ORIGINAL RESEARCH

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The Value of P wave dispersion in predicting reperfusion and infarct related artery patency in acute anterior myocardial infarction

Abstract

Purpose: The aim of this study is to investigate whether P wave dispersion (PWD), measured before, during and after fibrinolytic therapy (FT), is able to predict successful reperfusion and infarct related artery (IRA) patency in patients with acute anterior MI who received FT.

Methods: Sixty-eight patients who presented with acute anterior MI were enrolled in the study. An electrocardiogram was performed before and at 30, 60, 90 and 120 minutes after the start of FT. PWD was defined as the difference between maximum and minimum P wave duration on standard 12-lead surface electrocardiogram. A multivariate logistic regression model was used to assess whether PWD was predictor of IRA patency and ST-segment resolution (STR) on electrocardiogram.

Results: PWD₁₂₀ was significantly lower in patients with STR on electrocardiogram (38 patients) compared with those without STR (30 patients) (44.8 ± 11.5 vs. 52.9 ± 10.3 ms; $p < 0.001$). PWD₁₂₀ was found to be significantly lower in patients with patent IRA (31 patients) compared to those with occluded IRA (37 patients) (42.3 ± 9.7 vs. 53.5 ± 10.6 ms; $p < 0.001$). Logistic regression analysis revealed that PWD₁₂₀ significantly predicted STR and IRA patency. A ≥ 51.6 ms PWD₁₂₀ can predict an occluded IRA with a 87% sensitivity, ≥ 51 ms PWD₁₂₀ can predict no reperfusion with a 74% sensitivity.

Conclusion: PWD values, which were higher than 51 ms and 51.6 ms in patients who received fibrinolytic therapy, can serve as a marker of failed reperfusion and occluded IRA. PWD values, in combination with other reperfusion parameters, can contribute to the identification of rescue PCI candidates.

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A number of large clinical studies have demonstrated that achieving optimal coronary flow following thrombolysis in myocardial infarction (TIMI) reduces mortality, preserves left ventricular function and improves survival following acute myocardial infarction (MI) [1-4]. In addition, it is known that the prognosis of patients with persistent occlusion of the infarct related artery (IRA), despite lytic therapy, is poor compared with that of patients with recanalized coronary arteries [5-7]. Therefore, early detection of successful reperfusion and IRA patency in patients who received fibrinolytic therapy is of great importance in terms of prognosis and identification of candidates for rescue percutaneous coronary intervention (PCI) [8-9]. For this purpose, relief of chest pain, early peak of cardiac biomarkers, appearance of reperfusion arrhythmia and various electrocardiographic (ECG) changes are used as noninvasive biomarkers, among which ST segment resolution at 90 minutes is one of the most important markers of successful reperfusion and prognosis [10-13]. ST segment resolution is not always satisfactory to predict IRA patency and half of the patients without ST segment resolution have a patent IRA [14-15].

P wave dispersion (PWD) is defined as the difference between the maximum ($P_{\max}$) and minimum ($P_{\min}$) P wave duration on standard 12-lead ECG. PWD is a measurement of the heterogeneity of atrial refractoriness [16]. Prolongation of PWD is known to be an independent risk factor for atrial fibrillation (AF) and shows intra-atrial and inter-atrial non-uniform conduction [16-18].

The aim of this study was to investigate the value of PWD, measured via a 12-lead surface ECG, for predicting reperfusion and IRA patency in patients with acute anterior MI who were receiving thrombolytic therapy.

Methods

One hundred and three patients who were admitted to our hospital within the first six hours after acute anterior myocardial infarction and who received thrombolytic therapy were enrolled in this study. MI criteria were defined as follows: (1) chest pain lasting >30 minutes and admission to the coronary care unit <24 hours from the onset of chest pain, (2) ST-segment elevation ≥ 2 mm in at least two anterior electrocardiographic leads and (3) transient elevation of myocardial necrosis markers. Exclusion criteria included the presence of AF or flutter either before or after the assigned treatment, bundle branch block or any other intraventricular conduction abnormalities requiring permanent pace-maker insertion, preexcitation on admission or at the 24th hour ECG, cardiogenic shock, presence of either hypertrophic or dilated cardiomyopathy,

