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Gender-related changes in aortic geometry throughout life[†]

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Abstract

OBJECTIVES: Aortic geometry changes throughout life are not well defined. This investigation delineates aortic geometry across the adult age spectrum and determines the gender-related influence of aging on aortic morphometry.

METHODS: Contrast-enhanced computed tomography scans of all aortic segments in 195 subjects (94 women, 101 men, average age 57 ± 20 years) free of vascular disease were analysed. Lengths and diameters of each aortic segment as well as width, height and tortuosity of the thoracic aorta were compared between both genders.

RESULTS: Aortic diameters and lengths were larger in men than women ($P < 0.001$); however, after adjustment for body surface area (BSA), the ascending aorta and aortic arch revealed greater diameters in women than in men ($P = 0.001$ and $P = 0.011$, respectively). All aortic segment dimensions increased in a similar pattern with age for both genders, except the ascending aorta diameter, which increased +3.4% ($P < 0.001$) per decade in women and +2.6% ($P < 0.001$) per decade in men. Owing to more dynamic ascending aortic growth in women, absolute diameters were similar in both genders at an older age (>70 years old: 3.4 ± 0.3 vs 3.5 ± 0.3 cm, $P = 0.241$).

CONCLUSIONS: Female gender is associated with smaller aortic dimensions, but only at a young age. The dynamics of aortic growth throughout life are greater in women than in men. Gender-related changes in aortic geometry provide a hypothesis for the predominance of aortic dissection in young male patients, which normalizes between genders with increasing age.

Keywords: Aortic dissection • Imaging • Gender differences

INTRODUCTION

Acute aortic dissection type A (AADA) can occur at any age and is most commonly observed in patients between 50 and 80 years of age [1]. Both the International Registry of Acute Aortic Dissections (IRAD) [2] and the German Registry of Acute Aortic Dissection Type A [1] have identified significant gender- and age-related differences in the incidence of AADA, specifically, the facts that <25% of patients under 40 years of age with aortic dissection were females, and that the cut-off age for male dominance was 75 years (Fig. 1). While the recent Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) gender study provided data on the equal risk of aortic dissection in men and women with genetically triggered aortopathy [3], a novel hypothesis on gender differences in AADA incidence should be addressed.

Despite the growing interest in standardizing what constitutes as normal aortic dimensions, there are little data on gender- and

age-related aortic geometry changes [4–6]. Given the smaller absolute aortic dimensions in women than men and the significantly increasing risk of aortic events in aging females, we hypothesized that aortic geometry changes occur in different patterns in both genders. Our aim was to determine aortic geometry across the adult age spectrum and to investigate the gender-related influence of aging on aortic morphometry.

MATERIALS AND METHODS

Study population

The computed tomography (CT) database at the Hospital of the University of Pennsylvania was reviewed for patients who had undergone electrocardiogram-gated CT angiography (CTA) of all aortic segments at one time in the past 2 years. Excluded were patients with Marfan's syndrome, bicuspid aortic valve, severe atherosclerosis and any aortopathy. This retrospective study was approved by an institutional review committee. The need for informed consent was waived.

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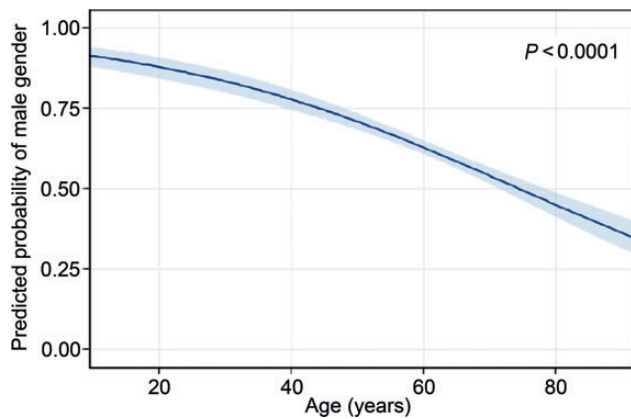


Figure 1: Predicted probability of male sex according to age in patients who underwent surgery for AADA. The blue area represents the 95% confidence interval. Analysis of 2137 patients enrolled in the German Registry of Acute Aortic Dissection Type A. Reproduced with permission from Rylski et al. [1].

