

# Prevalence of Aortic Dilatation in Patients with Bicuspid Aortic Valve According to Reference Values for the Argentine Population. Influence of the Indexing Method

*Prevalencia de dilatación aórtica en pacientes con válvula aórtica bicúspide según los valores de referencia de la población argentina. Influencia del método de indexación*

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## ABSTRACT

**Background:** A significant proportion of patients with bicuspid aortic valve (BAV) develop aortic dilatation predisposing to serious complications.

**Objective:** The aim of this study was to estimate the prevalence of aortic dilatation applying reference values for the Argentine population in patients with BAV, and the influence of different indexing methods [height, (H) and body surface area (BSA)]

**Methods:** A total of 581 adult patients with BAV were consecutively included in the study. Aortic dilatation was defined according to guideline criteria (Devereux formula) and the reference values suggested by the Measurement of Thoracic Aorta by Echocardiography in Argentina (MATEAR) registry.

**Results:** Mean age was  $44.9 \pm 16$  years and 68.7% were men. A high prevalence of aortic root or ascending aorta dilatation was observed based on MATEAR criteria (72.3% according to H and 61.5% according to BSA). This was significantly higher for the aortic root than the one obtained with the Devereux formula (H: 47% vs. 31.5%; BSA: 35.2% vs. 26.5%  $P < 0.001$ ). A systematic underestimation was found when indexing for BSA in patients with body mass index (BMI)  $> 25 \text{ kg/m}^2$  (57.8% of population).

**Conclusions:** When applying the reference values for the Argentine population the prevalence of aortic dilatation was high and significantly greater at the root than that determined by cutoff points originating in other populations. Systematic underestimation was observed when correcting for BSA in patients with BMI  $> 25 \text{ kg/m}^2$ , so indexing by H would be the most recommended option.

**Key words:** Bicuspid aortic valve - Thoracic aorta aneurysm - Prevalence - Body mass index - Height-Body Surface Area

## RESUMEN

**Introducción:** Una proporción significativa de los pacientes con válvula aórtica bicúspide (VAB) desarrollan una dilatación de la aorta que los predispone a serias complicaciones.

**Objetivos:** Estimar la prevalencia de dilatación aórtica aplicando los valores de referencia de la población argentina en pacientes con VAB y la influencia de los distintos métodos de indexación (talla, T, y superficie corporal, SC).

**Materiales y métodos:** Se incluyeron consecutivamente 581 pacientes adultos con VAB. Se definió la dilatación según el criterio propuesto por las guías (fórmulas de Devereux) y sobre la base de los valores propuestos por MATEAR (Medición de Aorta Torácica por Ecocardiografía en Argentina).

**Resultados:** La edad media fue de 44,9 años ( $\pm 16$ ), 68,7 % género masculino. Sobre la base de MATEAR se observó alta prevalencia de dilatación de la raíz aórtica o aorta ascendente (72,3 % según T y 61,5 % según SC) que resultó, en la raíz, mayor que la obtenida según las fórmulas de Devereux (T 47 % vs. 31,5 %; SC 35,2 % vs. 26,5 %  $p < 0,001$ ). Se observó una subestimación sistemática al indexar por SC en pacientes con índice de masa corporal  $> 25 \text{ kg/m}^2$  (57,8 % de la población).

**Conclusiones:** La prevalencia de dilatación aórtica, cuando aplicamos los valores de referencia para la población argentina, fue alta en la raíz y significativamente mayor que la determinada por puntos de corte originados en otras poblaciones. Se observó una subestimación sistemática al corregir por superficie corporal en pacientes con índice de masa corporal  $> 25 \text{ kg/m}^2$ , por lo que indexar por talla sería la opción más recomendable.

