Association between the sinus of Valsalva height and biometric parameters in patients with Marfan syndrome associated with aortic root aneurysm

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SUMMARY

Patients with Marfan syndrome and aortic root aneurysm require pre-surgical analysis of aortic root geometry for aortic reconstruction. The aim of this study is to perform the morphometric analysis of the sinus of Valsalva height and correlation between the former, age, weight, height, body mass index (BMI), and body surface area (BSA) in patients with Marfan syndrome and aortic root aneurysm. Data from 34 patients (28 men, 6 women) with Marfan syndrome and an ascending aortic diameter exceeding 45 cm were obtained using computed tomography angiography.

Gender-based differences were observed in the height of the left aortic sinus – by 47.23% (36.47±12.48 mm in men against 24.77±4.26 mm in women, p=0.0003). In men, a strong direct correlation has been identified between height and the right aortic sinus height (r=+0.75, p<0.0001), the posterior aortic sinus height (r=+0.71, p<0.0001), and the left aortic sinus height (r=+0.75, p<0.0001). Moderate reverse correlation has been discovered between the sinus of Valsalva height and BMI. No correlations have been identified between weight, BSA and the sinus of Valsalva height (p>0.05). In women, a strong direct correlation (Pearson) has been identified between age and the right aortic sinus height (r=+0.84, p=0.04), between weight and the left aortic sinus (r=+0.73, p=0.04) and between BSA and the left aortic sinus (r=+0.73, p=0.04).

Aortic sinus height in men increases with height and decreases with higher BMI and age. Weight and BSA do not affect the sinus of Valsalva height. In women, the sinus of Valsalva height is impacted by age, weight and BSA.

Key words: Sinus of Valsalva – Aorta – Computed tomography angiography – Marfan syndrome – Aneurysm

INTRODUCTION

Marfan syndrome is an inherited disease connected with fibrillin-1 gene defect (FBN1) (Renner et al., 2019). Patients with Marfan syndrome suf-

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fer from cardiovascular pathologies (Goyal et al., 2017; Grewal and Gittenberger-de Groot, 2018; Xuan et al., 2021). Aortic pathologies are reported in 90% of cases (Martín et al., 2020; Vanem et al., 2018). One of the forms of pathologies is the dilatation of the sinuses of Valsalva, which results in an aortic root aneurysm. In patients with Marfan syndrome and aortic root aneurysm, the mortality rate caused by aortic dissection without surgical intervention is 50% (Goyal et al., 2017). Most patients (90%, according to Goyal) require pre-emptive surgical intervention.

Reconstructive surgery options are valve-sparing aortic root replacement or valved conduit aortic root replacement (Pepper et al., 2020). Indications for surgery are aortic diameter of more than 50 mm or more than 45 mm with concurrent risks and a growth rate of more than 5 mm/year (Goyal et al., 2017; Martín et al., 2020). However, research shows that not only the diameter is a predictor for the dissection and it should not be the sole indicator for intervention (Wenzel et al., 2021). Age (Pape et al., 2007), height, weight (Wenzel et al., 2021), sex (Vanem et al., 2018) may also be predictors of dissection or lethality. In previous studies the connection between aortic diameter, age (Bahlmann et al., 2011) and anthropometric measurements (Nagpal et al., 2020) was mentioned. Most studies on the measurement of the sinus of Valsalva height are conducted in patients with aortic stenosis since this measurement is obligatory when qualifying patients for transcatheter aortic valve implantation (TAVI) (Francone et al., 2020). We have not found data on the sinus of Valsalva height in patients with Marfan syndrome associated with aortic root aneurysm. Nevertheless, pre-surgical planning of cardiovascular intervention for aortic root/ascending aortic reconstruction includes an analysis of aortic root geometry. The sinus of Valsalva height influences the choice of surgical intervention type: valve-sparing aortic root replacement or valved conduit aortic root replacement.

The study presents a morphometric analysis of the sinus of Valsalva height in patients with Marfan syndrome and aortic root aneurysm. We tried to establish a connection between age, weight, height, body mass index (BMI), and body surface area (BSA) and the sinus of Valsalva height in men and women with Marfan syndrome and aortic root aneurysm.

