The relationship between frontal QRS-T angle and premature ventricular contraction burden in ambulatory 24-hour Holter

Frontal QRS-T Açısı İle Ambulatuar 24 Saat Holterde Prematür Ventriküler Kontraksiyon Yükü Arasındaki İlişki

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ABSTRACT

Aim: Frequent premature ventricular contractions (PVCs) can cause impaired ventricular function or dilatation of ventricular cavities. The frontal plane QRS-T [f(QRS-T)] angle is an indicator of instability in the electrophysiological properties of the myocardium and is associated with arrhythmias. The present study aimed to investigate whether f(QRS-T) angle, as a marker of ventricular repolarization heterogeneity, predicts premature ventricular contraction burden in ambulatory 24-hour Holter.

Methods: The study included 100 patients. The patients were divided into two groups as 'frequent PVC' and 'seldom PVC' according to their PVC burden in 24-hour Holter monitoring. Laboratory and some ambulatory electrocardiography parameters, including frontal plane QRS-T angle, were compared between the two groups.

Results: Frontal QRS-T angle ($63.34\pm37.86°$ vs $23.46\pm14.29°$ p<0.001) was found to be wider in the Frequent PVC group. F(QRS-T) angle of $\geq 34°$ had a sensitivity of 82.2% and a specificity of 80% in indicating PVC load (AUC: 0.887 (0.824-0.950). In addition, a positive correlation was found between PVC burden and f(QRS-T) angle (r:0.429 p<0.001).

Conclusion: The widening of f(QRS-T) angle could perhaps be considered as a surrogate marker of increased PVC burden in 24-hour Holter monitoring. Measuring f(QRS-T) angle in 12-lead ECG in patients with PVC may be a warning sign for increased PVC burden.

Keywords: premature ventricular contraction, electrocardiography, frontal QRS-T angle

ÖZ

Amaç: Sık prematür ventriküler kontraksiyonlar (PVK), ventriküler fonksiyonun bozulmasına veya ventriküler kavitelerin genişlemesine neden olabilir. Frontal düzlem QRS-T [f(QRS-T)] açısı, miyokardın elektrofizyolojik özelliklerindeki kararsızlığın bir göstergesidir ve aritmilerle ilişkilidir. Bu çalışma, ventriküler repolarizasyon heterojenitesinin bir belirteci olarak f(QRS-T) açısının, ambulatuar 24 saatlik holterde prematüre ventriküler kasılma yükünü tahmin edip etmediğini araştırmayı amaçlamıştır.

Yöntem: Çalışmada 100 hasta mevcuttu. Hastalar 24 saatlik Holter izleminde PVK yüklerine göre "sık PVK" ve "nadir PVK" olarak iki gruba ayrıldı. Laboratuar ve frontal plan QRS-T açısı dahil olmak üzere bazı ambulatuar elektrokardiyografi parametreleri iki grup arasında karşılaştırıldı.

Bulgular: Frontal QRS-T açısı ($63.34\pm37.86°$'ye karşı $23.46\pm14.29°$ p<0.001) Sık PVK grubunda daha geniş bulundu. F(QRS-T) açısının $\geq 34°$ olması; PVK yükünü göstermede %82.2 duyarlılığa ve %80 özgüllüğe sahipti (AUC: 0.887 (0.824-0.950). Ayrıca PVK yükü ile f(QRS-T) açısı arasında pozitif korelasyon bulundu (r:0.429 p<0.001).

Sonuç: F(QRS-T) açısının genişlemesi, 24 saatlik Holter izleminde artmış PVK yükünün bir göstergesi olarak düşünülebilir. 12 derivasyonlu EKG'de PVK'sı olan hastalarda f(QRS-T) açısının ölçülmesi, artmış PVK yükü için uyarıcı bir bulgu olabilir.

Anahtar Sözcükler: prematür ventriküler kontraksiyon, elektrokardiyografi, frontal QRS-T açısı

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INTRODUCTION

Premature ventricular contractions (PVCs) are found in 40 to 75 percent of routine 24 to 48-hour Holter monitoring in healthy populations [1]. In the past, frequent PVCs were believed to have a benign clinical course in individuals without underlying structural heart disease [2]. Moreover, it was frequently advised to avoid beginning treatment unless the patient had symptoms or PVCs occurred frequently. However, recent evidence has revealed that frequent PVCs may cause impaired ventricular function or dilatation of ventricular cavities in some patients [3-5]. Indeed, some studies have found that frequent idiopathic PVCs are linked to an increased risk of death, whether the patient has structural heart disease or not [6-7].