Image analysis

One observer blinded to patient-identifying information performed the image analysis, using Aquarius Intuition (Terarecon, Inc., Foster City, CA, USA). A centre line was created from the aortic valve annulus to the aortic bifurcation. The aorta was divided into four segments by appropriated planes perpendicular to the centre line: (i) the ascending aorta, beginning at the plane corresponding to the nadirs of all three aortic cusps and extending to the plane immediately proximal to the origin of the brachiocephalic artery; (ii) the aortic arch, beginning at the plane immediately proximal to the origin of the brachiocephalic artery and extending to a plane immediately distal to the left sub-clavian artery's origin; (iii) the descending thoracic aorta, beginning at a plane immediately distal to the origin of the left sub-clavian artery and extending to a plane immediately proximal to the coeliac artery; and (iv) the abdominal aorta, beginning at a plane immediately proximal to the coeliac artery and extending to a plane at the aortic bifurcation (Fig. 2). Length and diameter were assessed in each aortic segment. Length was defined as the centre-line distance between the planes defined above. Diameter was calculated according to the cross-sectional aortic surface in reference to the aortic wall's outer surface at planes in the middle of each aforementioned aortic segment and at the following additional planes perpendicular to the centre line: (i) the sinus of Valsalva—defined as the plane depicting the largest sinus dimension; (ii) the proximal aortic arch—immediately proximal to the brachiocephalic artery orifice; and (iii) the distal aortic arch—immediately distally to the left sub-clavian artery orifice.

For the curvilinear part of the thoracic aorta, several shape descriptors corresponding to the centre-line points were assessed: (i) the thoracic aortic width (W)—distance between the point corresponding to all three aortic valve cusps and the analogous point at the transverse level in the descending thoracic aorta; (ii) the thoracic aortic height (H)—the length of the orthogonal projection of the centre-line inflection point at the top of the arch on the aortic width; (iii) H/W ratio—calculated as the height divided by the width; and (iv) the thoracic aortic tortuosity (T)—calculated as the incremental curve length of the centre line corresponding to the points defining the aortic width divided by the thoracic aortic width (Fig. 3).

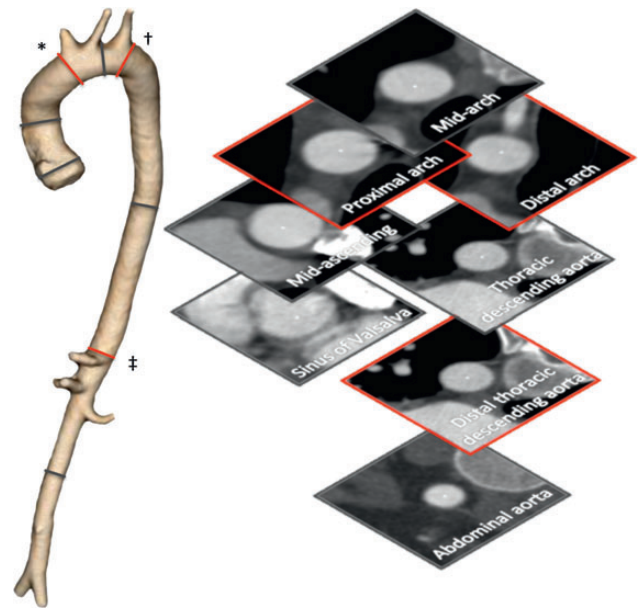


Figure 2: Segmentation of the aorta. Red planes correspond to the origin of the brachiocephalic artery (asterisk), left sub-clavian artery (dagger) and coeliac artery (double dagger), and divide the aorta into four segments of interest: the ascending aorta, aortic arch, descending thoracic aorta and abdominal aorta. Aortic diameters were assessed according to the cross-sectional aortic surface at all red and additional grey planes.

