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Original Article

Echocardiographic Evaluation of Axial Spondyloarthritis in Korea: Data From the Catholic Axial Spondyloarthritis Cohort

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Objective. Axial spondyloarthritis (axSpA) is often accompanied by cardiac manifestations, such as valvular heart disease. In this prospective cohort study, we evaluated the incidence of cardiac abnormalities in Korean axSpA patients by echocardiography. **Methods.** AxSpA patients were prospectively recruited from a single tertiary hospital. Baseline demographic, clinical, radiographic, and echocardiographic data were collected at the time of enrollment. Echocardiography evaluations were performed with a focus on valvular heart disease and systolic and diastolic function. Logistic regression analyses were used to identify factors associated with diastolic dysfunction in axSpA. **Results.** A total of 357 axSpA patients were included in the analyses, of whom 78 (21.8%) exhibited diastolic dysfunction, with no reports of systolic dysfunction. Thirteen patients (3.6%) had valvular heart disease, and aortic valve regurgitation (n = 5) and mitral valve regurgitation (n = 6) were most common. Multivariable logistic regression analyses indicated that older age and higher body mass index (BMI) were positively associated with diastolic dysfunction, whereas human leukocyte antigen (HLA)-B27 positivity was negatively associated with diastolic dysfunction. **Conclusion.** Valvular heart disease is infrequent in Korean axSpA patients. However, diastolic dysfunction is common in axSpA patients, and is significantly associated with older age, higher BMI, and HLA-B27. **(J Rheum Dis 2020;27:30-36)**

Key Words. Spondylarthropathies, Echocardiography, Heart failure, diastolic, Heart valve diseases

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis mainly affecting the axial joint. Concept of axSpA has been emerged to include early form of ankylosing spondylitis, non-radiographic axSpA, which do not accompanied obvious sacroiliitis detectable in plain radiography [1]. Ankylosing spondylitis is the prototype of spondyloarthritis (SpA), and SpA can accompany several extra-articular manifestations. Anterior uveitis is the most common extra-articular manifestation, and other manifestations such as inflammatory bowel disease (IBD), psoriasis, and dactylitis could occur in the course of the SpA. Cardiovascular manifestations have long been reported in ankylosing spondylitis patients [2-11]; however, most studies that have reported such results have been composed of small number of ankylosing spondylitis patients, with no inclusion of non-radiographic axSpA, a much broader disease entity than ankylosing spondylitis.

Several cardiovascular diseases have been reported in ankylosing spondylitis. A cohort study from Quebec found that ankylosing spondylitis patients were at increased risk for cardiovascular disease, including valvular heart disease, ischemic heart disease, and congestive heart failure [12]. A similar study from Sweden revealed a higher frequency of aortic valve regurgitation (AR) in

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ankylosing spondylitis patients compared to the general population, leading to a recommendation for routine echocardiography evaluation of ankylosing spondylitis patients [13]. More recently, a meta-analysis of cardiovascular studies in ankylosing spondylitis showed that diastolic dysfunction was more frequent in ankylosing spondylitis patients relative to healthy controls [14]. Similar findings from a retrospective cohort study in Canada demonstrated an increased risk for vascular death in ankylosing spondylitis patients relative to the general population [15]. Both valvular heart disease and diastolic dysfunction can cause symptomatic heart failure and eventually increase mortality. Given the strong link between cardiac manifestations and ankylosing spondylitis, early detection and management of the aforementioned cardiac manifestations may be important to prevent major cardiac adverse events.

Among Korean axSpA patients, cardiovascular diseases including valvular heart disease have not been evaluated. We assessed the incidence of cardiovascular disease in Korean axSpA patients by echocardiography. Clinical cofactors that may be predictive of diastolic dysfunction in axSpA were also evaluated.

MATERIALS AND METHODS

Study design

AxSpA patients were enrolled in the Catholic Axial Spondyloarthritis Cohort (CASCO), a prospective, longitudinal cohort of Seoul St. Mary's Hospital, Seoul, Korea. Inclusion criteria were as following: fulfillment of the modified New York criteria for ankylosing spondylitis or Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA [1,16], and >18 years of age. A total of 372 patients were enrolled from January 2015 to April 2017, of which 357 patients underwent echocardiography after enrollment to CASCO (15 patients refused to do echocardiography). Baseline demographic, laboratory, radiographic, disease activities, and functional index data were collected for all patients, with echocardiography performed within 1 month after enrollment. The study was conducted in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from each patient before enrollment. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (no. KC15OISI0012).

