Determinants and Prognostic Significance of Symptomatic Status in Patients with Moderately Dysfunctional Bicuspid Aortic Valves

Soo Youn Lee

Department of Medicine

The Graduate School, Yonsei University

Determinants and Prognostic Significance of Symptomatic Status in Patients with Moderately Dysfunctional Bicuspid Aortic Valves

Directed by Professor Chi Young Shim

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Soo Youn Lee

June 2016

This certifies that the Master's Thesis of
Soo Youn Lee is approved.

[Signature]

Thesis Supervisor : Chi Young Shim

[Signature]

Thesis Committee Member#1 : Kyung-Jong Yoo

[Signature]

Thesis Committee Member#2 : Geu-Ru Hong

The Graduate School
Yonsei University

June 2016

ACKNOWLEDGEMENTS

First of all, I am thankful to Professor Chi Young Shim for encouraging me to take training and for providing guidance concering from A to Z of echocardiography. She helped me in doing a lot of research and I came to know about so many new things. It has been an honor to learn from her, and I am pleased to have someone to look up to.

Secondly, I would also like to thank Professor Geu-Ru Hong for his valuable guidance. He helped me in attracting potentiality and having keen interest. His endless passion makes me march to scholarship. I'm very appreciate giving me chance and encouragement.

Finally, this project would not have been possible if Echo lab of Severance Cardiovascular Hospital did not have a support of many organizations. At various stages of my fellowship training period, their suggestion and criticism have contributed to the evolution of my capacity. Therefore I would like to extend sincere gratitude to all of them.

Written by Soo Youn Lee

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Determinants and Prognostic Significance of Symptomatic Status in Patients with Moderately Dysfunctional Bicuspid Aortic Valves

Soo Youn Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Chi Young Shim)

We aimed to identify the clinical and echocardiographic determinants of symptom status and its prognostic implication in patients with moderately dysfunctional bicuspid aortic valves (BAVs).

Among 1019 subjects in the BAV registry in a single tertiary care center, 128 patients (86 men, age 58±13 years) with moderately dysfunctional BAVs were comprehensively reviewed. The patients were divided into two groups based on their symptom status: asymptomatic (n=80) vs. symptomatic (n=48). The primary end-point was defined as a composite of aortic valve surgery, hospitalization for heart failure, and any cause of death. The symptomatic group was to have a higher proportion of females, hypertension, aortic stenosis, and aortopathy than the asymptomatic group. The symptomatic group showed lower e′ (5.5±1.7 vs. 6.5±2.2cm/s, p=0.003), higher E/e′ (13.2±4.8 vs.10.9±3.7, p=0.002), and larger left atrial volume index (29.5±11.5 vs. 24.6±9.1 ml/m^2, p=0.014) than the asymptomatic group. In the multivariable logistic regression, female (odds ratio [OR] 2.61, 95% confidence interval [CI] 1.03–6.53, p=0.041), hypertension (OR 2.78, 95% CI 1.08–7.21, p=0.032), moderate aortic stenosis (OR 5.33, 95% CI 1.89–15.01, p=0.002), E/e′>15 (OR 2.88, 95% CI 1.04–7.98, p=0.042), and aortopathy (OR 2.53, 95% CI 1.01–6.33, p=0.047) were independently correlated with symptom status. The symptomatic group showed a significantly lower event-free survival during the overall 8 years (51±9 vs. 69±8%, p=0.001). In moderately dysfunctional BAVs, the presence of moderate aortic stenosis, aortopathy, and diastolic dysfunction determines symptom status along with female gender and hypertension. Symptom status is associated with clinical outcomes.

Key words : bicuspid aortic valves; symptoms; prognosis; aortic stenosis; aortopathy

Determinants and Prognostic Significance of Symptomatic Status in Patients with Moderately Dysfunctional Bicuspid Aortic Valves

Soo Youn Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Chi Young Shim)

I. INTRODUCTION

Bicuspid aortic valve (BAV) is considered frequent progression to aortic valve stenosis (AS) and frequent aortic regurgitation requiring aortic valve replacement (AVR). Furthermore, dilatation of the aortic root and/or the ascending aorta (AA) occurs more frequently in patients with a bicuspid aortic valve (BAV) than it does in patients with a tricuspid aortic valve (TAV). Recent studies have demonstrated that left ventricular (LV) diastolic function is more impaired in subjects with a normally functioning BAV than subjects with a TAV in association with aortic dilatation and consequent aortic stiffness.[1-4] However, the clinical implications of diastolic dysfunction in BAV subjects with aortopathy are uncertain.

In patients with moderate to severe aortic stenosis (AS) or aortic regurgitation (AR), LV hypertrophy and diastolic dysfunction are quite common caused by the chronic pressure or volume overload and are related to impaired relaxation and increased LV chamber stiffness.[5,6]

The occurrence of symptoms and adverse events should be related to the global hemodynamic burden faced by the ventricle.[7] This global load not only includes the valvular load but also the pulsatile and steady components of arterial load, which are related with reduced arterial compliance and increased vascular resistance.[7] Recently, the clinical importance of diastolic dysfunction in patients with severe AS has been highlighted for understanding symptom status and predicting clinical outcomes.[8,9] Moreover, the importance of the valvular, arterial, and ventricular interplay in AV disease has been suggested for improving risk stratification and identifying patients who could benefit from an early elective aortic valve surgery.[10] Increased aortic stiffness was independently associated with elevated LV filling pressures, plasma brain natriuretic peptide level, and symptoms in AS.[11]

Therefore, we hypothesised that 1) the presence of symptoms

would be determined by BAV phenotypes or function, aortic phenotypes, or LV diastolic function in moderately dysfunctional BAVs and 2) symptomatic patients would show a worse clinical outcome than asymptomatic patients. In order to test our hypothesis, we reviewed clinical and echocardiographic characteristics and clinical events in patients with moderately dysfunctional BAVs.

