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Assessment of atrial electromechanical delay and echocardiographic parameters in patients with multiple sclerosis

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Abstract

Objective: Data on cardiovascular dysfunction is limited in the previous literature on patients with multiple sclerosis. In this study, we aimed to elucidate the cardiovascular parameters in multiple sclerosis patients by comparing the systolic-diastolic functions and atrial electro-mechanical delay compared to the control group. *Method:* A total of 37 patients with a diagnosis of relapsing-remitting multiple sclerosis and had Expanded Disability Status Scale (EDSS) scores between 0 – 3, and 20 individuals in the control group were included in the study. Seventeen of the MS patients (n=17) were taking immunomodulatory drugs and the other 20 did not receive any immunomodulatory agents. Patients with a diagnosis or clinical suspicion of cardiac dysfunction and using cardiotoxic medications were excluded. The measurement of systolic and diastolic function parameters was performed via M – Mode 2D transthoracic echocardiography, and Atrial electro-mechanical delay (AEMD) measurements were performed with tissue Doppler. *Results:* E' MV lateral and MV E/A values were determined to be higher in MS patients, who did not use immunomodulatory drugs, compared to the control group ($p<0.001$, $p=0.010$ respectively). E/E' MV lateral and MV AVmax values were determined to be significantly higher in the patient group using immunomodulators compared to the other two groups ($p=0.009$, $p=0.012$ respectively). PAs, PAI, left and right intraatrial EMG values were determined to be prolonged in MS patients using and not using drugs compared to the control group, but these values were not determined to be statistically significant.
Conclusion: We found that left ventricular diastolic function was impaired in MS patients compared to the control group, and right-left intra- and interatrial AEMD were similar. Based on these results, we recommend echocardiographic assessment for early detection of left ventricular diastolic dysfunction in MS patients.

Keywords: Multiple sclerosis, EDSS – expanded disability status scale, echocardiography, atrial electromechanical delay, cardiac dysfunction

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune central nervous system disease characterized by inflammation, demyelination, and axonal damage. Myelin sheaths, oligodendrocytes, axons, and nerve cells are damaged during the progression of the disease. The disease is often observed in young adults and has a chronic course with recurring attacks in nature.[1,2]

Patients with MS have a higher risk of cardiovascular disease, than the general population but data are limited. There are few studies in previous literature examining RV (right ventricle) and LV (left ventricle) functions, hence the results of these studies were found to be inconsistent.[3-5] Cardiovascular system disorders may be due to autonomic nervous system dysfunction and abnormalities in the cardiovascular sympathetic and parasympathetic system, increased oxidative stress, and systemic inflammation are common in MS patients.[6-8]

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In the study of Christiansen *et al*. (2010), between 1977 and 2006, normal cohorts of 13,963 MS patients and 66,407 individuals were followed up for cardiovascular disease and comorbidity. In the 1-year follow-up, a higher risk was found in the MS group regarding the risk of myocardial infarction, cerebrovascular disease, heart failure, and atrial fibrillation and flutter. In the next 2-30 years follow-up an increased risk for cerebrovascular disease and heart failure was detected in the MS group, and a decreased risk was observed in myocardial infarction. As a result, it has been shown that the risk of cardiovascular disease in MS patients is not very high, but was increased compared to the normal population.[9]

In an early study by Ziaber *et al*. (1997), 12 patients with MS with an EDSS score of 3 – 4, 12 patients with an EDSS score of 5 – 7, and a healthy control group of 12 people were compared in terms of myocardial functions. No significant difference was observed between all groups but ejection fraction (EF) decrease, stroke volume, and, cardiac output were significantly lower during the tilt test in patients with high EDSS scores. No significant difference was observed between the low EDSS score and the control group in terms of EF, cardiac output, and stroke volume.[10]

In the study of Olindo *et al*. (2002), MS patients and the control group were evaluated with radionuclide angiocardiography, which can be considered the gold standard for ejection fraction detection. A statistically significant decrease was observed in RV EF and LV EF values in MS patients compared to the control group. In terms of mean ejection fraction, no significant difference was observed between RRMS and SPMS and between men and women.[11]

Akgül *et al*. (2006), evaluated LV and RV functions of MS patients without cardiac symptoms and the control group with LV and RV standard echocardiography and tissue Doppler echocardiography. In addition, the myocardial performance index (MPI) of the patients was calculated. No significant difference was observed between the patient groups. The LV wall thickness of MS patients was significantly larger and the LV ejection fraction was significantly lower. However, mitral and tricuspid valve deceleration times and MPI values were significantly longer in MS patients compared to the control group.[2]

Atrial electro-mechanical delay (AEMD) is a parameter with an important place in the pathophysiology of atrial fibrillation, and it can be measured by non-invasive Doppler echocardiography (ECG). Atrial fibrillation is the most common rhythm disorder and is closely correlated with neurological diseases. Prolonged atrial conduction is associated with both the onset and recurrence of atrial fibrillation.

