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Original Article CARDIOLOGY

# Ventricular arrhythmias in mitral valve prolapse syndrome and their relationship with electrocardiographic repolarization parameters

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## ABSTRACT

**OBJECTIVE:** The aim of present study is to compare ventricular and supraventricular arrhythmia incidences in subjects with and without mitral valve prolapse (MVP) syndrome and to examine if an association exists between ventricular arrhythmias and repolarization parameters in patients with MVP syndrome.

**METHODS:** This cross-sectional study involved 41 subjects with MVP Syndrome and 41 subjects with palpitation but without MVP (control group). All subjects were subjected to lead-electrocardiogram, transthoracic echocardiography, and 24-h Holter monitoring to identify repolarization abnormalities, structural abnormalities, and supraventricular and ventricular arrhythmias. The QRS width, QTC interval, and Tpeak-Tend intervals were measured for each participant.

**RESULTS:** The number of subjects who had premature ventricular contractions (PVCs), couplets, and non-sustained ventricular tachycardia (NSVTs) was significantly higher in the MVP group compared to the control group. Left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) and left atrial diameter were also significantly higher in the MVP group than the control group. QRS width and Tpeak-Tend interval were also significantly higher in subjects with MVP than the controls. Correlation analysis showed a positive correlation between the severity of mitral regurgitation (MR) and the number of PVCs and couplets, while there was a significant correlation between left atrium (LA) diameter and the number of the PVCs and NSVTs.

**CONCLUSION:** Subjects with MVP experience ventricular arrhythmias more often including PVCs, couplets, and NSVTs compared to subjects without MVP. LVESD, LVEDD, LA diameter, QRS width, and Tpeak-Tend interval were increased in MVP subjects than those without MVP. There is an association between the severity of the MR and the frequency of the PVCs, couplets, or NSVTs.

*Keywords: Mitral valve prolapse; repolarization; ventricular arrhythmias.*

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Mitral valve prolapse (MVP) is characterized by abnormal bulging of the mitral valve leaflets into the left atrium (LA) during ventricular systole. Although MVP was initially considered (and is still often seen) as a benign disorder, several studies have demonstrated that it may lead to the development of endocarditis, sudden cardiac death, cerebrovascular events, and severe mitral regurgitation (MR) [1]. Both clinical and echocardio-

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graphic parameters are useful in identifying patients at high risk for these complications. Basso et al., [2] defined 43 individuals with MVP among 650 young adults (<40 years of age) with a sudden death. A female was the usual phenotype with a click at auscultation, bileaflet involvement of the mitral valve, T-wave abnormalities on inferior leads, and right bundle branch block-type or polymorphic arrhythmias on electrocardiograms. The incidence of sudden cardiac death in patients with MVP, which is twice the sudden death incidence of the healthy population, is 0.4% [3]. Although severe valvular dysfunction due to acute chordal rupture has been reported in some cases, the majority of sudden death events result from ventricular arrhythmias [4, 5]. The previous studies have reported an association between several structural abnormalities and sudden death, such as bileaflet prolapse, left ventricular wall fibrosis at the level of papillary muscles, papillary muscle fibrosis, and severe MR [6]. However, the relationship between repolarization parameters of the surface electrocardiogram and the frequency of ventricular and supraventricular arrhythmias is less clear.

One research showed wider dispersion of refractoriness among 32 patients with MVP and noted ventricular arrhythmias, whereas the QT interval was not extended [7]. However, one more research reported that among a group of 24 patients with an implantable cardioverter-defibrillator who had idiopathic out-of-hospital cardiac arrest, ten patients were identified with bileaflet MVP [8]. Patients with MVP in this group also had notably more potential to experience T-wave abnormalities and ventricular ectopy in comparison to those with normal mitral valves.

The primary aim of this study is to compare the incidence of ventricular and supraventricular arrhythmias in subjects with and without MVP and secondary aim is to investigate whether there was an association between ventricular arrhythmias and repolarization parameters in patients with MVP.

## MATERIALS AND METHODS

This cross-sectional study was conducted on subjects with MVP syndrome between April 2019 and July 2019. The study was approved by the Istanbul University Faculty of Medicine Ethics Committee (date: March 2019, decision no: 399). Written informed consent was obtained from all subjects. The study was approved by the Institutional Review Board and was conducted in accordance with the Helsinki Declaration (2013). Exclusion criteria were as follows: The presence of coronary artery disease, uncontrolled hypertension, dilated cardiomyopathy, left ventricular systolic dysfunction (ejection fraction <50%), heart failure with preserved EF, anemia, hyperthyroidism, hypothyroidism, active infection, and the presence of U wave on surface electrocardiogram. A group of subjects with palpitation, in whom the mitral valve was anatomically and functionally normal, was selected as the control group.

