QT dispersion in patients with rheumatic mitral stenosis and its relation with echocardiographic findings and serum NT-proBNP levels

Romatizmal mitral darlığı olan hastalarda QT dispersiyonu ve ekokardiyografik bulgular ve serum NT-proBNP düzeyi ile ilişkisi

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ABSTRACT

Objectives: We evaluated the value of QT interval dispersion in patients with rheumatic mitral stenosis (MS) in association with echocardiographic parameters and serum N-terminal pro brain natriuretic peptide (NT-proBNP) levels.

Study design: The study consisted of 46 patients (39 women, 7 men; mean age 46.9±9.7 years) with moderate-to-severe rheumatic MS. All patients underwent echocardiographic examination. Blood samples for NT-proBNP were collected immediately after ECG recording. QT interval and QRS complex were measured manually on standard 12-lead surface ECGs. Electrocardiographic and echocardiographic findings and serum NT-proBNP levels were compared with those of a control group consisting of 30 healthy subjects (26 women, 4 men; mean age 46.1±7.3 years).

Results: Compared to controls, serum NT-proBNP levels were significantly higher in MS patients (284.6±206.5 *vs.* 70.2±9.3 pg/ml, p<0.001). The mean QT interval, QTc interval, and QT dispersion were significantly prolonged in MS patients compared to controls (378±25 *vs.* 349±21, 420±22 *vs.* 401±19, and 61±21 *vs.* 38±15 msec, respectively; p<0.005). QT and QTc dispersions were negatively correlated with mitral valve area (QT: r=-0.311, p=0.03; QTc: r=-0.327, p=0.02), and positively correlated with serum NT-proBNP level (QT: r=0.583, p<0.001; QTc: r=0.637, p<0.001). QTc dispersion was also an independent predictor of serum NT-proBNP level in regression analysis (β=0.330, p=0.03).

Conclusion: Our results indicate that QT dispersion is related to the echocardiographic degree of rheumatic mitral valve disease and serum NT-proBNP levels in rheumatic MS. Being a noninvasive, easy, and inexpensive method, QT dispersion may be used as a complementary tool to the clinical and echocardiographic evaluation of patients with rheumatic MS.

ÖZET

Amaç: Romatizmal mitral darlığı olan hastalarda QT interval dispersiyonunun değeri ve ekokardiyografik bulgular ve serum N-terminal pro beyin natriüretik peptit (NT-proBNP) düzeyi ile ilişkisi araştırıldı.

Çalışma planı: Çalışmaya orta veya ileri derecede romatizmal mitral darlığı olan 46 hasta (39 kadın, 7 erkek; ort. yaş 46.9±9.7) alındı. Tüm hastalara ekokardiyografik inceleme yapıldı. Elektrokardiyografiden hemen sonra serum NT-proBNP ölçümü için kan alındı. QT intervali ve QRS kompleksi 12 derivasyonlu elektrokardiyografide el ile ölçülerek belirlendi. Hasta grubunun elektrokardiyografik ve ekokardiyografik bulguları ve serum NT-proBNP düzeyleri, 30 sağlıklı bireyden (26 kadın, 4 erkek; ort. yaş 46.1±7.3) oluşan kontrol grubuyla karşılaştırıldı.

Bulgular: Kontrol grubu ile karşılaştırıldığında, serum NT-proBNP düzeyi mitral darlığı olan hastalarda anlamlı derecede yüksek bulundu (284.6±206.5 ve 70.2±9.3 pg/ml, p<0.001). Ortalama QT intervali, QTc intervali ve QT dispersiyonu değerleri kontrol grubuna göre anlamlı derecede uzamış idi (sırasıyla, 378±25 ve 349±21, 420±22 ve 401±19, 61±21 ve 38±15 msn; p<0.005). QT ve QTc dispersiyonları mitral kapak alanıyla negatif (QT: r=-0.311, p=0.03; QTc: r=-0.327, p=0.02), serum NT-proBNP düzeyiyle pozitif ilişki gösterdi (QT: r=0.583, p<0.001; QTc: r=0.637, p<0.001). Regresyon analizinde, QTc dispersiyonu serum NT-proBNP düzeyinin bağımsız bir öngördürücüsü idi (β=0.330, p=0.03).