II.MATERIALS AND METHODS

1. Patients population

We retrospectively reviewed the echocardiographic database and medical records of patients with BAVs who were diagnosed from 2003 to 2015 at Severance Cardiovascular Hospital (Yonsei University College of Medicine, Seoul, Republic of Korea). During this period, a total of 1,019 patients with BAVs were identified. Among them, 208 patients who had moderate AS and/or AR on a transthoracic echocardiogram defined using current guidelines criteria[12,13] at the time of diagnosis were included in our study. Patients who had coronary artery disease defined as >50% narrowing in at least one coronary artery on an angiogram (n=38), a LV ejection fraction<50% (n=18), previous open heart surgery (n=4), concomitant other valvular disease of moderate or severe severity (n=6), infective endocarditis (n=6), hypertrophic cardiomyopathy (n=4), or end-stage renal disease (n=4) were excluded. Therefore, 128 patients (mean age 58±13 years, 86 men) were ultimately included in this study. All patients' medical records written by the physicians were carefully reviewed by 1 cardiologists. History of cardiac symptoms, including dyspnoea according to New York Heart Association classes, angina, syncope, or presyncope, reported at the time of the initial clinical and echocardiographic evaluation. Based on their presenting symptoms, including chest pain, dyspnoea, or syncope, the study population was divided into two groups: asymptomatic (n=80, 62.5%) vs. symptomatic (n=48, 37.5%; Figure 1). The institutional review board of Yonsei University College of Medicine approved the present study, which was conducted in compliance with the Declaration of Helsinki.

2. Echocardiographic assessment

All subjects underwent comprehensive transthoracic echocardiography using commercially available equipment. Standard

two-dimensional and Doppler measurements were performed per the recommendations of the American Society of Echocardiography guidelines.[14] A congenital BAV was diagnosed when only two cusps were unequivocally identified in systole and diastole in the short-axis view, with a clear "fish mouth" appearance during systole. We classified two BAV phenotypes based on the orientation of the free edge of the cusp defined as the anterior-posterior and right-left forms of BAV (BAV-AP and BAV-RL, respectively).[15] The severity of AS or AR were assessed using an integrated approach.[16,17] Mitral inflow velocities were obtained by pulse-wave Doppler in the apical four-chamber view. Early diastolic mitral inflow (E) velocity and the deceleration time of the E velocity were measured. Early diastolic mitral annular (e′) velocity was measured from the septal mitral annulus, and the E/e′ ratio, a measure of LV filling pressure, was calculated. For each quantitative parameter, three consecutive beats were averaged. All measurements of the aorta were performed according to the recommendations and on the QRS complex of the electrocardiogram.[18] The dimension of the Valsalva sinuses was measured perpendicular to the right and left (or non-) aortic sinuses. The sinotubular junction was measured where the aortic sinuses meet the tubular aorta. The AA was measured approximately 2 cm distal to the sinotubular junction. Aortopathy was defined as the predominant dilatation of the Valsalva sinuses or AA. Three aortic phenotypes were defined for all groups: (1) normal shape (Valsalva sinuses<39 mm and AA<Valsalva); (2) predominant dilatation of the Valsalva sinuses (Valsalva ≥39 mm and Valsalva>AA); and (3) predominant dilatation of the AA (AA≥39 mm and AA>Valsalva). End-systolic pressure was estimated as systolic blood pressure ×0.9, as described previously.[19-21] The effective arterial elastance (Ea), a global marker of arterial stiffness that encompasses both steady and pulsatile arterial load, was calculated as the end-systolic pressure divided by the stroke volume.[19-21] For the assessment of global LV afterload in AS patients, valvulo-arterial impedance (Zva) was calculated using a previously validated method.[22] Echocardiographic data were gathered and analysed by two independent investigators who were unaware of the subjects' clinical data.

3. Follwow-up

Follow-up information was obtained via review of the medical records or telephone interviews with the patients or their relatives. The primary end-point

was a composite of death, hospitalization for heart failure, and AV replacement. The clinical management of the patients was determined independently by their personal cardiologists.

4. Statistical analysis

Data are presented as the mean ± standard deviation or percentage unless otherwise specified. Differences between groups were compared using the Student's t-test, and categorical variables were tested by the Fisher's exact test or Pearson's chi-square test. In order to determine independent correlates of e′ velocity and aortic mechanical and functional properties, linear relations were verified using a simple linear regression analysis. A multiple logistic regression analysis was performed to assess the independent determinants for the presence of symptoms. All variables with suspected clinical relevance were entered, and variables were adjusted for age, gender, body mass index, and a history of hypertension or diabetes mellitus. Their incremental value was assessed by comparing the global chi-square values for each model. The Kaplan-Meier method was used for cumulative survival analysis with the log-rank test for assessing the statistical difference between the two groups according to the presence of each symptom. A two-sided p-value less than 0.05 was considered statistically significant.

