Original Article

Echocardiographic and Electrocardiographic Findings in Patients with Ankylosing Spondylitis without Cardiovascular Risk Factors

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Received 15 April 2019; Accepted 20 January 2020

Abstract

Background: *Ankylosing spondylitis (AS) is a chronic inflammatory condition associated with more cardiac manifestations than those in the normal population. In this study, we sought to determine the prevalence of cardiac involvement in patients suffering from AS without cardiovascular risk factors.*

Methods: *The present case-control study, conducted in 2 university hospitals in Tehran from January 2016 to December 2017, recruited 67 patients with AS and 40 age- and sex-matched healthy controls. The diagnosis of AS was based on the classification criteria of the Assessment of SpondyloArthritis International Society. All the participants were examined using transthoracic echocardiography and a standard 12-lead ECG. Baseline characteristics, echocardiographic findings, and ECG features were compared between the AS and control groups using univariate analyses.*

Results: *The median age was 33.5 ($IQR_{25\text{-}75\%}$: 20.5–59) years in the AS group and 35 ($IQR_{25\text{-}75\%}$: 26–59) years in the control group (P=0.301). The number of patients with left ventricular systolic and diastolic dysfunction was significantly higher in the patients with AS than in the controls (7.5% vs. 20.9%; P=0.067, and 22.9% vs. 5.0%; P=0.026, respectively). The number of individuals with a left-axis deviation and a left anterior fascicular block was significantly higher in the patients suffering from AS than in the control group. The number of patients with aortic valve involvement was comparable between the groups (P=0.332).*

Conclusion: *The most common cardiac involvement in our patients with AS was left ventricular dysfunction, followed by rhythm disturbances and aortic valve insufficiency. These findings were independent of age, AS severity, and disease duration. Therefore, the implementation of cardiovascular screening can be recommended for patients with AS.*

J Teh Univ Heart Ctr 2020;15(2):43-49

This paper should be cited as: Almasi S, Farahani B, Samiei N, Rezaei Y, Mahmoodi H, Qorbani M. Echocardiographic and Electrocardiographic Findings in Patients with Ankylosing Spondylitis without Cardiovascular Risk Factors. J Teh Univ Heart Ctr 2020;15(2):43-49.

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Keywords: *Spondylitis, ankylosing; Echocardiography; Electrocardiography; Ventricular dysfunction; Heart block; Aortic valve insufficiency*

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory condition affecting the spine and sacroiliac and peripheral joints; it begins in the second or third decades of life. Based on the latest meta-analysis, the prevalence of AS is found to be 16.7 per 10,000 in Asia, denoting the involvement of 4.63 to 4.98 million people.[1] The human leukocyte antigen (HLA) B27 presents in the majority of patients.[2] This disease is associated with extra-spinal manifestations including the involvement of the eye, gastrointestinal tract, cardiovascular system, pulmonary system, renal system, mental status, and blood.[2-5] It has been found that cardiovascular diseases (CVDs) and the associated risk factors are more common in patients afflicted with AS than in the normal population,[6-8] and it has also been shown to be associated with increased mortality by comparison with the normal population.[5]

Aortitis is the main cardiac involvement in patients with AS; it leads to aortic valve insufficiency and aortic root dilation,[9, 10] which may begin before the presence of clinical symptoms.[11] The involvement of the aorta extends to the interventricular septum and results in the development of conduction abnormalities, as the second most common cardiac diseases in patients with AS.[10] In addition to these common findings, some of the other structural and nonstructural CVDs that have been reported in patients with AS include left ventricular (LV) systolic and diastolic dysfunction,[12-16] valvular diseases,[2, 14, 17, 18] LV hypertrophy,[19] cardiac autonomic dysfunction,[20] coronary artery diseases,[21, 22] dilated cardiomyopathy,[3] and LV noncompaction cardiomyopathy.[23]

A relatively large cohort of Iranian patients with AS (n=320) found the incidence of heart diseases to be approximately 3%, but it failed to identify the type of CVDs.[24] On the other hand, cardiac arrhythmias were significantly more frequent in the controls than in the patients with AS.[24] No other cardiac involvement was reported in another study, in which all the participants were examined via echocardiography and ECG.[25]

Given the improper echocardiographic assessments in prior investigations in Iranian-based studies and the lack of data in this setting, we utilized echocardiographic and ECG modalities in the present case-control study firstly to identify the cardiac involvement in patients suffering from AS who were stable on medical therapy and without conventional cardiovascular risk factors and secondly to compare the findings with those in a group of age- and sex-matched controls.

