Relationship between R-wave peak time and no-reflow in ST elevation myocardial infarction treated with a primary percutaneous coronary intervention

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Objectives **Coronary no-reflow (NR) is observed in nearly half of ST segment elevation myocardial infarction (STEMI) patients who undergo a primary percutaneous coronary intervention (pPCI) despite epicardial coronary vessel patency. Several methods used to define NR include thrombolysis in myocardial infarction grade, corrected thrombolysis in myocardial infarction frame count, myocardial blush grade, ST-segment resolution, contrast echocardiography, and MRI. The aim of our study was to evaluate the relationship between NR and R-wave peak time (RWPT) measured from infarct-related artery leads**

Method **We enrolled 282 consecutive STEMI patients treated with pPCI in Kafkas University Hospital from January 2014 to January 2015. After exclusion, the remaining 233 patients were included in the study population**

Results **Patients were divided into two groups according to the development of NR. We observed that increased preprocedural (31 (27–37) vs 27 (21–30) p<0,001) and postprocedural RWPT(35±7 vs 22±6 p<0,001) was associated with the development of NR and preprocedural RWPT(OR: 1.254 95% CI: 1.104–1.425 p<0,001) was found to be independent predictor of NR. The association between postprocedural RWPT and angiographic NR was statistically noninferior to that between ST-segment resolution % and NR(difference between area under curves: 0.0232, p= 0.38)**

Conclusion **the present study is the first to report a significant correlation between NR and RWPT in STEMI patients treated with primary pPCI** *Coron Artery Dis* **28:326–331**

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Keywords: intrinsicoid deflection, no-reflow, ST-segment elevation myocardial infarction

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Introduction

Primary percutaneous coronary intervention (pPCI) is the best available reperfusion strategy in the setting of acute ST-segment elevation myocardial infarction (STEMI) and although 95% coronary vessel patency can be achieved, pPCI may fail to restore optimal myocardial reperfusion, known as coronary no-reflow (NR) [1]. NR is associated with larger myocardial infarct size, lower left ventricular ejection fraction, adverse left ventricular remodeling, and increased number of mechanical complications, heart failure, and death [2–4]. The precise pathophysiologic mechanisms underlying NR are unknown and are considered to be multifactorial. It may result because of ischemia reperfusion injury, larger infarct size, and endothelial dysfunction [5]. NR has been described in up to 60% of STEMI patients and its incidence has varied according to the diagnostic method used [1–5]. In clinical practice, the most preferred methods to define NR include thrombolysis in myocardial infarction (TIMI) grade, corrected TIMI frame count, myocardial blush grade (MBG), and ST-segment resolution (STR) [6–12].

R-wave peak time (RWPT), also known as intrinsicoid deflection time, was described by Macleod *et al.* [13] and defined as duration from onset of the QRS complex to the peak of the R wave. RWPT has several clinical implications including identification of ventricular hypertrophy, volume overload, conduction abnormalities, and differentiation of wide QRS complex tachycardia [13–*22*].

In the present study, we aimed to assess the potential relationship between angiographic NR and RWPT in STEMI patients treated with pPCI.

Patients and methods

Study population

The present study enrolled 282 consecutive patients with STEMI who underwent pPCI in Kafkas University Hospital from January 2014 to January 2015. STEMI was

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defined on the basis of the following criteria: ongoing ischemic symptoms (within 12 h), typical rise or fall in cardiac biomarkers, and a new ST elevation in two or more contiguous leads with leads V1, V2, and V3 measuring at least 0.2 mV or at least 0.1 mV in the remaining leads or a newly developed left bundle-branch block pattern [23].