Data on cardiovascular dysfunction is limited in the previous literature on patients with Multiple Sclerosis. Within the scope of this research, we aimed to elucidate the cardiovascular parameters in Multiple Sclerosis patients by comparing the systolic-diastolic functions and atrial electro-mechanical delay compared to the control group. We have utilized M – Mode Doppler, 2D transthoracic echocardiography with the systolic-diastolic function, and atrial electromechanical delay with the control group.

METHODS

A total of 37 patients aged 18 – 60 years old who applied to our institution with a diagnosis of relapsing-remitting multiple sclerosis according to McDonald Criteria *(2017)* between 01.01.2021 and 01.07.2021 have been enrolled in this research. Thirty seven patients with Expanded Disability Status Scale (EDSS) scores between 0 – 3, and 20 individuals in the control group were included in the study.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution with protocol number 1200 and informed consent has been obtained from all participants.

Half of the MS patients (n=17) were taking immunomodulatory drugs and the other half did not receive any immunomodulatory agents. Twenty patients, in the control group, were selected from subjects who applied to the outpatient clinic due to myalgia and headache.

Time of diagnosis, family history, blood pressure values, and EDSS of MS patients was recorded. Blood samples were obtained from all patients for biochemistry and hemogram tests including urea, creatinine, sodium, potassium, total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), troponin, creatine kinase-myocardial band (CK – MB).

Patients with relapsing MS, coronary artery disease (CAD), hypertension, previous cardiac surgery, cardiac valve diseases, stroke, diabetes mellitus (DM), and chronic renal failure (CRF) that may cause cardiac dysfunction were not included.

Additionally, individuals using cardiotoxic drugs (such as mitoxantrone) and subjects with sinuses were excluded from the study.

Electrocardiography and M – mode Doppler, 2D transthoracic echocardiography

All patients and the control group had undergone 12-lead electrocardiography, M – Mode, and 2D transthoracic echocardiography. ECG was recorded at a speed of 50 mm/sec and 20 mm/mV amplitude standardization. The measurements were based on the guidelines of the European Society of Cardiovascular Imaging and the American Society of Echocardiography. Left ventricular (LV) diameters were taken in the parasternal long-axis window by positioning the M – Mode cursor in the distal of mitral valve (MV) tips and perpendicular to the left ventricular long axis. Aorta and left atrium (LA) diameters were measured at the end-diastole and end-systole, respectively, from parasternal long-axis views. Left ventricular (LV) diastolic and systolic diameters, interventricular septum, and LV posterior wall thickness measurements were performed.

Left ventricular systolic function was calculated using apical 2 – chamber (A2C) and apical 4 – chamber (A4C) views by Simpson's method. LV-E wave velocities, LV-A wave velocity, and mitral valve deceleration time (DT) measurements were performed in A4C view with the pulse-Doppler (PW) cursor coinciding with the mitral valve tips. Early diastolic flow (E), atrial contraction signal (A), E/A ratio, and E deceleration time measurements were performed. Tissue Doppler measurements were performed with the tissue Doppler cursor coinciding with the septal and lateral corners of the mitral valve annulus in the A4C view.

The assessment of atrial electro-mechanical delay (AEMD), was obtained with the PW color Doppler method by placing the cursor on the lateral mitral annulus, septal and tricuspid annulus right ventricle lateral, in the apical four-chamber view. The monitor speed was set to 50 – 100 cm/sec. The time from the beginning of the P wave in the simultaneous ECG trace to the beginning of the A` vector in the tissue Doppler trace was accepted as AEMD. Left AEMD time (PAl) was measured from the images taken from the lateral part of the mitral annulus, septal AEMD time *(PAs)* was measured from the septum recordings, and right AEMD (PAt) time was measured from the recordings taken from the lateral tricuspid annulus. The difference between PAs-PAl, Pas,-PAt and PAl-PAt was defined as left intraatrial, interatrial and interatrial EMD, respectively.

Statistical analysis

Data were analyzed using the Statistics Package for Social Science (SPSS 23.0-IBM, NY, USA). Frequency tables and descriptive statistics were used in the interpretation of the findings. Parametric methods were used for measurement values suitable for normal distribution. Per parametric methods, the "Independent Sample-t" test (t-table value) was used to compare the values of two independent groups. The "ANOVA" test (F – table value) method was used to compare the measurement values of three or more independent groups. Non-parametric methods were used for measurement values unsuitable for normal distribution. Per non-parametric methods, the "Mann – Whitney U" test (Z – table value) was used to compare the values of two independent groups. The "Kruskal-Wallis H" test ($\chi 2$ -table value) was used to compare the measurement values of three or more independent groups. The P value was set at <0.05 for statistical significance.

RESULTS

Individuals were divided into three groups based on their diagnoses and immuno-modulatory drug usage (n=17 MS patients in the immuno-modulatory treatment group, 20 MS patients who were newly diagnosed or not on any treatment, and 20 individuals without MS in the control group). There was no statistically significant relationship between the control group regarding gender, smoking, presence of MS in family members, or cardiac disease history ($p>0.05$) (Table 1).

The mean age was 28.45±5.51 years in the MS patients using immunomodulatory drugs, 28.15±4.76 years in the MS patients not using drugs, and 30.00±5.54 years in the control group. No statistically significant difference was determined between the groups in terms of age and BMI (body mass index) (kg/m^2) values ($p>0.05$) (Table 2).