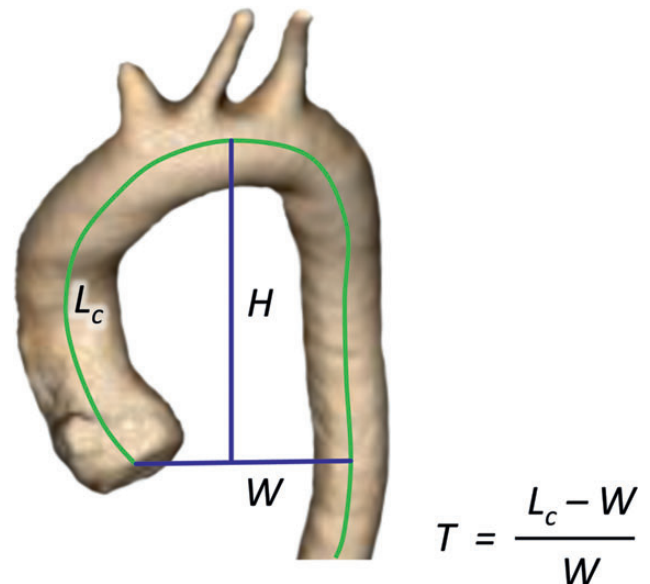


Figure 3: Geometric assessment of the thoracic aortic shape according to points on centre line (L_c). Tortuosity (T) is a ratio of the incremental curve length of the centre line corresponding to the points defining aortic width (W) divided by the thoracic aortic width. H indicates the thoracic aortic height.

Statistical analysis

Continuous data are reported as median \pm standard deviation, categorical variables are reported as counts and percentages. For comparison of continuous variables, Student's t -test was applied when normal distribution was present as tested by the Kolmogorov-Smirnov test. For not normally distributed variables, the Mann-Whitney rank sum test was employed. Categorical variables were compared using the χ^2 test. Aortic dimensions are given as absolute

values and indexed values, which are the ratios of absolute dimensions to the body surface area (BSA). BSA was calculated according to the Du Bois formula [7]. The association of BSA-indexed aortic dimensions (measurements divided by the BSA) with aging (Table 3, Fig. 4) was tested by linear regression models in each gender. All statistical calculations were performed using SigmaPlot 12 (Systat Software, San Jose, CA, USA).

RESULTS

Of 978 consecutive patients referred for CTA, scans of 195 adults (94 women, 101 men) ranging from 20 to 96 years were analysed. Indications for CTA studies were to evaluate chest pain ($n = 163$), post-traumatic diagnostic work-up ($n = 17$) and cancer staging ($n = 15$). Clinical details of our study cohort are summarized in