**Palabras clave:** Válvula aórtica bicúspide - Aorta torácica - Aneurisma - Prevalencia - Índice de masa corporal - Altura - Superficie corporal

## Abbreviations

<b>BAV</b>	Bicuspid Aortic Valve	<b>SD</b>	Standard deviation
<b>BMI</b>	Body Mass Index	<b>H</b>	Height
<b>BSA</b>	Body surface area		

REV ARGENT CARDIOL 2021;89:190-195. <http://dx.doi.org/10.7775/rac.v89.i3.20314>

Received: 02/02/2021 – Accepted: 04/07/2021

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**Sources of funding:** The present work did not receive any scholarship or funding.

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## INTRODUCTION

Bicuspid aortic valve (BAV) represents the most prevalent congenital heart disease, affecting 0.5% to 2% of the population. (1) Its most frequent complication is valve dysfunction. However, a significant proportion of patients have concomitant aortic root and/or ascending aorta dilation, predisposing to serious complications such as aortic dissection. Its prevalence, which depends on both the population studied and the criteria used to define it, is estimated between 35% and 80%, according to different series. (2)

There are different ways to define aortic dilation. The most accepted describes it as the presence of a diameter greater than that expected for age, gender and body size. Different studies (3, 4) and clinical practice guidelines (5, 6) agree on this definition, and use the cutoff point of 2 standard deviations above the mean of a healthy population, or the 95th percentile, to define the largest expected diameter. They also recognize that these values are influenced by age, gender, body size and, more recently, by ethnicity. (7)

Consequently, it is logical to think that the best way to determine the presence of aortic dilation is to use normal values obtained in the same population that is being evaluated and adjust the observations to age, gender, ethnicity and body size. In relation to this last parameter, there is controversy to date as to which is the best indexing method in adult patients. Initially, and by extension of the results obtained in pediatrics, body surface area (BSA) was proposed as a reference parameter. (3, 8) However, taking into account less height (H) variation in adulthood and the great variability of weight in some subjects, indexing by H was explored, with results at least equivalent to those of BSA. (9)

However, clinical practice guidelines continue to use absolute cutoff points, independently of age, gender, body size or ethnicity, for the indication of interventions on the aorta both in patients with aneurysms associated with bicuspid valve or other etiologies. (10, 11) The most recent guidelines only limit suggestions to adjustments in patients with extreme BSA. This could explain, in part, why 59% of the patients who presented events in the international registry of aortic dissections had smaller diameters than the 5.5 cm suggested for prophylactic intervention in the guidelines. (12)

The aim of the present study was to evaluate the prevalence of aortic dilation in patients with BAV based on the recently published normal reference values for the Argentine population (13) and to study the influence of the indexing method on its assessment. Optimizing the detection of this complication could lead to better follow-up and timely intervention.

## METHODS

The study analyzed the first transthoracic echocardiogram of adult patients (>18 years) with a diagnosis of BAV detected prospectively and consecutively between January 2015 and December 2019, at Hospital Italiano de Buenos

Aires. Patients undergoing cardiac surgery were excluded from the study. Whenever possible, the aortic annulus, aortic root, sinotubular junction, ascending aorta, aortic arch, and descending aorta were measured in all study participants. All measurements were made at end-diastole and from leading edge-to-leading edge, except for the annulus, which was measured at mid-systole from inner edge to inner edge, according to the recommendations of the Chamber Quantification Guide of the American Society of Echocardiography. (5) Measurements of the aortic root were made at the level of the sinuses of Valsalva in long parasternal axis view and those of the ascending aorta from the same view or one intercostal space higher, where the largest diameter could be observed. Ultrasound Phillips (Epiq, Affinity 50-70, HD 15, HD 11 and Sparq) machines with 1-5 Mhz transducer were used.

Demographic and anthropometric variables (body weight and H), cardiovascular risk factors and clinical history were collected. Body surface area was estimated using the Dubois formula. (14) The relationship between body weight and H was classified according to body mass index (BMI): overweight >25-30 kg/m<sup>2</sup> and obesity >30 kg/m<sup>2</sup>.

Aortic dilation was defined as the presence of a diameter >95th percentile of the normal value of each segment for the Argentine population (13) and above the value determined by the Devereux formula (4) applied to derive nomograms used by the American guidelines. (5) In both cases, the estimation implied correction for both BSA and H to assess the influence of the indexing method on the prevalence of aortic dilation.