Sonuç: Bulgularımız, romatizmal mitral darlığında QT dispersiyonunun, mitral kapak hastalığının ekokardiyografik derecesiyle ve serum NT-proBNP düzeyi ile ilişkili olduğunu gösterdi. İnvaziv olmaması, kolay ve ucuz bir yöntem olması nedeniyle, QT dispersiyonu mitral darlığının klinik ve ekokardiyografik değerlendirmesinde tamamlayıcı olarak kullanılabilir.

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Rheumatic mitral stenosis is still a prevalent disease in developing countries, causing significant morbidity and mortality.[1] These patients have reduced preload,[2] increased afterload,[3] and pulmonary artery hypertension.[4] Echocardiography and Doppler examinations are now the preferred imaging modalities for the diagnosis and quantification of the severity of the stenosis.[1] Brain natriuretic peptide and its N-terminal fragment are neurohormones synthesized and released mainly from the ventricular myocardium as a response to ventricular volume expansion and pressure overload, increases in ventricular filling pressures, and increased afterload.[5,6] Higher BNP levels are correlated with echocardiographic findings and reduced functional class in patients with MS.[7]

Dispersion of the QT interval, which is the difference between the longest and the shortest QT intervals in all electrocardiographic leads, is a reflection of regional variation in ventricular repolarization.[8] It is now well-recognized that myocardial stretch caused by increased intracardiac pressure slows conduction, enhances refractoriness, and can cause changes in electrophysiological properties of the heart.[9] These changes may lead to ventricular action potential prolongation and ventricular repolarization instability.[9] The QT interval on the surface ECG is an indirect measure of cardiac action potential duration.

In this study, we sought to investigate the relationship between QT dispersion, serum NT-proBNP levels and the echocardiographic degree of mitral stenosis in patients with rheumatic MS.

PATIENTS AND METHODS

Forty-six patients (39 women, 7 men; mean age 46.9±9.7 years) with moderate to severe MS, being followed-up in the outpatient clinic, were enrolled in the study between January and August 2009. The severity of MS was based on the mean gradient, systolic pulmonary artery pressure, and valve area according to the ACC/AHA guidelines for the management of patients with valvular heart disease.[1] The clinical status of each patient was graded according to the New York Heart Association classification system. Twenty-one patients had no symptoms and limitations in ordinary physical activity (NYHA class I). Of 25 symptomatic patients, 23 were NYHA class II and two were class III. None of the patients had pulmonary congestion. Medications included angiotensin converting enzyme inhibitor or angiotensin receptor blocker in 13 patients (28.3%), beta-blocker in 12 patients (26.1%), loop diuretic in 19 patients (41.3%), and calcium channel blocker in seven patients (15.2%).

Abbreviations:

ECG	*Electrocardiography*
MS	*Mitral stenosis*
BNP	*Brain natriuretic peptide*
JTc	*Corrected JT*
JTd	*JT dispersion*
LV	*Left ventricle*
NT	*N-terminal*
NYHA	*New York Heart Association*
PAP	*Pulmonary artery pressure*
QTc	*Corrected QT*
QTd	*QT dispersion*
RV	*Right ventricle*

We excluded patients having any the following conditions: mitral regurgitation or other valvular heart diseases more than mild in severity, hypertension, diabetes mellitus, hyperthyroidism, primary right heart disease, left ventricular hypertrophy, significant renal disease, respiratory disease, cardiomyopathy, history of myocardial infarction, angina or heart failure, abnormal serum electrolytes, ventricular preexcitation, atrial fibrillation, atrioventricular conduction block, or use of QT-prolonging drugs.

None of the patients had evidence for ischemic heart disease and all had a negative result on exercise stress testing. All subjects underwent a symptom-limited exercise treadmill test with the use of a standard Bruce protocol. Blood pressure was recorded every two minutes. Exercise was discontinued in the presence of fatigue, chest discomfort, dyspnoea, ST depression of ≥2 mm, significant arrhythmia, on patient request, or after completion of 15 minutes of the protocol (15.6 metabolic equivalents).

The control group consisted of 30 age- and sex-matched healthy subjects (26 women, 4 men; mean age 46.1±7.3 years), with normal physical examination, standard 12-lead ECG, negative stress test, and M-mode and two-dimensional color-Doppler echocardiography not showing any hemodynamically significant pathological flow or heart muscle dysfunction. Every control case was in sinus rhythm, and none were taking medications that are known to modify the QT interval.

