

Evaluation of Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with mitral valve stenosis before and after balloon valvuloplasty

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ABSTRACT

Objective: Sympathetic activity increases in patients with mitral stenosis (MS). The association between prolonged Tpeak-Tend (Tp-e) interval and increased sympathetic activity has been demonstrated. This study aimed to evaluate Tp-e interval, Tp-e/QT ratio, and Tp-e/corrected QT interval (QTc) ratio in patients with MS before and after balloon valvuloplasty.

Methods: Thirty patients with severe MS and 30 sex-, body mass index-, and age-matched healthy control subjects were enrolled. The severity of MS was defined following clinical, transthoracic, and transesophageal echocardiographic examinations. All patients underwent successful mitral balloon valvuloplasty. Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were measured using 12-lead electrocardiogram. First, the abovementioned parameters were compared between patients with MS and healthy control subjects. Second, these parameters were compared before and after balloon valvuloplasty in patients with MS.

Results: The mean Tp-e interval was significantly prolonged in patients with MS compared with healthy control subjects (85.02±9.12 ms vs. 75.38±6.04 ms; p<0.001). In addition, Tp-e/QT ratio and Tp-e/QTc ratio were significantly higher in patients with MS than in healthy control subjects (0.217±0.025 vs. 0.196±0.02 and 0.203±0.02 vs. 0.184±0.019; p<0.001). The mean valve area significantly increased after balloon valvuloplasty compared with that before balloon valvuloplasty (1.83±0.32 cm² vs. 1.18±0.15 cm²; p<0.001). Compared with those before balloon valvuloplasty, Tp-e interval (85.02±9.12 ms vs. 78.06±9.2 ms; p<0.001), Tp-e/QT ratio (0.217±0.02 vs. 0.201±0.02; p<0.001), and Tp-e/QTc ratio (0.203±0.02 vs. 0.184±0.02; p<0.001) decreased after balloon valvuloplasty.

Conclusion: We revealed that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio increased in patients with severe MS. Furthermore, balloon valvuloplasty had a favorable effect on parameters associated with myocardial repolarization. (*Anatol J Cardiol* 2017; 18: 353-60)

Keywords: Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, mitral valve stenosis

Introduction

In developing countries, rheumatic mitral stenosis (MS) remains a significant cause of morbidity and mortality (1). In severe MS, afterload and pulmonary artery pressure increase, whereas preload decreases (2-4). In patients with symptomatic severe MS, if the valve structure is appropriate, the currently recommended treatment is percutaneous mitral balloon valvuloplasty (PMBV) (1).

Surface electrocardiogram (ECG) is a cheap, easily accessible, and noninvasive diagnostic tool that is frequently used in cardiology. Careful and sufficient interpretation of ECGs provides a wide range of data for diagnosis and prognosis of many cardiac diseases. In many studies, surface ECG assessment techniques have been evaluated in patients at a high risk for

sudden cardiac arrest. Many parameters that predict the risk for ventricular arrhythmia (VA) in these patients can be assessed using surface ECGs. In addition, several ventricular repolarization (VR) markers can be evaluated using surface ECGs. The QT interval and its corrected QT interval (QTc), QT dispersion (QTd), Tpeak-Tend (Tp-e), and Tp-e/QT ratio are the most recognized predictors in clinical practice. These VR markers are important for evaluating the risk for developing malignant VAs in patients.

Tp-e is the interval between the peak of the T wave and the end of the T wave. The Tp-e interval is an index of total dispersion of repolarization (DOR) (5, 6). A prolonged Tp-e interval may predict VAs and mortality (7-9). The Tp-e/QT ratio is another novel predictor of cardiac arrhythmias.

