

A Potentially Useful Marker to Determine for Left Ventricular Dysfunction in Patients LBBB With Dilated Cardiomyopathy: Tpeak - Tend

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ABSTRACT

Introduction: It has been shown in various epidemiological studies that left bundle branch block (LBBB) is an independent risk factor for the cardiac mortality. In this study, we aimed to examine the relationship between left ventricular functions in patients with LBBB and the T peak-T end (Tp-e) interval which can be easily measured by using the ECG when patients are admitted to the hospital.

Materials and Method: In this study, 56 patients with LBBB were selected according to their echocardiographic (ECG) findings by using the retrospective scanning method. In line with this selection, patients were divided into two groups; such as EF<50% (60,2 ± 5,6) and EF>50% (58,1 ± 7). Tp-e/cTp-e intervals were measured by using surface electrocardiogram technique.

Results: According to our results, here was a negative correlation between Tp-e and EF in patients with LBBB and DCMP (r=-0,723, p=0,0001). We observed a positive correlation between Tp-e and LVEDD (r=0,394, p=0,035) and LVESD (r=0,478, p=0,009). In the correlation analysis, we observed a negative correlation between the cTp-e and EF values (r=-0,649, p=0,0001) and there was a positive correlation between cTp-e and LVEDD (r=0,587, p=0,001) as well as LVESD (r=0,558, p=0,002).

Conclusion: Consequently, Tp-e/cTp-e interval can be a useful parameter that can be used particularly in the determination and follow-up of the patients whose left ventricular functions have not yet been deteriorated. Furthermore, this value can be used to select patients who can benefit from the treatment and the optimal timing of resynchronization therapy.

Keywords: Left bundle branch block; Dilated Cardiomyopathy; Tpeak-Tend; ECG

LBBB Olan Dilate Kardiyomiyopati Hastalarında Sol Ventrikül Disfonksiyonunu Belirlemek için Potansiyel Olarak Faydalı Bir Marker : Tpeak - Tend

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ÖZET

Giriş: Sol dal bloğunun (LBBB) birçok epidemiyolojik çalışmada kardiyak mortalitenin bağımsız bir risk faktörü olduğu gösterilmiştir. Son yapılan çalışmalarda izole LBBB' a spesifik progresif kardiyomiyopati (KMP) gelişebileceği gösterilmiştir. Bu çalışmamızda LBBB olan hastalarda başvuru EKG sinde kolayca ölçülebilen T peak-T end (Tp-e) intervalinin sol ventrikül fonksiyonları ile ilişkisini araştırma amaçlanmıştır.

Hastalar ve Metod: Bu çalışmaya retrospektif tarama ile 56 LBBB hastası alınarak ekokardiyografik değerlerine göre; EF<50% ($60,2 \pm 5,6$) ve EF>50% ($58,1 \pm 7$) olarak 2 gruba bölünerek incelendi. Tp-e / cTp-e intervalleri yüzey elektrokardiyogramlarından bilgisayar ortamında hassas ölçümler elde etmek için bir dijital cetvel yardımıyla manuel olarak ölçüldü. Datalar hasta dosyalarından elde edilen ekokardiyografik parametrelerle kıyaslandı.

Bulgular: LBBB with DKMP hastalarında Tp-e ile EF arasında negatif korelasyon ($r=-0,723$, $p=0,0001$), SVDSÇ arasında ise pozitif korelasyon ($r=0,394$, $p=0,035$) ve SVSSÇ ile pozitif korelasyon ($r=0,478$, $p=0,009$) bulunmuştur. Korelasyon analizinde; cTp-e ile EF arasında negatif korelasyon ($r=-0,649$, $p=0,0001$), SVDSÇ arasında ise pozitif korelasyon ($r=0,587$, $p=0,001$) ve SVSSÇ ile pozitif korelasyon ($r=0,558$, $p=0,002$) bulunmuştur.

Sonuç: Sonuç olarak Tp-e/cTp-e intervali özellikle sol ventrikül fonksiyonları henüz bozulmamış hastaların belirlenmesinde, takibinde hatta tedaviden fayda görecektir hasta seçiminde ve resenkronizasyon tedavisinin optimal zamanlamasında potansiyel olarak faydalı olabilecek bir parametre olabilir.

