T Peak–T End Interval Alteration as Parameter of Successful Fibrinolysis in Patients with ST Segment Elevation Acute Myocardial Infarction

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Manuscript submitted: July 22, 2017; Revised and accepted for publication: September 24, 2017

ABSTRACT

Background: In STEMI patients, the duration of action potential dispersion occurs between normal and ischemic tissue due to the lengthening of the refractory period, causing transmural dispersion of repolarization, which could be detected with Tp-Te interval prolongation on the electrocardiogram (ECG). Benefits of fibrinolytic therapy in patients with STEMI has been demonstrated, with reduced mortality significantly and improve coronary patency in order to increase myocardial perfusion. The goal of this study was to determine Tp-Te interval alteration in STEMI patients before and after the fibrinolytic therapy between successful fibrinolysis compared to failed fibrinolysis.

Method: Cross-sectional study was conducted to collect ECG from medical records at Dr. Sardjito General Hospital in January–September 2016. STEMI patients with onset less than 12 hours whom reperfused with fibrinolytic therapy were registered. Tp-Te interval was measured before, soon after (0 minute), and 30 minutes after fibrinolysis with successful and failed results. The unpaired t-test analysis was used to compare Tp-Te interval alteration after fibrinolysis. Then, Δ Tp-Te cut-off value was determined to find sensitivity and specificity based on ROC.

Result: Among 84 patients enrolled in this study, 46 patients with successful fibrinolysis and 38 patients with failed fibrinolysis. Both of groups had Tp-Te interval prolongation before fibrinolysis, with mean value of 120.30 ± 13.02 ms in successful fibrinolysis group and 118.57 ± 15.24 ms in failed fibrinolysis group. In successful fibrinolysis group, Tp-Te interval reduced significantly with Δ Tp-Te value of 17.55 ± 13.35 ms on 0 minute and 20.85 ± 15.62 ms on 30 minutes after fibrinolysis, while in failed fibrinolysis group there was not a decrease of Tp-Te interval with Δ Tp-Te value of -0.77 ± 11.00 ms on 0 minute (p < 0.001) and -1.53 ± 14.35 ms on 30 minutes after fibrinolysis (p < 0.001). Cut-off value Δ Tp-Te 20 ms had sensitivity 52.2% and specificity 94.7% based on ROC, with strong discriminator value of AUC (0.888).

Conclusion: There was a greater reduction of Tp-Te interval in STEMI patients with successful fibrinolysis compared to failed fibrinolysis, so it may be used as a alternative parameter of successful fibrinolysis.

Keywords: STEMI; Tp-Te interval; fibrinolysis

INTISARI

Latar Belakang: Pada pasien dengan STEMI, durasi dispersi potensial aksi terjadi antara jaringan normal dan iskemik karene pemanjangan periode refrekter, menyebabkan dispersi transmural dari repolarisasi. Hal ini bisa dideteksi dari pemanjangan interval Tp-Te pada elektro kardiogram (EKG). Kegunaan terapi fibrinolisis pada pasien dengan STEMI telah ditunjukkan pada pasien dengan STEMI dengan penurunan angka kematian secara signifikan dan perbaikan patensi koroner untuk meningkatkan perfusi miokard. Tujuan penelitian ini untuk menentukan perubahan interval Tp-Te pada pasien STEMI sebelum dan sesudah terapi fibrinolisis, membandingkan antara yang sukses dan yang gagal.

