Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2020;45(3):880-890
DOI: 10.17826/cumj.690505

ARAŞTIRMA / RESEARCH

Could presystolic wave be a predictor for subclinical left ventricular diastolic dysfunction in ankylosing spondylitis?

Presistolik dalga ankilozan spondilitte subklinik sol ventrikül diyastolik disfonksiyonu için bir belirteç olabilir mi?

Çaglar Özmen[1], Neslihan Gökçen[2], Rabia Eker Akıllı[1], Cuma Yeşildaş[3], Ayhan Usal[1]

[1]Cukurova University, Faculty of Medicine, Department of Cardiology, Adana/Turkey
[2]Kocaeli University Research and Application Hospital, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Kocaeli/Turkey
[3]Mersin University, Faculty of Medicine, Department of Cardiology, Adana/Turkey

Cukurova Medical Journal 2020;45 (3):880-890

Abstract

Purpose: The aim of this study was to evaluate the clinical significance of presystolic wave in the detection of diastolic dysfunction in ankylosing spondylitis patients.
Materials and Methods: In this cross-sectional study, 59 patients and 65 healthy controls were included in the study. Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Metrology Index, Maastricht Ankylosing Spondylitis Enthesitis Score and Bath Ankylosing Spondylitis Functional Index was eveluated. The Doppler tissue-imaging and presystolic wave measurements were performed by same cardiologist who was blinded to study details.
Results: Presystolic wave was detected in 26.6% of the whole study population; in 37.3% of patients and 16.9% of the control group. When the patient and control groups were divided into two subgroups according to the presence or absence of presystolic wave; myocardial performance index, transmitral E wave velocity, E/A ratio, left ventricular outflow tract velocity and septal e' wave velocity were statistically significant in subjects with presence presystolic wave in both groups. In the univariate model, high c-reactive protein level, increased BASMI and BASFI scores and elevated myocardial performance index were determined as risk factors for the presence of presystolic wave in ankylosing spondylitis patients.
Conclusion: The assessment of presystolic wave on echocardiography examination may provide important information about the left ventricul diastolic function, which has a prognostic impact for ankylosing spondylitis patients.

Keywords:. Ankylosing spondylitis, diastolic dysfunction, heart failure, presystolic wave.

Öz

Amaç: Bu çalışmanın amacı, ankilozan spondilit hastalarında diyastolik disfonksiyonun saptanmasında presistolik dalganın önemini değerlendirmektir.
Gereç ve Yöntem: Kesitsel çalışmamıza 59 hasta ve 65 sağlıklı kontrol dahil edildi. Ankilozan Spondilit Hastalığı Aktivite Skoru, Bath Ankilozan Spondilit Metrology indeks, Maastricht Ankilozan Spondilit Entesit Skoru ve Bath Ankilozan Spondilit Fonksiyonel İndeksi değerlendirildi. Doppler doku görüntüleme ve presistolik dalga ölçümleri yapıldı.
Bulgular: Hastaların % 37.3'ünde ve kontrol grubunun % 16.9'unda olmak üzere tüm çalışma popülasyonunun% 26.6'sında presistolik dalga saptandı. Hasta ve kontrol grupları presistolik dalganın varlığına veya yokluğuna göre iki gruba ayrıldığında; miyokardiyal performans indeksi, transmitral E dalga hızı, E/A oranı, sol ventrikül çıkış yolu velositesi ve septal e 'dalga hızı, her iki grupta da presiktolik dalgası olanlarda istatistiksel olarak anlamlı oranda farklıydı. Tek değişkenli modelde, yüksek c-reaktif protein seviyesi, artmış BASMI ve BASFI skorları ve artmış miyokard performans indeksi, ankilozan spondilit hastalarında presistolik dalga varlığı için risk faktörü olarak belirlenmiştir.
Sonuç: Ekokardiyografik incelemede presistolik dalganın varlığı, ankilozan spondilit hastalarında prognostik önemi olan sol ventrikül diyastolik fonksiyonu hakkında önemli bilgiler sağlayabilir.

Anahtar kelimeler: Ankilozan spondilit, diyastolik fonksiyon bozukluğu, kalp yetmezliği, presistolik dalga

Yazışma Adresi/Address for Correspondence: Dr. Çaglar Özmen, Cukurova University Balcali Hospital, Faculty of Medicine, Department of Cardiology, Sarıcam/ Adana, Turkey E-mail: caglarozm@hotmail.com
Geliş tarihi/Received: 18.02.2020 Kabul tarihi/Accepted: 16.05.2020 Çevrimiçi yayın/Published online: 31.08.2020

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease, which affects not only the axial skeleton but also the organs and other systems including the cardiovascular system. Recently, many studies have investigated the impact of chronic inflammatory disorders on the cardiovascular system [1-3]. The involvement of the cardiovascular system in patients with AS increases mortality by approximately 2-fold compared to the general population [4,5].

What kind of cardiac involvement is expected in AS? According to studies, myocardial fibrosis and stiffness causing impaired diastolic function has been observed [6]. Ankylosing spondylitis has also been reported to be associated with an increased risk of cardiovascular diseases, including diseases of the aortic root and aortic valve, acute coronary syndromes (ACS), strokes, venous thromboembolism, and conduction abnormalities [7].

Even in the absence of clinical cardiovascular disease and the presence of normal ejection fraction (EF), diastolic dysfunction is reported in 9–45 % of patients with AS [8]. A disturbed filling pattern termed as diastolic left ventricular (LV) dysfunction is caused by impaired relaxation of the LV. This pattern may eventually lead to heart failure with preserved ejection fraction (HFpEF) [9]. Systemic inflammation is a significant risk factor for diastolic LV dysfunction and HFpEF, as it causes an increase in cardiomyocyte damage and cardiac collagen deposition in the cardiac structures [10].

