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Sex-specific considerations in defining aortic dilation: findings from the MATEAR study

Aspectos específicos de género en la definición de dilatación aórtica: resultados del estudio MATEAR

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Abstract

Objectives: *Patient body size and sex are significant factors in determining aortic dimensions. While females generally have smaller aortic dimensions, the criteria for surgical intervention in thoracic aortic aneurysms primarily rely on absolute diameters, disregarding sex-specific differences. The aim of this study was to compare sex differences in the upper limit of normal (ULN) and Z score in the population of a prospective nationwide multicenter registry and to determine the usefulness and fairness of guideline recommendations regarding aortic diameters in females.* **Methods:** *Transthoracic echocardiograms were performed on all patients enrolled measuring aortic dimensions at six levels following the current standard recommendations. Absolute diameters and indexed diameters by body surface area (BSA) and height were compared between males and females.* **Results:** *A total of 1,000 healthy adults were included, with an average age of 38.3 ± 12.7 years. Among them, 553 were females, and the majority were either Caucasian or Native American. Females exhibited lower values in all anthropometric parameters, echocardiographic measurements, and blood pressure. Analysis of aortic measurements revealed that females had lower absolute aortic diameters across all segments. However, when indexed parameters were examined in the aortic root and Sino tubular Junction, females demonstrated lower height-indexed diameters but higher BSA-indexed diameters. The ULN for females, correlating with a Z-score of 2.5, was determined to be 3.62 cm.* **Conclusion:** *Our study demonstrates the need for sex-specific considerations in defining aortic dilation, as females exhibit lower absolute aortic diameters but variations in indexed parameters, highlighting the limitations of using a universal cutoff value.*

Keywords: *Ascending aorta. Echocardiography. Female. Dimension. Reference values.*

Resumen

Objetivo: *Evaluar las diferencias de sexo en el límite superior de lo normal (ULN) y el puntaje Z de las dimensiones aórticas en una población de un registro multicéntrico nacional prospectivo, así como determinar la utilidad de las guías sobre los diámetros aórticos en mujeres.* **Métodos:** *Se realizaron ecocardiogramas transtorácicos en todos los pacientes enrolados, midiendo las dimensiones aórticas en seis niveles siguiendo las recomendaciones estándar actuales. Se compararon los diámetros absolutos y los diámetros indexados por área de superficie corporal (BSA) y altura entre hombres y mujeres.*

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Resultados: *Se incluyeron un total de 1,000 adultos sanos, con una edad promedio de 38.3 ± 12.7 años. De ellos, 553 eran mujeres, y la mayoría eran de origen caucásico o nativo americano. Las mujeres mostraron valores más bajos en todos los parámetros antropométricos, mediciones ecocardiográficas y presión arterial. El análisis de las mediciones aórticas reveló que las mujeres tenían diámetros aórticos absolutos más bajos en todos los segmentos. Sin embargo, cuando se examinaron los parámetros indexados en la raíz aórtica y la unión sino-tubular, las mujeres demostraron diámetros indexados por altura más bajos, pero diámetros indexados por BSA más altos. El ULN para las mujeres, correlacionado con un puntaje Z de 2.5, fue de 3.62 cm.* **Conclusiones:** *Nuestro estudio demuestra la necesidad de considerar las diferencias de sexo al definir la dilatación aórtica, ya que las mujeres exhiben diámetros aórticos absolutos más bajos, pero variaciones en los parámetros indexados, lo que resalta las limitaciones de utilizar un valor de corte universal.*

Palabras clave: *Aorta ascendente. Ecocardiografía. Sexo. Dimensión. Valores de referencia.*

Introduction

The definition of the threshold for aortic dilatation remains controversial. There is still debate over the normal diameters of thoracic aorta. Accurately diagnosing aortic root and ascending aorta (AA) dilatation relies on clearly defined normal values of aortic diameters. However, current indexing recommendations are based on studies with limitations, such as small sample size, non-standardized echocardiographic measurements, heterogeneous inclusion criteria, or lack of inclusion of non-Caucasian or overweight populations[1-5].

Although females are associated with smaller aortic dimensions, current guidelines do not take it into account to define aortic dilatation[6]. There is still controversy over whether the number 4 cm, frequently used to discriminate aortic dilation, is appropriate in females. Moreover, international guidelines for prophylactic surgical intervention for thoracic aortic (TA) aneurysms (TAA) are still based on absolute aortic diameter, even though aortic dimensions are influenced by age, sex, and body size.

To adjust for body size, it has been proposed to use Z scores or aortic diameters indexed by body surface area (BSA) or height. However, the calculation of Z scores is complex and their applicability across different populations is unclear[7-9].

