Comparing of Tp-Te Interval and Tp-Te/Qt Ratio in Patients with Preserved, Mid-Range and Reduced Ejection Fraction Heart Failure

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Abstract

BACKGROUND: Heart failure (HF) is classified in three class: HF with preserved EF (HFpEF); normal or LVEF ≥ 50%; HF with reduced EF (HFrEF); LEVF < 40% and newly HF mid-range EF (HFmrEF); LVEF 40-49%. On Electrocardiography (ECG) T wave, Tpeak-Tend (Tp-Te) interval reflects transmural dispersion of repolarisation (TDR) which of these indexes have been proposed as predictors of risk for ventricular arrhythmia (VA) in many cardiac diseases.

AIM: Aim of this study to asses these indices of TDR among three HF class.

METHODS: Total of 192 patients were included in this study.

RESULTS: Many of indices like Tp-Te, Tp-Te/QT wasn’t different between groups (P > 0.05). But mean Q-Tpeak (Qtp), S-Tend (S-T) and S-Tpeak (S-Tp) were found significantly different between groups (P < 0.05). Again S-T was found different according to having fragmented ORS (QRS) on ECG (P = 0.031). Comparing to mitral inflow E/A parameters showed significant differences for Tp-Te, Tp-Tec, Tp-Te/QTc and Tp-Tec/QTc parameters. Finally, we found correlations between S-T and white blood cell (WBC) (r = -0.171; P = 0.037) and S-Tp and WBC (r = -0.170; P = 0.038) and between S-T and IGRS (r = 0.158; P = 0.031).

CONCLUSIONS: We didn’t find differences for many of indices of TDR like Tp-Te interval between groups except Qtp, S-T, S-Tp intervals. Also, S-T and IGRS showed significant correlation. For prediction of ventricular arrhythmia and cardiovascular death newer indexes on ECG are needed to be established in the future which will make us facilitate to distinguish high risk patients.

Introduction

Heart failure (HF) is a clinical syndrome which shows typical symptoms and signs due to reducing cardiac output and increasing of intracardiac pressures in many circumstances. The prevalence of HF is nearly 1-2% of the general population. The HF is classified into 3 groups according to the measurement of the left ventricular ejection fraction (LVEF). HF with preserved EF (HFpEF): normal or LVEF ≥ 50%; HF with reduced EF (HFrEF): LEVF < 40% and HF with mid-range EF (HFmrEF): LVEF is between 40-49%. HFmrEF depicts a new group of patients with different which is a deserving attraction with different characteristic a treatment features [1], [2]. Mortality rates of cardiac failure for HFrEF, HFmrEF and HFpEF were accounted approximately with 154-115 and 87 deaths per 1000 person-year, respectively [3]. Sudden cardiac arrest or death (SCD) is one of the important cause of mortality in these patients because of reentrant ventricular arrhythmia (VA). This re-entry is being occurred highly due to local dispersion of myocardial repolarisation and this total ventricular dispersion of repolarisation (DVR) facilitates VA and cardiac arrest [4]. Cardiac myocardial transmural dispersion of repolarisation (TDR) or DVR was described in previous reports with three different myocardial cell layers: endocardial, epicardial and mid-myocardial M cells. M cells have
the longest action potential duration with prone to action potential prolongation with external factors. On surface Electrocardiography (ECG), the repolarization of the epicardial layer ends at the peak of T-wave but M cells' repolarization continue until the end of T wave and by measuring the time between the peak and end of the T wave, which is called as Tp-Te interval and reflects TDR [5], [6], [7]. QTc (corrected), Q-Tpeak (QTp), Tpeak-Tend (Tp-Te), and TP-Te/QT have been defined as predictors of risk for VA or SCD in various clinical scenarios like in HF patients, Brugada syndrome, hypertrophic cardiomyopathy, Long-QT syndrome and bradyarrhythmia or general population [8], [9], [10], [11], [12], [13]. The Tp-Tec interval and Tp-Tec/QT ratio were also found to be more accurate measurements of the TDR or DVR compared to the QT, QTd (QTDispersion), and Tp-Te interval [14]. Different cutoff values for Tp-Te interval have been proposed or found in previous studies [8], [15]. In groups of patients with increased risk of VA, the Tp-Te was often more than 100 millisecond (ms) in various clinical scenarios like acute myocardial infarction and HF [4], [16]. Although meaningful clinical usage of Tp-Te for prospective risk stratification for VA events and mortality in patients with cardiomyopathy has been demonstrated before, further risk stratification within three separate high-risk population with HF would be of clinical value [4]. Fragmented QRS (fQRS) is another risk predictor index on surface ECG for electro-mechanical dysynchrony, VA and SCD for patients with HF and hypertrophic cardiomyopathy [17], [18], [19], [20], [21], [22]. The purpose of this study was to assess if there is a distinction of various indices of TDR in three group of patients with HF (HfrEF- HmrfEF- HfpEF) and there is a relationship between fQRS and these indices in patients with HF.