The blood entering the LV during atrial systole produces a countercurrent along the septum towards the aortic valve. Early diastolic flow from the left atrium fills the ventricle centrally, whereas late diastolic flow enters the ventricle more posteriorly [11]. This results in a presystolic wave (PSW) in the left ventricular outflow tract (LVOT). A possible mechanism of PSW is related to left ventricular stiffness and impaired LV compliance [12]. The other mechanism for PSW is atrial contraction. The left atrium acts as a pump in late diastole. Therefore presence of PSW may be associated with atrial contraction and ventricular stiffness [13].

To the best of our knowledge, the frequency of PSW and the association between PSW and other echocardiographic (ECHO)-clinical parameters have not been studied in patients with AS. The hypothesis of this study was that the magnitude of this countercurrent in LVOT would be significantly affected by the compliance of the LV at the time of atrial contraction. It is very important to identify LV dysfunction as early as possible in order to determine the high risk of heart failure (HF) in patients with AS. Therefore, the aim of the current study was to investigate the association between the presence of PSW and the measurements of LV diastolic dysfunction, and to evaluate the clinical significance of PSW in the detection of diastolic dysfunction in AS patients.

MATERIALS AND METHODS

This cross-sectional study included fifty-nine patients with AS and an age and gender-matched 65 healthy control group with no medical history and who were on no medication. The AS patients were enrolled from the department of Physical Medicine and Rehabilitation of the Hospital of Cukurova University (Adana, Turkey) between Jully 2018 and December 2018. The study population was selected among the patients diagnosed with AS for at least 1 year. Stable patients other than acute exacerbation of the disease and patients over 18 years of age were included in the study. Exclusion criteria were as follows; i) valvular or congenital heart disease, ii) other cardiovascular diseases, iii) diabetes mellitus, iv) hypertension, v) current smokers, vi) excessive alcohol consumption (>120 g/day), vii) chronic obstructive pulmonary disease or cor pulmonale, viii) endocrinological disorders, and ix) systemic diseases including connective tissue disorders, hepatic and renal diseases, x) acute exacerbation of the AS. This study was approved by the Non-Interventional Clinical Research Ethics Committee of Cukurova University under the protocol number 79 at July 6th of 2018. All participants provided written informed consent before entering into study.

Measures and evaluations

The basic characteristics of the study population and clinical data were documented. Cardiovascular assessment was performed by a cardiologist, and the patients with AS were assessed by a rheumatologist. During admission, body mass index was calculated as soon as possible after obtaining informed consent from the patients. Patients using the antirheumatic

drugs were also included in the study and were instructed to discontinue the antirheumatic drugs 48 hours before the echocardiographic examination.

Ankylosing Spondylitis Disease Activity Score (ASDAS)

Disease activity was evaluated in AS patients with the Ankylosing Spondylitis Disease Activity Score (ASDAS), which consists of numeric rating scores of back pain, peripheral pain/swelling, patient self-assessment of global disease activity, duration of morning stiffness, and C-reactive protein (CRP) level. The cut-off values based on ASDAS are accepted as <1.3 indicating inactive disease, ≥1.3−≤2.1 moderate disease activity, ≥2.1−≤3.5 high disease activity, and >3.5, very high disease activity [14,15].

Bath Ankylosing Spondylitis Metrology Index (BASMI)

Axial mobility was evaluated with the Bath Ankylosing Spondylitis Metrology Index (BASMI). The tragus to wall distance, lumbar flexion (modified Schober), lateral lumbar flexion, and maximal intermalleolar distance, and cervical rotation are assessed and each item is scored on a 3-point scale from 0 to 2. Higher scores indicate decreased mobility [16]. The functional status of AS patients was assessed with the Bath Ankylosing Spondylitis Functional Index (BASFI), which contains 10 items related to daily living activities. High scores indicate lower function [17-19].

Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

The enthesitis was evaluated in accordance with the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), which assesses 13 entheses (spinous processes of 5th lumbar vertebra, bilateral of 1st and 7th costochondral joint, spina iliaca anterosuperior, crista iliaca, spina iliaca posterior, proximal insertion of Achilles tendons). Each region is scored 0 or 1, giving a total score of 0 to 13. High scores indicate clinically important enthesitis [20].

Echocardiographic evaluation

The echocardiographic examination was performed using the Vivid S5 cardiovascular ultrasound system with a 3S 1.5 - 3.6 MHz transthoracic probe (GE Medical Systems, Buckinghamshire, UK). Echocardiographic data were recorded during end-expiratory apnea. Conventional B-mode and pulsed Doppler parameters were measured according to the American Society of Echocardiography guidelines [21].

Left Ventricular EF were derived from biplane apical views using the modified Simpson's rule algorithm and estimation of ejection fraction by M-mode in parasternal long and short axis [22]. Aortic root measurements were performed at the annular plane in all cases. Diastolic and systolic interventricular septal (IVS) thickness, posterior wall (PW) thickness, and left ventricular end-diastolic (LVDD) and left ventricular end-systolic (LVSD) diameters were measured on the parasternal long-axis views. All measurements were performed on M-mode images.

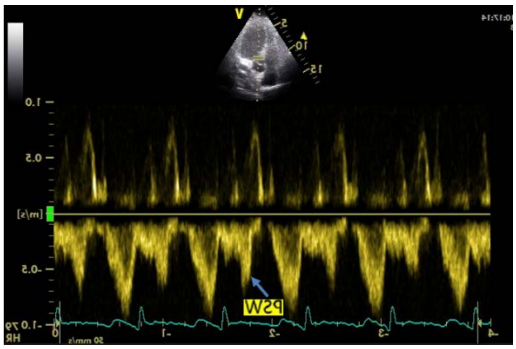

Figure 1. Typical appearance of a PSW on pulse-wave Doppler examination of the LVOT.