The MATEAR Study, a national prospective registry of echocardiographic aortic dimensions in apparently healthy subjects in Argentina, aimed to define upper normal limits (UNL) of the thoracic aorta in the Argentinian population[10]. The objective of this study was to compare the upper ULN and Z score between sexes in the population of the MATEAR Study and to determine the usefulness and fairness of guideline recommendations regarding aortic diameters in females.

Materials and methods

The MATEAR Study was a prospective, observational, multi-center study that involved 53 accredited echocardiography laboratories of the Argentine Society of Cardiology (SAC). The protocol for this registry has been previously published[10]. Briefly, between February 2018 and June 2019, 1,000 consecutive healthy adult individuals were enrolled, excluding those with hypertension, a history of major cardiovascular risk factors, TAA, any degree of aortic stenosis or regurgitation, previous cardiac surgery, pregnancy, family history of genetic aortopathies and/or bicuspid aortic valve, competitive sport participants, and smokers.

To assess the covariates of interest, relevant clinical variables were collected for each patient, including demographic and anthropometric data, blood pressure, and cardiovascular history (personal and of first-degree family members). The BSA was calculated using the Dubois formula. Each patient underwent a comprehensive transthoracic echocardiogram following standard protocols based on ASE/EACVI guidelines to rule out unknown cardiovascular diseases[11]. TA diameters were measured at the aortic annulus, sinuses of Valsalva, sinotubular junction, and proximal tubular AA (at 1 cm above STJ). The annulus was measured at mid-systole (inner to inner edge method) and all others at end-diastole (leading to leading edge) (Fig. 1). Only subjects with complete aortic measurements (from annulus to proximal tubular AA) were included in the study. Aortic measurements were performed on-site and confirmed offline by two experienced readers. Finally, the offline measurements were included in the analysis.

Absolute diameters and indexed diameters by BSA and height were compared between males and females, as well as the estimated upper limit of normal (ULN), to analyze discrepancies of the recommended ULN (4 cm) for female individuals.

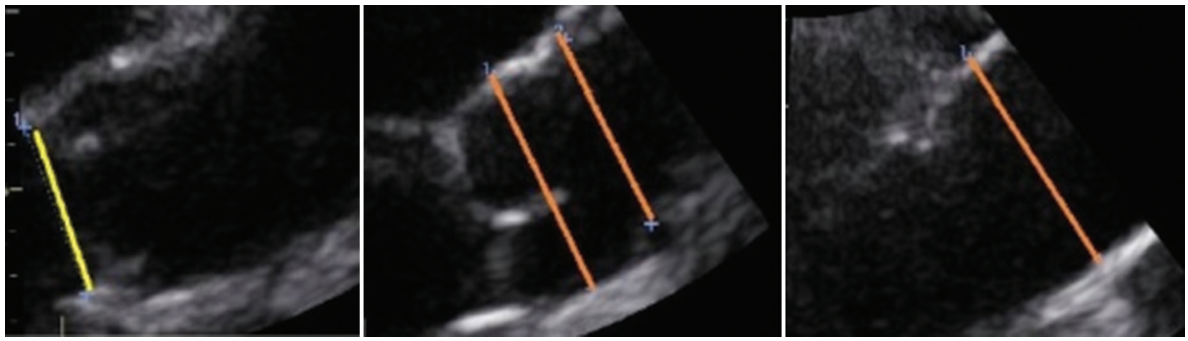

Figure 1. Measurements of the aorta. From left to right: the annulus was measured at mid-systole (inner-to-inner edge, depicted in yellow), Sinuses of Valsalva, sinotubular junction, and ascending aorta were measured at end-diastole (leading-to-leading edge).

The registry obtained ethical approval from the bioethics committee of the SAC, and every participant provided written informed consent. The research adhered to the guidelines for medical investigations outlined in the Declaration of Helsinki, the Good Clinical Practice Guidelines, and the current ethical regulations.

Statistical analysis

The analyses were performed by sex. The normality of distribution for continuous variables was evaluated using the Kolmogorov-Smirnov test. Reference values were defined as the values within the 2.5th-97.5th percentile, with the ULN being set at the upper reference value. Proportions were used to express discrete variables, while mean and standard deviation were used for continuous variables with normal distribution, and median and interquartile range for those with non-normal distribution. Student's t-test and Mann–Whitney test were utilized to compare continuous variables with parametric and non-parametric distributions, respectively. The statistical analyses were performed using R software, with a two-tailed $p < 0.05$ considered significant.

