GENDER VARIATIONS IN THE MECHANICAL PROPERTIES OF ASCENDING AORTIC ANEURYSMS

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ABSTRACT
The present study aimed to examine gender variations in the mechanical properties of ascending aortic aneurysms. Fresh tissue from ten patients undergoing graft replacement of the ascending aorta was classified according to gender and direction. The specimens were submitted to mechanical testing beyond rupture with evaluation of failure stress (tensile strength), failure strain (extensibility), and peak elastic modulus (maximum tissue stiffness). Failure strain was independent of gender in both circumferential and longitudinal specimens. Failure stress and peak elastic modulus were higher in male than female patients in circumferential, but not in longitudinal specimens. Tissue thickness did not vary with gender. In both genders, failure stress and peak elastic modulus were significantly higher in the circumferential compared to the longitudinal direction. The present findings relating to gender variations in the rupture properties of aneurysmal tissue may be responsible for the increased rupture risk documented by epidemiologic studies in women, because rupture develops when hemodynamic stresses overcome the aortic wall strength.

KEY WORDS
Biomechanics, ascending aortic aneurysms, gender, risk of rupture.

1. Introduction
Ascending aortic aneurysm (AsAA) is a lethal disease. Aneurysm and dissection of the ascending aorta is related with a high degree of morbidity, mortality, and medical expenditure, despite sustained improvements in diagnostic and surgical procedures [1,2]. Nevertheless, they have not captured historically the same level of attention as that given to diseases of more functional organs [3]. However, the prevalence of aortic aneurysms appears to be rising, which may reflect improvements in imaging techniques as well as heightened clinical awareness of the disease.

Three general guidelines are suggested for all patients with clinically recognized thoracic aortic aneurysms [4]. Hypertension [5] is a risk factor known to increase rupture risk but also a factor that can be controlled in most patients. Second, symptomatic aneurysms and those complicated by dissection are more likely to rupture, thus requiring urgent assessment for repair. Finally, asymptomatic thoracic aortic aneurysms with diameters of 6 cm or greater are at increased risk of eventual rupture and may be regarded for elective repair as acceptable surgical candidates [6-10].

Despite the prevalence of men over women with AsAA in epidemiologic studies [6-8], a higher fraction of women among patients with ruptured AsAA have been reported, identifying the female gender as a predictor of negative events, i.e. dissection or rupture, and recommending that variations excluding patient size may account for the higher risk documented in females [9]. We put forward that gender may have a specific impact on the mechanical properties of AsAA wall tissue, and the purpose of our study was to test this hypothesis.

This study was, consequently, undertaken to explore gender-specific variations in strength and stiffness, i.e. in the mechanical properties of AsAA wall tissue, with particular consideration to potentially pertinent association with the increased risk of negative effects found in females. The present findings relating to gender variations in the failure properties of aneurysmal tissue may be responsible for the increased risk of rupture in women, because rupture develops when hemodynamic stresses overcome the strength of aortic wall [10,11].

2. Materials and Methods
2.1 Aortic Tissue Collection
Full-thickness ascending aortic wall specimens were obtained from ten patients (age: 67±3 years, male/female ratio: 5/5; AsAA diameter: 5.4±0.1 cm, mean ± standard error of the mean (SEM)), undergoing elective surgery for degenerative (non-dissecting) AsAA at the Department of Cardiothoracic Surgery of the Athens Medical Center, under informed consent following local ethic guidelines. Biopsies were obtained fresh in the operating room from AsAA at the point of maximum diameter. The age and sex
of the patients were collected from clinical charts, and peak preoperative transverse AsAA diameter as assessed during magnetic resonance imaging, computed tomography, or echocardiography. No bias to the selection of patients was made with respect to age.

The tissue specimens were stored in refrigerated saline solution at 4°C immediately after harvesting. Within 24 hours of excision, the aortic tissue was equilibrated to room temperature by immersion in physiologic saline solution for mechanical testing. Dogbone-shaped tissue strips were cut, yielding a total of 214 specimens with circumferential (CIRC: n=105) and longitudinal (LONG: n=109) orientation with respect to the intact aorta. The typical specimen size was 3.5 cm long and 1.0 cm wide, with the middle region tapered to 0.3 cm, as in earlier studies from our laboratory [10,11]. Aortic specimens were allocated into two groups according to gender: male (CIRC: n=50, LONG: n=57) vs. female (CIRC: n=55, LONG: n=52).