A statistically significant difference has been observed in terms of the time of diagnosis. The group of patients who were under medical treatment had significantly higher disease duration compared to the group not using drugs. In group 1 (n=17) patients had been using interferon beta 1a, glatiramer acetate, and dimethyl fumarate as immuno-modulator treatment.

Table 1: Demographic data of the study patients

Variables	MS patients with medical treatment(n=17)		MS patients without medical treatment(n=20)		Control subjects (n=20)		p-value
	N	%	n	%	n	%	
Sex							
Female	10	58.8	13	65.0	12	60.0	χ^2=0.174
Male	7	41.2	7	35.0	8	40.0	p=0.917
Smoking							
+	2	11.8	2	10.0	3	15.0	χ^2=0.238
-	15	88.2	18	90..0	17	85.0	p=0.888
Family history of MS							
+	2	11.8	1	5.0	#	#	χ^2=0.564
-	15	88.2	19	95.0	#	#	p=0.452
Family history of CVD							
+	6	35.3	7	35.0	9	45.0	χ^2=0.533
-	11	64.7	13	65.0	11	55.0	p=0.766

MS= Multiple sclerosis; CVD= cardiovascular disease

There was a statistically significant difference between the groups in terms of E' MV lateral and MV E/A values (p<0.001, p=0.010 respectively). E' MV lateral and MV E/A values of MS patients not using immunomodulatory drugs were determined to be significantly higher compared to the control group (Tables 3 and 4). Additionally, the A'MV medial (m/s) value is statistically significantly lower in MS patients who do not use drugs compared to the control group (p=0.036) (Table 4).

A statistically significant difference was determined between the groups in terms of E/E' MV lateral and MV A Vmax values (p=0.009, p=0.012 respectively). As a result of Bonferroni-corrected pairwise comparisons performed to determine the group from which the significant difference originated, E/E' MV lateral and MV A Vmax values of the control group and the MS patient group not using drugs were determined to be significantly lower compared to the patient group using drugs (Table 4).

PAs, PAl, and left and right intraatrial EMD values were determined to be prolonged in MS patients using and not using drugs compared to the control group but this finding was not statistically significant (Table 5).

Cerebral lesion involvement of MS patients in the first and second groups was examined (thin section MRI, in 1 mm MIP TRA sequence). According to MAGNIMS criteria cerebral lesions were classified as lesions up to 20 number 1,

Table 2: Age, BMI, and diagnosis time of the study patients

Variables	MS patients with medical treatment (n=17)		MS patients without medical treatment (n=20)		Control subjects (n=20)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
Age (years)	27.6±4.1	29 [5]	28.2±4.8	28 [6]	30±5.5	31 [7]	F=1.280 p=0.286
BMI (kg/m^2)	24.6±3.6	24.97 [5.58]	25.1±4.4	24,4 [5,57]	25.3±5.7	23.51 [4.73]	F=0.108 p=0.897
Diagnosis time (years)	**3.12±1.22**	**3.0 [2.0]**	**1.20±0.41**	**1,0 [0,0]**	#	#	**Z=-5.037 p=<0.001**

SD=Standard deviation; IQR= interquartile range; BMI= body mass index.

Table 3: Echocardiographic and clinical data of the study patients

Variables	MS patients with medical treatment (n=20) (1)		MS patients without medical treatment (n=20) (2)		Control subjects (n=20) (3)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
SBP (mmHg)	124.6±10.6	122 [10]	120.4±8.6	122 [20]	126.4±9.9	130 [14.5]	χ^2=4.694 p=0.096
DBP (mmHg)	77±7	80 [10]	75.3±5.8	77.5 [10]	75.6±7.8	77.5 [7.5]	χ^2=0.581 p=0.748
HR (bpm)	81.1±10.9	80 [9]	72.7±13.8	72 [19]	72.7±14.2	72.5 [15]	F=2.457 p=0.095
PWD (ms)	0.9±0.4	1 [0.5]	0.8±0.4	0.5 [0.5]	1±0.4	1 [0.75]	χ^2=1.945 p=0.378
CK-MB (U/L)	1.5±1.1	1.2 [0.7]	0.9±0.3	0.8 [0.25]	1.1±0.6	0.95 [0.8]	χ^2=4.511 p=0.105
Troponin (ng/L)	2.0±1.3	2 [1]	1.9±1.0	2 [1]	1.5±0.8	1 [1]	χ^2=3.569 p=0.168
E' MV lateral (m/s)	**0.12±0.04**	**0.13 [0.07]**	**0.15±0.05**	**0.15 [0.06]**	**0.09±0.03**	**0.08 [0.05]**	**F=9.076 p=<0.001 [2-3]**
E' MV medial (m/s)	0.10±0.03	0.10 [0.04]	0.10±0.03	0.11 [0.05]	0.09±0.03	0.09 [0.04]	F=1.599 p=0.211
HDL	49.2±12.5	51 [18]	56.3±11.3	57.5 [20]	49.8±3.3	50 [4]	χ^2=4.069 p=0.131
Triglyceride	114.7±52.8	99 [52]	122±64.9	110 [51]	106.4±36.3	95 [32.5]	χ^2=0.564 p=0.754
LDL	113.9±31.4	103 [20]	125.3±46.7	118 [71.5]	110.1±30.2	102.5 [27.5]	χ^2=0.948 p=0.623
Total cholesterol	180.5±41.5	175 [28]	198.2±66.7	181.5 [74.5]	179.9±25.4	175 [30]	χ^2=0.611 p=0.737