The Doppler tissue-imaging (DTI) program was set to the pulsed-wave Doppler mode. Filters were set to exclude high-frequency signals, and the Nyquist limit was adjusted to a velocity range of 15 cm/s - 20 cm/s. The transthoracic echocardiographic parameters used to assess diastolic LV function included peak early filling velocity (E-wave) divided by late diastolic filling velocity (A-wave) and isovolumetric relaxation time (IVRT). Septal e' velocity and septal a' velocity were measured, then the e'/a' ratio was calculated to estimate LV filling pressure. The IVRT is an interval in the cardiac cycle, from the aortic component of the second heart sound, that is, closure of the aortic valve, to onset of filling by opening of the mitral valve. The isovolumetric contraction time (IVCT) was defined as the time interval from the mitral valve closure at end diastole, to the aortic valve opening. The ejection time (ET) was defined as the time interval from aortic valve opening to aortic valve closing at end systole [23]. The myocardial performance index (MPI) was calculated using the formula, MPI= (IVCT+ IVRT)/ET [24].

The ascending aorta wall motion velocities were assessed during the cardiac cycle. Aortic wall systolic velocity (SAo, cm/s) and aortic wall early diastolic retraction velocity (EAo, cm/s) were obtained from the records.

Pulse-wave spectral Doppler of the LVOT was evaluated by placing the pulse-wave sample volume in the LVOT, approximately 1 cm from the aortic valve. PSW preceding the LVOT flow was also investigated (Figure 1).

Table 1. Baseline characteristics, clinical variables and ECHO parameters of the study population

	Patients (n=59)	**Healthy controls (n=65)**	**p**
Age (years)a	44.0 (36.0−52.0)	45.0 (29.5−56.5)	0.625
Height (cm)a	168.0 (160.0−174.0)	170.0 (163.0−177.0)	0.164
Weight (kg)a	79.0 (70.0−87.0)	77.0 (68.5−85.0)	0.132
BMI (kg/m2)a	27.5 (24.3−32.0)	25.1 (23.1−27.5)	0.077
Gender (Males)	51 (57.3)	67 (63.8)	0.272
Systolic BP (mmHg)	124.9±6.1	121.4±7.4	0.283
Diastolic BP (mmHg)	76.7±4.1	74.9±6.2	0.473
EF (%)	62.9±2.9	64.7±2.5	**0.006**
IVS (mm)	9.8±1.4	9.6±1.2	0.257
PW (mm)	9.4±1.2	9.2±0.9	0.321
LVDD (mm)	45.7±3.8	43.4±3.4	**0.021**
LVSD (mm)	29.4±3.5	29.9±3.7	0.432
LA anteroposterior diameter (mm)	33.1±3.4	32.8±2.4	0.541
LA minor-axis dimension (mm)	34.2±3.7	33.6±2.6	0.365
LA major-axis dimension (mm)	42.8±6.1	41.5±4.0	0.156
LVOT diameter (mm)	22.9±2.6	23.4±1.7	0.673
AoS (mm)	29.8±2.4	31.2±2.2	0.615
AoD (mm)	27.9±2.4	29.1±2.1	0.349
Aortic root (mm)	27.2±2.4	27.3±2.1	0.872
MPI	0.41±0.11	0.38±0.08	**0.045**
Sinus valsalva (mm)	31.2±3.1	31.9±2.2	0.527
E (cm/s)	76.0±18.0	73.0±22.0	0.085
A (cm/s)	86.6±34.0	82.0±32.0	0.124
E/A ratio	0.9±0.27	0.8±0.22	**0.037**
LVOT VTI (cm)	17.4±4.5	20.3±3.2	**0.024**
DT (ms)	193.4±16.5	204.7±20.4	0.154
LVOT velocity (m/s)	92.6±12.4	100.5±14.4	0.120
IVCT (ms)	101.3±23.4	97.7±12.7	0.472
IVRT (ms)	94.9±21.7	112.3±20.7	**0.004**
Septal e' (cm/s)	7.3±0.12	6.4±0.18	0.065
Septal a' (cm/s)	7.6±0.18	7.1±0.12	0.279
e'/a' ratio	1.02±0.25	0.86±0.23	0.145
SAo (m/s)	5.1±0.36	4.4±0.32	0.075
EAo (m/s)	4.5±0.12	4.2±0.2	0.580
CRP (mg/dL)	1.0±0.8	0.8±0.3	**<0.001**

[a]Values are given as median (interquartile range).; [b]Values are given as n (%).

AoD: Ascending aorta diastolic diameter; AoS: Ascending aorta systolic diameter; BMI: Body Mass Index; BP: Blood pressure; CRP: C-reactive protein; DT: Deceleration time; EAo: Aortic wall early diastolic retraction velocity; EF: Ejection fraction; IVCT: Isovolumic contraction time; IVRT: Isovolumetric relaxation time; IVS: Interventricular septum; LA: Left atrium; LVDD: Left ventricular end-diastolic diameters; LVOT VTI: Left ventricular outflow tract velocity time integral; LVSD: Left ventricular end-systolic diameters; MPI: Myocardial performance index; PW: Posterior wall, Sao: Aortic wall systolic velocity.

