Original Article

Predictors of no- reflow during primary angioplasty for acute myocardial infarction, from Medical College Hospital, Trivandrum

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ARTICLE INFO

ABSTRACT

Background: Primary angioplasty (PCI) for acute myocardial infarction is associated with no-reflow phenomenon, in about 5–25% of cases. Here we analysed the factors predicting no reflow .

Methods: This was a case control study of consecutive patients with acute myocardial infarction who underwent Primary PCI from August 2014 to February 2015.

Results: Of 181 patients who underwent primary PCI, 47 (25.9%) showed an angiographic no-reflow phenomenon. The mean age was 59.19 ± 10.25 years and females were 11%.

Univariate predictors of no reflow were age >60 years (OR = 6.146, 95%CI 2.937–12.86, P = 0<0.001), reperfusion time >6 h (OR = 21.94, 95%CI 9.402–51.2, P = <0.001), low initial TIMI flow ($\leq$1) (OR = 12.12, 95%CI 4.117–35.65, P < 0.001), low initial TMPG flow ($\leq$1) (OR = 36.19, 95%CI 4.847–270.2, P < 0.001) a high thrombus burden (OR = 11.04,95%CI 5.124–23.8, P < 0.001), a long target lesion (OR = 8.54, 95%CI 3.794–19.23, P < 0.001), Killip Class III/IV(OR = 2.937,95%CI 1.112–7.756,P = 0.025) and overlap stenting (OR = 3.733,95%CI 1.186–11.75,P = 0.017).

Multiple stepwise logistic regression analysis predictors were: longer reperfusion time > 6 h (OR = 13.844, 95%CI 3.214–59.636, P = <0.001), age >60 years (OR = 8.886, 95%CI 2.145–36.80, P = 0.003), a long target lesion (OR = 8.637, 95%CI 1.975–37.768, P = 0.004), low initial TIMI flow ($\leq$1) (OR = 20.861, 95%CI 1.739– 250.290, P = 0.017).

Conclusions: It is important to minimize trauma to the vessel, avoid repetitive balloon dilatations use direct stenting and use the shortest stent if possible.

1. Introduction

Primary angioplasty is an effective treatment for myocardial infarction in that it effectively and rapidly opens up the infarct related artery and provides sufficient information about the disease in the other major epicardial coronary arteries. In spite of its effectiveness in certain patients and in spite of having a TIMI 3 flow, patients experience a phenomenon called no-reflow. This phenomenon is associated with arrhythmias, poor in-hospital survival and poor one year survival[1,2] and has been found to occur in 5 to 25 percent of cases.[3,4]

2. What is no-reflow?

The phenomenon of no-reflow is defined as inadequate myocardial perfusion through a given segment of coronary circulation without angiographic evidence of mechanical vessel obstruction.[7] Occlusion and reperfusion leads to no-reflow.

3. No-reflow in 2016

No-reflow has attracted a great deal of interest, even in 2016. Researchers from London have completed a *meta*-analysis on the use of intravenous and intracoronary adenosine in patients with no-reflow.[5] They calculated the pooled relative risk via a fixed effect *meta*-analysis. They studied the effect of adenosine administration on all-cause mortality, non-fatal myocardial infarction, and congestive heart failure. They analysed 13 randomized controlled trials. In patients who received intra-coronary adenosine, the incidence of no-reflow was reduced and

the incidence of new onset heart failure was reduced significantly. Intravenous adenosine did not improve the incidence of no-reflow or new heart failure.

Another recent study examined the predictors of no-reflow from a large cohort.[6] The authors analysed data from 781 consecutive patients who had undergone primary angioplasty from 2008 to 2012. Of these, 189 patients had no-reflow. The patients who had no-reflow were older, lower TIMI flows and a higher thrombus score (more than 4). According to the multivariate analysis, the presence of cardiogenic shock, age of more than 60 years, thrombus score of more than 4 and balloon time of more than 360 min were independent predictors of no-reflow.

4. Stenting and no-reflow

17% of patients developed no-reflow immediately after stenting.[6]

4.1. Death and reinfarction

Patients with no-reflow had a higher incidence of death at 12 months. (13% versus 6% $p < 0.003$).[6]

With this background we decided to publish our study on no-reflow.