Collected data

Baseline demographic characteristics including current age, age at the time of axSpA diagnosis, sex, height, and weight were collected at the time of enrollment. Clinical parameters including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), pain visual analogue scale (VAS), patient's global assessment, and physician's global assessment were recorded. EuroQol-5 dimensions (EQ-5D) and EQ-VAS were measured to access health-related quality of life. EQ-5D was converted into a 'time trade-off' value according to Korean reference data [17]. Very high ASDAS-CRP and elevated BASDAI were defined as >3.5 and 4.0 units, respectively [18,19].

Laboratory data included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and human leukocyte antigen (HLA)-B27. Electronic medical records of each patient were reviewed to assess current medications, comorbidities, and extra-articular manifestations. Extra-articular manifestations were deemed positive if at least once it was present in the course of the disease. The ASAS nonsteroidal anti-inflammatory drug index was calculated according to ASAS guidelines [20].

Radiographic assessment

Baseline grade of sacroiliitis was measured using plain radiography of the pelvis. Lateral radiographies of the cervical and lumbar spine were used to calculate the modified Stoke AS Spinal Score (mSASSS) and syndesmophyte [21]. The squaring score for the cervical vertebrae was excluded from the mSASSS because the anterior border of these vertebrae can be naturally concave [22]. Each radiography was provided to the assessor in a Digital Imaging and Communications in Medicine file after erasing the patient's information. mSASSS was performed by a trained rheumatologist (Min).

Echocardiography

Transthoracic echocardiography (TTE) was performed by an experienced cardiologist (Youn). Valvular regurgitation was divided into mild, moderate, and severe. Diastolic dysfunction was judged by measuring the E/A ratio, deceleration time, and E/E' ratio, and classified into grades I to IV [23]. Right ventricular systolic pressure was measured if tricuspid regurgitation was present, and the pressure gradient was calculated using the modified Bernoulli equation [24]. Groups were divided into axSpA

Table 1. Baseline characteristics of axSpA patients with and without diastolic dysfunction

