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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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Keywords: Heart Failure; Transmural dispersion; Tp-Te interval; fQRS; Tp-Te/QT

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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. 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-Te) and S-Tpeak (S-Tp) were found significantly different between groups (P < 0.05). Again S-Te was found different according to having fragmented QRS (fQRS) on ECG (P = 0.031). Comparing to mitral inflow E/A parameters showed significant differences for Tp-Te, Tp-Tec, Tp-Te/QT, Tp-Te/QTc and Tp-Tec/QTc parameters. Finally, we found correlations between S-Te 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-Te and fQRS (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-Te, S-Tp intervals. Also, S-Te and fQRS 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

Hear 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 (LEVF). 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 dyssynchrony, VA, SCD and poor prognosis 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- HfmrEF- 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%), HFmrEF (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.

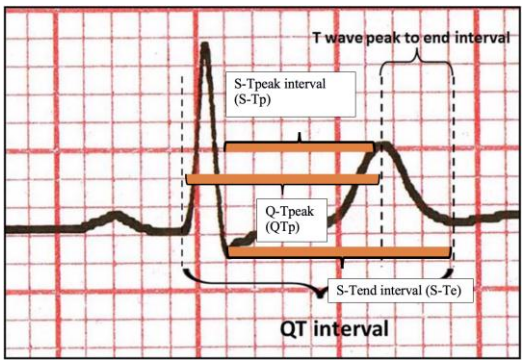

Figure 1: Demonstration of the T wave peak to end and QT intervals [24]

Other novel indexes were described as S-Tend (S-Te) interval and S-Tpeak 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].

fQRS 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).

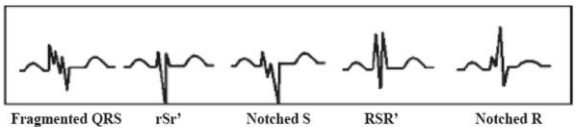

Figure 2: Different types of fragmented QRS (fQRS) [23]

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, 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 (%, per cent). 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 descriptives analysis of some features of groups

Features	Count	LVEF% < 40 Group 1 n:66 (34.4%)	LVEF% 40-49 Group 2 n:69 (35.9%)	LVEF% >50 Group 3 n:57 (29.7%)	Total n:192 (100%)	*P*¥
Gender						
Women	Count & percent in total	20 (10%)	27(14%)	21 (10%)	68 (35%)	
Male	Count & percent in total	46 (24%)	42 (22%)	36 (19%)	124 (65%)	0.543 *
Age	Mean ± SD	71.5 ± 13.2	68.8 ± 13.3	67.6 ± 13.3	69.4 ± 13.3	0.086 #
	Min: 22 Max: 97				Min: 22 Max: 97	
S-BP (mmHg)	Mean ± SD	127 ± 26.5	132 ± 25.4	135 ± 27.2		0.568 #
	Median (25%-75%)	130 (110-148)	128 (110-150)	130 (120-160)		
D-BP (mmHg)	Mean ± SD	69 ± 14.5	67 ± 14.5	71 ± 12.7		0.574 #
	Median (25%-75%)	70 (60-81)	70(60-80)	70(62-80)		
Pulse rate per minute	Mean ± SD	99 ± 22.7	98 ± 26.4	82 ± 19.2		0.001 #
	Median (25%-75%)	98 (84-114)	94 (79-114)	79 (69-98)		
LVEF %	Mean ± SD Min: 18 Max: 58	31 ± 5.5	44 ± 2.9	53 ± 2.8		0.001 #
	Median (25%-75%)	32 (26-36)	45 (41-47)	53 (51-55)		
NT-ProBNP	Mean±SD	310 ± 116.9	305 ± 120.5	330 ± 135.7		ns #
NYHA 1-2	Count & percent in total	46 (23.9 %)	44 (22.9%)	40 (24.4%)		ns #
NYHA 3-4	Count & percent in total	20 (10.4%)	25 (13.0%)	17 (8.8%)		ns #
LVDD (mm)	Mean ± SD	54 ± 6.8	51 ± 7.9	49 ± 6.1		0.002 #
	Median (25%-75%)	53 (49-60)	51 (46-54.5)	51 (46-54.7)		
LVSD (mm)	Mean ± SD	40 ± 8.1	35 ± 7.7	32 ± 6.5		0.001 #
	Median (25%-75%)	39 (33-47)	35 (29-40)	32 (27-35)		
IVS (mm)	Mean ± SD	10 ± 1.6	10 ± 1.4	10 ± 1.3		0.782 #
	Median (25%-75%)	10 (10-11)	11 (10-12)	11 (10-11)		
DM (missing n = 6)	Count & percent in total	27 (15%)	37 (20%)	16 (8%)	80 (43.2%)	0.006*
HT (missing n = 8)	Count & percent in total	45 (25%)	46 (25%)	29 (16%)	120 (65.6%)	0.017*
HPL (missing n = 16)	Count & percent in total	16 (9%)	21 (12%)	23 (13%)	60 (34.3%)	0.173*
CAD (missing n = 13)	Count & percent in total	39 (22%)	40 (22%)	28 (16%)	107 (60.1%)	0.071*
AF	Count & percent in total	14 (7%)	21 (11%)	11 (6%)	46 (24.1%)	
SR	Count & percent in total	51 (27%)	48 (25%)	46 (24%)	145 (75.9%)	0.291*