Sympathetic activity increases in patients with MS (10). Increased sympathetic activity stimulates renin release from

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the kidney (11) and increases the heart rate (10). The effects of PMBV on the autonomic nervous system activity in patients with MS have been evaluated by heart rate variability (HRV) analysis (12). Significant improvement has been shown in HRV parameters after PMBV (12). In the literature, there are very few studies that have evaluated VR parameters in patients with MS. A study showed that QTd was significantly prolonged in patients with MS compared with control subjects (13). To date, no study has evaluated Tp-e interval and Tp-e/QT ratio in MS. This study aimed to investigate Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with MS before and after PMBV.

Methods

Study population

This cross-sectional study aimed to evaluate the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with MS. Forty-five consecutive patients with severe rheumatic MS who underwent successful PMBV between January 2015 and January 2017 were prospectively enrolled. All the patients were symptomatic because of severe rheumatic MS and their mitral valve area (MVA) were ≤ 1.5 cm². Exclusion criteria were having a significant aortic valve disease, coronary heart disease, atrial fibrillation, bundle branch block or evidence of any other intraventricular conduction defect, previous pacemaker implantation, electrolyte abnormalities, ECGs without a clearly analyzable QT segment, diabetes mellitus, thyroid disorders, left ventricular hypertrophy, and taking any chronotropic medication such as beta-blockers. Accordingly, 11 patients with atrial fibrillation, three with extensive negative T waves on ECGs, and one with diabetes mellitus were excluded. Thus, the study population comprised 30 patients with severe rheumatic MS with sinus rhythm (MS group) and 30 sex-, body mass index (BMI)-, and age-matched healthy control subjects (control group).

At the beginning of the study, a detailed cardiovascular and systemic examination was performed for all subjects. Demographic data and anthropometric measurements, including those of height, weight, and BMI, of each individual were recorded. A 12-lead ECG at 50 mm/s (paper speed) and transthoracic echocardiography using Vivid S5 with the GE 3S-RS Probe (GE Healthcare) were performed for each subject. Each subject's blood pressure was measured two times consecutively at 5-min intervals in the sitting position, and the mean value was used for the analysis.

Biochemical parameters, including serum creatinine, fasting blood glucose, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglyceride, were assessed for all subjects. The local Ethics Committee approved the study, and the study was conducted according to the principles of the Declaration of Helsinki. Moreover, informed consent was obtained from each subject.

Electrocardiography

Using a standard ECG system (Nihon Kohden ECG-1250 Cardiofax S), 12-lead ECGs were obtained in the supine position,

with a paper speed of 50 mm/s and a voltage of 10 mm/mV, before and 24 h after PMBV. The QT interval was defined as the time between the beginning of the Q wave and the end of the T wave. Subjects with negative T waves on their ECGs were excluded. To reduce the error margin, all ECGs were scanned and recorded using a personal computer. Measurements were performed using the Pixelmator 3.6 software after $\times 400\%$ magnification. The QTc interval was calculated using Bazett's formula (14). The Tp-e interval was measured from the peak of the T wave to the end of the T wave using the best available T wave in lead V5 (7). T wave in V4 or V6 were used for measurement of Tp-e interval when V5 was not suitable for analysis. The end of the T wave was defined as the intersection of the tangent to the downslope of the T wave and isoelectric line (15). From these measurements, the Tp-e/QT ratio and Tp-e/QTc ratio were calculated. Assessments of ECGs were performed by two independent cardiologists, who were blinded to the group designation. The inter- and intraobserver coefficients of variation were 2.8% and 2.2%, respectively.

Echocardiography

Transthoracic echocardiographic studies were performed using Vivid S5 with the GE 3S-RS Probe (GE Healthcare) before and 24 h after PMBV. The left ventricular internal dimensions, wall thicknesses, and left atrial diameters (LADs) were measured according to the recommendations of the American Society of Echocardiography (16). MVA was measured using continuous wave Doppler and pressure half-time (PHT) and planimetry methods. The diastolic pressure gradient was estimated based on the transmitral velocity flow curve using the simplified Bernoulli equation (17). To evaluate intracardiac thrombus, transesophageal echocardiography was routinely performed for all patients before the procedure.