Methods

Study Population

The study consisted of 192 patients who were admitted to our institute with HF between November 2016 and May 2017. After the diagnosis of HF was made according to the previous guideline [1]. Demographic data including age and sex and clinic data of history of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HPL), coronary artery disease (CAD), baseline rhythm of ECG (atrial fibrillation (AF) or sinus rhythm (SR), as well as laboratory data and used medication and being on a diet were obtained at baseline. Patients were classified to their baseline LVEF measurements as HfrEF (LVEF < 40%), HmrfEF (LVEF: 40-49%) and HfpEF (LVEF > 50%). Patients with prior pacemaker implantation, cancer, or other major illnesses were excluded. Patients with abnormal thyroid function test, abnormal electrolyte values and on antiarrhythmic drug treatment were also excluded.

Approval of Ethics Committee

The study protocol was approved by the Ethics Committee at Afyon Kocatepe University, and informed consent was obtained from each patient.

ECG

All 12-lead ECGs were recorded using a General Electric MAC 5000 (GE Healthcare, Milwaukee, WI, USA) at 25 mm/s with standard lead positions. All records were magnified by 200%, and QT intervals were measured. Automated ECG analysis of the baseline ECG was performed at a central laboratory (GE Healthcare, Wauwatosa, WI, USA) using the commercially available GE Healthcare Marquette 12SL ECG analysis program, which uses validated algorithms for measurement [23]. To eliminate both interobserver variability and bias, all measurements were measured in each of the 12 leads by a single observer who was blinded to all clinical findings. QT intervals were taken to be from the onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the intersection of the tangent to the down slope of the T wave and the isoelectric line when not followed by a U wave or if distinct from the following U wave. If a U wave followed the T wave, the T-wave offset was measured as the nadir between the T and U Waves. The Tp-Te interval was defined as the interval from the peak of the T wave to the end of T wave [24]. Q-Tpeak (QTP) was measured from onset of QRS to peak of T wave, and in the case of negative or biphasic T waves, Q-Tpeak (QTP) was measured to the nadir of the T-wave. The Tp-Te value reported was the average value of obtained in all precordial leads. The Tp-Te/QT ratio was calculated as the ratio of Tp-Te in that lead to the corresponding QT interval.

Figure 1: Demonstration of the T wave peak to end and QT intervals [24]

Other novel indexes were described as STpeak (S-Te) interval and STpeak interval (S-Tp). S-Te and S-Tp were measured from nadir of S wave to
peak of T and end of T wave in precordial limbs (Figure 1). Bazett’s formula (n/ RR) was applied to the all the indices to find heart rate corrected form which was shown as ‘c’ in this text (for example QTc) [25]. The corrected intervals are expressed in the same units as the original parameters, as recommended by Molnar et al., [26].

IQRs included various RSR patterns and was defined by the presence of an additional R wave (R prime), notching in nadir of the S wave, notching of R wave, or the presence of more than one R prime (fragmentation) in two contiguous leads corresponding to a major myocardial segment [23] (Figure 2).

![Fragmented QRS (IQRs) [23]](image)

**Figure 2: Different types of fragmented QRS (IQRs) [23]**

**Echocardiography**

A Vivid 5 pro echocardiographic unit (GE, USA) with 3,5 MHz probe was used. The echocardiographic study was performed in standard accepted positions which all of the echocardiographic measurements (M-mode, two-dimensional and Doppler echocardiography), were performed and/or reviewed by experienced staff cardiologists, in compliant with the recommendation of the American Society of Echocardiography. Mitral inflow was determined by continuous and pulse wave Doppler echocardiography at the tips of the mitral leaflets. Early diastolic mitral peak flow velocity (E), late diastolic mitral peak flow velocity (A), E/A ratio were measured. Left ventricular diastolic dysfunction (LVD-Dys) was defined as a mitral continuous-wave (CW) Doppler E<A as compliant with the recommendation of previous guideline [27, 28].

**Statistical analysis**

Continuous variables were expressed as mean ± SD (Standard deviation), and categorical variables were presented as frequencies (%). Continuous and categorical measures were compared with t-tests or 2 statistics, as appropriated. For correlations, appropriate calculations were done. A p value < 0.05 was accepted as a statistically significant. All analyses were performed using SPSS Version 16.0 (SPSS Inc. Chicago, IL, USA).

**Results**

**Baseline descriptive analysis**

The 192 patients were included in our study with 68 women (35.4%) and 124 men (64.6%). Many of baseline features which were borne in Table 1 were similar between groups except pulse rate, left ventricular end-diastolic diameter (LVDD) and left ventricular end-systolic diameter (LVSD) which were higher in first group (for pulse rate P = 0.001; for LVDD P = 0.002; for LVSD P = 0.001, respectively). History of HPL, CAD, AF and SR ratios were similar between groups (for all P value > 0.05) however DM was found higher in group 2 (P = 0.006), and HT was found higher in group 1 and 2 (P = 0.017).