abnormal thyroid functions, previously known congestive heart failure, congenital cardiac abnormalities, requirement for rescue angioplasty/stenting, severe valvular heart disease, previous beta blocker and other anti-arrhythmic drug usage and presence of unmeasurable P waves in more than four leads on any ECG. Thirty five patients who did not meet these criteria were excluded from the study and 68 patients (55 males, 13 females; mean age 54 ± 11.1) who met the criteria were divided into groups according to the presence of ST segment resolution on ECG and IRA patency. A signed informed consent form was obtained from each patient. The study was approved by the local ethics committee.

Treatment Protocol

Each patient was given tissue plasminogen activator-Alteplase (t-pA, Actlyse; Boeringer Ingelheim, Germany) as thrombolytic therapy. A dose of 15 mg intravenous bolus of Alteplase, followed by 0.75 mg/kg over 30 minutes (not to exceed 50 mg) and then 0.5 mg/kg over 60 minutes (not to exceed 35 mg), with a total dose not exceeding 100 mg, was administered. All patients also received 100-325 mg acetylsalicylic acid, low-flow nasal oxygen and a bolus of 60U/kg heparin followed by infusion of 12U/kg heparin, for 24-48 hours. Intravenous nitroglycerin and oral metoprolol (50-100 mg) were administered to the patients with normal heart rate and blood pressure values. Clopidogrel was given at a dose of 300 mg to patients aged ≤ 75 years and at a dose of 75 mg to those aged ≥ 75 years followed by 75 mg/day. None of the patients received antiarrhythmic drugs or calcium channel blockers. Reperfusion criteria were defined as follows: a complete relief of chest pain, development of reperfusion arrhythmia and $\geq 70\%$ ST segment resolution on ECG after thrombolytic therapy. Coronary angiography was performed the next day for patients in whom reperfusion was achieved. Patients who had <70% ST segment resolution at 120 minutes and ongoing chest pain underwent immediate coronary angiography. A 12-lead electrocardiogram (ECG) was performed at 0 and 30, 60, 90 and 120 minutes after the start of fibrinolytic therapy.

Echocardiography was performed to all patients within 48 hours. Two-dimensional echocardiographic measurements were performed according to standards outlined by the American Society of Echocardiography [19]. LA size was measured at end-systole in M-mode when ultrasound beam is perpendicular to the LA walls. The LV ejection fraction (EF) was calculated according to the Simpson method [20].

Electrocardiographic measurements

All standard 12-lead ECGs were obtained using a recorder (Agilent, Andover, MA, USA) set at a 50 mm/s paper speed and 20 mm/mV standardization. All measurements of P-wave duration were calculated blindly by two observers. P waves on all derivations were measured on 12-lead surface ECG. The onset of the P wave was defined as the point of first visible upward slope from baseline for positive waveforms and as the point of first downward slope from baseline for negative waveforms. The return to the baseline was considered as the end of the P wave. The $P_{\max}$ measured in any of the 12 leads of the surface ECG was used as the longest atrial conduction time and $P_{\min}$ measured in any of the 12 leads of the surface ECG was used as the shortest atrial conduction time. The mean P-wave duration for at least three complexes was calculated for each lead. P wave measurement could not be performed in each case because of low amplitude P waves in one or two of 12 leads in the ECG. Biphasic P waves were measured to the time of final return to baseline. ST-segment deviation was measured with a handheld caliper and magnifying glass at 80 milliseconds after the J-point in all available leads. The TP-segment was considered the preferred iso-electric baseline and ST-segment deviation was measured to the nearest 0.05 mV. ST segment resolution was calculated and expressed as a percentage with this formula: (baseline ST elevation-90 minute ST elevation)/baseline ST elevation. Intra- and inter-observer variability were obtained from random 40 ECG recordings. Intra- and inter-observer variability for PWD were 3.2% and 3.5%, respectively.