A new indicator of ventricular repolarization heterogeneity known as the frontal QRS-T [f(QRS-T)] angle is defined as the angle between the directions of ventricular depolarization and repolarization [8]. It also possesses an important advantage in that it can be quickly determined from an automated electrocardiogram (ECG) interpretation. The prognostic value of the f(QRS-T) angle has been demonstrated in various populations [9,10]. Additionally, according to earlier studies, the abnormal widening of this angle has been linked to sudden cardiac death (SCD) in specific patient populations [11]. An increased f(QRST) angle is a sign of electrophysiological instability in the myocardium and is linked to a worsening cardiac prognosis and mortality [12,13].

In this study, we aimed to examine the correlation between the f(QRS-T) angle in surface ECG and PVC burden estimated from ambulatory 24-hour Holter monitoring.

MATERIAL AND METHODS

Study population

We retrospectively evaluated one hundred patients who underwent 24-hour rhythm Holter monitoring for palpitations. ECG and rhythm Holter recordings were acquired and baseline demographic and clinical characteristics were examined. Exclusion criteria included severe valvular heart disease, prior myocardial infarction, thyroid disorder, permanent pacemaker therapy, heart failure, hypertrophic cardiomyopathy, bundle branch block, electrolyte disturbance, atrial fibrillation and any medication usage that might affect the ECG such as Beta blockers, antiarrhythmics or proarrhythmic drugs. The local ethics committee granted approval for the study (Antalya Education and Research Hospital, Protocol No:2022/23 Decision No:2/8, January 20, 2022).

Holter monitoring

Holter recordings were performed using a three-channel digital recorder (DMS 300-3A Holter ECG Recorders). During the Holter monitoring, all patients were informed to carry on with their ordinary routine and to refrain from drinking coffee or smoking. The Holter recordings were manually edited and analyzed for PVCs, and the number of PVCs was recorded. The PVC burden was calculated as the total number of PVCs divided by the number of all QRS complexes, during 24-hour Holter monitoring. Previous research has reported that the lowest PVC burden linked to reversible cardiomyopathy was 10% [14]; therefore, patients with a frequency of > 10% PVCs/24 h were classified as 'frequent PVC' (n = 50), while those with a frequency of < 10% PVCs/24 h were classified as 'seldom PVC' (n = 50).

The modified Simpson's technique was used to calculate the ejection fraction (EF). A board-certified cardiologist performed the echocardiographic studies.

Electrocardiography

ECGs of the patients were taken just before the rhythm Holter. In the supine position, a 12-lead surface ECG (Nihon Kohden Corporation, Cardiofax M Model ECG-1250) was recorded at a voltage of 10 mm/s and a paper speed of 25 mm/s. The intervals, axis and heart rates were evaluated from the standard ECG. Furthermore, all ECGs were uploaded to a computer and analyzed with x400 percent magnification using the Adobe Photoshop software to reduce incorrect measurements. The P and QRS durations were transcribed from the computer interpretation of the ECG. All the measurements were validated by an investigator. The QT interval was measured from the beginning of the QRS complex to the end

of the T wave and adjusted for heart rate using the Bazett formula: cQT=QT√ (R-R interval). Tp-e intervals were evaluated from precordial leads and described as the interval from the peak of the T wave to the end of the T wave. This data was used to compute the Tp-e/QTc ratio. The QRS axis and T-wave axis were identified in the automatic analysis of the ECG device. The absolute difference between the frontal plane QRS axis and T axis was used to calculate the f(QRS-T) angle (Figure 1). If the angle was more than 180°, it was subtracted from 360° [15].
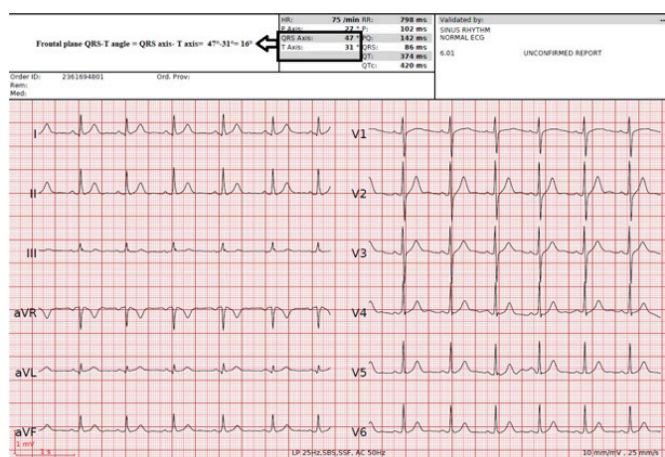