Statistical analysis

The statistical analysis was performed with IBM SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). Conformity of the data to normal distribution was checked using the Shapiro−Wilk test. Descriptive statistics were used to determine the median (interquartile range) of the parameters. Between group and subgroup comparisons of clinical and echocardiographic variables were evaluated using the Mann−Whitney U test for continuous variables and the Chi−square test for categorical variables. Binary logistic regression analysis was used to determine the risk factors for the presence of PSW. The association of the clinical variables and ECHO parameters was assessed with Spearman's correlation analysis. The strength of the correlation was determined as very weak (r_s=0−0.19), weak (r_s=0.20−0.39), moderate (r_s=0.40−0.59), strong (r_s=0.60−0.79), or very strong (r_s=0.80−1.0). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

A total of fifty-nine patients and 65 healthy control subjects were included in the study. The baseline characteristics and clinical variables of the study population are given in Table 1. The median age was 44 years in the patient group and 45 years in the control group (p=0.806). The medication used by patients was reported as non-steroid anti-inflammatory drugs (NSAID) by 57.6%, and biological disease modifying antirheumatic drugs by 42.4%. Within the patients taking biological disease modifying antirheumatic drugs, 17.1% of them had taken sulfasalazine, 11.2% had taken methotrexate, 8.1% had taken leflunomide and 6.0% had taken hydroxychloroquine. PSW was detected in 26.6% of the whole study population; in 37.3% of patients and 16.9% of the control group (x^2=0.01). When PSW was assessed according to the treatment of patients, higher rates of PSW were determined in patients using biological disease modifying antirheumatic drugs (x^2=0.05). PSW was determined in 26.5% of patients using NSAIDs and in 52.0% of patients using biological disease modifying antirheumatic drugs.

In the comparisons of ECHO parameters between patients and control subjects; EF, LVOT VTI and IVRT values were statistically significantly higher in the control group (EF: % 62.9±2.9 in patients, % 64.7±2.5 in controls, p=0.006; LVOT VTI: 17.4±4.5cm in patients, 20.3±3.2cm in controls, p=0.024; IVRT: 94.9±21.7ms in patients, 112.3±20.7ms in controls, p= 0.004). E/A ratio, MPI and LVDD were statistically significantly higher in patients than the control group (E/A ratio: 0.9±0.27 in patients, 0.8±0.22 in controls, p=0.037; MPI: 0.41±0.11 in patients, 0.38±0.08 in controls, p= 0.045; LVDD: 45.7±3.8mm in patients, 43.4±3.4mm in controls, p=0.021). No statistically significant difference was determined between the groups in respect of transmitral E and A wave velocity, DT, ICT, septal a' and e' wave velocity, LVOT velocity, e'/a' ratio and aortic wall systolic velocity (SAo) (table 1).

When the patients and control groups were separated into two subgroups according to the presence or absence of PSW, the MPI, transmitral E wave velocity, E/A ratio, LVOT velocity, septal e' wave velocity, and aortic wall systolic velocity (SAo) values were statistically significant in the subjects of both groups with presence PSW (figure 2). LVOT diameter and IVRT were determined to be significant in the only patient group, and transmitral A wave velocity, IVCT and e'/a' ratio were statistically significant only in the control group (table 2). CRP levels were statistically significant in the subjects of both patients and control groups with presence of PSW. In our study, e'/a' ratio < 1.0 was observed in 54.5% of AS patients with presence PSW.

Binary logistic regression analysis was performed to define the variables which were significant for the presence of PSW in AS patients. In the univariate model, a high CRP level, increased BASMI and BASFI, high LVOT diameter, elevated MPI, and high LVOT velocity were determined as risk factors for the presence of PSW in patients (table 3). In the multivariate model, a high CRP level, high LVOT diameter, elevated MPI, and high LVOT velocity were determined as risk factors for the presence of PSW in AS patients after adjustments for age and gender. In the multivariate model, high LVOT velocity (OR 1.05; 95% CI:1.00−1.09, p=0.05) was found to be the most significant risk factor in the control group after adjustments for age and gender.

In the correlation analysis of clinical parameters with ECHO variables, the ASDAS (r=0.52, p=0.02) and MASES scores (r=0.49, p=0.02) were significantly correlated with EF. The MASES scores were found to be correlated with LA major-axis dimension (r=0.48, p=0.02), transmitral A wave velocity (r=−0.52, p=0.04) and E/A (r=0.54, p=0.009).