Coronary angiography

All patients underwent coronary angiography on multiple projections using the Judkins' technique [21]. Cineangiography was performed by hand injection through diagnostic 6 Fr Judkins' catheters. Iopromide contrast (Ultravist- 370; Schering AG, Berlin, Germany) was used in all patients. Angiographic procedure was performed using a computer based automated coronary analysis system (DCI-S; Philips Medical Imaging Systems, Eindhoven, Netherlands). Anterograde perfusion of the infarct-related artery was graded according to the classification system of the thrombolysis in myocardial infarction (TIMI) trial (grade 0 = no anterograde perfusion, grade 1 = minimal perfusion, grade 2 = partial perfusion and grade 3 = complete perfusion) [22]. IRA was considered as patent if TIMI flow grade was 2 or 3 and as occluded if TIMI flow grade was 0 and 1.

Statistical Analysis

All statistical analyses were carried out using SPSS statistical software (version 11.0, SPSS, Chicago, Illinois, USA). Data are presented as mean $\pm$ SD. Statistical comparison of quantitative data was performed by independent sample t-test. Categorical variables were summarized as percentages and were compared with the Chi-square test and Mann Whitney U test where appropriate. A multivariate logistic regression model was used to assess whether PWD measured at 0, 30, 60, 90 and 120 minutes was predictor of IRA patency and ST-segment resolution on ECG. A p value of <0.05 was considered statistically significant.

Results

Table 1 shows clinical and demographic characteristics of the patients.

ST-segment resolution occurred on ECG in 38 (55.8%) patients of the study group, whereas 30 (44.2%) patients had no ST-segment resolution on ECG. Following coronary angiography, the IRA was found to be patent in 31 (45.5%) patients but occluded in 37 (54.5%) patients. It was found that

TABLE 1. Clinical and demographic characteristics of the study group

Characteristics	Mean $\pm$ SD
Age (year)	54 $\pm$ 11.1
Sex (Male/female)	55/13
Smoking (%)	71
Hypertension (%)	28
Diabetes mellitus (%)	22
Dyslipidemia (%)	21
Obesity (%)	30
History of familial CAD (%)	31
SBP (mmHg)	129.9 $\pm$ 21.1
DBP (mmHg)	76.4 $\pm$ 14.1
HR (beat/min)	80 $\pm$ 18
Time to therapy (hour)	3.4 $\pm$ 1.5
LVEF (%)	42.6 $\pm$ 9.2
LA (mm)	39.7 $\pm$ 3.5
<i>Number of involved vessels</i>	
LAD (n)	68
Cx (n)	21
RCA (n)	13

Abbreviations: CAD, coronary artery disease, Cx, circumflex artery, DBP, diastolic blood pressure, HR, heart rate, LA, left atrium, LAD, left anterior descending artery, RCA, right coronary artery, LVEF, left ventricular ejection fraction, SBP, systolic blood pressure.

FIGURE 1. ROC curves showing diagnostic accuracy of PWD 120 to predict ST segment resolution (A) and PWD 120 to predict IRA patency.

56% had single vessel disease, 25% had two vessel disease and 19% had three vessel disease. Twenty-seven of 30 patients who underwent immediate coronary angiography because of failed thrombolysis had occluded IRA. Twenty-eight of 38 patients who had ST segment resolution on ECG had patent IRA. Table 1 shows the rate of coronary artery involvement. It was also found that chest pain in the patients with ST-segment resolution on ECG was relieved after thrombolytic therapy. Nine patients developed atrial fibrillation during their hospital stay. Rescue PCI was performed in patients who failed to show signs of reperfusion.

When the patients were divided into groups according to the presence of ST-segment resolution on ECG, PWD measured at 120 minutes was found to be significantly lower in patients with ST-segment resolution on ECG compared with that found in patients without ST-segment resolution on ECG (Table 2). In comparison, there were no significant differences in PWD measured at 0, 30, 60 and 90 minutes between patients with and without ST-segment resolution. When the patients were grouped according to IRA patency, PWD measured at 120 minutes was significantly lower in patients with patent

IRA compared with those with occluded IRA (Table 3). In comparison, there were no significant differences in PWD measured at 0, 30, 60 and 90 minutes between both groups. Multivariate regression analysis revealed that PWD₁₂₀ could predict IRA patency and ST-segment resolution on ECG (OR:0.907, CI:0.856 to 0.960; $p=0.001$; OR: 0.942, CI: 0.896 to 0.991; $p=0.02$, respectively).

