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FOCUS ISSUE: FRONTIERS IN HEART VALVE IMAGING

ORIGINAL RESEARCH

Hemodynamic Patterns for Symptomatic Presentations of Severe Aortic Stenosis

Sung-Ji Park, MD, PhD,* Maurice Enriquez-Sarano, MD,† Sung-A Chang, MD, PhD,* Jin-Oh Choi, MD, PhD,* Sang-Chol Lee, MD, PhD,* Seung Woo Park, MD, PhD,* Duk-Kyung Kim, MD, PhD,* Eun-Seok Jeon, MD, PhD,* Jae K. Oh, MD*†

Seoul, Korea; and Rochester, Minnesota

OBJECTIVES The aim of this study was to investigate intracardiac hemodynamic idiosyncrasies responsible for various presentations of severe aortic stenosis (AS).

BACKGROUND Syncope, dyspnea, and chest pain are well-established indications for aortic valve replacement in patients with severe AS. Patients' survival is limited once they develop symptoms from AS, and survival depends on what type of symptoms a patient develops. We hypothesized that there would be a relationship between the type of AS symptoms and intracardiac hemodynamics as well as AS severity.

METHODS We analyzed 498 patients (men: 58.4%, 66 ± 12 years of age) with severe AS and normal left ventricular ejection fraction from 2003 to 2009 who had comprehensive echocardiography examination for AS. The study population was divided into 4 groups based on presenting symptom(s) (341 in group I, asymptomatic; 15 in group II, syncope; 110 in group III, dyspnea; 32 in group IV, chest pain). Echocardiographic measurements for cardiac structure, function, and intracardiac hemodynamic parameters were compared among these 4 groups.

RESULTS Mean aortic valve pressure gradient and aortic valve area were 57.1 ± 15.2 mm Hg and 0.74 ± 0.19 cm^2, respectively. AS severity based on mean gradient and aortic valve area was similar among 4 groups. Compared with the asymptomatic group, symptomatic patients were older and had lower cardiac output, and higher E/e' ratio while having a similar aortic valve area and gradient. Group II (syncope) displayed smaller LV dimension, stroke volume, cardiac output, left atrial volume index, and E/e' ratio. Conversely, group III (dyspnea) was found to have the worst diastolic function with largest left atrial volume index and highest E/e' ratio.

CONCLUSIONS Among patients with severe AS, their symptoms are often linked to specific hemodynamic patterns associated with AS: smaller left ventricular cavity and reduced output for syncope versus more advanced diastolic dysfunction for dyspnea. Hence, comprehensive intracardiac hemodynamics including diastolic function and stroke volume need to be evaluated in addition to aortic valve area and pressure gradient for assessment of AS. (J Am Coll Cardiol Img 2013;6:137–46) © 2013 by the American College of Cardiology Foundation

From the *Cardiovascular Imaging Center, Cardiac and Vascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; and the †Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota. Dr. Enriquez-Sarano has served on the advisory board of Valtech Inc., and has received a grant from Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Aortic stenosis (AS) is the most common valvular heart disease in the elderly characterized by fixed aortic valve narrowing, left ventricular (LV) remodeling with hypertrophy, and progressive diastolic dysfunction (1). The cardinal manifestations of AS include syncope, chest pain, and dyspnea. It has been well described that patients' survival is limited once they develop symptoms from AS, and survival after the onset of a symptom depends on what type of symptoms a patient develops (2). Therefore, the onset or presence of these symptoms are the class I indication for surgical indication, but without any distinction among symptoms. Because the survival duration without aortic valve replacement depends on the type of symptoms in severe AS, we hypothesized that there would be a relationship between the type of AS symptoms and intracardiac hemodynamics as well as the severity of AS. The fact that patients with dyspnea have the worst prognosis suggests that these patients do have the worst intracardiac hemodynamics and more severe AS than do the patients with other symptoms (2). However, little is known about the relationship between AS symptoms and intracardiac hemodynamics. Nor do we understand why specific symptoms develop and whether the severity of AS (within the severe AS category) or the cardiac response to AS determines the occurrence of specific symptoms. The objective of this study was to assess how a particular symptom in patients with severe AS is related to intracardiac as well as aortic valvular hemodynamics.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
LA = left atrial
LAVI = left atrial volume index
LV = left ventricular
SV = stroke volume

METHODS

Study population. A prospective registry commenced in 2003 and using a standard case report form has included all consecutive patients with AS undergoing echocardiography at a major tertiary cardiac and vascular center in Korea. Clinical and echocardiographic follow-up data on study patients were collected annually and entered into the database. Subjects who had severe AS and normal LV ejection fraction (>50%) in transthoracic echocardiogram were included in our study. Severe AS was defined as aortic valve area (by the continuity equation) <1 cm^2 as previously published (3).

Exclusion criteria included previous aortic valve replacement, concomitant other valvular disease of moderate or severe severity, coronary artery disease defined as >50% narrowing in at least 1 coronary artery in an angiogram, history of myocardial infarction, acute coronary syndrome, and end-stage renal disease on chronic dialysis. The study was approved by the regional ethics committee. From 2003 to 2009, 498 patients (mean age: 66 ± 12 years of age) with severe AS met the criteria for inclusion in this study (Fig. 1).

All patients' medical records written by the primary physician(s) were carefully reviewed by 1 cardiologist. The study population was divided into 4 groups based on their predominant presenting symptom at baseline (group I, asymptomatic; group II, syncope; group III, dyspnea; group IV, chest pain). Patients with pre-syncope were also included in group II. Patients with chest heaviness or chest discomfort were included in group IV.