**Highlight key points**

- Subjects with MVP syndrome have been observed to have a higher frequency of ventricular arrhythmias as well as having enlarged left ventricular and left atrial diameter and more severe MR regarding the subject without MVP.
- QRS width and Tpeak-Tend interval were higher in subjects with MVP than the ones without MVP.
- The number of the subjects having PVCs, couplets, and NSVTs was found to be higher in the MVP group.

Demographic data and anthropometric measurements, including weight, height, and body mass index (BMI) of the study subjects were recorded on enrollment. All study subjects underwent standardized transthoracic echocardiography (Vivid 7, GE Healthcare, Horton, Norway) and 12-lead electrocardiography. MVP was defined as the displacement of the margin of one or more mitral valve leaflets beyond the annular plane (>2 mm) during systole, determined from the parasternal long-axis view [9]. Simpson's method in a two-dimensional echocardiographic apical four-chamber view was used to assess left ventricular ejection fraction as recommended by the American Society of Echocardiography guidelines [10]. The parasternal long-axis view was used to measure left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD), and LA diameter measurements. Effective regurgitant orifice area (EROA), regurgitant volume (RVOL), and regurgitant fraction (RF) were recorded for the evaluation of MR severity. Definitions of severity were as follows: EROA <0.2 $cm^2$, RVOL, and <30 mL RF <30% were defined as grade 1 MR; EROA 0.2–0.29 $cm^2$, RVOL 30–44 mL, and RF 30–39% were defined as grade 2 MR; EROA 0.30–0.39 $cm^2$, RVOL 45–59 mL, and RF 40–49% were defined as grade 3 MR; and finally EROA ≥0.4 $cm^2$ RVOL ≥60 mL, and RF ≥50% were defined as grade 4 MR [11]. All images were archived and evaluated by two independent cardiologists. Accordingly, heart rate, QRS width, QT distances, and Tpeak-Tend intervals were cal-

culated manually. QT intervals were measured from the earliest QRS deflection to the end of the T-wave, determined by the return to isoelectric baseline. During normal sinus rhythm, QT and RR intervals were averaged over three consecutive complexes. In other rhythms, QT and RR intervals were averaged over all complexes on 6-s rhythm strips or lead II of the 12-lead ECGs. QT intervals were only measured in ECGs which showed clearly discernable endings of T waves. QT intervals were corrected for heart rate using Bazett's correction (QTC), per standard clinical practice. The Tangent method was used for Tpeak-end interval measurement from leads with a T wave amplitude of >1.5 mm, and Bazett formula was used for corrected Tpeak-end interval measurement. For this purpose, the time from the peak of the T-wave to the intersection between the tangent at the steepest point of the T-wave and the isoelectric line was measured digitally in milliseconds with the software Cardio Calipers Version 3.3 (Iconico, Inc., New York, NY, USA) [12].

All subjects underwent 24-h rhythm Holter monitoring with a commercially available Holter monitoring system (DMS300-3A, DM Systems (Beijing) Co., Ltd.) for the detection of any ventricular or supraventricular arrhythmias. Premature ventricular contractions (PVC) and supraventricular premature beats, sustained and non-sustained ventricular tachycardia (NSVT), and supraventricular tachycardia (SVT) were evaluated. NSVT was defined as 3–30 consecutive PVCs with a heart rate of >100 bpm. >30 consecutive PVCs with a heart rate of >100 bpm were defined as sustained ventricular tachycardia.

### Primary Outcome

Subjects with and without MVP were compared with respect to surface electrocardiogram, transthoracic echocardiography, and Holter monitoring parameters. The difference between MVP subjects and the controls with regard to these parameters was the primary outcome measure of this study. The association between the ventricular arrhythmias on Holter monitoring and selected echocardiographic and electrocardiography parameters was the secondary outcome measure.

### Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to test data distribution. Homogeneity of variances was assessed with the Levene test. Data are given as mean±standard deviation for continuous variables, and as frequency (percentage) for categorical variables. Continuous variables were compared using the independent samples t-test, and categorical variables were compared using Pearson Chi-square test. Depending on normality of distribution of selected variables, the Spearman or Pearson correlation analyses were performed to investigate the association between the number of PVCs, supraventricular premature contractions, couplets, NSVT, and several other echocardiographic and electrocardiographic measurements. p=0.05 or lower were defined to be statistically significant.

