Acta Neurol Scand 2006: 114: 114–118 DOI: 10.1111/j.1600-0404.2006.00662.x

ACTA NEUROLOGICA
SCANDINAVICA

Subclinical left ventricular dysfunction in multiple sclerosis

Akgül F, Mclek İ, Duman T, Seyfelì E, Seydaliyeva T, Yalçın F. Subclinical left ventricular dysfunction in multiple sclerosis. Acta Neurol Scand 2006: 114: 114–118. © Blackwell Munksgaard 2006.

Objectives – To investigate the left (LV) and right ventricular (RV) function in multiple sclerosis (MS) using standard echocardiography and Doppler tissue imaging (DTI). *Materials and methods* – A total of 41 patients with definite MS and 32 healthy controls were included in the study. *Results* – LV end-systolic dimension was increased and LV ejection fraction was decreased in MS patients compared with controls ($P < 0.05$). LV end-diastolic dimension was increased in MS patients, however, did not reach significance. Among DTI parameters, mitral annular peak early diastolic velocity to peak late diastolic velocity ratio (Em/Am) was decreased in MS patients, but not reach statistical significance. No significant differences in tricuspid annular Em/Am ratio was found between MS patients and controls. A statistically significant increase of DTI derived LV myocardial performance index was found in MS patients as compared with controls. RV myocardial performance index showed a tendency to be increased in MS patients, however, did not reach significance. *Conclusions* – These findings suggest subclinical LV dysfunction and preserved RV function in patients with MS.

Ferit Akgül[1], İsmet Mclek[2], Taşkın Duman[2], Ergün Seyfelì[1], Tunzale Seydaliyeva[1], Fatih Yalçın[1]

[1]Mustafa Kemal University, Faculty of Medicine, Department of Cardiology, Antakya, Turkey; [2]Mustafa Kemal University, Faculty of Medicine, Department of Neurology, Antakya, Turkey

Key words: Multiple sclerosis, ventricular function, tissue doppler

Assist. Prof. Dr. Ferit Akgül, Mustafa Kemal Üniversitesi, Tıp Fakültesi, Arastırma ve Uygulama Hastanesi, Kardiyoloji Anabilim Dalı, Antakya, Turkey
Tel: 090 532 656 5518
Fax: 090 326 6143834
e-mail: feritakgul1@yahoo.ca

Accepted for publication March 23, 2006

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. Although MS causes functional abnormalities in different organs of the body including the urinary bladder, lungs and the gastrointestinal tract, the effect of MS on cardiac function is not well known (1–3). There are only a few studies in the literature related to function of the left or right ventricles and the findings have been conflicting (4–8). Several authors have reported dysfunction of the left and right ventricles in patients with MS (4, 5, 8). On the other hand, others have reported a normal left ventricular (LV) function (6, 7). Recently, Doppler tissue imaging (DTI), a new technique of echocardiography, has been used to evaluate ventricular function (9). DTI-derived myocardial performance index (MPI), is defined as the sum of the isovolumetric relaxation time (IVRT) and isovolumetric contraction time (IVCT) divided by ejection time has been reported to reflect combined systolic and diastolic cardiac function (10). It is prolonged in many ventricular dysfunctions, in the absence of clinical signs of the disease (11, 12). The index was shown to reflect disease severity and to have prognostic value (13). In this study, we evaluated left and right ventricular (RV) function using standard echocardiography and DTI in MS patients without signs or symptoms of cardiac involvement. We also calculated DTI-derived MPI of the left and right ventricles.

Materials and methods

A total of 41 patients with definite MS according to the criteria of Poser et al. were included into the study (14). None of the patients had ever received cardiotoxic treatments. Thirty-two gender and age-matched healthy subjects were used as a control group. All patients and healthy subjects gave informed consent to participate in the study, which had the approval of our local ethics committee. All patients underwent a neurological examination according to Kurtzke and an Expanded Disability Status Scale (EDSS) score was created for each of them by an experienced neurologist (15). All patients and controls underwent chest radiography, electrocardiography and echocardiography.