Echocardiographic evaluation. Comprehensive transthoracic echocardiography (M-mode, 2-dimensional, and Doppler) was performed using commercially available equipment (Vivid 7, GE Medical Systems, Milwaukee, Wisconsin; Acuson 512, Siemens Medical Solutions, Mountain View, California; or Sonos 5500, Philips Medical Systems, Andover, Massachusetts). Maximal aortic jet velocity was recorded from the apical, right parasternal, or suprasternal window that yielded the highest-velocity signal. End diastole was defined as the frame with the largest cavity area near the QRS interval and end systole as the frame with the smallest cavity area. LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction were calculated from 2-dimensional recordings using the modified biplane Simpson method (4). Relative wall thickness and LV mass were calculated as described previously (5,6). Left atrial (LA) volume was assessed by the modified biplane area-length method and was indexed to body surface area. LV stroke volume was derived as the cross-sectional area of the LV outflow tract × time-velocity integral of the LV outflow tract flow by pulse wave Doppler (7). Cardiac output was calculated as the product of LV stroke volume and heart rate. Mean aortic gradient and aortic valve area (by the continuity equation) were obtained as previously reported (8) and described in the guidelines of the American Society of Echocardiography (7,9). LV stroke work loss was expressed as a percentage and calculated as 100 × mean transvalvular aortic valve pressure gradient/(mean transvalvular aortic pressure gradient + sys-

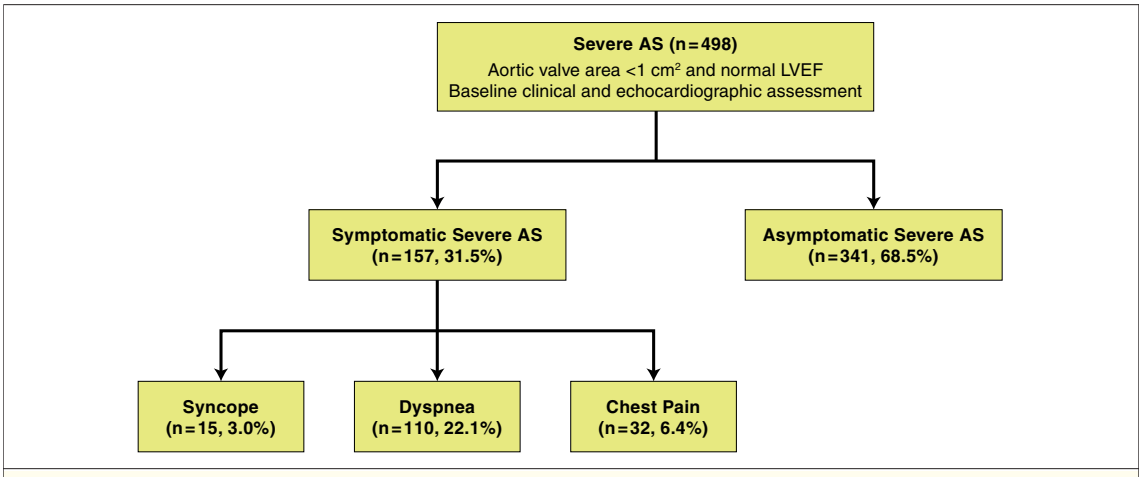

Figure 1. Description of Study Population

AS = aortic stenosis; EF = ejection fraction; LV = left ventricular.

tolic blood pressure) (10). Early diastolic mitral inflow velocity (E) was measured using the pulsed wave Doppler. The tissue Doppler-derived early diastolic mitral annular velocity (e′) was measured from the septal corner of the mitral annulus in the apical 4-chamber view. Deceleration time of early transmitral flow velocity was also measured. As an index of LV filling pressure, E/e′ was calculated. The average of 3 consecutive Doppler signals was used.

Statistical analysis. Continuous variables are listed as mean ± SD or median (Q1, Q3). Categorical variables are presented as frequencies and group percentages.

Differences between asymptomatic groups and symptomatic groups were assessed using Wilcoxon rank sum test for comparing 2 independent samples.

Differences among 4 groups were assessed using Kruskal-Wallis test for continuous variables and chi-square test or Fisher exact test for categorical variables. For the comparison of the continuous variables among groups according to presenting symptoms, we used 1-way analysis of variance. Post hoc pairwise comparisons were adjusted for multiple comparisons using the Dunnett significant difference method. We assessed univariate regression with presence of symptoms or presence of dyspnea as a nominal dependent variable and other parameters as independent variables. Multiple logistic regression analysis was used to assess independent determinants of presence of symptoms and presence of dyspnea. For multivariate analysis, significant p value variables in univariate analysis and other important clinical variables irrespective of their univariate p value were included in the model. Generalized logit model for nominal response data was used to assess the association of presence of dyspnea and clinical and echocardiographic parameters among 4 different groups. Group III (dyspnea) served as the reference group.