SD=Standard deviation; IQR= interquartile range; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; PWD=p-wave dispersion; CK-MB:Creatine Kinase-Myocardial Band; E'=early diastolic mitral annular velocity; MV=mitral valve.

between 21 – 50 number 2, between 51 – 100 number 3, and lesions over 100 number 4). The number of E'MV lateral (m/s) lesions between 21 – 50 and 51 – 100 was higher than the control group (number of lesions=0) (p=0.007). The number of MV E/A lesions 1-20 is higher than in the control group (p=0.004). However, there was no significant increase in these values according to the increase in the number of cerebral MRI lesions (Table 6).

Spinal lesions (in the STIR sequence) were classified as lesions up to 10 number 1, and those with more than 10 were indicated as 2. It was checked whether there was a correlation between the parameters of the echo results according to the lesion load. Those with nucleus tractus solitarius (NTS) involvement were added as NTS present:1 absent:0. This parameter was also compared with the echo results. E/E' MV lateral spinal MRI lesions between 1 and 10 were higher than the control group, and those with more than 10 lesions were higher than the control group (p=0.007) (Table 7). There was no correlation between the increase in spinal MRI lesions and these parameters.

In patients with nucleus tractus solitorius involvement, A' MV lateral (m/s) is higher in this region than in those without cerebral MRI

Table 4: Echocardiographic data of the study patients

Variables	MS patients with medical treatment (n=20) (1)		MS patients without medical treatment (n=20) (2)		Control subjects (n=20) (3)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
A' MV lateral(m/s)	0.08±0.03	0.09 [0.05]	0.09±0.03	0.08 [0.03]	0.09±0.02	0.09 [0.03]	F=0.045 p=0.956
A' MV medial(m/s)	**0.09±0.03**	**0.09 [0.03]**	**0.07±0.03**	**0.07 [0.04]**	**0.09±0.02**	**0.09 [0.03]**	**F=3.529 p=0.036 [2-3]**
E/E' MV lateral	**8.22±2.83**	**7.8 [4.7]**	**6.68±1.77**	**6.4 [1.9]**	**6.05±1.69**	**5.2 [2.3]**	**χ^2=7.454 p=0.024 [2,3-1]**
E/E' MV medial	8.27±2,2.17	8.11 [1.74]	7.91±1.90	7.29 [3.16]	8.41±2.73	8.1 [3.93]	χ^2=0.166 p=0.920
MV E Vmax(m/s)	0.78±0.21	0.77 [0.3]	0.87±0.20	0.83 [0.27]	0.84±0.21	0.82 [0.16]	χ^2=1.828 p=0.401
MV A Vmax(m/s)	**0.80±0.20**	**0.8 [0.3]**	**0.64±0.15**	**0.6 [0.2]**	**0.63±0.15**	**0.6 [0.1]**	**χ^2=8.811 p=0.012 [2,3-1]**
MV E/A	**1.25±0.36**	**1.28 [0.31]**	**1.40±0.36**	**1.42 [0.59]**	**1.08±0.24**	**1.05 [0.38]**	**F=4.915 p=0.011 [2-3]**
LA diameter(cm)	2.77±0.48	2.77 [0.5]	2.90±0.47	2.88 [0.53]	2.75±0.41	2.72 [0.73]	F=0.668 p=0.517
IVS d(cm)	0.87±0.23	0.84 [0.4]	0.87±0.18	0.85 [0.2]	0.83±0.11	0.81 [0.14]	F=0.361 p=0.699
IVS s(cm)	1.04±0.24	0.96 [0.2]	1.07±0.31	1.09 [0.53]	1.04±0.21	1.07 [0.26]	F=0.128 p=0.880
LV HR(bpm)	82.1±13.9	80 [12]	72.7±13.8	72 [19]	73±14.4	75 [16.5]	F=2.636 p=0.081
LVEF (%)	59.6±12.8	56.6 [21.2]	59.4±12	57.3 [16.2]	55.2±16.3	58.05 [25.25]	F=0.623 p=0.540

S.D.=Standard deviation; IQR= interquartile range; MV=mitral valve; E=mitral inflow early diastolic velocity; A=mitral inflow late diastolic velocity; E'=early diastolic mitral annular velocity; A'=late (atrial) diastolic mitral annular velocity; LA=left atrial; IVS d=interventricular septum thickness diastolic; IVS s=interventricular septum thickness sistolic; LV=left ventricle; LV HR;left ventricular heart rate; LVEF=left ventricular ejection fraction.

involvement (p=0.033). Left and right intraatrial EMD is higher in patients with nucleus tractus solitarius involvement (p=0.048 and p=0.012, respectively) (Table 8).