Patients with a history of coronary artery disease, heart failure, valvular insufficiency, or stenosis more than the mild degree except ischemic mitral regurgitation, cardiomyopathy (hypertrophic or dilated), renal replacement therapy, cardiogenic shock, and failure of reperfusion therapy were excluded from the study. The patients with ECG problems because of poor image quality, bundle-branch block, second-degree and third-degree AV block, QRS duration (QRSD) of more than 120 ms, and QS pattern on admission were also excluded. A total of remaining 233 patients were included in the study population. The clinical findings and medical history of the patients were recorded. Dual antiplatelet therapy, statin, β-blockers, and angiotensin-converting enzyme inhibitors were administered to all patients without contraindications. All patients were monitored at the coronary care unit for at least 24 h after pPCI. The study protocol was reviewed and approved by the Local Ethics Committee of University in accordance with the Declaration of Helsinki.

ECG analysis

Twelve-lead ECG, which was recorded at a speed of 25 mm/s and a voltage of 10 mm/mV, was obtained from all patients at admission and 60 min after pPCI, and all measurements were obtained from these ECG papers. Preprocedural and postprocedural (at 60 min) ECG papers were scanned and analyzed using digital image processing software (*http://imagej.nih.gov/ij/*). All measurements were performed by two independent cardiologists blinded to other patients' clinical information. QRSD and RWPT were measured from the beginning of the QRS complex to the J point and from the beginning of the QRS complex to the R-peak, respectively; the average of three consecutive beats from V5 to V6 leads in anterior STEMI, D2-AVF leads in inferior STEMI, and D1-AVL leads in high lateral STEMI that had the longest duration was recorded. The durations were given as milliseconds (ms). The sum of the preprocedural and postprocedural ST-segment elevation ($\sum STE_{PRE}$, $\sum STE_{POST}$) was measured 20 ms after the end of the QRS complex of the infarct-related artery (IRA) leads.

Coronary angiography

All patients underwent selective coronary angiography using the Judkins percutaneous trans-femoral technique. All patients received, on a routine basis, 300 mg acetylsalicylic acid and a 600 mg loading dose of clopidogrel before the intervention and unfractionated heparin during the intervention. The decision as to whether to use tirofiban was left to the operator's discretion. Culprit lesions were treated with stent implantation and balloon angioplasty if necessary. Coronary angiograms were recorded in digital media for quantitative analysis (Dicom-viewer; MedCom GmbH, Darmstadt, Germany). Digital angiograms were analyzed by two independent and experienced interventional cardiologists, who were blinded to all data. In case of disagreement, the final decision was made by consensus.

Coronary blood flow patterns before and after pPCI were subjected to a thorough evaluation on the basis of TIMI flow grade using grades 0, 1, 2, and 3 [6]. MBG was assessed according to the technique defined by Van't Hof *et al.* [24]. Thrombus burden was assessed according to the TIMI thrombus grading scale ranging from grade 0 (no thrombus) to grade 5 (very large thrombus causes vessel occlusion). Patients with grade 5 thrombus were reclassified from grade 0 to grade 4 after recanalization with guide wire or small balloon [25]. We defined the angiographic NR phenomenon as a coronary TIMI flow grade of 2 or less after a vessel was recanalized or TIMI flow grade 3 together with a final MBG of less than 2, as described in previous studies [1–12].

Statistical analyses

Data were analyzed using SPSS, version 17.0 (SPSS Inc, Chicago, Illinois, USA). Normality of the data distribution was analyzed using the Kolmogorov–Smirnov test. The numerical variables with a normal distribution were presented as mean ± SD, whereas those without a normal distribution were presented as median (interquartile range). Categorical variables were presented as number and %. Continuous variables between the two groups were compared using the Student *t*-test or the Mann–Whitney *U*-test. Categorical data were compared using the χ^2 or the Fisher exact test. Statistical significance was defined as a P value less than 0.05. Multivariate logistic regression analysis was carried out to identify the independent predictors of NR using variables that showed a marginal association with it on univariate testing. Receiver-operating characteristic (ROC) analysis was used to detect the cut-off value of STR% and $RWPT_{PRE}$ in the prediction of NR. The De Longs test was used to compare the ROC curve of STR% with $RWPT_{POST}$ and $QRSD_{POST}$.