*: Chi-Square test. #: Independent samples non-parametric Kruskal-Wallis test. ¥ : P < 0,05 is accepted statistically significant. SD: Standard deviation, mm: millimetre, S-BP: Systolic blood pressure, D-BP: Diastolic Blood pressure, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association functional classification, LVDD: Left ventricular diastolic diameter, LVSD: Left ventricular systolic diameter, IVS: interventricular septum, DM: Diabetes mellitus, HT: Hypertension, HPL: Hyperlipidemia, CAD: Coronary artery disease, AF: Atrial fibrillation, SR: Sinus rhythm.

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 T time (*P* = 0.002) and between group 1 versus (vs) 3 and 2 vs 3 (*P* = 0.009 and *P* = 0.042, respectively) for QT time.

Table 2: Baseline frequency and descriptives analysis of groups

Features	Count	LVEF% < 40 Group 1 n:66 (34.4%)	LVEF% 40-49 Group 2 n:69 (35.9%)	LVEF% > 50 Group 3 n:57 (29.7%)	Total n:192 (100%)	*P*¥
PW (mm)	Mean ± SD	9.8 ± 1.4	10.4± 1.2	10.3 ± 1.3	10 ± 1.3	0.332#
LA (mm)	Mean ± SD	45 ± 8.2	41± 8.0	41 ± 9.6	42 ± 8.6	0.047#
RV (mm)	Mean ± SD	31 ± 5.9	29 ± 5.9	27 ± 3.6	29 ± 5.5	0.075#
RA (mm)	Mean ± SD	34 ± 6.7	31 ± 7.4	31 ± 10.1	32 ± 8.0	0.067#
P time (ms)	Mean ± SD	70 ± 41.2	62± 46.1	79 ± 43.5	70 ± 44.0	0.067#
QRS time (ms)	Mean ± SD	91 ± 16.5	90 ± 12.7	88 ± 13.7	90 ± 14.4	0.542#
T time (ms)	Mean ± SD	127 ± 29.0	141 ± 41.7	148 ± 35.0	138 ± 36.6	0.003#
QT time (ms)	Mean ± SD	345 ± 49.9	348 ± 53.8	375 ± 54.6	355 ± 54.0	0.007#
fQRS	Present count & percent in total	37 (19.3%)	40 (20.8%)	28 (14.5%)	105 (55%)	0.566*
	None count & percent in total	28 (14.6%)	29 (15.1%)	29 (15.1%)	86 (45%)	

*: Chi-Square test. #: Independent samples non-parametric Kruskal-Wallis test. ¥ : P < 0,05 is accepted statistically significant. SD: Standard deviation, mm: millimetre, ms: millisecond, PW: Left posterior ventricular wall, LA: Left atrium four-chamber diameter, RV: Right ventricular four-chamber diameter, RA: Right atrium four-chamber diameter, fQRS: Fragmented QRS.

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

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

Features	Count	LVEF%<40 Group 1	LVEF%40-49 Group 2	LVEF%>50 Group 3	Total	*P*¥
		n:66 (34.4%)	n:69 (35.9%)	n:57 (29.7%)	n:192 (100%)	
S-Tp (ms)	Mean±SD	222.0 ± 43.0	219.7± 42.3	241.3 ± 53.3	227.0 ± 46.8 Min:120 msn Max: 502 msn	0.032
	Median (25%-75%)	220 (193-240)	220 (200-243)	240 (207-260)		
S-Tpc (ms)	Mean ± SD	279.6 ± 42.7	277.6 ± 35.8	276.2 ± 45.5	277.9 ± 41.0 Min:170 msn Max:435 msn	0.631
	Median (25%-75%)	278 (257-308)	275 (251-304)	268 (240-307)		
S-Te (ms)	Mean ± SD	296.0 ± 47.5	296.7 ± 47.8	318.9 ± 56.7	303.1 ± 51.3 Min: 199 msn Max: 582 msn	0.028
	Median (25%-75%)	288 (266-320)	292 (271-320)	320 (280-358)		
S-Tec (ms)	Mean ± SD Min: 18 Max: 58	370.8 ± 48.8	376.4 ± 44.2	365.7 ± 45.4	371.3 ± 46.1 Min: 235 msn Max: 544 msn	0.432
	Median (25%-75%)	372 (342-403)	374 (342-404)	360 (336-399)		

¥: *P* < 0,05 is accepted statistically significant. S-Tp: Measurement from nadir S wave to T peak. S-Te: Measurement from nadir S wave to T end. SD: Standard deviation, ms: millisecond, c: Heart rate-corrected form with Bazett's formula (n/ RR).