Anahtar Kelimeler: LBBB; Dilate Kardiyomiyopati; T peak-Tend; EKG

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INTRODUCTION

Despite the recent developments, heart failure is a major and an increasingly growing public health problem [1]. It has been shown in various epidemiological studies that left bundle branch block (LBBB) is an independent risk factor for the cardiac mortality [2]. In recent studies, progressive cardiomyopathy (CMP) can develop specific to the isolated LBBB [3]. Widespread myocardial damage and fibrosis or the disruptions of intercellular communication in dilated cardiomyopathy (DCMP) patients are appropriate substrates for the reentry mechanism which is responsible for majority of the major arrhythmias [4]. LBBB leads to delay in the mechanical activation of the left ventricle and it negatively affects both systolic and diastolic functions [5]. As a result of this synchronization disorder in the presence of LBBB, intraventricular asynchrony causes the paradoxical septal motion by leading to volume-pressure relationship changes [6]. It has been shown in various echocardiographic studies that isolated LBBB has negative effects on systolic and diastolic functions in asymptomatic individuals. Isolated LBBB shows its negative effects by increasing the diameter of the end-diastolic and decreasing the ejection fraction (EF) [7]. Furthermore, LBBB has direct effects on electromechanical functions as well as it affects the global ventricular function by causing the changes in the coronary perfusion [8]. LBBB has effects on the myocardial structure, functions and the perfusion and thus there can be anteroseptal and septal perfusion defects in the myocardial perfusion scintigraphy despite the absence of the coronary artery disease [9]. There are various hypotheses which try to explain the close relationship between the LBBB and the heart failure. Different zones of the heart show changes in mechanical functions in the presence of LBBB. These changes can lead to increase in the feedback action potential time and dispersion of the membrane recovery. This sets the

stage for the ventricular arrhythmias by increasing the recovery dispersion as a result of the formation of short and long intervals between heart beats [10].

Myocardial repolarization is deteriorated in the congestive heart failure independent of the etiology of the cardiomyopathy [11]. In DCMP, the basic factor for malignant arrhythmias is the presence of the myocardial substrate which is responsible for the reentry mechanism. There should be deterioration in the repolarization of tissues and/or signal transduction in order to observe the reentry mechanism [12]. These deteriorations direct researchers to consider the ST-T alterations in ECG can be fatal arrhythmic findings and they can detect the deteriorations of the repolarization and depolarization via various invasive and non-invasive tests [13,14]. Interval between the apex point and the endpoint of the T wave in the ECG is known as the Tpeak- Tend (Tp-e) interval and it is a noninvasive parameter which can be used to evaluate the myocardial repolarization. Tp-e/corrected (Tp-e/cTp-e) interval is more effective in the prediction of the future ventricular arrhythmias compared to QT dispersion. It has been shown that the increase in this parameter is associated with the cardiovascular deaths [15].

Scientific results show that LBBB has negative effects on the perfusion of the heart, systolic, diastolic performance, and hemodynamics. However, it has not yet been clarified whether or not LBBB is a predictor or a reason or a result of the myocardial dysfunction. New research to be done on this subject will be useful to understand the answers of these questions, to appropriately select patients who can benefit from treatments, and to optimize the timing of the resynchronization therapy. In this study, we aimed to examine the relationship between left ventricular functions in patients with LBBB and the T peak-T end (Tp-e) interval which can be easily measured by using the ECG when patients are admitted to the hospital.

PATIENTS AND METHODS

Study Population

In this study, we retrospectively scanned 280 patients with ICD code who were admitted to Necmettin Erbakan University, Meram Medical Faculty, and Cardiology clinic with heart failure symptoms. Coronary angiography was applied to these patients between January and April 2016. It was detected that 178 of these patients did not have a severe coronary artery disease and who were not ischemic DCMP patients. Totally 56 patients were identified according to their ECG recordings. According to the ECG values of patients with LBBB, patients were divided into two groups such as Group 1 (EF<50%) and Group 2 (EF>50%). We obtained approval from Ethics Committee of Necmettin Erbakan University Clinical Investigations. We conducted the study in line with the ethical principles described by the Declaration of Helsinki. The demographic and clinical characteristics of patients were obtained from patient recordings.