Results

The study population included 233 STEMI patients (mean age: 63 ± 11 years; 20.2% women) who underwent pPCI. The baseline characteristics of all patients are listed in Table 1. Patients were divided into two groups according to the development of angiographic NR. The patients in the NR group ($n = 99$) were older and had a higher incidence of hypertension (HT), diabetes mellitus (DM), and smoking than the patients in the reflow group

Table 1 Baseline characteristics of all patients ($N = 233$)

	All patients [n (%)]
Age (years) (mean ± SD)	63 ± 11
Sex (female)	20.2 (47)
Hypertension	44.6 (104)
Diabetes mellitus	32.2 (75)
Dyslipidemia	27.9 (65)
Smoking	56.2 (131)
Family history	26.2 (61)
Heart rate (/min) [median (interquartile range)]	71 (62–83)
Systolic blood pressure (mmHg) [median (interquartile range)]	138 (126–156)
FGL (mg/dl) [median (interquartile range)]	107 (94–125)
Creatinine (mg/dl) (mean ± SD)	0.89 ± 0.18
CRP (mg/dl) [median (interquartile range)]	0.56 (0.18–1.27)
Total cholesterol (mg/dl) [median (interquartile range)]	168 (149–190)
Hemoglobin (g/dl)	14.8 ± 1.7
Platelet (10^3/mm^3) [median (interquartile range)]	191 (171–241)
White blood cell (10^3/μl) (mean ± SD)	11.4 ± 3.3
STR (70%)	41.6 (97)
STR (50%)	71.7 (167)
IRA of LAD	36.5 (85)
Three vessels disease	12 (28)
No-reflow	42.4 (99)
LVEF (%) [median (interquartile range)]	47 (40–52)

CRP, C-reactive protein; FGL, indicates fasting glucose level; IRA, infarct-related artery; LAD, left anterior descending; LVEF, left ventricular ejection fraction; STR, ST-segment resolution.

($n = 134$). Increased symptom to balloon time, involvement of left anterior descending (LAD) as an IRA, presence of three-vessel disease, longer lesion length, preprocedural TIMI 0, and TIMI thrombus grade 2–4 were found more frequently in the NR group than in the reflow group. The baseline characteristics, clinical, angiographic, and laboratory findings of the two groups are summarized in Table 2.

The NR group had lower STR% and higher Q wave on admission ECG than the reflow group. $RWPT_{PRE}$, $RWPT_{POST}$, $QRSD_{PRE}$, and $QRSD_{POST}$ were longer in the NR group than the reflow group. The ECG findings of reflow and NR groups are compared in Table 3. Postprocedural corrected TIMI frame count in IRA was higher in the NR group than the reflow group. Spearman's correlation analysis showed that there was a moderate correlation between $RWPT_{PRE} - cTFC$ (r: 0.348; $P < 0.001$), $QRSD_{PRE} - cTFC$ (r: 0.327; $P < 0.001$), and $QRSD_{POST} - cTFC$ (r: 0.359; $P < 0.001$) and a strong correlation between $RWPT_{POST} - cTFC$ (r: 0.558; $P < 0.001$).

Multivariate logistic regression analysis was used to determine the independent predictors of NR. Univariate analysis showed that age, hypertension, DM, smoking, involvement of LAD as IRA, symptom to balloon time, preprocedural TIMI 0, thrombus grade of 3 or more, stent length, Q wave on admission, STR%, $RWPT_{PRE}$, and $QRSD_{PRE}$ were associated significantly with NR, but in multivariate analysis, symptom to balloon time, preprocedural TIMI 0, STR%, and $RWPT_{PRE}$ were found to be independent predictors of NR (Table 4). The cut-off values of STR% and $RWPT_{PRE}$ to predict NR were 64.8 with a sensitivity of 82.1% and a specificity of 80.8% [area under the curve (AUC): 0.924; $P < 0.001$] and 28.2