## Statistical analysis

Discrete variables are expressed as absolute and relative frequency. Continuous variables with normal distribution are expressed as mean and standard deviation (SD), and those with non-normal distribution, as median and interquartile range.

To study the concordance between the different indexing methods, Cohen's kappa index and the Bland-Altman graphic representation were used. (15, 16) The degree of agreement according to Cohen's kappa value was: 0-0.2: irrelevant; >0.2-0.4: low; >0.4-0.6: moderate; >0.6-0.8: good and >0.8-1: very good.

STATA 13.1 software package (StataCorp LP, College Station, TX) was used for the analysis. A two-tailed p value <0.05 was considered significant.

## Ethical considerations

The protocol was approved by the ethics committee of our institution.

## RESULTS

The study included 581 patients with diagnosis of BAV by transthoracic color Doppler echocardiography. Mean age was 44.9±16 years and 68.7% were men. Two hundred and thirty-three patients (40.1%) were overweight, a comorbidity significantly more frequent the older the age quartile (27% in 17-32 years vs. 51.4% between 57-86 years, p <0.001), while 103 (17.7%) were obese. Demographic and anthropometric variables, as well as risk factors, are described in Table 1.

Mean aortic root diameter was 3.57±0.56 cm and 3.7±0.68 cm at the level of the ascending aorta. These

diameters were significantly larger the older the age quartile ( $3.23 \pm 0.45$  cm and  $3.18 \pm 0.58$  cm in 17-32 years patients vs.  $3.83 \pm 0.52$  cm and  $4.07 \pm 0.57$  cm in those between 57-86 years, for the aortic root and ascending aorta, respectively,  $p < 0.001$ ). The remaining echocardiographic variables, where aortic diameters are detailed for the other segments, are shown in Table 2.

Using absolute cutoff points as definition of aortic dilation, we found that 22% and 31.5% of the patients presented dilation greater than 4 cm at the aortic root and ascending aorta level, respectively. Only 5.4% and 12% had dilation greater than 4.5 cm in the same locations; 35.8% had aortic root or ascending aorta greater than 4 cm and only 13.4% greater than 4.5 cm.

#### Estimation of the prevalence of aortic dilation based on the absolute and indexed cutoff points postulated for the Argentine population

Based on the absolute cutoff points proposed by the MATEAR registry, adjusted for gender, but independent of body size, 39% of the patients had root dilation and 59.8% ascending aorta dilation. The proportion of patients affected in the remaining segments was: aortic annulus 17.6%, sinotubular junction 31.8%, aortic arch 31.3%, and descending aorta 4.7%. At least one segment was dilated in 63.9% of patients.

When cutoff points indexed by gender and body size were considered, the proportion of patients with aortic root dilation was 35.2% and 47% according to BSA and H. The most frequently involved segment was the ascending aorta with 57% dilation according to BSA and 63.1% according to H. In 61.5% of cases patients had dilation of the aortic root or ascending aorta corrected by BSA and this percentage increased to 72.3% after correcting for H. The same estimations at the level of the aortic annulus, sinotubular junction, aortic arch and descending aorta, can be observed in Table 3 and their graphic representation

**Table 1.** General population characteristics

	n = 581
Age, years	44.85 ± 15.98
Male gender, n (%)	399 (68.7)
Body surface area, m <sup>2</sup>	1.87 ± 0.22
Height, m	1.7 ± 0.1
Weight, kg	75.97 ± 15.59
BMI, n (%)	
<25 kg/m <sup>2</sup>	245 (42.2)
25-30 kg/m <sup>2</sup>	233 (40.1)
>30 kg/m <sup>2</sup>	103 (17.7)
Hypertension, n (%)	182 (31.3)
Dyslipidemia, n (%)	127 (22)
Smoking, n(%)	62 (10.7)
Ex-smoker, n(%)	80 (13.8)
Diabetes, n (%)	12 (2.1)
End-stage kidney disease, n (%)	9 (1.5)

SD: Standard deviation; BMI: Body Mass Index.

