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Comparison of frontal QRS-T angle in mitral valve prolapse without arrhythmic phenotype with healthy individuals

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Abstract

Mitral valve prolapse (MVP) is generally known as a benign disease with a good prognosis. Patients with the arrhythmic MVP (AMVP) phenotype have an increased risk of ventricular arrhythmia and sudden cardiac death. The frontal QRS-T angle is a new indicator, related to malign arrhythmias and cardiac death risk in various diseases. This study aimed to compare the frontal QRS-T angle of patients with MVP without the AMVP phenotype with that of healthy subjects. Fifty MVP patients without the AMVP phenotype, identified through a retrospective review of medical records, constituted the MVP group, and 50 healthy individuals constituted the control group. Frontal QRS-T angle and other electrocardiography and echocardiography parameters were compared between the groups. The groups were similar in terms of demographic characteristics and laboratory results. Frontal QRS-T angle was similar in both groups (30±37° vs 28±24°, p=0.56). There was also no difference in other electrocardiographic and echocardiographic parameters between the groups. In MVP patients without the AMVP phenotype, the frontal QRS-T angle does not change compared to healthy individuals. The risk of ventricular arrhythmia and sudden cardiac death in this patient population appears to be similar to that in healthy individuals.

Keywords: Electrocardiography, cardiac arrhythmias, arrhythmic mitral valve prolapse, frontal QRS-T angle, myocardial repolarization

Introduction

Mitral valve prolapse (MVP) represents a prevalent condition affecting the mitral valve, constituting the most frequent cardiac valve anomaly and serving as the primary reason for mitral regurgitation (MR) [1]. Its prevalence in the general population is 0.6-3% [1]. The diagnosis of MVP is often made by suspecting a mid-to-late systolic click heard on cardiac auscultation and a subsequent mid-to-late systolic murmur and confirming it with echocardiography. Sometimes it is detected incidentally during echocardiography examinations performed for other indications. Although most patients with MVP are asymptomatic, symptomatic patients may complain of palpitations, chest pain, dizziness, dyspnea, and exercise intolerance. Significant MR or cardiac arrhythmias account for many of the symptoms. MVP patients generally do not have poor outcomes, and patients who do not have severe degenerative MR or left ventricular systolic dysfunction can expect a normal lifespan [2]. Nevertheless, a minority of patients with MVP are at heightened risk for ventricular arrhythmias (VA) and sudden cardiac death (SCD) [3]. Research on SCD victims and patients with significant VA has shed light on various arrhythmic risk factors and potential substrates for VA in individuals with MVP [4-6]. Patients with MVP who are at high risk for arrhythmias are classified as having arrhythmic MVP (AMVP) syndrome (also called malignant MVP), within which two distinct phenotypes have been recognized [7]. The first of the AMVP phenotypes is severe degenerative MR. Patients with this phenotype exhibit a heightened risk of VA and SCD when compared to normal individuals, irrespective of the morphology of the mitral valve [8]. The second phenotype of AMVP is characterized by severe myxomatous MVP, irrespective of the severity of MR. Significant myxomatous degeneration of leaflets, diffuse leaflet redundancy, increased length and thickness of the leaflets, along with mitral annular disjunction (MAD) and bicuspid leaflet involvement are the most common characteristics of this AMVP

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phenotype [9]. MAD appears to be a significant element of this AMVP phenotype and carries a considerable negative prognostic impact. Electrocardiographic (ECG) features of this phenotype include prolongation of corrected QT interval (QTc), ST segment depressions, negative/biphasic T waves in inferior leads, and premature ventricular complexes (PVC). The occurrence of arrhythmias is not influenced by the severity of MR, gender, left ventricular systolic function, or involvement of the bicuspid valve leaflets [9]. Patients exhibiting the AMVP phenotype require additional assessment for the risk of VA. In instances where patients show refractoriness or have contraindications to antiarrhythmic drugs, catheter ablation may lower the risk of VA and SCD [7]. Furthermore, it is advised that MVP patients who are recovering from SCD or have persistent ventricular tachycardia should consider implanting a cardioverter-defibrillator [7].

Assessing an individual's risk of SCD due to life-threatening arrhythmias continues to be a complex challenge. For this purpose, studies have been conducted on many methods, and research on new methods continues. The frontal QRS-T (fQRS-T) angle represents a new ECG parameter that can be readily identified through standard ECG [10]. It represents the heterogeneity of myocardial electrical activity, and its prognostic significance has been established across diverse populations [10]. The literature lacks studies investigating the fQRS-T angle in patients MVP. The present study aimed to compare the fQRS-T angle of MVP patients without AMVP phenotype and healthy controls.