Table 2 Demographic, clinical, laboratory, and coronary angiographic characteristics of patients with no-reflow and without no-reflow with *P* value

	n (%)		
	Patients without NR ($n = 134$)	Patients with NR ($n = 99$)	P value
Age (years) (mean ± SD)	61 ± 12	65 ± 11	0.035
Sex (female)	16.4 (22)	25.3 (25)	0.097
Hypertension	37.3 (50)	54.5 (54)	0.009
Diabetes mellitus	22.4 (30)	45.5 (45)	< 0.001
Dyslipidemia	23.9 (32)	33.3 (33)	0.112
Smoking	48.5 (65)	66.7 (66)	0.006
Family history	25.4 (34)	27.3 (27)	0.744
Heart rate (/min) [median (interquartile range)]	71 (53–83)	71 (68–83)	0.135
Systolic blood pressure (mmHg) [median (interquartile range)]	137 (115–156)	142 (132–149)	0.421
FGL (mg/dl) [median (interquartile range)]	103 (92–117)	117 (98–132)	< 0.001
Creatinine (mg/dl) (mean ± SD)	0.89 ± 0.20	0.90 ± 0.16	0.573
Hemoglobin (g/dl) (mean ± SD)	14.8 ± 1.6	14.8 ± 1.7	0.835
Platelet (10^3/mm^3) [median (interquartile range)]	195 (165–234)	191 (182–256)	0.065
White blood cell (10^3/μl) (mean ± SD)	11.1 ± 3.4	11.8 ± 3.1	0.072
Peak CK-MB (mg/dl) [median (interquartile range)]	140 (98–256)	262 (195–349)	< 0.001
Total cholesterol (mg/dl) [median (interquartile range)]	169 (154–205)	166 (149–187)	0.131
CRP (mg/dl) [median (interquartile range)]	0.24 (0.13–1.41)	0.69 (0.40–1.20)	< 0.001
Symptom to balloon time (h) (mean ± SD)	2.3 ± 0.8	3.2 ± 0.6	< 0.001
IRA of LAD	29.9 (40)	45.5 (45)	0.014
Three-vessel disease	4.5 (6)	22.2 (22)	< 0.001
Proximal lesion	53.7 (72)	58.6 (58)	0.461
Preprocedural TIMI 0	52.2 (70)	84.8 (84)	< 0.001
Thrombus grade ≥ 3	36.6 (49)	81.8 (81)	< 0.001
Stent length (mm) [median (interquartile range)]	23 (18–25)	28 (23–33)	< 0.001
Postprocedural IRA TFC [median (interquartile range)]	13 (10–14)	23 (16–32)	< 0.001
LVEF (%) [median (interquartile range)]	48 (44–52)	44 (35–50)	< 0.001

CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; FGL, fasting glucose level; IRA, infarct-related artery; LAD, left anterior descending; LVEF, left ventricular ejection fraction; TFC, TIMI frame count; TIMI, thrombolysis in myocardial infarction.

Table 3 ECG characteristics of patients with no-reflow and without no-reflow with *P* value

	Patients without NR ($n=134$)	Patients with NR ($n=99$)	*P* value
Q wave on admission [*n* (%)]	20.9 (28)	59.6 (59)	<0.001
$\sum STE_{PRE}$ [median (interquartile range)]	8.5 (6.4–20.1)	8.7 (4.9–11.7)	0.150
$\sum STE_{POST}$ [median (interquartile range)]	2.1 (1.2–3.4)	3.9 (2.5–7.6)	<0.001
STR (%) [median (interquartile range)]	75.3 (68–86.1)	46.6 (25.3–62.5)	<0.001
STR (70%) [*n* (%)]	68.7 (92)	5.1 (5)	<0.001
STR (50%) [*n* (%)]	100 (134)	33.3 (33)	<0.001
$QRSD_{PRE}$ (ms) (mean ± SD)	91 ± 14	100 ± 13	<0.001
$QRSD_{POST}$ (ms) (mean ± SD)	84 ± 14	105 ± 13	<0.001
$RWPT_{PRE}$ (ms) [median (interquartile range)]	27 (21–30)	31 (27–37)	<0.001
$RWPT_{POST}$ (ms) (mean ± SD)	22 ± 6	35 ± 7	<0.001

NR, no-reflow; $QRSD_{POST}$, postprocedural QRS duration; $QRSD_{PRE}$, preprocedural QRS duration; $RWPT_{post}$, postprocedural R-wave peak time; $RWPT_{PRE}$, preprocedural R-wave peak time; STR, ST-segment resolution.