**Table 2.** Echocardiographic characteristics

Type of BAV, n (%)	RCL-LCL	392 (72.3)
	RCL-NCL	77 (14.2)
	LCL-NCL	17 (3.1)
	Without raphe	56 (10.3)
Stenosis, n (%)	absence	418 (71.9)
	Mi-MiMo	80 (13.8)
	Mo	38 (6.5)
	Mo-S	18 (3.1)
	S	27 (4.6)
Insufficiency, n (%)	absence	150 (25.8)
	Mi-MiMo	287 (49.4)
	Mo	96 (16.5)
	Mo-S	26 (4.5)
	S	22 (3.8)
Aortic annulus diameter, cm		2.24 ± 0.24
Aortic root diameter, cm		3.57 ± 0.56
STJ diameter, cm		3.12 ± 0.53
Ascending aorta diameter, cm		3.7 ± 0.68
Aortic coarctation		17 (2.9)

BAV: Bicuspid aortic valve; RCV: Right coronary leaflet; LCL: Left coronary leaflet; NCL: Non-coronary leaflet; Mi: Mild; MiMo: Mild-to-moderate; Mo: Moderate; Mo-S: Moderate-to-severe; S: Severe; STJ: Sinotubular junction.

in Figure 1. The proportion of patients with at least one dilated segment was 61.5% and 72.3% according to BSA and H.

The prevalence of aortic dilation according to gender evidenced significant differences when comparing the aortic root and sinotubular junction, both when indexing by BSA as well as by H. Aortic root involvement was higher in men (39.3% vs. 25.9% and 51.1% vs. 37.9%, according to BSA and H,  $p = 0.002$ ), and in women sinotubular junction involvement was more prevalent (35% vs. 20% and 45.7% vs. 32.8%, according to BSA and H,  $p = 0.04$ ). The differences were not significant at the level of the aortic annulus, ascending aorta, aortic arch and descending aorta.

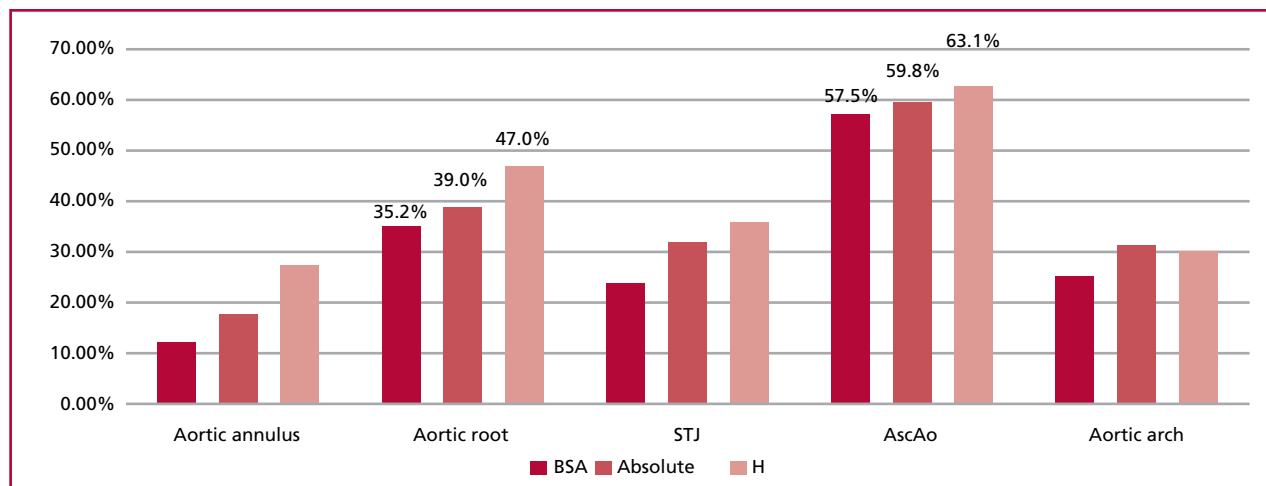
#### Comparison between the prevalence of aortic dilation according to reference values for the Argentine population and those suggested in the guidelines (obtained from the United States population)