III RESULTS

1. Demographic characteristics

The demographic characteristics of the patients according to their symptom status are presented in Table 1. Among 128 patients, 80 (62.5%) patients were asymptomatic, and 48 (37.5%) patients were symptomatic. Although there were no significant differences in age, body mass index, systolic blood pressures, or pulse pressure between the two groups, the symptomatic group had a higher proportion of females, hypertension, and use of diuretics than did the asymptomatic group. The major cause of their symptoms in the symptomatic patients was dyspnea (64.6%), but New York Heart Association (NYHA) class III or IV dyspnea was rare (6.5%).

2. Echocardiographic characteristics

Table 2 shows the echocardiographic characteristics of the two groups. Of the patients with moderately dysfunctional BAVs, approximately one-third of patients displayed the A-P type of BAV, and there was no difference in the prevalence of the BAV phenotype between the two groups. The symptomatic group had a higher prevalence of moderate AS than the asymptomatic group

(72.9 vs. 43.8%, p=0.002). Accordingly, more moderate AR patients were classified into the asymptomatic group.

Symptomatic patients showed a significantly higher prevalence of aortopathy than the asymptomatic patients (70.8 vs. 47.5%, p=0.011). Among the three aortic phenotypes, there was a significantly higher prevalence of the predominant AA in the symptomatic group than the other group (58.3 vs. 37.5 %, p=0.028). Aortic diameters tended to be larger in patients with symptoms than those without symptoms at the site of the tubular portion of the AA with a marginal statistical significance. In terms of noninvasively derived arterial stiffness, the effective arterial elastancewas significantly higher in symptomatic patients than those without symptoms (1.8±0.4 vs. 1.5±0.5 mmHg/ml, p=0.002). Likewise, valvulo-arterial impedance calculated in AS patients (n=85) was higher in the symptomatic group (4.7±1.7 vs. 3.9±1.3 mmHg/ml/m^2, p=0.013).

Symptomatic patients had a smaller LV end-diastolic dimension and higher relative wall thickness than asymptomatic patients. There were no significant differences in LV mass index or LV ejection fraction (LVEF). The symptomatic group was revealed to possess more advanced LV diastolic dysfunction with a larger left atrium volume index, a lower e` velocity, and a higher E/e′ ratio than the asymptomatic group. Regarding the vascular-ventricular interaction, there were significant correlations between the structural and functional properties of the AA and LV diastolic indices. The AA diameters were well correlated with e′ velocity (r=-0.368, p<0.001) and E/e′ (r=0.179, p=0.043). The effective arterial elastance also revealed significant correlations with e′ velocity (r=-0.214, p=0.015) and E/e′ (r=0.181, p=0.041).

3. Determinants of symptomatic status

The percentages of symptom presentation according to gender, moderate AS, or aortopathy are demonstrated in Figure 2. In patients with moderate AS, female patients displayed a higher symptom presentation (62.5 vs. 39.6%, p=0.034) and had a higher E/e′ (13.6±4.8 vs. 11.5±3.6, p=0.027) than male patients. In patients with aortopathy, female patients had higher E/e′ (13.6±4.4 vs. 11.4±4.4, p=0.039) than male patients. Although, overall male patients were revealed to have a lower prevalence of symptoms than female patients, male patients with moderate AS (between males, p=0.006) or aortopathy (between males, p=0.003) had dramatic increases in their symptom presentation.

Female gender, moderate AS, and the presence of aortopathy provided incremental predictive values for the symptomatic status in patients with moderately dysfunctional BAVs over a combination of clinical variables, including age, body mass index, and the presence of hypertension or diabetes mellitus (Figure 3).

When adjusting for confounding factors in the multivariable logistic regression analysis, female (odds ratio [OR] 2.61, 95% confidence interval [CI] 1.04 to 6.53, p=0.041), hypertension (OR 2.78, 95% CI 1.08 to 7.21, p=0.032), moderate AS (OR 5.33, 95% CI 1.89 to 15.01, p=0.002), aortopathy (OR 2.53, 95% CI 1.01 to 6.33, p=0.047), and E/e′>15 (OR 2.88, 95% CI 1.04 to 7.98, p=0.042) were associated with the symptomatic status of moderately dysfunctional BAV (Table 3).

4. Prognostic significance of symptomaticstatus

During a mean of 41 ± 27 months of follow-up, adverse clinical events occurred in 31 (24.2%) patients. In symptomatic patients, AV surgery was performed more frequently (31.3 vs. 12.5%, p=0.012), and hospitalization for heart failure occurred more often (14.6 vs. 3.8%, p=0.04). There was no significant difference in all-cause mortality between the two groups. The presence of symptoms was associated with reduced event-free survival during follow-up (56±9 vs. 71±8%, log-rank p=0.001).

