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Prolonged P wave peak time is associated with the severity of coronary artery disease in patients with non-ST segment elevation myocardial infarction

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ABSTRACT

Background: Multi-vessel coronary artery disease (CAD) is associated with worse outcome in non-ST segment elevation myocardial infarction (NSTEMI) patients. Depending on the severity of CAD, there may be prolongation of atrial depolarization time as a result of left ventricular dysfunction and atrial ischemia. Therefore, we aimed to study whether the severity of CAD can be predicted with the P wave peak time (PWPT) in the electrocardiography (ECG) obtained during the diagnosis in NSTEMI patients.
Method: A total of 162 patients were included. The coronary angiography records of all patients were analyzed and SYNTAX scores were calculated. Patients were divided into two groups, according to CAD severity. In addition to well-known P wave parameters, PWPT, defined as the time from the beginning of the P wave to its peak, was measured in the leads D_{II} and V_1.
Results: The PWPTs in the leads D_{II} and V_1 were significantly longer in the group with severe CAD (71 ± 13 vs. 61 ± 12, $p < 0.001$, 63 ± 24 vs. 53 ± 18, $p = 0.024$, respectively). PWPT was found to be an independent predictor of severe CAD and the best cut-off value of PWPT in the lead D_{II} was 69.6 ms with sensitivity of 58.3% and specificity of 78.9%.
Conclusion: Our findings show that prolonged PWPT, which is a parameter easily obtainable from the ECG, is associated with severe CAD. Recognition of NSTEMI patients with severe CAD at the time of diagnosis before performing coronary angiography may be important for the planning of treatment.

Introduction

Non-ST segment elevation myocardial infarction (NSTEMI) patients form a significant proportion of patients with acute coronary syndrome (ACS), and approximately half of these patients have multi-vessel disease, which is associated with increased mortality and morbidity [1]. Early recognition of patients with multi-vessel disease is important for interventional and medical treatment planning, especially in centers without a catheter laboratory.

The SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) scoring system (http://www.syntaxscore.com/calculator/start.htm) is the most commonly used system to assess the severity of coronary artery disease (CAD). The number of lesions, localization, and functional effect are evaluated in order to provide guidance on the optimal treatment option. A high SYNTAX score is associated with increased mortality [2]. Therefore, attempts to predict patients with severe CAD before performing coronary angiography (CAG) may contribute to improving the prognosis of these patients.

Changes in the P wave duration (PWD), indicating atrial depolarization, are known to demonstrate abnormal inter- and intra-atrial conduction times [3]. Previous studies have assessed the change in PWD in ischemic heart disease, but there are limited data regarding their relationship with the severity of CAD [4–6]. P wave peak time (PWPT) is a newly introduced electrocardiographic parameter that has been shown to be associated with no-reflow in patients with ACS [7]. This study tests the hypothesis that prolonged atrial conduction time may occur due to

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left ventricular dysfunction and atrial ischemia caused by severe CAD [8,9]. Therefore, we aimed to study whether the severity of CAD can be predicted with the PWPT in the electrocardiography (ECG) obtained during diagnosis in NSTEMI patients.

Methods

Study population

A total of 193 consecutive NSTEMI patients without history of CAD admitted to the cardiology department of Kafkas University of Medical Faculty from January 2018 to December 2018 were retrospectively screened. Patients with known or newly diagnosed degenerative or rheumatic valvular disease (n = 3), end-stage renal failure on renal replacement treatment (n = 4), atrial dysrhythmias including atrial fibrillation/flutter/tachycardia (n = 11), second- and third-degree atrioventricular block (n = 1), and those with inappropriate ECG due to poor image quality (e.g. baseline drift or missing leads) (n = 12) were excluded. After exclusion, 162 patients constituted the study population. Baseline demographic data and laboratory findings were obtained from the electronic database system of the hospital. The SYNTAX score of all included patients was calculated and the number of patients with left main coronary artery (LMCA) lesions and three-vessel disease were determined. LMCA lesion was defined as stenosis ≥50% and three-vessel disease was defined as stenosis ≥70% in all three coronary arteries. Echocardiographic examination was performed in all patients during the hospital stay. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson method, and the left atrial anteroposterior diameter was measured according to the current guidelines. The study protocol was reviewed and approved by the ethics committee of our institution in accordance with the principles of the Helsinki Declaration.