Figure 1: An example of the illustration and measurement of frontal plane QRS -T angle

STATISTICAL ANALYSIS

We evaluate statistical analysis with the SPSS software v27.0.1 (SPSS, Inc., Chicago, Illinois). The descriptive data was summarized as percentage frequencies for categorical variables and mean standard deviation (SD) for continuous variables. The variables were analyzed using analytical (Shapiro-Wilk test) and visual methods to determine whether they were normally distributed. Student's t-test was used to compare normally distributed measurements for independent samples, and Mann Whitney's U-test was used for comparisons of medians.

We obtained the optimal Youden index cut-off for best sensitivity and specificity by performing receiver operating characteristic (ROC) curve analysis, to assess whether the f(QRS-T) angle is useful to predict that PVC exposure; the corresponding area under the curve (AUC) was calculated. In addition, Pearson correlations were used to explore binary relationships between PVC exposure and frontal QRS-T angles. P < 0.05 was taken as the cut-off for significance, accompanied by a 95% confidence interval (CI).

RESULTS

This study included one hundred patients who underwent 24-hour rhythm Holter monitoring due to palpitation. The patients were divided into two groups based on their PVC burden in Holter monitoring: 'frequent PVC' and 'seldom PVC'. The mean PVC burden was 20.37±9.01% in the Frequent PVC group, and 2.04±1.34% in the Seldom PVC group. The study population's baseline demographics, laboratory results and echocardiographic characteristics are described in Table 1. There was no statistical difference between the groups.

Table 1: Comparisons of demographic characteristics, laboratory findings, and echocardiography parameters

	Seldom PVC	Frequent PVC	P value
Age, years	53.22±17.81	55.50±13.81	0.704
Gender			
-Male, n (%)	24 (48)	28 (56)	0.423
Diabetes mellitus n (%)	19 (38)	26 (52)	0.159
Hypertension, n (%)	26 (52)	31 (62)	0.313
Smoking, n (%)	19 (38)	25 (50)	0.227
Coronary artery disease, n (%)	16 (32)	21 (42)	0.300
Hemoglobin, g/dl	13.75±3.23	16.45±2.32	0.319
WBC, (K/ μl)x 103	8.49±2.73	7.45±2.41	0.198
Platelet , (K/ μl)x 103	278.68±56.14	273.06±67.22	0.080
Neutrophil to lymphocyte ratio	2.59±2.41	1.93±0.68	0.579
Fasting blood glucose, mg/dL	116.18±55.29	104.14±41.16	0.187
Creatinine, mg/dL	0.93±0.16	1.05±0.48	0.084
Sodium, mmol/L	139.66±2.71	140.14±3.39	0.494
Potassium, mmol/L	4.86±4.08	6.89±1.44	0.354
HDL, mg/dl	51.64±11.65	53.92±12.48	0.785
LDL, mg/dl	114.58±35.19	105.90±34.81	0.140
Triglyceride, mg/dl	145.63±64.76	154.50±75.47	0.899
TSH, mU/L	1.83 (2)	1.46 (2)	0.825
LVEF,%	60.70±4.28	59.10±5.01	0.090
Heart Rate, bpm	79.58±15.81	75.16±12.67	0.262

(PVC: premature ventricular contractions WBC: White blood cell, HDL: High-density lipoprotein cholesterol, LDL: Low density lipoprotein cholesterol, TSH: Thyroid Stimulating Hormone, LVEF: left ventricular ejection fraction)