Blood lipid parameters LDL, HDL, triglyceride, and total cholesterol were added as cardiovascular risk factors (Table 3). These parameters were also compared between groups. However, no statistical significance was found between the groups.

No signs of autonomic involvement or orthostatic hypotension were detected in any of the patients.

DISCUSSION

Within the scope of this research, we have compared AEMD periods, which are predictive in assessing atrial functions, in both MS patients and the control group. Due to the limited data on cardiovascular function in MS, we tried to assess atrial functions. We determined that some parameters demonstrating left ventricular diastolic dysfunction in MS patients (with or without immunomodulatory drug use) were impaired compared to the control group, and right-left intra- and interatrial AEMD were similar.

We determined a significant difference in

Table 5: Atrial conduction time intervals of the study patients

Variables	MS patients with medical treatment (n=20)		MS patients without medical treatment (n=20)		Control subjects (n=20)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
Pas(ms)	78.94±30.31	66.0 [28.0]	70.90±16.68	72.0 [28.0]	63.20±11.56	66.0 [17.5]	χ^2=2.923 p=0.232
Pal(ms)	68.35±26.47	55.0 [33.0]	64.45±23.65	66.0 [36.0]	61.05±13.43	61.0 [11.0]	χ^2=0.418 p=0.811
PAt(ms)	66.88±19.20	72.0 [22.0]	69.30±14.16	66.0 [22.0]	69.25±14.03	66.0 [19.0]	F=0.137 p=0.872
Left intraatrial EMD (ms)	20.24±16.90	22.0 [15.0]	18.95±14.77	14.0 [27.5]	12.75±7.69	11.0 [8.5]	χ^2=1.302 p=0.522
Right intraatrial EMD (ms)	17.94±17.04	11.0 [17.0]	18.20±10.84	17.0 [11.0]	14.35±10.49	11.0 [16.5]	χ^2=1.657 p=0.437
İnteratrial EMD (ms)	14.88±12.06	11.0 [11.0]	19.95±14.71	17.0 [22.5]	16.00±12.38	17.0 [16.5]	χ^2=0.786 p=0.675

PAs=mitral septal annulus PA duration; PAl=mitral lateral annulus PA duration; PAt=tricuspid lateral annulus PA duration; EMD=electromechanical delay.

left ventricular diastolic dysfunction findings in MS patients compared to the control group. This difference was greater in the group using immuno-modulatory drugs with a longer duration of disease. Left ventricular systolic function, left atrium function, and right ventricular function were similar.

Autonomous system disorders in MS can be elaborated as bladder, intestinal, and sexual dysfunction, sweating, thermoregulation, and pupillary abnormalities and are considered as the causes of CV dysfunction.[3] In addition to autonomous system involvement, the mechanisms of impaired CV function in MS patients can be considered as the presence of cardiomyocyte structure change, physical insufficiency, oxidative stress, endothelial dysfunction, and associated cardiovascular risk factors.[1,2]

The main mechanism responsible for the deterioration of cardiac function may be muscle proteins with impaired structure, such as the involvement of myocyte structure and muscle diseases expressed in the myocardium.[4] Mitochondrial dysfunction, which leads to the disruption of myelin production in the central nervous system, is also present in cardiac cells and contributes to the disruption of cardiac function.[5,6] Risk factors such as smoking, dyslipidemia, and lack of exercise are more frequently observed in patients with MS.[7] The higher mortality rate of MS patients compared to the general population may be associated with a higher incidence of CV.[8]

In previous research, a decrease in left ventricular ejection fraction correlated with EDSS score was reported.[11,12] In our study, we could not determine any difference in ejection fraction values because we included patients with EDSS 0 – 3. Despite the fact that most studies have reported disorders in left ventricular functions, there are also controversial data.[10-12]

Several published articles indicated an increase in the frequency of arrhythmia in MS patients.[12] Especially, the risk of developing atrial fibrillation has increased after high-dose corticosteroid treatment.[13] Although fingolimod is generally known as the cause of bradycardia, it has been reported in the literature that it causes paroxysmal atrial fibrillation.[14]

In our study, no statistically significant AEMD was determined between the MS patient groups and the control group using and not using immuno-modulators, but the left and right intraatrial EMD values were determined to be longer compared to the control group. There are some observational studies in the literature reporting that the risk of AF was reduced in MS.[15,16] It was considered that this may be due to the frequency of female gender in the MS patient group and/or may be associated