**Table 1: Baseline frequency and descriptive analysis of some features of groups**

| Features | Count | LVEF% | LVEF% | LVEF% | Total n=192 (100%) |
|----------|-------|-------|-------|-------|--------------------|
| Gender   |       |       |       |       | ns                 |
| Women    | 116   | 34.4% | 68    | 21    | 10 (35%)           |
|          | 40    | 40.1% | 124   | 36    | 19 (62%)           |
|          |       |       |       |       | ns                 |
| Male Age |       |       |       |       | ns                 |
| Count & | 754   | 46.2% | 124   | 36    | 19 (62%)           |
| percent |       |       |       |       | ns                 |
| Mean ± SD| 5.4±0.8 | 51.7±7.9 | 49.6±1.1 | 51±4.6 | 46.7±5.4 |
| NT, ProBNP | 203 | 42.9% | 79    | 24    | 12 (36%)           |
| NYHA 1-2 |       |       |       |       | ns                 |
| Count & | 107   | 42.4% | 79    | 24    | 12 (36%)           |
| percent |       |       |       |       | ns                 |
| Mean ± SD| 40±8.1 | 35±7.7 | 32±6.5 | 32±6.5 | 32±6.5 |
| LVDD (mm) |       |       |       |       | ns                 |
| Median (25%-75%) | 40±8.1 | 35±7.7 | 32±6.5 | 32±6.5 | 32±6.5 |
| Median | 51±4.6 | 46.4±5.4 | 51±4.6 | 46.4±5.4 | 51±4.6 |
| LVSD (mm) |       |       |       |       | ns                 |
| Median (25%-75%) | 40±8.1 | 35±7.7 | 32±6.5 | 32±6.5 | 32±6.5 |
| Median | 51±4.6 | 46.4±5.4 | 51±4.6 | 46.4±5.4 | 51±4.6 |
| IVS (mm) |       |       |       |       | ns                 |
| Median (25%-75%) | 40±8.1 | 35±7.7 | 32±6.5 | 32±6.5 | 32±6.5 |
| Median | 51±4.6 | 46.4±5.4 | 51±4.6 | 46.4±5.4 | 51±4.6 |

As shown in Table 2 there wasn’t a significant difference between groups for interventricular septum
(IVS), posterior wall (PW), right atrium (RA), right ventricular (RV) dimensions, P-time, QRS-time and fQRS (all \( P > 0.05 \)). But there were significant differences for left atrium diameter (LA), T wave time and QT time \( (P = 0.047, P = 0.003, P = 0.007, \) respectively). However, after cross-tabulation between groups the adjusted significance was found \( (P > 0.05) \) for LA. After then we compared the groups each other for T and QT times we found significant difference only in between group 1 and 3 for QT time \( (P = 0.002) \) and between group 1 versus (vs) 3 and 2 vs 3 \( (P = 0.009 \text{ and } P = 0.042, \) respectively) for QT time.

Table 2: Baseline frequency and descriptives analysis of groups

| Features      | Count | LVEF=40 Group 1 | LVEF=40-49 Group 2 | LVEF=50 Group 3 | Total n=192 (100%) |
|---------------|-------|-----------------|--------------------|----------------|-------------------|
| IVS (mm)     | Mean ± SD | 9.8 ± 0.14 | 10.45 ± 1.2 | 10.13 ± 1.3 | 10 ± 1.3 | 0.302 |
| LA (mm)      | Mean ± SD | 45 ± 6.2 | 41 ± 6.1 | 42 ± 8.6 | 42 ± 8.6 | 0.047* |
| RV (mm)      | Mean ± SD | 31 ± 5.9 | 30 ± 5.9 | 27 ± 3.6 | 27 ± 3.6 | 0.075* |
| RA (mm)      | Mean ± SD | 34 ± 6.7 | 31 ± 7.4 | 31 ± 10.1 | 32 ± 8.6 | 0.067 |
| P-time (ms)  | Mean ± SD | 70 ± 14.2 | 62 ± 14.6 | 70 ± 14.0 | 70 ± 14.0 | 0.067 |
| QTc time (ms)| Mean ± SD | 91 ± 16.5 | 90 ± 12.7 | 86 ± 13.7 | 90 ± 14.4 | 0.542 |
| Group 1 vs. Group 3  | n=66 (34.6%) | n=69 (35.3%) | n=69 (35.3%) | n=192 (100%) |       |
| Present count & percent in total | 37 (19.1%) | 30 (15.1%) | 29 (15.1%) | 86 (45%) | 0.565 |
| None count & percent in total | 28 (14.6%) | 39 (20.3%) | 39 (20.3%) | 85 (45%) |        |

As shown in Table 3 we found the significant difference between groups for only QTP and RR interval measurements \( (QTP: 271.5 ± 51.0 \text{ ms vs } 272.4 ± 45.1 \text{ ms vs } 293.1 ± 53.1 \text{ ms}; P = 0.028 \text{ and RR interval}; P = 0.0001) \).