PMBV

Right and left heart catheterization was performed to measure baseline hemodynamic parameters. PMBV was performed via the transvenous (antegrade) approach through the femoral vein using a transseptal Brockenbrough needle, following the technique described by Inoue et al. (18). Successful PMBV was defined as the final MVA of >1.5 cm² or an increase in MVA by 50% without significant mitral regurgitation ($>2+$) (19).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). Normal distribution of variables was evaluated using Shapiro-Wilk test. Numerical variables with a normal distribution were presented as the mean \pm standard deviation and those with a skewed distribution were presented as the median (Q1-Q3); categorical variables were presented as percentages. For normally distributed numerical variables, an independent sample t-test was performed, and for non-normally distributed numerical variables, Mann-Whitney U test was performed for

Table 1. Baseline characteristics of the study groups.			
Parameters	Control group (n=30)	Mitral stenosis (n=30)	P
Age, years	41.13±5.37	43.47±12.60	0.239*
Body mass index, kg/m ²	22.17 (21.23-24.40)	23.7 (20.16-25.45)	0.519#
Gender, n (%)			
Female	23 (76.7%)	23 (76.7%)	
Male	7 (23.3%)	7 (23.3%)	1.00
Hypertension	0	5 (16.7%)	0.052
Systolic BP	109.13±7.54	109.70±8.15	0.781*
Diastolic BP	72.23±4.80	73.53±4.78	0.298*
Diabetes mellitus	0	0	
MVA, Pressure half time, cm ²	–	1.18±0.15	–
MVA, Planimetry, cm ²	–	1.19±0.14	–
Serum creatinin, mg/dL	0.89±0.11	0.77±0.17	0.002*
LVEF, %	65.44±3.57	66.50±6.70	0.002*
LVEDD, mm	46.0 (43.75-48.0)	45.0 (43.0-48.0)	0.284#
IST, mm	9.0 (9.0-10.0)	9.0 (8.0-10.0)	0.922#
LAD, mm	33.47±3.27	45.21±6.29	<0.001*

P<0.05 is statistically significant; *Independent sample t-test; #Mann-Whitney U test. IST- interventricular septum thickness, LAD- left atrial diameter LVEDD- left ventricular end-diastolic diameter, LVEF- left ventricular ejection fraction, MVA- mitral valve area.

inter-group comparisons. Chi-square test and Fisher's exact chi-square test were used for comparing categorical variables. For repeated measurements, paired sample t-test and Wilcoxon signed rank tests were used to evaluate the significance of the difference in parameters with normal and skewed distribution, respectively. Correlation was performed using Pearson correlation coefficient. Univariate analysis of variance was used to evaluate the association among the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio with several clinical and echocardiographic variables. A post-hoc power analysis was performed using PASS 11 (NCSS, LLC. Kaysville, Utah). A two-tailed p value of <0.05 was considered to be statistically significant.

Results

In this study, we enrolled 30 consecutive patients with severe rheumatic MS [23 females (76.7%); mean age, 43.47±12.60 years] and 30 healthy control subjects [23 females (76.7%); mean age, 41.13±5.37 years]. Baseline characteristics, including age, sex, and BMI, were similar between both the groups. Furthermore, there were no statistically significant differences regarding left ventricular end-diastolic dimension and interventricular septal thickness between the two groups. LADs were significantly higher in the MS group than in the control group (45.21±6.29 vs. 33.47±3.27; p<0.001). Among patients with MS, five (16.7%) had hypertension (HT; p=0.052). However, there were no statistically significant differences between both the groups with respect to mean systolic blood pressure (109.70±8.15 mm Hg vs. 109.13±7.54

mm Hg; p=0.781) and diastolic blood pressure (73.53±4.78 mm Hg vs. 72.23±4.80 mm Hg; p=0.298) values. Of the five patients, three used amlodipine and the other two used indapamide. The blood pressure values of these patients with HT were within normal limits. None of these patients had left ventricular hypertrophy. MVA values of all patients were <1.5 cm². The mean MVA values, measured by PHT and planimetry methods, were 1.18±0.15 cm² and 1.19±0.14 cm², respectively, in patients with MS. There were statistically significant differences with regard to left ventricular ejection fraction and serum creatinine levels, but all values were within normal limits. The baseline characteristics of the study population are given in Table 1.