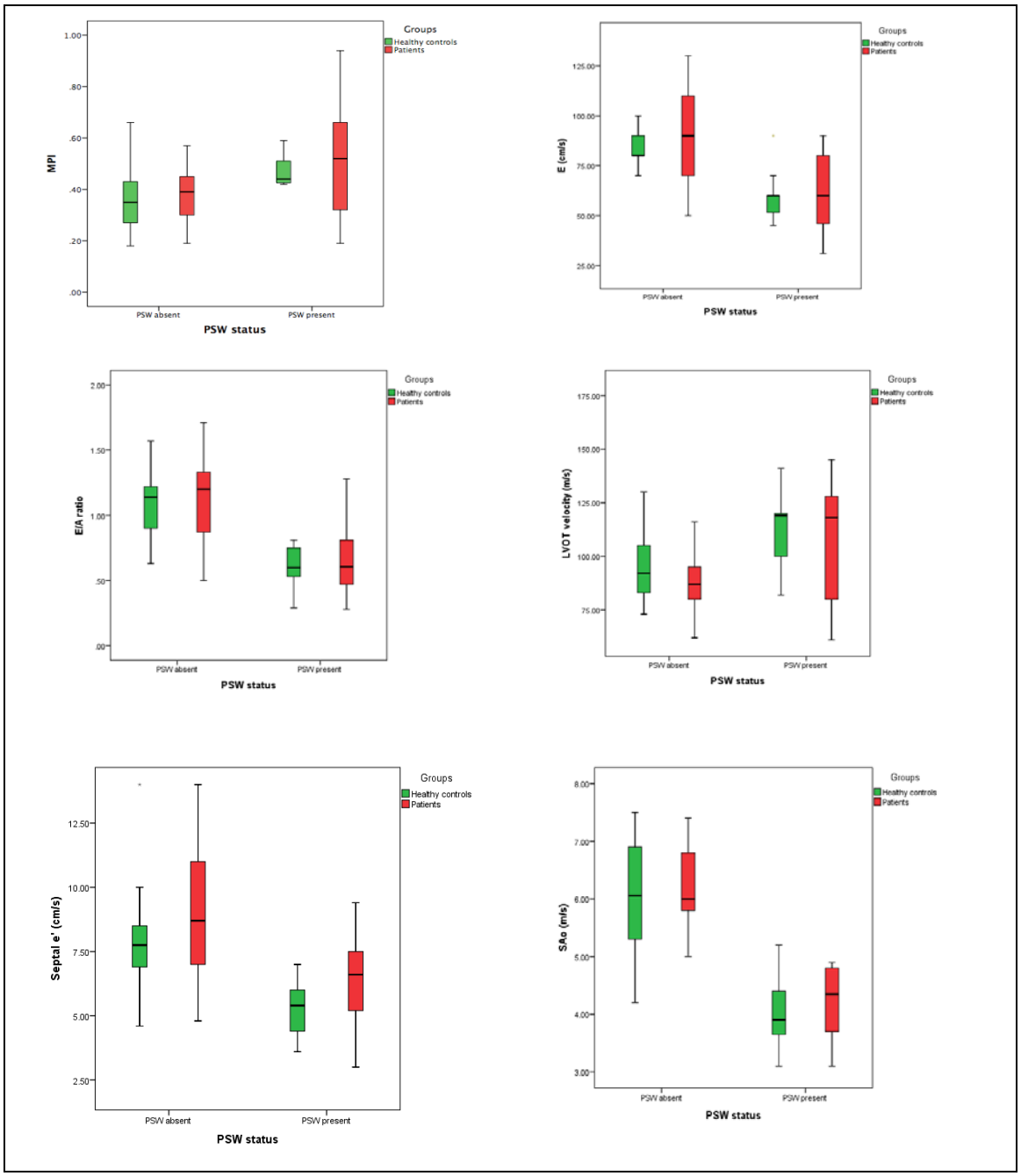

Figure 2. The comparison of the AS patient group and the control group according to the presence or absence of PSW in respect of the ECHO parameters.,

LVOT: Left ventricular outflow tract; MPI: Myocardial performance index; PSW: Presystolic wave; Sao: Aortic wall systolic velocity.

Table 2. The comparison of the ECHO parameters between groups according to the absent or present of PSW

	Patients		p	Controls		p
	PSW absent	PSW present		PSW absent	PSW present	
EF (%)	64.0 (60.0−65.0)	62.0 (60.0−65.0)	0.155	65.0 (64.0−66.0)	65.0 (64.0−66.0)	0.929
IVS (mm)	9.0 (9.0−10.0)	10.0 (9.0−11.0)	0.150	9.0 (9.0−11.0)	10.0 (9.0−11.0)	0.464
PW (mm)	9.0 (8.5−10.0)	9.8 (8.4−10.0)	0.390	9.0 (9.0−10.0)	9.0 (9.0−9.0)	0.473
LVDD (mm)	45.0 (43.5−47.0)	48.0 (44.0−50.3)	0.077	44.5 (42.0−46.0)	42.0 (39.0−47.0)	0.224
LVSD (mm)	30.0 (26.5−31.0)	30.0 (28.0−32.3)	0.131	31.0 (27.8−32.0)	30.0 (26.0−33.0)	0.556
LA anteroposterior diameter (mm)	33.0 (30.5−34.5)	34.0 (30.8−36.0)	0.372	33.0 (31.8−34.0)	33.0 (31.0−35.0)	0.852
LA minor-axis dimension (mm)	35.0 (31.0−37.0)	34.0 (32.0−37.0)	0.608	34.0 (32.8−36.0)	34.0 (30.0−36.0)	0.683
LA major-axis dimension (mm)	43.0 (37.5−46.5)	46.0 (42.5−47.3)	0.074	41.5 (39.0−45.0)	43.0 (41.0−45.0)	0.758
LVOT diameter (mm)	22.0 (19.5−24.0)	25.0 (22.0−26.0)	0.005	24.0 (23.0−24.0)	23.0 (22.0−26.0)	0.738
AoS (mm)	30.0 (28.3−32.0)	29.3 (28.0−31.2)	0.893	31.0 (30.0−33.0)	33.0 (28.0−34.0)	0.507
AoD (mm)	28.0 (26.0−30.0)	27.0 (26.0−29.5)	0.968	30.0 (28.0−31.0)	31.0 (26.0−32.0)	0.123
Aortic root (mm)	27.0 (25.0−29.0)	27.0 (25.0−29.3)	0.782	27.0 (26.0−29.0)	29.0 (25.0−30.0)	0.081
MPI	0.39 (0.29−0.45)	0.52 (0.32−0.68)	0.018	0.35 (0.27−0.43)	0.44 (0.42−0.56)	0.009
Sinus valsalva (mm)	31.0 (29.0−33.5)	31.5 (29.0−34.0)	0.717	32.0 (31.0−33.0)	34.0 (32.0−34.0)	0.117
E (cm/s)	90.0(70.0−110.0)	60.0 (45.0−80.0)	<0.001	80.0 (80.0−90.0)	60.0 (51.0−60.0)	<0.001
A (cm/s)	80.0(65.0−100.0)	94.0 (70.0−110.0)	0.161	80.0 (70.0−90.0)	90.0 (80.0−110.0)	0.048
E/A ratio	1.2 (0.86−1.33)	0.6 (0.47−0.85)	<0.001	1.1 (0.9−1.2)	0.6 (0.5−0.75)	<0.001
LVOT VTI (cm)	18.2 (15.5−22.1)	16.5 (15.0−19.1)	0.095	19.6 (17.6−24.0)	23.0 (16.7−24.0)	0.972
DT (ms)	203.1 (171-217)	188.3 (154-209)	0.074	217.1 (171-228)	196.3 (164-209)	0.084
LVOT velocity (m/s)	87.0 (79.5−98.0)	118.0(79.5−129.3)	0.009	92.0(83.0−106.3)	119.0(90.0−120.0)	0.040
IVCT (ms)	96.0(71.5−112.5)	120.0(81.0−111.8)	0.224	90.0 (77.3−110.0)	110.0(98.0−120.0)	0.017
IVRT (ms)	116.0(94.5−175.0)	90.0 (85.5−117.3)	0.004	110.0(95.0−120.0)	120.0(110.0−120.0)	0.218
Septal e' (cm/s)	8.7 (7.0−11.5)	6.6 (5.2−7.6)	<0.001	7.8 (6.9−8.5)	5.4 (4.0−6.3)	<0.001
Septal a' (cm/s)	8.3 (7.0−10.0)	6.9 (5.6−9.3)	0.058	7.0 (6.0−9.0)	7.2 (6.8−7.9)	0.750
e'/a' ratio	1.09 (0.75−1.39)	0.95 (0.82−1.10)	0.233	1.10 (0.79−1.26)	0.72 (0.57−0.95)	0.013
SAo (m/s)	6.0 (5.8−6.8)	4.4 (3.7−4.8)	<0.001	6.1 (5.3−6.9)	3.9 (3.6−4.6)	<0.001
EAo (m/s)	4.3 (3.9−5.0)	4.7 (3.7−5.1)	0.649	4.4 (3.9−5.0)	4.1 (3.6−4.8)	0.540