MATERIALS AND METHODS

A retrospective study included analysis of pre-operative contrast-enhanced CT images of the aorta in patients with Marfan syndrome. The data had been taken from the registry of the Cardiac Surgery Department of Lviv Regional Clinical Hospital between 2019 and 2021. Inclusion criteria: patients over 18 years old, with diagnosed Marfan syndrome (based on Ghent nosology or genetic testing) (Renner et al., 2019), and with sinuses of Valsalva diameter of more than 45 cm (posterior sinus). Exclusion criteria: congenital heart defects, reconstructive surgeries of the ascending aorta, prosthetic aortic valve, incomplete anthropometric details of patients, and inappropriate image quality. Analysis of the 128 DICOM exams revealed that 34 patients met the criteria (28 men, 6 women). They were later divided into two groups based on gender.

CT angiography of the aorta was conducted on LightSpeed 64 VCT XT (General Electric, Boston, USA) with ECG synchronisation and Ultravist 470 (Bayer Healthcare, Berlin, Germany). Measurement of the sinus of Valsalva height was performed from the lower point of aortic valve cusps in the area of the left ventricular outflow tract (LVOT) up to the projection of the sinotubular junction (Hennessey et al., 2020). Image analysis has been conducted independently by two radiologists using radiology imaging viewer software RadiAnt DICOM Viewer v.5.0.2 (Poznan, Poland) in double-oblique projection (Francone et al., 2020). The sinus of Valsalva height is presented in cm. Clinical data of patients: sex, age, weight, and height, BMI and BSA (Mosteller formula).

The study was conducted in compliance with the ethical standards of the 1964 Helsinki Declaration and approved by the Bioethics Commission of Lviv National Medical University (Protocol No. 10 of 20 December 2021). Formal informed consent of the patients is not required.

Statistical analysis was conducted in R Commander (version 2.7-2. GNU General Public Li-

cense, Ontario, Canada) and SPSS (version 22.0. IBM Corp. Armonk, NY, USA). Student's t- test was used to analyze average values of biometric measurements (Gaussian data distribution). Calculation of pair connections between age and anthropometric indicators and the sinus of Valsalva height has been conducted using Pearson's linear correlation. The multiple connection between independent variables – biometric measurements (age, weight, height, BMI, BSA) and dependent variables – the sinus of Valsalva height – was examined with the help of multiple regression analysis. In all studies, $p<0.05$ was considered valid.

RESULTS

In men with Marfan syndrome and aortic root aneurysm (average age – 56.61±16.11 years, height 1.78±0.09 m, n=28), the average values of the height of the posterior and right aortic sinuses were practically on the same level (Fig. 1, Fig. 2). The average value of left aortic sinus height was slightly lower and equaled 36.47±12.48 mm. In women (average age 44.33±13.08 years, height 1.67±0.05 m, n=6), the height of posterior and right aortic sinuses is higher in comparison with the left sinus (Table 1). Gender-based differences were observed in the height of left aortic sinus