Subjects belonging to both the groups had sinus rhythm, and the 12-lead resting ECG results of each subject were normal. The mean Tp-e interval was significantly prolonged in the MS group compared with the control group (85.02±9.12 ms vs. 75.38±6.04 ms; p<0.001). The Tp-e/QT (0.217±0.025 vs. 0.196±0.002; p<0.001) and Tp-e/QTc (0.203±0.02 vs. 0.184±0.019; p<0.001) ratios were significantly higher in the MS group than in the control group (Fig. 1). QT (392.93±34.36 ms vs. 384.64±22.27 ms; p=0.272) and QTc (415.73±21.43 ms vs. 410.83±24.12 ms; p=0.409) intervals were similar between the MS and control groups. Tp-e, Tp-e/QT, and Tp-e/QTc parameters of the study groups are given in Table 2.

PMBV was successful in all the patients. In all the patients, MVA was measured using both PHT and planimetry methods before and 24 h after PMBV. MVA, measured using PHT and planimetry methods, significantly increased after PMBV (1.18±0.15

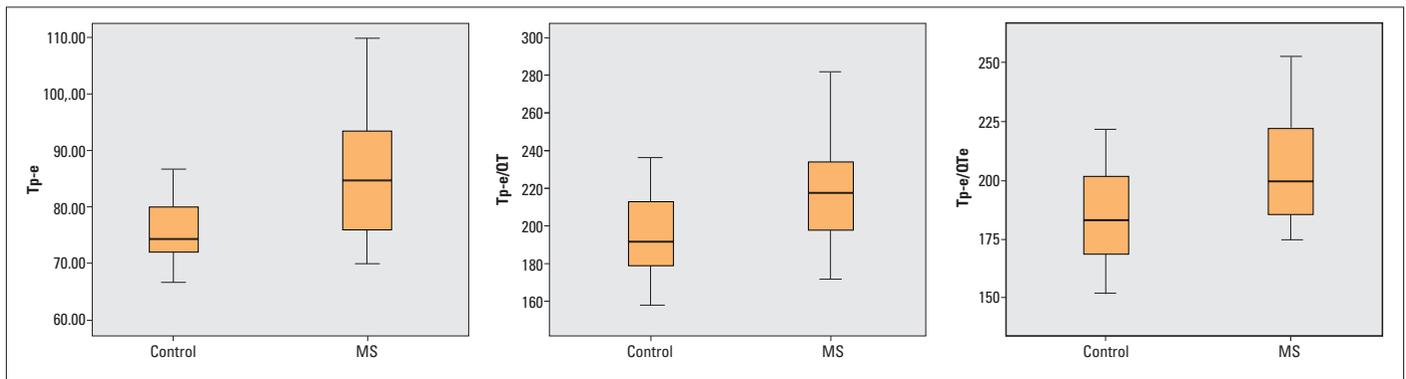


Figure 1. Mean Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in patients with MS than in healthy control subjects. (MS, mitral stenosis; QTc, corrected QT interval; Tp-e, T-peak to T-end)

cm² vs. 1.83±0.32 cm² and 1.19±0.14 cm² vs. 1.87±0.28 cm², respectively; $p<0.001$). Furthermore, compared with before PMBV, the mean transmitral pressure gradient significantly decreased after PMBV (12.32±5.56 mm Hg vs. 4.93±2.01 mm Hg; $p<0.001$).