All reported p values were 2-sided, and a p value <0.05 was considered statistically significant. SPSS (version 15.0, SPSS Inc., Chicago, Illinois) was used for all statistical analyses. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Clinical and echocardiographic characteristics. The total population included 498 patients (291 were men [58.4%], with a mean age of 66 ± 12 years) of whom 157 were symptomatic and 341 were asymptomatic. Baseline characteristics of total patients are shown in Table 1. In the total cohort, mean LV ejection fraction was 64.6 ± 6.7% and mean aortic valve area (AVA) was 0.74 ± 0.19 cm^2. When the symptomatic patients were compared with the asymptomatic patients, the symptomatic group was older. The severity of AS, as determined by AVA, peak velocity, and mean gradient, was not significantly different between symptomatic and asymptomatic patients. However, diastolic parameters of E, e′, and E/e′ ratio were significantly different. E and E/e′ ratio were significantly higher in the symptomatic AS patients group versus the asymptomatic AS patients group.

The study population was divided into 4 groups based on their presenting major symptoms at baseline (group I, asymptomatic [n = 341, 68.5%], group II, syncope [n = 15, 3.0%]; group III,

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Table 1. Clinical and Echocardiographic Findings in Severe AS Patients

	Symptomatic Severe AS (n = 157)	Asymptomatic Severe AS (n = 341)	p Value*
Age, yrs	68.1 ± 11.0	64.6 ± 12.6	**0.002**
Male	88 (56.1)	203 (59.5)	0.291
Height, cm	159.7 ± 9.4	160.8 ± 12.7	0.128
Weight, kg	61.1 ± 11.1	63.8 ± 30.5	0.1
BSA, m^2	1.63 ± 0.18	1.66 ± 0.24	0.353
BMI, kg/m^2	23.9 ± 3.5	24.6 ± 13.6	0.516
SBP, mm Hg	125.2 ± 20.6	124.9 ± 18.3	0.878
DBP, mm Hg	70.9 ± 12.4	72.3 ± 13.3	0.362
HR, beats/min	74.5 ± 14.1	75.2 ± 15.3	0.363
Comorbidities			
HT	75 (47.8)	146 (42.8)	0.543
DM	39 (24.8)	58 (17)	0.192
HyperC	21 (13.4)	44 (12.9)	0.865
AV parameters			
Mean PG, mm Hg	57.7 ± 15.4	56.8 ± 15.2	0.240
Vmax, m/s	4.92 ± 0.60	4.86 ± 0.63	0.105
AVA, cm^2	0.72 ± 0.19	0.75 ± 0.18	0.053
AVAI, cm^2/m^2	0.44 ± 0.12	0.46 ± 0.11	0.174
SWL, %	31.6 ± 6.7	31.2 ± 6.6	0.323
Echo parameters			
LVIDd, mm	51.4 ± 6.2	52.0 ± 6.1	0.462
LVIDs, mm	30.1 ± 5.5	30.9 ± 5.1	0.656
IVSd, mm	11.9 ± 2.7	11.5 ± 2.6	0.211
LVPWd, mm	11.3 ± 1.9	11.0 ± 1.7	0.161
LAVI, ml/m^2	52.1 ± 16.7	49.9 ± 17.8	0.285
RWT	0.45 ± 0.10	0.43 ± 0.08	0.216
LVMI, g/m^2	145.2 ± 45.0	140.1 ± 46.8	0.225
LVEF, %	65.1 ± 7.2	64.4 ± 6.5	0.933
SV, ml	88.6 ± 20.5	86.9 ± 20.8	0.504
CO, l/min	5.9 ± 1.5	6.3 ± 1.7	**0.025**
SV index, ml/m^2	52.6 ± 12.1	55.3 ± 12.9	0.504
CI, $l/min/m^2$	3.7 ± 0.93	3.8 ± 1.08	0.161
E, m/s	0.88 ± 0.34	0.78 ± 0.30	**0.0008**
A, m/s	0.97 ± 0.30	0.96 ± 0.30	0.648
E/A	0.95 ± 0.46	0.85 ± 0.52	0.066
e′, m/s	0.047 ± 0.02	0.057 ± 0.02	**<0.0001**
E/e′	19.5 ± 6.83	14.1 ± 4.67	**<0.0001**

Values are mean ± SD or n (%). **Bold** values are statistically significant. *$p < 0.05$ by Wilcoxon rank sum test for comparing 2 independent samples (continuous variable), chi-square test or Fisher exact test (categorical variables).

A = late transmitral flow velocity; AS = aortic stenosis; AV = aortic valve; AVA = aortic valve area; AVAI = aortic valve area index; BSA = body surface area; BMI = body mass index; CI = cardiac index; CO = cardiac output; DBP = diastolic blood pressure; DM = diabetes mellitus; E = early transmitral flow velocity; e′ = early diastolic mitral annular velocity; E/e′ = E/e′ ratio; EA = EA ratio; HR = heart rate; HT = hypertension; HyperC = hypercholesterolemia; IVSd = interventricular septal thickness; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVIDd = left ventricular end-diastolic dimension; LVIDS = left ventricular end-systolic dimension; LVMI = left ventricular mass index; LVPWd = left ventricular posterior wall thickness; mean PG = aortic valve mean pressure gradient; RWT = relative wall thickness; SBP = systolic blood pressure; SV = stroke volume; SWL = stroke work loss; Vmax = aortic valve maximum velocity.

dyspnea [n = 110, 22.1%]; group IV, chest pain [n = 32, 6.4%]). In group III, 37 (34%) patients also had chest heaviness or chest discomfort.

