ORIGINAL ARTICLE

The association between severe mitral stenosis and the size of the aortic root and the ascending thoracic aorta

Ciddi derecede ağır mitral stenozu, aort kökü ve çıkan torasik aort arasındaki ilişki

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ABSTRACT

Objective: The aim of this study was to examine the role of isolated rheumatic mitral stenosis (MS) in remodeling of the aorta at various locations.

Methods: In this prospective study, patients who were to undergo transesophageal echocardiography for various indications were screened. The study participants were classified into 2 groups according to the presence of MS with a valve area ≤1.5 cm^2. Factors associated with the index dimensions of the aorta at the levels of the annulus, root, sinotubular junction (STJ), and the proximal ascending portion (5 cm from the annulus) were evaluated. Multivariate linear models were constructed including factors that affect the size of the aorta at any of the aforementioned levels. Pearson's correlation coefficient was used to investigate the association between mitral valve area, mitral valve gradient, and dimensions of the aorta.

Results: A total of 179 men and 354 women were enrolled. Eighty-four patients had MS (15.8%). The patients with MS were younger and less likely to have hypertension. In univariate analysis, patients with MS had a smaller annulus and STJ (p=0.003 and p=0.043, respectively). Multivariate analysis indicated that MS was correlated with a smaller indexed size of the aortic annulus, yielding a regression coefficient value of 0.541 (p=0.005).

Conclusion: The presence of significant stenosis at the level of the mitral valve is associated with a smaller diameter in the aortic annulus. It is yet to be clarified whether this phenomenon occurs due to chronic, long-standing, low stroke volume or involvement of the aortic annulus in the fibrotic process of mitral disease.

ÖZET

Amaç: Bu çalışmanın amacı değişik yerleşimlerdeki aortun yeniden biçimlendirilmesinde izole mitral stenozun (MS) rolünü incelemekti.

Yöntemler: Bu prospektif çalışmada değişik endikasyonlar için transözofageal ekokardiyografi yapılacak hastalar tarandı. Çalışma katılımcıları mitral kapak alanı ≤1.5 cm^2 olan hastalar MS olup olmadıklarına göre 2 grupta sınıflandırıldı. Aort halkası, aort kökü, sinotübüler bileşke (STB) ve çıkan aortun aort halkasından 5 cm uzaklıktaki proksimal kısmının boyutlarıyla ilişkili faktörler değerlendirildi. Yukarıda belirtilen seviyelerin herhangi birinde aortun boyutunu etkileyen faktörleri içeren çok değişkenli doğrusal modeller oluşturuldu. Mitral kapak alanı, mitral kapak gradyanı ve aortun boyutları arasındaki ilişkiyi araştırmak için Pearson korelasyon katsayısı kullanıldı.

Bulgular: Toplam 179 erkek ve 354 kadın çalışmaya alındı. Hastaların 84'ünde (%15.8) MS mevcuttu. MS hastaları daha genç ve hipertansiyon olma ihtimalleri daha düşüktü. Tek değişkenli analizde MS'li hastaların aort halkası ve STB'si daha ufaktı (sırasıyla, p=0.003 ve p=0.043). Çok değişkenli analizde MS daha küçük aort halkasıyla ilişkili olup regresyon katsayısının 0.541 olmasına neden olmuştur (p=0.005).

Sonuç: Mitral kapak düzeyinde önemli stenozun varlığı aort halkasının daha küçük çaplı olmasıyla ilişkilidir. Bu olgunun kronik, uzun süreli düşük atım hacim veya aort halkasının mitral hastalıktaki fibrotik sürece mi bağlı olduğu henüz açıklığa kavuşturulmamıştır.