According to the reference values for age, gender and body size proposed by Devereux (5) and endorsed by US guidelines, (6) the prevalence of aortic root dilation in this population was 26.5% when indexed by BSA and 31.5% when indexed by H. This prevalence was significantly lower than that obtained according to the MATEAR registry in this segment (35.2% according to BSA and 47% according to H,  $p < 0.001$ ). The concordance between these two methods according to Cohen's kappa index 0.64 (95% CI 0.57-0.71) only showed a moderate-to-good degree of agreement. This comparison was not made in other segments since the nomograms proposed by Devereux are described only for the aortic root.

**Table 3.** Prevalence of aortic dilation by segment according to the MATEAR registry. Analysis of concordance between indexing methods

	n	Dilation according to BS	Dilation according to BS	Cohen's Kappa Index (CI 95%)			
				Global	BMI < 25 kg/m <sup>2</sup>	BMI 25-30 kg/m <sup>2</sup>	BMI >30 kg/m <sup>2</sup>
Aortic annulus, n (%)	317	38 (12.1)	38 (12.1)	0.36 (0.24-0.47)	0.64 (0.47-0.82)	0.27 (0.13-0.41)	0.17 (0-0.35)
Aortic root, n (%)	566	199 (35.2)	199 (35.2)	0.65 (0.59-0.71)	0.82 (0.75-0.9)	0.68 (0.59-0.77)	0.25 (0.13-0.37)
Sinotubular junction, n (%)	309	74 (23.9)	74 (23.9)	0.64 (0.55-0.73)	0.76 (0.64-0.89)	0.63 (0.50-0.76)	0.42 (0.20-0.65)
Ascending Ao, n (%)	511	294 (57.5)	294 (57.5)	0.73 (0.67-0.79)	0.81 (0.73-0.88)	0.76 (0.66-0.85)	0.51 (0.35-0.67)
Aortic arch, n (%)	359	90 (25.1)	90 (25.1)	0.79 (0.72-0.86)	0.85 (0.74-0.96)	0.85 (0.76-0.94)	0.53 (0.33-0.74)
Descending Ao, n (%)	128	3 (2.3)	3 (2.3)	0.66 (0.29-1)	1 (1-1)	0.66 (0.02/1)	0.45 (0-1)

Ao: Aorta; BMI: Body mass index; BSA: Body surface area; H: Height



SJT: Sinotubular junction.; Ao: Aorta; Asc: Ascending; BSA: Body surface area; H: Height:

BSA refers to indexing by body surface area, H to indexing by height and Absolute to indexing by values adjusted to gender, but not to body size.

**Fig. 1.** Prevalence of aortic dilation by segment. Influence of the indexing method.

### Comparison of the different indexing methods by body size and their effect on prevalence of dilation estimation

The agreement between indexing by BSA or H at the aortic root and the ascending aorta level was evaluated according to the values proposed by the MATEAR registry. For this registry, Cohen's kappa index was first used, showing moderate-to-good degree of agreement for the global population. However, when stratifying according to BMI, a progressive loss of agreement was observed. While for the population with BMI <25 kg/m<sup>2</sup> the concordance was very good, it was only moderate-to-good for the 25-30 kg/m<sup>2</sup> range and low-to-moderate for the group with BMI >30 kg/m<sup>2</sup> (Table 3).

When studying the degree of agreement according to the Bland-Altman method, a systematic underestimation of the prevalence of aortic dilation was observed when indexing by BSA compared to indexing by H. At the aortic root level, the mean difference was  $-0.05 \pm 0.11 \text{ cm}^2$  for the normal weight group,  $-0.23 \pm 0.08 \text{ cm}^2$  for the overweight group and  $-0.38 \pm 0.09 \text{ cm}^2$  for the group with BMI >30 kg/m<sup>2</sup> (Figure 2). At the level of the ascending aorta, the mean difference in these three groups was  $-0.05 \pm 0.11$

cm,  $-0.24 \pm 0.08 \text{ cm}$  and  $0.39 \pm 0.09 \text{ cm}$ , respectively. This implied that when indexing by BSA, both for the aortic root and the ascending aorta measurements, 50% of patients had underestimations greater than 3%, 12% and 19% in the normal weight, overweight and obesity groups, respectively.