Table 4: Independent samples Kruskal-Wallis and Pearson Chi-Square test results

| Features      | Count | LVEF=40 Group 1 | LVEF=40-49 Group 2 | LVEF=50 Group 3 | Total n=192 (100%) |
|---------------|-------|-----------------|--------------------|----------------|-------------------|
| S-Tp (ms)     | Mean±SD | 220.9 ± 43.0 | 217.9 ± 43.9 | 241.3 ± 53.9 | 277.0 ± 46.8 | 0.052 |
| Median (25%-75%) | 220 (193-240) | 220 (200-243) | 240 (207-260) |       |       |
| S-Tpc (ms)    | Mean±SD | 279.6 ± 42.2 | 277.6 ± 43.6 | 276.2 ± 45.5 | 277.3 ± 41.0 | 0.631 |
| Median (25%-75%) | 275 (260-308) | 275 (261-304) | 269 (240-307) |       |       |
| S-Te (ms)     | Mean±SD | 296.0 ± 47.5 | 296.7 ± 47.8 | 318.9 ± 56.7 | 303.1 ± 51.3 | 0.028 |
| Median (25%-75%) | 285 (265-320) | 292 (271-320) | 320 (260-358) |       |       |
| S-Tcp (ms)    | Mean±SD | 370.8 ± 44.8 | 376.4 ± 44.2 | 365.7 ± 45.4 | 371.3 ± 46.1 | 0.432 |
| Median (25%-75%) | 372 (342-403) | 374 (342-404) | 360 (336-399) |       |       |

Table 5: Comparing to groups with each other for S-Tp and S-Tpc

| Groups         | Adj.Sig. \( P \) for S-Tp | Adj.Sig. \( P \) for S-Tpc |
|----------------|---------------------------|--------------------------|
| Group 1 vs. Group 2 | > 0.05                     | > 0.05                    |
| Group 1 vs. Group 3 | 0.043                     | 0.077                    |
| Group 2 vs. Group 3 | 0.081                    | 0.054                    |

Table 6 shows the comparing of incidents of TDR according to having of iQRS or not on surface ECG. Only S-Tp was found significantly different between groups \( (309.2 ± 47.4 \text{ ms versus } 295.5 ± 55.0 \text{ ms}; P = 0.031) \).

This Table showed us iQRS was found relevant only with S-Tp and not with Tpc and other important indices. Finally, we made correlation analysis and we found significant correlation between S-Tp and WBC \( (r = -0.171; P = 0.037) \) and S-Tp and WBC \( (r = -0.170; P = 0.038) \) and between S-Tp and iQRS \( (r = 0.158; P = 0.031) \).
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Table 6: Differences of incidents of TDR according to having fQRS or not on surface ECG showed only S-Te was significantly different between groups

| Variable of indices | Count | fQRS Present | TDR | fQRS None | P |
|---------------------|-------|--------------|-----|-----------|---|
| QTc (ms)            | Mean ± SD | 459.5 ± 37.5 | 442.0 ± 41.8 | 0.544 |
| QTp (ms)            | Mean ± SD | 232.7 ± 43.8 | 272.8 ± 57.1 | 0.197 |
| QTe (ms)            | Mean ± SD | 343.6 ± 44.9 | 342.2 ± 47.3 | 0.780 |
| Tp-Te (ms)          | Mean ± SD | 78.0 ± 17.6  | 73.6 ± 17.2  | 0.098 |
| Tp-Tc (ms)          | Mean ± SD | 95.1 ± 24.0  | 92.3 ± 24.1  | 0.339 |
| Tp-Tc/QT            | Mean ± SD | 0.216 ± 0.05 | 0.214 ± 0.05 | 0.481 |
| Tp-Tc/QTc           | Mean ± SD | 0.162 ± 0.07 | 0.170 ± 0.04 | 0.256 |
| Tp/Te               | Mean ± SD | 0.214 ± 0.05 | 0.215 ± 0.05 | 0.720 |
| S-Tc                | Mean ± SD | 279.6 ± 39.8 | 275.7 ± 42.6 | 0.415 |
| S-Te                | Mean ± SD | 309.2 ± 47.4 | 295.5 ± 55.0 | 0.031 |
| S-Tc/Te             | Mean ± SD | 374.0 ± 44.2 | 368.0 ± 48.5 | 0.250 |

Note: Non-parametric Mann-Whitney U test. *: Chi-square test. * P < 0.05 is accepted statistically significant. SD: Standard deviation, ms: milliseconds, c: Heart rate-corrected form with Bazett’s formula (n RR), IQRS: Fragmented QRS.