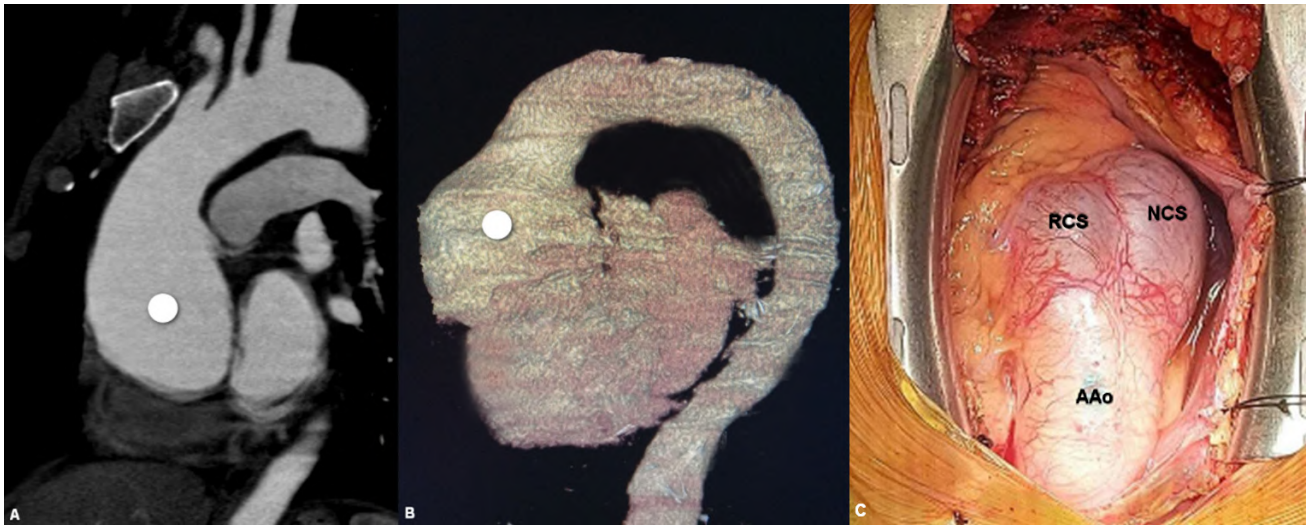


Fig. 1.- Computed tomography and intraoperative images demonstrating aortic root aneurysm in patient with Marfan syndrome. (**A**) A curved multiplanar reformatted view. (**B**) Volumetric rendering (3D reconstruction). (**C**) Intraoperative imaging of the right coronary sinus (RCS), the posterior or non-coronary sinus (NCS), and ascending aorta (AAo).

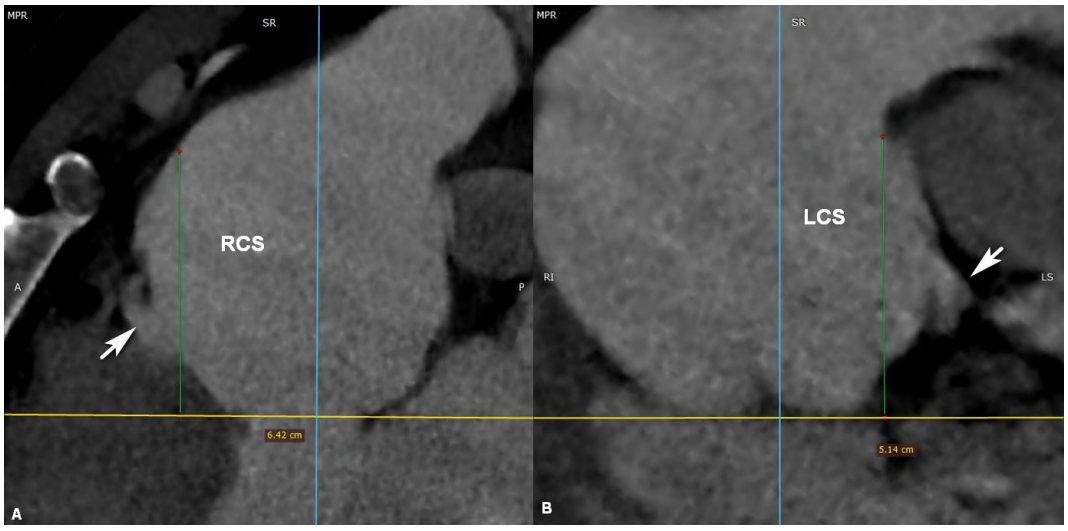


Fig. 2.- Computed tomography images of the measurement of the sinus of Valsalva height in male with Marfan syndrome and aortic root aneurysm. (**A**) The height of the right coronary sinus (RCS) and (**B**) the left coronary sinus with the appropriate coronary arteries (white arrow).