When the patients were divided into 4 groups based on presenting symptom(s) at baseline, there were no differences in their demographics, including sex, body mass index, systolic and diastolic blood pressures, heart rate, and comorbidities (Table 2). Baseline echocardiographic parameters of 4 groups are shown in Table 3. The severity of AS, as determined by AVA, peak velocity, and mean gradient, was not significantly different among the 4 groups. There were no significant differences in LV end-systolic dimension, LV wall thickness, LV mass index, relative wall thickness, and ejection fraction. However, group II (syncope) patients had significantly smaller LV end-diastolic dimension, lower stroke volume (SV), cardiac output, and left atrial volume index (LAVI) than did the other groups (Table 3, Fig. 2). There was a significant difference between 4 groups regarding diastolic dysfunction parameters of E velocity, e′ velocity, and E/e′ ratio. E velocity was highest and e′ velocity was lowest in group III with presenting symptom of dyspnea, resulting in the highest E/e′ (i.e., estimated filling pressure) in that group. Consistent with preceding data, LAVI was largest in group III when compared to other groups. E/e′ ratio was significantly lower in group II than that in the other groups, indicating lower filling pressure in patients presenting with syncope.

Among 498 patients, 259 patients had coronary computed tomography angiography or coronary angiography that showed no significant coronary artery disease. Of those 259, 92 were symptomatic and 167 were asymptomatic. There were no differences in the demographics among the 4 groups. In this subgroup of patients with known normal coronary anatomy, results regarding intracardiac hemodynamics and cardiac structures were the same as those found in the total patients.

When LAVI, SV, stroke volume index, and E/e′ ratio were stratified by sex and median age in 4 different groups, LAVI was smaller in group II and largest in group III, when compared to other groups, regardless of sex and age (Fig. 3).

E/e′ ratio was significantly lower in group II than in other the groups, and it was highest in group III regardless sex and age (Fig. 4).

By multiple logistic regression analysis, E/e′ ratio, LAVI, cardiac output, and SV index were independent determinants of presence of symptoms in severe AS patients (Table 4). To assess the association of presence of dyspnea and clinical and echocardiographic parameters, we used the generalized logit model for nominal response data. Group III (dyspnea) is the reference group. E/e′ ratio was significantly different between group I (asymptomatic) and group III (dyspnea). Also, E/e′

Table 2. Clinical Characteristics in 4 Groups

	Group I: Asymptomatic (n = 341)	Group II: Syncope (n = 15)	Group III: DOE (n = 110)	Group IV: Chest Pain (n = 32)	p Value*
Age, yrs	64.6 ± 12.6	68.2 ± 11.7	67.9 ± 11.4	68.9 ± 9.7	**0.020**
Male	203 (59.5)	10 (66.7)	55 (50)	23 (71.9)	0.103
Height, cm	160.8 ± 12.7	161.2 ± 8.9	158.5 ± 9.1	162.8 ± 9.7	0.063
Weight, kg	63.8 ± 30.5	60.4 ± 9.7	60.5 ± 10.9	63.7 ± 12.4	0.338
BSA, m^2	1.66 ± 0.24	1.63 ± 0.16	1.61 ± 0.17	1.68 ± 0.18	0.921
BMI, kg/m^2	24.6 ± 13.6	23.2 ± 2.6	24.0 ± 3.5	24.0 ± 3.7	0.828
SBP, mm Hg	124.9 ± 18.3	122.0 ± 20.3	127.5 ± 20.9	118.6 ± 18.7	0.050
DBP, mm Hg	72.3 ± 13.3	73.7 ± 9.0	71.8 ± 12.9	66.3 ± 10.7	0.10
HR, beats/min	75.2 ± 15.3	75.7 ± 14.0	75.2 ± 14.1	71.7 ± 14.2	0.092
Comorbidities					
HT	146 (42.8)	5 (33.3)	50 (45.5)	20 (62.5)	0.507
DM	58 (17)	3 (20)	23 (23.7)	13 (13.4)	0.138
HyperC	44 (12.9)	1 (6.7)	14 (12.7)	6 (18.8)	0.614

Values are mean ± SD or n (%). **Bold** values are statistically significant. *$p < 0.05$ by Kruskal-Wallis test (continuous variable), chi-square test, or Fisher exact test (categorical variables).
DOE = dyspnea on exertion; other abbreviations as in Table 1.

ratio was significantly different between group IV (chest pain) and group III (dyspnea). E/e′ ratio was an important factor influencing the presence of dyspnea among the 4 different groups (group I, asymptomatic; group II, syncope; group III, dyspnea; group IV, chest pain) (Table 5).