Electrocardiographic analysis

The standard 12 lead ECG was obtained for each patient with amplitude of 10 mm/mV, paper speed of 25 mm/s, and filter range of 0.15–100 Hz. Regardless of the symptoms of ischemia, patients' first ECG strips were scanned and transferred to the computer. ImageJ digital image processing software (imagej.nih.gov/ij/) was used to analyze ECG measurements. All ECG measurements and calculation of SYNTAX scores were performed by two experienced cardiologists who were blinded to the patients' clinical data, and in the event of disagreement, the third cardiologist was consulted.

The beginning of the P wave was determined as the point of upward or downward deviation from the isoelectric line, and the end was determined as the return point to the baseline of the deviation. TP interval was accepted as an isoelectric line, where there were no positive or negative deflections. The time from the beginning of the P wave to its peak was defined as PWPT, it was measured in the leads D_{II} and V_1, and it was given as a mean of three consecutive beats (Fig. 1) [7]. In case of biphasic P wave morphology, which was defined as P wave with positive and negative deflections, PWPT was measured from the beginning of the P wave to the nadir of the negative deflection. The maximum and minimum P wave duration (PWD_{max} and PWD_{min}, respectively) were also measured and the algebraic difference between the two was defined as the P wave dispersion (PW_{DISP}). The duration of the terminal negative part of the P wave measured in the lead V_1 was multiplied by the amplitude of the same part, and in this way P wave terminal force (PWTF) was calculated. Partial interatrial block (IAB) was defined as PWD longer than 120 ms. Advanced IAB was defined as PWD longer than 120 ms concomitant with notch or biphasic P wave in at least two of three the inferior leads. The QRS duration was defined as the interval from the beginning of the QRS complex to the J point, and the longest duration was recorded. ST segment depression ≥1 mm in at least two contiguous leads and ST segment elevation ≥0.5 mm in the lead aVR were included regarding ST segment deviation. T wave showing ≥1 mm negative deflection from the isoelectric line in at least two contiguous leads other than aVR was defined as T wave inversion.

Statistical analyses

The data was analyzed with SPSS statistical software version 21.0 (SPSS Inc., Chicago, Illinois). The normality of continuous variables was analyzed using the Kolmogorov–Smirnov test. The continuous variables with normal distribution were reported as mean ± standard deviation, and those without normal distribution were reported as a median (interquartile range). Categorical variables were presented as numbers and percentages (%). The continuous variables between two independent groups were compared by the Student's *t*-test or the Mann–Whitney *U* test. The Chi-squared test or Fisher's exact test were used to compare categorical data. Statistical significance was assumed

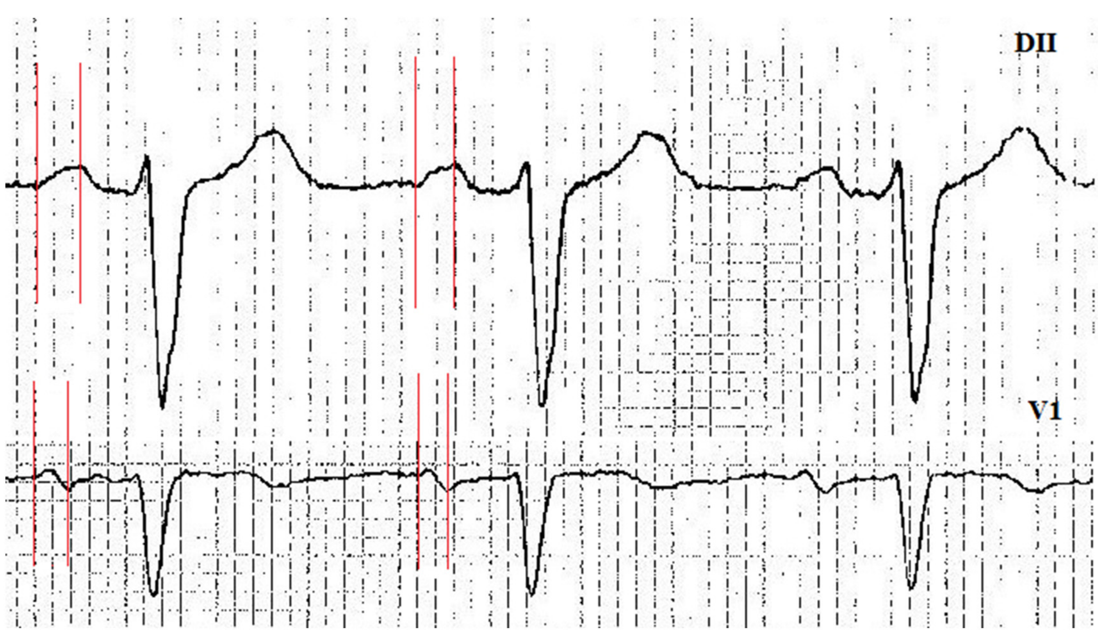

Fig. 1. Measurement of the P wave peak time (PWPT) in the leads D_{II} and V_1.