### DISCUSSION

The population of our study had mean age of  $44.9 \pm 16$  years, consistent with that reported in referral centers like ours, but greater than that reported in community studies and that of the MATEAR study population ( $38.3 \pm 12.7$  years). (13, 17) The proportion of male patients, as well as the prevalence of risk factors and echocardiographic characteristics was similar to those reported for this group of patients.

As expected, the prevalence of aortic dilation was different depending on the definition used. When absolute cutoff points independent of age, gender and body size were used, approximately one out of every 3 patients had aortic root or ascending aorta diameter greater than 4 cm (35.8%) and only one in 7 patients greater than 4.5 cm (13.4%).

Using the cutoff points described for the Argentine



population revealed a high prevalence of aortic dilation, regardless of the indexing method. According to absolute cutoff points only adjusted for gender, aortic dilation was estimated as 39% at the aortic root level.

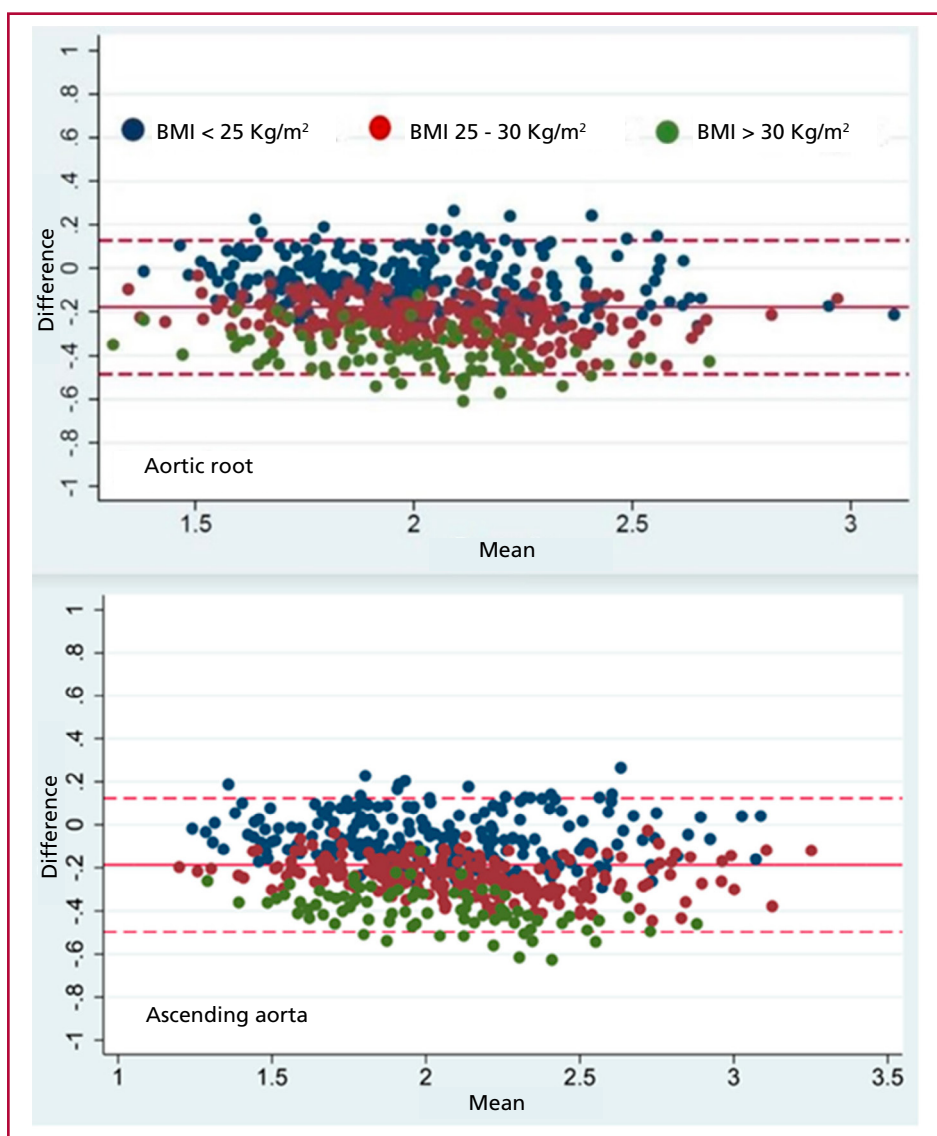
Unlike the studies by Roman and Devereux that only report data for the aortic root, the MATEAR registry provides reference limits for each of the aortic segments. This is of particular importance in the setting of bicuspid aortic disease, where the most affected segment is the ascending aorta. In that segment, the prevalence was 59.8% according to the 95th percentile for each gender. The rest of the segments involved in decreasing order were: sinotubular junction, 31.8%, aortic arch, 31.3% and descending aorta only 4.7%. The rest of the segments involved in decreasing order were: sinotubular junction, 31.8%, aortic arch 31.3%, and descending aorta, 4.7%. Of these the frequency of aortic arch involvement stands out as it is not usually described in patients with BAV. However, only in