Table 3. Echocardiographic Parameters in 4 Groups

	Group I: Asymptomatic (n = 341)	Group II: Syncope (n = 15)	Group III: DOE (n = 110)	Group IV: Chest Pain (n = 32)	p Value*
AV parameters					
Mean PG, mm Hg	56.8 ± 15.2	57.7 ± 17.5	58.2 ± 16.1	55.7 ± 11.9	0.803
Vmax, m/s	4.86 ± 0.63	4.93 ± 0.80	4.94 ± 0.60	4.84 ± 0.51	0.651
AVA, cm^2	0.75 ± 0.18	0.71 ± 0.19	0.71 ± 0.18	0.76 ± 0.22	0.155
AVAI, cm^2/m^2	0.46 ± 0.11	0.43 ± 0.10	0.44 ± 0.12	0.45 ± 0.11	0.667
SWL, %	31.2 ± 6.6	33.1 ± 7.4	31.3 ± 7.0	31.9 ± 5.1	0.732
Echo parameters					
LVIDd, mm	52.0 ± 6.1†	47.4 ± 4.2	51.9 ± 6.6†	51.6 ± 4.8	**0.043**
LVIDs, mm	30.9 ± 5.1	27.9 ± 3.8	30.3 ± 5.9	30.5 ± 4.3	0.141
IVSd, mm	11.5 ± 2.6	12.0 ± 2.1	11.9 ± 3.0	11.8 ± 1.5	0.499
LVPWd, mm	11.0 ± 1.7	11.5 ± 1.4	11.3 ± 2.1	11.4 ± 1.3	0.369
LAVI, ml/m^2	49.9 ± 17.8†	35.2 ± 7.8	54.1 ± 16.5†	53.1 ± 16.2†	**0.003**
RWT	0.43 ± 0.08†	0.49 ± 0.09	0.44 ± 0.11	0.44 ± 0.06	0.058
LVMI, g/m^2	140.1 ± 46.8	129.3 ± 24.2	148.6 ± 48.9	141.3 ± 36.7	0.306
LVEF, %	64.4 ± 6.5	64.5 ± 6.8	65.3 ± 7.6	64.9 ± 6.0	0.647
SV, ml	86.9 ± 20.8	74.7 ± 14.6	89.0 ± 19.4†	93.9 ± 24.2†	**0.044**
CO, l/min	6.3 ± 1.7†	5.2 ± 1.0	5.8 ± 1.4	6.4 ± 1.9†	**0.033**
SV index, ml/m^2	52.6 ± 12.1	44.8 ± 10.8	56.5 ± 13.1†	56.2 ± 11.0†	**0.009**
CI, $l/min/m^2$	3.8 ± 1.1	3.1 ± 0.6	3.7 ± 0.9	3.8 ± 0.8	0.137
E, m/s	0.78 ± 0.30	0.66 ± 0.18	0.94 ± 0.36†	0.80 ± 0.27	**<0.0001**
A, m/s	0.96 ± 0.30	0.98 ± 0.23	0.99 ± 0.32	0.90 ± 0.26	0.492
E/A	0.85 ± 0.52	0.72 ± 0.31	0.98 ± 0.48	0.93 ± 0.46	0.074
e′, m/s	0.057 ± 0.02	0.056 ± 0.03	0.044 ± 0.01†	0.053 ± 0.014	**<0.0001**
E/e′	14.1 ± 4.67	14.2 ± 6.67	21.3 ± 6.20†	15.8 ± 6.39	**<0.0001**

Values are mean ± SD. **Bold** values are statistically significant. *$p < 0.05$ by Kruskal-Wallis test (continuous variable). †$p < 0.05$ versus group II (syncope) as reference group adjusted multiple comparison corrected by Dunnett.
Abbreviations as in Tables 1 and 2.

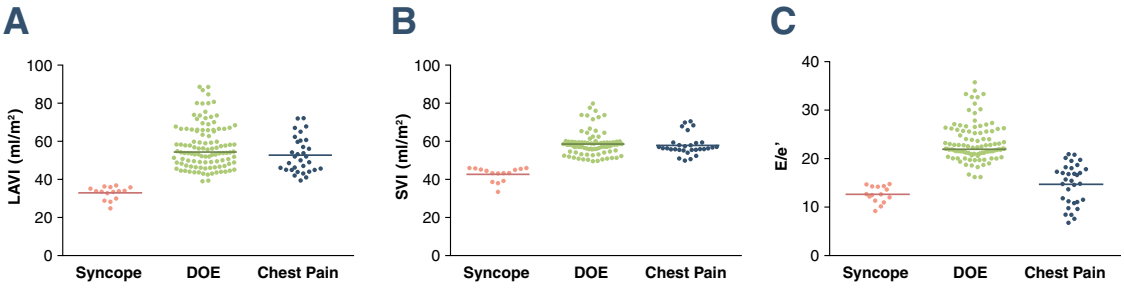

Figure 2. LAVI, SVI, and E/e′ Ratio in Patients With Different Symptoms

(A) Left atrial volume index (LAVI); **(B)** stroke volume index (SVI); **(C)** E/e′ ratio. Data are listed as mean ± SD. Chest pain = symptomatic patients presenting as chest pain; DOE = symptomatic patients presenting as dyspnea on exertion; syncope = symptomatic patients presenting as syncope.

DISCUSSION

The principal finding of this study was that there is a characteristic intracardiac hemodynamic profile for each presenting symptoms (syncope, dyspnea, and chest pain) in patients with severe AS, despite a similar AVA and aortic valve mean pressure gradient. This result suggests that there are superimposed mechanisms for development of a particular symptom in patients with severe AS. Larger LA volume, lower cardiac output, lower SV index, and higher E/e′ ratio were independent determi-