Values are given as median (interquartile range).

AoD: Ascending aorta diastolic diameter; AoS: Ascending aorta systolic diameter; DT: Deceleration time; EAo: Aortic wall early diastolic retraction velocity; EF: Ejection fraction; IVCT: Isovolumic contraction time; IVRT: Isovolumetric relaxation time; IVS: Interventricular septum; LA: Left atrium; LVDD: Left ventricular end-diastolic diameters; LVOT VTI: Left ventricular outflow tract velocity time integral; LVSD: Left ventricular end-systolic diameters; MPI: Myocardial performance index; PW: Posterior wall, Sao: Aortic wall systolic velocity.

Table 3. Modeling association of risk factors of the presence of PSW in AS patients

			Adjusted Models			
Variables	**Univariate Models**		**Model 1**		**Model 2**	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
CRP	1.98 (0.93−4.15)	0.08	3.90 (1.25−12.20)	0.02	3.88 (1.23−12.23)	0.02
BASMI	1.23 (0.98−1.54)	0.08	1.60 (0.94−2.72)	0.08	1.68 (0.93−3.05)	0.08
BASFI	1.27 (0.98−1.65)	0.07	–	–	–	–
LVOT diameter	1.39 (1.09−1.76)	0.008	2.07 (1.25−3.41)	0.004	1.85 (1.20−2.83)	0.005
MPI	1.65 (1.53−2.36)	0.06	2.00 (1.23−3.28)	0.005	1.83 (1.16−2.88)	0.009
LVOT velocity	1.05 (1.02−1.08)	0.003	1.08 (1.01−1.14)	0.02	1.06 (1.02−1.11)	0.007

Model 1: Age and sex adjusted ORs were given; Model 2: Age, sex and body mass index adjusted ORs were given.
BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; LVOT: Left ventricular outflow tract; MPI:Myocardial performance index

DISCUSSION

In the current study, the presence of PSW with diastolic LV dysfunction was evaluated and the results were compared between an AS patient group and a healthy control group. The main findings of the study were that the presence of PSW was significantly associated with the diastolic dysfunction parameters of LV in AS patients, and the presence of PSW was also a predictor of higher inflammation in AS patients. To the best of our knowledge, the present study is the first study in literature to show the significance of PSW in AS patients and to determine an independent association between PSW and LV diastolic dysfunction.

The most valuable diagnostic tool for diastolic dysfunction (DD) is still a matter of debate. A meta-analysis by Heslinga et al. [8] showed the importance of applying ASE criteria to determine DD in patients with AS. In the current study, DD was also diagnosed according to ASE criteria. According to a cohort study by Sveälv et al. [25] using conventional pulsed-wave and tissue Doppler, 12% of AS patients were determined to have DD. But in our study, no difference was found between the groups in respect of LV diastolic dysfunction parameters.

The exact physiology of a PSW in the LVOT has not been fully elucidated. It is thought to be a vortex flow pattern formed by diastolic blood flow, but it is not due to the flow across the aortic valve [26]. The other mechanism for PSW is mitral transmission time. Transmission depends on LV stiffness in diastole and therefore PSW has been found to be a marker of impaired LV compliance [27].

The relationship between LV diastolic dysfunction and PSW presence has been shown in previous studies. Mittal et al. [27] evaluated PSW velocity in subjects with mild hypertension and those who were normotensive. A significant positive correlation was determined between PSW and transmitral A wave velocity, and a significant inverse relationship between PSW and the E/A ratio. In this study, they also reported that PSW was a marker of impaired LV compliance. Akyuz et al. [28] showed that the presence of PSW and increased PSW velocity in hypertensive patients were related to subclinical LV dysfunction. In the present study, LV diastolic dysfunction was observed in AS patients with PSW.

Myocardial performance index is an important measurement to show systolic and diastolic functions of the ventricle, which is easily obtained on transthoracic echocardiography (TTE). According to the MPI, a deterioration in LV function can be identified before overt HF [29]. The strong independent association between CRP levels, a well-established marker of inflammation and DD may indicate that inflammation plays a prominent role in the development of DD. In the current study, increased MPI and high CRP levels may be predictors of the presence of PSW in both groups. As a result of univariate analysis, high CRP levels (as an indicator of inflammation) and increased MPI values (associated with diastolic dysfunction) were strongly associated with the presence of PSW. As a result, a relationship between PSW and diastolic dysfunction may be established in AS patients.