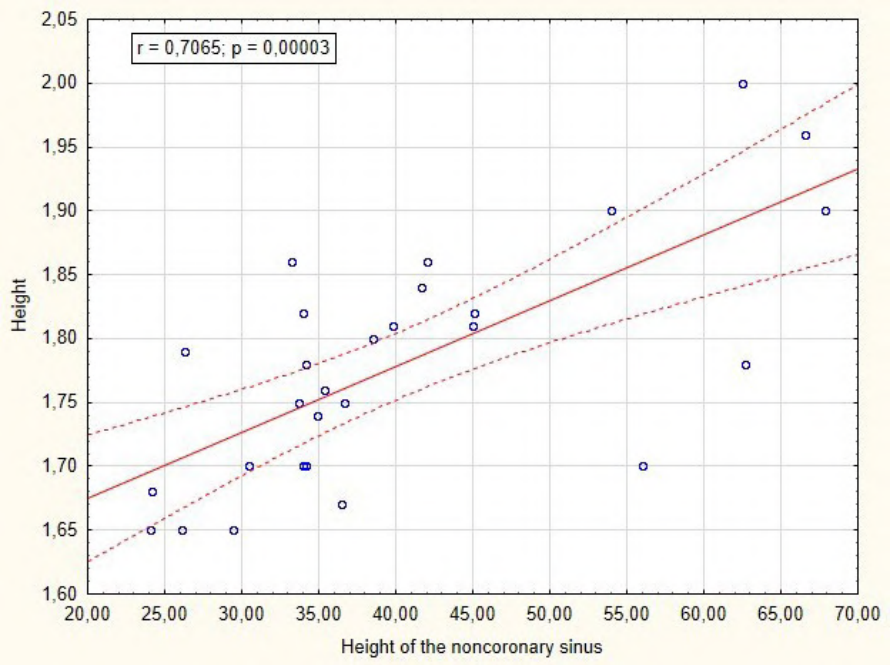
– by 47.23% (36.47±12.48 mm in men against 24.77±4.26 mm in women, p=0.0003). The height of the right and posterior sinuses of Valsalva in men is higher than in women with no statistical significance (p>0.05).

Significant correlation between height and the sinus of Valsalva height has been identified (Pearson). In men, strong direct correlation has been determined between height and the right aortic sinus height (r=+0.75, p<0.0001), the posterior aortic sinus height (r=+0.71, p<0.0001), the left aortic sinus height (r=+0.75, p<0.0001) (Table 2, Graphic 1). Moderate reverse correlation has been identified between the sinus of Valsalva height and BMI (correlation coefficient varied between r=-0.55, p=0.002 for the right aortic sinus height and up to r=-0.39, p=0.042 for the posterior aortic sinus height). No correlations have been discovered between weight, BSA and the sinus of Valsalva height (p>0.05). Moderate reverse correlation was found between age and the right aortic sinus height (r=-0.60, p=0.001), the posterior aortic sinus height (r=-0.50, p=0.006) and the left aortic sinus height (r=-0.48, p=0.009) (Graphic 2). Logically, significant correlations were proved between the height of the right, left and posterior sinuses of Valsalva (p<0.0001).

In women, strong direct correlation (Pearson) has been identified between age and the right aortic sinus height (r=+0.84, p=0.04), between weight and the left aortic sinus height (r=+0.73, p=0.04) and between BSA and the left aortic sinus height (r=+0.73, p=0.04) (Tab. 3, Graphic 3). Direct correlation was found between age and the left aortic sinus height (r=+0.41); between weight and the posterior (r=+0.55) and the right aortic sinus height (r=+0.49). BMI is directly correlated with all sinuses of Valsalva height (for the posterior (r=+0.55), the left (r=+0.52) and the right (r=+0.49)). The same correlation was detected between BSA value and the posterior aortic sinus height(r=+0.54) and the right aortic sinus height (r=+0.51).

Table 1. Comparison of blood vessel indicators in men and women with Marfan syndrome and aortic root aneurysm (M±SD, mm).

Indicators	Men (n=28)	Women (n=6)	p	Difference by gender (%)
Posterior aortic sinus height	40.33±12.76	34.23±9.33	0.19	17.82
Left aortic sinus height	36.47±12.48	24.77±4.26	0.0003	47.23
Right aortic sinus height	39.41±16.40	32.22±9.63	0.16	22.32