Compared with those before PMBV, the Tp-e interval (85.02±9.12 ms vs. 78.02±9.2 ms; $p<0.001$), Tp-e/QT ratio (0.217±0.025 vs. 0.201±0.02; $p<0.001$), and Tp-e/QTc ratio (0.203±0.02 vs. 0.184±0.02; $p<0.001$) significantly decreased after PMBV in patients with MS (Fig. 2). The QT and QTc intervals did not show a statistically significant change after PMBV ($p>0.05$). Changes in variables before and after PMBV in patients with MS are shown in Table 3.

Univariate analysis of variance was used to evaluate the association between the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio and BMI, HT, sex, and LAD. Only LAD was associated with the Tp-e interval ($p=0.024$) and the Tp-e/QT ratio ($p=0.035$). There was no statistically significant association between LAD and the Tp-e/QTc ratio ($p>0.05$). Moreover, there were no statistically significant associations between BMI, HT, and sex and the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio ($p>0.05$; Fig. 3).

There were no significant correlations between the increment in MVA and decrement in mean transmitral pressure gradient with respect to the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio after PMBV [MVA vs. Tp-e interval ($r=0.091$, $p=0.688$), MVA vs. Tp-e/QT ratio ($r=0.007$, $p=0.974$), MVA vs. Tp-e/QTc ratio

($r=0.081$, $p=0.720$), mean transmitral pressure gradient vs. Tp-e ($r=0.054$, $p=0.820$), mean transmitral pressure gradient vs. Tp-e/QT ratio ($r=0.021$, $p=0.929$), and mean transmitral pressure gradient vs. Tp-e/QTc ratio ($r=0.079$, $p=0.527$)].

Discussion

In the literature, there are very few studies that have examined the predictors of VA in patients with MS. In this study, we evaluated the VR parameters in patients with severe MS and compared with those in healthy control subjects. The study results show that many parameters associated with VR in patients with MS were impaired. This is the first study in the literature to evaluate the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with MS. Our study results also indicate that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were prolonged in patients with MS compared with those in healthy control subjects. In addition, we demonstrated that treatment may have a favorable effect on VR parameters in patients with MS.

An important measurement of ventricular DOR is the Tp-e interval measured on surface ECGs (20, 21). Moreover, Tp-e reflects both the left ventricle epicardial and endocardial DOR (22). Prolongation of the Tp-e interval indicates greater DOR and therefore increased susceptibility to malignant VA (23, 24). The association between Tp-e and sudden cardiac death has been previously demonstrated (25). Another novel index to predict cardiac arrhythmias is the Tp-e/QT ratio (26). This is the ratio of the Tp-e interval, which is a measure of the transmural dispersion of VR, to the QT interval, which is a measure of the spatial dispersion of VR (26). Therefore, these parameters have been evaluated for many diseases. Tokatlı et al. (27) investigated that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were prolonged in patients with diabetes mellitus. In another study, the association between coronary slow flow and a prolonged Tp-e interval was shown (28). Yayla et al. (29) found that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were increased in patients with severe aortic stenosis.

In the literature, there is no study that evaluates sudden and unexplained deaths owing to repolarization abnormality in rheu-

Table 2. Comparison of the Tp-e, Tp-e/QT and Tp-e/QTc parameters among study groups.

Parameters	Control group (n=30)	Mitral stenosis (n=30)	P
Tp-e, ms	74.28 (71.5-80.0)	84.72 (76.39-93.33)	<0.001 [#]
QT, ms	383.33 (371.43-400.0)	388.33 (368.75-410.0)	0.272 [#]
QTc, ms	410.83±24.12	415.73±21.43	0.409 [*]
Tp-e/QT	0.196±0.02	0.217±0.025	<0.001 [*]
Tp-e/QTc	0.184±0.019	0.203±0.02	<0.001 [*]

QTc-corrected QT interval-Tp-e-peak and the end of the T wave; $P<0.05$ is statistically significant; [#]Independent sample t-test; ^{*}Mann-Whitney U test