6 (1.6%) and in 3 (0.8%) patients it exceeded 4 cm and 4.5 cm, respectively, and it was always associated with dilation of the aortic root or ascending aorta.

In addition, by adjusting for BSA and H, it was possible to verify a higher prevalence of aortic root involvement compared with that estimated according to the Devereux formula, which demonstrates the importance of having estimated reference values in the local population.

Also, systematically and in all the segments, it was seen that BSA indexing yielded prevalence values lower than absolute values and those indexed by H. As an example, the involvement of the ascending aorta was 59.8% for values not indexed to body size, 57.5% according to BSA and 63.1% according to H. At this point, it is important to highlight that 57.8% of the patients in our cohort had BMI >25 kg/m<sup>2</sup>, similar to the 60% prevalence reported in the MATEAR registry. This implies an increase in body size at the expense

**Fig. 2.** Bland-Altman. Concordance between the indexing methods by body surface area and height, stratified by body mass index



A systematic underestimation of indexed aortic diameters and, therefore, of the presence of aortic dilation, is observed when indexing by body surface area in relation to indexing by height.

of a parameter that varies in an acquired manner in almost 2 out of 3 patients, and could explain the variability between methods.

The concordance between both forms of indexing showed that it ranged only from moderate-to-good for the general population. When stratifying by BMI, a progressive loss was found the higher the stratum, and it ranged from low-to-moderate in obese patients. Similarly, the Bland-Altman method showed a systematic underestimation of aortic involvement when indexing by BSA in relation to indexing by H. Taking into account the prevalence of overweight and obesity in our population, the greater variability of weight compared with H and a very good agreement between methods in non-overweight patients, we believe that always indexing by H could be the most appropriate method.

### Limitations

It was not possible to obtain measurements of all segments in all the patients. However, they could be collected in 97% of the cases for aortic root and in 88% for the ascending aorta.

The cutoff points proposed by the MATEAR registry are not adjusted for age, which could translate into a slight overestimation of the prevalence of aortic dilation.

Although from a theoretical point of view, indexing by body size and especially by H seems the most appropriate option, whether this strategy translates into a clinical practice benefit remains to be evaluated.

### CONCLUSIONS

When the reference values for the Argentine population were applied, the prevalence of aortic dilation was high and significantly higher at root level than that determined by cutoff points originating in other populations.

When studying the influence of indexing methods, a systematic underestimation was observed when correcting for BSA in both overweight and obese patients. Considering the very good concordance between indexing by H and BSA in non-overweight patients and the high prevalence of overweight in this population, always indexing by H would be the most recommended option.

### Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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