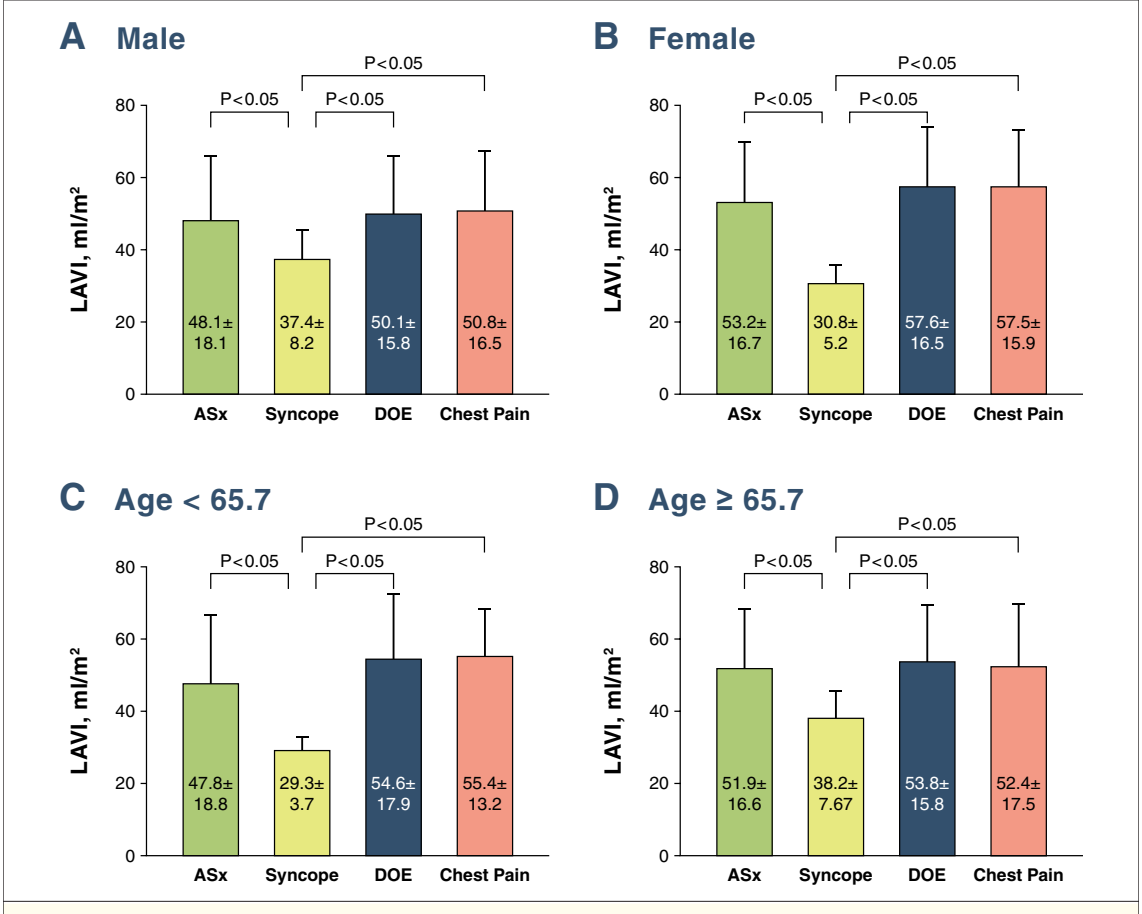

Figure 3. LAVI in Patients With Different Symptoms Stratified by Sex and Age

(A) Male; **(B)** female; **(C)** age <65.7 years; **(D)** age ≥65.7 years. Values are mean ± SD. $p < 0.05$ versus group II (syncope) as reference group. Adjusted multiple comparison corrected by Dunnett. ASx = asymptomatic group; other abbreviations as in Figure 2.

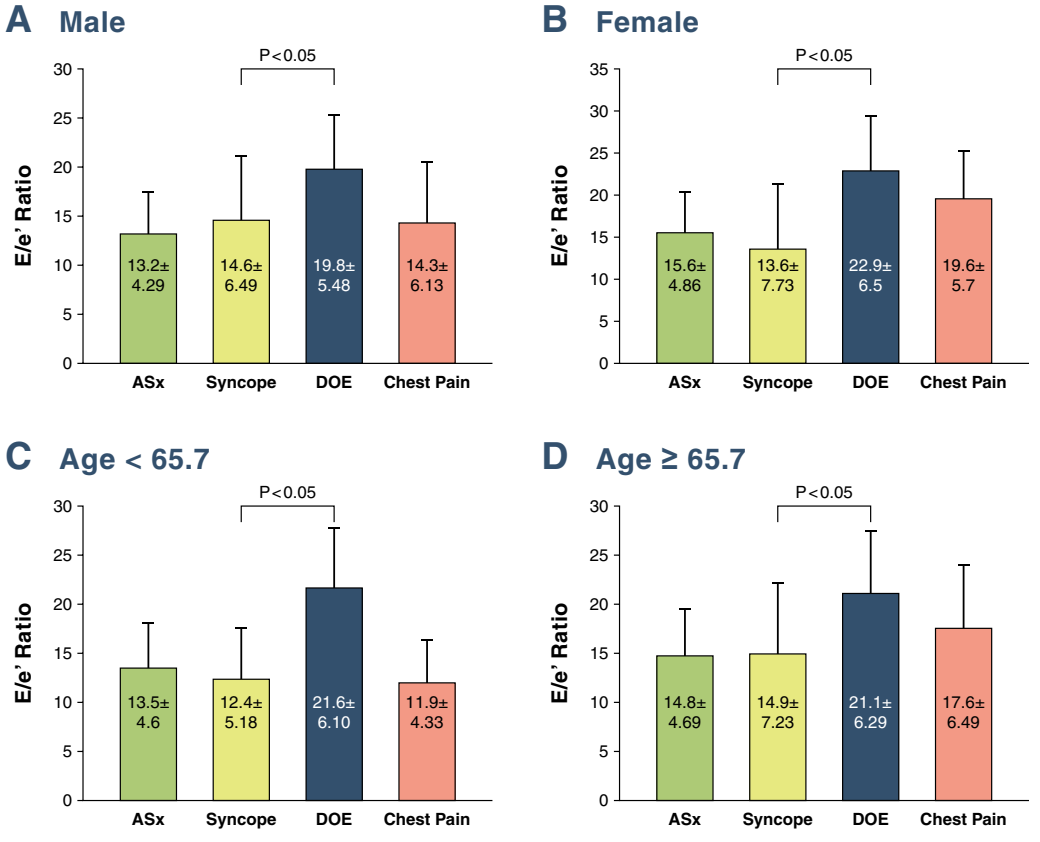

Figure 4. E/e′ Ratio in Patients With Different Symptoms Stratified by Sex and Age