**Table 1.** Demographic data of the study groups

| | MVP syndrome n=41 | | Control group n=41 | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age (years) | 42.5±12.8 | | 35.7±14.9 | | **0.30** |
| Gender (male) | 21 | 51.2 | 15 | 36.6 | 0.266 |
| BMI (kg/m$^2$) | 24.67±3.81 | | 24.04±3.88 | | 0.465 |
| Hypertension | 9 | 22.0 | 5 | 12.2 | 0.379 |
| Diabetes mellitus | 0 | 0 | 2 | 4.9 | 0.494 |
| The use of beta-blockers | 19 | 46.3 | 3 | 7.3 | **<0.001** |

Data are presented as mean±standard deviation for continuous variables and as frequency for categorical variables. BMI: Body mass index; MVP: Mitral valve prolapse.

## RESULTS

A total of 41 subjects with MVP (mean age 42.5±12.8 years, 51.2% male) and 41 controls (mean age 35.7±14.9 years, 36.6% male) were enrolled in this study. The demographic features of the subjects with MVP and the controls are presented in Table 1. There were no significant differences between the groups with respect to gender, BMI, presence of diabetes, and hypertension. Subjects with MVP were more frequently on beta-blocker treatment compared to controls (46.3% vs. 7.3%, p<0.001).

The results of transthoracic echocardiography measurements are presented in Table 2. Both LVESD (32.2±3.5 mm vs. 28.4±3.5, p<0.001) and LVEDD (48.8±5.1 mm vs. 44.2±4.6, p<0.001) were significantly higher in subjects with MVP compared to the controls. LA diameter was also significantly higher in the MVP

**Table 2.** Echocardiographic findings

| | MVP syndrome n=41 | Control group n=41 | p |
|---|---|---|---|
| EF (%) | 63.8±4.7 | 64.4±3.7 | 0.522 |
| LVEDD (mm) | 48.8±5.1 | 44.2±4.6 | **<0.001** |
| LVESD (mm) | 32.2±3.5 | 28.4±3.5 | **<0.001** |
| LA diameter (mm) | 37.8±6.7 | 32.8±3.5 | **<0.001** |
| Mitral regurgitation, n (%) | | | **<0.001** |
| None | 0 (0) | 27 (65.8) | |
| Minimal | 8 (19.5) | 14 (34.2) | |
| 1 (+) | 9 (21.9) | 0 (0) | |
| 2 (+) | 11 (26.8) | 0 (0) | |
| 3 (+) | 7 (17.1) | 0 (0) | |
| 4 (+) | 6 (14.6) | 0 (0) | |

LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; EF: Ejection fraction; MVP: Mitral valve prolapse; LA: Left atrium.

**Table 3.** 12 lead electrocardiogram findings

| | MVP syndrome n=41 | Control group n=41 | p |
|---|---|---|---|
| Heart rate (beats/min) | 75.4±13.3 | 77.9±9.6 | 0.337 |
| QRS width (msn) | 97.8±12.1 | 89.3±9.5 | **0.001** |
| QTC distance (msn) | 418.5±28.4 | 408.2±18.5 | 0.056 |
| T peak-tend interval (msn) | 80.0±16.3 | 69.8±8.7 | **0.001** |

MVP: Mitral valve prolapse.

group than the controls (37.8±6.7 mm vs. 32.8±3.5 mm, p<0.001). There were no subjects with an MR ≥1° in the control group. However, 21.9% of subjects with MVP had 1 (+) MR, 26.8% had 2 (+) MR, 17.1% had 3 (+) MR, and 14.6% had 4 (+) MR.

Twelve-lead surface electrocardiography parameters are presented in Table 3. QRS width (97.8±12.1 m vs. 89.3±9.5 m, p=0.001) and Tpeak-Tend interval (80. 0±16.3 m vs. 69.8±8.7 m, p=0.001) were significantly higher in subjects with MVP than controls. QTC was similar in the two groups.

24 h Holter monitoring data revealed that the number of the subjects experiencing PVCs, couplets, and NSVTs was significantly higher in the MVP group compared to the control group (Table 4). Correlation analysis showed that the severity of MR (r=0.268, p=0.015) and LA diameter (0.245, p=0.026) were significantly correlated with the number of the PVCs (Table 5). Furthermore, MR severity was significantly correlated with the number of couplets (r=0.255, p=0.021) and LA diameter was correlated with the number of NSVTs (r=0.267, p=0.015).