Transthoracic echocardiography was performed with a GE Vingmed Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway). All measurements were performed by the same cardiologist on frozen images from three to five cardiac cycles using the available software package of the ultrasound system. All measurements were taken according to recommendations of the American Society of Echocardiographists (16).

DTI was performed from the apical four-chamber view using a frame rates of >80/s. Myocardial velocity profiles of the lateral mitral annulus were obtained by placing the sample volume at the junction of the mitral valve annulus and lateral myocardial wall. Myocardial velocities of the lateral tricuspid annulus were obtained similarly by placing the sample volume at the junction of the tricuspid annulus and RV free wall. Peak mitral annular systolic (S_m), early diastolic (E_m) and late diastolic velocities (A_m) were measured and the ratio of early to late diastolic mitral annular velocities (E_m/A_m) was calculated. Similar measurements were made for peak tricuspid S_m, E_m and A_m. E_m/A_m was then calculated. Mitral annular E_m wave deceleration time, IVRT, IVCT and S_m wave duration (ejection time) were measured. Thereafter, DTI-derived LV MPI was calculated (Fig. 1). Similarly, tricuspid annular E_m wave deceleration time, IVRT, IVCT and ejection time were measured. Then, RV DTI-derived MPI was calculated.

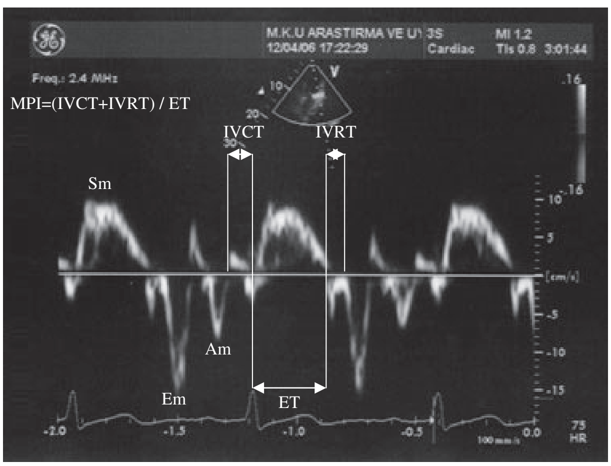

Figure 1. Time intervals of the myocardial performance index (MPI) derived with pulsed wave tissue Doppler echocardiography. MPI was calculated as the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) divided by ejection time (ET).

All statistical analyses were performed using commercially available SPSS version 10.0. Categorical variables were presented numerically and for statistical analysis chi-square test was used. All clinical and echocardiographic variables are presented as mean ± SD. The values for patients and controls were compared with each other using unpaired Student's *t*-test. The Spearman bivariate correlation test was used to determine the correlation between two numerical variables. $P < 0.05$ was considered significant.

Results

Clinical findings

The clinical and demographic features of the two groups are shown in Table 1. The patients and control subjects were well matched with each other for age, sex and body mass index. There was no significant difference in blood pressures, resting heart rates, fasting plasma glucose, total cholesterol or triglyceride levels between the two groups

Echocardiography

Left atrial diameter, RV diastolic dimension (RV DD) and LV end-diastolic dimension (LV EDD) were similar in patient and control groups (Table 2). However, MS patients had larger LV end-systolic dimension (LV ESD) and LV wall thickness when compared with healthy subjects ($P < 0.05$). LV ejection fraction was decreased in MS patients compared with healthy subjects ($P < 0.05$). Though LV fractional shortening was lower in MS patients than those of controls, the difference was not statistically significant. Five MS patients showed a diffuse LV dysfunction with reduced ejection

Table 1 Clinical and demographic data (mean ± SD)