Discussion

Repolarisation parameters on ECG

In an earlier report by Sicouri and Antzelevitch identified distinct functional four type ventricular cells in a canine model, endocardial, M cells (in deep subepicardium layer), epicardial and Purkinje fibres. They found that action-potential duration-rate relation in which of cells in the M region relative to cells in neighbouring tissues is such that a prominent dispersion of repolarisation and refractoriness develops that area when stimulation rate is slowed. Intramural reentry during ischemia and bradycardia-induced could be facilitated by that midmyocardial reentry which occurs by delays of activation [7]. Yan et al., found that repolarization of the M cell was at the nearly same time with the end of the T wave, whereas repolarization of the epicardial cells was at the same time with the peak of the T wave in canine ventricle model so that the interval between the peak and the end of the T wave (Tp-Te) depicts the TDR (difference in repolarization times between epicardium and the M region). The Action-potential duration (APD) of endocardial cells was usually intermediate. Ascending part of T wave is drawn by voltage gradient difference between M cell-epicardial cell and descending part is drawn by difference between endocardial cell-M cell. When the T wave is upright, the epicardial response is the earliest to repolarise and the M cell action potential is the last. It concluded that the duration of the M cell action potential determines the QT interval, whereas the duration of the epicardial action potential determines the QTp (QTP) interval. QT dispersion is used a parameter to determine ventricular arrhythmia risk. Also measuring Tp-Te interval depicts the TDR. Transmembrane action potentials (APs) recorded from the right ventricle are usually longer than those from the left, and APs from the apical regions are generally longer than the base region. These apico-basal repolarisation gradients have been proposed to determine the electrocardiographic T wave [5, 6, 12, 29]. According to these studies, the Tp-Te interval in precordial ECG leads was suggested to depicts the index of TDR. More recent studies have also provided to help estimation of TDR in more complex T waves, including negative, biphasic and triphasic T waves [30].

Clinical Implications of Repolarisation Indices

Patients with non-heart failure

Conlon et al., found mean Tp-Te and Tp-Te/QT ratio significantly were prolonged in patients with coronary artery ectasia comparing to control group (Tp-Te: 95.6 ± 9.01 ms vs. 84.5 ± 6.2 ms and Tp-Te/QT: 0.22 ± 0.02 vs. 0.20 ± 0.01, P < 0.05 for all) [31]. Tenekcioglu et al., found mean Tp-Te, Tp-Te/QT and Tp-Te/QTc ratio were significantly higher in patients with coronary slow flow phenomenon (Tp-Te: 85 ± 13.7 ms vs. 74 ± 9.9 ms and Tp-Te/QT: 0.24 ± 0.03 vs. 0.20 ± 0.02 and Tp-Te/QTc: 0.20 ± 0.03 vs 0.17 ± 0.02 all of P-value < 0.001) [32]. Can Yontar et al., demonstrated mean Tp-Te, Tp-Te/QT ratio, Tp-Te/QTc ratio were higher in patients with mitral valve prolapse comparing to normal healthy patients (Tp-Te: 100.2 ± 22.1 ms vs. 74.6 ± 10.2 ms; Tp-Te/QT: 0.24 ± 0.0 vs. 0.20 ± 0.0; all P-value < 0.001) [24]. Castro Hevia et al. found Tp-Te interval is a suitable risk predictor for VA in patients with Brugada syndrome (BS). Most of these arrhythmia recurrences were in patients maximum QTc > 460 ms, and an average value of Tp-Te > 100 ms. The Tp-Te and Tp-Te dispersion were significantly longer in patients experiencing a recurrence compared with those did not (104.4 and 35.6 ms vs 87.4 and 23.2 ms; P = 0.006 and P = 0.03; respectively) [10]. These results were congruent with another trial with BS. Tp-Te duration in lead V1 (87 ± 30 ms vs. 71 ± 21 ms; P = 0.017) was significantly longer and Tp-Te/QT ratio (0.24 vs. 0.19; P = 0.019) was significantly larger in patients with VA. They found a cutoff value of Tp-Te ≥ 77 ms and Tp-Te/QT ratio of ≥ 0.205 for predicting cardiac events with a good sensitivity and specificity level [33]. In hypertrophic cardiomyopathy patients with VA events, mean Tp-Te interval and Tp-Te/QTc ratio were longer than without events and control group (Tp-Te: 82.6 ± 9.8 ms vs. 74.6 ± 9.3 ms; Tp-Te/QTc: 0.202 ± 0.01vs.0.181 ± 0; P < 0.001 for all) [34]. Another trial which included acute ST-elevation myocardial patients with coronary interventional therapy showed pre-coronary intervention (pre-CI) Tp-Te was prolonged in patients that died during follow-up. The optimal cutoff point was determined to be 100 ms for the pre-CI Tp-Te [16]. In acquired bradycardic patients The QT interval, QTc interval, and Tp-Te interval were closely related to the risk of Torsade de Points (TdP). The best single discriminator for TdP
was the Tp-Te. Also, having a Tp-Te $\geq 85$ ms with Long-QT2-like morphology almost were proposed to predict the occurrence of TdP [13].