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The size of the proximal aorta correlates with the diameter of the coronary arteries and has a prognostic role in the occurrence of cardiovascular events.[1–3] Remodeling of the proximal aorta occurs due to structural changes in the collagen-rich tissue of the aortic wall secondary to chronic shear forces exerted by luminal pressure. Such remodeling is generally observed in chronic hypertension, although other factors, such as inherent weakness of the aortic wall in collagen disease (e.g., Marfan syndrome) can play a significant role in its pathophysiology.[4] The ascending aorta has an important function in vascular hemodynamics and left ventricular (LV) afterload changes, as histological/structural characteristics of the aorta can inversely affect the central pulse pressure and progression of systolic heart failure.[5]

Abbreviations:

IQR	*Interquartile range*
LV	*Left ventricle*
MS	*Mitral stenosis*
MVA	*Mitral valve area*
STJ	*Sinotubular junction*
TEE	*Transesophageal echocardiography*

Reverse remodeling of the proximal ascending aorta may also occur in conditions where the systolic stroke volume of the LV is diminished. A smaller aorta is reported in patients with systolic heart failure and it carries a relatively poorer prognosis. In other cardiac diseases, obstructive pathology of the mitral valve is associated with reduced systolic stroke of the left heart.[6,7] Mitral stenosis (MS) is a common consequence of acute rheumatic fever in developing countries; however, the narrowing of the valve and the subsequent hemodynamic changes that develop can take 20 to 40 years to evolve.[8–11] MS is hemodynamically accompanied by LV under-filling and a smaller stroke volume.[12,13] It was observed that the size of the ascending aorta in the patient population diagnosed with MS appeared to be smaller, and this study was designed to test this observation. To the best of our knowledge, neither clinical nor pathological studies have drawn attention to any association between aortic diameter and MS. Reverse remodeling of the proximal ascending aorta secondary to MS has not been clearly established. There is little in the literature on this issue at present.

This is the first prospective, observational study that aimed to investigate a correlation between the diameter of the proximal aorta measured using transesophageal echocardiography (TEE) and MS. It was hypothesized that the presence of significant MS inversely affects the dimensions of the proximal ascending aorta.

METHODS

This prospective, cross-sectional observational study was undertaken over a period of 12 months at a university-affiliated cardiac imaging clinic. The institutional review board and the ethics committee approved the protocol for its scientific merit and ethical standards. A research team member approached eligible patients and obtained informed, written consent after full disclosure of the study protocol and objectives. Collected clinical information was treated carefully to ensure patient privacy.

Patients aged between 18 and 80 years who were to undergo TEE for any indication between August 1, 2016 and July 31, 2017 were screened for enrollment. The exclusion criteria were patients with Marfan syndrome, bicuspid aortic valve, any degree of aortic stenosis, rheumatic involvement of the aortic valve, non-rheumatic mitral valve pathologies, or prior open-heart surgery. Commissural fusion and diastolic doming of the mitral valve leaflets were considered signs of rheumatic MS. Participants were classified into 2 groups: Group I comprised patients with significant MS [mitral valve area (MVA) ≤1.5 cm^2) and Group II was made up of patients without significant MS (MVA >1.5 cm^2).

The relevant demographic, anthropometric, and medical history data were recorded. Clinical information, including Framingham's coronary risk factors (hypertension, diabetes mellitus, smoking, hyperlipidemia, and family history of coronary disease), congestive heart failure, atrial fibrillation, cerebrovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease, as well as medication history were also collected.

An experienced cardiologist with special training in echocardiography performed and interpreted all of the TEE examinations. MVA was calculated using a combination of planimetry and the pressure half-time method. Doppler studies were utilized to measure trans-mitral valve gradients. The diameter of the ascending aorta was measured at the levels of the annulus, root, sinotubular junction (STJ), and 5 cm distal to the aortic annulus. The primary endpoint for the current study was the indexed diameter of the aorta measured at 4 levels: a) annulus, b) root, c) STJ, and d) proximal ascending aorta. Indexed values were calculated by dividing the absolute measurements by the

body surface area. The body surface area was calculated for every patient using the Mosteller formula as a product of height and weight.[14]