Variables	Total axSpA (n=357)	AxSpA without diastolic dysfunction (n=279)	AxSpA with diastolic dysfunction (n=78)	p-value
Age (yr)	38.0 [31.0; 46.0]	35.0 [28.0; 41.5]	50.0 [44.0; 56.0]	<0.001
Disease duration (yr)	6.1 [2.3; 11.3]	5.7 [1.9; 10.4]	9.2 [4.0; 13.2]	0.003
Male sex	271 (75.9)	208 (74.6)	63 (80.8)	0.324
BMI (kg/m^2)	23.7 [21.7; 26.0]	23.5 [21.5; 25.9]	24.7 [22.9; 26.8]	0.004
Obesity (≥25)	124 (35.3)	92 (33.7)	32 (41.0)	0.289
Current smoker	96 (27.9)	75 (28.1)	21 (27.3)	1.000
Current alcohol drinker	239 (69.5)	193 (72.0)	46 (60.5)	0.075
Uveitis	161 (46.7)	114 (42.7)	47 (60.3)	0.009
IBD	5 (1.5)	1 (0.4)	4 (5.1)	0.011
Dactylitis	27 (7.8)	20 (7.5)	7 (9.0)	0.850
Psoriasis	16 (4.6)	13 (4.9)	3 (3.8)	0.943
BASDAI (0~10)	2.6 [1.6; 4.1]	2.6 [1.6; 4.0]	3.1 [1.4; 5.0]	0.443
Elevated BASDAI (≥4)	100 (29.2)	72 (27.2)	28 (35.9)	0.177
ASDAS-CRP (0~10)	1.7 [1.2; 2.3]	1.7 [1.1; 2.3]	2.0 [1.3; 2.5]	0.104
Very high ASDAS-CRP (≥3.5)	19 (5.5)	11 (4.2)	8 (10.3)	0.073
BASFI (0~10)	0.3 [0.0; 1.3]	0.2 [0.0; 1.1]	0.9 [0.1; 2.6]	<0.001
EQ-5D-TTO (0~1)	0.8 [0.8; 0.8]	0.8 [0.8; 0.8]	0.8 [0.7; 0.8]	0.070
EQ-VAS (0~100)	75.0 [60.0; 85.0]	75.0 [65.0; 86.0]	75.0 [60.0; 81.0]	0.218
PGA (0~10)	3.0 [1.0; 5.0]	2.0 [1.0; 5.0]	3.5 [1.0; 5.0]	0.063
PhyGA (0~10)	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	2.0 [1.0; 4.0]	0.075
Pain VAS (0~10)	2.0 [1.0; 4.0]	2.0 [1.0; 4.0]	3.0 [1.0; 5.0]	0.361
Peripheral arthritis	28 (8.2)	21 (7.9)	7 (9.1)	0.926
Comorbidity				
HTN	35 (9.8)	21 (7.5)	14 (17.9)	0.012
DM	10 (2.8)	2 (0.7)	8 (10.3)	<0.001
Dyslipidemia	8 (2.2)	5 (1.8)	3 (3.8)	0.515
Current medication				
NSAID index (0~100)	50.0 [0.0; 50.0]	50.0 [0.0; 50.0]	50.0 [0.0; 100.0]	0.454
Sulfasalazine	122 (34.2)	100 (35.8)	22 (28.2)	0.262
TNF-α blocker	167 (46.8)	123 (44.1)	44 (56.4)	0.072
ESR (mm/h)	11.0 [5.0; 19.0]	11.0 [5.0; 19.0]	12.0 [7.0; 22.0]	0.144
CRP (mg/dL)	0.1 [0.0; 0.3]	0.1 [0.0; 0.3]	0.1 [0.0; 0.5]	0.329
HLA-B27 positive	311 (93.4)	253 (95.5)	58 (85.3)	0.006
Baseline mean grade of sacroiliitis	2.5 [1.5; 3.0]	2.5 [1.5; 3.0]	3.0 [2.0; 4.0]	0.002
Ankylosing spondylitis (satisfying mNY criteria)	262 (73.4)	200 (71.7)	62 (79.5)	0.217
mSASSS (0~72)	4.0 [0.0; 14.0]	2.0 [0.0; 10.0]	15.0 [7.0; 47.0]	<0.001
Syndemophyte count (0~24)	1.0 [0.0; 5.0]	0.0 [0.0; 3.0]	5.0 [2.0; 17.0]	<0.001
TTE				
Valvular heart disease	13 (3.6)	7 (2.5)	6 (7.7)	0.069
AR	5 (1.4)	2 (0.7)	3 (3.8)	0.125
LVEF (%)	62.9 [60.0; 65.0]	62.9 [60.0; 65.0]	62.2 [60.0; 65.0]	0.757
Sm (cm/s)	8.3 [7.5; 9.1]	8.4 [7.5; 9.1]	8.1 [7.0; 9.1]	0.206
E/A ratio	1.3 [1.1; 1.6]	1.4 [1.2; 1.7]	0.9 [0.8; 0.9]	<0.001
DT (msec)	180.0 [154.5; 199.5]	173.0 [149.0; 187.0]	201.5 [183.0; 229.0]	<0.001
E/E′ ratio	6.9 [6.1; 8.1]	6.7 [6.0; 7.7]	8.0 [6.7; 9.6]	<0.001
RVSP (mmHg)	23.0 [19.0; 24.0]	22.0 [19.0; 24.0]	23.0 [20.0; 26.0]	0.222

Values are presented as median [inter-quartile range] or number (%). axSpA: axial spondyloarthritis, BMI: body mass index, IBD: inflammatory bowel disease, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, CRP: C-reactive protein, BASFI: Bath Ankylosing Spondylitis Functional Index, EQ-5D: EuroQol-5 dimensions, TTO: time trade-off, VAS: visual analogue scale, PGA: patient global assessment, PhyGA: physician global assessment, HTN: hypertension, DM: diabetes mellitus, NSAID: nonsteroidal anti-inflammatory drug, TNF: tumor necrosis factor, ESR: erythrocyte sedimentation rate, HLA: human leukocyte antigen, mNY: modified New York, mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score, TTE: transthoracic echocardiography, AR: aortic valve regurgitation, LVEF: left ventricular ejection fraction, Sm: mitral annular peak systolic velocity, DT: deceleration time, RVSP: right ventricular systolic pressure.

with and without diastolic dysfunction.

Statistical analyses

Normality was checked for each continuous variable, and then the data were compared using Student's t or Mann–Whitney tests. The results are presented as median and inter-quartile range. Categorical variables were compared using chi-square or Fisher's exact tests. Comparisons between multiple independent groups were done by ANOVA. Logistic regression analyses were used to identify factors associated with diastolic dysfunction. Factors significant at $p < 0.05$ in univariate analyses were included in multivariate regression analyses using backward stepwise regression; p-values < 0.05 were considered statistically significant. All tests were performed using R (R for Windows 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of axSpA patients and comparison between axSpA patients with and without diastolic dysfunction