Table 1. Baseline clinicalcharacteristics

	Asymptomatic (n=80)	Symptomatic (n=48)	p-value
Age, years	57±14	59±12	0.314
Female	19(23.8)	23(47.9)	0.006
Body mass index, kg/m^2	23.3±4.6	24.1±3.0	0.287
Systolic BP, mmHg	123.9±14.7	127.8±18.2	0.186
Diastolic BP, mmHg	75.6±9.7	81.0±12.4	0.012
Pulse pressure, mmHg	48.3±12.1	46.8±12.4	0.511
Co-morbidities			
Hypertension	22 (27.5)	24 (50.0)	0.013
Diabetes mellitus	10 (12.5)	9 (18.8)	0.442
Dyslipidemia	8 (10.0)	10 (20.8)	0.116
Atrial fibrillation	4(5.0)	4 (8.3)	0.472
Chronic kidney disease	6(7.5)	6(12.5)	0.364
Medications			
Diuretics	13(16.3)	18 (37.5)	0.01
β-blocker	8 (10.0)	11(22.9)	0.07
CCB	37 (46.3)	22 (45.8)	1
ACEi/ARB	37(46.3)	22 (45.8)	1
Symptoms			
Chest pain, or discomfort	0	15(31.3)	
Dyspnea			
NHYA Class (1/2/3/4)	80(100)/0/0/0	15(31.3)/31(64.6)/2(4.2)/0	
Pre-syncope, or syncope	0	4(8.3)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; NYHA, New York Heart Association

Table 2. Echocardiographic characteristics

	Asymptomatic (n=80)	Symptomatic (n=48)	p-value
BAV phenotype, n (%)			
A-P type	55 (68.8)	31 (64.6)	0.669
R-L type	25 (31.3)	17 (35.4)	
BAV dysfunction, n (%)			
Moderate AS	35 (43.8)	35 (72.9)	0.002
Moderate AR	36 (45.0)	7 (14.6)	<0.001
Moderate AS with AR	9 (11.3)	6 (12.5)	0.521
Aorta phenotype, n (%)			
Overall aortopathy	38 (47.5)	34 (70.8)	0.011
Normal shape	42 (52.5)	14 (29.2)	0.011
Predominant sinus Valsalva	8 (10.0)	6 (12.5)	0.772
Predominant ascending aorta	30 (37.5)	28 (58.3)	0.028
Aorta dimension, mm			
Sinus of Valsalva	34.3 ± 5.1	34.5± 5.2	0.902
Sinotubularjunction	29.9 ± 4.7	30.5 ±4.4	0.451
Tubular portion of AA	38.6 ± 6.2	40.8 ± 6.1	0.055
Effective arterial elastance,mmHg/ml	1.5 ± 0.5	1.8 ± 0.4	0.002
Valvuloarterial impedance, mmHg/ml/m^2	3.9±1.3	4.7±1.7	0.013
Echocardiography data			
Aortic valve area, cm^2	1.25 ± 0.41	1.19 ± 0.37	0.484
Mean pressure gradient, mmHg	28 ± 7	30 ± 6	0.178
LVEDD, mm	51.3 ±5.3	49.0 ±4.5	0.015
LVESD, mm	33.1 ± 5.1	31.6 ±4.5	0.098
LAVI, ml/m^2	24.6 ±9.1	29.5 ±11.5	0.014
RWT	0.39 ±0.06	0.42 ±0.06	0.028
LVMI, g/m^2	111.5 ± 21.7	109.4 ± 25.3	0.607
LVEF, %	67.0 ± 5.9	67.2 ±6.2	0.855
E velocity, m/s	0.66±0.18	0.68±0.21	0.542
Deceleration time, msec	215 ±41	216 ±39	0.899

A velocity , m/s	0.71±0.19	0.76 ±0.23	0.231
e` velocity, cm/s	6.5 ±2.2	5.5 ±1.7	0.007
A` velocity, cm/s	8.6 ±1.7	8.0 ±1.7	0.105
S` velocity, cm/s	6.7 ±1.4	5.9 ±1.5	0.003
E/e`	10.9 ±3.7	13.2 ± 4.8	0.002
RVSP, mmHg	25.6 ± 5.7	27.1 ± 6.3	0.188

Values are mean (±SD). LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVSD, interventricualrseptal diameter; LVPWD, left ventricular posterior wall diameter; LAVI, left atrial voumeindex; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; E, early diastolic mitral inflow; e`, early diastolic mitral annular; A, late diastolic mitral inflow; A` , late diastolic mitral annular; S` peak systolic mitral annular; RVSP, right ventricular systolic pressure.

Table 3. Determinants of symptom status in logistic regression analysis

	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Clinical characteristics				
Age	1.01 (0.99-1.04)	0.312	0.98 (0.95-1.02)	0.366
Female	2.95 (1.37-6.35)	0.006	2.61 (1.04-6.53)	0.041
Body mass index	1.05 (0.96-1.15)	0.303	1.01 (0.92-1.12)	0.768
Hypertension	2.64 (1.25-5.58)	0.011	2.78 (1.08-7.21)	0.032
Diabetes mellitus	1.62 (0.61-4.31)	0.338	0.59 (0.12-2.57)	0.697
Echocardiographic characteristics				
BAV phenotype (A-P type)	1.21 (0.57-2.57)	0.627		
Moderate AS	4.79 (1.92-11.96)	0.001	5.33 (1.89-15.01)	0.002
Moderate AR	0.29 (0.13-0.63)	0.002		
AA dimension (mm)	1.06 (1.00-1.13)	0.048		
Presence of aortopathy	2.68 (1.25-5.75)	0.011	2.53 (1.01-6.33)	0.047
LVEF	1.01 (0.95-1.07)	0.854	0.97 (0.90-1.04)	0.38
LVMI	1.00 (0.93-1.01)	0.838	0.99(0.97-1.01)	0.483
LAVI	1.05 (1.01-1.09)	0.013		
E/e`	1.14 (1.04-1.25)	0.005		
e` velocity	0.77 (0.63-0.94)	0.01		
E/e`>15	2.83 (1.20-6.69)	0.017	2.88 (1.04-7.98)	0.042