Table 1
The baseline characteristics and laboratory results of all patients and patients classified according to severity of CAD.

	All patients (n: 162)		Patients with severe CAD (n: 48)		Patients without severe CAD (n: 114)		p value
Age, years	64	±12	67	±12	63	±12	0.092
Male gender, n (%)	103	(63.6)	25	(52.1)	78	(68.4)	0.048
Diabetes mellitus, n (%)	45	(27.8)	17	(35.4)	28	(24.6)	0.159
Hypertension, n (%)	99	(61.1)	33	(68.8)	66	(57.9)	0.196
Dyslipidaemia, n (%)	60	(37.0)	20	(41.7)	40	(35.1)	0.428
Smoking, n (%)	79	(48.8)	26	(54.2)	53	(46.5)	0.372
Heart rate, bpm	73	±13	74	±12	73	±14	0.477
Systolic blood pressure, mmHg	135	±24	137	±24	134	24	0.289
LVEF, %	56	±9	54	±9	57	±9	0.037
Left atrial diameter, mm	38	±5	39	±4	37	±5	0.017
Haemoglobin, g/dL	14	±2	13	±2	14	±2	0.183
White blood cell count, 10^3/μL	9	±3	9	±3	9	±3	0.923
Platelet count, 10^3/L	228	(202–276)	225	(210–277)	229	(202–276)	0.843
Glucose, mg/dL	116	(97–155)	123	(104–156)	111	(96–150)	0.070
Creatinine, mg/dL	1.01	±0.67	1.16	±1.05	0.94	±0.40	0.820
Sodium, mmol/L	139	±4	139	±4	139	±4	0.495
Potassium, mmol/L	3.9	±0.5	3.9	±0.5	4.0	±0.5	0.198
Total cholesterol (mg/dL)	156	(132–188)	160	(140–190)	153	(130–184)	0.385
LDL cholesterol (mg/dL)	101	±31	103	±31	100	±31	0.494
HDL cholesterol (mg/dL)	36	±9	35	±8	37	±9	0.447
TG cholesterol (mg/dL)	109	(78–163)	118	(91–172)	102	(76–162)	0.082
CK-MB (ng/mL) on admission	34	(21–57)	36	(23–55)	32	(21–69)	0.011
C-Reactive protein (mg/dL)	0.49	(0.25–1.25)	0.78	(0.37–2.46)	0.45	(0.21–1.11)	0.496

Abbreviations: CAD; coronary artery disease, LVEF; left ventricular ejection fraction, LDL; low density lipoprotein, HDL; high density lipoprotein, TG; triglyceride, CK-MB; creatine kinase-MB isoenzymes.

for p value <0.05. The Pearson correlation coefficient was used to evaluate continuous variables with normal distribution, and the Spearman's rank correlation coefficient was used to evaluate variables without normal distribution. To identify the independent predictors of the severity of CAD, multivariate logistic regression analyses were performed using demographic and electrocardiographic parameters, which were obtained on patients' hospital admission. A receiver operating curve (ROC) analysis was used to define PWPT values, which predicted severe CAD with the best specificity and sensitivity.

Results

The study population consisted of 162 NSTEMI patients who were hospitalized and underwent CAG. Patients were divided into two groups. Patients with SYNTAX score ≥ 23, and/or three-vessel disease, and/or LMCA disease were defined as the group with severe CAD (n = 48 patients). There were more women in the group with severe CAD. There was no significant difference between the patients in terms of age, diabetes mellitus, hypertension, dyslipidemia and smoking (Table 1). Concerning the laboratory parameters, creatine kinase myocardial band (CK-MB) was significantly higher in the group with severe CAD, but there was no difference in other parameters between the groups. Heart rate and systolic blood pressure were similar. In the echocardiographic evaluation of the patients, LVEF was lower in the group with severe CAD (54 ± 9 vs. 57 ± 9; p = 0.037) and the left atrial (LA) diameter was increased (39 ± 4 vs. 37 ± 5, p = 0.017).