In order to conduct the statistical analysis, the distribution of all of the numerical variables was tested using the Kolmogorov-Smirnov test; the data for variables that lacked normal distribution were presented as median [interquartile range (IQR)]. Categorical variables were stated as frequencies with percentages. The comparison of categorical variables between the groups of patients with MS and those without MS was performed using a chi-square analysis or Fischer's exact test, as appropriate. The non-parametric Mann-Whitney U test was used to compare the difference in the median of numerical variables. Variables affecting the size of the aorta at any level with a p value <0.05 were included in multivariable linear regression models. Gender, age, hypertension, beta-blockers, and MS were identified as the independent variables to be evaluated for their effect on the indexed dimensions of the aorta at each level. A p value <0.05 was considered statistically significant. All of the data were analyzed using IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp., Armonk, NY, USA).

RESULTS

After screening 1080 patients, 179 men and 354 women were eligible to be included in the study. The female/male ratio in Group I patients with MS was 0.83,

Table 1. Gender distribution, comorbid diseases and medication history of patients according to the presence of mitral stenosis observed on transthoracic echocardiography

	Without MS (n=449)		With MS (n=84)		OR	Lower	Upper	*p*
	n	%	n	%				
Gender								
Male	160	32.0	19	17.2	1.894	1.097	3.271	0.023
Female	289	68.0	65	82.8				
Hypertension	291	65.0	38	45.2	0.446	0.278	0.714	0.001
Diabetes mellitus	114	25.4	12	14.3	0.488	0.256	0.933	0.026
Hyperlipidemia	92	20.5	11	13.1	0.583	0.297	1.144	0.133
Neoplastic disease	5	1.1	0	0.0				1.000
Chronic kidney disease	31	6.9	3	3.6	0.481	0.144	1.610	0.336
Congestive heart failure	78	17.4	1	1.2	0.057	0.008	0.418	<0.001
Coronary artery disease	121	26.9	14	16.7	0.540	0.294	0.995	0.055
Cerebrovascular accident	26	5.8	5	6.0	1.027	0.383	2.756	1.000
COPD	12	2.7	1	1.2	0.438	0.056	3.412	0.703
Active smoking	66	14.7	10	11.9	0.782	0.384	1.591	0.611
Atrial fibrillation	33	7.3	27	32.1	5.943	3.330	10.60	<0.001
Mitral regurgitation	71	15.8	12	14.3	0.887	0.458	1.720	0.870
Tricuspid regurgitation	44	9.8	18	21.4	2.510	1.368	4.606	0.005
Aortic diameter >4.0 cm	34	7.6	2	2.4	0.288	0.068	1.224	0.097
Beta blockers	225	50.1	49	58.3	1.388	0.866	2.224	0.191
Digoxin	30	6.7	17	20.2	3.535	1.848	6.762	<0.001
Calcium channel blockers	94	20.9	18	21.4	1.027	0.582	1.814	0.875
Acetylsalicylic acid	232	51.7	38	45.2	0.769	0.482	1.228	0.286
Statins	203	45.2	24	28.6	0.483	0.290	0.803	0.005
ACE inhibitors/ARBs	209	46.5	26	31.0	0.513	0.311	0.844	0.005
Diuretics	136	30.3	37	44.0	1.806	1.123	2.906	0.016

COPD: Chronic obstructive pulmonary disease; MS: Mitral stenosis; ACE: Angiotensin-converting-enzyme; ARB: Angiotensin receptor blocker.

which was significantly larger than the ratio of 0.68 observed in Group II patients without MS (p=0.023). Furthermore, patients in Group I, with a median age of 54 years (IQR: 14) were significantly younger than the patients in Group II, where the median age was 61 years old (IQR: 14) (p=0.002). Characteristically, there was less hypertension, diabetes, and congestive heart failure, and a greater frequency of atrial fibrillation and concomitant tricuspid regurgitation among Group I patients than in Group II (Table 1). As expected, the Group I patients with MS were less likely to be taking statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and more likely to be treated with digitalis and diuretics (Table 1).