OR, odds ratio; CI, confidence interval; BAV, bicuspid aortic valve; A-P, anterior-posterior; AS, aortic stenosis; AR, aortic regurgitation; AA, ascending aorta; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; E, early diastolic mitral inflow; e`, early diastolic mitral annular

Table 4. Clinical outcomes according to symptom status

	Asymptomatic (n=80)	Symptomatic (n=48)	p-value
Composite outcome	14(17.5)	17(35.4)	0.032
Aortic valve surgery	10 (12.5)	15 (31.3)	0.012
Surgery for aortic valve only	3(3.8)	7 (14.6)	0.04
Surgery for aortic valve and aortic root	7 (8.8)	8 (16.7)	0.256
Hospitalization for heart failure	3 (3.8)	7 (14.6)	0.04
All-cause mortality	4 (5.0)	2 (4.2)	1

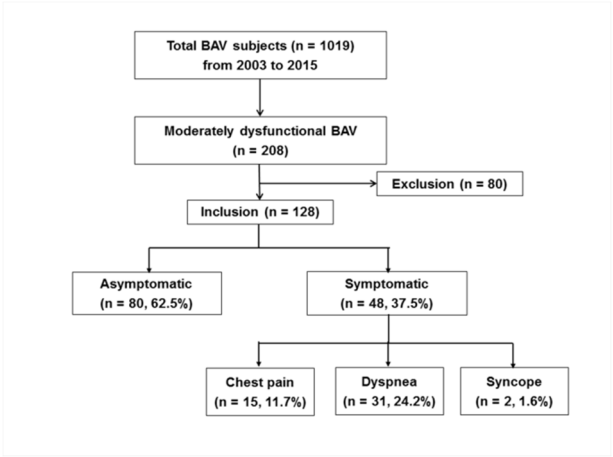

Figure 1. Description of the study population.

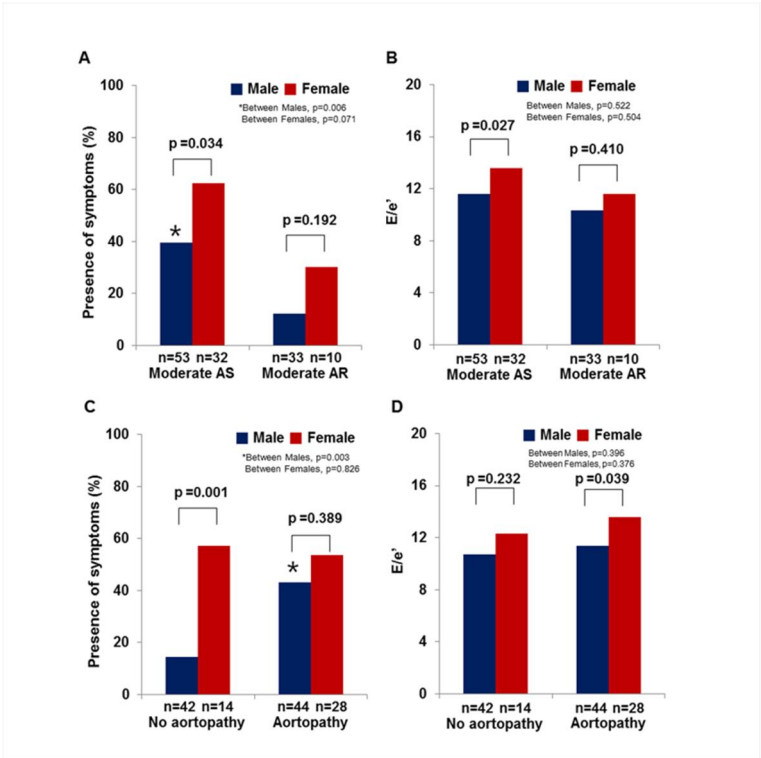

Figure 2. Presence of symptoms and E/e′ according to gender, BAV function, and aortopathy

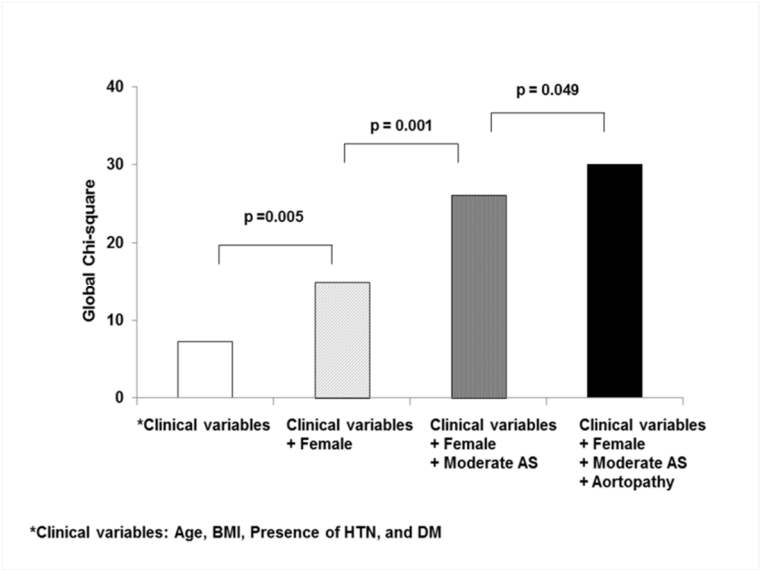

Figure 3. Incremental values for the presence of moderate AS and aortopathy in addition to clinical variables for the prediction of symptom status in patients with moderately dysfunctional BAVs.