	Controls ($n = 32$)	Multiple sclerosis ($n = 41$)	*P*-value
Age (years)	32.3 ± 11.8	33.5 ± 10.2	NS
Women/men	22:10	28:13	NS
SBP (mmHg)	107.5 ± 12.9	112.2 ± 11.8	NS
DBP (mmHg)	70.1 ± 6.4	72.2 ± 7.2	NS
Heart rate (beats per minute)	72.0 ± 12.1	73.8 ± 10.1	NS
Body mass index (kg/m^2)	22.6 ± 3.8	23.4 ± 4.1	NS
Fasting plasma glucose (mg/dl)	84.1 ± 8.2	87 ± 7.8	NS
Total cholesterol (mg/dl)	181.6 ± 39.3	172.1 ± 43.6	NS
Triglycerides (mg/dl)	143.6 ± 61.4	126.7 ± 57.3	NS
Disease duration (years)	–	6.4 ± 6.5	–
EDSS score	–	3.7 ± 1.4	–

SBP, systolic blood pressure; DBP, diastolic blood pressure; EDSS, Expanded Disability Status Scale; NS, statistically not significant.

Table 2 Comparison of echocardiographic parameters of patients and controls (mean ± SD)

	Controls	Multiple sclerosis	*P*-value
Left atrium (cm)	3.0 ± 0.4	3.0 ± 0.4	NS
RV DD (cm)	2.1 ± 0.2	2.3 ± 0.2	NS
LV EDD (cm)	4.5 ± 0.4	4.6 ± 0.4	NS
LV ESD (cm)	2.7 ± 0.3	2.9 ± 0.3	0.038
Septum (cm)	0.76 ± 0.9	0.81 ± 1.0	0.02
LV fractional shortening (%)	39 ± 3.6	0.37 ± 5.2	0.09
LV ejection fraction (%)	69.9 ± 4.6	66.0 ± 6.8	0.006

RV DD, right ventricular diameter at diastole; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; NS, statistically not significant.

fraction (< 55%). None of the patients had segmental LV dysfunction. No correlation was found between LV ejection fraction and disease duration or EDSS score ($P = 0.26$ and 0.71).

The mitral lateral annular S_m, E_m, the E_m/A_m ratio, IVCT and ejection time were statistically similar in MS patients and controls (Table 3). However, the E_m deceleration time, IVRT and MPI were prolonged in MS patients compared with controls ($P < 0.05$). Though A_m was increased in MS patients than controls, the difference was not statistically significant.

In the right ventricle, DTI assessment at tricuspid annulus showed an increase E_m deceleration time in the MS group compared with the control group ($P < 0.05$) (Table 3). However, tricuspid lateral annular S_m, E_m, A_m, the E_m/A_m ratio, IVRT, IVCT, ejection time and MPI were similar for MS and control groups. Among MS patients, no correlation was found between LV or RV MPI and disease duration ($P = 0.54$ and 0.89) or EDSS score ($P = 0.74$ and 0.91).

Table 3 Comparisons of mitral and tricuspid annular tissue Doppler velocities among the patients and controls (mean ± SD)

	Controls	Multiple sclerosis	*P*-value
Mitral annular tissue Doppler velocities			
S_m (cm/s)	9.6 ± 1.7	9.2 ± 1.6	NS
E_m(cm/s)	15.1 ± 2.0	14.7 ± 3.6	NS
A_m(cm/s)	7.4 ± 2.5	8.2 ± 2.9	0.08
E_m/A_m	2.1 ± 0.9	1.8 ± 1.0	NS
$E_m$deceleration time (ms)	142.2 ± 18.4	160.9 ± 18.0	0.02
IVRT (ms)	46.2 ± 11.3	60.3 ± 18.2	0.001
IVCT (ms)	72.9 ± 19.8	71.0 ± 16.6	NS
Ejection time (ms)	285.6 ± 18.1	286.1 ± 20.1	NS
MPI	0.41 ± 0.06	0.46 ± 0.1	0.04
Tricuspid annular tissue Doppler velocities			
S_m (cm/s)	12.1 ± 1.5	12.0 ± 1.7	NS
E_m(cm/s)	13.5 ± 2.7	12.2 ± 2.9	0.09
A_m(cm/s)	12.6 ± 4.2	12.9 ± 3.9	NS
E_m/A_m	1.1 ± 0.4	1.0 ± 0.4	NS
$E_m$deceleration time (ms)	140.1 ± 15.8	166.8 ± 26.9	0.007
IVRT (ms)	70.1 ± 25.0	75.0 ± 33.1	NS
IVCT (ms)	55.1 ± 8.6	58.4 ± 10.3	NS
Ejection time (ms)	277.4 ± 14.9	280.6 ± 18.6	NS
MPI	0.45 ± 0.07	0.47 ± 0.1	NS

S_m, peak systolic velocity; E_m, peak early diastolic velocity; A_m, peak late diastolic velocity; IVRT, isovolumic relaxation time; IVCT, isovolumic contraction time; MPI, myocardial performance index; NS, statistically not significant.