In univariate analysis, the patients in Group I with MS had a smaller indexed annulus dimension, with a median of 11.29 mm (IQR: 2.00) compared to 11.84 mm (IQR: 2.00) in Group II without MS (p=0.003). With regard to the dimension of the aortic root index, the median diameter was 16.25 mm (IQR: 3.00) in Group I, which was comparable to a median of 17.01 mm (IQR: 3.00) in patients without MS (p=0.117). The median index dimension of the STJ was 14.05 mm (IQR: 3.00) in patients with MS which was significantly smaller than the median of 14.60 mm (IQR: 3.00) in Group II patients (p=0.043). There was no difference between the 2 groups with regard to the indexed diameter of the proximal ascending aorta (p=0.259). Figure 1 depicts the indexed size of the ascending aorta at 4 levels in Group I patients with MS compared with those in Group II without MS. Scatter plots demonstrating the correlation between MVA (Fig. 2) and peak transvalvular gradient (Fig. 3) and the index diameters of the aortic annulus, root, STJ, and the proximal ascending aorta showed a poor correlation between these 2 variables and the indexed

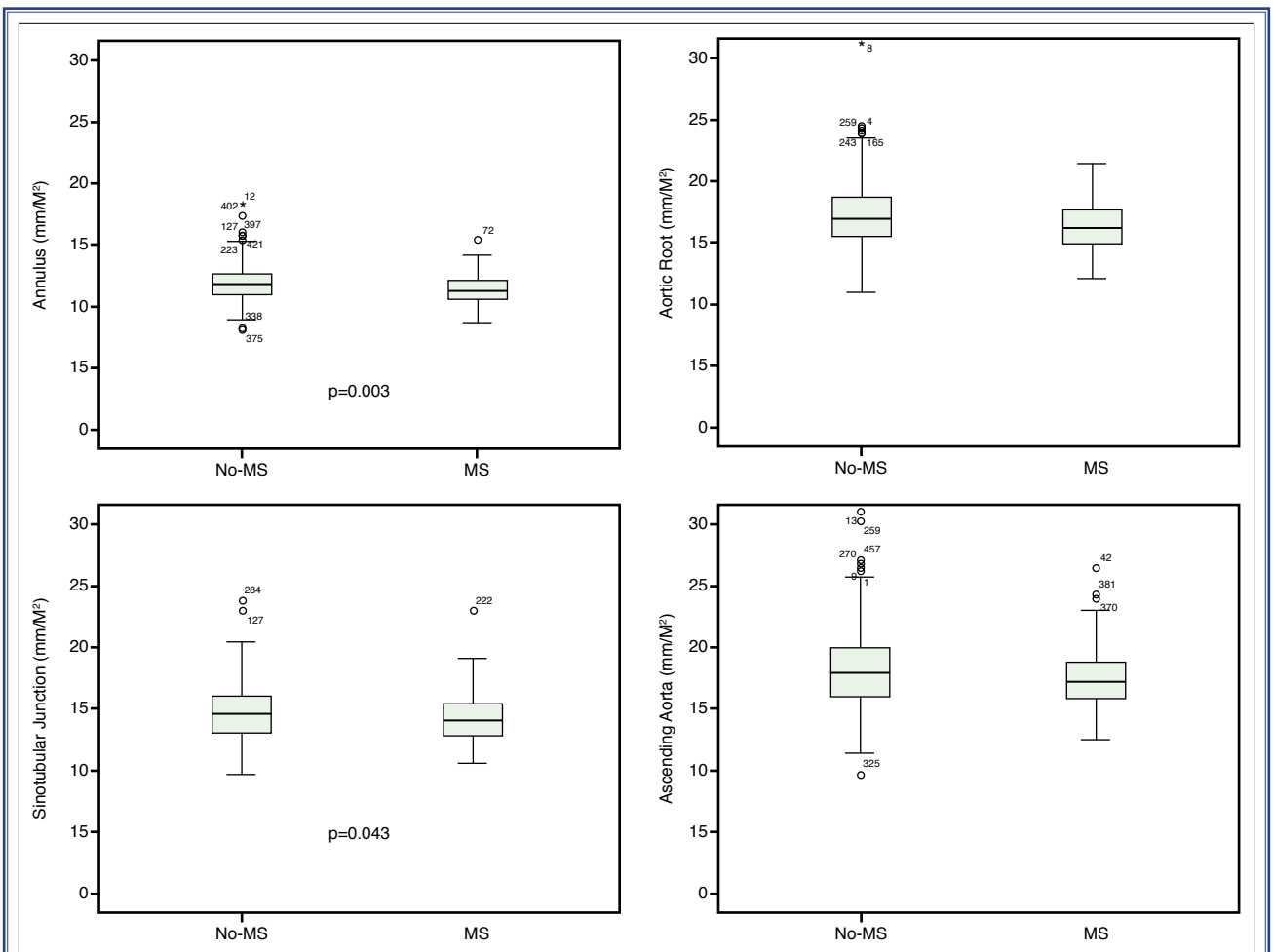

Figure 1. The indexed size of the ascending aorta at 4 levels in Group I patients with mitral stenosis (MS) compared with the corresponding values in Group II without MS.