Metode: Penelitian potong lintang dilakukan untuk mengumpulkan EKG dari rekam medis di RSUP Dr Sardjito antara Januari-September 2016. Pasien STEMI dengan awitan kurang dari 12 jam yang menjalani fibrinolisis didaftar dalam analisis. Interval Tp-Te diukur sebelum, segera setelah (menit 0) dan 30 menit setelah fibrinolisis, dengan hasil sukses dan gagal. Analisis uji T tak berpasangan digunakan untuk membandingkan perubahan interval Tp-Te setelah fibrinolisis. Nilai cut-off Δ Tp-Te digunakan untuk menentukan sensitivitas dan spesifisitas berdasarkan kurva ROC. Hasil: Sebanyak 84 pasien didaftarkan dalam penelitian ini, 46 pasien dengan fibrinolisis sukses dan 38 pasien dengan fibrinolisis gagal. Kedua kelompok mempunyai pemanjangan interval Tp-Te sebelum fibrinolisis, dengan rerata 120,30±13,02 milidetik pada kelompok fibrinolisis sukses dan 118,57±15,24 milidetik pada kelompok fibrinolisis gagal.Pada kelompok fibrinolisis sukses, interval Tp-Te menurun secara signifikan dengan nilai ∆Tp-Te 17,55±13,35 milidetik pada menit 0 dan 20,85±15,62 milidetik pada menit 30 setelah fibrinolisis, sedangkan pada kelompok fibrinolisis gagal tidak terdapat penurunan interval Tp-Te dengan nilai Δ Tp-Te -0,77 \pm 11,00 milidetik pada menit 0 (p<0,001) dan -1,53 ±14,35 milidetik pada 30 menit setelah fibrinolisis (p <0,001). Nilai cut-off Δ Tp-Te 20 milidetik mempunyai sensitivitas 52,2% dan spesifisitas 94,7% berdasarkan kurva ROC, dengan nilai diskriminator kuat AUC (0,888).

Kesimpulan: Terdapat penurunan interval Tp-Te lebih besar pada pasien STEMI dengan fibrinolisis sukses dibandingkan pada yang fibrinolisis gagal, sehingga interval Tp-Te dapat digunakan sebagai alternatif parameter keberhasilan fibrinolisis.

INTRODUCTION

Coronary artery disease (CAD) is still the number one cause of mortality worldwide, with more than 7 million deaths due to CAD each year, which represented 12.8% of all causes of death.¹ ST elevation acute myocardial infarction (STEMI) is a clinical syndrome, which is a spectrum of acute coronary syndrome (ACS), which is defined by the characteristic symptoms of myocardial ischemia related with ST segment elevation in electrocardiography (ECG) and afterward followed with myocardial necrosis.

Myocardial ischemia causes metabolic changes and ion exchange. This cellular processes will lengthen repolarization and shorten the action potential in myocardium ischemic area.²

Differences in the duration of action potentials between normal and ischemic tissue due to the lengthening of the refractory period raises electrophysiological inhomogenity in the ventricular myocardium and improves transmural dispersion of repolarization. This process may act as a predisposing factor reentry arrhythmias. This arrhythmia is the most common cause of death in STEMI patients.^{3,4} Several studies show a decrease in mortality due to STEMI, along with the increase use of reperfusion therapy, the availability of percutaneous coronary intervention (PCI) facilities, modernantithrombotic therapy and secondary prevention.⁵ Benefits of fibrinolytic therapy in patients with STEMI has been demonstrated, with significant reduction of mortality by administration of fibrinolytic therapy.⁶ Traditional variables that had been used to assess response to fibrinolytic therapy was still less precision.⁷

Dispersion of repolarization increase can be detected by a peak interval prolongation Tpeak - Tend (Tp-Te) on 12 lead electrocardiogram examination. Tp-Te interval is a time interval measured from the top of the T wave to the end of the T wave In some studies, Tp-Te interval is proposed as a marker of increased risk of ventricular arrhythmias in patients with various conditions, including acute myocardial infarction.^{8,9,10} Another study said that STEMI patients who performed the reperfusion with primary PCI, rescue PCI and successful fibrinolysis, duration of repolarization is significantlydecreased as assessed by Tp-Te. In addition, Tp-Te interval can be a response parameter and marker of successful reperfusion.¹¹ However, until now there is no study evaluating the Tp-Te interval and the change in STEMI patients who performed fibrinolysis with successful and failed results and propose amendments Tp-Te interval as a parameter of successful fibrinolysis.

The aim of this study was to determine Tp-Te interval alteration in STEMI patients before and after the fibrinolytic therapy between successful fibrinolysis compared to failed fibrinolysis.

METHODS

This is an analytic observational study with cross sectional method on two unpaired groups. Data were obtained retrospectively to see Tp-Te interval change in STEMI patients who received fibrinolysis with successful and failed results. The study took place in the Medical Record Installation Dr. Sardjito General Hospital in January–September 2016 for collection of secondary data.

