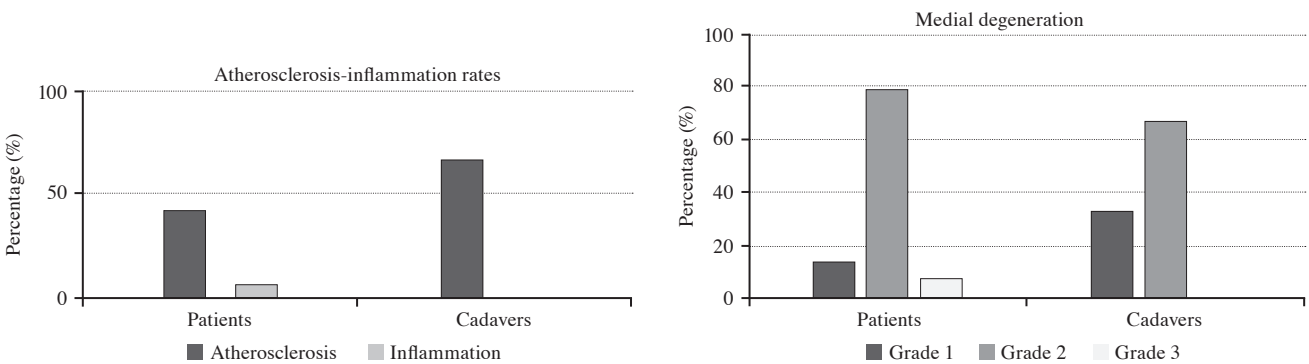

Figure 4. The histopathological findings of the tissue samples of the patients and cadavers.

Table 3. Uniaxial tensile test force-displacement data and statistical analysis of the patients with ascending aortic aneurysm and control group (cadaver)

	Ei (MPa) *(Elasticity modulus for first region slope of stress-strain curves)*			Es (MPa) *(Elasticity modulus for linear region slope of stress-strain curves close to rupture)*		
	Mean	Min-Max	*p*	Mean	Min-Max	*p*
Longitudinal (n=37)	1.0833000	0.38000-2.20770		3.3336500	1.15190-7.07000	
	Patients: 1.17 / Control: 1.07		0.061	*Patients: 3.70 / Control: 3.97*		0.933
Circumflex (n=38)	1.2751500	0.43490-2.76850		3.4437000	1.33010-7.04280	
	Patients: 1.41 / Control: 1.09			*Patients: 3.95 / Control: 3.38*		
Great curvature (n=42)	1.1904500	0.38000-2.7685		3.4437000	1.79700-7.07000	
	Patients: 1.37 / Control: 1.12		0.203	*Patients: 3.81 / Control: 4.15*		0.407
Small curvature (n=33)	1.1500000	0.51910-2.20770		3.3336500	1.15190-7.04280	
	Patients: 1.22 / Control: 1.03			*Patients: 3.86 / Control: 3.12*		
Patients (n=49)	1.2035500	0.51910-2.24010	**0.028**	3.4229500	1.15190-7.07000	0.609
Control (n=26)	1.1261500	0.38000-2.76850		3.4038500	1.24100-6.63610	

Ei: The first regions of the curves; Es: The second elastic modulus based on the slopes of the linear region close to rupturing; p value <0.05 significant.

For the definition of medial degeneration, four pathological findings were identified and analyzed by an expert pathology team: decrease in smooth muscle cells, presence of fibrosis, mucin deposition, and elastic fiber content (Figure 3). In addition, pathological findings such as atherosclerosis and inflammation were examined. No statistically significant difference was found in these parameters between the groups (Table 2). Medial degeneration and atherosclerosis, the main histopathological changes encountered in aortic dilatation, were also similar between the groups (p>0.05) (Figure 4).

At the beginning of the uniaxial tensile test, (Ei) values were found to be significantly higher in patients with AAA compared to cadavers (p=0.028), while elastic modulus immediately before rupture (Es) showed similar results in both groups (p=0.609) (Table 3).