ECG diagnosis criteria for LBBB are as follows; 1) QRS duration longer than 120 ms, 2) Wide notched R wave in Lateral leads (V5-V6, D1 and aVL), 3) Small r wave or absence of the r wave in right precordial leads (V1-V2), 4) Absence of the septal q wave in Left precordial leads (V5-V6), and according to some researchers 60 msn longer intrinsic deflection duration [16].

Exclusion criteria

We excluded patients who did not have ECG or echocardiography recordings, whose recordings cannot be evaluated, who had DCMP due to ischemic heart disease and heart valve disease, who were ICD implanted for the secondary protection, who were ICD implanted for

arrhythmogenic right ventricular cardiomyopathy, who had hematological disorders, history of myocardial infarction, valvular heart disease, atrial fibrillation, who were using antiarrhythmic drugs and digoxin.

Measurement of Tp-e, cTp-e, QT, cQT, and QRS intervals from the 12-Lead ECG

We preferred the recordings at least the 12-lead ECG tracing at 25 mm/s paper speed at 10 mm/mV amplitude. All ECG recordings were transferred to computer by using a scanner with 800 dpi solubility. We used a computer program to calculate the Tp-e/cTp-e intervals and highly sensitive measurements were done by using a digital ruler or vernier caliper manual measuring tool (Figure 1). We measured the Tp-e and QT intervals in lead V5. We respectively measured leads V4 or V6 in case the V5 was not appropriate [17]. We defined the end of the T wave as the intersection of the tangent to the downslope of the T wave and the isoelectric line. We measured T wave offset as between T and U waves in case U wave followed the T wave. On the other hand, we excluded the lead from the study in case the T wave amplitude was lower than 1.5 mm in a particular lead. We measured the QT interval from the earliest onset of the QRS complex to the endpoint of the T wave. We corrected our measurements according to the Bazett formula. Two independent cardiologists conducted the ECG measurements and they were blinded to the recordings of patients. Intra-observer and inter-observer variabilities were estimated by analyzing the randomized 10 ECG measurements and two independent cardiologists repeated the measurements. Blinded investigators analyzed all ECG tracings obtained by another investigator in order to evaluate inter-observed variations. Reproducibility for the measurements of the Tp-e interval and Tp-e dispersion was examined in 20 randomly selected ECG recordings by two cardiologists. Intraobserver and interobserver variability were estimated by measuring Lin's concordance correlation coefficient. Concordance correlation coefficients were 0.958 [95% CI=0.936–0.984] for the Tp-e interval and 0.975 [95% CI=0.952–0.986] for the Tp-e dispersion within the same observer. Concordance correlation coefficients were 0.978 [95% CI=0.954–0.993] for the Tp-e interval and 0.966 [95% CI=0.927–0.983] for the Tp-e dispersion between the two observers.

Statistical Analyses

We used SPSS (Statistical Package for Social Sciences) for Windows 18.0 in order to conduct statistical analyses. When we evaluated the findings of the study, we represented the parametric variables as mean±standard deviation, and categorical variables as percentage. Parametric variables were evaluated by using Student-t test and categorical variables were evaluated by using Chi-square test. The relationship between variables was assessed by using Pearson correlation analysis for normally distributed data and by Spearman's correlation analysis for the data which are not normally distributed. Results were evaluated between 95% confidence interval and the significance was accepted as $p<0.05$.

RESULTS

Characteristics of groups can be seen in Table 1. Groups were not significantly different from each other in terms of their ages ($60,2 \pm 5,6$ versus $58,1 \pm 7$), genders [Male;16 (51,8%) or 16 (59,2%), Female; 13 (48,1%) or 11 (40,7%)], body mass index (BMI) values ($24,8 \pm 2,5$ or $25,6 \pm 2$), systolic and diastolic blood pressure values ($68,6 \pm 7,6$ versus $69,1 \pm 8,2$). Besides, there was also no significant difference between groups in terms of risk factors and medications.

