



ORIGINAL ARTICLE

## Predictors of No-Reflow Phenomenon after Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction Patients

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### ABSTRACT

**Background:** Despite the recent progress in percutaneous coronary intervention (PCI), a proportion of patients develop epicardial coronary artery reperfusion but not myocardial reperfusion after primary percutaneous coronary intervention (PPCI), known as no-reflow (NR). This study is conducted to identify simple clinical factors, laboratory, angiographic findings, and procedural features that predict no-reflow phenomenon (NR) in patients with STEMI who undergo PCI.

**Methods:** We investigated a total of 444 patients who underwent PCI for acute STEMI in a Specialized medical hospital, at Mansoura university between January 2015 to April 2020 as a retrospective and prospective comparative cross-sectional study.

**Results:** Longer total ischemic time, pathologic Q waves, absence of ST-segment resolution  $\geq 50$ , higher CKMB, higher platelet distribution width (PDW), higher CHA2DS2-VASC risk score, lower EF %, low initial TIMI flow grade, lower myocardial blush grade, high thrombus grade, higher SYNTAX score, higher culprit lesion length, large vessel diameter, complex occlusion, increased number of infarct-related artery stents, the higher maximal inflation pressure of stent, pre-balloon dilatation and post-balloon dilatation and higher contrast were found as significant predictors for the development of NR. The previous independent risk factors can correctly predict NR by 88.2%

**Conclusions:** The NR predictors in this study might be useful in targeting patients who could benefit from aggressive pharmaco-invasive therapy. Prevention of NR is always better than treatment as the development of NR is associated with high morbidity and mortality rates.

**Key Words:** No-reflow phenomenon; ST-segment elevation myocardial infarction; Primary percutaneous coronary intervention.



### INTRODUCTION

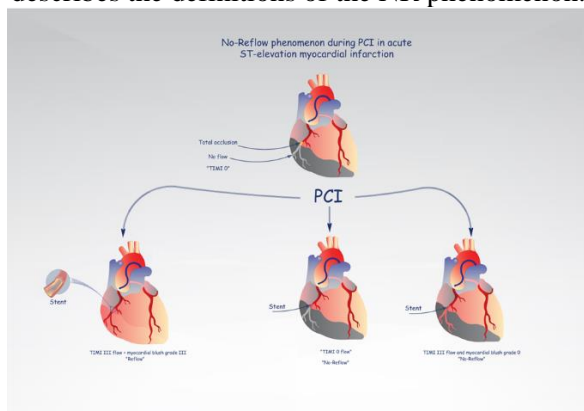
The main part of the treatment of acute STEMI is the rapid restoration of the perfusion of IRA, leading to the slogan 'Time is the Myocardium, Time is Life'. Additionally, it is important to mention that the necrotic part of the myocardium cannot undergo restoration however, it is associated with reperfusion injuries and even the NR phenomenon[1].

Despite the effectiveness of PPCI in certain patients, some patients may face a phenomenon

which is named no-reflow. In addition, this phenomenon has been noticed to have an association with poor hospital survival, poor one-year survival as well as arrhythmias. Furthermore, it has been found to happen in 5-25% of cases [2].

It has been reported that no-reflow is known as final thrombolysis in myocardial infarction flow grade (TIMI) <III or TIMI III flow with MBG 0 or 1 in absence of mechanical obstruction. In addition, TIMI flow grade has been known to be the easiest as

well as the most commonly used method to evaluate the success of PCI in the case of STEMI (1). **Figure 1** describes the definitions of the NR phenomenon.



**Figure 1** Shows the definition of the No-reflow phenomenon.

It has been reported that the prediction of patients having a risk for no-reflow can have benefits from prevention. In addition, awareness of the risks will result in using of certain techniques which can improve the no-reflow degree [3].

This study is aimed to identify simple clinical factors, laboratory, angiographic findings, and procedural features that predict no-reflow phenomenon in patients with STEMI who undergo PCI in the cardiovascular medicine department at Mansoura Specialized Medical Hospital.