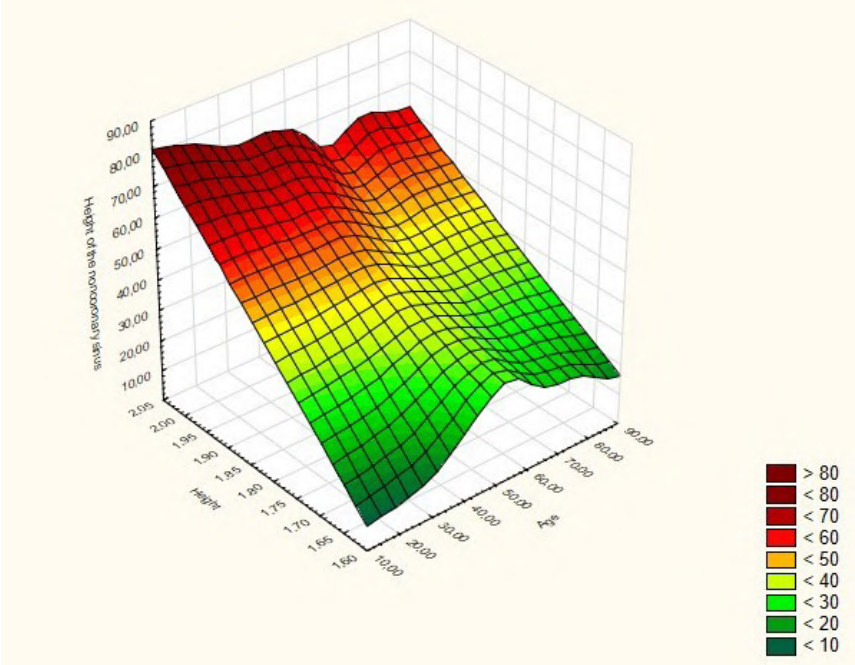


Graphic 1.- Correlation between height and posterior aortic sinus height indicators in men with aortic root aneurysm and Marfan syndrome.

Multiple regression analysis of the sinus of Valsalva height with a choice of optimal set of independent predictors (age, height, weight, BMI, BSA) in men with Marfan syndrome and aortic root aneurysm has confirmed several influences. The posterior aortic sinus height has been proven to be strongly influenced by age (reverse influence) and all anthropometric measurements (direct influence of height and BMI and reverse influence of weight and BSA): R=+0.81 with p<0.0002 (Fisher's exact test) and standard error of evaluation (SEE) 8.33. Adjusted coefficient of multiple determination R2adj=+0.57 points to the influence of these independent predictors on the posterior aortic sinus height in 57.4% cases. The left aortic sinus height has been strongly influenced by a set of 4

Table 2. Correlation (r) between the blood vessel, age and anthropometric indicators in men with Marfan syndrome and aortic root aneurysm. BMI: body mass index, BSA: body surface area.

Indicators		Posterior aortic sinus height	Left aortic sinus height	Right aortic sinus height
Age	r	-0.50	-0.48	-0.60
	p	0.006	0.009	0.001
Height	r	0.71	0.70	0.75
	p	<0.0001	<0.0001	<0.0001
Weight	r	-0.02	-0.06	-0.18
	p	0.93	0.76	0.35
BMI	r	-0.39	-0.42	-0.55
	p	0.042	0.024	0.002
BSA	r	0.18	0.13	0.05
	p	0.35	0.50	0.82
Posterior aortic sinus height	r		0.90	0.90
	p		<0.0001	<0.0001
Left aortic sinus height	r	0.90		0.89
	p	<0.0001		<0.0001
Right aortic sinus height	r	0.90	0.89	
	p	<0.0001	<0.0001	