Discussion

Abnormalities of parasympathetic or sympathetic cardiovascular tests are common in patients with MS, ranging from 13% to 80% (17–19). However, cardiovascular symptoms are uncommon and reports related to functions of the left or right ventricles are conflicting (4–8, 19). Strotmann et al. reported that LV function was not affected in patients with MS (7). However, Ziaber et al. reported a significant decrease in LV ejection fraction of MS patients with a high EDSS score when compared with normal subjects (8). They believed that the decrease in LV ejection fraction in patients with a high EDSS score might be related to dysfunction of the autonomic nervous system. In a radionuclide angiocardiography study Olindo et al. showed that MS patients had a decreased LV ejection fraction compared with control subjects (5). Another study by Beer et al. reported that some MS patients had a reduced LV ejection fraction measured with MR imaging study (4). There are only two studies in the literature related to evaluation of the diastolic function of the left ventricule using echocardiography in patients with MS (6, 7). The diastolic parameters of left ventricle were found to be normal in both these studies.

In our study, cardiac symptoms were not noted in any patients with MS. Transthoracic two-dimensional echocardiography showed increased LV ESD and decreased LV ejection fraction in MS patients when compared with control subjects. Although the mitral annular E_m/A_m ratio was decreased in MS patients, it was not statistically significant. This may be related to the wide range of age in the study group that may lead to a heterogeneous spectrum of mitral annular tissue Doppler velocity patterns that render subtle changes in mitral annular diastolic velocity difficult to detect. In the present study, we found a significant LV E_m deceleration time prolongation in patients with MS compared with control subjects. We explained this finding with LV relaxation impairment that was seen in the early stage of the ventricular dysfunction.

To our knowledge, this the first study that applies MPI to examine subclinical ventricular dysfunction in MS. MPI provides assessment of overall ventricular function that combines systolic and diastolic time intervals (10). In our study, we confirmed LV dysfunction using this new echocardiographic index.

Olindo et al. showed that MS patients had a decreased RV ejection fraction compared with control subjects using radionuclide angiocardiography (5). In the current study, we did not find any abnormality in RV systolic or diastolic function indicated by normal tricuspid annular systolic and diastolic myocardial velocities, as well as a normal tricuspid annular E_m/A_m ratio in patients with MS. We confirmed the presence of normal combined RV systolic and diastolic function with normal MPI. The discrepancies between the results of Olindo et al. and ours might be due to differences in the technique that was used.

The pathophysiological mechanism responsible for LV dysfunction was not clear. In our study, we excluded patients who were on medication with cardiotoxic drugs such as anticholinergic, α-blocking or tricyclic antidepressant agents. As disease duration and EDSS score were not correlated with LV ejection fraction and MPI, decreased physical load does not seem to play an important role on ventricular dysfunction in patients with MS.

Previous studies have shown that a variety of autoimmune diseases such as thyroiditis, myasthenia gravis or uveitis occur more frequently in MS patients than in the general population (20–22). Animal studies have shown that a single viral agent could result in both induction of autoimmunity and inflammatory demyelination of the central nervous system (23). In MS patients, a single agent may also be responsible for induction of different autoimmune diseases and inflammatory demyelination. This agent may induce myocarditis and lead to impairment in myocardial function in some MS patients.

Conclusions

Standard echocardiography and DTI-derived MPI findings suggest subclinical LV dysfunction and preserved RV function in MS patients. Further studies are required to establish the underlying mechanism and its clinical significance.

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