Methods

The current case-control study, conducted from January 2016 to December 2017, recruited 67 patients with AS and 40 age- and sex-matched healthy individuals as controls. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (identification number: 1006). All cases with AS were consecutively selected from among the patients who visited our rheumatologic diseases clinic in a tertiary care center. Patients were diagnosed with AS when they fulfilled the criteria of this chronic inflammatory condition based on the modified New York criteria for AS.[26] In addition, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[27] and the Bath Ankylosing Spondylitis Functional Index (BASFI)[28] were calculated for all the participating patients. The BASDAI was employed to determine active diseases (BASDAI score >4). All the patients were on medical therapy for AS and had stable conditions. The exclusion criteria were comprised of hypertension, diabetes mellitus, dyslipidemia, renal failure, chronic pulmonary diseases, other rheumatologic diseases, any known CVDs including congenital heart diseases, and the consumption of cardiovascular medications. Control individuals were selected from asymptomatic patients without cardiovascular risk factors and any known CVDs. The inclusion criteria consisted of referral for evaluations for probable cardiac diseases before employment in organizations (a requirement for insurance validity) and participation in sporting events. All the study subjects were examined using echocardiography and ECG for an evaluation of their cardiac status.

All the patients were examined and evaluated using conventional transthoracic echocardiography and tissue Doppler imaging (TDI) parameters for an assessment of their cardiac systolic and diastolic functions, any valvular involvement, aortic involvement, and pulmonary artery pressure measurements (Vivid S5, GE Healthcare, Horten, Norway). Additionally, the echocardiographer was free to evaluate the patients' heart and related vessels in all views to find any concomitant abnormalities. The pulsed-wave spectral mode was used for the TDI parameters.

The TDI modality from the apical 4-chamber view allowed the measurement of peak myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities (cm/s) for the corresponding LV lateral wall, septal segments, and right ventricular free wall. The Em/Am ratio was consequently calculated for either of the corresponding segments. All the values were measured in 3 separate beats and then averaged. The identification of LV diastolic dysfunction

was based on the 2009 guideline of the American Society of Echocardiography.[29] The patients with a septal e′ of less than 8 and/or a lateral e′ of less than 10 were considered to have diastolic dysfunction. Moreover, the cases with E/e′ of 8 or less, between 9 and 12, and 13 or more were regarded as grades I, II, and III diastolic dysfunction, respectively. The LV ejection fraction was estimated using the Simpson method. During the echocardiographic evaluation, a single-lead ECG was superimposed on imaging.

Regarding valvular involvement, a moderate or greater degree of valvular regurgitation was reported as valvular insufficiency. Any degrees of valvular stenosis were also reported. Also evaluated and reported was the prolapse of the mitral valve.

Standard 12-lead ECGs were obtained simultaneously using a recorder at a paper speed of 25 mm/s and a scale of 10 mm/mV standardization. A single cardiologist, blinded to the clinical status of the patients, interpreted all the ECGs. The interpretation of the ECGs included any changes leading to the alteration in the electrical activity of the heart.

The normality of the continuous variables was assessed using the Kolmogorov–Smirnov test. The categorical data were presented as numbers (percentages) and the continuous variables as the mean±the standard deviation or the median (interquartile ranges$_{25\text{-}75\%}$), as appropriate. The continuous variables were compared between the groups using the t-test or the Mann–Whitney U tests, as appropriate. The categorical variables were analyzed using the χ^2 test or the Fisher exact test. On the basis of a 95% confidence interval, a power of 80%, a level of significance of 0.05, and a case to control ratio of 0.7, the sample size was calculated based on 45% and 18% rates of LV diastolic dysfunction in the AS and control groups, respectively.[30] All the data were analyzed using the Statistical Package for the Social Science Base, version 21.0 (SPSS, IBM, NY). Two-sided P values were calculated.