We found the mean Tp-Te in total population as 76.0 ± 17.5 ms with minimum: 40 ms and maximum: 120 ms and didn't show any difference between groups (Tp-Te: 73.4 ± 15.4 ms vs. 77.5 ± 19.0 ms vs. 77.2 ± 17.9 ms; *P* = 0.291) with all kind of new indexes of TDR as QTpc, Tp-Tec, Tp-Te/QT, Tp-Te/ QTc, Tp-Tec/QTc and PR interval (QTpc: *P* = 0.644*;* Tp-Te > 100 ms: *P* > 0.05; Tp-Tec: *P* = 0.213; Tp-Te/QT: *P* = 0.463; Tp-Te/QTc: *P* = 0.253; Tp-Tec/QTc: *P* = 0.367, PR: *P* = 0.547).

After then again comparing to groups for QTp and RR interval between each other showed there was a significant difference only in between group 1 and 3 for QTp time (*P* = 0.049) and however in group 1 vs 3 and 2 vs 3 (*P* = 0.0001 for both) for RR interval time.

As shown in Table 4 and Table 5 when comparing to groups for new indices we found the significant differences for S-Tp and S-Te measurements (S-Tp: 222.0 ± 43.0 ms vs. 219.7 ± 42.3 ms vs. 241.3 ± 53.3 ms; *P* = 0.032; S-Te: 296.0 ± 47.5 ms vs. 296.7 ± 47.8 ms vs. 318.9 ± 56.7 ms; *P* = 0.028). But S-Tpc (*P* = 0.631) and S-Tec (*P* = 0.432) weren't found to be different between groups.

Again we compared the groups each other for S-Te and S-Tp and found there was a significant difference only in between group 1 and 3 for S-Te time (*P* = 0.043). Other many of the biochemistry features and list of used drugs were not different between groups (for all *P* value > 0.05), however ratio of used of mineralocorticoid receptor antagonist (MRA) drugs, blood urea nitrogen (BUN), creatinine, glucose and WBC levels were found significantly different between groups (for all *P*-value < 0.05).

When comparing of incidents of TDR according to having of E/A < 1.0 (LVD-Dys) that we found significant differences between groups for Tp-Te, Tp-Tec, Tp-Te/QT, Tp-Te/QTc and Tp-Tec/QTc (*P* = 0.005, *P* = 0.003, *P* = 0.002, *P* = 0.016, *P* = 0.002, respectively). LVD-Dys was found a significant predictor of many of arrhythmic indices.

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

Groups	Adj.Sig. *P*¥ for S-Te	Adj.Sig. *P*¥ for S-Tp
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

¥: *P* < 0,05 is accepted statistically significant.

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

This Table showed us fQRS was found relevant only with S-Te however not with Tp-Te and other important indices. Finally, we made correlation analysis and we found significant correlation between S-Te and WBC (r = - 0,171; *P* = 0,037) and S-Tp and WBC (r = - 0,170; *P* = 0,038) and between S-Te and fQRS (r = 0,158; *P* = 0,031).

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 n: 105 (55%)	fQRS None n: 86 (45%)	*P*[#,*]
QTc (ms)	Mean ± SD	439.5 ± 37.5	442.0 ± 41.8	0.544
QTp (ms)	Mean ± SD	282.7 ± 43.8	272.8 ± 57.1	0.197
QTpc (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-Tec (ms)	Mean ± SD	95.1 ± 24.0	92.3 ± 24.1	0.339
Tp-Te/QT	Mean ± SD	0.216 ± 0.05	0.214 ± 0.05	0.481
Tp-Te/QTc	Mean±SD	0.182 ± 0.07	0.170 ± 0.04	0.256
Tp-Tec/ QTc	Mean±SD	0.214 ± 0.05	0.215 ± 0.05	0.720
S-Tp (ms)	Mean±SD	230.7 ± 43.5	222.3 ± 50.4	0.157
S-Tpc (ms)	Mean±SD	279.6 ± 39.8	275.7 ± 42.6	0.415
S-Te (ms)	Mean±SD	309.2 ± 47.4	295.5 ± 55.0	0.031
S-Tec (ms)	Mean±SD	374.0 ± 44.2	368.0 ± 48.5	0.250

[#]: Non-parametric Mann-Whitney U test. [*]: Chi-Square Test. [*]: *P* < 0,05 is accepted statistically significant. SD: Standard deviation, ms: millisecond, c: Heart rate-corrected form with Bazett's formula (n/ RR). fQRS: 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 renentry 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 Q-Tpeak (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 Repolarization 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: 95.5 ± 9.01 ms vs. 84 ± 5.62 ms and Tp-Te/QT: 0.22 ± 0.02 vs. 0.20 ± 0.01, *P* < 0.05 for all) [31]. Tenekecioglu 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 who 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 TpTe/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 vs.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 Pointes (TdP). The best single discriminator for TdP

was the Tp-Te. Also, having a Tp-Te ≥ 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-Tec 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 HFrEF and HFpEF showed the significant difference but HFmrEF was same with HFrEF and HFpEF. For S-Te again HFrEF and HFpEF showed the significant difference, but HFmrEF was same with HFrEF and HFpEF. However for S-Tp although HFmrEF wasn't different from HFrEF but different from HFpEF and again HFpEF was different from HFrEF. 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 indices 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 fQRS 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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