### METHODS

We investigated a total of 444 patients who underwent PCI for acute STEMI in our catheterization laboratory in the cardiovascular medicine department at Mansoura specialized internal medicine hospital between January 2015 to April 2020 as a retrospective and prospective comparative cross-sectional study. Twenty-six patients were excluded as they didn't fulfill the inclusion criteria. Written informed consent was obtained from all participants, the study was approved by the research ethics committee of the Faculty of Medicine, Mansoura University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The included patients in our study were allocated into two groups in accordance with the NR occurrence. The patients included in Group I had NR and on the other hand, the patients included in group II had a final grade of TIMI flow 3. Additionally, it is significant to mention that NR was identified as a final flow grade of TIMI less than 3 or with TIMI 3

distal flow but with TMBG 0 or 1 without any dissection or spasm.

Clinical outcomes were assessed in accordance with the standard protocol, and all the cases included in our study were followed up (1, 3, and 6, months) at an outpatient clinic.

### Inclusion and exclusion criteria:

The inclusion criteria were STEMI patients for PCI according to the universal definition. The Exclusion criteria were patients who received conservative treatment for spasm of the coronary artery or 50% or less of diameter stenosis of the culprit lesion with normal blood flow in the coronary artery, patients that needed emergency surgical revascularization for severe left main coronary artery or multivessel disease.

Comparative analysis between two groups of normal flow and no-reflow with full history regarding age, gender, risk factors (diabetes mellitus (DM), hypertension (HTN), and smoking, family history of coronary artery disease), total ischemic time and CHA2DS2-VASC risk score.

Electrocardiography (ECG) was analyzed for ST segment elevations, pathologic Q waves, bundle branch block, and the presence of an arrhythmia. Echocardiography study for ejection fraction and complications.

Laboratory data were analyzed for CKMB and PDW

Coronary angiography was assessed for lesion characteristics as follows: IRA, lesion location, type of occlusion, culprit lesion length, vessel diameter, TIMI flow, MBG, thrombus grade, SYNTAX score I utilizing [www.syntaxscore.com](http://www.syntaxscore.com) from the baseline angiogram, number of stents, contrast volume, inflation pressure, pre, and post balloon dilatation.

### STATISTICAL ANALYSIS

Data were collected and processed and introduced to the computer and analyzed utilizing IBM SPSS for Windows, Version 22.0. The presentation of the Qualitative data was carried out utilizing numbers and percentages. The presentation of Quantitative data was carried out utilizing mean, and standard deviation after normality testing utilizing the Kolmogorov-Smirnov test. The level of Significance of the attained results was judged at (0.05).

The Qualitative data were analyzed by the following two methods; the Chi-Square test for comparison of 2 or more groups and the Monte Carlo test as correction for the Chi-Square test when more

than 25% of cells have a count less than 5 in tables (>2\*2).

Quantitative data between groups were analyzed by the Student t-test which was used to compare 2 independent groups of parametric variables while the Mann-Whitney U test was used to compare 2 independent groups of non-parametric tests.

The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using ROC curve analysis. Sensitivity and Specificity were detected from the curve and PPV, NPV, and accuracy were calculated through cross-tabulation.

**RESULTS**

The present study was cross sectional study carried out on STEMI patients for PCI to identify simple clinical factors, angiographic findings, and procedural features that predict NR phenomenon in patients with STEMI who undergo PCI. The total examined patients 444 from them 26 were excluded as they did not meet inclusion criteria, then the total studied groups were 418 patients that were classified into 2 groups according to TIMI flow into reflow group including patients with TIMI flow 3 (85.4% of the studied sample) and patients with TIMI Flow less than or equal to 2 (NR group) and represents 14.6% of the studied sample with 9.8% mortality.

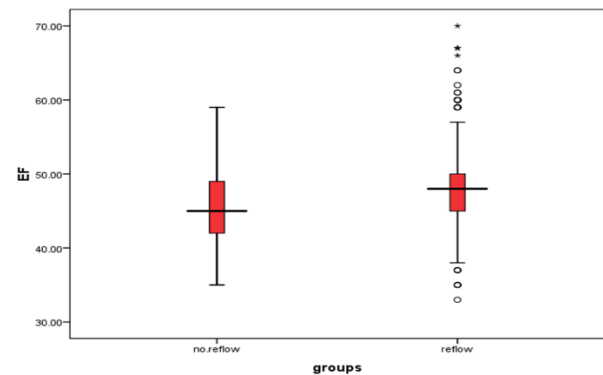
In the present study, we found that old age, sex, HTN, DM, smoking, and family history of CAD were insignificantly associated with the NR phenomenon.