On the basis of ROC curve analysis; a 51.6 ms or higher PWD₁₂₀ was found to predict an occluded IRA with a 87% sensitivity (95% CI, 70.1-96.3; $p<0.001$, area under curve 0.79). A 51 ms and higher PWD₁₂₀ was found to predict no reperfusion on ECG with a 74% sensitivity (95% CI, 56.9-86.6; $p=0.003$, area under curve 0.71) (Figure 1).

The sensitivity and specificity of ECG resolution in predicting IRA patency were 73% and 90%, respectively. The sensitivity and specificity of PWD₁₂₀ in predicting IRA patency were near the ECG resolution as 65% and 87% respectively. When both IRA patency and ECG resolution in predicting IRA patency were combined, the sensitivity and specificity were 89% and 85%, respectively.

TABLE 2. Comparison of P wave dispersion obtained at during and after thrombolytic therapy and left atrium and ejection fraction according to ECG resolution.

PWD	Resolution (+) (n=38)	Resolution (-) (n=30)	P
PWD 0 (ms)	46.2±15.2	51.5±13.8	0.75
PWD 30 (ms)	47.2±12.8	47.0±12.3	0.57
PWD 60 (ms)	46.5±14.5	47.9±9.6	0.28
PWD 90 (ms)	43.9±13.3	48.3±11.2	0.16
PWD 120 (ms)	44.8±11.5	52.9±10.3	<0.001
LA (mm)	39.6±3.8	39.7±3.2	0.92
EF (%)	42.3±9.4	43.2±9.1	0.68

Abbreviations: PWD, P wave dispersion, LA, left atrium, EF, ejection fraction.

Discussion

Patients in whom successful reperfusion and IRA patency was achieved with thrombolytic therapy were found to present lower PWD values compared with pretreatment values. Additionally, a decrease in PWD, measured at 120 minutes after the start of thrombolytic therapy, may serve as an effective predictor for ST-segment resolution on ECG and IRA patency with coronary angiography.

The goal of thrombolysis is to restore normal myocardial perfusion (TIMI 3 flow to the IRA with associated full tissue perfusion) within 60 to 90 minutes. TIMI 3 flow in the IRA after thrombolysis has been associated with decreased mortality as well as decreased incidence of congestive cardiac failure, recurrent ischemia and improved left ventricular ejection fraction [23]. Prognosis after ST elevation MI has been shown to relate directly to the delay between onset of symptoms and reperfusion therapy [1] and final infarct size [24].

It has been reported that reperfusion fails to occur at all in 25% of patients [25-27] and in 50-70% of patients at 90 minutes after thrombolytic administration [25,28]. Even though ST segment resolution is considered as the hallmark for successful reperfusion and prognosis, false negative ST segment resolution may occur in patients with patent IRA, who have normal epicardial flow but microvascular dysfunction and obstruction [29]. Noninvasive electrocardiographic markers such as reperfusion arrhythmias, single lead ST-segment recovery, and continuous segment monitorization contribute to determination of IRA patency and reperfusion [30].

The occurrence rate of atrial fibrillation during acute MI ranges between 10% and 20% and develops for many reasons including left ventricle dysfunction with hemodynamic impairment [31-35], atrial ischemia or infarction, right ventricular infarction, acute hypoxia, hypokalemia [35-37]. In a study

TABLE 3. Comparison of P wave dispersion obtained during and after thrombolytic therapy and left atrium diameter and ejection fraction according to infarct related artery patency.