dimensions of the aorta at all levels. The aortic annulus was positively related to MVA (r=0.285; p=0.030). Aortic root and STJ measurements were also correlated positively with MVA (r=0.372, p=0.001; r=0.282, p=0.022, respectively). The ascending aorta was also positively correlated with MVA in Pearson's correlation analysis (r=0.422; p<0.001) (Fig. 2).

Pearson's correlation coefficient analysis revealed that the peak mitral valve gradient was negatively associated with the aortic root and the ascending aorta (r=-0.217, p=0.023; r=-0.311; p=0.001, respectively). However, there was no significant correlation between peak mitral gradient and the aortic annulus or the STJ (r=-0.106, p=0.357; r=-0.134, p=0.192, respectively) (Fig. 3).

Four multivariate linear regression models were constructed to assess the independent role of MS with the indexed diameters of the ascending aorta. All variables with a p value <0.05 in univariate analysis in the comparison of the aortic size at all levels, including age, gender, hypertension, and beta blocker use, were selected as independent variables for adjustment in model. MS was found to be correlated with a smaller indexed size of the aortic annulus with a regression coefficient value of 0.541 (p=0.005). Additionally, there was a trend suggesting a smaller aortic root size in patients with MS (p=0.094). Moreover, women had a smaller indexed diameter of the aortic root and the STJ. Similarly, age positively correlated with the dimensions of the aorta above annulus (p<0.001).

DISCUSSION

To the best of our knowledge, the present cross-sectional study is the first to investigate the relationship