Results

The median age was 33.5 (IQR$_{25\text{-}75\%}$: 20.5–59) years in the AS group and 35 (IQR$_{25\text{-}75\%}$: 26–59) years in the control group (P=0.301). The mean duration of the disease was 9.58±5.56 years, and 38.8% of the patients were on the regimen of anti-tumor necrosis factor (TNF) therapy. The other baseline values are summarized in Table 1.

The mean of the LV lateral wall Em/Am ratio was significantly lower in the AS group than in the control group (1.37±0.69 vs. 2.06±1.44; P<0.001). The number of patients with diastolic dysfunction (septal Em/Am ratio <1) was comparable between the AS and control groups (30.0% vs. 44.8%; P=0.130). The mean of the Em/Am ratio in the septal and RV free wall segments, as well as the number of individuals with an Em/Am ratio of less than 1, was comparable between the patients with AS and the controls. There was a trend among the patients with AS, compared with the controls, toward having greater E/e′ values (8.81±4.62 vs. 7.27±3.14 mmHg; P=0.073). The rate of LV diastolic dysfunction in the patients suffering from AS was significantly higher than that in the controls (20.9% vs. 5.0%; P=0.026). Furthermore, the cases with AS had lower LV ejection fractions than the controls (P=0.020), and LV systolic dysfunction (defined as an LV ejection fraction <55%) was more frequent in the AS group than in the control group (7.5% vs. 20.9%; P=0.067).

Aortic root dilation was observed in 4.5% of the controls and none of those in the AS group (P=0.291). A 36-year-old man with AS was diagnosed with aortic root dilation along with aortic valve insufficiency. The patient underwent surgery; however, he did not survive this fatal complication. (His AS duration was 8 years with a BASDAI score of 8.2, associated with LV diastolic dysfunction and without any cardiac rhythm disturbances.)

The number of patients with aortic valve insufficiency was comparable between the 2 groups (P=0.332). No patients had pericardium thickening, and only 1 patient in the AS group had pericardial effusion. There were no significant differences between the groups regarding significant heart valve diseases. The other echocardiographic findings of the study participants are tabulated in Table 2.

Based on ECG examinations, all the study participants

Table 1. Baseline characteristics in the patients and the controls*, **

	Control (n=40)	AS (n=67)	P*
Age (y)	33.5 (20.5-59)	35 (26-59)	0.301
Male	30 (75.0)	56 (83.6)	0.280
Positive HLA-B27	NA	47 (70.1)	NA
Duration of AS (y)	NA	9.52±5.53	NA
BASDAI	NA	2.82±1.65	NA
BASDAI ≥4	NA	19 (28.4)	NA
BASFI	NA	2.18±1.66	NA
Anti-TNF therapy	NA	26 (38.8)	NA

*Data are presented as the mean±the SD, the median (interquartile ranges 25-75%), or numbers (%).
**All the comparisons are calculated using the χ^2 test or the Mann–Whitney U rank sum test.
AS, Ankylosing spondylitis; HLA, Human leukocyte antigen; NA, Not applicable; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; TNF, Tumor necrosis factors

Table 2. Echocardiographic parameters evaluating structural heart diseases in the patients and the controls*, **