Subjects

Inclusion criteria in this study were STEMI patient at first time with onset within 12 hours and receive reperfusion therapy with fibrinolysis, aged 18-80 years, with complete data on the patient's medical record. While exclusion criteria of this research is atrial fibrillation, atrial flutter, ECG with LBBB, total AV block, pacing rhythm, or pre-excitation, chronic heart failure, valvular heart disease, congenital heart disease, electrolyte disturbances, drug history amiodarone and digitalis, duration QRS more than 12 ms in the ECG, and T-wave in the ECG difficult to assess.

ECG Recording

ECG recording done by using a standard 12 lead ECG with a speed of 25 mm / sec and gain of 10 mm/mV by medical or paramedical personnel in the emergency department of Dr. Sardjito General Hospital accordance with the standard operating procedures of ECG collection. ECG data is used in STEMI patients with fibrinolysis action is ECG data when admission or pre- and post-fibrinolysis counted 90 minutes since the fibrinolysis started. ECG data is scanned in order to be processed digitally with a Canon brand scanner Canoscan Lide 110.



Figure 1.Measurement of Tp-Teinterval (source:Erikssen et al., 2012)¹²

Tp-Te Interval Measurement

Tp-Te measurements performed on precordial leads. Measurements were done using standard ECG at V₅, V₄ and V₆ lead. In previous study, V₅ lead is a measurement having high precision(Figure 1). If the calculation is not possible in V₅, the alternative calculation of Tp-Te interval in a sequence can be calculated from V₄ and then V₆.^{13,14} In the case of the T wave disturbed by waves U, Te is defined as nadir between the T wave with wave U. T wave with low voltage <0.1 mV is not analyzed.¹⁵

Statistical Analysis

The data obtained will be analyzed using the software SPSS for Windows version 18.0. The baseline characteristics are shown as mean or amount in figures and percentages. A comparative analysis was conducted between the 2 groups with paired t test in each group (pre and post-fibrinolysis) and unpaired t test to compare between the two groups of fibrinolysis success and failure or test Mann-Whitney and Wilcoxon two numeric variables when the data is not normal to see whether there is a significant difference between the two variables with a proficiency level of significance value of p < 0.05. Analysis of confounding variables will be performed by multivariate analysis with multiple linear regression analysis. Further changes in the value, expressed in delta, is used to find the limit value using receiver operator characteristics

(ROC) curves then prepared a sensitivityspecificity curve to help determine the sensitivity and specificity of the limit value.

RESULT

In this study there were 84 patients enrolled and met the inclusion and exclusion criteria. It was then divided into two following groups, successful fibrinolysis with 46 patients (54.76%) and failed fibrinolysis in 38 patients (45.24%). Of the subjects of this study, there were a total of 77 male patients and 7 (8.33%) patients were female. The mean age at all subject was 56.63 ± 10.023 years. Average onset all the subjects were 4.36 ± 2.143 hours. Table 1 shows the baseline characteristics based on fibrinolysis results.

In this study, we obtained Tp-Te interval prolongation prior to the action of fibrinolysis in both groups of subjects, i.e. both in successful fibrinolysis group and failed fibrinolysis group, 120.30 ± 13.02 ms and 118.57 ± 15.24 ms, respectively. Table 2 shows the comparison of Tp-Te interval comparison before fibrinolysis, 0 minute, and 30 minutes after fibrinolysis in successful fibrinolysis group.

In this study, Tp-Te interval evaluation was performed at 0 minutes (instantaneous) and 30 minutes after fibrinolysis. The Tp-Te interval value after successful fibrinolysis experienced significant reduction, both at 0 minute and at 30 minutes after fibrinolysis, 17.55 ± 13.35 ms and 20.85 ± 15.62 ms respectively. Tp-Te interval reduction was not found in the failed fibrinolysis group, otherwise