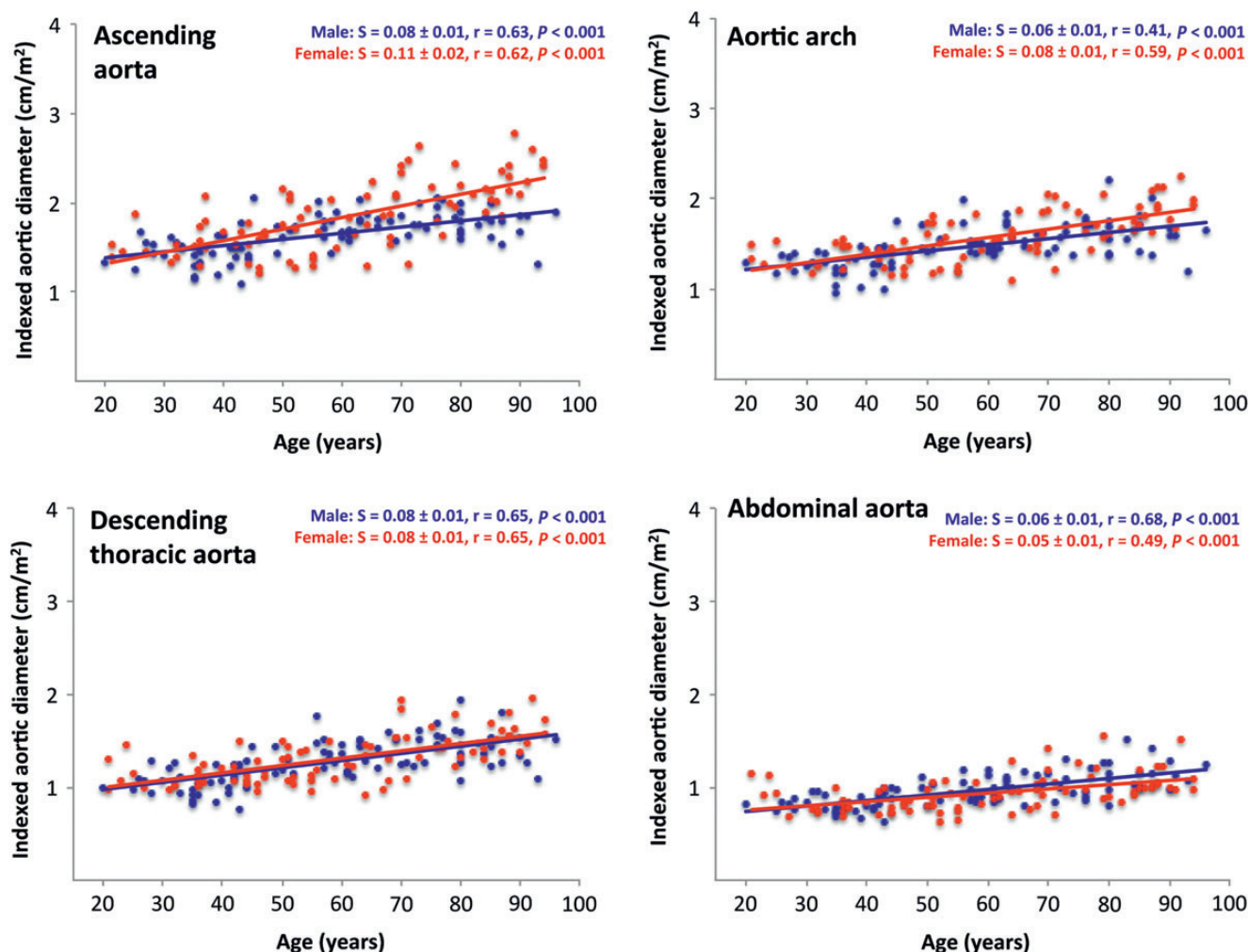


Figure 4: Gender-specific aortic diameters adjusted to the body surface area in relation to age.

Table 1: Clinical characteristics

	All (n = 195)	Male (n = 101)	Female (n = 94)	P-value
Age (years)	57 ± 20	57 ± 20	56 ± 20	0.395
Body surface area (m ²)	1.92 ± 0.34	2.02 ± 0.36	1.74 ± 0.24	<0.001
Blood pressure (mmHg)				
Systolic	122 ± 14	123 ± 13	120 ± 14	0.465
Diastolic	72 ± 11	72 ± 12	72 ± 11	0.989
Hypertension	85 (44)	43 (43)	42 (45)	0.767
Hypercholesterolaemia	56 (29)	26 (26)	30 (32)	0.427
Diabetes mellitus	30 (15)	11 (11)	14 (15)	0.535
Current smoking	24 (12)	13 (13)	11 (12)	0.976

Data are medians ± standard deviation or number of subjects (%).

Table 1. The median age was 57 ± 20 years and did not differ between genders. Men had significantly larger BSA (2.02 ± 0.36 vs 1.74 ± 0.24 m², $P < 0.001$). Overall, both genders' rates of cardiovascular risk factors were similarly distributed.

Gender-related differences in aortic dimensions

Aortic diameters and lengths were greater in men than women at all segments ($P < 0.001$, Table 2). The averaged gender-related absolute diameter difference ranged between 0.2 and 0.3 cm. When indexed by BSA, the diameters of the ascending aorta and the aortic arch were greater in women than in men (1.8 ± 0.3 vs 1.6 ± 0.2 cm/m², $P = 0.001$ and 1.6 ± 0.3 vs 1.4 ± 0.2 cm/m², $P = 0.011$, respectively). All other diameters and lengths were similar.