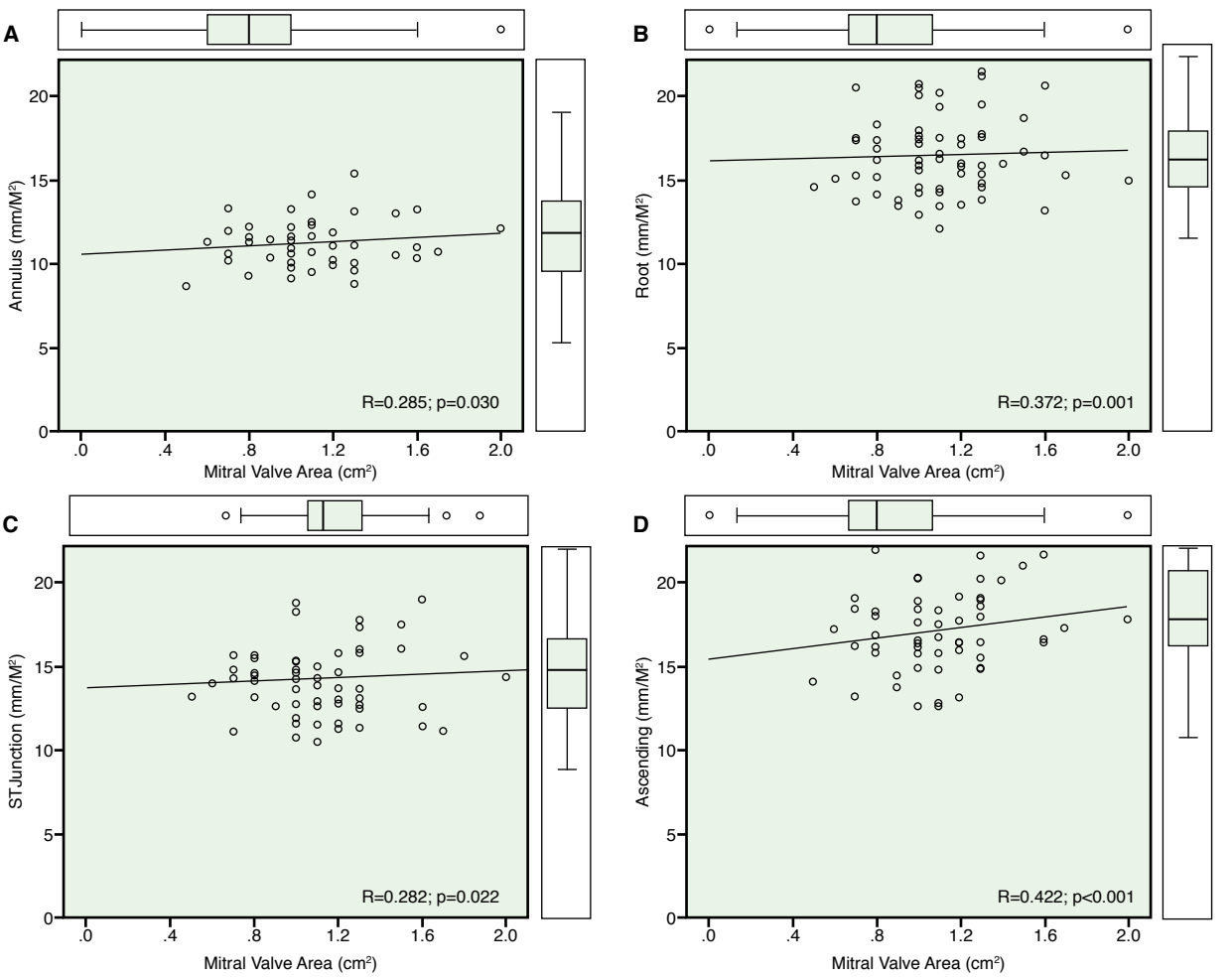

Figure 2. Scatter plots illustrating the correlation between mitral valve area and the indexed sizes of the ascending aorta at 4 levels.