The electrocardiographic parameters of the patients are detailed in Table 2. The duration of QRS was longer (104 ± 9 vs. 99 ± 12; p = 0.022) and the percentage of patients with ST depression was higher (11 patients (24.4%) vs. 12 patients (11.3%); p = 0.040) in the group with severe CAD. The PWD_{max} was longer in the group with severe CAD (124 ± 14 vs. 116 ± 19; p = 0.030), but there were no significant differences between the groups in terms of PWD_{min}, PWTF, and PW_{DISP}. The PWPT in the leads D_{II} and V_1 were significantly longer in the group

Table 2
Angiographic and electrocardiographic findings of all patients and patients stratified according to the severity of CAD.

		All patients (n: 162)		Patients with severe CAD (n: 48)		Patients without severe CAD (n: 114)		p value
SYNTAX Score		15	(9.0–22.5)	25.5	(23.8–30.0)	12.0	(8.0–16.0)	<0.001
Patients with LMCA lesion, n (%)		12	(7.4)	12	(25)	0	(0)	<0.001
Three vessel disease, n (%)		20	(12.3)	20	(41.7)	0	(0)	<0.001
QRS duration, ms		101	±11	104	±9	99	±12	0.022
ST depression, n (%)		25	(15.4)	12	(25.0)	13	(11.4)	0.040
ST elevation in aVR, n (%)		21	(13.0)	10	(20.8)	11	(9.6)	0.073
T wave negative, n (%)		50	(30.9)	13	(27.1)	37	(32.5)	0.509
PWD_{max}, ms		118	±18	124	±14	116	±19	0.030
PWD_{min}, ms		77	±17	79	±16	77	±17	0.412
PW_{DISP}, ms		41	(25–54)	41	(36–54)	41	(24–55)	0.297
IAB, n (%)		17	(10.5)	7	(14.6)	10	(8.8)	0.270
PW morphology in the lead V_I	Negative, n (%)	57	(35.2)	13	(27.1)	44	(38.6)	
	Positive, n (%)	14	(8.6)		(6.3)	11	(9.6)	
	Biphasic, n (%)	91	(56.2)	32	(66.7)	59	(51.8)	
PWTF in the lead V_I, ms		40	(22–58)	41	(29–63)	39	(22–56)	0.344
PWPT in the lead D_{II}, ms		64	±13	71	±13	61	±12	<0.001
PWPT in the lead V_I, ms		56	±21	63	±24	53	±18	0.024

Abbreviations: CAD; coronary artery disease, LMCA; left main coronary artery, PWD_{max}; the maximum P wave duration, PWD_{min}; minimum P wave duration, PW_{DISP}; P wave dispersion, IAB; interatrial block, PWTF; P wave terminal force, PWPT; P wave peak time.

Table 3
Univariable and multivariable logistic regression analysis for the prediction of severe CAD.

Univariable analysis			Multivariable analysis	
	p value	OR (95% CI)	p value	OR (95% CI)
Gender	0.050	0.502(0.252–1.001)	–	–
ST segment depression	0.045	2.534(1.023–6.279)	–	–
QRS duration	0.014	1.045(1.009–1.082)	–	–
PWD_{max}	0.010	1.030(1.007–1.054)	–	–
PWPT in the lead D_{II}	<0.001	1.066(1.034–1.100)	<0.001	1.066(1.030–1.102)

All clinically relevant parameters were included in the model. Abbreviations: CAD; coronary artery disease, PWD_{max}; maximum P wave duration, PWPT; P wave peak time.

with severe CAD (71 ± 13 vs. 61 ± 12; p < 0.001, 63 ± 24 vs. 53 ± 18; p = 0.024, respectively). The number of patients with IAB was quite low. Although IAB was higher in the group with severe CAD (7 patients (14.6%) vs. 10 patients (8.8%); p = 0.270), a statistical significance was not reached.

In univariable analysis; sex, QRS duration, PWD_{max}, PWPT in lead D_{II}, and ST segment depression were found to be related with severe CAD (Table 3). In multivariate regression analysis, the PWPT was found to be an independent predictor of severe CAD (Odds ratio (OR): 1.066 per 1 ms increase, 95% Confidence Interval (CI): 1.030–1.102; p < 0.001). The correlation analysis of P wave parameters with age, LA diameter, LVEF and SYNTAX score is presented in Table 4. The SYNTAX score was positively correlated with PWPT in the leads D_{II} and V_1, but not with PWTF and PW_{DISP}. Further, PWD_{max}, PW_{DISP}, and PWPT in the lead D_{II} were positively correlated with LA diameter.