Table 2 shows the ambulatory ECG parameters of both groups. The Frequent PVC group had longer QRS duration (p=0.001), QT interval (p=0.001) and

QTc intervals (p=0.012). Moreover, Tp-e interval (75.84±14.84 vs 86.50±14.29, p= 0.001) and Tp-e/QTc ratio (0.18±0.03 vs 0.20±0.03 p = 0.016) were significantly increased in the Frequent PVC group. The frequency of fragmented QRS was considerably higher in the Frequent PVC group (28% vs 36%, p =0.043). Regarding to HRV time domain indices (SDNN, SDNN, RMSSD, pNN50), there was no noticeable differences across the groups.

Table 2: Ambulatory electrocardiography parameters of patients

	Seldom PVC	Frequent PVC	P value
P duration, msec	108.24±18.08	115.30±24.11	0.15
QRS duration, msec	91.56±13.96	99.48±11.49	0.001
QT interval, msec	368.20±31.97	395.68±46.68	0.001
cQT interval, msec	418.78±25.14	438.04±36.03	0.012
Tp-e, msec	75.84±14.84	86.50±14.29	0.001
Tp-e/cQT ratio	0.18±0.03	0.20±0.03	0.020
Presence of fragmented QRS, n (%)	9 (28)	18 (36)	0.043
Frontal QRS-T angle, (°) degrees	23.46±14.29	63.34±37.86	<0.001
PVC (%)	2.04±1.34	20.37±9.01	<0.001
HRV time domain indices			
SDNN ms	121.94±30.96	119.76±33.47	0.756
SDANN ms	120.14±37.87	118.88±46.69	0.749
RMSSD ms	34.24±18.96	34.22±19.09	0.882
pNN50 %	10.36±9.34	9.68±12.27	0.498

(PVC: premature ventricular contractions, cQT: corrected QT, Tp-e: T wave peak-to-end interval, HRV: heart rate variability, SDNN: standard deviation of all normal-to-normal RR intervals, SDANN: standard deviation of 5-min mean RR intervals, RMSSD: the square root of the mean of the squares of the differences between successive normal-to-normal RR intervals, pNN50: percentage of successive normal RR intervals exceeding 50 ms)
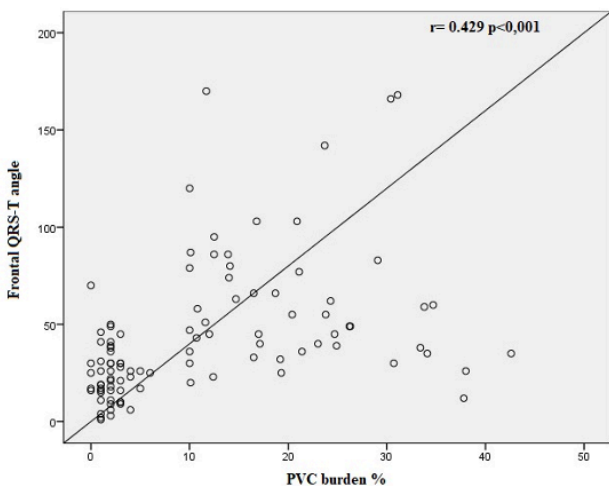
Figure 2: Correlation between PVC burden and Frontal QRS-T angle.