	Before valvuloplasty	After valvuloplasty	P
Tp-e, ms	84.72 (76.39-93.33)	74.29 (71.5-86.66)	<0.001 [#]
QT, ms	388.33 (368.75-410.0)	386.74 (360.0-400.0)	0.375 [#]
QTc, ms	415.73±21.43	412.20±24.07	0.319 [*]
Tp-e/QT	0.217±0.025	0.201±0.02	<0.001 [*]
Tp-e/QTc	0.203±0.02	0.184±0.02	<0.001 [*]
MVA, Pressure half time, cm ²	1.18±0.15	1.83±0.32	<0.001 [*]
MVA, Planimetry, cm ²	1.19±0.14	1.87±0.28	<0.001 [*]
TMG, mm Hg	10.2 (7.75-15.0)	4.55 (4.0-5.8)	<0.001 [#]

QTc-corrected QT interval; Tp-e-peak and the end of the T wave. MVA- mitral valve area, TMG- transmitral mean gradient; P<0.05 is statistically significant; [#]Paired sample t-test; ^{*}Wilcoxon Signed Rank test

matic MS and provides us with direct data regarding this issue. Parameters that measure VR in patients with MS have been evaluated in a few studies. In a study by Kılıçkesmez et al. (13), the mean QT interval, QTc interval, and QTd were found to be significantly higher in patients with MS than in healthy control subjects. In the literature, there is no study that evaluates the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with MS. In this study, we found significant increment in the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with MS compared with those in healthy control subjects. These findings may be related with an increased sympathetic activity in patients with MS. Sympathetic activity increases in patients with MS (10). Yagishita et al. (22) evaluated endocardial and epicardial DOR and its effects on Tp-e with sympathetic activation. They also reported that sympathetic nerve stimulation increased Tp-e, and Tp-e was strongly correlated with epicardial and endocardial DOR during sympathetic nerve activation (22). In our study, increased sympathetic activity owing to MS had negative effects on VR.

Another important aspect of our study was the comparison of Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients

with MS before and after PMBV. In severe MS, cardiac output is reduced, possibly leading to an increase in sympathetic nervous activity (10). PMBV is the standard treatment modality for appropriate patients with MS. Following PMBV, sympathetic activity may decrease and DOR may improve. Ashino et al. (10) microneurographically evaluated muscle sympathetic nerve activity in patients with MS and normal sinus rhythm before and after PMBV. They also measured sympathetic nerve activity in healthy control subjects and demonstrated that muscle sympathetic nerve activity increased in patients with MS, and this increment was reduced to normal limits 1 week after valvuloplasty (10). They also found that sympathetic activity remained within normal limits 6 months after valvuloplasty in patients with MS (10). In our study, significant improvement in VR parameters was observed after 24 h of successful PMBV. Therefore, it can be considered that the electrophysiological changes that result from hemodynamic improvement and decrease of sympathetic activity after PMBV can occur much earlier. Another study examined the HRV parameters in patients with MS to evaluate the effect of PMBV on cardiac autonomic functions (12). All patients