5. When does no-reflow develop?

Temporary occlusion of the artery, a prerequisite condition for no-reflow, may be produced in the experimental setting occur during reperfusion of an infarct-related artery or following percutaneous coronary intervention.[7,8] No-reflow is associated with abnormal tissue perfusion, and persistent no-reflow is associated with higher clinical complication rates[8,9]. The concept of coronary no-reflow was first described in experimental models in 1966[10] and then in the clinical setting of reperfusion after myocardial infarction in 1985.[10,11]

No-reflow has been documented in 30% of patients after thrombolysis or mechanical intervention for acute myocardial infarction[8,9,12]. Compared to similar patients with adequate reflow, those with no-reflow are more likely to exhibit congestive heart failure early after myocardial infarction and demonstrate progressive left ventricular cavity dilatation in the convalescent stage of the infarction.[8,9] Persistent no-reflow has been associated with increased mortality and a high incidence of recurrent myocardial infarction.[13,14] Hence, the predictors of no-reflow would be helpful in identifying patients at high risk and those with a higher chance of death.

6. Materials and methods

6.1. Aim

To identify the predictors of no-reflow/slow-flow during primary percutaneous coronary intervention in patients with acute myocardial infarction in our institution.

This is a case control study of consecutive patients with acute myocardial infarction who were admitted to MCH Trivandrum and underwent primary PCI from August 2014 to February 2015.

6.2. Inclusion criteria

Patients admitted to MCH Trivandrum with a diagnosis of acute ST elevation myocardial infarction within 12 h of onset of symptoms who underwent primary PCI were included. The patients were classified as those with no-reflow and those without no-reflow.

- Cases: The patients were considered to exhibit a no-reflow phenomenon if blood flow in the IRA (infarct related artery) was a TIMI ≤2 flow despite successful dilatation and in the absence of mechanical complications, such as dissection, spasm or extensive angiographically evident distal embolization, at the completion of the procedure.
- Controls: Patients who did not have no-reflow/slow-flow phenomenon and had a TIMI III flow at the completion of the procedure.

Study Site: Medical College Hospital Thiruvananthapuram.

This hospital is a tertiary care government hospital and is an important referral hospital in Kerala; it caters to patients mainly from South Kerala. We care for a large population and see patients from all over South Kerala. Hence, a sample population that is taken from this hospital might be representative of the population in South Kerala.

In all of the patients a detailed history was obtained, and a physical, electrocardiographic, echocardiographic and laboratory examination was performed and the relevant catheterization data were collected prospectively from the Trivandrum MCH cath registry (a computerized registry started in December 2013).

7. Definitions

New myocardial infarction was defined as new ischemic symptoms that lasted >20 min and new or recurrent ST-segment elevation or depression >1 mm in at least 2 contiguous leads that was associated with a > 20% increase in the cardiac biomarker values that was not attributable to the evolution of the index myocardial infarction.

Post-procedural bleeding was considered to be any overt and actionable haemorrhage not related to coronary artery bypass graft with a ≥3 g/dl decrease in haemoglobin that required a prompt evaluation by a health care professional and led to an increased level of care. Bleeding was further categorized as access site related or non–access site related according to its relationship to the arterial vascular access.

No-reflow: Angiographic evidence of the reopening of an occluded coronary artery with an acute reduction in coronary flow (TIMI grade 0–1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.

Slow flow: Lesser degrees of flow impairment (TIMI grade 2) are generally referred to as "slow-flow."

High thrombus burden: was defined as thrombus grade 4 and grade 5.

Long target lesions: were defined as target lesions that were more than 20 mm in length.

8. Laboratory and echocardiographic evaluation

All of the subjects underwent routine investigations that included a haemogram, electrocardiogram, renal function tests and liver function tests at the time of admission to the ICCU. All patients underwent an echocardiogram once they were stabilized.

9. Inclusion criteria

Patients who were at least 18 years of age who presented within 12 h of the onset of chest pain with a STEMI defined as an ST-segment elevation of 1 mm of more in two or more contiguous leads, a new left bundle-branch block, or a true posterior MI with ST-segment depression of at least 1 mm were included in the study

10. Exclusion criteria

Patients with an AMI onset of >12 h, patients who were treated conservatively for coronary artery spasm or had a < 50% diameter stenosis of the culprit lesion with normal coronary blood flow, patients who had undergone CABG (post coronary bypass grafting), patients who were taking anticoagulation medications for any reason, and patients who had undergone a rescue PCI were excluded.