**Patients with heart failure**

An investigation by Morin et al. found increased Tp-Te was associated with 14% increase in risk for VA ($P = 0.04$), and Tp-Tec was found to be more powerful predictor ($P < 0.01$) in 327 HFrEF patients. Increasing of Tp-Tec was associated with a 19% increase in the risk of death ($P < 0.01$). The cutoff point of Tp-Te was 103.5 ms for VA and 126.7 ms for all-cause mortality in 2 years [4]. Lellouche et al. found baseline QTc dispersion and Tp–Te dispersion was significantly higher in patients with ICD (intracardiac defibrillator) therapy after a 1-year follow-up ($P = 0.08$). After multivariate analysis postimplantation Tp–Te was the only independent predictor of ICD therapy ($P = 0.02$). A cutoff point of Tp–Te: 110 ms level had specificity 74% and sensitivity 77% in predicting ICD therapy [35]. Evaluation of 101 consecutive patients with HF by Xue et al., after CRT-D (cardiac resynchronisation therapy-intracardiac defibrillator) therapy Tp-Te was shortened (107 ± 23 ms at baseline to 94 ± 24 ms at the 1-year follow-up). Shortened Tp-Te group experienced lower VA episodes, compared to non-shortened Tp-Te (12% vs. 39%, $P = 0.002$) [36].

**In general population risk stratification**

Panikkath et al., showed Tp-Te, QTc, QRS dispersion and Tp-Te/QT ratio were significantly prolonged in SCD cases compared to control (Tp-Te: 89.4 ms vs 76.1 ms; Tp-Te/QT: 0.22 vs 0.19; $P < 0.05$ for all) [8]. Tp-Te was proved to be a good risk predictor for VA in various cardiac diseases including HF patients. None of these trials didn’t compare heart failure patients according to their LVEF which was our prime aim.

**A clinical and echocardiographic feature of our study population**

Newly classification of HF patients in three groups attracted attention on new HF class which named HfMrEF [1]. HfMrEF has different features comparing to HfPef and HFrEF [2]. Our main aim was to find interesting results from this new group for indexes of TDR and fQRS. We found our HfMrEF patients have many features somewhat different from HfPef but nearly the same characteristics with HFrEF. Previous reports stated HfMrEF tends to have a higher rate of HT, DM and CAD and increased LV diastolic stiffness compared to HfPef [3]. DM and HT were seen more in HfMrEF and HFrEF than HfPef ($P < 0.05$). But CAD was seen the same in three groups ($P > 0.05$). LV-Dys was found same in groups ($P > 0.005$). Patients with HFrEF had higher creatinine level than others ($P < 0.0001$).

Although we determined the cutoff level of Tp-Te > 100 ms as a higher, but our examination found only 11.5% of patients had Tp-Te value higher than cutoff level. Mean Tp-Te was found 76 ms in our patients which was lower than the accepted cutoff levels in other reports including HF patients even reference predictive level for SCD for the general population [4], [8], [35], [36]. But Tp-Tec levels were found higher than some previous cutoff levels [13], [33]. Other important indices like QT, QTc, Tp-Te/QT, Tp-Te/QTc, Tp-Tec/QTc didn’t show any significant difference between groups. When looking into results more precisely in tables, our mean Tp-Te/ QT and Tp-Te/QTc values in all groups were found higher than important cutoff levels in some trials [8], [24], [31], [32], [34]. But after careful examination, some indices were found meaningful higher than accepted cutoff points according to some trials, mean Tp-Te/QT level in our HfMrEF patients was higher than patients with BS. [33] However after an investigation of newer indices in this study which was including Qtp, S-Tp, S-Te as well as their heart rate corrected forms QTPc, S-Tpc, S-Te showed only QTP, S-Tp and S-Te were significantly different between groups (All for $P$-value < 0.05, in Table 3-4). For QTP HfRFEF and HfPef showed the significant difference but HfMrEF was same with HfRFEF and HfPef. For S-Tp again HfRFEF and HfPef showed the significant difference, but HfMrEF was same with HfRFEF and HfPef. However for S-Tp although HfMrEF wasn’t different from HfRFEF but different from HfPef and again HfPef was different from HfRFEF. Which is the useful distinct index between these three groups, S-Tp or S-Te or QTP? Exactly what is the value of these new indexes in prediction for VA or serious events in HF patients, we don’t know now. Patients with HfPef had more prolonged QTP, S-Te, and S-Tp than others which may imply more protected LVEF shows some different depolarisation-repolarisation features than HfMr and HFrEF. We need to investigate these indexes in a prospective study with more patients to find true answers. Another finding of our study was about the relationship between fQRS and indexes of TDR showed there was a significant relationship between fQRS and S-Te with important correlation ($P = 0.031$). Again important indexes were found relevant, but we need more studies on how we can use them in real life for prognosis of patients. And finally, patients with LVD-days had a significant relationship with prolonged Tp-Te and some other indices (in table 7) which may suggest that this kind of indices can use to show stages progressive ventricular disease with other subtle traces like diastolic dysfunction.

**Limitations**

Some important limitations of this study should be mentioned. This study was a cross-sectional study to find differences of TDR on ECG. In
conjunction with different level of LVEF, some of the previously reported indexes of TDR were supposed to be different, but we could not find. But we could find different newer indexes of TDR. Maybe low number of patients with rather missing data for some measurement which could affect to find real differences of these indexes of TDR we showed some interesting data for TDR indices in three different HF groups and finally we can say there are a needed more trials with more patients to establish and evaluate difference or relationship among these indices deeply.