	Control (n=40)	AS (n=67)	P
LV lateral wall E, cm/s	15.10±3.61	13.59±4.47	0.074
LV lateral wall A, cm/s	8.80±2.81	11.12±3.57	<0.001
LV lateral wall S, cm/s	9.71±2.28	10.15±2.84	0.413
LV lateral wall Em/Am ratio	2.06±1.44	1.37±0.69	<0.001
LV lateral wall Em/Am ratio <1	3 (7.5)	27 (40.3)	<0.001
Septal wall E, cm/s	10.58±2.69	11.91±3.74	0.062
Septal wall A, cm/s	8.43±2.22	10.81±3.28	<0.001
Septal wall S, cm/s	7.71±2.02	9.68±2.43	<0.001
Septal Em/Am ratio	1.36±0.59	1.21±0.57	0.193
Septal Em/Am ratio <1	12 (30.0)	30 (44.8)	0.130
RV free wall E, cm/s	12.92±3.70	12.59±3.70	0.657
RV free wall A, cm/s	12.52±3.51	13.55±4.04	0.194
RV free wall S, cm/s	12.47±1.94	13.28±2.67	0.103
RV free wall Em/Am ratio	1.12±0.49	1.03±0.48	0.385
RV free wall Em/Am ratio <1	16 (40.0)	37 (55.2)	0.128
LVEF, %	59.25±2.66	56.63±6.64	0.020
LVEF <55%	3 (7.5)	14 (20.9)	0.067
E/e′	7.27±3.14	8.81±4.62	0.073
LV diastolic dysfunction	2 (5.0)	14 (22.9)	0.026
LVESD, mm	2.97±0.50	3.05±0.52	0.459
LVEDD, mm	4.65±0.37	4.75±0.59	0.347
PAP, mmHg	23.40±3.29	24.43±5.38	0.276
Aortic root dilation	0	3 (4.5)	0.291
Pericardial effusion	0	1 (1.5)	1
Mitral valve involvement			0.548
Prolapse	2 (5.0)	6 (9.0)	
Stenosis	0	1 (1.5)	
Aortic valve involvement			0.332
Regurgitation	2 (5)	6 (9)	
Stenosis	1 (2.5)	0	
Tricuspid valve involvement			0.419
Regurgitation	31 (77.5)	52 (77.6)	
Stenosis	1 (2.5)	0	
Pulmonary valve involvement			0.238
Regurgitation	0	2 (3.0)	
Stenosis	1 (2.5)	0	

*Data are presented as the mean±the SD or numbers (%).
**All the comparisons are calculated using the χ^2 test, the Fisher exact test, or the t-test.
AS, Ankylosing spondylitis; LV, Left ventricle; E, Early diastolic velocity; A, Late diastolic velocity; Em/Am ratio, Early diastolic/late diastolic velocity ratio; E/e′, Mitral early diastolic flow velocity/average E septal and lateral wall flow velocity; RV, Right ventricle; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; LVEDD, Left ventricular end-diastolic diameter; PAP, Pulmonary arterial pressure; LA, Left atrium; RV, Right ventricle; RA, Right atrium

Table 3. Electrocardiographic findings in the patients and the controls*, **

	Control (n=40)	AS (n=67)	P
Hear rate, beats/min	75.15±12.19	74.11±13.98	0.700
Right-axis deviation	0	1 (1.5)	1
Left-axis deviation	0	7 (10.4)	0.044
Left anterior fascicular block	0	11 (16.4)	0.007

Data are presented as the mean±the SD or numbers (%).
**All the comparisons are calculated using the χ^2 test, the Fisher exact test, or the *t*-test.

were in the sinus rhythm. The number of individuals with a left-axis deviation and a left anterior fascicular block was significantly higher in the AS group than in the control group (10.4% vs. 0; P=0.044 and 16.4% vs. 0; P=0.007, correspondingly). The PR and QT intervals and the QRS complex were normal in both study groups (Table 3).

The patients were categorized into 2 groups based on the median of their disease duration (34 patients ≥9 years and 33 patients <9 years of AS duration). The number of patients with BASDAI scores of 4 or greater was higher in the long-standing AS group (38.2% vs. 18.2%; P=0.069). A decreased LV ejection fraction was more common among the cases with long-standing AS (29.4% vs. 12.1%; P=0.084). Aortic insufficiency was twice as frequent in the long-standing AS group (11.8% vs. 6.0%; P=0.351). There was also a trend among the patients with long-standing AS toward having LV diastolic dysfunction more frequently (12.1% vs. 29.4%; P=0.082). The other echocardiographic findings were comparable between the 2 groups based on AS duration. The patients in the long-standing AS group exhibited left-axis deviation more frequently (17.6% vs. 3.0%; P=0.051). There was a trend in the long-standing AS group toward having left anterior fascicular block more frequently (23.5% vs. 9.1%; P=0.111).