Frontal QRS-T angle (63.34±37.86° vs 23.46±14.29° p<0.001) was found to be wider in the Frequent PVC group. A positive correlation was found between PVC burden and f(QRS-T) angle (r:0.429 p<0.001) (Figure 2). ROC curve analysis was performed to determine the best cut-off value for detecting the PVC burden of the frontal QRS-T angle. An f(QRS-T) angle of ≥ 34° had a sensitivity of 82.2% and a specificity of 80% in indicating PVC burden (AUC: 0.887 (0.824-0.950) (Figure 3).
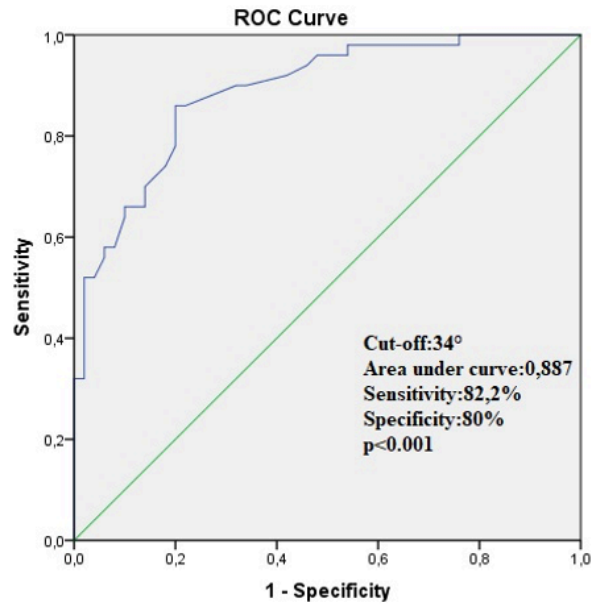
Figure 3: Receiver operating characteristics curve analysis of frontal plane QRS-T angle to predict PVC burden

DISCUSSION

This study demonstrated that the f(QRS-T) angle calculated from surface ECG is a predictor of increased PVC burden. Furthermore, Tp-e intervals and Tp-e/QTc ratio were significantly higher in patients with frequent PVC burden. However, HRV domain indexes were similar between the groups.

Even though it has been traditionally considered that frequent PVCs were associated with a good prognosis in patients without structural heart disease [2], this has not always been demonstrated to be the case. There have been studies that show the presence of PVC is linked to a higher risk of cardiac events and mortality in people that have not been assessed for structural heart disease [16]. The increased daily total burden of PVCs can cause severe cardiac problems, such as syncope,

heart failure and angina.

PVCs are the most common ventricular arrhythmias and despite the high prevalence, in most patients, no cause can be identified. Although PVCs are more common in the elderly and in men, they can also occur in healthy individuals. There are a number of mechanisms responsible for PVC and although some of the underlying mechanisms have been clarified, it is still unclear why some people have a higher frequency of PVC than others, or why some people notice the symptoms, but others do not. PVCs may be felt as palpitations or dizziness. They can also cause chest pain, fainting, fatigue, presyncope, dyspnea or hyperventilation following exercise. Despite there being a number of symptoms associated with PVCs, on occasion they do not cause any symptoms at all and the absence of symptoms is not always a good prognosis. Even in cases where no symptoms are present, it is unquestionably necessary to evaluate using rhythm Holter monitoring if PVCs are found in the surface ECG of the patients, or if the ejection fraction is low in the transthoracic echocardiography. Treatment should be started if the PVC percentage is found to be high in 24-hour rhythm Holter monitoring, even if the patient is asymptomatic. However, 24-hour Holter monitoring may not always be sufficient to show the actual PVC burden. It might be necessary to use some ECG parameters that demonstrate the patient's PVC burden and localization.

PVCs are thought to contribute to the development of malignant arrhythmias. They may transform into ventricular arrhythmias due to a variety of factors that impair the myocardial electrical stability, such as electrolyte disturbance or increased sympathetic activity. In addition, frequent PVCs may cause left ventricular dysfunction and dilatation, leading to the development of ventricular arrhythmia, with mechanisms such as increased automaticity, re-entry and triggered activity [17]. While many studies cannot provide an absolute limit to identify patients at risk of developing PVC induced cardiomyopathy (PIC), at least a 10% PVC burden are at sufficient risk for development of PIC [14]. Regular follow-ups should be performed to assess of ejection fraction and LV dimensions, as well as to prevent future arrhythmic events.