Table1. Baseline characteristics based on fibrinolysis results in STEMI patients

	Fibring			
Variables	Successful (n=46)	Failed (n=38)	P value	
Gender, n(%)				
Male	42 (91.30%)	35 (92.11%)	1.000	
Female	4 (8.70%)	3 (7.89%)		
Age in year (mean±SD)	56.11 ± 9.907	57.26 ± 10.258	0.602	
Onset in hour (mean±SD)	4.28 ± 2.126	4.45 ± 2.190	0.728	
Infarct location, n(%)				
Anterior	18 (39.13%)	30 (78.95%)	<0.001	
Non-anterior	28 (60.87%)	8 (21.05%)		
Fibrinolytic agent, n(%)				
Streptokinase	35 (76.09%)	29 (76.32%)	1.000	
Alteplase	11 (23.91%)	9 (23.68%)		
Diabetes mellitus, n(%)	7 (15.22%)	9 (23.68%)	0.406	
Hypertension, n(%)	25 (54.35%)	26 (68.42%)	1.000	
Smoker, n(%)	36 (78.26%)	28 (73.68%)	0.797	
Family history, n(%)	2 (4.35%)	1 (2.63%)	1.000	
Hyperlipidemia, n(%)	9 (19.57%)	9 (23.68%)	0.790	

Note: SD= standard deviation

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Table 2.Tp-Te interval comparison before fibrinolysis, 0 minute, and 30 minutes after fibrinolysis based on the success of fibrinolysis

Variables	Successful fibrinolysis (n=46)	Failed fibrinolysis (n=38)	P value*
Before fibrinolysis, mean±SD	120.30 ± 13.02	118.57 ± 15.24	0.576
0 minute after fibrinolysis, mean±SD	102.76 ± 13.17	119.34 ± 16.38	<0.001
30 minutes after fibrinolysis, mean±SD	99.46 ± 13.95	120.11 ± 20.43	<0.001

*Unpaired T test, Tp-Te interval in units of milisecond (ms)

Tabel 3.	Comparison	of Tp-Te	interval change	es (ΔT	p-Te) based or	n the outcome	e of fibrinol	ysis
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	n	Mean±SD	P value*	
ΔTp-Te before and 0 minute after fibrinolys	is			
Successful	46	17.55 ± 13.35	-0.001	
Failed	38	-0.77 ± 11.00	<0.001	
ΔTp-Te before and 30 minutes after fibrinol	ysis			
Successful	46	20.85 ± 15.62	<0.001	
Failed	38	-1.53 ± 14.35	<0.001	

*Unpaired T test, Tp-Te interval in units of milisecond (ms)

there was little Tp-Te interval prolongation, with the changes obtained was equal to -0.77 \pm 11.00 ms at 0 min and -1.53 \pm 14.35 ms at 30 minutes after fibrinolysis. Table 3 shows the comparison of Tp-Te interval changes (Δ Tp-Te) based on the outcome of fibrinolysis.

The ROC curve showed that Tp-Te interval changes (Δ Tp-Te) had a strong discriminator value with area under the curve (AUC) of 0.888. In this study, the cut-off value proposed as a parameter of successful fibrinolysis based on the ROC curve is 20 ms. The value gave 52.2% sensitivity and 94.7% specificity, based on ROC curve analysis. Figure 2 and 3 showed the ROC analysis.

DISCUSSION

The baseline characteristics of the subjects of this study showed that the percentage of hypertension, diabetes mellitus, family history, hyperlipidemia, and smoking did not differ between the two groups. The risk factors of smoking was found in 78.26% of successful fibrinolysis group and as much as 73.68% in the failed fibrinolysis group. This number is very large, thus requiring special attention in cardiovascular disease prevention program. In addition, a high percentage of smokers subjects associated with increased mortality and arrhythmias.¹⁴

The mean onset of STEMI in each group was 4.28 ± 2.126 hours on the successful fibrinolysis group and 4.45 ± 2.19 hours in the failed fibrinolysis group. There are significant differences in infarct location of the two groups, in which the percentage of anterior infarct location in the failed fibrinolysis group more than the successful fibrinolysis. This corresponds with the results of previous studies by Lopeset al.¹⁶ that the anterior infarct location into one of the predictors of failed fibrinolysis. Nevertheless, infarct location does not affect the Tp-Te interval at baseline.