Table 6: Cerebral lesion involvement of MS patients

Variables	0 (n=20)		1-20 (n=13)		21-50 (n=13)		51-100 (n=8)		>100 (n=3)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
E' MV lateral(m/s)	**0.09±0.03**	**0.1 [0.1]**	**0.16±0.04**	**0.16 [0.04]**	**0.13±0.05**	**0.13 [0.08]**	**0.10±0.04**	**0.09 [0.07]**	**0.09±0.03**	**0.09 [0.05]**	**F=3.949 p=0.007 [0-2/0-3]**
E' MV medial(m/s)	0.09±0.03	0.09 [0.04]	0.11±0.02	0.11 [0.03]	0.1±0.04	0.1 [0.06]	0.09±0.04	0.09 [0.05]	0.08±0.02	0.08 [0.03]	F=1.596 p=0.189
A' MV lateral(m/s)	0.09±0.02	0.09 [0.03]	0.08±0.03	0.08 [0.03]	0.09±0.03	0.08 [0.03]	0.09±0.03	0.09 [0.04]	0.08±0.03	0.07 [0.06]	F=0.511 p=0.728
A' MV medial(m/s)	0.07±0.03	0.07 [0.04]	0.09±0.03	0.09 [0.03]	0.08±0.02	0.08 [0.04]	0.10±0.03	0.1 [0.04]	0.10±0.01	0.11 [0.03]	F=2.312 p=0.070
E/E' MV lateral	6.05±1.7	5.2 [2.34]	7.24±2.6	6.39 [1.64]	7.38±2.2	6.51 [1.61]	7.96±3.0	7.3 [3.22]	6.56±1.1	6.10 [5.96]	χ^2=6.102 p=0.192
E/E' MV medial	8.41±2.7	8.1 [4.06]	8.04±1.7	8.11 [2.21]	7.59±1.65	7.23 [1.83]	8.43±2.12	8.07 [2.78]	9.36±4.21	8.56 [8.31]	χ^2=0.678 p=0.954
MV E Vmax(m/s)	0.84±0.2	0.82 [0.16]	0.9±0.17	0.83 [0.2]	0.8±0.2	0.77 [0.28]	0.78±0.22	0.71 [0.28]	0.73±0.36	0.82 [0.7]	χ^2=3.084 p=0.544
MV A Vmax(m/s)	0.63±0.14	0.61 [0.14]	0.63±0.11	0.65 [0.12]	0.69±0.2	0.65 [0.13]	0.85±0.26	0.89 [0.36]	0.79±0.20	0.80 [0.26]	χ^2=7.133 p=0.129
MV E/A	**1.08±0.2**	**1.05 [0.39]**	**1.49±0.29**	**1.43 [0.45]**	**1.36±0.39**	**1.18 [0.66]**	**1.13±0.31**	**1.1 [0.38]**	**1.09±0.41**	**1.28 [0.76]**	**F=4.327 p=0.004 [1-0]**
LA diameter(cm)	2.75±0.4	2.72 [0.75]	2.76±0.53	2.74 [0.54]	2.78±0.4	2.84 [0.43]	3.06±0.51	3.08 [0.82]	2.91±0.43	2.95 [0.85]	F=0.760 p=0.556
IVS d(cm)	0.83±0.11	0.81 [0.15]	0.8±0.21	0.78 [0.17]	0.88±0.19	0.85 [0.35]	0.98±0.22	1.04 [0.26]	0.85±0.09	0.87 [0.17]	F=1.472 p=0.224
IVS s(cm)	1.04±0.20	1.07 [0.26]	1.03±0.25	1.03 [0.29]	1.01±0.22	0.99 [0.25]	1.22±0.39	1.18 [0.66]	0.94±0.12	0.87 [0.2]	F=1.205 p=0.320
LV HR(bpm)	72.9±14.4	75 [16.75]	74.38±11.72	76 [12]	72.77±16.26	71 [18]	86.25±13.55	82.5 [11.5]	82±12.49	78 [24]	F=1.624 p=0.182
LVEF (%)	55.23±16.3	58.05 [26.43]	61.34±11.59	56.6 [18.1]	58.15±13.62	56.6 [18.8]	61.6±12.05	61.85 [17.85]	52.13±10.67	47 [19.4]	F=0.649 p=0.630

Pas(ms)	63.2±11.6	66 [17.75]	70.38±19.05	77 [22]	69.62±19.74	66 [17]	85±26.28	83 [36]	86.67±49.74	61 [89]	χ^2=5.576 p=0.233
Pal(ms)	61.1±13.4	61 [11.0]	57.23±19.69	55 [33]	65.85±23.34	61 [17]	69.88±29.17	69 [49.5]	97.33±19.55	99 [39]	χ^2=6.661 p=0.155
PAt(ms)	69.3±14.0	66 [20.5]	65.92±15.92	66 [22]	70.46±13.81	72 [11]	65.5±23.03	63.5 [41]	75.33±13.58	77 [27]	F=0.355 p=0.839
Left intraatrial EMD(ms)	12.75±7.7	11 [9.75]	19.92±16.51	22 [29]	16.08±14.57	11 [16]	16.63±10.53	19.5 [13.5]	40.67±16.92	45 [33]	χ^2=6.668 p=0.155
Right intraatrial EMD(ms)	14.4±10.5	11 [16.75]	16.46±12.55	16 [11]	15.31±12.82	11 [16]	22.25±12.86	20 [17]	26±26.46	16 [50]	χ^2=2.992 p=0.559
İnteratrial EMD(ms)	16.0±12.4	17 [16.75]	17.77±14.83	16 [17]	18.62±14.27	17 [17]	14.13±11.8	8.5 [13.5]	22±14.93	16 [28]	χ^2=0.641 p=0.958

SD=Standard deviation; IQR= interquartile range; MV=mitral valve; E=mitral inflow early diastolic velocity; A=mitral inflow late diastolic velocity; E'=early diastolic mitral annular velocity; A'=late (atrial) diastolic mitral annular velocity; LA=left atrial; IVS d=interventricular septum thickness diastolic; IVS s=interventricular septum thickness sistolic; LV=left ventricle; LV HR:left ventricular heart rate; LVEF=left ventricular ejection fraction; PAs=mitral septal annulus PA duration; PAl=mitral lateral annulus PA duration; PAt=tricuspid lateral annulus PA duration; EMD=electromechanical delay.

with decreased aerobic capacity because of the inactivity in the patients.