Subject details were collected by a cardiologist blinded to the serum NT-proBNP levels, QT dispersion, and echocardiographic findings at the time of enrollment. Heart rate, blood pressure, cardiac rhythm, body mass index (weight in kg/height in m^2), age, gender, and current medications were recorded. The study protocol was approved by the local research ethics committee and all patients gave written informed consent.

Echocardiographic examination

All patients underwent cardiac echocardiography using a standard protocol on a commercially available

system (Vivid i, GE Vingmed Ultrasound, Horten, Norway). All measurements were made according to the guidelines of the American Society of Echocardiography.[10] Rheumatic valvular disease was diagnosed based on echocardiographic detection of typical B-mode features such as thickening of the valve leaflets and chordal apparatus, restricted leaflet separation, diastolic doming of the anterior mitral leaflet, and upward movement of the posterior mitral leaflet in early diastole.[11] The mean pressure gradient across the mitral valve was determined using the simplified Bernoulli equation. Mitral valve area was measured by planimetry and pressure half-time methods.[12,13] Pulmonary artery pressure was estimated measuring the velocity of the tricuspid regurgitant jet. Right atrial pressure was estimated from the resting inferior vena cava diameter with changes during respiration.[14]

Measurement of the QT interval

A standard 12-lead surface ECG was obtained (Hewlett Packard pagewriter, model M 1702-69502, USA) at a speed of 50 mm/sec for the measurement of QRS complex duration and QT, JT, and RR intervals. All measurements were performed manually by two cardiologists blinded to the patients' symptom status, echocardiographic results, and serum NT-proBNP levels. All parameters were measured in all leads and for two consecutive cycles, and the average value was taken for each lead. The QT interval was measured from the onset of the Q wave to the end of the T wave. If the end of the T wave could not be clearly determined, this lead was excluded from analysis. The QRS complex duration was measured from the beginning of QRS to the end. The JT interval was obtained from the formula JT= QT-QRS. Heart rate-corrected QT and JT intervals were derived from the Bazett's formula. QT and JT dispersions were defined as the difference between the longest and shortest QT and JT intervals, respectively.

The interobserver variability for QT dispersion was 9.7±3.6 msec. The intraobserver variability (based on 15 randomly selected ECGs reviewed by the same observer twice) was 7.9±2.9 msec for the QT dispersion.

Measurement of NT-proBNP

Blood samples were collected by venipuncture into tubes containing potassium EDTA immediately after ECG recording and centrifuged within half an hour at -4 °C. Plasma was stored at -80 °C and NT-proBNP was measured using an established radioimmunoassay[15] on an Immulite 1000 Turbo Analyzer (Siemens). The detection range for NT-proBNP was 0.1-125 pg/ml.

Statistical analysis

All statistical analyses were made using the SPSS 10 software package for Windows. All results were expressed as mean±standard deviation for continuous variables and as percentages for categorical data. Analysis of normality was made with the Kolmogorov-Smirnov test. Associations between variables were examined with the Mann-Whitney U-test. Correlations between all variables were calculated with the Pearson correlation coefficient. Comparisons between the groups were made by use of one-way analysis of variance. After univariate analysis, a stepwise multiple linear regression analysis was made to identify the independent predictors of the NT-proBNP level. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and echocardiographic characteristics of the patient and control groups are presented in Table 1. The two groups were similar with respect to age, gender, body mass index, LV ejection fraction, and fractional shortening (p>0.05). All patients and controls had normal LV systolic function. Patients with MS had significantly higher LV, right ventricular, and left atrium dimensions and peak systolic PAP.

Patients with MS had a lower exercise capacity than control subjects (6.9±1.3 min *vs*. 8.1±0.9 min, p<0.005). Minimum and maximum exercise times were 2 and 10 minutes in patients with MS, respectively.

Serum NT-proBNP level was markedly higher in MS patients (284.6±206.5 *vs*. 70.2±9.3 pg/ml, p<0.001). It was also significantly higher in patients with NYHA class II-III compared to class I patients (357.9±300.9 *vs*. 197.3±157.1 pg/ml, p<0.05).

In correlation analysis, plasma NT-proBNP level exhibited significant negative correlations with exercise duration (r=-0.572, p<0.001) and mitral valve area (r=-0.444, p=0.002), and positive correlations with RV diameter (r=0.352, p<0.05), mitral valve gradient (r=0.477, p=0.001), PAP (r=0.655, p<0.001), QTcd (r=0.637, p<0.001), and JTcd (r=0.403, p= 0.005) in MS patients.