Material and Methods

Study Design and Data Collection

The study was designed as a single-center, observational, case-control study. The study population consisted of two groups: MVP and the control group. The MVP group consisted of patients with MVP who did not exhibit an arrhythmic phenotype. The patients were identified through a retrospective review of individuals who had applied to the cardiology outpatient clinic from September 2023 to September 2024 and were diagnosed with MVP. Following the screening, 102 patients with MVP were identified, and out of these, 50 met the study's inclusion criteria and were thus selected for the MVP group. The control group included 50 healthy individuals who applied to the cardiology outpatient clinic for a medical report and were given a healthy report. Demographic and clinical characteristics, laboratory test results, ECG, transthoracic echocardiography, and Holter monitoring data of the MVP patients and healthy individuals were gathered from individual patient records and the hospital's electronic database. Patients with any cardiovascular and cerebrovascular disease, diabetes mellitus, renal failure, serious valvular disease other than MVP, electrolyte abnormalities, history of presyncope or syncope, family history of SCD, and any other condition or medication use known to alter cardiac conduction/repolarization were excluded. Individuals with ECG artifacts, non-sinus rhythm, bundle-branch block, QTc prolongation, ST segment depressions, and negative/biphasic T waves in inferior leads were also excluded.

MVP diagnostic criterion was defined as prolapse of one or both mitral valve leaflets 2 mm or more in systole above the annular plane of the valve on echocardiography [1]. The AMVP phenotype was defined as follows; QTc prolongation, ST segment depressions, negative/biphasic T waves in inferior leads, myxomatous disease with marked leaflet redundancy, MAD, bicuspid leaflet involvement, frequent and/or complex VA on Holter monitoring. In the study, MAD is defined by the detachment of the mitral annulus supporting the posterior mitral leaflet, from the ventricular myocardium during systole, observed in the parasternal long-axis view on echocardiography [7]. If >440 milliseconds in men and >460 milliseconds in women, QTc was considered prolonged. Frequent and/or complex VA was defined as the presence of PVC comprising ≥5% of all heartbeats or the presence of nonsustained/sustained ventricular tachycardia and ventricular fibrillation.

The fQRS-T angle is determined by calculating the angle difference between the frontal QRS axis and the T wave axis, as reported automatically by the electrocardiography machine [11]. If the result was >180°, the value was subtracted from 360. ECG readings were assessed and validated by two cardiologists who were unaware of the participants' information.

Ethics Committee Approval

The Ethics Committee for Non-interventional Clinical Research of Kütahya Health Sciences University approved the study (Date: 30.09.2024, Decision No: 2024/11-15). The research was conducted adhering to the ethical standards and the principles outlined in the Declaration of Helsinki.

Statistical Analysis

The SPSS program version 23.0 was used for statistical analysis. Numerical variables are expressed as mean±standard deviation. A comparison of two independent groups was performed using Student's t-test or Mann-Whitney U test, depending on the distribution. Categorical variables were compared using the Pearson chi-squared test. In all analyses, a p-value of less than 0.05 was deemed to indicate statistical significance.

Results

Table 1 displays a comparison between the demographic and clinical characteristics of the patient group and the control group. The groups were similar in terms of age, gender distribution, smoking, hemoglobin, plasma high-sensitivity C-reactive protein, fasting glucose and creatinine levels, and estimated glomerular filtration rate. Table 2 displays a comparison of the ECG and echocardiography parameters across two groups. The fQRS-T angle was similar in both groups (p=0.56). No differences were observed between the groups in terms of heart rate, PR interval, QRS duration, QTc interval, P wave, QRS and T wave axes, left atrium diameter, left ventricular end-diastolic and end-systolic diameters, and left ventricular ejection fraction.