A strong positive relationship was determined between PSW and MPI. A negative association was also observed between PSW and several ECHO parameters including transmitral E wave velocity, E/A ratio, IVRT, septal e' wave velocity, and aortic wall systolic velocity. Accordingly, it can be concluded that presystolic flow velocities in LVOT are also affected by the relaxation properties of the LV and transmitral flow velocity during left atrial contraction.

Isovolumetric relaxation time is dependent on the rate of active relaxation and mean left atrial pressure [30]. In the present study, PSW was in inverse correlation with IVRT in the AS patients. Accordingly, PSW was influenced by active isovolumetric relaxation and left atrial pressure. The E wave deceleration time depends on mean left atrial pressure, left atrial compliance and LV compliance during early filling [31]. A less compliant ventricle is likely to have a greater increase in pressure and therefore, a greater velocity of flow towards LVOT. Conversely, in the current study, no significant relationship between PSW and DT was found in AS patients. The reverse correlation between PSW and transmitral flow E/A ratio could be explained by different factors including myocardial relaxation, diastolic suction of the LV and left atrial pressure at the time of mitral valve opening, affecting E wave velocity [32]. With confirmation of these results, this little-known echocardiographic parameter could provide prognostic information for AS patients with LV diastolic dysfunction.

Inflammation is known to affect the endocardium and myocardium and cause diastolic LV dysfunction through many different pathophysiological mechanisms. First, inflammation compromise LV relaxation function by affecting the extracellular matrix that causes increased fibrosis and reduced elasticity [33]. Second, inflammation may cause hypertrophy of the LV as the heart compensates for increased pressure in the ventricles and damage in the myocardium and endocardium [34]. The results of the present study demonstrated that a high CRP level, and increased BASMI and BASFI were risk factors for the presence of PSW in AS patients. According to these results, it can be claimed that the presence of PSW could lead to LVD in AS patients, especially in those with high disease activity.

There is currently no available treatment to reduce morbidity and mortality in HFpEF. In the current study, while 57.6% of patients used NSAIDs, 42.4% used biological disease modifying antirheumatic drugs. The presence of PSW was found at a higher rate in patients using biological disease modifying antirheumatic drugs. Therefore, NSAIDs may have a protective role against PSW. As there are no studies on this subject in literature, there is a need for future studies to investigate the effect of anti-inflammatory therapy on diastolic LV function and PSW.

The accurate diagnosis of DD is complex and requires appropriate criteria. Okan et al. [35] found that DD was observed in the majority of AS patients without any cardiovascular disease. In a previous study, e'/a' ratio < 1.0 was observed in 45% of the patients, and in the present study, e'/a' ratio < 1.0 was observed in 54.5% of AS patients with PSW. However, this was a lower rate than the e'/a' ratio determined in the control group. This could have been due to greater a' velocity and lower e' velocity probably reflecting a combination of impaired early diastolic relaxation and greater atrial contraction in PSW patients.

It is increasingly recognized that diastolic LV dysfunction plays an important role in the development of HF. None of the previous studies have found a significant difference in EF (precursor for systolic LV function) between AS patients and control subjects. This may suggest that, primarily, changes in diastolic properties lead to HF in AS. The results of this study showed that impaired DD was detected in AS patients with PSW, and a strong correlation was determined between DD parameters and the presence of PSW. In the light of these results, it can be suggested that the presence of PSW reflecting LV diastolic dysfunction may be an early predictor of cardiac involvement in patients with AS before the emergence of any clinical signs.

The current study has several limitations. First, the study was a single center prospective study, and so the size of the study population was relatively small. Second, patients with known cardiac disease, hypertension and diabetes mellitus were excluded from the study, although these are important risk factors for diastolic LV dysfunction. Therefore it is plausible that the presence of diastolic LV dysfunction was underestimated due to the selection of included patients. Third, the study was not blinded, which could have led to suspicion bias. The main reason for this is that AS patients often have visible deformities, which makes it impossible to blind the entire study. Fourth, the use of rheumatological medicine might have influenced the

findings. It is advised to avoid the use of both NSAIDs and TNF-α inhibitors in symptomatic HF, although the effect of NSAIDs and TNF-α inhibitors on diastolic LV dysfunction is currently unknown [8]. Fifth, measurements were not taken of pulmonary venous flow, LV mass and volume of the left atrium, which are also parameters in the ASE criteria [36]. Sixth, we could not use LV strain for correction of LV dystolic functions. Therefore, the study results cannot be extrapolated to the general population. A final limitation of the study was that diastolic dysfunction was detected non-invasively.