Tp-e and Electrocardiographic Analysis Results

Tp-e interval values of Group 1 and Group 2 were respectively $98,2 \pm 8,2$ ms and $83,2 \pm 8,8$ ms (Table 2). This difference was statistically significant ($p=0,001$). Tp-e interval dispersion values of Group 1 and Group 2 were respectively $37,1 \pm 15,4$ ms and $23,1 \pm 12,8$ ms. This difference was statistically significant ($p=0,002$). cTp-e interval dispersion values of Group 1 and Group 2 were respectively $104,9 \pm 9$ ms and $89,4 \pm 10$ ms. This difference was statistically significant ($p=0,005$). Besides, QRS duration values of Group 1 and Group 2 were

respectively $134,5 \pm 8$ ms and $133,9 \pm 9$ ms. However, this difference was not statistically significant. QT interval values of Group 1 and Group 2 were respectively $380,2 \pm 21,9$ ms and $357,1 \pm 23,1$ ms. This difference was statistically significant ($p=0,001$) (Table 2). cQT interval values of Group 1 and Group 2 were respectively $398,5 \pm 16,1$ ms and $383,4 \pm 17,3$ ms. This difference was statistically significant ($p=0,001$) (Table 2).

Echocardiography Results and Comparisons of Mean Values

According to our findings, we found the IVS values as $0,98 \pm 0,1$ and $99,9 \pm 0,1$; respectively in Group 1 and Group 2 (Table 3). PW values were found as $0,83 \pm 0,1$ and $0,84 \pm 0,1$; respectively in Group 1 and Group2 (Table 3). There was no significant difference between groups. Mean EF values were shown as percentages (%) and we found EF values as $32,4 \pm 3,7$ and $58,2 \pm 4,1$ respectively in Group 1 and Group 2. There was a significant difference between groups ($p=0,001$) (Table 3). In our study, mean LVEDD values were shown as $5,94 \pm 0,42$ cm and $5,08 \pm 0,60$ cm respectively in Group 1 and Group 2. There was a significant difference between groups ($p=0,001$) (Table 3). In our study, mean LVESD values were shown as $3,98 \pm 0,33$ cm and $3,20 \pm 0,51$ cm respectively in Group 1 and Group 2. There was a significant difference between groups ($p=0,001$) (Table 3).

Correlation Analysis Findings

The difference between the echocardiography and electrocardiography findings were compared by using the Pearson or Spearman correlation tests and only the significant results are shown in **Figure 2**. In Group 1, there was a negative correlation between the Tp-e and EF values ($r=-0,723$, $p=0,0001$) and there was a positive correlation between Tp-e and LVEDD ($r=0,394$, $p=0,035$) as well as LVESD ($r=0,478$, $p=0,009$). Similarly, we also detected a negative correlation between cTpe and EF values ($r=-0,649$, $p=0,0001$) and positive

correlation between cTpe and LVEDD ($r=0,587$, $p=0,001$) as well as LVESD ($r=0,558$, $p=0,002$). Meanwhile, there was a negative correlation between Tp-e dispersion and EF values ($r=-0,597$, $p=0,0001$). Besides, we found a positive correlation between Tp-e dispersion and LVEDD ($r=0,443$, $p=0,001$) as well as LVESD ($r=0,622$, $p=0,001$) (Table 4).

We did not detect the Tp-e and echocardiographic values in Group 2. However, when we conducted the population analysis, we found a negative correlation between the Tp-e and EF ($r=-0,737$, $p=0,0001$). On the other hand, there was a positive correlation between the T-pe and LVEDD ($r=0,594$, $p=0,0001$) as well as LVESD ($r=0,692$, $p=0,0001$). Similarly, we detected a positive correlation between cTp-e and SVEF ($r=-0,424$, $p=0,001$) and there was a negative correlation between cTp-e and LVEDD ($r=0,594$, $p=0,0001$) as well as LVESD ($r=0,692$, $p=0,0001$). There was a positive correlation between Tp-e and EF ($r=-0,597$, $p=0,0001$) and there was a negative correlation between cTp-e and LVEDD ($r=0,443$, $p=0,001$) as well as LVESD ($r=0,622$, $p=0,001$) (Table 4).

DISCUSSION

To our knowledge, this is the first study that provides a Tp-e interval evaluation in patients with LBBB. Baldasseroni et al. showed that the presence of LBBB increased the risk of 1 year all-cause mortality by 36% in the Italian Network CHF Registry [18]. Various studies have shown the poor prognosis relationship between LBBB and elongated QT interval which can lead to malign ventricular arrhythmias [19]. Tabatabaei P et al. stated that QT elongation in patients with LBBB depends mostly on the repolarization than the depolarization and QT interval measurement is frequently overestimated [20]. Similar to other studies, we also detected significantly increased QT interval in patients with LBBB together with DCMP. Crow et al. found that the elongation of the JT interval which reflects the repolarization independent of the QRS duration is a prognostic parameter for cardiac events. In our study,

we did not show significant difference among groups in terms of their QRS durations. However, it is interesting that the significant elongation of QT intervals leads to deteriorations of repolarizations in these patients [21].