Among the 372 axSpA patients enrolled in the CASCO study, 357 were examined by TTE. Of these, 74 were diagnosed with grade I diastolic dysfunction, and 4 were classified with grade II (Table 1). AxSpA patients with diastolic dysfunction were older than those without diastolic dysfunction and had a longer disease duration. Body mass index (BMI) was also higher in axSpA patients with diastolic dysfunction, who also had a frequent history of uveitis and combined IBD. Comorbid diseases, hypertension (HTN), and diabetes mellitus (DM) were more frequently observed in axSpA patients with diastolic dysfunction. Baseline radiographic structural changes in the axial joint, mean grade of sacroiliitis, mSASSS, and syndesmophyte count were all more severe in axSpA patients with diastolic dysfunction (Table 1). Valvular heart diseases were apparent in 13 patients, of which AR (n=5, three mild and two moderate) and mitral valve regurgitation (MR; n=6, five mild, and one moderate) were most common (Supplementary Table 1). All axSpA patients with AR satisfied modified New York criteria for ankylosing spondylitis. The prevalence of AR in ankylosing spondylitis patients of CASCO was generally lower than that of a Swedish study on ankylosing spondylitis (Supplementary Table 2) [13]. Although direct comparison of valvular heart disease frequency between axSpA patients and healthy controls was impossible, the crude prevalence of valvular heart disease in CASCO was higher than the general population of Korea (3.60% vs. 0.11%) [25]. The prevalence of diastolic dysfunction showed a tendency to increase with age, whereas valvular disease did not (Table 2).

Predictors of diastolic dysfunction in axSpA patients

Logistic regression analyses were used to identify variables associated with diastolic dysfunction in axSpA. In univariate regression analyses, age, disease duration, BMI, history of uveitis, IBD, very high ASDAS-CRP, BASFI, HTN, DM, mean grade of sacroiliitis, syndesmophyte count, and co-existence of valvular heart disease were all associated with increased risk for diastolic dysfunction, whereas HLA-B27 positivity was inversely correlated with diastolic dysfunction (Table 3). Multivariate regression analyses indicated that older age, higher BMI, and HLA-B27 negativity increased the odds of diastolic dysfunction in axSpA (Table 3).

DISCUSSION

We described the echocardiographic findings of axSpA patients in Korea, and identified predictors of diastolic

Table 2. Frequencies of diastolic dysfunction and valvular heart diease by age in axSpA

Cardiac manifestations	Age category						p-value
	<30 (n=80)	30~39 (n=119)	40~49 (n=100)	50~59 (n=44)	60~69 (n=12)	≥70 (n=2)	
Diastolic dysfunction	0 (0.0)	9 (7.6)	26 (26.0)	30 (68.2)	11 (91.7)	2 (100.0)	<0.001
T*	a	a	b	c	c	c	
Valvular heart disease	2 (2.5)	2 (1.7)	4 (4.0)	3 (6.8)	2 (16.7)	0 (0.0)	0.118

Values are presented as number (%). axSpA: axial spondyloarthritis. *The same letters indicate non-significant difference between groups based on Bonferroni multiple comparison test.

Table 3. Univariate and multivariate logistic regression analysis of predicting diastolic dysfunction in axSpA

Variables	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (yr)	1.20	1.15, 1.26	<0.001	1.21	1.15, 1.27	<0.001
Male sex	1.43	0.77, 2.68	0.258			
Disease duration (yr)	1.06	1.02, 1.10	0.001			
BMI (kg/m^2)	1.11	1.02, 1.19	0.011	1.14	1.01, 1.28	0.030
Alcohol drinker	0.60	0.35, 1.01	0.056			
Current smoker	0.96	0.54, 1.69	0.888			
Uveitis history	2.03	1.22, 3.40	0.007			
IBD	14.32	1.58, 130.11	0.018			
Elevated BASDAI (≥4)	1.50	0.88, 2.57	0.137			
Very high ASDAS-CRP (>3.5)	2.64	1.02, 6.81	0.045			
BASFI	1.45	1.23, 1.72	<0.001			
HTN	2.69	1.30, 5.57	0.008			
DM	15.83	3.29, 76.20	0.001	5.54	0.93, 32.92	0.060
Dyslipidemia	2.19	0.51, 9.38	0.290			
HLA-B27 positive	0.28	0.11, 0.67	0.004	0.23	0.06, 0.93	0.039
Mean grade of sacroiliitis	1.50	1.16, 1.94	0.002			
mSASSS	1.04	1.03, 1.05	<0.001			
Syndesmophyte count	1.12	1.08, 1.16	<0.001			
Valvular heart disease	3.24	1.06, 9.93	0.040			

axSpA: axial spondyloarthritis, OR: odd ratio, CI: confidence interval, BMI: body mass index, IBD: inflammatory bowel disease, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, CRP: C-reactive protein, BASFI: Bath Ankylosing Spondylitis Functional Index, HTN: hypertension, DM: diabetes mellitus, HLA: human leukocyte antigen, mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score.