The result of the present study demonstrated that LV diastolic dysfunction parameters were strongly correlated with PSW in patients with AS. An important point that the assessment of PSW on echocardiography can provide important information about the LV diastolic function.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ÇÖ; Veri toplama: ÇÖ, Veri analizi ve yorumlama: CY, AU; Yazı taslağı: NG; İçeriğin eleştirel incelenmesi: CY, ÇÖ; Son onay ve sorumluluk: ÇÖ, NG, REA, CY, AU; Teknik ve malzeme desteği: REA; Süpervizyon: REA; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Çukurova Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulundan 06.07.2018 tarih ve 79 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design : ÇÖ; Data acquisition: ÇÖ; Data analysis and interpretation: CY, AU; Drafting manuscript: NG; Critical revision of manuscript: CY, ÇÖ; Final approval and accountability: ÇÖ, NG, REA, CY, AU; Technical or material support: REA; Supervision: REA; Securing funding (if available): n/a.
Ethical Approval: For this study, ethics approval was obtained from Çukurova University Faculty of Medicine non-interventional clinical research ethics committee with Decision No. 79 dated 06.07.2018.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. McCarey D, Sturrock RD. Comparison of cardiovascular risk in ankylosing spondylitis and rheumatoid arthritis. Clin Exp Rheumatol. 2009;27:124–6.
2. DeMizio DJ, Geraldino-Pardilla LB. Autoimmunity and inflammation link to cardiovascular disease risk in rheumatoid arthritis. Rheumatol Ther. 2020;7:19-33.
3. Chou CH, Lin MC, Peng CL, Wu YC, Sung FC, Kao CH et al. A nationwide population-based retrospective cohort study: increased risk of acute coronary syndrome in patients with ankylosing spondylitis. Scand J Rheumatol. 2011;43:132–6.
4. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitisis related to disease activity. Ann Rheum Dis. 2011;70:1921–5.
5. Hung YM, Chang WP, Wei JCC, Chou P, Yung P, -Wang P. Midlife ankylosing spondylitis increases the risk of cardiovascular diseases in males 5 years later: a national population-based study. Medicine (Baltimore). 2016;9518:e3596.
6. Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum. 2004;34:585–92.
7. Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. Ann Intern Med. 2015;163: 409.
8. Heslinga SC, Van Dongen CJ, Konings TC, Peters MJ, Van der Horst-Bruinsma IE, Smulders YM et al. Diastolic left ventricular dysfunction in ankylosing spondylitis–a systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44:14–9.
9. Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. J Card Fail. 2007;13:569–76.
10. Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding. Cells. 2020;9:242.
11. Bryg RJ, Williams GA, Labovitz AJ. Effect of aging on left ventricular diastolic filling in normal subjects. Am J Cardiol. 1987;59:971-974.
12. Korkmaz L, Akyüz AR, Gurbak I, Erkan H, Dursun I, Celik S. Presystolic A wave may predict increased arterial stiffness in asymptomatic individuals. Blood Press Monit. 2016;21:144–8.
13. Joshi KR, Kabirdas D, Romero-Corral A, Shah M, Figueredo VM, Pressman GS. Clinical significance of a presystolic wave on Doppler examination of the left ventricular outflow tract. Am J Cardiol. 2014; 114:1599–1602.
14. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. 2011;70:47-53.
15. Machado PM, Landewé R, Heijde DV. Assessment of SpondyloArthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis. 2018;77:1539-40.
16. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694–8.
17. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68 Suppl 2:ii1-44.

18. Calin A, Jones SD, Garrett SL, Kennedy LG. Bath Ankylosing Spondylitis Functional Index. Br J Rheumatol. 1995;34:793–4.
19. Ozer HT, Sarpel T, Gulek B, Alparslan ZN, Erken E. The Turkish version of the Bath Ankylosing Spondylitis Functional Index: reliability and validity. Clin Rheumatol. 2005; 24:123-8.
20. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewé R, van ver Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis. 2003;62:127–32.
21. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019;32:1-64.
22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification. Eur J Echocardiogr. 2006;7:79-108.
23. Biering-Sørensen T, Mogelvang R, Schnohr P, Jensen JS. Cardiac time intervals measured by tissue doppler imaging m-mode: association with hypertension, left ventricular geometry, and future ischemic cardiovascular diseases. J Am Heart Assoc. 2016;19:5.
24. Tei C1, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function - a study in normals and dilated cardiomyopathy. J Cardiol. 1995;26:357-366.
25. Sveälv BG, Täng MS, Klingberg E, Forsblad-d'Elia H, Bergfeldt L. Prevalence of diastolic dysfunction in patients with ankylosing spondylitis: a cross-sectional study. Scand J Rheumatol. 2015;44:111-7.
26. Armstrong WF, Ryan T, Feigenbaum H. Feigenbaum's Echocardiography. Philadelphia, Wolters Kluwer, 2010.
27. Mittal SR, Pancholi N. Left ventricular outflow tract presystolic flow velocity--another marker of left ventricular diastolic function. Int J Cardiovasc Imaging. 2002;18:249–256.
28. Akyüz AR, Turan T, Gürbak İ, Korkmaz L, Ağaç MT, Çelik Ş. The relationship between presystolic wave and subclinical left ventricular dysfunction in asymptomatic hypertensive patients. Blood Press Monit. 2016;2:277–281.
29. Adar A, Kırış A, Bülbül Y, Bektaş H, Acat M, Casim H, Onalan O et al. Association of fragmented QRS with subclinical left ventricular dysfunction in patients with obstructive sleep apnea. Med Princ Pract. 2015;24:376–81.
30. Vizzardi E, Bonadei I, Teli M, Caretta G, Maiandi C, Madureri A, et al. Usefulness of left atrial diametres and volumes for the evaluation of left ventricular diastolic function. Recenti Prog Med. 2009;100:294-8.
31. Otto A. Smiseth. Evaluation of left ventricular diastolic function: state of the art after 35 years with Doppler assessment. J Echocardiogr. 2018;16:55–64.
32. Ommen SR, Nishimura RA. A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: update 2003. Heart. 2003;89:18-23.
33. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: partII: causal mechanisms and treatment. Circulation. 2002;105:1503–8.
34. Cuspidi C, Sala C, Muiesan ML, De Luca N, Schillaci G. Right ventricular hypertrophy in systemic hypertension: an updated review of clinical studies. J Hypertens. 2013;31:858–65.
35. Okan T, Sari I, Akar S, Cece H, Goldeli O, Guneri S et al. Ventricular diastolic function of ankylosing spondylitis patients by using conventional pulsed wave Doppler, myocardial performance index and tissue Doppler imaging. Echocardiography 2008;25:47–56.
36. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiog. 2009;22:107-33.