Table 2 presents echocardiographic and electrocardiographic features and NT-proBNP levels of patients according to the severity of MS. Left ventricular dimension

Table 1. Clinical, echocardiographic characteristics, NT-proBNP levels and repolarization parameters in patients and controls

	Mitral stenosis (n=46)			Controls (n=30)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			46.9±9.7			46.1±7.3	N S
Sex							N S
Male	7	15.2		4	13.3		
Female	39	84.8		26	86.7		
Body mass index (kg/m^2)			27.6±4.6			26.9±4.8	N S
Smoking	9	19.6		15	50.0		**<0.001**
NYHA class							**<0.001**
I	21	45.7		30	100.0		
II	23	50.0		–			
III	2	4.4		–			
Left ventricular end-diastolic diameter (cm)			4.6±0.4			4.3±0.3	**<0.05**
Left ventricular end-systolic diameter (cm)			3.0±0.5			2.8±0.2	**<0.001**
Ejection fraction (%)			63.2±2.7			64.4±2.1	N.S
Right ventricular end-diastolic diameter (cm)			2.3±0.2			2.0±0.2	**<0.001**
Left atrial diameter (cm)			4.3±0.4			3.0±0.6	**<0.001**
Mitral valve area (cm^2)			1.6±0.2			4.2±0.4	**<0.001**
Range			09-2.0			3.7-4.8	**<0.001**
Mitral valve mean gradient (mmHg)			6.5±3.7			2.7±1.9	**<0.001**
Systolic pulmonary artery pressure (mmHg)			37.8±12.6			22.5±4.5	**<0.001**
NT-proBNP (pg/ml)			284.6±206.5			70.2±9.3	**<0.001**
Median			250			62	**<0.001**
25th/50 percentil			132/423			49/76	**<0.001**
Potassium (mmol/l)			4.1±1.3			4.2±0.9	N S
Calcium (mg/dl)			8.9±0.4			9.1±0.6	N S

NS: Not significant; NYHA: New York Heart Association; NT-proBNP: N-terminal fragment brain natriuretic peptide.

was similar in patients with mild, moderate, and severe MS. Right ventricular and left atrium dimensions, mitral valve gradient, peak PAP, and QTc dispersion increased significantly in proportion to the severity of MS. Although NT-proBNP level increased with severity of MS, this difference was not statistically significant.

Table 2. Echocardiographic and electrocardiographic characteristics and NT-proBNP levels according to the degree of mitral stenosis

	Mild MS (n=13)	Moderate MS (n=23)	Severe MS (n=10)	*p*
Mitral valve area (cm^2)	1.8±0.2	1.4±0.1	0.9±0.1	**<0.01**
Left ventricular end-diastolic diameter (cm)	4.3±0.5	4.6±0.4	4.7±0.4	0.12
Right ventricular end-diastolic diameter (cm)	2.2±0.1	2.4±0.2	2.7±0.3	**<0.05**
Left atrial diameter (cm)	4.1±0.5	4.4±0.3	4.6±0.3	**0.03**
Mitral valve mean gradient (mmHg)	5.1±2.2	6.6±2.9	11.4±4.5	**<0.01**
Systolic pulmonary artery pressure (mmHg)	31.7±9.9	39.9±5.8	48.5±10.2	**<0.05**
NT-proBNP (pg/ml)	193.5±110.6	326.8±161.4	457.0±376.1	0.08
QTc dispersion (msec)	59.7±16.5	62.6±18.8	87.3±35.2	**<0.05**

MS: Mitral stenosis; NT-proBNP: N-terminal fragment brain natriuretic peptide.

Table 3. Repolarization parameters in patients and controls

	Mitral stenosis (n=46)	Controls (n=30)	*p*
QT minimum (msec)	344±26	312±23	**<0.001**
$QT_{corrected}$ minimum (msec)	382±20	363±17	**<0.005**
QT maximum (msec)	405±26	378±23	**<0.001**
$QT_{corrected}$ maximum (msec)	451±31	434±27	**<0.005**
QT mean (msec)	378±25	349±21	**<0.005**
$QT_{corrected}$ mean (msec)	420±22	401±19	**<0.005**
QT dispersion (msec)	61±21	38±15	**<0.001**
JT minimum (msec)	268±31	242±19	**<0.001**
$JT_{corrected}$ minimum (msec)	268±31	247±16	**<0.005**
JT maximum (msec)	325±28	291±25	**<0.005**
$JT_{corrected}$ maximum (msec)	361±27	342±17	**<0.005**
JT mean (msec)	298±27	265±26	**<0.005**
$JT_{corrected}$ mean (msec)	331±20	302±19	**<0.001**
JT dispersion (msec)	57±19	34±17	**<0.001**
QRS duration (msec)	79±9	81.3±8	N S

Table 3 summarizes the differences in repolarization parameters of patients with MS and the control group. Except for similar QRS duration, all repolarization parameters were significantly prolonged in patients with MS.