(A) Male; **(B)** female; **(C)** age <65.7 years; **(D)** age ≥65.7 years. Values are mean ± SD. p < 0.05 versus group II (syncope) as reference group. Adjusted multiple comparison corrected by Dunnett. Abbreviations as in Figures 2 and 3.

nants of the presence of symptoms in our study patients with severe AS. The patients who presented with dyspnea (group III) had the worst diastolic function and the highest filling pressure, evidenced by largest LA volume, lowest e′, highest E, and highest E/e′ ratio. On the other hand, the patients who presented with syncope (group II) were found to have reduced SV and better preserved diastolic function without increased filling pressure.

In the setting of hemodynamically significant AS, the spectrum of diastolic abnormalities are known to be present, including increased myocardial stiffness, reduced LV compliance, increased LV mass, and elevated LV end-diastolic and LA pa-

Table 4. Independent Determinants of Presence of Symptoms in the Multiple Logistic Regression Analysis

		Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
Parameters	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > Chi-Square**	**Point Estimate**	**95% Wald CI**	
Age, yrs	1	0.0205	0.0192	1.1379	0.2861	1.021	0.983	1.06
Male	1	−0.0385	0.3136	0.0151	0.9023	0.926	0.271	3.166
BSA, m^2	1	−0.0183	0.0234	0.6153	0.4328	0.982	0.938	1.028
SBP, mm Hg	1	0.0188	0.0101	3.4442	0.0635	1.019	0.999	1.039
E/e′	1	**0.2795**	**0.0494**	**32.0474**	**<0.0001**	**1.322**	**1.20**	**1.457**
LAVI, ml/m^2	1	**−0.0223**	**0.0135**	**12.719**	**0.0092**	**0.978**	**1.052**	**1.114**
CO, l/min	1	**−0.7956**	**0.1885**	**17.8198**	**<0.0001**	**0.451**	**0.312**	**0.653**
SVI, ml/m^2	1	**0.0908**	**0.0249**	**13.2585**	**0.0003**	**1.095**	**1.043**	**1.15**

p Value determined by multiple logistic regression analysis. **Bold** values are statistically significant.
CI = confidence interval; DF = degrees of freedom; Pr = probability; other abbreviations as in Table 1.

Table 5. Association of Presence of Dyspnea in the Generalized Logit Model for Nominal Response Data

			Analysis of Maximum Likelihood Estimates				
Parameter	**Groups***	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > Chi-Square**	**Adjusted p Value**
Age	I	1	−0.0224	0.0222	1.0188	0.3128	0.938
	II	1	0.025	0.0577	0.1881	0.6645	1.000
	IV	1	0.019	0.0413	0.2113	0.6458	1.000
BSA	I	1	−0.00213	0.0315	0.0046	0.946	1.000
	II	1	0.0787	0.1092	0.5197	0.471	1.000
	IV	1	0.0466	0.0518	0.8076	0.3688	1.000
DBP	I	1	−0.0333	0.0178	3.4963	0.0615	0.185
	II	1	0.0082	0.0574	0.0205	0.8863	1.000
	IV	1	−0.0663	0.0327	4.098	0.0429	0.129
HR	I	1	0.0174	0.0168	1.0725	0.3004	0.901
	II	1	−0.00612	0.0635	0.0093	0.9233	1.000
	IV	1	−0.0205	0.0321	0.4099	0.522	1.000
DM	I	1	1.0188	0.6275	2.6355	0.1045	0.313
	II	1	1.0561	1.4618	0.522	0.47	1.000
	IV	1	2.744	0.9405	8.5128	0.0035	0.011
LVIDd	I	1	−0.0569	0.0436	1.705	0.1916	0.575
	II	1	−0.2963	0.1546	3.672	0.0553	0.166
	IV	1	−0.0392	0.0822	0.2278	0.6331	1.000
LVMI	I	1	−0.00227	0.00402	0.3193	0.5721	1.000
	II	1	0.000538	0.00964	0.0031	0.9555	1.000
	IV	1	0.00105	0.00723	0.0212	0.8842	1.000
E/e′	I	1	**−0.3531**	**0.0629**	**31.5473**	**<0.0001**	**<0.0001**
	II	1	−0.2346	0.1996	1.3809	0.2399	0.720
	IV	1	**−0.3397**	**0.1034**	**10.7869**	**0.001**	**0.003**
LAVI	I	1	0.0315	0.0148	4.4984	0.0339	0.102
	II	1	−0.0276	0.0575	0.2302	0.6314	1.000
	IV	1	0.0424	0.0266	2.5366	0.1112	0.334
SVI	I	1	−0.0202	0.0177	1.3093	0.2525	0.758
	II	1	−0.1278	0.0708	3.2564	0.0711	0.213
	IV	1	−0.0013	0.0302	0.0018	0.9658	1.000

All p values were corrected by Bonferroni method due to multiple testing. *Group I = asymptomatic; group II = syncope; group III = dyspnea (reference group); group IV = chest pain.
Abbreviations as in Tables 1 and 4.

rameters (6). Also, it has been shown that moderate to severe diastolic dysfunction is an independent predictor of increased morbidity and mortality in patients with AS (11). Although Bruch et al. (12) demonstrated impairment of diastolic function using tissue Doppler imaging in symptomatic patients with advanced AS and LV hypertrophy, our study demonstrates that the extent of diastolic dysfunction as well as SV and cardiac output appear to be responsible for the presenting symptoms in this group.