In predicting severe CAD, the ROC curve analysis was performed, and it revealed that the cut-off value of PWPT in lead D_{II} was 69.6 ms with sensitivity of 58.3% and specificity of 78.9% (area under curve (AUC): 0.708, 95% CI: 0.631–0.776, p < 0.001). The PWPT in lead V_1 was 58.8 ms with sensitivity of 64.4% and specificity of 64.1% (AUC: 0.617, 95% CI: 0.533–0.695, p = 0.03) (Fig. 2).

Discussion

In this study, it is shown that the prolongation of PWPT is associated with CAD severity determined with SYNTAX score in patients with NSTEMI. To the best of our knowledge, this is the first study to show that there is a moderate correlation between PWPT and CAD severity and that PWPT in the lead D_{II} is an independent predictor of severe CAD.

NSTEMI patients have poor endpoints in general, but it has been shown that multi-vessel CAD is associated with worse clinical outcomes than single CAD in patients with NSTEMI [10]. Therefore, predicting severe CAD in these patients may be valuable for risk classification and management. Although normal ECG is rarely observed during angina episodes in NSTEMI patients, ECG has a low sensitivity and specificity in the diagnosis of NSTEMI, and approximately half of the patients may not have any electrocardiographic sign of ischemia [11]. Nonetheless, in patients who have severe CAD, it has been shown that ST-T wave changes, including ST segment depression, transient ST segment elevation, T wave inversion, and ST segment elevation in the lead aVR are more common [12,13]. Consistent with previous studies, ST segment depression was more common in patients with high SYNTAX scores in our study. In addition to ST-T wave changes, the QRS duration in NSTEMI patients could be evaluated despite the fact that being less commonly used. The QRS duration may prolong due to the delay of transmission in the myocyte and Purkinje system. Our results are consistent with prior studies that demonstrated the relationship between CAD severity and QRS duration, with the QRS duration being longer in patients with severe CAD compared to those with non-severe CAD [14].

Other than the classical ST-T segment changes, to date several P wave parameters have been investigated in stable CAD and acute myocardial infarction patients. It has been shown that the inflated balloon-induced acute ischemia during percutaneous transluminal coronary angioplasty or spontaneous angina episodes might simultaneously cause prolongation of PW_{DISP}, and/or PWD_{max} [15,16]. The relationship between CAD and electrocardiographic P wave parameters is mostly based on two basic pathophysiological mechanisms [9,17,18]. The first is the atrial ischemia and/or scar due to CAD. The other is systolic and diastolic dysfunction due to left ventricular ischemia that gives rise to increased left ventricular end-diastolic pressure. Consequently, increased LA pressure and/or volume loading and the prolongation in atrial depolarization time may be seen [8]. In accordance with previous studies, we observed that the PWD_{max} was correlated with CAD severity. However, the PWTF and PW_{DISP} were not correlated with CAD severity in our study patients. In one study, the PW_{DISP} was increased in patients with a high Gensini score who underwent elective percutaneous coronary angioplasty compared to patients with normal coronary arteries [9]. In our study, PW_{DISP} was similar between the patients with and without severe CAD. The PW_{DISP} seems to be an important parameter in distinguishing patients with normal coronaries and patients with coronary lesions, but may not be sufficiently discriminative in patients with baseline coronary ischemia. The relationship between CAD severity and PWTF has been established previously. However, in these studies, the patients had LVEF of <40% and a high average LA diameter [19,20]. In our study, patients who had severe CAD did not have an abnormal PWTF compared to non-severe CAD patients. The reason for no difference between the groups in terms of PWTF could be the better LVEF and the smaller LA dimensions.

PWPT has been introduced as a newly ECG parameter. In a study by Çağdaş and colleagues, prolonged PWPT was associated with imperfect reperfusion in acute anterior ST elevation myocardial infarction patients [7]. The study finding was explained by the way that the acute ischemia may deteriorate atrial depolarization by impairing the blood supply to the atrium or by affecting the left ventricular hemodynamics, resulting in the prolongation of the P wave parameters. Given that ischemia could prolong the PWPT, we hypothesized that the patients with NSTEMI and severe coronary disease could have a prolonged PWPT due to impaired perfusion. As expected, in the present study, we observed that the PWPT in the lead D_{II} was correlated with severe CAD, and the PWPT was found to be an independent predictor of severe CAD. In our study, findings associated with acute ischemia such as ST

Table 4
Correlation analysis of the electrographic P wave parameters.