When the patients with AS were categorized into groups based on the BASDAI levels (<4 vs. ≥4) and the use of anti-TNF therapy, there were no significant differences between the subgroups with regard to all echocardiographic and ECG parameters. Similarly, when the patients suffering from AS were divided into groups based on age (32 patients <35 years old vs. 35 patients ≥35 years old), all the variables were comparable between the subgroups, except for a septal Em/Am ratio of smaller than 1, which was significantly higher in the patients older than 35 years of age (57.1% vs. 31.2%; P=0.033).

Discussion

In this case-control study, we showed that patients with AS, in comparison with a healthy population, have an increased prevalence of systolic and diastolic dysfunction as measured by conventional and TDI echocardiography. We also observed aortic root dilation (4.5%) and aortic valve insufficiency (9%) in our patients with AS; the differences with the control group were, however, nonsignificant. Our patients with AS had a higher frequency of left anterior fascicular block (16.4%) and left-axis deviation (10.4%) than our control group, confirming the relatively high burden of CVDs in patients afflicted with AS compared with a healthy population.

The most common instances of cardiac involvement in patients with AS are aortic root dilation, aortic valve insufficiency, and conduction abnormalities.[10] Using echocardiography and standard 12-lead ECG, Klingberg et al.[18] examined 187 patients with AS and showed that the cases had a relatively high frequency of aortic regurgitation (18%) and conduction abnormalities (13%). In a Swedish cohort study,[31] AS increased the risk of cardiac rhythm disturbances and aortic valve insufficiency during a 6-year follow-up. Elsewhere, a 25-year follow-up of 68 patients with AS showed an incidence rate of 33% of cardiac conduction abnormalities.[32] In our study, the frequency of aortic valve insufficiency and left anterior fascicular block was 9% and 16.4%, respectively. These findings are in accordance with previous studies, although the rates of such events have been found to be influenced by the follow-up duration and the continuity of patients' examination at routine visits.[32]

Aortopathies are the major consequence of AS that may lead to fatal complications. A male patient in the present cohort developed aortic dilation and subsequent dissection, and he died postoperatively. Moyssakis et al.[33] evaluated aortic stiffness via echocardiography in 57 patients with AS and reported that aortic distensibility, an indicator of aortic stiffness, was significantly decreased in the patients with AS by comparison with the controls ($2.21\pm0.24\times10^{-6}$ cm^2 dyn^{-1} vs. $2.58\pm0.19\times10^{-6}$ cm^2 dyn^{-1}; P<0.001). Biesbroek et al.,[34] having examined patients suffering from AS with echocardiography and cardiac magnetic resonance imaging, observed aortic root dilatation in 14% of their study population. In a prospective study on patients with AS examined with the aid of transesophageal echocardiography, Roldan et al.[9] found a 25% incidence rate of aortic root dilation. All these findings underscore the need for a definite screening of patients if complications are to be prevented.

ECG has also been used to evaluate the detailed aspects of cardiac dysrhythmia in patients with AS. Bengtsson et al.[31] evaluated the risk of cardiac arrhythmias in different spondyloarthropathies and found that AS increased the risk of atrioventricular block, atrial fibrillation, and pacemaker implantation during a 6-year follow-up (HR: 2.3, 1.3, and 2.1, correspondingly). Acar et al.[12] demonstrated that the maximum P-wave duration and P-wave dispersion in their patients with AS were significantly higher than those in their healthy controls (103.85±6.10 vs. 97.52±6.79 ms; P<0.001 and 48.65±6.17 vs. 40.98±5.37 ms; P<0.001, respectively). In their investigation, Dik et al.[11] observed 6 (4.6%) patients with first-degree heart block, 2 (1.6%) with bundle branch blocks, and 38 (29.2%) with prolonged QRS-complex durations. They also found that disease duration was associated with the PR interval and the QRS duration. In another case-control study, the QT interval was comparable between the cases with AS and the controls and also in subgroups of AS (Stage 3 vs. Stage 4); nonetheless, heart rate, T-wave duration, and the root mean square recessive difference were significantly different between the cases in stages 3 and 4 and the controls.[35] Gunes et al.[17] found bundle branch block and left-axis deviation in 12%