## DISCUSSION

The present study shows that subjects with MVP syndrome not only have a higher frequency of ventricular arrhythmias but also have larger left ventricular and left atrial diameter and more severe MR compared to subjects without MVP. QRS width and Tpeak-Tend interval were also higher in subjects with MVP than those without MVP. Moreover, the number of the subjects experiencing PVCs, couplets, and NSVTs was significantly higher in the MVP group compared to the control group. The number of PVCs was associated with the severity of MR and the diameter of the LA. On the other hand, the number of couplets was correlated with the severity of MR and the number of the NSVTs was correlated with the diameter of the LA.

MVP is a complex disorder presenting mainly with valve pathology, which ranges within a wide spectrum; from fibroelastic deficiency and localized prolapse of an isolated scallop to myxomatous Barlow's disease where the valve leaflets are thickened, chordee are elongated and multiple scallops are prolapsed [13]. Non-specific symptoms such as chest pain, dyspnea, palpitations, syncope, and anxiety are frequently encountered in subjects with MVP [14]. Although the mechanism(s) leading to the development of symptoms are yet to be elucidated, autonomic nervous system dysfunction has been suggested as the cause of the symptoms in several reports [15–17]. The studies conducted by Boudoulas et al. [15, 16] have shown increased adrenergic tonus and a hypersensitive response to adrenergic stimulation in subjects with symptomatic MVP.

MVP has been reported to be associated with sudden cardiac death as a result of ventricular arrhythmias. In a cohort of 24 patients with out-of-hospital sudden death (in which of none of the subjects had myocardial ischemia, cardiomyopathy, or evidence of channelopathy) is was found that 42% of the subjects had bileaflet MVP [8]. In that study, patients with MVP were more likely to

**Table 4.** Comparison of the frequency of the ventricular and supraventricular arrhythmias on Holter monitoring between the study groups

| | MVP syndrome n=41 (%) | | Control group n=41 (%) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Ventricular premature beat | 28 | 68.3 | 8 | 22.2 | <**0.001** |
| Couplet | 12 | 29.3 | 0 | 0 | <**0.001** |
| Non-sustained ventricular tachycardia | 7 | 17.1 | 0 | 0 | **0.012** |
| Supraventricular premature beat | 31 | 75.6 | 22 | 53.7 | 0.064 |
| AF rhythm | 9 | 22 | 3 | 7.3 | 0.116 |

AF: Atrial fibrillation; MVP: Mitral valve prolapse.

**Table 5.** Correlation between the number of PVCs, couplets, and NSVTs and selected echocardiography and electrocardiography parameters

| | PVC | | Couplet | | NSVT | |
|---|---|---|---|---|---|---|
| | r | p | r | p | r | p |
| Severity of MR | 0.268 | **0.015** | 0.255 | **0.021** | 0.202 | 0.069 |
| LA diameter | 0.245 | **0.026** | 0.101 | 0.182 | 0.267 | **0.015** |
| LVEDD | 0.060 | 0.592 | 0.011 | 0.920 | 0.006 | 0.988 |
| LVESD | 0.052 | 0.644 | 0.011 | 0.922 | 0.061 | 0.588 |
| $T_{peak}$-$T_{end}$ interval | 0.074 | 0.506 | 0.069 | 0.535 | 0.158 | 0.157 |
| QRS width | 0.147 | 0.162 | 0.123 | 0.273 | 0.150 | 0.180 |
| $QT_C$ interval | 0.046 | 0.679 | 0.053 | 0.633 | 0.075 | 0.503 |

LA: Left atrium; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; MR: Mitral regurgitation; PVC: Premature ventricular contractions; NSVT: Non-sustained ventricular tachycardia.

have T-wave abnormalities and ventricular ectopic beats than those with normal mitral valves. An increased burden of PVCs, bigeminy, and NSVT has been noted in subjects who suffered from out of hospital cardiac arrest with MVP compared to those without MVP [8]. Several studies using electrophysiology mapping have indicated that PVCs in subjects with MVP predominately originate from the left ventricular papillary muscles and fascicles [18]. Severe MR and worsening functional class were also identified as predictors of increased risk for sudden death in subjects with MVP [19]. The Framingham Heart Study, which compared 84 patients with MVP to 3403 control subjects without MVP based on existing two-dimensional echocardiographic criteria, has shown that MVP without significant MR was not associated with atrial or ventricular arrhythmia risk [20]. Yet, one other study showed a completely different situation for patients with isolated MVP without MR. Lethal ventricular arrhythmias in patients with MVP have been noted, but their prevalence in registries has differed among series, from <1% to 7% of all sudden cardiac deaths [2, 8]. A probable origin of malignant arrhythmia was defined using pathology and magnetic resonance imaging. Researchers identified patchy fibrosis interspersed within surviving hypertrophic cardiomyocytes at the level of the papillary muscles and adjacent free wall and at the inferobasal basal wall (in keeping with the morphology of the ventricular arrhythmia). The potential pathophysiology of malignant arrhythmia in MVP [21] decreased later in the same group. A strong association for the mitral annular disjunction systolic curling of the posterior mitral valve leaflet, and ultimately, myocardial fibrosis was reported. Mechanical stretch caused by myocardial fibrosis served as a substrate for malignant arrhythmias.