		Age	LA	LVEF	SYNTAX
PWD_{max}	r value	0.037	0.302	−0.127	0.231
	p value	0.640	0.000	0.109	0.003
PW_{DISP}	r value	0.036	0.312	−0.265	0.109
	p value	0.647	0.000	0.001	0.169
PWTF	r value	0.057	0.110	−0.064	0.021
	p value	0.492	0.183	0.440	0.801
PWPT in the lead D_{II}	r value	0.061	0.335	−0.197	0.412
	p value	0.443	0.000	0.012	0.000
PWPT in the lead V_1	r value	0.156	0.073	0.010	0.252
	p value	0.059	0.377	0.903	0.002

Abbreviations: LA; left atrium, LVEF; left ventricular ejection fraction, PWD_{max}; maximum P wave duration, PW_{DISP}; P wave dispersion, PWTF; P wave terminal force, PWPT; P wave peak time.

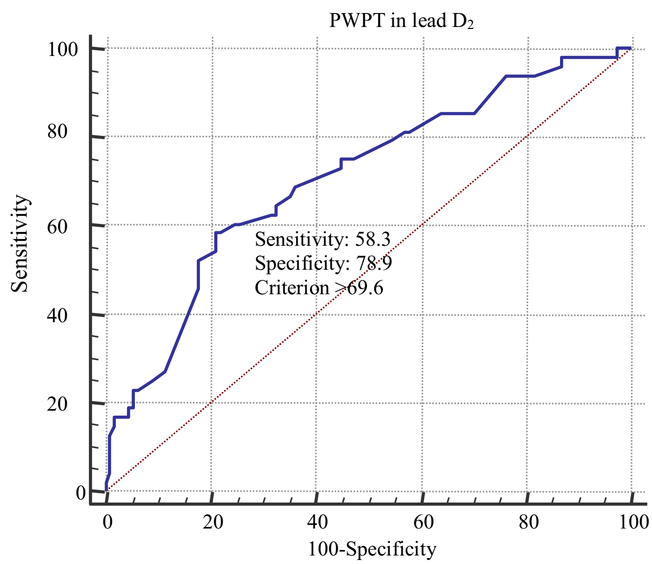

Fig. 2. Receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off value of the P wave peak time (PWPT) in the lead D_{II} for prediction of severe coronary artery disease (CAD). Abbreviations: PWPT; P wave peak time, CAD; coronary artery disease.

depression, ST elevation in the lead aVR, and CK-MB levels were higher in patients with a high SYNTAX score. Therefore, the prolonged PWPT could be a finding of acute ischemia as well as CAD severity.

IAB is a finding from P wave abnormality that is associated with adverse clinical outcomes. It has been recently shown that multi-vessel CAD is associated with IAB [8]. Consistent with previous studies, the rate of patients with IAB was higher in patients with a high SYNTAX score in our study, but the difference was not statistically significant. This finding may be due to the small number of patients with IAB. PWPT is prolonged before IAB development, which may be considered to be a more advanced stage in atrial conduction disorders, and the relationship of PWPT with the severity of CAD may provide information about the severity of CAD without block development.

Limitations

Our study did not include prognostic information because of a retrospective design. The lack of diastolic dysfunction evaluation, which is known to have an effect on atrial P wave parameters, is another limitation. Since there were very few new-onset atrial fibrillation cases in our study, we could not determine the relationship. The exclusion of patients with a history of percutaneous coronary intervention and/or coronary aorta bypass grafting indicates that it is not appropriate to generalize our results to the overall CAD population. The low number of patients included in this study and the low AUC value of PWPT may limit the clinical utility of PWPT, so it needs to be validated by further studies.

Conclusion

NSTEMI has poor endpoints, especially in patients that have multi-vessel/severe CAD. The diagnosis of CAD severity using non-invasive tools could be useful, especially in non-invasive centers. The ECG is easily accessible, interpretable, and applicable in all patients, and it is a diagnostic tool that can be assessed by most healthcare professionals. To predict severity of CAD in patients with NSTEMI, the PWPT seems to be a more useful tool among the P wave parameters and this relationship may be important in the management of the patient.

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