Changes in the repolarization potential of the myocardium may cause predisposition to malignant ventricular arrhythmias and may lead to SCD. Even though the QT interval has traditionally been used to assess myocardial repolarization, correct calculation of the QT interval is challenging, and the measurement's reproducibility is poor [18]. Although QT dispersion is used to measure ventricular refractoriness dispersion, it does not directly reflect the regional heterogeneity of cardiac repolarization [19]. The Tp-e interval is now regarded as a ventricular repolarization marker. Furthermore, it was discovered that patients with Brugada syndrome had a higher risk of mortality if their Tp-e interval was prolonged. [20]. Yayla et al. found significant reductions in the Tp-e/QTc ratio and Tp-e interval after successful radiofrequency ablation (RFA) (p<0.001) in patients with a PVC burden >5% at 24-hour Holter follow-ups. [21]. In light of this data, the longer Tp-e interval in patients with frequent PVCs suggests a higher risk of malignant arrhythmia. Nevertheless, the Tp-e interval is an unreliable parameter as it is affected by changes in heart rate and body weight [22]. The Tp-e/QTc ratio has recently been proposed as a more accurate predictor of repolarization and it is unaffected by changes in heart rate [22]. In our study, the Tp-e/QTc ratio was significantly higher in the Frequent PVC group, which is consistent with the literature. However, it is challenging to calculate the Tp-e/QTc ratio accurately, and sophisticated software programs as well as specific tools such as rulers and magnifiers are required.

Recently, some new ECG parameters have been used to evaluate myocardial repolarization. F(QRS-T) angle, which shows ventricular conduction heterogeneity, is one of these parameters. [8,9]. According to some studies, myocardial repolarization parameters, such as QTc interval and T wave inversion, were found to be less accurate and repeatable than this novel parameter [11]. Moreover, the abnormal widening of this angle may in fact be a sign of a number of cardiac events [23].

The QRS-T angle can be calculated with two different methods: spatial and frontal QRS-T angle. Spatial angle is more challenging to calculate and necessitates sophisticated computer programs;

furthermore, it cannot be measured routinely from surface ECG. On the other hand, the automatic report section of ECG devices makes it simple to calculate the frontal QRS-T angle. In our study, we preferred the f(QRS-T) angle, since it has been shown in various studies that it can be used instead of spatial QRS-T angle for risk assessment [24].

Although 24-hour rhythm monitoring is considered the gold standard method for assessing PVC frequency, recent evidence has shown that there may be significant daily variation and that at least six days of rhythm monitoring may be required to determine the maximum daily PVC frequency [25]. This situation reveals the necessity for long-term monitoring to determine the true frequency of PVC in patients, however not every clinic has the required supplies of Holter devices that can be used for long-term monitoring of every patient. In this study, it was found that patients with a high PVC burden had a significantly higher f(QRS-T) angle. It was also determined that f(QRS-T) angle ≥34° predicted the presence of increased PVC burden, with 82.2% sensitivity and 80% specificity. According to this finding, the presence of f(QRS-T) angle of ≥34° in the surface ECGs of patients who are compliant with palpitations and have at least one PVC on their surface ECG is significant and may indicate an increased PVC burden. In these patients, long-term and more frequent Holter monitoring may be considered to determine the accurate PVC burden.

Limitations: The comparatively small number of registered patients is the study's most important limitation. If the sample size of the study had been larger, more consistent results could be obtained. The center where the study was conducted was a tertiary care facility, with many patients presenting in the heart clinic, however it would have required much time and resources to enrol select patients who were neither taking medication or presenting structural heart diseases. Another major limitation was the retrospective design of the study. Owing to the observational nature of the design, only associations can be drawn and no causal relationships can be established. One point not assessed in the study is that the patients' serious cardiac events, such as cardiac mortality and arrhythmias, were not monitored.

Therefore, since patients could not be followed up for prospective arrhythmic events, the correlation between f(QRS-T) angle and cardiac events could not be assessed. If long-term follow-ups could be done with more patients, the long-term cardiac events could be evaluated more clearly. In addition, this single center study in a tertiary heart center where many patients apply should have its findings validated in multicentre studies, involving greater patient populations and longer follow-ups. Despite these limitations, this research has raised a number of questions that require further investigation.

Conclusion: Frequent PVCs have a negative effect on myocardial repolarization parameters and may predispose these patients to malignant arrhythmias. As a simple and easily obtained ECG parameter, f(QRS-T) angle may be used in predicting PVC burden. Measuring the f(QRS-T) angle in the 12-lead ECG in patients with PVC may be a warning sign for increased PVC burden and will encourage increased frequency and duration of Holter monitoring, and a review of treatment regimens.

ORCID and Author contributions: GK (0000-0002-6058-5501): Concept and Design, Data collection, Literature search, Manuscript Writing, Analysis. GÇ (0000-0001-9768-918X): Interpretation and Critical Review.

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