Impact of aging on aortic dimensions

The dimensions of all aortic segments significantly increased with each decade of life (Table 3). Total aortic length increased at a rate of 0.98 ± 0.07 cm/10 years ($P < 0.001$). Diameter increase rates ranged between 0.06 and 0.11 cm/10 years.

When indexed by BSA, gender-related differences in growth rates throughout life were observed in the ascending aorta and aortic arch (Fig. 4, Table 3). The ascending aorta length increase rate per decade was +2.9% ($P < 0.001$) in women and +2.5% ($P < 0.001$) in men; the diameter increase rate was +3.4% ($P < 0.001$) in women and +2.6% ($P < 0.001$) in men. BSA-indexed ascending aortic diameter was similar in both genders at a young age, but the women's higher diameter increase rate led to significantly higher indexed diameter in senior women than men (>70

Table 2: Gender differences in aortic dimensions

	Absolute values (cm)			Indexed values (cm/m ²)		
	Male	Female	P-value	Male	Female	P-value
Ascending aorta						
Diameter	3.4 ± 0.4	3.1 ± 0.5	<0.001	1.6 ± 0.2	1.8 ± 0.3	0.001
Length	8.4 ± 1.1	7.6 ± 1.0	<0.001	4.2 ± 0.7	4.3 ± 0.9	0.102
Aortic arch						
Diameter	3.0 ± 0.3	2.7 ± 0.3	<0.001	1.4 ± 0.2	1.6 ± 0.3	0.011
Length	3.7 ± 0.8	3.2 ± 0.7	<0.001	1.8 ± 0.4	1.8 ± 0.5	0.297
Descending thoracic aorta						
Diameter	2.5 ± 0.3	2.3 ± 0.3	<0.001	1.3 ± 0.2	1.3 ± 0.2	0.316
Length	23.5 ± 2.9	21.2 ± 2.2	<0.001	11.6 ± 1.9	12.0 ± 1.9	0.080
Abdominal aorta						
Diameter	1.9 ± 0.3	1.6 ± 0.3	<0.001	0.9 ± 0.2	0.9 ± 0.2	0.206
Length	14.4 ± 2.5	12.8 ± 2.0	<0.001	7.1 ± 1.3	7.3 ± 1.5	0.090

Table 3: Gender-specific influence of aging on aortic segment dimensions indexed to body surface area

	Male (n = 101)			Female (n = 94)		
	β	% change	R	β	% change	R
Ascending aorta						
Diameter	0.08 ± 0.01*	2.4	0.63	0.11 ± 0.02*	3.5	0.62
Length	0.21 ± 0.03*	2.5	0.59	0.22 ± 0.04*	2.9	0.50
Aortic arch						
Diameter	0.06 ± 0.01*	2.0	0.41	0.08 ± 0.01*	2.9	0.59
Length	0.09 ± 0.02*	2.6	0.46	0.11 ± 0.02*	3.4	0.48
Descending thoracic aorta						
Diameter	0.08 ± 0.01*	3.3	0.65	0.08 ± 0.01*	3.4	0.65
Length	0.55 ± 0.09*	2.4	0.57	0.45 ± 0.09*	2.1	0.47
Abdominal aorta						
Diameter	0.06 ± 0.01*	3.4	0.68	0.05 ± 0.01*	3.1	0.49
Length	0.19 ± 0.07 [†]	1.4	0.28	0.19 ± 0.08 [‡]	1.5	0.25

The association between BSA-indexed aortic dimensions and aging was tested by the linear regression model. Regression coefficient β is given for a change in centimetre per 10 years per square metre of BSA. Percentage changes are calculated per 10 years with respect to median values (presented in Table 2) adopted as a reference.

* $P < 0.001$.

[†] $P < 0.01$.

[‡] $P < 0.05$.