As regards total ischemic time from symptom onset to wire crossing, longer total ischemic time is significantly associated with NR (OR=1.68, 95% CI:1.21-2.33).

Regarding ECG, the presence of pathologic Q waves at admission ECG (OR=3.86, 95% CI:1.96-7.62) and absence of ST-segment elevation resolution (STR) ≥ 50(OR=4.41, 95% CI:1.51-2.81) was significantly associated with NR as shown in.

As regards the CHA2DS2-VASC risk score, a higher score is associated with NR (OR=2.05, 95% CI:1.51-2.81) as shown in.

As regards echocardiography; the present study shows a significantly increased incidence of no-reflow with low EF (OR=0.931, 95%CI:0.881-0.985) as shown in figure 2.



**Figure 2** Box and Whisker plot showing median EF among studied groups.

Regarding laboratory results, higher CKMB (OR=1.001, 95% CI:1.0-1.002) and higher PDW (OR=1.66, 95% CI:1.009-2.75) were significantly associated with NR.

Regarding the coronary angiography; low initial TIMI flow grade (OR=0.067, 95% CI :(0.002-1.95) and low myocardial blush grade (OR=0.006, 95% CI:0.001-0.077) as shown in table 1. High SYNTAX score (OR=1.43, 95% CI: 1.24-1.65), high thrombus burden (OR=3.29, 95% CI :2.18-4.98), culprit lesion length (OR=1.09 ,95% CI:1.026-1.178), vessel diameter (OR=5.1395% CI: 0.659-39.96) and complex occlusion (OR =1.0, 95% CI: 0.89-4.2) as shown in table 2. Preballoon dilation(OR=2.3, 95% CI:1.05-5.05), post balloon dilation (OR=4.16, 95% CI :1.49-11.56), maximal inflation pressure of stent(OR=1.39, 95%CI :1.09-1.79), number of stents of IRA(OR=1.92, 95% CI:1.072-3.45) and contrast volume(OR=1.01, 95% CI:1.002-1.02) as shown in table 3 were statistically significant associated with NR with overall percent predicted=88.0%, as shown in table 4.

**Table 1** Association between no reflow and initial TIMI flow, TFC, myocardial blush and collateral flow grade among studied cases.

	Total number =418	No reflow N=61(%)	Reflow N=357(%)	test of significance	p-value
Initial TIMI flow 0/1	88	30(49.2)	58(16.2)	$\chi^2=33.99$	P<0.001*

	Total number =418	No reflow N=61(%)	Reflow N=357(%)	test of significance	p-value
2/3	330	31(50.8)	299(83.8)		
Myocardial blush grade				FET	p<0.001*
<2	61	60(98.4)	1(0.3)		
≥2	357	1(1.6)	356(99.7)		

Used tests: Chi-Square test and Fischer exact test(FET)\*statistically significant TIMI (Thrombolysis in Myocardial Infarction)

**Table 2** Association between NR and lesion characteristics among studied cases.

	Total number =418	No reflow (N=61)	Reflow (N=357)	test of significance	p-value
Infarction related artery				$\chi^2=1.71$	p=0.425
LAD					
RCA	282	43(70.5)	239(66.9)		
LCX	106	12(19.7)	94(26.3)		
	30	6(9.8)	24(6.7)		
Culprit lesion length	21.40±6.75	27.75±8.49	20.33±5.77	t=18.97	p<0.001*
Vessel diameter	3.13±0.23	3.32±0.26	3.10±0.21	t=12.56	p<0.001*
Thrombus grade				MC	p<0.001*
0	3	0(0.0)	3(0.8)		
1	9	0(0.0)	9(2.5)		
2	22	1(1.6)	21(5.9)		
3	249	22(36.1)	227(63.6)		
4	108	23(37.7)	85(23.8)		
5	27	15(24.6)	12(3.4)		
Thrombus grade				MC	P<0.001*
Grade 0(Nil)	3	0(0.0)	3(0.8)		
Low (grade 1/2)	31	1(1.6)	30(8.4)		
Moderate (grade 3)	249	22(36.1)	227(63.6)		
High (grade 4/5)	135	38(62.3)	97(27.2)		
<4	283	23(37.7)	260(72.8)	$\chi^2=29.39$	p<0.001*
≥4	135	38(62.3)	97(27.2)		
SYNTAX score mean±SD	23.48±3.89	27.46±3.52	22.80±3.54	t=9.51	P<0.001*
Lesion type				$\chi^2=1.39$	p=0.238
Eccentric	221	28(45.9)	193(54.1)		
Concentric	197	33(54.1)	164(45.9)		
Type of occlusion				MC	P<0.001*
Total	27	25(40.9)	2(0.6)		
Tapered	77	9(14.8)	68(19.0)		
Subtotal	174	5(8.2)	169(47.3)		
Cut off	140	22(36.1)	118(33.1)		
Lesion location				MC	p=0.06
Proximal	199	34(55.7)	165(46.2)		
Ostial	16	2(3.3)	14(3.9)		
Mid	134	22(36.1)	112(31.4)		
Distal	69	3(4.9)	66(18.5)		