Even though clinicians commonly use QT/cQT interval, this measurement can be insufficiently measured and inadequately interpreted in LBBB patients. Therefore, Tabatabaei P et al. showed that JT interval measurement should be used to obtain the right ventricular repolarization measurement and it can be better also for the risk stratification [20,22].

It has been specified that the Tp-e/ cTp-e dispersion is a better predictor than the QT interval and it is independent of QRS duration. The starting point of our study is to examine the importance of the Tp-e/ cTp-e dispersion in the population with DCMP together with LBBB. One of the most important findings of our study is that the Tp-e/ cTp-e dispersion was significantly higher in patients with DCMP and LBBB compared to HF patients without LBBB. It has been shown that LBBB associated repolarization disorders increase the mortality risk [23,24] and this lets us think that cTp-e can be easy and clinically useful parameter in patients with LBBB and DCMP.

It was reported higher rates of non-ischemic etiology, progressive LV dilatation, lower ejection fraction, increased symptomatology, and worse survival in patients with LBBB and DCMP compared to patients with normal intraventricular conduction [25]. According to our analysis, LBBB is associated with a LV dilatation and the lower ejection fraction in patients with DCMP.

Vaillant C et al. conducted a study in order to find the answer to the question “Can LBBB lead to DCMP?”. They included patients who had at least 5 years of typical complete LBBB (sinus rhythm) and who had EF a >50% when they were diagnosed with bundle branch block diagnosis, whose EF values decreased to 40% and lower in time, who had a NYHA II-IV

functional capacity, who had a prominent mechanical dyssynchrony in LV, who had a unexplained cardiomyopathy, who were CRT transplanted and who positively responded to CRT transplantation (decrease in the $EF \geq 45\%$ and NYHA class). According to the evaluation, the mean duration from the detection of LBBB to KY development was 11.6 years. Before the CRT implantation, QRS durations of all of these patients were >150 msn. It was detected that 84% of these patients ($n=5$) had normal coronary structures. After the CRT was implanted, it was shown that there was an improvement in the functional capacity and mean EF values. Furthermore, it increased from $\%31 \pm 12$ to $\%56 \pm 8$ after 12 months [3]. In our study, we showed a significant correlation cTp-e interval and EF, LVEDD and LVESD in patients with LBBB together with DCMP.

It has been shown that extended Tp-e is associated with increased mortality in congenital and acquired Long QT syndrome [26], hypertrophic cardiomyopathy [27], and coronary artery disease [28]. It was attributed to hypertrophy and conduction disorders.

In this regard, patients with LBBB and DCMP have common features. It has been known that the scar tissue shows heterogeneous distribution in the non-ischemic DCMP and this leads to the reentry mechanism and provides an appropriate substrate for ventricular arrhythmias [29]. It has been shown that the heterogeneous activation of the myocardium and the scar lead to arrhythmic events and mortality. These events have been shown in various heart diseases primarily in coronary artery heart disease and other such as cardiomyopathy, congenital heart disease, Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy [30].

This shows that Tp-e interval evaluation in patients with LBBB should not be ignored. Tp-e definition in patients with LBBB and DCMP has not yet been clarified. The correlation that we detect can allow us to use Tp-e values effectively in the determination and follow-up the patients particularly whose left ventricle functions have not yet been deteriorated.

Furthermore, it also allows us to appropriately select patients who will be benefited from the treatment and optimize the timing of the resynchronization therapy.

Limitations of the Study

There are some important limitations in our study. First of all, our study was a retrospective study and thus ECG was not performed in order to evaluate the Tpe interval that was the basic parameter that should be assessed in this study. Secondly, clinical parameters including the drug use were obtained from ECG recordings and the alterations of these parameters in time were not evaluated. Thirdly, patients were not followed up in terms of their arrhythmic events and clinical outcomes. Finally, we had less number of patients and thus were restricted in the interpretation of our findings .