Also, no clear clinical consensus has been achieved on the cardiac effects of immuno-modulatory agents in the treatment group. Immuno-modulatory treatments were heterogeneous in the MS group receiving treatment (dimethyl fumarate, glatiramer acetate). The effect of immunomodulatory drugs on the cardiovascular system of the disease is not clear. Although the duration of the disease from the first diagnosis up to our day was found to be longer in the treatment group. It is not possible to know the initiation of the disease process before the first attack.[17,18]

The relatively low number of study population could be counted as a limitation of our study. On the other hand, the stregths could be elaborated as: while there have been reported cases of cardiovascular dysfunction in MS ranging from subclinical to sudden death, studies focusing on the various aspects of cardiac evaluation and correlation to cardiac function in MS patients are limited. In addition, awareness of such conditions may also help in guiding the selection of therapy given the potential for cardiac toxicity with agents such as fingolimod and mitoxantrone hence the relevance of evaluating and subtyping cardiovascular dysfunction in MS patients.

In conclusion, in our study, we determined that left ventricular diastolic function was impaired in MS patients compared to the control group, and right-left intra- and interatrial AEMD were similar. Based on these results, we recommend echocardiographic assessment for early detection of left ventricular diastolic dysfunction in MS patients.

DISCLOSURE

Ethics: This study is approved by the ethics committee of our institution and informed consent has been obtained from all participants.

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Table 7: Spinal lesions (in the STIR sequence)

Variables	0 (n=26)		1-10 (n=25)		>10 (n=6)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
E' MV lateral(m/s)	0.13±0.05	0.13 [0.09]	0.11±0.04	0.10 [0.06]	0.12±0.06	0.12 [0.11]	F=2.440 p=0.097
E' MV medial(m/s)	0.09±0.03	0.09 [0.04]	0.09±0.03	0.1 [0.05]	0.1±0.03	0.09 [0.05]	F=0.318 p=0.729
A' MV lateral(m/s)	0.09±0.02	0.08 [0.03]	0.09±0.03	0.08 [0.04]	0.08±0.02	0.08 [0.03]	F=0.229 p=0.796
A' MV medial(m/s)	0.08±0.03	0.08 [0.04]	0.09±0.02	0.09 [0.03]	0.09±0.03	0.1 [0.03]	F=1.737 p=0.186
E/E' MV lateral	**5.98±1.51**	**5.52 [1.49]**	**7.48±2.54**	**6.51 [3.70]**	**8.62±2.3**	**8.95 [4.37]**	**χ^2=9.871 p=0.007 [1-0/2-0]**
E/E' MV medial	8.45±2.56	8.09 [3.79]	8.13±2.10	7.78 [2.65]	7.3±1.47	7.17 [2.56]	χ^2=0.746 p=0.689
MV E Vmax(m/s)	0.86±0.21	0.83 [0.18]	0.82±0.21	0.82 [0.32]	0.74±0.14	0.71 [0.24]	χ^2=1.619 p=0.445
MV A Vmax(m/s)	0.65±0.14	0.64 [0.18]	0.70±0.22	0.62 [0.35]	0.78±0.15	0.86 [0.25]	χ^2=2.775 p=0.250
MV E/A	1.15±0.28	1.10 [0.42]	1.35±0.37	1.38 [0.60]	1.26±0.32	1.22 [0.40]	F=2.228 p=0.118
LA diameter(cm)	2.77±0.48	2.70 [0.72]	2.85±0.42	2.88 [0.71]	2.83±0.49	2.81 [0.73]	F=0.203 p=0.817
IVS d(cm)	0.84±0.15	0.83 [0.15]	0.88±0.19	0.85 [0.29]	0.84±0.28	0.72 [0.52]	F=0.374 p=0.690
IVS s(cm)	1.00±0.24	1.05 [0.33]	1.09±0.23	1.05 [0.37]	1.06±0.37	0.94 [0.42]	F=0.682 p=0.510
LV HR(bpm)	73.96±15.2	76 [18]	74.72±13.07	72 [15]	86.17±14.19	81.5 [27]	F=1.881 p=0.162
LVEF (%)	56.90±15.52	58.7 [24.15]	59.06±11.76	58 [17.25]	58.48±15.69	55 [33.82]	F=0.155 p=0.857
Pas(ms)	66.65±15.25	66 [18.25]	71.56±21.44	72 [25]	83.67±36.27	66 [73.5]	χ^2=0.895 p=0.639
Pal(ms)	61.15±14.84	61 [12.75]	67.40±25.62	66 [39]	66.17±28.15	55 [44.25]	χ^2=0.548 p=0.761
PAt(ms)	70.27±14.90	66 [22]	67.56±16.17	66 [16]	65.33±17.4	66.5 [28.75]	F=0.331 p=0.720
Left intraatrial EMD (ms)	14.04±10.72	11 [12.25]	20.32±16.04	17 [29.5]	17.5±13.37	16.5 [18]	χ^2=1.483 p=0.476
Right intraatrial EMD (ms)	15.92±12.39	11 [19]	16.80±10.90	16 [11]	20.33±21.73	11 [42.5]	χ^2=0.316 p=0.854
İnteratrial EMD (ms)	15.88±13.35	16.5 [17]	19.84±13.42	16 [22]	10.5±8.36	8.5 [14]	χ^2=2.105 p=0.349