2.2 Mechanical Tests

Mechanical tests of the aortic specimens were carried out with Vitrodyne V1000 Universal Tester (Liveco Inc, Burlington, VT, USA), as previously reported by our group [10-14]. Briefly, the specimens were mounted between the grips of tensile tester, with the use of sandpaper to avoid slippage, and subjected to a continuously rising tensile load along their long axis at a fixed extension rate of 100 μm/s until failure (rupture) of the aortic tissue. The mechanical test data were excluded when failure did not occur in the tapered region of the specimens and when the latter slipped from the grips. The majority of specimens tested exhibited two ruptures (refer to Fig. 1 for a representative example). First ruptured the inner layers of aortic wall and then the outer; only data from the first rupture were evaluated. To sustain normal tissue hydration, specimens were immersed in a physiologic saline bath, regulated to 37°C by means of a heater coil (1130A, PolyScience, Niles, IL, USA).

Following placement in the tensile tester, the initial dimensions of the aortic specimens were recorded at the no-load state; their initial width and thickness determined optically by a laser beam micrometer (LS-3100, Keyence Corp, Osaka, Japan) with 1-μm resolution. Due to the non-uniform dimensions of specimens, four measurements were taken in the tapered region and averaged. The extension of specimens and the tensile load exerted during testing were measured with a sampling frequency of 50 Hz. The tensile tester used load cells with 0.25-g resolution for the evaluation of load. Extension in the tapered region of specimens was measured with 1-μm accuracy by a pair of piezoelectric crystals (Sonometrics Corp, London, Ontario, Canada), glued on the adventitial side of the tissue.

2.3 Data Processing

Data processing involved the assessment of engineering strain, true stress, and elastic modulus [10-14]. Engineering (infinitesimal) strain ε was calculated by subtracting unity from the stretch ratio λ:

$$\varepsilon = \lambda - 1, \quad \lambda = |l|/l_0,$$

the latter being the specimens deformed length at each tensile load divided by their initial length at no-load. True (Cauchy) stress σ was calculated, upon the assumption of tissue incompressibility, as the applied load exerted to the aortic specimens times their stretch ratio divided by their initial tapered width and thickness:

$$\sigma = F\lambda/wt$$

Passive stiffness of the AsAA tissue was quantified in terms of the elastic modulus $M$, which was calculated as the first derivative of stress with respect to strain:

$$M = d\sigma/d\varepsilon$$

Failure stress $\sigma_f$, i.e. tensile strength, and failure strain $\varepsilon_f$, an index of tissue extensibility, were taken as the stress and strain at failure, whereas peak elastic modulus $M_f$ was taken as the maximum slope of stress-strain curve attained prior to failure (refer to Fig. 1 for a graphic presentation of the definitions used for the mechanical parameters).

![Fig. 1. Representative stress-strain curve of an AsAA specimen, showing multiple aortic ruptures. Symbols $\sigma_f$, $\varepsilon_f$, and $M_f$ denote failure stress, failure strain, and peak elastic modulus, respectively.](image-url)

Mechanical parameters were averaged and presented as mean ± SEM. The two-tailed unpaired student’s t-test was used for comparisons of failure stress and strain, peak elastic modulus, and aortic wall thickness among genders and directions with SPSS v13.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was set at $p<0.05$. 

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3. Results

Gender variations in age (67±4 vs. 66±4 years, p>0.2) and AsAA diameter (5.5±0.2 vs. 5.2±0.2 cm, p>0.2) among male and female patients were non-significant.

Failure stress σf did not differ with gender in the LONG direction (Fig. 2; 123.7±7.1 N/cm2 vs. 120.4±6.8 N/cm2, p>0.2), while it was higher in male than female tissue in the CIRC direction (Fig. 2; 211.3±11.3 N/cm2 vs. 159.0±8.9 N/cm2, p<0.001).

Failure Stress (N/cm²)

Fig. 2. Gender (male vs. female) and directional (CIRC vs. LONG) variations in failure stress σf of AsAA tissue.

Similarly to failure stress σf, peak elastic modulus Mp was higher in male than female tissue in the CIRC (Fig. 3; 1119.4±84.2 N/cm² vs. 869.2±50.4 N/cm², p<0.001) but not in the LONG direction (Fig. 3; 600.7±33.5 N/cm² vs. 606.2±38.9 N/cm², p>0.2).