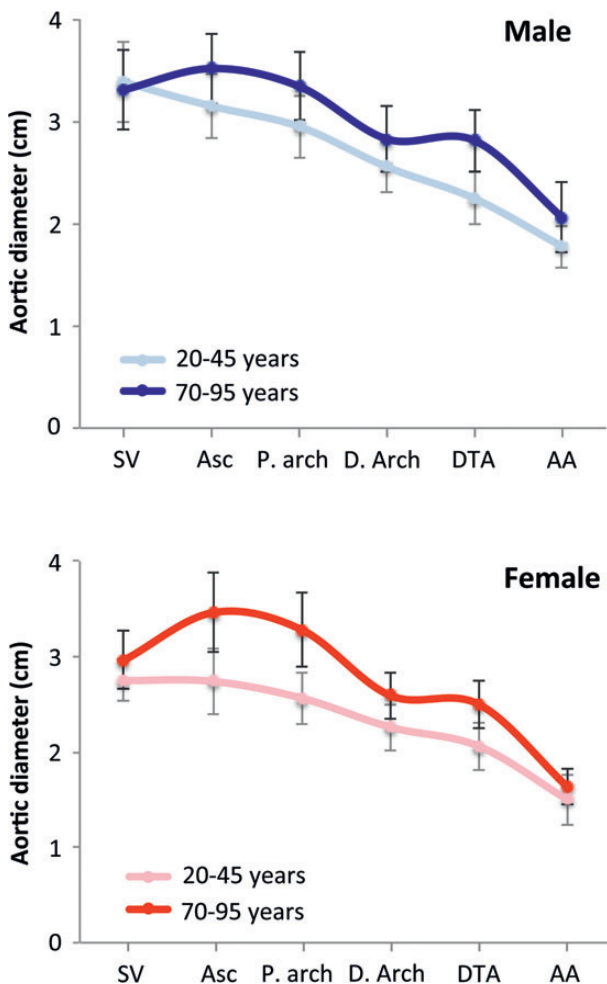


Figure 5: Gender-stratified absolute aortic diameters in young (20–45 years old) and senior (70–95 years old) adults. The greatest average absolute diameter difference was noted in the ascending aorta: 0.72 cm in women and 0.37 cm in men. SV: Sinus of Valsalva; Asc: ascending aorta; P. arch: proximal aortic arch; D. Arch: distal aortic arch; DTA: descending thoracic aorta; AA: abdominal aorta.

years old: 2.4 ± 0.4 vs 1.8 ± 0.4 cm/m², $P = 0.019$). Furthermore, significantly smaller absolute ascending diameter in females compared with males was observed only in younger adults (<45 years old: 2.6 ± 0.4 vs 3.1 ± 0.3 , $P = 0.002$), and this difference was not detectable in older patients (>70 years old: 3.4 ± 0.3 vs 3.5 ± 0.3 , $P = 0.241$). The incidence of hypertension was similar in senior females and males (20/30 vs 20/32, $P = 0.732$). Aortic arch growth revealed a similar gender-dependent growth pattern, whereas the descending thoracic and abdominal aortic dimension increase was homogeneous between genders (Table 3). The effect of different patterns of aortic diameter increase is depicted in Fig. 5, which delineates the diameters of young (20–45 years old) and senior (70–95 years old) adults in gender-stratified fashion. The greatest average absolute diameter increase was identified in the ascending aorta: 0.72 cm in women and 0.37 cm in men.

Thoracic aortic shape

The curvilinear part of the thoracic aorta showed greater absolute width (7.1 ± 1.3 vs 6.4 ± 1.1 cm, $P < 0.001$) and height (8.3 ± 1.4 vs

7.6 ± 1.2 , $P < 0.001$) in men than women. When indexed by BSA, women had greater aortic dimensions, but these differences did not reach statistical significance ($P = 0.089$ and $P = 0.103$, respectively). Both height and width increased with age in both genders in a similar manner (+8% per decade). The height to width ratio and thoracic aortic tortuosity were similar in both genders and were not associated with aging (H/W male: $r = 0.06$, $P = 0.584$, female: $r = 0.01$, $P = 0.948$; tortuosity: male: $r = 0.05$, $P = 0.615$, female: $r = 0.1$, $P = 0.323$).