Used tests: Student t test , Monte Carlo test (MC), Chi-Square test \*statistically significant SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery)

**Table 3** Technique of reperfusion among studied groups.

	Total number N=418	No reflow N=61	Reflow (N=357)	test of significance	P Value
Direct stenting				$\chi^2=3.14$	P=0.076
no	137	26(42.6)	111(31.1)		
yes	281	35(57.4)	246(68.9)		
Pre-balloon dilatation	74	18(29.5)	56(15.7)	$\chi^2=6.83$	p=0.009*
Post-balloon dilatation	25	12(19.7)	13(3.6)	$\chi^2=23.81$	p<0.001*
Maximal inflation pressure of stent	14.93±1.64	16.42±1.99	14.68±1.43	t=2.5	p<0.001*
Number of IRA stents				MC	p<0.001*
1	350	44(72.1)	306(85.7)		
2	60	12(19.7)	48(13.4)		
3	7	4(6.6)	3(0.8)		
4	1	1(1.6)	0(0.0)		
Contrast volume	126.48±50.97	178.03±68.55	117.68±41.45	t=17.81	p<0.001*

Used tests: Fischer exact test (FET), Student t test, Monte Carlo test\*MC), Chi-Square test \*statistically significant

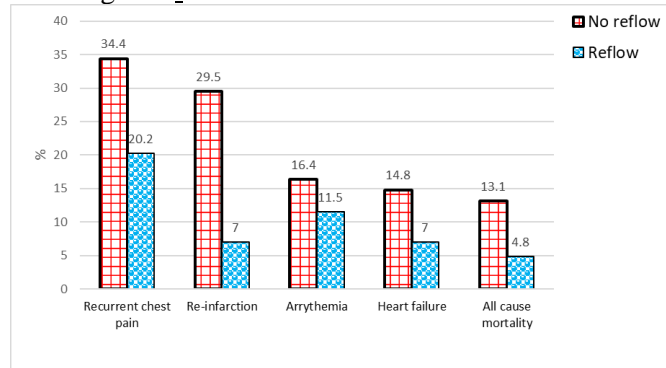
IRA(infarct related artery)

**Table 4** Predictors for no reflow among studied cases.

Predictors	B	P	Odds ratio (95% CI)
EF %	-0.071	0.013*	0.931(0.881-0.985)
Myocardial blush grade	-5.06	<0.001*	0.006(0.001-0.077)
Culprit lesion length	0.095	0.007*	1.09(1.026-1.178)
Vessel diameter	1.64	0.118	5.13(0.659-39.96)
Contrast volume	0.01	0.02*	1.01(1.002-1.02)
Thrombus grade $\geq 4$	1.19	<0.001*	3.29(2.18-4.98)
Number of IRA stents	0.653	0.03*	1.92(1.07-3.45)
Type of occlusion	1.05	0.06	1.0(0.89-4.2)
Total ischemic time (min) from symptom onset to wire crossing in PCI	0.519	0.002*	1.68(1.21-2.33)
Pre-infarction angina	0.902	0.06	2.46(0.99-4.29)
CKMB(IU/L)	0.001	0.004*	1.001(1.0-1.002)
PDW (fl)	0.511	0.046*	1.66(1.009-2.75)
Maximal inflation pressure of stent	0.335	0.009*	1.39(1.09-1.79)
Syntax score	0.357	<0.001*	1.43(1.24-1.65)
Presence of pathologic Q waves in admission ECG	1.35	<0.001*	3.86(1.96-7.62)
Absence of STR $\geq 50$	1.48	<0.001*	4.41(1.51-2.81)
CHA2DS2-VASc Risk Criteria	0.722	<0.001*	2.05(1.51-2.81)
Pre-balloon dilatation	0.835	0.037*	2.30(1.05-5.05)
Post-balloon dilatation	1.426	0.006*	4.16(1.49-11.56)
Overall percent predicted=88.0%			