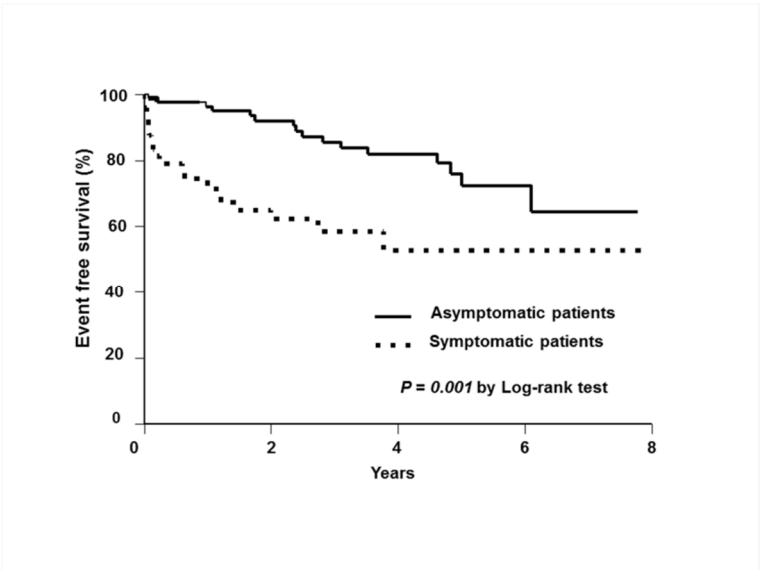

Figure 4. Kaplan-Meier survival curves showing the poorer prognosis of patients with symptoms compared to those without.

IV DISCUSSION

The principal findings in the present study are that 1) symptoms were more prevalent in female patients, patients with hypertension, moderate AS, or aortopathy in association with consequent LV diastolic dysfunction in patients with moderately dysfunctional BAVs, and 2) symptomatic status in patients with moderately dysfunctional BAVs was associated with a poor clinical outcome. The results of our study demonstrated the clinical importance of BAV aortopathy in conjunction with other clinical factors that may affect increased LV afterload and consequent LV diastolic dysfunction. Therefore, risk stratification, more careful follow-up, and identifying candidates for early AV surgery are needed in patients with moderately dysfunctional BAVs.

Pathologic hypertrophy can lead to coronary microvascular dysfunction despite the angiographically unobstructed coronary arteries.[23] When ventricular dilatation becomes detectable, pathological alterations such as reduced coronary blood flow per mass of myocardium have already occurred.[24] A recent study demonstrated that, in patients with AS without obstructive CAD, angina is related to impaired coronary microvascular function using adenosine-stress cardiac magnetic resonance.[25] Quantified myocardial contrast echocardiography has shown myocardial blood flow in the subendocardium to be reduced in patient with AS, and reduction of flow is associated with increased cardiomyocyte apoptosis that lead to heart failure through oxygen demand-supply imbalance.[26]

The importance of heart failure with preserved ejection fraction is increasingly recognised.[27,28] These patients most likely have heart failure due to LV diastolic dysfunction and tend to be older, to be female, and to have a history of hypertension.[27,28] Central aortic stiffness and the ventricular response to elevated LV afterload are highly linked to the pathogenesis of heart failure with preserved ejection fraction.[21,29,30] If there is AV disease in subjects who are vulnerable to heart failure, symptoms may occur easily because of further pressure and volume overloads on the LV. Moreover, if subjects with AV disease have dilatation of the proximal aorta and consequent central aortic stiffness, symptoms related to heart failure or AV disease can be further aggravated. In this study, the complaint symptoms of the 37.5% of patients with moderately dysfunctional BAVs were related to heart failure or AV disease. Symptomatic patients included more female patients and those with a higher prevalence of hypertension. Our results are in accordance

with the generally proven risk factors for heart failure with preserved ejection fraction.[27,28] Symptomatic patients in this study possessed significantly elevated effective arterial elastance and valvulo-arterial impedance than the asymptomatic patients. Therefore, vascular stiffening combined with elevated systolic loads from AV disease, especially in moderate AS, may importantly contribute to the clinical features of patients with moderately dysfunctional BAVs. Furthermore, the symptomatic patients showed a worse clinical outcome than the asymptomatic patients. Although, the relatively higher prevalence of symptomatic patients was probably influenced by the characteristics of the study population enrolled in a tertiary care center, the present data proved a prognostic difference according to symptom status.

Several possible mechanisms can be discussed further about female gender as one of the symptom determinants in patients with moderate dysfunctional BAVs. In a previous study of 408 consecutive patients with isolated severe AS undergoing AV replacement, women were more symptomatic than men, but the affected women were also older and had smaller valve areas and higher mean pressure gradients than men.[31] Female patients were more symptomatic than male patients (23/42, 54.8 % vs. 25/86, 29.1%, p=0.006), even though the indexed AV area (0.73±0.24 vs. 0.73±0.22 cm^2/m^2, p=0.974) and mean pressure gradient across the AV (28.7±7.0 vs. 29.9±5.8 mmHg, p=0.391) did not differ by gender in the present study population. Female patients with moderately dysfunctional BAVs displayed more impaired LV diastolic functional parameters including e′ velocity (5.6±1.9 vs. 6.5±2.2 cm/s, p=0.026) and E/e′ (13.2±4.6 vs. 11.1±4.1, p=0.010) compared to male patients. Our results were consistent with a few previous studies that demonstrated the importance of diastolic dysfunction to symptom status in severe AS, although the previous studies did not show gender-specific differences.[8,32]