Conclusion

Scientific results show that LBBB has negative effects on the perfusion of the heart, systolic, diastolic performance, and hemodynamics. However, it has not yet been clarified whether or not LBBB is a predictor or reason or result of myocardial dysfunction. New research to be done on this subject will be useful to understand the answers of these questions, to select of the patients who can benefit from treatments, and to optimize the timing of the resynchronization therapy. The main emphasis of our study is the prolongation of the Tp-e in patients with LBBB and DCMP together with deteriorated systolic dysfunction. However, the determination of the cut-off value is the issue of further advanced studies. Our patient group did not have a sufficient sensitivity with the only one parameter (Tp-e). Therefore, it is possible to use other clinical and laboratory parameters.

Conflict Of Interest

The authors reported no conflict of interest related to this article.

Authorship Contributions

Concept/Design: AI

Analysis/Interpretation: AI

Data Acquisition: ALS

Writting: AI

Critical Revision: AI

Final Approval: All of authors

Abbreviations

ACEi : Angiotensin converting enzyme inhibitor

ARB: Angiotensin receptor blocker

DCMP: Dilated cardiomyopathy

DM: Diabetes mellitus

EKG: Electrocardiography

ICD: Implantable cardioverter defibrillator

CAD: Coronary artery disease

LBBB: Left bundle branch block

LVEDD: Left ventricular end-diastolic diameter

LVESD: Left ventricular end-systolic diameter

EF: Left ventricular ejection fraction

Tp-e: Tpeak-Tend

CTp-e: corrected Tpeak-Tend

cQT: corrected QT

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Figure Legends

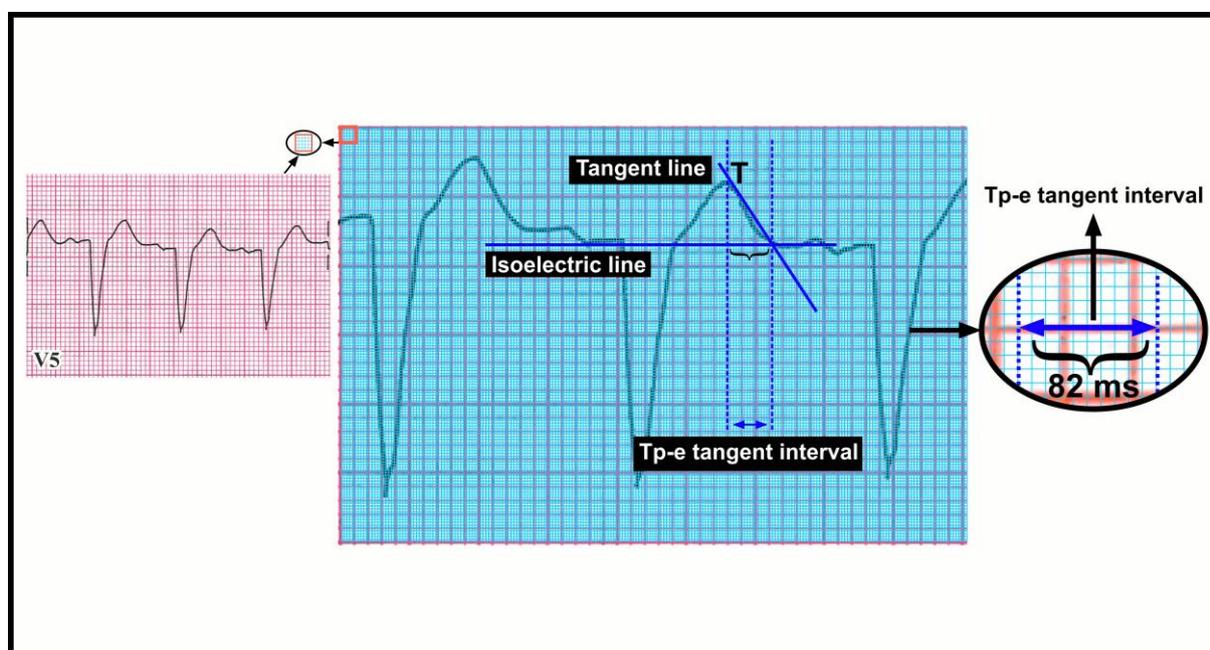


Figure 1. Measurement of the Tp-e interval by using the tangent method

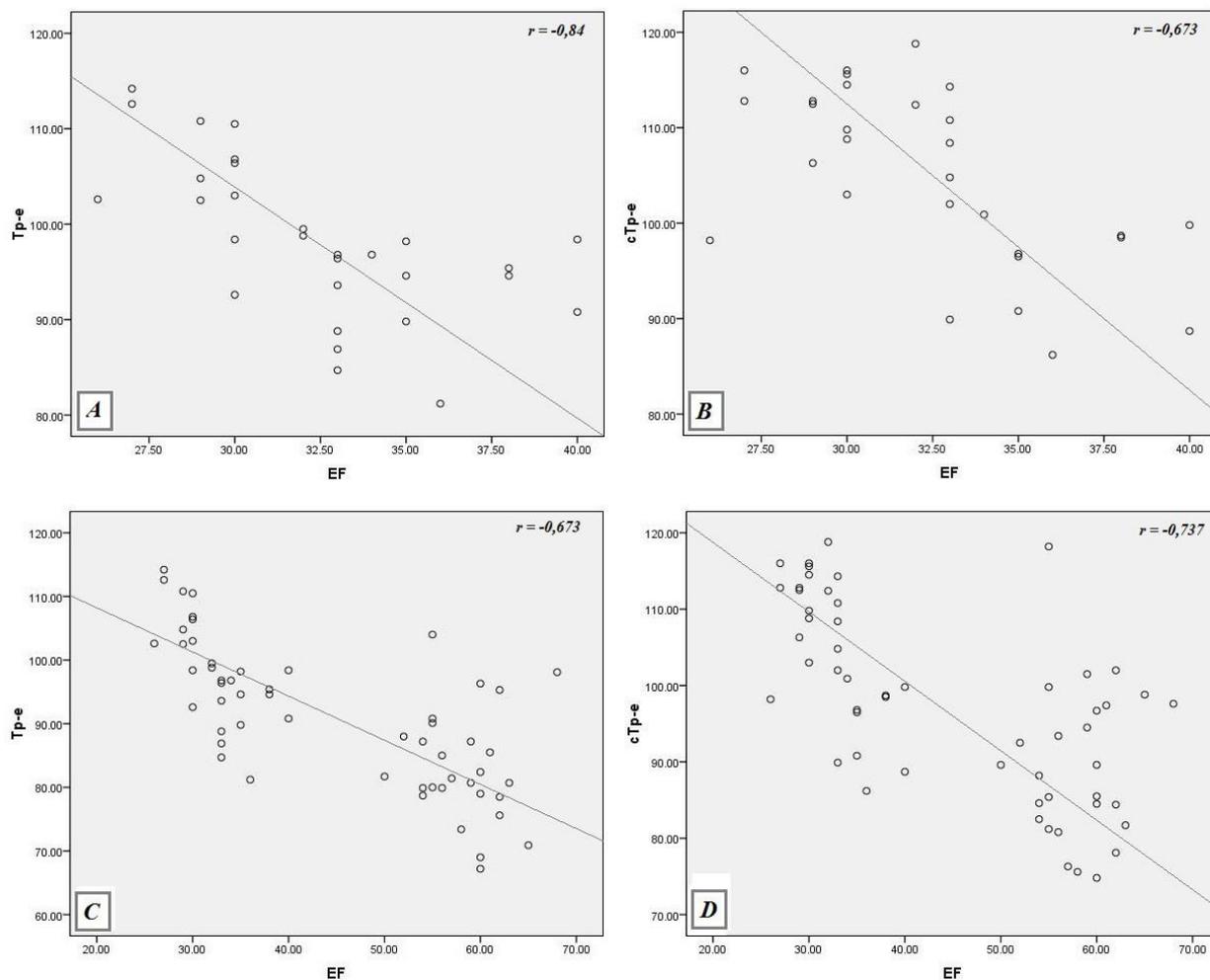


Figure 2. A:Correlation between Tp-e Interval and ejection fraction (EF) in Group 1. B: Correlation between cTp-e Interval and ejection fraction (EF) in Group 1. C:Correlation between Tp-e Interval and ejection fraction (EF) in all populations. D: Correlation between cTp-e Interval and ejection fraction (EF) in all populations.