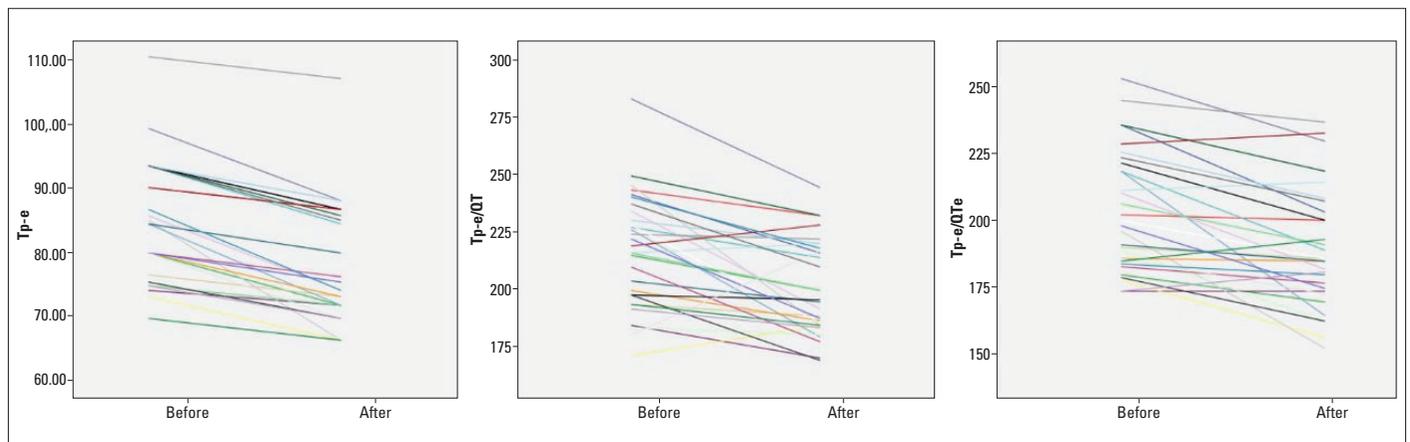


Figure 2. Mean Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly decreased after PMBV in patients with MS (PMBV, percutaneous mitral balloon valvuloplasty; QTc, corrected QT interval; Tp-e, T-peak to T-end)