In conclusion, although in our study mean TP-Te interval levels were lower than other reports and didn’t show any differences between three different HF groups. QTP, S-Te, S-TP intervals were found to be different between the HF groups. S-Te and IQRS showed a correlation. For prediction of VA and cardiovascular death newer indexes on ECG are needed to be established in the future which will make us facilitate to distinguish high risk patients. Maybe Pathological and electrophysiological feature of TDR must be evaluated in the future.

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References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37:2129-2200. https://doi.org/10.1093/eurheartj/ehw128 PMid:27206819

2. Vedin O, Lam CSP, Koh AS, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction a nationwide cohort study. Circ Heart Fail. 2017; 10:e003975. https://doi.org/10.1161/CIRCHEARTFAILURE.117.003875 PMid:28615366

3. Lam CSP and Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%). European Journal of Heart Failure. 2014; 16:1049-1055. https://doi.org/10.1002/ejhf.159 PMid:25210008

4. Morin DP, Saad MN, Shams OM, et al. Relationships between the T-peak to T-end interval, ventricular tachycardia, and death in left ventricular systolic dysfunction. Europace. 2012; 14: 1172-1179. https://doi.org/10.1093/europace/eur246 PMid:22277646

5. Dogan M, Yiginer O, Degirmencioglu G, Un H. Transmural dispersion of repolarization: a complementary index for cardiac inhomogeneity. J Geriatr Cardiol. 2016; 13:99-100. PMid:26918022 PMcid:PMC4753021

6. Ophoth T, Coronel R, Janse M.J. Is there a significant transmural gradient in repolarization time in the intact heart? Repolarization Gradients in the Intact. Heart. Circ Arrhythm Electrophysiol. 2009; 2:89-96. https://doi.org/10.1161/CIRCEP.108.825356 PMid:19808447

7. Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, Gintant GA, Liu DW. Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. Circulation Research. 1991; 69(6):1427-49. https://doi.org/10.1161/01.RES.69.6.1427 PMid:1659499

8. Panikkath R, Reinier K, Uy-Evano A, et al. Prolonged peak-to-end interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol. 2011; 4:441-447. https://doi.org/10.1161/CIRCEP.110.960568 PMid:21593198 PMcid:PMC3175947

9. Porthan K, Viltasalo M, Toivonen L, et al. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. Circ Arrhythm Electrophysiol. 2013; 6:690-696. https://doi.org/10.1161/CIRCEP.113.000556 PMid:23881778

10. Hevia JC, Antzelevitch C, Bárázga FT, et al. Tpeak and Tpeak-end dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada Syndrome. J Am Coll Cardiol. 2006; 47(9):1828-1834. https://doi.org/10.1016/j.jacc.2005.12.049 PMid:16682308 PMcid:PMC1474075

11. Shimizu M, Ino H, Yasuokei K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin Cardiol. 2002; 25(7):335-339. https://doi.org/10.1002/clc.490250706 PMid:12109867

12. Yan GX and Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998; 98(18):1928-1936. https://doi.org/10.1161/01.CIR.98.18.1928 PMid:9799215

13. Topilski I, Rogowski O, Rosso R, et al. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. J. Am. Coll. Cardiol. 2007; 49(3):320-328. https://doi.org/10.1016/j.jacc.2006.08.058 PMid:17239713

14. Karaman K, Karayakalı M, Erken E, et al. Assessment of myocardial repolarisation parameters in patients with familial Mediterranean fever. A Cardiovascular Journal of Africa. 2017; 28(3): 154-168. https://doi.org/10.5830/CVJA.2016-074 PMid:28759086 PMcid:PMC5558142

15. Chua KCM, Rusinaru C, Reinier K, et al. Tpeak-to-Tend interval corrected for heart rate: A more precise measure of increased sudden death risk? Towards an improved sudden death risk prediction. Heart Rhythm 2016; 13(11):2181-2185. https://doi.org/10.1016/j.hrthm.2016.08.022 PMid:27523774 PMcid:PMC5100825

16. Haarmark C, Hansen PR, Vedel-Larsen E, et al. The prognostic value of the Tpeak-toTend interval in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Journal of Electrocardiology 2011; 42(6):555-560. https://doi.org/10.1016/j.jelectrocard.2009.06.009 PMid:19643432

17. Ozcan S, Cakmak HA, Ikitimur B, et al. The prognostic significance of narrow fragmented QRS on admission electrocardiogram in patients hospitalized for decompensated systolic heart failure. Clin. Cardiol. 2013; 36(9):560-564. https://doi.org/10.1002/cjic.22153 PMid:23754185

18. Igarashi M, Tada H, Yamasaki H, et al. Fragmented QRS is a novel risk factor for ventricular arrhythmic events after receiving cardiac resynchronization therapy in nonischemic cardiomyopathy. Journal of Cardiovascular Electrophysiology. 2016; 28(3):327-335. https://doi.org/10.1111/jcp.13132 PMid:27925329