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Table 1. Comparison of demographic characteristics and laboratory parameters of MVP patients and controls

Variables	MVP (n=50)	Control (n=50)	p-value
Age, years	34.3±10.5	34.8±8.4	0.85
Female, n (%)	32 (64)	28 (56)	0.75
Current smoking, n (%)	12 (24)	16 (32)	0.65
Hemoglobin, g/dL	13.3±2.1	13.4±1.8	0.75
hs-CRP, mg/L	2.1±1.1	1.9±0.9	0.54
Fasting plasma glucose, mg/dL	92±6	88±5	0.49
Creatinine, mg/dL	1.13±0.12	1.08±0.10	0.36
eGFR, mL/min/1.73 m²	96±8	94±9	0.82

MVP: mitral valve prolapse, hs-CRP: high-sensitivity C-reactive protein, eGFR: estimated glomerular filtration rate

Table 2. Comparison of the electrocardiography and echocardiography parameters between groups

Variables	MVP (n=50)	Control (n=50)	p-value
Electrocardiography parameters			
Heart rate, bpm	77±12	75±11	0.62
PR interval, ms	149±21	146±13	0.25
QRS duration, ms	89±11	90±11	0.87
QT interval, ms	373±19	371±23	0.58
Corrected QT interval, ms	407±23	403±20	0.58
P axis, °	48±25	46±21	0.59
QRS axis, °	46±26	54±32	0.22
T axis, °	46±28	40±15	0.54
Frontal QRS-T angle, °	30±37	28±24	0.56
Echocardiography parameters			
LVEDD, mm	48±12	46±9	0.48
LVESD, mm	31±8	28±6	0.33
LVEF, %	65±5	63±4	0.49
LA diameter, mm	38±4	32±5	0.25

MVP: mitral valve prolapse, LA: left atrium, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic diameter, MVP: mitral valve prolapse

Discussion

In cases of MVP, symptoms are typically absent or mild; however, when they do occur, they are generally nonspecific. Although it is mostly benign, MVP can result in complications such as MR, left ventricular dysfunction, and various arrhythmias, including atrial fibrillation and VA, which can cause SCD [1]. The lifetime serious complication rate is 30%. Complex PVC has been reported in 50% of adults with MVP. Individuals with MVP have a survival rate similar to the overall population, with the prognosis largely hinging on the severity of MR [12]. Patients with MVP may experience a range of atrial or VA, although the likelihood of these arrhythmias occurring is generally low for most individuals [9]. Severe VA observed in MVP cause an increased risk of cardiovascular mortality [9]. Patients with MVP and MR exhibit a higher incidence of VA compared to those with MVP alone and clinically significant MR is an independent predictor of VA [13,14]. The absence of MR does not reduce the risk of arrhythmia to the level of the general population, and PVC occurs more frequently in patients without MR than in the general population [9]. Evidence linking MVP with SCD is generally based on autopsy series or evaluation of SCD victims. The annual risk of developing SCD in patients with MVP is between 0.1 to 0.4%, three times higher than that of the general population, and the presence of significant MR results in a 50 to 100 times increased risk [3]. This rate is much higher in young athletes. It has been suggested that an an arrhythmogenic event, generally ventricular fibrillation is generally responsible for the SCD that develops in patients with MVP. SCD in elderly patients with MVP is primarily attributed to secondary cardiac changes related to MVP, whereas such changes are typically not present in younger patients with MVP. Given that MVP is a prevalent valve variant among the general population, it is probable that the total number of patients with MVP who experience SCD is comparatively higher [12]. A post-mortem study using strict morphological diagnostic criteria for MVP showed that 7% of juvenile SCD cases were associated with MVP [15]. MVP has been noted as the sole cardiac abnormality in certain SCD victims and some SCD survivors [4,16]. MVP is also the sole cardiac abnormality found in 8% to 16% of individuals with refractory ventricular tachycardia. [17]. The actual incidence of SCD resulting from MVP may differ based on the evaluation methods and the clinical data available, potentially leading to an underestimation of its frequency. All these data raise suspicions that MVP, especially without MR, may not be a disease with a benign prognosis as thought.

There are also studies in the literature showing that MVP without significant MR is not associated with an increased risk of atrial or VA [1]. However, there are also studies showing an increased risk of VA and SCD in a group of MVP patients without significant MR [3]. The clinical presentation of these patients, defined as arrhythmic MVP syndrome, is usually as follows: young adults (mostly women), QTc prolongation, ST segment depressions, biphasic/negative T waves in inferior ECG leads, myxomatous degeneration with marked leaflet redundancy, excess leaflet length and thickness, MAD, bicuspid leaflet involvement, frequent and/or complex VA on Holter monitoring and/or exercise testing [4,9,15,16]. Several mechanisms have been proposed for the development of VA in patients with