dysfunction. Diastolic dysfunction was relatively common in axSpA patients (21.8%), and, of note, HLA-B27 positivity was inversely associated with diastolic dysfunction in axSpA. By contrast, other associated factors including age, BMI, HTN, and DM are well known risk factors of diastolic dysfunction [26]. In univariate regression analyses, structural damage in the axial joint, mean grade of sacroiliitis, mSASSS, and syndesmophyte count were positively associated with diastolic dysfunction. Structural damage such as sacroiliitis, mSASSS, and syndesmophyte progress naturally in conjunction with axSpA. Therefore, progression in structural damage to the spine or sacroiliac joint may simply be the result of prolonged disease duration or older age, and independent associations between structural damage in axSpA and diastolic dysfunction have yet to be established. Previous studies suggested potential role of HLA-B27 on cardiac manifestations of axSpA [6,10], aortic regurgitation and conduction system abnormality, however the exact role of HLA-B27 on cardiac problem of axSpA is not revealed yet. There are several differences between HLA-B27 positive and negative axSpA patients [27], and pathogenesis of HLA-B27 positive and negative axSpA would be differ. Further research is necessary to confirm the negative association between diastolic dysfunction and HLA-B27, including basic research that investigates the role of HLA-B27 in the context of diastolic dysfunction in axSpA patients.

Diastolic dysfunction without symptoms of heart failure along with normal systolic function is termed preclinical diastolic dysfunction [28]. The influence of diastolic dysfunction on mortality is well established, with moderate to severe diastolic dysfunction strongly associated with increased mortality, whereas mild diastolic dysfunction is not [29,30]. In grade I diastolic dysfunction, left ventricle ejection fraction (LVEF) predicts the occurrence of heart failure symptoms [31]. However, in the present study, all axSpA patients exhibited LVEF within the normal reference ranges. In addition, the vast majority (94.9%) of axSpA patients with diastolic dysfunction were classified as having grade I disease, without accompanying symptoms of heart failure. Although diastolic dysfunction was relatively common in axSpA patients in the present study, its severity was mild and the clinical significance of this finding remains uncertain.

Valvular heart disease, particularly AR, is considered an important extra-articular manifestation in ankylosing spondylitis patients [2,4,6]. A recent study from Sweden reported an increased prevalence of AR in ankylosing spondylitis patients relative to healthy controls, and Klingberg et al. [13] claimed to check echocardiography routinely in ankylosing spondylitis patients. However, the prevalence of AR was lower in the present study than in the Swedish study, and none of the non-radiographic axSpA patients had valvular heart disease. This implies that routine screening using TTE may not be suitable for axSpA patients in Korea.

This study had several limitations. For example, the study population was relatively small; however, it differed significantly from previous studies that were limited to ankylosing spondylitis patients. The present study represents the first evaluation of cardiac manifestation in whole axSpA patients, not limited to ankylosing spondylitis. Second, the design was cross-sectional, and thus we were unable to assess long-term prognosis of axSpA patients in the context of diastolic dysfunction. As the CASCO study is an ongoing prospective, longitudinal cohort study, assessment of disease prognosis in axSpA patients with and without diastolic dysfunction is possible in subsequent analyses. Third, proper age- and sex-matched healthy controls were not available. Therefore, direct comparisons of the prevalence of valvular heart disease and diastolic dysfunction in axSpA patients and healthy controls was not possible.

CONCLUSION

Although revealing prevalence of cardiac manifestation in Korean ankylosing spondylitis patients exists [32], this study provides the first echocardiographic findings which categorized and described cardiac manifestation in Korean axSpA patients. Incidence of AR was less frequent than that seen in Western country. By contrast, diastolic dysfunction was relatively common in Korean axSpA patients, although its severity was mostly mild (grade I) with all patients being asymptomatic. Based on these findings, routine use of TTE might not be suitable in Korean axSpA patients. However, it may be useful for detecting diastolic dysfunction in a subset of axSpA patients, particularly those with HLA-B27 negativity, higher BMI, and older age.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

H.K.M. drafted the manuscript, carried out data collection and analysis. J.L., J.H.J., S.K.K., and H.J.Y. collected and analyzed the data. S.H.P. designed the study, interpreted the results, and revised the manuscript. All authors were involved in critically revising the final preparation. All authors approved the final version to be published.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2020.27.1.30.

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