Statement of ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Argentinian Society of Cardiology I Review Board has approved our project. Every participant of the MATEAR study provided written informed consent.

Results

The study included 1,000 healthy adult individuals (mean age: 38.3 ± 12.7 years), of whom 553 were females (56.7% Caucasian, 38.3% Native Americans). Table 1 presents the baseline characteristics of the study population segregated by sex. Females had a mean age of 39.1 ± 13.4 years, while males had a slightly lower mean age of 37.2 ± 12.3 years ($p = 0.02$). Females had lower values in all anthropometric parameters, were approximately 13 cm shorter than males, and exhibited lower left ventricular diameters, ventricular mass, septal thickness, and average blood pressure. Aortic measurements at the six levels indicated that females had lower absolute aortic diameters in all aortic segments. However, when indexed parameters were analyzed in the aortic root and STJ, females demonstrated lower height-indexed diameters but higher BSA-indexed diameters (Table 2 and Fig. 2). In terms of the Z score evaluation, we observed that the recommended ULN of 4 cm was higher in females than in males, with a Z score equivalent to 3.61 and 2.34, respectively. In addition, our registry found the ULN in females to be 3.62 cm, corresponding to a Z score of 2.5.

Discussion

The present study adds to previous research by indicating that sex-specific thresholds are needed to accurately define aortic dilatation, contributing to the overall knowledge on differences in vascular dimensions between females and males.

Patients with a dilated thoracic aorta face a significant risk for aortic complications, such as aortic dissection or rupture, which are associated with high mortality

Table 1. Baseline MATEAR's population characteristics by sex

Variable	Total (n = 1000)	Females (n = 553)	Males (n = 447)	p
Age, y	38.3 ± 12.9	39.1 ± 13.4	37.2 ± 12.3	0.02
Weight, kg	74.4 ± 16.8	67.3 ± 14.5	83.2 ± 15.3	< 0.0001
Height, cm	167.4 ± 9.5	161.5 ± 6.0	174.6 ± 7.7	< 0.0001
BSA- Dubois, m^2	1.8 ± 0.2	1.7 ± 0.2	2.0 ± 0.2	< 0.0001
BMI, kg/m^2	26.4 ± 5.1	25.8 ± 5.4	27.2 ± 7.4	< 0.0001
MBP, mmHg	85.5 ± 7.3	83.5 ± 7.4	86.8 ± 7.1	< 0.0001
LV EF, %	64.8 ± 5.0	65.3 ± 4.9	64.1 ± 5.1	0.0003
LAVI, ml/m^2	23.5 ± 6.8	23.4 ± 6.4	23.8 ± 7.2	NS
LVMass, g/m^2	70.6 ± 13.2	67.1 ± 13.0	75.0 ± 13.1	< 0.0001
RWT	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	NS
LVEDD, cm	4.6 ± 0.4	4.4 ± 0.4	4.8 ± 0.4	< 0.0001
LVESD, cm	2.8 ± 0.4	2.7 ± 0.4	2.9 ± 0.4	< 0.0001
Septal Th, cm	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	< 0.0001

BSA: body surface area; BMI: body mass index; MBP: mean blood pressure, LVEF: left ventricle ejection fraction; LAVI: left atrial volume index; LVMass: left ventricle mass; RWT: relative wall thickness; LVEDD: left ventricle end-diastolic diameter; LVESD: left ventricle end-systolic diameter; Septal Th: septal thickness.