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AMVP phenotype. Myocardial fibrosis, particularly affecting the inferobasal left ventricular myocardium and papillary muscles, has been described in pathologic and cardiac magnetic resonance imaging (MRI) studies with late gadolinium enhancement and has been demonstrated in some patients with MVP, particularly those with complex VA or SCD [15,18]. Fibrosis formation has been associated with mechanical tension secondary to MAD and hypermobility of the mitral valve apparatus due to posterior systolic buckling [19,20]. MAD-VA link is assumed to be secondary to local fibrosis induced by tension [19]. MAD can be present in healthy individuals, and it has been demonstrated that a MAD measurement greater than 6-8.5 millimeters increases the risk of arrhythmia. Fibrosis, friction lesions, mechanical contact of leaflets to the myocardium, and myocardial stretching can lead to VA through re-entry or triggered activity mechanisms. These findings suggest that cardiac MRI is promising for arrhythmic risk stratification beyond traditional electrophysiologic markers by identifying fibrosis. It has been shown that sympathetic activity is increased, vagal activity is decreased, and catecholamine levels are increased in MVP patients with VA [21]. This autonomic dysfunction observed in MVP patients contributes to the increase in ectopic activity in the ventricular myocardium [21]. PVC originating from the papillary muscle, the fascicular system, and the outflow tract may be a trigger for ventricular fibrillation [21]. Studies have demonstrated that patients with MVP may experience VA, characterized by a wider distribution of refractoriness, even though the QTc interval remains normal [22]. This finding suggests that regional variations in repolarization duration could be a contributing factor to VA and SCD in MVP. Electrophysiological studies have also been utilized to comprehend the role of arrhythmias in patients with MVP. In one analysis, the probability of inducible sustained monomorphic ventricular tachycardia in patients with nonsustained ventricular tachycardia was found to be 6% [23].

The fQRS-T angle is the angular difference between the ventricular depolarization (QRS) and repolarization (T) axes as measured on a 12-lead ECG [11]. A widened fQRS-T angle is indicative of electrophysiological heterogeneity in the myocardium and is associated with an increased risk of VA and cardiovascular mortality [10]. The fQRS-T angle is one of the powerful predictors of cardiovascular death, and SCD in the general population [24,25]. The biggest advantage of the fQRS-T angle is that it can be easily calculated from automatic measurements of the standard 12-lead ECG without the need for any additional processing.

Although other clinical risk factors for SCD, such as the presence of flail mitral leaflets or significant MR, have been suggested, no specific recommendations for risk stratification of patients with MVP have been defined. Additionally, there is a lack of information to identify patients with MVP at high risk for VA and SCD. Currently, there is no definitive predictor of malignant VA, and the combination of risk factors that pose the greatest threat remains unclear. High-risk MVP patients constitute a small portion of a much larger population traditionally considered low-risk patients. The early detection of the risk for arrhythmic events and the provision of early preventive interventions are key components in managing patients with MVP. In this study, I compared fQRS-T angles with healthy individuals to evaluate the risk of developing VA in patients with MVP who do not have an arrhythmic phenotype and are considered to have a benign prognosis. Although the fQRS-T angle has been studied in many cardiovascular diseases, there is no study in the literature comparing the fQRS-T angle in MVP patients with healthy individuals. As a result of our study, the fQRS-T angles of MVP patients were found to be similar to those of healthy individuals. Also, QTc intervals, another indicator of VA risk, were similar between groups. I believe this study's findings are attributable to the lack of MAD and associated left ventricular myocardial fibrosis in our patient cohort, which did not exhibit features of an arrhythmic phenotype. Moreover, excluding patients with long QTc or significant MR from the study may have influenced the outcome, given that the heterogeneity of myocardial depolarization and repolarization remained unaltered. This study is the first on this subject and will shed light on future studies.

Our study has several limitations. A prospective study design and a larger patient population may increase the reliability of the results. The inclusion of the patient group with AMVP phenotype into the study could have clarified the AMVP-fQRS-T angle relationship. In addition, investigating myocardial fibrosis with cardiac MRI in a prospective study may provide the opportunity to exclude the possible effects of myocardial fibrosis on the fQRS-T angle.

Conclusion

In conclusion, the fQRS-T angle in MVP patients without arrhythmic phenotype is similar to that in healthy subjects. This finding supports previous studies suggesting a low risk of VA and SCD in this patient population.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The Ethics Committee for Non-interventional Clinical Research of Kütahya Health Sciences University approved the study (Date: 30.09.2024, Decision No: 2024/11-15).

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