This study showed an increase in ventricular repolarization dispersion in acute phase of STEMI, assessed with intervals Tp-Te. There is no consensus regarding the normal value Tp-Te interval, but on the setting of myocardial infarction, value Tp-Te interval of more than 100 ms are considered prolonged and associated with increased risk



Figure 3. Sensitivity and specificity chart of Δ Tp-Te interval at 30 minutes after fibrinolysis



Figure 2. The ROC of Δ Tp-Te at 30 minutesto success of fibrinolysis

of arrhythmias.^{13,17} In this study, obtained Tp-Te interval prolongation prior to the action of fibrinolysis in both groups of subjects, both in successful fibrinolysis group and failed fibrinolysis group, respectively 120.30 ± 13.02 ms, and 118.57 ± 15.24 ms. This is according to a study conducted by Shentar et al.¹² that compared normal individuals and STEMI patients, where there were lengthening of Tp-Te interval and Tp-Te/QT ratio in STEMI patients with a mean Tp-Te interval of 110 ms and the value of Tp-Te> 100 ms and the ratio Tp- Te/QT > 0.3 increases the risk of malignant ventricular arrhythmias in STEMI patients.

The main objective of fibrinolytic therapy in STEMI patients is achieving and maintaining coronary patency to improve left ventricular function and reduce mortality. Although the benefits of the use of fibrinolytic agents has been documented to reduce mortality in STEMI, the mechanism is still being debated, most likely through an improvement in the mechanical and electrical functions.¹⁸ Past studies by Lopes et al.¹⁶ showed that successful fibrinolysis reduced QT dispersion in STEMI patients. But until now there has not been studies evaluating the Tp-Te interval before and after fibrinolysis.

This is consistent with research done by John et al.¹¹ and Mahbubi¹⁹ in which there is a decrease Tp-Te interval after reperfusion action, either by primary PCI or successful fibrinolysis. Moreno et al.¹⁸ demonstrated the beneficial effects of reperfusion in addition to the reduction of infarct size and improvement of myocardial function. In patients with a successful fibrinolysis outcome (TIMI 3 flow) shows more stable electrical substrate compared to persistent occlusion. Achievement of early patency correlates with reduced incidence of arrhythmias and cardiovascular death.

The same result was reported by Dey et al.²⁰ in which the decrease Tp-Te interval after reperfusion reduces the risk of ventricular arrhythmias, but it can not predict mortality within 30 days and heart failure.

Based on the ROC, it was found that ΔTp -Te has a strong discriminator value with AUC 0.888. In this study, the cut-off valueproposed as a parameter of successful fibrinolysis is based on the ROC curve and the curve of the sensitivity-specificity, is the change interval Tp-Te (ΔTp-Te) of 20 ms with 52.2% sensitivity and 94.7% specificity. It is based on the consideration that the average Δ Tp-Te achieved on successful fibrinolysis group at 30 minutes after fibrinolysis revolves around these values. The limit value of 20 ms is also thought of as a value that can be observed more easily on the EKG. A span of 30 minutes after fibrinolysis is used as a reference in calculating Δ Tp-Te based on research by Vrachatis et al.²¹, in which the TIMI 3 flow on successful fibrinolysis achieved within 90-120 minutes after starting fibrinolysis. With this result, Tp-Te interval can be an alternative parameter in assessing the success of fibrinolysis.

Limitations of this study is the ECG recording was not conducted prospectively, so less guarantee timely. The study also does not use angiographic parameters as the gold standard of the arterial flow patency resulting in less accurate in evaluating the diagnostic value of Tp-Te interval.

CONCLUSION

There was a greater reduction of Tp-Te interval in STEMI patients with successful fibrinolysis compared to failed fibrinolysis, so it may be used as a alternative parameter of successful fibrinolysis with sensitivity 52.2% and specificity 94.7%.

ACKNOWLEDGEMENT

Authors thank dr. Erdiansyah Zulyadaini and dr. Mustika Mahbubi for their ideas, companion and assistance in some data collection during this study. This study was conducted with ethical clearance from the Ethical Committee of Faculty of Medicine Universitas Gadjah Mada.

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