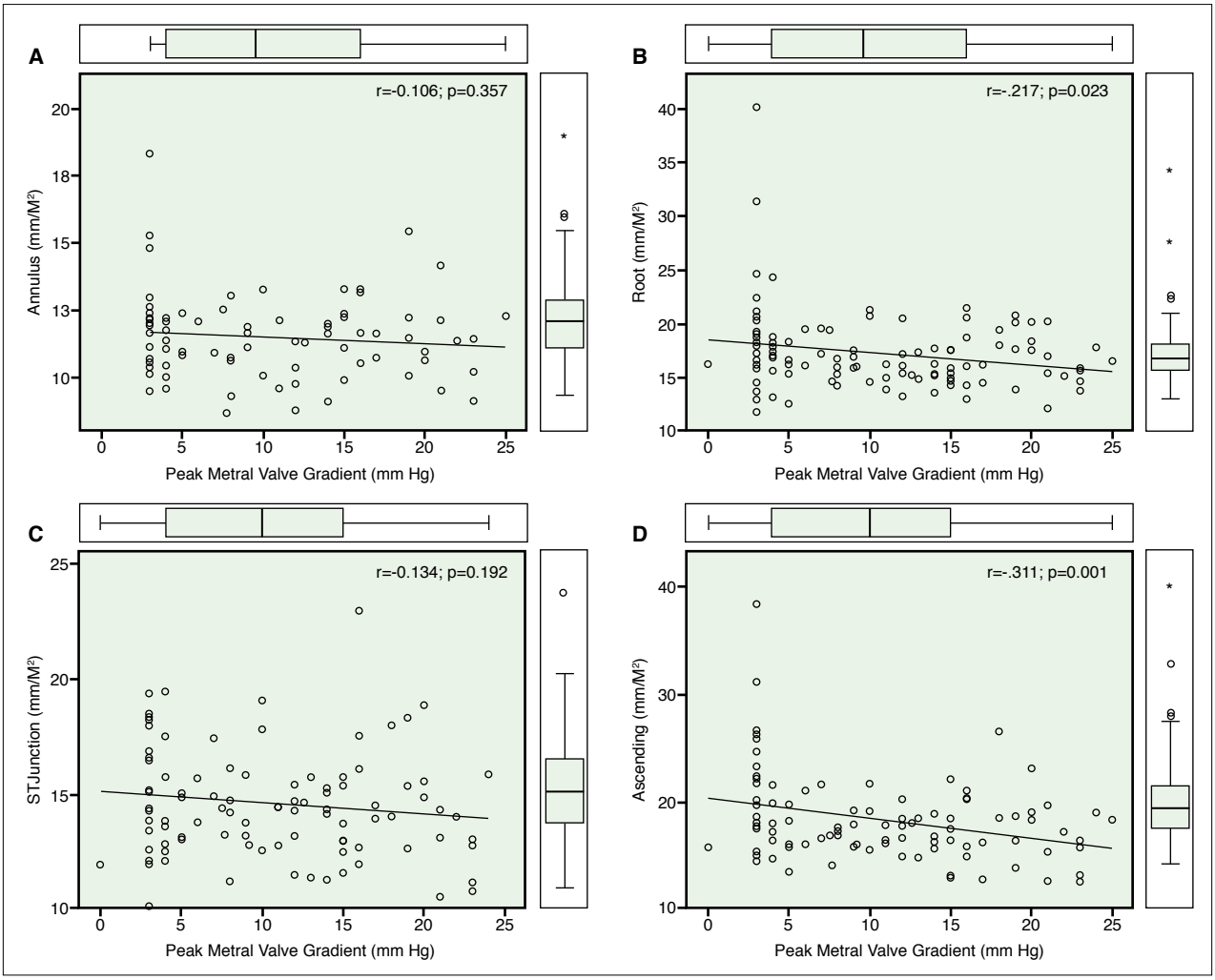

Figure 3. Scatter plots demonstrating the correlation between peak transvalvular gradient and the indexed size of the ascending aorta at 4 levels.

between isolated MS, MVA, and peak mitral valve gradient and the diameter of the aorta at 4 different levels. Overall, we found MS to be negatively correlated with the annular dimension of the aorta. Moreover, gender, hypertension, and consumption of beta adrenergic blocking agents were demonstrated to be associated with various indexed dimensions of aorta.

Proximal aortic diameter has been shown to be associated with risk of incident coronary heart disease, stroke, cardiovascular events, and all-cause mortality.[1,3] A smaller aortic root size may occur due to reverse remodeling of the aortic root as a result of disrupted hemodynamics[15,16] or extensive atheromatous change to the ascending aorta secondary to altered intercellular communications within the aortic wall. Several studies indicated that valvular and/or supravalvular aortic stenosis and a markedly narrowed aortic root are less common complications of homozygous familial hypercholesterolemia.[17,18] Likewise, coarctation of the aorta is frequently reported in patients with mitral valve abnormalities.[19–21] Rosenquist[22] examined autopsy specimens of 53 patients with a diagnosis of coarctation of the aorta. He noticed that only 9 had a mitral valve of normal size and configuration. In the remaining specimens, the mitral valve demonstrated an abnormal size and/or configuration.