Despite the evidence regarding the role of MR in predicting ventricular arrhythmias and sudden cardiac death in subjects with MVP, the impact of the left ventricular and left atrial diameter and the presence of baseline electrocardiographic abnormalities on ventricular and supraventricular arrhythmias are unclear. Consistent with the majority of the previous data, our results indicate that the number of PVCs and couplets increase in subjects with MVP in accordance with the severity of the MR. Furthermore, our findings indicate that left atrial diameter may also be associated with the number of PVCs, and also, NSVTs recorded through Holter monitoring. Nevertheless, we failed to demonstrate any relationship between LVESD or LVEDD with the frequency of PVCs, couplets, or NSVTs. One possible explanation for the lack of an association between LV diameter and the ventricular arrhythmias might be that both LVESD and LVEDD were within the physiological range in our subjects with MVP. We also found that the number of subjects with supraventricular premature beats was similar in subjects with and without MVP; however, there was a trend toward a higher frequency of supraventricular premature beats in the MVP group. Higher left atrial diameter might be associated with this trend in subjects with MVP.

Our results have shown that subjects with MVP have a wider QRS complex and a longer Tpeak-Tend interval than those without MVP. Nonetheless, there was no significant correlation between the frequency of ventricular and supraventricular arrhythmias and QRS width of Tpeak-Tend interval. A possible explanation for this might be that, despite the statistically significant difference in QRS width and Tpeak-Tend interval between subjects with and without MVP, both measurements were within physiological range even in subjects with MVP. On the other hand, beta-blocker treatment was more frequent in subjects with MVP compared to the controls. Beta-blocker use could have reduced the prevalence of ventricular arrhythmias in the MVP group.

The prevalence of atrial fibrillation (AF) is also known to be increased in subjects with MVP [22, 23]. Increased left atrial diameter, a high degree of MR, and age are among the risk factors for AF development. In this study, five patients had paroxysmal AF and four patients had persistent AF in the MVP group, while three patients had paroxysmal AF in the control group. There were more AF patients in the MVP group than controls; however, the difference between the groups was not statistically significant. The limited number of patients and the higher frequency of beta-blocker use in the MVP group may have contributed to the lack of statistical significance.

These findings suggest that subjects with MVP more frequently experience ventricular arrhythmias than those without MVP; and that, echocardiographic parameters, including the LA diameter and assessment of the severity of the MR, may provide important clues concerning the presence of ventricular arrhythmias in these subjects. However, it appears that QRS width, QTC interval, and Tpeak-Tend interval are less useful in the evaluation of the ventricular arrhythmias in subjects with MVP.

## Study Limitations

There are some limitations that need to be mentioned. The sample size is relatively small. Another limitation of this study – although minor – is that 24-h Holter monitoring may not always be sufficient to identify the frequency of ventricular and supraventricular arrhythmias. Prolonged cardiac monitoring may provide additional data concerning the prevalence of ventricular arrhythmias in subjects with MVP.

## Conclusion

Subjects with MVP more frequently have ventricular arrhythmias, including PVCs, couplets, and NSVTs compared to subjects without MVP. LVESD, LVEDD, LA diameter, QRS width, and Tpeak-Tend interval are increased in MVP subjects compared to those without MVP. The severity of the MR and LA diameter are associated with the frequency of PVCs, couplets, or NSVTs. Consequently, our findings suggest that echocardiographic assessment, including the evaluation of MR severity and the measurement of the LA diameter, may provide important clues concerning the presence or risk of ventricular arrhythmias.

**Ethics Committee Approval:** The Istanbul University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 22.03.2019, number: 399).

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Authorship Contributions:** Concept – BE, AE; Design – BE, EC; Supervision – BE, AE; Fundings – BE; Materials – RD, HO; Data collection and/or processing – EC, HO; Analysis and/or interpretation – RD, BE, AE; Literature review – HO, RD; Writing – BE, EC; Critical review – AE, BE, EC.

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