Previous studies have reported that LV longitudinal relaxation was significantly impaired and estimated LV filling pressure was elevated in BAV subjects without significant valvular dysfunction.[1,3,4] There is noticeable central aortic stiffness in BAV subjects compared with TAV controls.[2] Moreover, independent correlations between the parameters of LV diastolic function and the indices of aortic mechanical function have been established in subjects with BAV.[3] Consistently, the present study demonstrated good correlations between the structural and functional properties of the AA and LV diastolic indices. We believe that the valvular, arterial, and ventricular interplay is more important in patients

with moderately dysfunctional BAVs than in subjects with normally functioning BAVs because either diastolic dysfunction or aortic stiffness may result in substantial clinical events.

There are several limitations to this study. First, the present study is a retrospective analysis; thus, an assessment of symptoms is dependent upon the accuracy of the medical records. Symptomatic patients were evaluated according to their NYHA class. An investigation into the potential confounding between symptomatic status and exercise capacity will be required in order to thoroughly interpret the data. However, the mean age of the study population was 58.1±13.6 years-old; therefore, we suspect the number of patients who were asymptomatic because of avoiding activities would not represent a large portion of our patients. Second, this study was conducted in a tertiary care center, which might raise suspicion that the study population may have a relatively higher prevalence of co-morbidities versus the general population. However, the prevalence of hypertension, the most important co-morbidity influencing the results, was not high (35.9%). In addition, the patients with coronary artery disease or specific co-morbidities influencing clinical outcomes were excluded. Third, this study included moderate AS with AR patients. Mixed aortic valve disease is found to be associated with a high rate of adverse events in patients with tricuspid aortic valve patients.[33] However, the prevalence moderate AS with AR was not significant different in both groups (11.3% vs. 12.5%, p=0.521). Fourth, classification of the aortopathy and the evaluation of mechanical function only depended on the transthoracic echocardiography, although recent studies suggest that multidetector computed tomography or magnetic resonance imaging allows for an appropriate assessment of the extent of aortopathy and functional alteration of the aorta.[34]

V. CONCLUSIONS

In patients with moderately dysfunctional BAVs, symptom status is independently associated with female gender; the presence of hypertension, moderate AS, or aortopathy; and consequent LV diastolic dysfunction. Moreover, the presence of symptoms in moderately dysfunctional BAV patients is associated with a worse clinical outcome.

References

1. Santarpia G, Scognamiglio G, Di Salvo G, D'Alto M, Sarubbi B, Romeo E, et al. Aortic and left ventricular remodeling in patients with bicuspid aortic valve without significant valvular dysfunction: a prospective study. Int J Cardiol 2012;158:347-52.
2. Shim CY, Cho IJ, Yang WI, Kang MK, Park S, Ha JW, et al. Central aortic stiffness and its association with ascending aorta dilation in subjects with a bicuspid aortic valve. J Am Soc Echocardiogr 2011;24:847-52.
3. Lee SY, Shim CY, Hong GR, Seo J, Cho I, Cho IJ, et al. Association of Aortic Phenotypes and Mechanical Function With Left Ventricular Diastolic Function in Subjects With Normally Functioning Bicuspid Aortic Valves and Comparison to Subjects With Tricuspid Aortic Valves. Am J Cardiol 2015;116:1547-54.
4. Weismann CG, Lombardi KC, Grell BS, Northrup V, Sugeng L. Aortic stiffness and left ventricular diastolic function in children with well-functioning bicuspid aortic valves. Eur Heart J Cardiovasc Imaging 2016;17:225-30.
5. Zaid RR, Barker CM, Little SH, Nagueh SF. Pre- and post-operative diastolic dysfunction in patients with valvular heart disease: diagnosis and therapeutic implications. J Am Coll Cardiol 2013;62:1922-30.
6. Villari B, Hess OM, Kaufmann P, Krogmann ON, Grimm J, Krayenbuehl HP. Effect of aortic valve stenosis (pressure overload) and regurgitation (volume overload) on left ventricular systolic and diastolic function. Am J Cardiol 1992;69:927-34.
7. Pibarot P, Dumesnil JG. Aortic stenosis: look globally, think globally. JACC Cardiovasc Imaging 2009;2:400-3.
8. Park SJ, Enriquez-Sarano M, Chang SA, Choi JO, Lee SC, Park SW, et al. Hemodynamic patterns for symptomatic presentations of severe aortic stenosis. JACC Cardiovasc Imaging 2013;6:137-46.
9. Biner S, Rafique AM, Goykhman P, Morrissey RP, Naghi J, Siegel RJ. Prognostic value of E/E' ratio in patients with unoperated severe aortic stenosis. JACC Cardiovasc Imaging 2010;3:899-907.
10. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and

ventricular interplay. Heart 2010;96:1364-71.
11. Weisz SH, Magne J, Dulgheru R, Caso P, Pierard LA, Lancellotti P. Carotid artery and aortic stiffness evaluation in aortic stenosis. J Am Soc Echocardiogr 2014;27:385-92.
12. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.
13. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1-23; quiz 101-2.
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
15. Kang JW, Song HG, Yang DH, Baek S, Kim DH, Song JM, et al. Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction and bicuspid aortopathy: comprehensive evaluation using MDCT and echocardiography. JACC Cardiovasc Imaging 2013;6:150-61.
16. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.
17. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1-25.
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the