of their study population, while the QT interval and the P-wave dispersions were not significantly different between the patients with AS and the control group. Aksoy et al.[36] reported a high prevalence of supraventricular arrhythmia in their patients with AS compared with their controls (39% vs. 10%; P=0.020).

In our study, we found significant differences concerning bundle branch block and left-axis deviation between our AS and control groups, but the QRS duration and the PR interval were comparable between the 2 groups. Further, we observed a higher incidence of left-axis deviation in our patients with AS, who also exhibited a higher trend toward developing bundle branch block. Given the diverse distribution of dysrhythmias in patients suffering from AS, it appears that cardiac rhythm disturbances can account for a major portion of CVD burden in patients with AS, indicating the need for more accurate evaluations with a view to determining the incidence and predictors of AS and applying preventive and therapeutic modalities in daily practice.

Echocardiographic examinations have been increasingly implemented in patients with different rheumatologic diseases with the aim of evaluating cardiac functions and structures.[37-39] The systolic and diastolic functions of the heart have been found to be impaired in patients with AS in addition to classic aortopathies and arrhythmias. Kiris et al.[13] found that their patients with AS had LV systolic asynchrony, which might lead to cardiovascular events. In contrast, several studies have shown that the LV ejection fraction is comparable between cases with AS and controls.[16, 33, 40] Svealv et al.[41] demonstrated infrequent LV diastolic dysfunction (12% mild dysfunction) among 187 patients with AS. In the current study, the patients with AS had lower LV ejection fractions than the controls, although the difference did not reach statistical significance. Based on a meta-analysis,[42] LV diastolic dysfunction has been observed in patients with AS; however, there has been no prospective study to show the prognostic implications of this phenomenon.

Speckle-tracking echocardiography and TDI parameters have also ushered in further assessments of myocardial functions. Ustun et al.[16] evaluated 26 patients with AS with speckle-tracking echocardiography, which illustrated decreased levels of systolic and diastolic strains. With the use of TDI, Acar et al.[12] demonstrated LV diastolic dysfunction in a group of 40 patients with AS. Moyssakis et al.[33] examined 57 patients with AS using conventional and TDI echocardiography. They showed that the myocardial performance index, an indicator of LV global systolic and diastolic functions, was higher among their patients with AS than among their healthy population (0.39±0.03 vs. 0.37±0.03; P<0.010), although the LV ejection fractions were comparable between the 2 groups.[33] In light of these findings, it appears that large-scale studies are required to evaluate cardiac functions in patients with AS via conventional, TDI, and speckle-tracking echocardiography not only to provide more precise findings regarding confounding factors but also to evaluate the clinical relevance of such findings in daily practice.

There are some major limitations in the current study that should be taken into consideration in the interpretation of its results. Firstly, although we recruited consecutive patients with AS that visited our clinic, our sample size was small. Secondly, we did not use new approaches for the evaluation of diastolic dysfunction; therefore, our results may not represent the true number of patients with diastolic dysfunction. Thirdly, the small number of patients with diastolic dysfunction precluded us from evaluating its predictors in our cohort.

Conclusion

In the current cohort of patients suffering from AS without cardiovascular risk factors, the most common cardiac involvement was LV systolic and diastolic dysfunction, followed by left anterior fascicular block, left-axis deviation, and aortic valve insufficiency, correspondingly, based on echocardiographic and ECG examinations. Furthermore, due to the lack of any significant differences between major cardiac pathologies and disease severity, patients' age, and the duration of AS, it might be of utmost importance to implement serial screening modalities for detecting CVDs in patients with AS.

Acknowledgments

The study was approved and supported by Iran University of Medical Sciences.

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