EF(ejection fraction), PDW(platelet distribution width)

As regards outcomes, the present study illustrated that there is statistically significant association between 6 months recurrent chest pain, re-infarction, heart failure, all-cause mortality, and presence NR among studied cases, with 29.5% of cases with no reflow have higher incidence of re-infarction after 6 months versus 7% among cases with reflow, Recurrent chest pain, heart failure and all causes mortality show also higher frequency among cases with no reflow (34.4%, 14.8%, 13.1%, respectively) as shown in figure 3.



**Figure 3** MACE distribution within 180 days among studied groups.

### DISCUSSION

NR phenomenon has a multifactorial etiology and generally can be recognized by 4 different groups: (1) Ischemic injury, (2) Distal athero-thrombotic embolization, (3) The coronary microcirculation susceptibility to injury, and (4) Reperfusion injury. Furthermore, distal embolization has been recognized to occur due to the migration of debris (endothelial cells, thrombi, and lipid matrix) downstream from the lry lesion, resulting in microvascular obstruction and causing more injury [3].

The present study is conducted to recognize simple clinical factors, laboratory, procedural features, and angiographic findings which can provide a prediction of the NR phenomenon in the cases suffering from STEMI who have PCI in a Specialized medical hospital, Mansoura university.

The present study reported the incidence of NR phenomenon as 14.6%. Rossington et al, [4] reported it ranges from 11 to 41%. The present study couldn't find statistically significant differences between the studied groups regarding age, sex, hypertension, diabetes, smoking, and family history of ischemic heart disease (IHD).

In the present study, the main factor for a prolonged total ischemic time was the patient's delay. The absence of general awareness regarding chest pain differentiation, delay in looking for medical advice, particularly in women, and poverty were factors prompting the occurrence of the patient's delay, the same reasons demonstrated by Ayad [5]. Our study demonstrated a significant

association between prolonged ischemic time and NR.

Regarding ECG analysis, STR <50% should be considered indicative of NR. Our study showed that the absence of STR ≥50 was significantly associated with NR. Waks et al, [6] demonstrated an association between the appearance of new Q waves on the presenting ECG and NR. In line with the present study that showed the presence of pathologic Q wave was significantly associated with NR.

Regarding laboratory analysis, the present study demonstrated that mean peak CPK and CKMB are significantly higher among cases with NR. In agreement with Liang et al [7] that illustrated that peak CPK was higher in patients with NR. Our study illustrates a statistically significant higher mean PDW among cases with NR. In line with our study, Zhang et al [8] illustrated that PDW is an independent predictor of NR.

As regards CHA2DS2-VASc, Zhang et al [9] demonstrated that though the CHADS2, CHA2DS2-VASc, and CHA2DS2-VASc-HSF scores can all be utilized as simple tools to make predictions of NR phenomenon, their findings represent that the CHA2DS2-VASc-HSF score showed the highest predictive value. Consequently, this score may be an ideal tool for the prediction of high-risk cases. this is in concordance with our study that showed an increased score of CHA2DS2-VASc Risk Criteria was significantly associated with NR (Sensitivity 86.2%, Specificity 51.2%).

Lower left ventricular EF (LVEF) of 11 studies [10] was correlated with the possibility of the

development of NR. Additionally, Low EF of LV was correlated with poor prognosis [11]. In our study, there is a statistically significantly lower mean EF among cases with NR (45.67) versus (47.57) among cases with reflow (Sensitivity 63.3%, Specificity 51.5%).