European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
19. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028-34.
20. Shim CY, Park S, Choi EY, Hong GR, Choi D, Jang Y, et al. The relationship between ventricular-vascular uncoupling during exercise and impaired left ventricular longitudinal functional reserve in hypertensive patients. J Am Soc Hypertens 2013;7:198-205.
21. Shim CY. Arterial-cardiac interaction: the concept and implications. J Cardiovasc Ultrasound 2011;19:62-6.
22. Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. J Am Coll Cardiol 2005;46:291-8.
23. Gould KL, Carabello BA. Why angina in aortic stenosis with normal coronary arteriograms? Circulation 2003;107:3121-3.
24. Johnson LL, Sciacca RR, Ellis K, Weiss MB, Cannon PJ. Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. Circulation 1978;57:582-90.
25. Ahn JH, Kim SM, Park SJ, Jeong DS, Woo MA, Jung SH, et al. Coronary Microvascular Dysfunction as a Mechanism of Angina in Severe AS: Prospective Adenosine-Stress CMR Study. J Am Coll Cardiol 2016;67:1412-22.
26. Galiuto L, Lotrionte M, Crea F, Anselmi A, Biondi-Zoccai GG, De Giorgio F, et al. Impaired coronary and myocardial flow in severe aortic stenosis is associated with increased apoptosis: a transthoracic Doppler and myocardial contrast echocardiography study. Heart 2006;92:208-12.
27. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.
28. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
29. Shim CY, Park S, Choi D, Yang WI, Cho IJ, Choi EY, et al. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. J Am Coll Cardiol 2011;57:1226-33.

30. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36-46.
31. Fuchs C, Mascherbauer J, Rosenhek R, Pernicka E, Klaar U, Scholten C, et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis. Heart 2010;96:539-45.
32. Dahl JS, Christensen NL, Videbaek L, Poulsen MK, Carter-Storch R, Hey TM, et al. Left ventricular diastolic function is associated with symptom status in severe aortic valve stenosis. Circ Cardiovasc Imaging 2014;7:142-8.
33. Egbe AC, Poterucha JT, Warnes CA. Mixed aortic valve disease: midterm outcome and predictors of adverse events. Eur Heart J 2016; doi:10.1093/eurheartj/ehw079.
34. Wassmuth R, von Knobelsdorff-Brenkenhoff F, Gruettner H, Utz W, Schulz-Menger J. Cardiac magnetic resonance imaging of congenital bicuspid aortic valves and associated aortic pathologies in adults. Eur Heart J Cardiovasc Imaging 2014;15:673-9.

ABSTRACT(IN KOREAN)

중등도의 이엽성 대동맥 판막 질환에서 증상을 결정하는 인자와 예후에 미치는 영향

<지도교수 심지영>

연세대학교 대학원 의학과

이수연

이 연구의 목적은 대동맥 판막질환에서 증상을 결정하는 임상적 특징과 심초음파의 계측인자를 알아보고 예후와의 연관성을 알아보고자 한다. 3차 병원에서 이엽성 대동맥판막 레지스트리의 1019명의 환자 중에 중등도의 이엽성 대동맥 판막질환이 있는 128명의 환자(86명의 남자, 58±13세)를 살펴보았다. 환자군을 증상이 있는 그룹과(80명) 무증상 그룹(48명)으로 나누었다. 주요 종료점을 대동맥 판막 수술과 심부전으로 인한 입원, 그리고 사망으로 정의하였다. 증상이 있는 그룹은 무증상 그룹에 비하여 여성, 고혈압 환자, 대동맥 협착, 대동맥 병증이 비율이 높았다. 증상이 있는 그룹은, 없는 그룹에 비하여, 낮은 e` 5.5±1.7 vs. 6.5±2.2cm/s, p=0.003), 높은 E/e´ (13.2±4.8 vs.10.9±3.7, p=0.002), 큰 left atrial volume index (29.5±11.5 vs. 24.6±9.1 ml/m^2, p=0.014) 를 보였다. 다변량 로지스틱 회귀분석에서는, 여성 (odds ratio [OR] 2.61, 95% confidence interval [CI] 1.03–6.53, p=0.041), 고혈압 (OR 2.78, 95% CI 1.08–7.21, p=0.032), 중등도의 대동맥 판막 협착증(OR 5.33, 95% CI 1.89–15.01, p=0.002), E/e´>15 (OR 2.88, 95% CI 1.04–7.98, p=0.042), 대동맥병증 (OR 2.53, 95% CI 1.01–6.33, p=0.047) 이 독립적으로 증상과 관련이 있었다. 증상이 있는 그룹은 8년 동안 유의미하게 낮은 생존률을 보였다 (51±9 vs. 69±8%, p=0.001). 중등도의 이엽성 대동맥 판막 질환에서여성, 고혈압, 중등도의 대동맥 판막 협착, 대동맥병증, 좌심실의 이완성 기능 저하가 증상을 결정하는 인자이며, 증상이 있는 경우 좋지 않은 예후와 관련이 있음을 알 수 있었다.

핵심되는 말: 이엽성 대동맥 판막; 증상; 예후; 대동맥 판막 협착; 대동맥병증