Peak Elastic Modulus (N/cm²)

Fig. 3. Gender (male vs. female) and directional (CIRC vs. LONG) variations in peak elastic modulus Mp of AsAA tissue.

Variations in failure strain (Fig. 4; CIRC: 0.58±0.02 vs. 0.54±0.02, p>0.2; LONG: 0.52±0.02 vs. 0.51±0.02, p>0.2) and thickness (Fig. 5; 1.72±0.03 mm vs. 1.70±0.04 mm, p>0.2) with gender were non-significant.

Significant variations in failure stress σf were found among the CIRC and LONG directions in both males (Fig. 2; 211.3±11.3 N/cm² vs. 123.7±7.1 N/cm², p<0.001) and females (Fig. 2; 159.0±8.9 N/cm² vs. 120.4±7.1 N/cm², p<0.001). As with failure stress σf, peak elastic modulus Mp of ATAA tissue was found to be significantly higher in CIRC than LONG specimens in male (Fig. 3; 1119.4±84.2 N/cm² vs. 600.7±33.5 N/cm², p<0.001) and female patients (Fig. 3; 869.2±50.4 N/cm² vs. 606.2±38.9 N/cm², p<0.001). Opposite to failure stress σf and peak elastic modulus Mp, directional variations in failure strain εf were insignificant in both males (Fig. 4; 0.58±0.02 vs. 0.52±0.02, p>0.2) and females (Fig. 4; 0.54±0.02 vs. 0.51±0.02, p>0.2).

Failure Strain (-)

Fig. 4. Gender (male vs. female) and directional (CIRC vs. LONG) variations in failure strain εf of AsAA tissue.

Thickess (mm)

Fig. 5. Gender (male vs. female) variations in thickness of AsAA tissue.

4. Discussion

Preceding epidemiologic studies [6-8] have reported a higher percentage of women among patients with ruptured AsAA. Coady et al. [7] and Davies et al. [8] in particular documented that the cumulative and yearly risks of aortic dissection and rupture rose markedly with enlarged vessel diameter over the 5-cm limit, but a higher likelihood of negative outcomes in women was inferred by their multivariate analysis. Besides Elefteriades group, Juvonen et al. [6] found in univariate analysis a greater proportion of female patients with ruptured thoracic aortic aneurysms that was not, however, evident in their multivariate model. Davies et al. [8] conjectured that the identification of female gender as a significant predictor of negative events might be partly ascribed to gender variations in mean body size, with a certain aortic diameter constituting relatively greater size and thus danger in women, whose body frame is smaller, than that of men. When changes in risk were next scrutinized according to patient body size, this group inferred that the additional risk related with female gender was not a mere consequence of the small patient body dimensions [9].

This result implies that the high risk found in women may be explained by causative parameters excluding body size, such as the modified activity of inflammatory mediators in presence of higher estrogen levels [15] and the increased proximal thoracic aortic stiffness in elder women [16]. The hypothesis of this study was that gender has a direct effect on the mechanical properties of AsAA wall tissue and that changes in these properties may be accountable for the high
risk in women, as rupture is a biomechanical phenomenon occurring when the hemodynamic forces acting on the aortic wall overcome its strength [10,11].

Accordingly, the present study determined gender and directional variations in the mechanical properties of AsAA tissue in vitro and our data indicated that in comparison to female tissue, male tissue was stronger, stiffer, but evenly extensible in CIRC specimens. Gender changes in failure strain, failure stress, and peak elastic modulus of LONG specimens were non-significant and tissue thickness did not vary between males and females. As regards directional variations, identical ones were noted for both genders, i.e. we found that the tensile strength and maximum stiffness of AsAA tissue were significantly lower along the LONG than the CIRC direction, while tissue extensibility did not display significant variations among the two directions. The directional variations in our rupture data confirmed those in previous studies from our group [10,11].

Similar to the presently-reported gender variations, i.e. decreased failure stress but with no information on stiffness and extensibility, were recently reported for abdominal aortic aneurysms [17].

5. Conclusion

It is inferred from our findings that tensile strength and maximum tissue stiffness were higher in male than female patients in CIRC but not in LONG specimens. The present findings, relating to gender variations in the tensile strength of AsAA tissue, may be responsible for the increased risk of rupture in women, as rupture occurs when hemodynamic loads overcome the strength of aortic wall tissue.

References