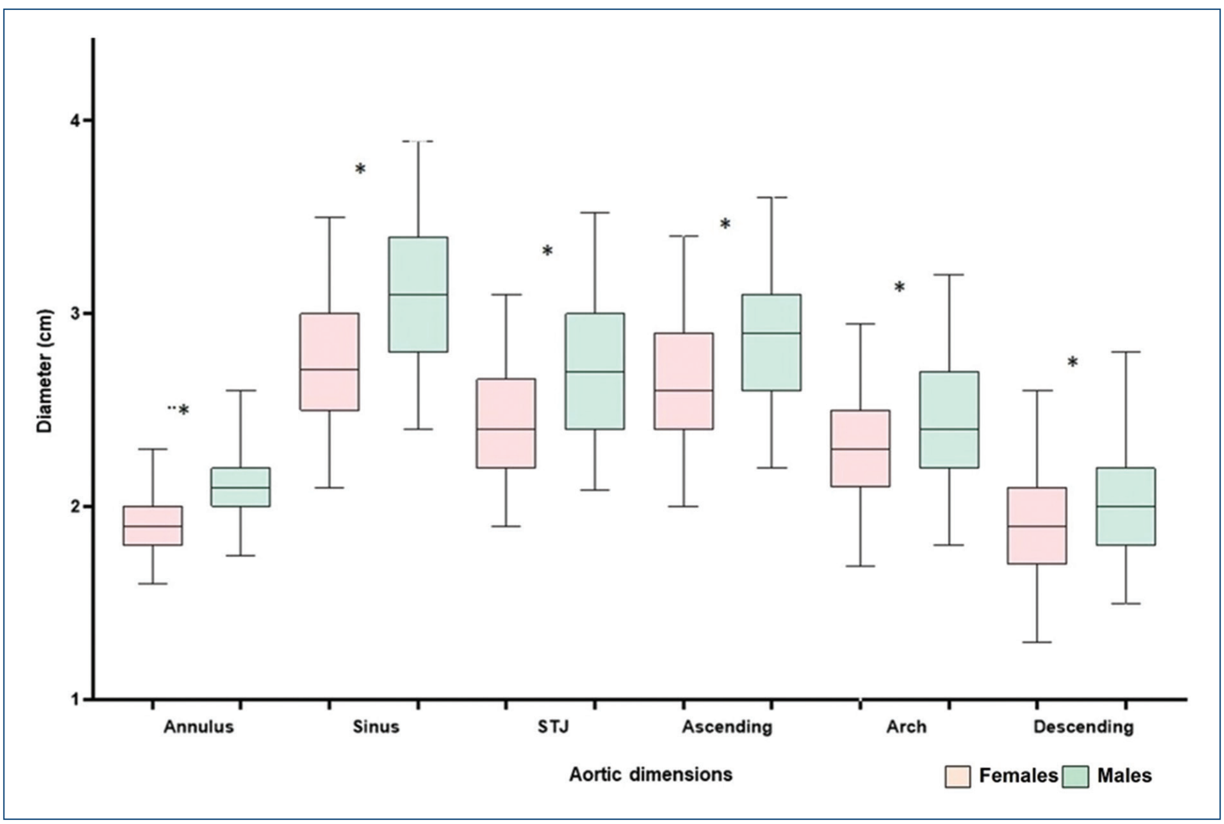

Figure 2. Comparison of absolute aortic diameters between males and females. The box plot displays the mean along with the 2.5th and 97.5th percentiles (p2.5 and p97.5, respectively). An asterisk (*) indicates significance at $p < 0.0001$.

Table 2. Aortic dimensions at the 6 levels by sex

Aortic dimensions	Females		Males		p
	(Mean SD)	P97.5	(Mean SD)	P97.5	
Annulus (cm)	1.93 ± 0.18	2.30	2.12 ± 0.20	2.60	< 0.0001
Annulus/BSA (cm/m^2)	1.13 ± 0.13	1.38	1.07 ± 0.11	1.30	< 0.0001
Annulus/height (cm/m)	1.19 ± 0.11	1.42	1.22 ± 0.10	1.45	0.0005
Sinus (cm)	2.77 ± 0.34	3.50	3.11 ± 0.38	3.89	< 0.0001
Sinus/BSA (cm/m^2)	1.62 ± 0.24	2.11	1.56 ± 0.21	1.97	0.0001
Sinus/height (cm/m)	1.72 ± 0.21	2.18	1.78 ± 0.21	2.20	< 0.0001
STJ (cm)	2.45 ± 0.31	3.10	2.74 ± 0.37	3.50	< 0.0001
STJ/BSA (cm/m^2)	1.43 ± 0.21	1.87	1.38 ± 0.20	1.84	< 0.0001
STJ/height (cm/m)	1.52 ± 0.19	1.93	1.57 ± 0.21	2.01	< 0.0001
Ascending (cm)	2.65 ± 0.35	3.40	2.88 ± 0.36	3.60	< 0.0001
Ascending/BSA (cm/m^2)	1.54 ± 0.22	2.00	1.45 ± 0.19	1.86	< 0.0001
Ascending/height (cm/m)	1.64 ± 0.21	2.09	1.65 ± 0.20	2.08	0.37
Aortic arch (cm)	2.27 ± 0.31	2.93	2.46 ± 0.33	3.20	< 0.0001
Aortic arch/BSA (cm/m^2)	1.32 ± 0.19	1.75	1.23 ± 0.18	1.64	< 0.0001
Aortic arch/height (cm/m)	1.37 ± 0.29	1.83	1.39 ± 0.24	1.84	0.29
Descending (cm)	1.91 ± 0.31	2.60	2.06 ± 0.33	2.80	< 0.0001
Descending/BSA (cm/m^2)	1.11 ± 0.18	1.50	1.03 ± 0.17	1.40	< 0.0001
Descending/height (cm/m)	1.15 ± 0.27	1.62	1.16 ± 0.23	1.60	0.43