Table 4 Independent predictors of no-reflow with univariate and multivariate *P* value, odds ratio with 95% confidence interval

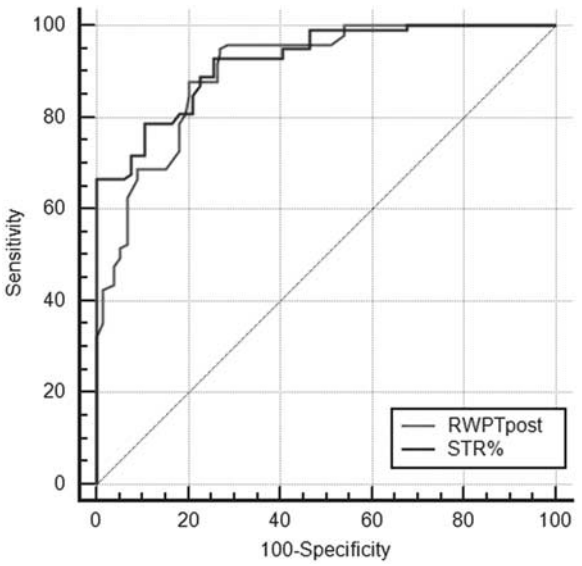
	Univariate			Multivariate		
	P value	OR	95% CI	*P* value	OR	95% CI
Age	0.035	1.024	1.001–1.047	0.109	0.962	0.917–1.009
Hypertension	0.009	2.016	1.189–3.419	0.124	0.388	0.116–1.296
Diabetes mellitus	<0.001	2.889	1.639–5.093	0.052	3.379	0.990–11.541
Smoking	0.006	2.123	1.24–3.636	0.463	1.492	0.512–4.343
Symptom balloon time	<0.001	4.457	2.865–6.933	0.001	7.869	2.337–26.490
IRA of LAD	0.014	1.958	1.139–3.366	0.160	0.283	0.049–1.647
Preprocedural TIMI 0	<0.001	5.120	2.685–9.764	0.012	6.288	1.492–26.492
Thrombus grade ≥ 3	<0.001	7.806	4.199–14.511	0.090	2.786	0.852–9.116
Stent length	<0.001	1.223	1.150–1.3	0.953	0.997	0.892–1.113
Q wave on admission	<0.001	5.584	3.131–9.957	0.053	0.165	0.027–1.027
STR (%)	<0.001	0.871	0.84–0.903	<0.001	0.848	0.791–0.908
$RWPT_{PRE}$	<0.001	1.134	1.084–1.186	<0.001	1.254	1.104–1.425
$QRSD_{PRE}$	<0.001	1.051	1.029–1.074	0.192	0.963	0.910–1.019

CI, confidence interval; IRA, infarct-related artery; LAD, left anterior descending; OR, odds ratio; $QRSD_{PRE}$, preprocedural QRS duration; $RWPT_{PRE}$, preprocedural R-wave peak time; STR, ST-segment resolution; TIMI, thrombolysis in myocardial infarction.

with a sensitivity of 61.6% and a specificity of 56% (AUC: 0.697; $P<0.001$), respectively.

ROC curves of STR% (AUC: 0.924; $P<0.001$), $RWPT_{POST}$ (AUC: 0.904; $P<0.001$), and $QRSD_{POST}$ (AUC: 0.855; $P<0.001$) were compared (Fig. 1). There was no statistically significant difference between AUC of $RWPT_{POST}$ and STR% (difference between area: 0.0232, $P=0.38$); AUC of $RWPT_{POST}$ was significantly higher than $QRSD_{POST}$ (difference between area: 0.286, $P<0.001$).