19. Brenyo A, Pietraask G, Barsheshet A, et al. QRS fragmentation and the risk of sudden cardiac death in MADIT II. J Cardiovasc Electrophysiology. 2012; 23(12):1343-1348. https://doi.org/10.1111/j.1540-8167.2012.02390.x PMid:22805297
20. Ozcan F, Turak O, Canpolat U, et al. Fragmented QRS predicts the arrhythmic events in patients with heart failure undergoing ICD implantation for primary prophylaxis: more fragments more appropriate ICD shocks. Ann Noninvasive Electrocardiol. 2014; 19(4):351-357. https://doi.org/10.1016/j.aniec.2014.12.014 PMid:24920012

21. Özyılmaz S, Akgül Ö, Uyarel H, et al. Assessment of the association between the presence of fragmented QRS and the predicted risk score of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy. Anatol J Cardiol. 2017; 18:54-61. https://doi.org/10.14744/AnatolJCardiol.2017.7593

22. Sinha SK, Bhagat K, Asif M, et al. Fragmented QRS as a marker of electrical dyssynchrony to predict inter-ventricular conduction defect by subsequent echocardiographic assessment in symptomatic patients of non-ischemic dilated cardiomyopathy. Cardiol Res. 2016; 7(4):140-145. https://doi.org/10.14740/cr495w PMid:28197282 PMCid:PMC5295578

23. Xue JX, Gao W, Chen Y, et al. Study of repolarization heterogeneity and electrocardiographic morphology with a modeling approach. J Electrocardiol. 2008; 41:581-7. https://doi.org/10.1016/j.jelectrocard.2008.07.027 PMid:18804785

24. Yontar OC, Karaagac K, Tenekecioglu E, et al. Assessment of ventricular repolarization inhomogeneity in patients with mitral valve prolapse: value of T wave peak to end interval. Int J Clin Exp Med. 2014; 7(8):2173-2178. PMid:25232403 PMCid:PMC4161563

25. Bazett HC. An analysis of the time relation of electrocardiograms. Heart 1920; 7:353-367.

26. Molnar J, Weiss JS, Rosenthal JE. The missing second: what is the correct unit for the flow TP? Canadian journal of cardiology. 1995; 11(7):537-8. https://doi.org/10.1016/S0828-9149(95)00603-1

27. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. American Society of echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. J Am Soc Echocardiogr. 1989; 2:358-367. https://doi.org/10.1016/S0894-7317(89)80014-8

28. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009; 22:107-133. https://doi.org/10.1016/j.echo.2008.11.023 PMid:19187653

29. Opthof T, Coronel R, Janse MJ. Is there a significant transmural gradient in repolarization time in the intact heart? Repolarization gradients in the intact heart. Circ Arrhythmia Electrophysiolog. 2009; 2:89-96. https://doi.org/10.1016/CIRCEP.108.825356 PMid:19808447

30. Antzelevitch C, Viskin S, Shimizu W, et al. Does Tpeak–Tend provide an index of transmural dispersion of repolarization? Heart Rhythm. 2007; 4(8):1114-1119. https://doi.org/10.1016/j.hrthm.2007.05.028 PMid:17675094 PMCid:PMC1994816

31. Conlona R, Tannera R, Davida S, et al. Evaluation of the TP-te interval, QTc and P-wave dispersion in patients with coronary artery Ectasia. Cardiol Res. 2017; 8(6):280-285. https://doi.org/10.14740/cr631w PMid:29317970 PMCid:PMC5755659

32. Tenekecioglu E, Karaagac K, Yontar OC, et al. Evaluation of TP-te interval and TP–Te/QT ratio in patients with coronary slow flow TP–Te/QT ratio and coronary slow flow. Eurasian J Med. 2015; 47:104-8. https://doi.org/10.5152/eurasianmed.2015.72 PMid:26169494 PMCid:PMC4494444

33. Zumhagen S, Zeidler EM, Stallmeyer B, et al. Tpeak–Tend interval and Tpeak–Tend/QT ratio in patients with Brugada syndrome. Europace. 2016; 18:1866-1872. PMid:26941339

34. Akboğa MK, Balci KG, Yılmaz S, et al. Tp-e interval and Tp-e/QT ratio as novel surrogate markers for prediction of ventricular arrhythmia events in hypertrophic cardiomyopathy. Anatol J Cardiol. 2017; 18:48-53. https://doi.org/10.14744/AnatolJCardiol.2017.7581

35. Lellouche N, De Diego C, Akopyan G, et al. Changes and predictive value of dispersion of repolarization parameters for appropriate therapy in patients with biventricular implantable cardioverter-defibrillators. Heart Rhythm. 2007; 4: 1274-1283 https://doi.org/10.1016/j.hrthm.2007.06.012 PMid:17905332

36. Xue C, Hua W, Chi C, et al. Acute and chronic changes and predictive value of tpeak-tend for ventricular arrhythmia risk in cardiac resynchronization therapy patients. Chin Med J. 2016; 129:2204-2211. https://doi.org/10.4103/0366-9699.189916 PMid:27625093 PMCid:PMC5022342