Correlations of QT and QTc dispersions with basal echocardiographic variables and NT-proBNP levels are shown in Table 4. Both QT and QTc dispersions were positively correlated with RV diameter, PAP, and NT-proBNP level, and negatively correlated with mitral valve area. In addition, QTc was correlated with mean mitral valve gradient. Correlation between QTc and NT-proBNP level is illustrated in Fig. 1.

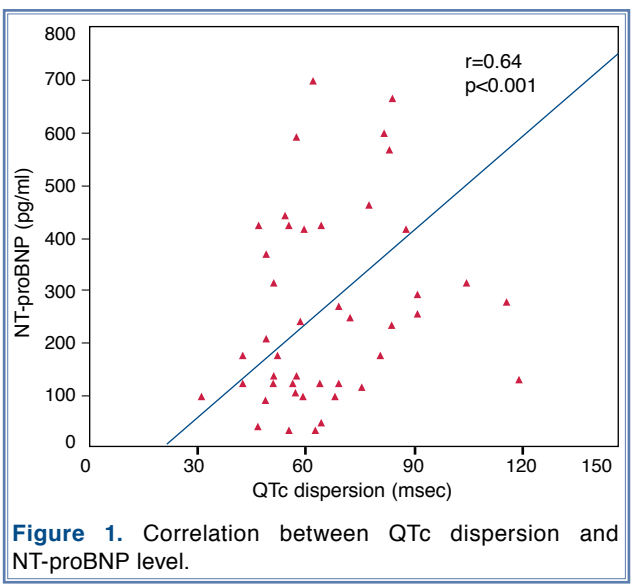

Figure 1. Correlation between QTc dispersion and NT-proBNP level.

Univariate correlation analysis revealed a statistically significant positive correlation between plasma NT-proBNP level and QTc dispersion ($r=0.535$, $p<0.05$) and peak PAP ($r=0.427$, $p<0.05$) for the entire study population. Plasma NT-proBNP level was not in correlation with dimensions of the LV, RV, and left atrium, mitral valve area, exercise duration, age, and sex. In stepwise multiple linear regression model that was adjusted to age, only QTc dispersion ($\beta=0.330$, $p=0.03$) and peak PAP ($\beta=0.379$, $p=0.02$) were associated with plasma NT-proBNP level.

DISCUSSION

This study confirms that QT dispersion on the ECG is significantly increased in patients with MS compared with normal subjects and demonstrates that prolonged QT dispersion is associated with increased NT-proBNP levels and echocardiographic degree of MS. To the best of our knowledge, this is the first study to report QT dispersion and an association between the QT dispersion and serum NT-proBNP levels and echocardiographic parameters in patients with rheumatic MS.

Echocardiography and Doppler examinations are essential for the diagnosis and quantification of the severity of stenosis.[1] Previous studies of MS have re-

Table 4. Correlations of basal QT and QTc dispersions with echocardiographic variables and NT-proBNP levels

	QT dispersion		QTc dispersion	
	r	*p*	r	*p*
Left atrial diameter	0.196	0.192	0.190	0.205
Left ventricular end-diastolic diameter	-0.128	0.397	-0.131	0.387
Right ventricular end-diastolic diameter	0.311	**0.03**	0.387	**0.008**
Mitral valve area	-0.311	**0.03**	-0.327	**0.02**
Mitral valve mean gradient	0.192	0.201	0.301	**0.04**
Systolic pulmonary artery pressure	0.501	**<0.001**	0.598	**<0.001**
NT-proBNP	0.583	**<0.001**	0.637	**<0.001**

NT-proBNP: N-terminal fragment brain natriuretic peptide.