SD=Standard deviation; IQR= interquartile range; MV=mitral valve; E=mitral inflow early diastolic velocity; A=mitral inflow late diastolic velocity; E'=early diastolic mitral annular velocity; A'=late (atrial) diastolic mitral annular velocity; LA=left atrial; IVS d=interventricular septum thickness diastolic; IVS s=interventricular septum thickness sistolic; LV=left ventricle; LV HR;left ventricular heart rate; LVEF=left ventricular ejection fraction; PAs=mitral septal annulus PA duration; PAl=mitral lateral annulus PA duration; PAt=tricuspid lateral annulus PA duration; EMD=electromechanical delay.

Table 8: Nucleus tractus solitarius involvement

Variables	No (n=51) (1)		Yes (n=6) (2)		p-value
	$\overline{X}$ ± SD	Median [IQR]	$\overline{X}$ ± SD	Median [IQR]	
E' MV lateral(m/s)	0.12±0.05	0.12 [0.07]	0.12±0.04	0.13 [0.07]	t=-0.251 p=0.803
E' MV medial(m/s)	0.09±0.03	0.09 [0.05]	0.1±0.03	0.11 [0.05]	t =-0.785 p=0.436
A' MV lateral(m/s)	**0.08±0.02**	**0.08 [0.03]**	**0.11±0.04**	**0.11 [0.06]**	t **=-2.192 p=0.033**
A' MV medial(m/s)	0.08±0.03	0.09 [0.04]	0.10±0.04	0.09 [0.04]	t =-1.244 p=0.219
E/E' MV lateral	6.82±2.18	6.11 [2.52]	7.77±2.97	7.09 [2.91]	u=-0.923 p=0.967
E/E' MV medial	8.22±2.36	7.69 [3.03]	7.9±1.37	7.9 [2.05]	u =-0.130 p=0.909
MV E Vmax(m/s)	0.83±0.2	0.81 [0.3]	0.82±0.24	0.83 [0.27]	u =-0.039 p=0.969
MV A Vmax(m/s)	0.68±0.17	0.65 [0.13]	0.71±0.26	0.57 [0.14]	u =-0.013 p=0.990
MV E/A	1.24±0.35	1.18 [0.61]	1.28±0.32	1.25 [0.27]	t =-0.246 p=0.806
LA diameter(cm)	2.83±0.46	2.81 [0.7]	2.67±0.32	2.81 [0.46]	t =0.846 p=0.401
IVS d(cm)	0.85±0.16	0.85 [0.28]	0.92±0.27	0.91 [0.47]	t =-0.968 p=0.337
IVS s(cm)	1.05±0.24	1.03 [0.36]	1.09±0.39	1.03 [0.34]	t =-0.435 p=0.665
LV HR(bpm)	74.82±14.5	76 [16]	82±12.98	76.5 [24]	t =-1.156 p=0.253
LVEF (%)	57.99±13.39	56.6 [18.5]	58.25±18.33	58.55 [31.5]	t =-0.043 p=0.966
Pas(ms)	68.18±17.12	66 [28]	91.17±38.48	77 [72]	u =-1.414 p=0.157
Pal(ms)	63.76±20.57	61 [39]	70±29.62	63.5 [55]	u =-0.366 p=0.715
PAt(ms)	68.84±14.51	66 [22]	66.17±24.26	74.5 [49]	t =0.396 p=0.693
Left intraatrial EMD(ms)	**16.02±13.27**	**11 [28]**	**26.83±14.27**	**22 [27]**	**u =-1.976 p=0.048**
Right intraatrial EMD(ms)	**14.70±10.28**	**11 [16]**	**34.33±18.94**	**36.5 [27]**	**u =-2.518 p=0.012**
İnteratrial EMD(ms)	17.74±13.50	16 [27]	11.17±7.44	8.5 [12]	u =-0.993 p=0.321

S.D.=Standard deviation; IQR= interquartile range; MV=mitral valve; E=mitral inflow early diastolic velocity; A=mitral inflow late diastolic velocity; E'=early diastolic mitral annular velocity; A'=late (atrial) diastolic mitral annular velocity; LA=left atrial; IVS d=interventricular septum thickness diastolic; IVS s=interventricular septum thickness sistolic; LV=left ventricle; LV HR;left ventricular heart rate; LVEF=left ventricular ejection fraction; PAs=mitral septal annulus PA duration; PAl=mitral lateral annulus PA duration; PAt=tricuspid lateral annulus PA duration; EMD=electromechanical delay.

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