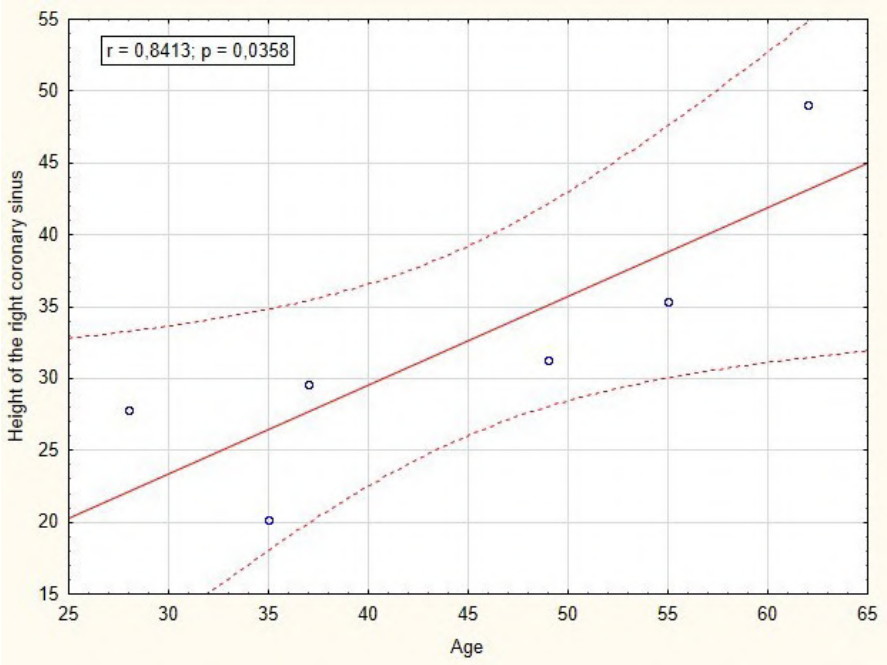


Graphic 2.- Correlation between height, age and posterior aortic sinus height indicators in men with aortic root aneurysm and Marfan syndrome.

independent predictors: direct influence of height and weight, and reverse influence of age and BSA. Multiple correlation coefficient accounted for R=+0.81 with p<0.0002 (Fisher's exact test) and SEE=8.12. Adjusted coefficient of multiple determination R2adj=+0.57 proves influence of independent predictors on the left aortic sinus height in 57.5% cases of this group. The right aortic sinus height depends on height, BSA (strong direct influence), age, weight, BMI (direct reverse influence): R=+0.875, p<0.0001, SEE=8.78. Adjusted coefficient of multiple determination R2adj=+0.71

Table 3. Correlation (r) between the sinus of Valsalva height, age and anthropometric indicators in women with Marfan syndrome and aortic root aneurysm. BMI: body mass index, BSA: body surface area.

Indicators		Posterior aortic sinus height	Left aortic sinus height	Right aortic sinus height
Age	r	0.28	0.41	0.84
	p	0.59	0.42	0.04
Height	r	-0.19	-0.01	-0.17
	p	0.72	0.98	0.74
Weight	r	0.55	0.73	0.49
	p	0.26	0.04	0.32
BMI	r	0.55	0.52	0.49
	p	0.26	0.29	0.33
BSA	r	0.54	0.73	0.51
	p	0.26	0.04	0.30
Posterior aortic sinus height	r		-0.21	0.17
	p		0.69	0.74
Left aortic sinus height	r	-0.21		0.77
	p	0.69		0.07
Right aortic sinus height	r	0.17	0.77	
	p	0.74	0.07	
	p	0.63	0.03	0.08



Graphic 3.- Correlation between age and the right aortic sinus height indicators in women with Marfan syndrome and aortic root aneurysm (Height, Age, Height of the right coronary sinus).

proves influence of independent predictors on the right aortic sinus height in 71.3% cases of this group.

Relevant risk analysis in comparison groups did not prove a significantly higher risk of abnormal values of the studied parameters of aortic sinus height in women with aortic root aneurysm compared with men who have the same pathology: RR was in the range of 0.32 to 1.07 ($p>0.05$).

DISCUSSION

Morphometric analysis of the sinus of Valsalva height in patients with Marfan syndrome and aortic root aneurysm identified higher values of the left aortic sinus in men than in women ($p=0.0003$). The height of the right and posterior sinus of Valsalva in men was also higher, yet without statistical significance ($p>0.05$). A correlation has been identified between age, weight, height, BMI, BSA and the sinus of Valsalva height separately in the group of men and the group of women. In men, a strong direct correlation between height and the right, left and posterior aortic sinuses height has been determined ($p<0.0001$). Moderate reverse correlation has been confirmed between BMI and the height of posterior sinus ($p=0.002$) and left sinus ($p=0.042$).