Fig. 1



ROC curve comparison of STR and $RWPT_{POST}$. Difference between AUC of STR% (AUC: 0.924; $P<0.001$) and $RWPT_{POST}$ (AUC: 0.904; $P<0.001$) was 0.0232, with a *P* value of 0.38. AUC, area under curve; ROC, receiver-operating characteristic; $RWPT_{POST}$, postprocedural R-wave peak time; STR, ST-segment resolution.

Discussion

Our study showed that $RWPT_{PRE}$ and $RWPT_{POST}$ were significantly associated with the NR phenomenon and $RWPT_{PRE}$ was found to be an independent predictor for NR. Also, the association between angiographic NR and $RWPT_{POST}$ was statistically equal to NR and STR% in the ROC curve comparison.

In clinical practice, angiographic NR was defined as postprocedural TIMI flow grade of less than 3 or TIMI flow grade of 3 with MBG below 2 [12]. According to this definition, 42.4% ($n=99$) of our study population had NR. Consistent with the results of previous studies [1–5], we found that older age, a history of DM, and smoking

were associated with increased development of NR. There is lack of evidence on the relationship between NR and HT, but our study showed that a history of HT was more prevalent in patients with NR. This divergent result could be explained by the relationship between HT, endothelial dysfunction [26], coronary slow flow [27], and increased atherosclerotic burden [28] in stable coronary artery disease. In our study, patients with NR had a larger infarct size (higher symptom to balloon time, peak creatine kinase-myocardial band level, more frequent involvement of LAD as IRA, decreased left ventricular ejection fraction) and higher thrombus burden as shown in previous studies [1–4,29]. Also, symptom to balloon time and preprocedural TIMI 0 were found to be independent predictors of NR.

ECG has a unique value in the diagnosis of STEMI and success of reperfusion. In clinical practice, the most used ECG parameter to define reperfusion success is postprocedural STR. STR below 70% at 60 min is a marker of NR and a rapid STR is a highly specific (91%) and sensitive (77%) parameter of myocardial reperfusion [9,11]. In our study, STR% at 60 min after pPCI was significantly lower in patients with NR. In our study, we evaluated preprocedural and postprocedural RWPT and QRSD, and found that these parameters were significantly higher in the NR group. $RWPT_{PRE}$ was found to be an independent predictor of NR, but not $QRSD_{PRE}$. Also, NR caused significant prolongation in RWPT and QRSD. AUC of $RWPT_{POST}$ was statistically not different from STR% and higher than $QRSD_{POST}$. As QRSD was previously shown to be associated with NR [30]; to our knowledge, RWPT was not examined in the development of NR in STEMI patients. Myocardial ischemia-induced prolongation of QRSD is explained by conduction delay in Purkinje fiber and ventricular myocytes [31,32]. On the basis of previous data, prolongation of RWPT can be attributed to ventricular enlargement because of systolic or diastolic overload [13–19] and conduction abnormalities [20–22]. The superiority of RWPT measured from IRA leads over QRSD in association with NR could be explained by localized conduction delay in myocardial ischemia/infarction. Because STEMI causes segmental myocardial infarction associated with IRA and the QRS complex represents whole ventricular depolarization, QRSD could be less sensitive than RWPT that obtained from IRA leads to show localized infarction-related conduction delay.

Conclusion

The present study has three main observations. First, RWPT was associated with NR and surpassed QRSD. Second, $RWPT_{PRE}$ could predict angiographic NR before pPCI. Third, the association between $RWPT_{POST}$ and angiographic NR was statistically noninferior to that between STR% and NR.

Limitations

The present study has a cross sectional design; hence, it does not provide prognostic data. Reperfusion success was evaluated only by visual assessment and a more specific and sensitive method such as coronary flow reserve, contrast echocardiography, or cardiac MRI was not used.

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Conflicts of interest

There are no conflicts of interest.

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