DISCUSSION

In the current study, we investigated the natural properties of AAAs and histopathologically and biomechanically compared dilated aortic tissues of patients with AAA and the non-pathological aortic tissues of cadavers. The main finding of this study was that the tissues of the ascending aortic aneurysm were much more rigid, although no significant histopathological changes were detected. In addition, the mean age and male predominance are consistent with the literature.[6]

The histopathological changes reported in aortic dilatation are mainly medial and atherosclerotic degeneration.[7] In previous studies, histopathological changes associated with medial degeneration were examined based on four parameters: decrease in smooth muscle cells, presence of fibrosis, mucin deposition, and elastic fiber content.[8] The present study focused on these four parameters for medial degeneration. Similar studies examining AAA histopathologies observed differences in medial degeneration and elastin fragmentation.[9] In some studies, the examination was recommended to be done in detail with electron microscopy.[10] In our study, we observed no statistically significant difference between the AAA and control groups in terms of medial degeneration and related histopathological changes. However, the lack of a statistically significant difference, particularly for medial degeneration, can be attributed to the small sample size.

In a study, Okamoto et al.[11] showed that mechanical properties could be used in mathematical models of the dilated ascending aorta to predict regional and transmural stress distributions. Vorp et al.,[12] using the uniaxial tensile test, found that AAA and potential aneurysm rupture were associated with stiffening and weakening of the aortic wall. Uniaxial tensile tests are insufficient to reproduce the physiological state and evaluate the anisotropic behavior of the tissue.[13,14]

However, researchers have widely used these tests, as they are easy-to-apply and can be evaluated without tissue damage.[15] In the next stage of our study, the uniaxial tensile test was preferred for similar reasons, and stress-strain curves obtained from force-displacement data in AAA tissues were examined.

In the study of Khanafer et al.,[3] in longitudinal orientation, the maximum elastic modulus was different for the greater and lesser curvatures and more remarkable in the circumferential than in the longitudinal direction. Ferrera et al.[15] also reported that the mean elastic modulus in circumflex orientation had higher values in the greater and lesser curvatures. In another study, Cosentino et al.[16] used finite element analysis and the biaxial tensile test and found no significant difference in material response between the longitudinal and circumferential directions. In our study, we showed no significant difference between the samples from different orientations and regions. However, the Ei values were significantly higher in the AAA group, while there was no significant difference in the Es values between the groups.

In the study of Garcia-Herrera et al.,[17] healthy aortic tissue from organ donors was compared and, similarly, tensile stress was found to be higher in the patients with AAAs. In this study, pathology did not significantly affect rupture parameters in the biomechanical examination. However, tensile strength obtained with stress data was evaluated instead of the elastic modulus, indicating the harmony between stress and strain.

In the current study, due to the definition of the elastic modulus, the high Ei values in patients with AAA suggest that the mechanical structure of the ascending aorta in this group becomes more rigid by moving away from elasticity. Rigidity would cause an increase in the effect of pressure in the ascending aorta. The lack of a difference in Es values between the AAA and control groups shows similar biomechanical properties before rupture. On the other hand, there was no histopathological finding that could explain these biomechanical findings between the two groups. This finding suggests that AAAs may occur due to purely structural reasons. The unique structure of biological tissues indicates that it is not simple to predict the occurrence and the course of the aneurysm in the ascending aorta.

The single-center design with a relatively small sample size and having cadaveric tissues as the control group are the main limitations to this study. In accordance with the national regulations and the conditions of our hospital, cadaver tissues were used as the most suitable tissue sample for comparison. Similar conditions were attempted to be achieved between the excised aortic tissues and cadaver tissues for the study. However, it is well established that the tissues lose their flexibility after treatment with 10% formalin. Since the detailed medical history and cardiac examinations of the cadaver samples used in the study were unknown, some data could not be compared between the two groups. Due to the conditions of our hospital, the uniaxial tensile test was applied in our study. However, while considering the elastic structure of biological tissues, a three-dimensional mechanical evaluation may obtain more relevant results.

In conclusion, our study results show that the tissue is more rigid in ascending aortic aneurysms. On the other hand, biological tissues exhibit a complex behavior in which the distribution, arrangement, and ratio of elastin and collagen fibers can lead to non-linear and isotropic properties. In this study, we observed no significant change in the histopathological structure of the tissue. However, further studies are needed to confirm these findings.

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Ethics Committee Approval: The study protocol was approved by the Kocaeli University Non-Interventional Clinical Research Ethics Committee (date: 04.06.2020, no: GOAKEK-2020/4.11 2020/75). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept- design-control-writing-review-references: A.D.; Concept and idea- design-supervision: O.O.; Data collection and processing: Z.T.; Writing the article: B.A.; Uniaxial tensile test and data analyze: A.C., İ.M.; Pathological evaluation, scoring and data analyze: A.T.E., U.K.

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