There is also evidence regarding the mitral valve and the aorta in patients who were suffering from hypoplastic left heart syndrome. Sathanandam et al.[23] found in a study of 100 patients that the variants MS-aortic atresia and mitral atresia-aortic atresia were associated with a smaller ascending aorta. In addition, Mori et al.[24] reported that 13 patients required aortic annular enlargement due to underlying hypoplasia of the aortic annulus

in a study of 71 patients undergoing aortic valve replacement. Nine out of these 13 patients were suffering from concomitant hemodynamically significant MS. This report added to our own anecdotal observations of a lower incidence of aneurysmal dilation of the aorta among the cohort of patients suffering from MS.

Ercan et al.[25] studied 66 patients and described an association between MS and the elastic properties of the aortic wall. Using strain and distensibility as a surrogate marker of elasticity, they found a strong correlation between the distensibility of the aortic wall and MVA ($p<0.001$; $r=0.40$). Moreover, aortic wall strain was also associated with MVA ($p=0.002$; $r=0.31$), indicating that MS might have contributed to impaired aortic elasticity. These findings are consistent with the results of current study, which indicated a weak but significant correlation between the indexed dimension of the ascending aorta and MVA (Fig. 2). We also observed an inverse correlation between the peak mitral valve gradient and the indexed size of the aortic dimensions.

Beta blockers have been shown to decrease aortic dilation at the level of the sinus of Valsalva in patients with Marfan syndrome.[26] Likewise, beta blocker therapy has been reported to result in near-normalization of aortic growth velocity in patients with confirmed Marfan syndrome.[27] A decreased stroke volume and the negative inotropic effect of beta blockers are believed to contribute to the beneficial effects.[28] In the current study, significant narrowing of the annulus and the root of the aorta was found to correlate with the presence of MS. It should be considered that the development of elastin lamellae in the media of elastic-type arteries like the aorta appears to be modulated by mechanical factors such as flow.[29] In children suffering from congenital complete heart block, aortic dilatation can develop due long-term exposure to large stroke volumes.[16] After implantation of a pacemaker in these children and normalizing the stroke volume, the size of the ascending aorta regressed. In addition, a decreasing LV end-systolic dimension has been demonstrated to be a long-term adverse outcome of rheumatic MS.[30] On that basis, decreased aortic flow may be responsible for the occurrence of tubular hypoplasia of the aorta. Thus, a possible explanation for the smaller diameters of the aorta is the diminished blood flow to the ascending aorta from the LV.

In our study, hypertension was associated with a larger proximal aortic size in univariate analysis. It was shown that the aortic diameter in hypertensive patients was significantly larger (+0.9 mm) than in normotensive individuals.[31] In another study, Vasan et al.[32] found that the aortic root dimension was directly associated with mean arterial and diastolic blood pressure, and inversely related to pulse and systolic blood pressure. While there was a positive correlation between hypertension and the indexed diameter of the ascending aorta, the dimensions of the aortic annulus were negatively affected by the presence of hypertension. In our patient population, even after adjusting for other confounding variables, hypertension was inversely associated with the indexed dimension of the annulus in multivariate analysis. It should also be noted that myocardial fibrosis is a common sequel of rheumatic fever.[33] Though we did not include patients with rheumatic involvement of the aortic valve, the extension of rheumatic changes to the aortic-mitral curtain cannot be excluded.

In conclusion, our study demonstrated that rheumatic MS was independently associated with a smaller indexed size of the aortic annulus. However, having rheumatic MS was not independently associated with aortic root, STJ and the proximal ascending aorta.

The present study has limitations. The results may include some potential bias due to the single-center design; thus, it may not be possible to generalize the findings of our study. In addition, this was only a cross-sectional study without a longitudinal follow up. Our control group comprised patients who were undergoing TEE for various indications and were not healthy control subjects.

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Keywords: Aortic annulus; ascending aorta; echocardiography; mitral stenosis; rheumatic heart disease.

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