**Fajar et al [12]** demonstrated that initial flow of TIMI equal or less than 1, multivessel disease, collateral flow, and increased thrombus burden had a significant association with the possibility of development of the NR. Furthermore, in comparison with other covariates, thrombus burden and TIMI flow showed the highest correlation for the NR phenomenon. The NR phenomenon with a large size of infarct has been demonstrated to be more common in cases having increased thrombus burden [13], decreased TIMI flow, and collateral flow [14]. In our study, there is a statistically significant association between higher incidence of NR and the following; initial TIMI flow grade 0/1 (49.2% versus 16.2% for cases with no-reflow and reflow respectively), presence of high thrombus grade (62.3% among cases with NR have thrombus grade more than or equal to 4 versus 27.2% among cases with reflow (Sensitivity 72.4% , Specificity 69.4% ) .

**Sadek et al [15]** demonstrated that the SYNTAX score is a predictor of the NR phenomenon in the cases with acute MI that were managed by PCI, in line with our study that showed the median SYNTAX score among cases with NR was significantly higher than cases with reflow (Sensitivity 85.5%, Specificity 81.2%).

**Liang et al [7]** confirmed that the length of the lesion and reference lumen diameter have been correlated with development of the NR phenomenon. Additionally, they reported that many factors may clarify these outcomes. Firstly, large vessels can provide accommodation of big quantities of thrombus or plaque lipid. Additionally, it is important to mention that the bigger the affected vessels are , the slower the velocity of flow, and the longer the lesion reveals the bigger quantity of plaque burden and thrombus [16]. Second, longer lesion specifies the utilization of longer length of stent. Hong et al [17] detected that longer the length of the stent has been correlated with prolapse of plaque that was established to be correlated with myonecrosis subsequent to stenting and the NR phenomenon [18]. This would explain that the present study found there is a statistically significant association observed between NR and culprit lesion

length (Sensitivity 86.1% ,Specificity 61.3%) and vessel diameter.

Hong et al,[19] illustrated that maximal inflation pressures of stent did not have significant effect on the NR incidence. The present study showed that maximal inflation pressures of stent correlates well with no-reflow phenomenon incidence (Sensitivity 72.4%, Specificity 69.4%). This controversy could be explained by the inflation pressure were higher in our study than the previous study especially in NR group, that probably compresses and squeezes the underlying soft plaque and thrombi contributing to NR phenomenon.

Our study demonstrates that mean contrast volume among cases with NR was 178.03 versus 117.68 among cases with reflow (Sensitivity 95.8%, Specificity 51.6%) with a significant correlation. In concordance with our study, Ding et al [20] illustrated that the contrast agent dose may be a risk factor for slow/NR after PCI. When the dose was greater than 160 ml, the risk of slow/NR increased significantly.

**Ndrepepa et al, [21]** found that NR in STEMI patients after primary PCI was associated with a significant reduction in myocardial salvage, larger infarct size, worse LVEF at 6 months, and an increased risk of 1-year mortality. Normalization of blood flow occurred within 6 months of reperfusion in four of five patients who did not have reflow after PCI. When compared to patients who had normal blood flow restored within 6 months of PCI, the persistence of compromised tissue perfusion was associated with worse left ventricular function. Our study illustrated that there is a statistically significant association between 6 months of recurrent chest pain, re-infarction incidence, heart failure, all-cause mortality and the presence of no-reflow among studied cases with 29.5% of cases with no-reflow having a higher incidence of re-infarction-after-6 months versus 7% among cases with reflow. Recurrent chest pain, heart failure, and all-cause mortality show also higher frequency among cases with no-reflow (34.4%, 14.8%, and 13.1%, respectively) as shown in figure 3.

## CONCLUSIONS

Longer total ischemic time from symptom onset to wire crossing in PPCI, pathologic Q waves, absence of ST-segment resolution( STR)  $\geq 50$ , higher CKMB, higher PDW, higher CHA2DS2-VASC risk criteria, lower EF %, low initial TIMI flow grade, lower MBG, high thrombus grade, higher SYNTAX score, higher culprit lesion length, large vessel

diameter, complex occlusion, increased number of infarct-related artery stents, the higher maximal inflation pressure of stent, pre-balloon dilatation and post-balloon dilatation and higher contrast volume were found as significant predictors for the development of NR. The main recommendation is that prevention is always better than treatment and the NR phenomenon should be predicted and successfully treated to improve myocardial salvage and improve outcomes.

**Conflict of Interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**Financial Disclosures:** None

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