Role of filling pressures in patients with severe AS. In patients with AS, diastolic dysfunction was observed in at least 50% of patients with preserved systolic function and in 100% of patients with depressed function (13,14). Elevated filling pressure may induce symptoms such as dyspnea under exertion or even at rest resulting in pulmonary venous congestion. Indeed, a previous study (15) demonstrated that enhanced early diastolic filling (indicating increased filling pressure) distinguishes symptomatic from asymptomatic patients with AS.

In our study, LV filling pressure was estimated by E/e′ ratio obtained from echocardiography. The ratio (E/e′) of early transmitral flow velocity (E) to early diastolic septal mitral annular velocity (e′) has been shown to be a reliable noninvasive method of estimation of LV filling pressure (16–18). Increased value of E/e′ ratio accurately predicted elevated filling pressures in moderate to severe AS (12), and the E/e′ ratio has been reported to predict the prognosis of patients in a variety of cardiac diseases including AS (19–22).

Our present study demonstrated an important relationship between diastolic dysfunction and typical symptoms in severe AS. Our group has shown that increased E/e′ ratio was an independent predictor of outcome even after aortic valve replacement in patients symptomatic severe AS (22). The worse diastolic dysfunction and higher estimated filling pressure in dyspnea group are most likely due to coexisting myocardial abnormality in addition to severe AS, because diastolic dysfunction is relatively common in the elderly even without aortic valve stenosis or LV hypertrophy. This provides a possible explanation for the worse prognosis found in patients with higher E/e′ after aortic valve replacement. The onset of angina, syncope, and dyspnea has been shown to correlate with an average time to death of 5, 3, and 2 years, respectively (23). This clinical course has been derived primarily from postmortem studies on adults with acquired AS (23). The clinical spectrum of AS is broad, and patients with the same AVA can have different symptoms and intracardiac hemodynamics. Our data emphasize the importance of diastolic dysfunction in the natural history and its role in presenting symptoms of patients with severe AS. Because diastolic dysfunction is a common abnormality in the elderly even without AS, it is possible that those patients with pre-existing diastolic dysfunction or who are susceptible for diastolic dysfunction independent of AS are more likely present with dyspnea. Such patients may present with dyspnea even in the setting of nonsevere AS. It will be helpful if future investigations can address the question of whether aortic valve replacement can improve symptoms and survival of the patients with dyspnea and less than severe AS. This study also emphasizes the importance of assessing diastolic function as well as SV as a part of evaluation of AS, because they are intimately related to the patient's presenting symptoms and clinical outcome.

Study limitations. Several potential limitations in our study must be noted. First, the number of patients with syncope was relatively small. However, syncope is a less frequent symptom than dyspnea or chest pain. Despite the small number, our finding that decreased stroke volume and relatively lower filling pressure are responsible for syncope is an important observation. Increased filling pressure may be necessary to compensate for vasodilation when it occurs in patients with severe AS. Second, the patients with coronary artery disease were not included in our study. In the presence of coronary artery disease, chest pain may be more common when increased filling pressure can induce myocardial ischemia and/or ventricular arrhythmias. Therefore, intracardiac hemodynamic characteristics may be different in patients with severe AS and coronary artery disease. Third, the number of patients with syncope or chest pain was relatively small compared with the number of patients with dyspnea. This relatively small number might have introduced a possibility of selection bias. Fourth, the patients with LV systolic dysfunction were not included in our study to avoid hemodynamic changes related to LV systolic dysfunction. Therefore, our study results are not applicable to the patients with LV systolic dysfunction. Fifth, all intracardiac hemodynamics and AS severity were derived from echocardiographic measurements that can be operator- and patient-dependent. However, these noninvasive hemodynamic parameters have been well validated (8).

Finally, this study was conducted in a single referral tertiary hospital with a cardiac imaging center. Many patients of our study were referred for evaluation of murmur from other smaller hospitals. Those patients did not have any symptoms except for murmur. In addition, the exclusion of patients with coronary artery disease may have contributed to a large number of asymptomatic patients. Therefore, numbers of asymptomatic patients were relatively high.

CONCLUSIONS

In patients with anatomically severe AS, development of a particular symptom is linked to specific hemodynamic patterns. In the patients with severe AS who develop dyspnea, markedly altered LV diastolic function with increased filling pressure was present. On the other hand, the patients who develop syncope present with reduced SV along with smaller LV and LA. Hence, comprehensive intracardiac hemodynamics including diastolic function need to be evaluated in addition to AVA and pressure gradient for assessment of AS.

Reprint requests and correspondence: Dr. Seung Woo Park, Cardiovascular Imaging Center, Cardiac and Vascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea. *E-mail: parksmc@gmail.com.* OR Dr. Jae K. Oh, Cardiac and Vascular Center, Samsung Medical Center, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea; OR Dr. Jae K. Oh, Integrated Cardiac Imaging Center, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. *E-mail: oh.jae@mayo.edu.*

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