PWD	IRA patency (+) (n=31)	IRA patency (-) (n=37)	P
PWD 0 (ms)	47.9±14.9	49.1±14.7	0.75
PWD 30 (ms)	46.9±12.4	47.3±12.7	0.58
PWD 60 (ms)	45.3±14.0	48.6±11.4	0.13
PWD 90 (ms)	43.5±13.1	47.8±11.4	0.16
PWD 120 (ms)	42.3±9.7	53.5±10.7	0.001
LA (mm)	39.5±3.2	39.8±3.8	0.88
EF (%)	43.4±9.2	39.7±3.8	0.55

Abbreviations: IRA, infarct related artery, PWD, P wave dispersion, LA, left atrium, EF, ejection fraction.

including 2,475 patients admitted to the hospital with AMI, it was found that AF during AMI occurred in 297 patients (12%) [38]. In our study, AF developed in 9 of 60 patients (8.3%) during their hospital stay. Several studies have investigated the effects of primary PCI on PWD in AMI patients. In one of these studies, Celik *et al.* demonstrated that PWD on 12-lead surface ECG measured before and after PCI was significantly lower after PCI than pre-intervention values in 125 patients undergoing primary PCI. When the patients were grouped according to TIMI perfusion grade (TMPG), a significant decrease was found in patients with TMPG 3 [39]. In another study, Akdemir *et al.* compared the effects of fibrinolytic therapy versus PCI on PWD in patients with acute anterior myocardial infarction who received successful reperfusion therapy [31]. In the mentioned study, there was a significant decrease in PWD in patients treated with PCI whereas the decrease in patients treated with fibrinolytic therapy did not reach statistical significance. In this study, we found a significant decrease in PWD after fibrinolytic therapy compared to pretreatment values in patients with signs of successful reperfusion, a finding which is consistent with that of Celik and Akdemir *et al.* No significant difference was found between patients without ST segment resolution on ECG and those with occluded IRA. Unlike the results of these studies, our study demonstrated that PWD measured at 120 minutes after the start of thrombolytic therapy could predict ST-segment resolution on ECG and IRA patency. This result indicates that, if supported by other findings of reperfusion, it may serve as a new noninvasive parameter to predict reperfusion. In our study, we also found similar sensitivity and specificity values of PWD₁₂₀ compared with ST segment resolution. The sensitivity of combination of both parameters was higher than parameters separately in predicting IRA patency.

Biphasic P waves in lead V1 and V2 may suggest LA overload [40]. These differences in biphasic P waves may be an explanation for prolonged PWD in some situations. In our study, there was no difference in biphasic P waves in V1 or V2 leads. Reperfusion of coronary flow is necessary to resuscitate the ischemic myocardium. It is known that predictors of atrial fibrillation after acute myocardial infarction include decreased ejection fraction, age and KILLIP class [33-34]. Additionally, Baykan *et al.* found that $P_{\max}$ and PWD are also predictors of AF in acute anterior MI [41]. In our study, AF developed in nine patients in whom PWD measured at 120 minutes was above 51 ms during their hospital stay. Ejection fraction values were higher and left atrium diameters were lower in patients who had patent IRA than those with occluded IRA although did not reach statistically significant. In addition to these findings, PWD was found to be lower and EF was improved after thrombolytic therapy in patients with signs of successful reperfusion and patent IRA. A patent IRA and successful reperfusion should result in reversal of ischemia in a shorter period of time and restoration of coronary flow can be achieved by better preservation of ventricular function. In addition, increased PWD in patients with failed reperfusion after fibrinolytic therapy might also be a result of both hemodynamic impairment and ongoing tissue ischemia, which causes inhomogeneous and discontinuous atrial conduction.

Study Limitations

The main limitation of the present study was the small number of patients included. Our study was restricted to the anterior localization, which also restricted the applicability of the results. Patients with other than anterior localization of the myocardial infarction were excluded from the study because sinus node artery and AV node artery arise from the right coronary artery. Dilaveris *et al.* concluded that the manual measurement of the P wave duration in standard 12-lead ECGs is feasible, and more stable and reliable when performed on a high resolution screen of a digital ECG system than with the more conventional methods involving paper printed ECGs [42]. P wave dispersion was measured on paper printed ECGs. Although the method used to calculate PWD is time consuming, it becomes easier with repetitive measurements. Although 90 minutes after fibrinolytic therapy is standard time for rescue PCI in most centers, PWD was measured at 120 minutes in our study - an another potential limitation of our study.

In conclusion, PWD values, which were found to be lower compared with pretreatment values in patients who received fibrinolytic therapy, can be a marker of successful reperfusion and patent IRA. PWD values, in combination with other

reperfusion parameters, can contribute to the identification of rescue PCI candidates.

Acknowledgments

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