ported an association between the echocardiographic findings and functional class and increase in plasma levels of NT-proBNP.[7] Watanabe et al.[16] suggested plasma BNP levels as a useful clinical marker in determining optimal surgical timing in patients with valvular heart disease. In our study, NT-proBNP level was higher in patients with MS than that of healthy subjects and was correlated with echocardiographic findings. There was a positive correlation with, mitral valve mean gradient, RV dimension, PAP, and negative correlation with mitral valve area. Although the amount of BNP secreted from the atria is very small compared to that from the ventricles in patients with congestive heart failure, BNP is also secreted from the atria.[17]

Previous studies showed that plasma BNP levels were elevated in patients with LV overload in proportion to the degree of LV dysfunction[18] or LV hypertrophy.[19] In the presence of elevated PAP, this represents a serious impediment to RV emptying, with eventual development of RV dysfunction and dilatation. It has been shown that plasma BNP levels are elevated in association with RV pressure overload and increased RV end-diastolic volume and PAP.[20] An experimental study demonstrated that BNP was secreted mainly from the RV in hypoxic pulmonary hypertension.[21] Lang et al.[22] reported that plasma BNP levels were elevated in proportion to the degree of hypoxemia in chronic obstructive pulmonary disease. They speculated that BNP release was triggered by the increased pressure and volume load on the right side of the heart. In our study, plasma NT-proBNP levels were correlated with RV diameter and PAP in patients with MS, suggesting that NT-proBNP secretion is influenced by the severity of increased PAP and RV dysfunction. However, NT-proBNP levels were not correlated with LV variables such as LV end-diastolic diameter and ejection fraction, suggesting that the LV remains unaffected in patient with MS.

The interlead variability in QT interval duration on the standard 12-lead ECG, known as QT dispersion, is a simple, noninvasive method for detecting regional differences in ventricular recovery times of excitability. The QT interval is modified by the preceding R-R interval, autonomic nervous tone,[23] and mechanical load on cardiac muscle.[24] Experimental studies confirmed that QT dispersion is significantly correlated with dispersion of ventricular recovery time, measured directly from the myocardium.[25] It has been proposed that QT and JT dispersions represent a measure of the heterogeneity of ventricular repolarization, and the importance of the latter in the development of ventricular arrhythmias has been shown in previous studies.[26,27]

A majority of studies have shown increased QT dispersion in various cardiac diseases. Compared with healthy controls, increased QT dispersion has been reported in heart failure and LV dysfunction,[28-30] LV hypertrophy of varying origin,[31,32] isolated aortic stenosis,[33] and mitral valve prolapse.[34] However, we found no reports on QT dispersion and its correlation with plasma BNP levels in patients with MS. In our study, QT dispersion was significantly prolonged in MS patients compared to control subjects. It was positively correlated with RV end-diastolic dimension, PAP, serum NT-proBNP level, and negatively correlated with mitral valve area. These results suggest that QT dispersion is influenced by the severity of mitral valve disease. Being a nonin-

vasive and easy measurement, QT dispersion can be broadly and repeatedly assessed in all patients. As an inexpensive method in monitoring disease severity, QT dispersion may be used as a complementary tool in the clinical and echocardiographic evaluation of patients with MS.

These findings may indicate that changes in the RV, as a result of RV overload, are associated with increases in NT-proBNP secretion and these ventricular stretches might affect ventricular repolarization, which is determined by the QT interval. Another mechanism that has been proposed to play a significant role in the prolongation of QT dispersion and increased NT-proBNP secretion in MS patients is related to the presence of autonomic dysfunction, increased adrenergic activity, and papillary muscle traction.[35] Sympathetic stimulation can cause prolonged dispersion through regional shortening or prolongation of the refractory period.[36] Gornick et al.[37] demonstrated papillary muscle traction leading to significant regional repolarization changes in the ventricle in a canine heart model. However, further studies are necessary to understand the exact mechanisms.

Study limitations

Limitations of the present study include the relatively small number of patients and manual measurements of the QT and JT intervals.

In conclusion, echocardiography is the most accurate approach to the diagnosis and evaluation of MS and serum NT-proBNP levels correlate well with echocardiographic findings.[1] QT dispersion is closely related to echocardiographic findings and serum NT-proBNP levels in patients with MS and can be used as a complementary marker of disease severity. The clinical significance of our finding should be assessed in further prospective studies addressing the role of QT dispersion in monitoring disease severity and progression.

Conflict-of-interest issues regarding the authorship or article: None declared

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