Values are expressed as the mean ± standard deviation. T-test statistics for comparing means. P97.5: 97.5th percentile point.
BSA: body surface area; STJ: sinotubular junction.

rates[12,13]. Timely diagnosis is crucial for these patients, even though they may remain asymptomatic. Despite our long-standing understanding that factors such as body size, height, weight, and sex play a role in determining aortic diameters, it is only recently that the guidelines of aortic disease have begun to incorporate sex differentiation in the diagnostic of aortic dilatation[12,14]. Consequently, a uniform cutoff value of 4 cm has been widely used without considering individual variations[12].

Sex-specific differences in aortic dimensions and in aortic diseases have been described, prompting the question of whether specific considerations for management based on sex are warranted[15]. Bons et al. suggested that sex-specific distribution values of TA diameters may be beneficial in clinical practice, particularly for elderly patients[16]. Our study found that females were 13 cm shorter and had lower absolute aortic diameters across all segments compared to males, which aligns with previous research[4,17,18]. The AHA guidelines published in 2022 for aortic diseases diagnosis and management only suggested using height or BSA-indexation of aortic root or ascending aortic diameter only in patients significantly deviating from the average[14]. Unfortunately, when introducing the definition of aortic dilatation, these guidelines only provided an example for "a man in his 40s who would be expected to have an average aortic root diameter of 3.5 cm.[12]" Encouragingly, this year's guidelines for multimodality assessment of the aorta took a step forward by considering different thresholds to define aortic dilatation in males and in females (> 40 mm in adults and > 34 mm in female adults or > 22 mm/m^2)[19]. Typically, aortic dilatation is defined using a Z score of 2, equivalent to 4 cm[12,14]. Nevertheless, our findings suggest the necessity of a lower threshold for females, given that a diameter of 4 cm corresponded to a Z score of 3.61 standard deviations above the predicted mean normal diameter for this specific group. Counting solely on a 4 cm cutoff value could potentially result in the underdiagnosis of aortic dilatation in females. This notion also implies the utilization of absolute thresholds for aortic repair.

Even though TAAs are less prevalent in females compared to males, the consequences are often more severe for females. The IRAD registry found that females with aortic dissections experienced higher mortality rates and exhibited distinct differences in imaging findings and surgical approaches. Hormonal and mechanical influences have been proposed as potential explanations for the observed sex differences in aortic pathology, yet the exact underlying mechanisms remain unknown[15].

Despite these findings, the influence of sex on TA disease is incompletely characterized. The underrepresentation of females in cardiovascular trials and the lack of consideration of sex differences in guidelines are well-known issues[20]. This oversight could potentially result in the underdiagnosis of aortic dilatation in females. Given that females typically have smaller physical statures and aortic diameters, it raises the question as to why we still employ the same cut-off values to define aortic dilatation and determine the need for surgery. Forbes et al. found that thoracic aneurysms of equivalent diameters were proportionately larger in females than in males[21]. They suggested an approximately 1 cm lower treatment threshold in females than in males with TAA.

We believe that the optimal method for defining aortic dilatation may vary depending on the characteristics of the study population, but sex should always be considered. By considering sex-specific differences, we can improve the accuracy of diagnoses and facilitate appropriate referral for timely treatment.

Limitations

This was a cross-sectional study designed to provide reference values, and as such, it does not allow for the investigation of causal relationships or prognostic implications of the findings. In addition, the generalizability of our results may be limited by the population specificity, as our findings are based on a local cohort and may be influenced by ethnic variations. This restricts the applicability of our reference values to other populations with different ethnic compositions. Furthermore, we encountered difficulties in including patients older than 65 years who did not meet the exclusion criteria, primarily due to the high prevalence of arterial hypertension and other cardiovascular risk factors in this age group. This limitation could affect the representativeness of our results in older populations, and future studies should aim to address this gap. Nonetheless, the findings remain relevant for populations with characteristics similar to those in our study cohort.

Conclusion

Our findings suggest the need to reassess commonly used reference values by considering sex in the definition of aortic dilatation. We have contributed to providing a portion of the missing data necessary for reassessing local reference values.

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Author contributions

C. Carrero, F. Ash: Conception and design of the project. C. Carrero, I. Constantin, G. Masson: Data collection. C. Carrero, M.G. Matta: Data analysis and interpretation, Drafting the article. C. Carrero: Drafting the tables. C. Carrero, M.G. Matta, I. Constantin, G. Masson, F. Ash: Critical revision of the article.

Data availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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