DISCUSSION

Investigators of the two largest registries for aortic dissection type A have recently identified age- and gender-related differences in the presentation, management and outcomes of AADA patients [1, 2]. One of the most interesting findings from these studies was the unequal gender distribution of AADA across the lifespan. They observed that over 75% of patients under 40 years old were male. Interestingly, this disproportion disappeared in senior patients. IRAD investigators have suggested that over half of aortic dissections occurring in young patients are genetically triggered [8], and this might explain the striking gender differences observed. However, the GenTAC data revealed opposite results, with only 32% females among those patients with genetically triggered thoracic aortopathies and equal frequency between genders in those with aortic dissection [3].

The aim of the present study was to delineate aortic geometry changes throughout life and to determine which gender-related differences, if any, might explain the different patterns of AADA incidence in both genders. To reduce the body mass bias, we adjusted aortic dimensions to BSA, which was previously found to be more closely associated with aortic diameter than the body mass index [5, 9]. The findings of the present study can be summarized as follows:

- (i) All absolute aortic segment dimensions were larger in men compared with women. After adjustment for BSA, ascending aorta and aortic arch diameters were greater in women than in men.
- (ii) Aortic diameters and lengths increased with age in both genders in a similar pattern; however, women displayed a significantly greater increase in the size of the ascending and aortic arch segments with age than men.
- (iii) Owing to more dynamic ascending aortic growth in women, absolute diameters at an older age were similar in both genders.
- (iv) Height and width of the thoracic aorta increased with age in both genders but their ratio (H/W) and aortic tortuosity were not associated with aging.

Relationship to previous studies

The average aortic diameters found in the current study are comparable to the dimensions previously reported [4–6, 10]. Our findings that aortic dimensions relate to age confirm previous results [5, 6, 10, 11]. Previous investigations on the relationship between aortic diameter and gender generally showed that male gender is associated with a larger aortic diameter [5, 6, 12], which is in accordance with our results. Hager *et al.* [12] observed this association in the ascending aorta but not in the sinus segment nor in

the proximal aortic arch. Investigators who analysed CT studies taken for coronary calcium quantification reported on larger diameters of both the ascending and descending thoracic aorta in men compared with women [5, 6]. In our study, all absolute aortic dimensions were larger in men than in women; however, after adjusting for BSA, these differences were not significant and, moreover, the indexed ascending aortic diameter was greater in women.

Gender- and age-related differences in aortic geometry

The data on gender-specific aortic dimension changes related to age are limited. Wolak *et al.* [5] found in patients categorized by BSA that older men had larger aortas than women of similar age, but the difference was smaller in younger populations. Agmon *et al.* [9] demonstrated that the increase rate of the ascending aortic diameter in an aging population was similar in both genders. However, both studies are not directly comparable with our investigation because of a different patient risk profile demonstrated by the diverse indication for CT diagnostics (coronary artery calcium scanning in the Wolak *et al.* report vs post-traumatic diagnostics and chest pain evaluation in our cohort), as well as the lack of data on younger patients (<50 years old) in the work done by Agmon *et al.* In our study, there were no differences in aortic diameters adjusted to BSA between both genders, except for the ascending aorta diameter, which was larger in women. This was the result of a higher diameter growth rate in women compared with men. This also affected absolute diameter values, which were significantly larger only in young men compared with women at a similar age. In older patients absolute ascending diameters were similar in both genders.

Our results do not explain the reasons for the higher ascending aortic growth rate among women in later periods of life. However, hormonal changes might play a role in it, as there is evidence that oestrogen affects connective tissue structure by slowing down the natural reduction of arterial compliance with age [13]. Hormone replacement therapy in postmenopausal women has been shown to decrease stiffness of the aorta and large arteries [14, 15]. These findings might explain older women's greater aortic growth rate observed particularly in the proximal aortic segments, most likely due to higher blood pressure and more turbulent flow in those segments.

Thoracic aorta shape

Several investigators recently demonstrated the geometry of the curvilinear part of the thoracic aorta. Craiem *et al.* [4] showed that both aging and hypertension lead to unfolding of the thoracic aorta with increments in aortic width, reduced tortuosity and no change in aortic arch height. Elongation and widening of the thoracic aorta with aging were also observed in magnetic resonance imaging-based study [10] as well as in a study on exclusively non-hypertensive patients [11]. To date, data quantifying the thoracic aortic shape in men and women separately have been unavailable. The current study confirms previous results on the increase in thoracic aortic width and height with aging. We detected no gender-related differences regarding the height and width

increase with age; however, we did observe greater elongation of the ascending aorta and aortic arch in women.