Reverse moderate correlation has been identified between age and the height of the right ($p=0.001$), posterior ($p=0.006$) and left aortic sinus ($p=0.009$). In women, age had a direct influence on the right aortic sinus height ($p=0.04$), weight and BSA affected the left aortic sinus height ($p=0.04$). Direct moderate correlation (from $r=+0.41$ to $r=+0.55$) has been established between age and the left aortic sinus height; between height, BSA and the posterior and right aortic sinus height; a correlation between BMI and the height of all aortic sinuses has not been proven due to limited sampling ($n=6$). Nevertheless, we consider it necessary to mention those correlations between age and anthropometric details and the sinus of Valsalva height. They might be important, when modelling an identical situation with more extensive sampling.

Multiple regression analysis has proven that the posterior aortic sinus height in men is strongly influenced by height and BMI and is reversely influenced by age, weight and BSA. The left aortic sinus height is strongly influenced by age and weight and is reversely affected by age and BSA. The right aortic sinus height is strongly influenced by height and BSA and is reversely influenced by age, weight and BMI.

These findings go in line with the statement that age has an influence on aortic dimensions (Erbel, 2006; Forte et al., 2020; Nagpal et al., 2020). In particular, the coronary sinus of Valsalva height in men is higher than in women (Stolzmann et al., 2009). It has been established that in patients with Marfan syndrome and aortic root aneurysm, age and height influence sinuses of Valsalva size just as in patients without diagnosed connective tissue disorders (Bahlmann et al., 2011; Nagpal et al., 2020; Plonek et al., 2019). The identified reverse correlation between age and sinus height proves that the value of aortic sinus height decreases with increased age in men with Marfan syndrome and aortic root aneurysm. Gender-based correlation between BSA and aortic size remains debatable (Forte et al., 2020; Nagpal et al., 2020). The question of correlation between biometric measurements and sinuses of Valsalva height in patients with Marfan syndrome and aortic root aneurysm still stands.

The sinus of Valsalva height is essential when planning cardiac surgeries for aortic root/ascending aortic aneurysms. Among all thoracic aortic aneurysms, the aneurysm of this segment is the most commonplace (approximately 60% of cases) (Nagpal et al., 2020). As of today, two options for aortic root aneurysm surgeries are available: valve-sparing aortic root replacement or remodeling (David operation, Yacoub procedure, Urbanski operation, neocuspidalization by Ozaki) and valved conduit aortic root replacement (Bentall-de-Bono surgery, full root technique, Wheat procedure) (Hennessey et al., 2020; Task et al., 2014; Valdis et al., 2019). Almost all procedures (except Wheat procedure, Ozaki procedure) require reimplantation of coronary ostia (Pidvalna et al., 2022). The criteria for selecting the type of surgery are the following: the higher the sinuses of Valsalva height, the higher the chances of a valve-sparing procedure. The lower the sinuses

of Valsalva height, the stronger the recommendations for valve-replacement surgery. For cardiologists, another critical indicator is the height of the posterior sinus, which is located close to the septum and right atrium. Adequate morphometric assessment of the aortic root ensures higher chances of a successful procedure and the functioning of a reconstructed aortic segment.

The analysis was conducted for each vessel parameter (dependent predictors) with a selection of an optimal set of independent predictors (age and anthropometric indicators). As a result of the present study, groups of independent predictors were formed, which had a valid strong influence on the values of the sinus of Valsalva height in persons with Marfan syndrome and aortic root aneurysm, which is proven by relevant validity criteria. Nevertheless, the study has its limitations. Firstly, it includes persons in their middle adulthood, which should be considered when assessing the influence of age on aortic dimensions. Secondly, a small sampling of women (n=6) had an effect on the unconfirmed correlation between age, anthropometric indicators and aortic sinus height. Thirdly, we did not assess the anatomy of the aortic valve (bicuspid or tricuspid), which may affect the aortic root geometry.

To conclude, the significant valid correlation has been identified between anthropometric indicators and the sinus of Valsalva height based on data of CT images of patients with Marfan syndrome and aortic root aneurysms. Aortic sinus height in men increases with increased height and decreases with increased BMI and age. Weight and BSA do not affect the height of sinuses of Valsalva. In women, the height of aortic sinuses is influenced by age, weight and BSA.

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