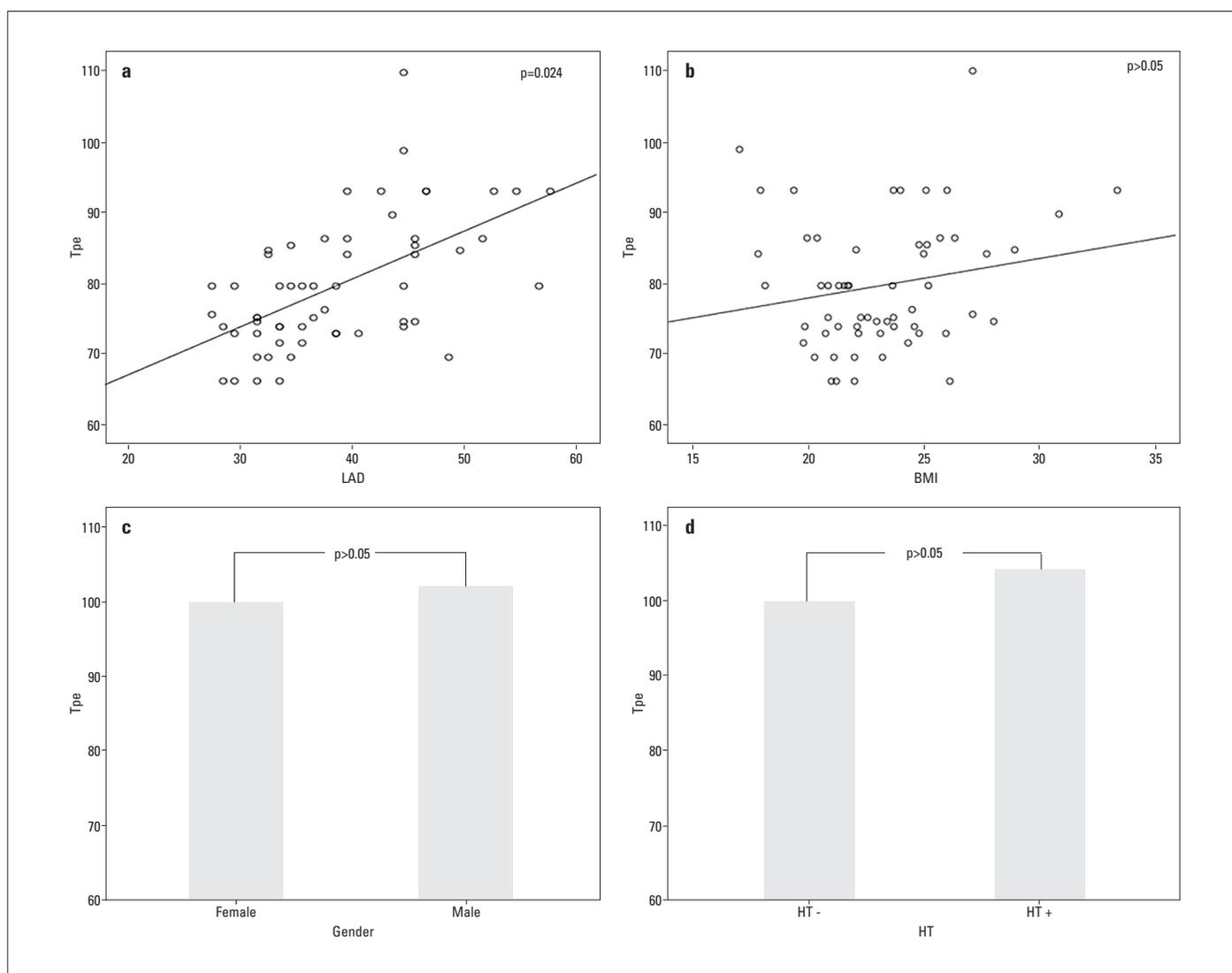


Figure 3. Univariate analysis of variance between Tp-e and (a) LAD, (b) BMI, (c) sex, and (d) HT. Only LAD was associated with the Tp-e interval. (BMI, body mass index; HT, hypertension; LAD, left atrial diameter; Tp-e, T-peak to T-end)

underwent 24-h Holter ambulatory ECG monitoring 1 day before PMBV and 1 day and 1 month after PMBV in this study. They investigated that HRV parameters in patients with MS improved 1 day after PMBV (12). In our study, we revealed that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios in patients with MS were significantly decreased after PMBV. Consequently, it can be conceivable that in patients with MS, the improvement in these parameters after PMBV would be because of the reduction in sympathetic activity.

Results of the univariate analysis of variance revealed that LAD was associated with the Tp-e interval and Tp-e/QT ratio. A previous study showed that LA volumes were higher in elderly athletes with early repolarization patterns in ECGs than in those without early repolarization (30). It has been determined that there is a correlation between some HRV parameters and LAD in patients with MS (12). Thus, LAD appears to be associated with both cardiac autonomic functions and VR. In our study, LAD was

an important parameter that affected VR. In correlation analysis, there were no significant correlations of the increment in MVA and decrement in mean transmitral pressure gradient with the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio after PMBV, possibly because of the successful implementation of PMBV for each patient.

Study limitations

The demonstration of impaired VR with different parameters in patients with MS was the main aspect of our study. However, our study has some limitations. The number of patients in our study is relatively low. However, the group sample sizes of 30 achieve 98% power to detect a difference between repeated measures with a significance level (alpha) of 0.05 using a two-sided paired t-test. In addition, the study did not have long-term follow-ups to assess the clinical significance of VR abnormalities and how long these favorable effects of PMBV persisted

in VR parameters. Further long-term prospective studies are required to reveal the exact pathophysiologic mechanisms and clinical impacts of impaired VR in patients with MS.

Conclusion

We observed that several VR parameters are impaired in patients with severe MS. Our study also shows that PMBV may have a favorable effect on parameters associated with VR. The reduction in sympathetic activity after PMBV may provide improvements in the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. Large randomized studies are necessary to demonstrate the prognostic value of the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with MS.

Authorship contributions: Concept – M.D.; Design – M.D., K.İ.; Supervision – K.U.M.; Materials – K.İ.; Data collection &/or processing – K.İ.; Analysis &/or interpretation – K.U.M.; Literature search – M.D.; Writing – M.D., K.İ.; Critical review – K.U.M.

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