Aortic geometry's impact on acute aortic dissection type A incidence

Hypertension, connective tissue disorders and aortic aneurysm are well-established risk factors for ascending aortic dissection [16–18]. Interestingly, both hypertension and connective tissue disorders fail to explain the very low rate of women among young AADA patients and a similar gender distribution in older ones. For example epidemiological studies usually report on similar or an even higher age-adjusted hypertension prevalence in men than women [19, 20]. Furthermore, GenTAC investigators observed no gender-related differences in the incidence of aortic dissection in patients with connective tissue disorders [3]. Last but not least, patients presenting with AADA usually do not have a genuine aortic aneurysm [21, 22], probably due to the fact that patients with a diagnosed ascending aneurysm undergo elective aortic replacement according to the diameter threshold of 5.5 cm as recommended in current guidelines [23]. Our study on non-aneurysmal aortas showing age- and gender-related changes in aortic geometry provides a hypothesis for the predominance of aortic dissection in young male patients, which normalizes between genders with increasing age. The smaller aortic dimensions in young females may be protective against aortic dissection. Owing to the more dynamic aortic growth in women, they attain similar absolute ascending aortic dimensions at an older age—thus their risk of AADA resembles that risk in men at a similar age.

Study limitations

The cross-sectional design of our study is the major limitation, as it precludes drawing a definitive conclusion regarding age-related morphometric changes. Further studies with a longitudinal design seem to be necessary. Furthermore, our study cohort does not enable us to generalize results to define normal aortic geometry for male or female individuals separately; however, since cardiovascular risk factors are equally distributed in both groups and we had excluded patients with aortopathies from the analysis, the gender-related differences we have documented might indeed be representative for the majority of our population.

CONCLUSIONS

Female gender is associated with smaller aortic dimensions at a young age, which may help protect against aortic dissection. Aortic growth dynamics throughout life are greater in women than in men. Gender-related changes in aortic geometry provide a hypothesis for the predominance of aortic dissection in young male patients, which normalizes between genders with increasing age.

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Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr. J Holfeld (Innsbruck, Austria): Professor Czerny had to leave for the main board meeting. I have his comments for you here. His first question is: Why do you think that female aortas grow faster in later periods of life? Could hormonal changes be responsible for that? Are there any data?

Dr Rylski: We do not have any data on it; this is purely a CT study. We do not know if genetic or hormonal factors might explain these differences.

Dr Holfeld: Do you know whether the aortic valves in your patients were bicuspid or tricuspid? It would be very interesting to know if the bicuspids have longer ascending aortas as compared to the tricuspid patients.

Dr Rylski: Bicuspid valve patients and patients with severe aortic valve calcification were excluded from the study, so I cannot say anything about them.

Dr Holfeld: And one more question. Do you have any measurements for comparing your aortas to patients having sustained acute type A aortic dissection (if you had previous CT scans before dissection), in order to find out whether the pre-type A aortas were longer? This would be my (Professor Czerny's) clinical impression and would add to your paper if there is any answer to that.

Dr Rylski: It is an excellent comment. We are indeed working on a study which shows how the diameter and length of the aorta changes when it dissects, according to CTs done coincidentally in patients who later developed type A dissection. We have found very interesting results such as an increase in diameter of 20% just because of the dissection. We will address this point in our project.

Dr Holfeld: And then there is one comment for your future work. It should be a stimulus for later investigations. The arch angulation throughout life would be an interesting subject, especially with respect to TEVAR, particularly in younger patients in whom, irrespective of gender, the arch is very steep, which is usually not the case in elderly patients.

Dr C. Hagl (Munich, Germany): Do you have any idea about the incidence of hypertension in the patients, comparing the women to the men?

Dr Rylski: We compared hypertension in female versus male patients, and there was pretty much the same rate. We did not exclude patients with hypertension because a lot of older patients have high blood pressure.