11. Sampling techniques

Determination of Sample Size requirement for Case – Control Studies
Let

q_3

f	be the prevalence of exposure to the factor in the population. In most epidemiological studies of rare diseases,the prevalence of the exposure factor in the control group provides a good approximation of f
R	Relative Risk of disease regared as important to detect.
P3	Prevalence of the exposure factor among the cases It is estimated as $\frac{fR}{1+f(R-1)}$
q_3	$1-p_3$
μ	$\frac{f}{2}\left\{1+\frac{R}{[1+f(R-1)]}\right\}$
Z alpha	This is the Z value corresponding to the alpha error. When looking this up in a table, You must always use the two-tailed value,unless you have a good reason for. choosing a 1-sided test.For example,if alpha is 0.01,0.05.or 0.10 the corresponding (two tailed) Z values are 2.58,1.96,and 1.65 respectively.
Z beta	This is the Z value corresponding to the beta error.The Z-value for beta is always based on a one-tailed test. (ask if you are really interested in why!)So if the beta is 0.05,0.10,0.20 pr 0.30,the corresponding Z values are 1.65,1.28,o.85 and 0.52 respectively.

Formula

$$n = \left[\frac{Z_\alpha\sqrt{2\mu(1-\mu)}+Z_\beta\sqrt{f(1-f)+p_3q_3}}{f-p_3}\right]^2$$

Data Collection (prospectively collected from Trivandrum MCH cath registry)

- Baseline characteristics, including relevant details of the PCI will be collected prospectively from the cath registry.

12. Data analysis

The data thus collected would be used to assess the predictors of no-reflow/slow-flow in patients with primary PCI via odd's ratio, univariate and multivariate analyses.

The protocol has been cleared by the Research Committee and has been cleared by the Institutional Ethical Committee. The patient records will be kept confidential at all points of time. Patient consent was obtained from all patients.

13. Statistical analysis

The database that was used for data collection was Microsoft Access, the spreadsheet that was used for export and data conversion was Microsoft Excel. The data were analysed with SPSS (open source).

The graphs have been prepared with Microsoft Excel.

The Chi square test was used to compare categorical variables and Student's *t*-test was used for comparisons between means (continuous variables).

Significance was assumed at p < 0.05.

Univariate and multivariate analyses for significant variables were performed. The odds ratio for different predictors was calculated. The confidence intervals were stated and their statistical significance was calculated. The significant variables that were identified in the univariate analysis (except CPK MB, see below) were included in the multivariate analysis with the variable as the independent variable and no-reflow as the dependent variable. The results are stated below.

14. Results

A total of 181 patients with a diagnosis of ST elevation myocardial infarction were admitted to the Intensive Coronary Care Unit, MCH Trivandrum, and underwent primary PCI from August 2014 to February 2015.

14.1. Baseline characteristics

The baseline parameters that have a continuous distribution are given in Table 1 and the categorical parameters are given in Table 2.

Important baseline characteristics were as follows:

The mean age was 59.19 ± 10.25 years old.

Males were predominant, accounting for almost 88.9% of the study population.

A history of Type 2 diabetes mellitus and systemic arterial hypertension were present in 40.3% and 33.1% of the population, respectively.

Dyslipidaemia was present in 63% of the population

6. Patients in the study cohort exhibited anterior wall myocardial infarctions (43.6%) and inferior wall myocardial infarctions (55.2%).

A positive family history of CAD was present in 9.9% of the population.

The mean ejection fraction of the study cohort was $51.93 \pm 9.51\%$

The baseline mean creatinine was 0.99 ± 0.23 mg/dl

14.2. Baseline clinical characteristics

In the 181 patients who had undergone primary PCI, 47 (25.9%) showed an angiographic no-reflow phenomenon. The baseline clinical characteristics are shown in Tables 1 and 2 (Fig. 1)

Table 1
Baseline clinical data in the no-reflow and reflow groups – continuous variables (N = 181).

	No-reflow (N = 47)		Reflow (N = 134)		t	p
	mean	sd	mean	sd		
Age	63.19	9.62	55.19	10.88	4.462	< 0.001
DBP	78.43	15.60	78.82	11.42	0.185	0.854
SBP	129.11	33.20	127.74	25.31	0.293	0.770
Peak CKMB	403.00	144.15	234.71	136.21	7.178	< 0.001
EF	50.82	9.32	53.05	9.71	1.340	0.182
Urea	29.32	11.10	27.38	11.26	1.019	0.309
Creatinine	0.99	0.24	0.99	0.22	0.038	0.970
Total Cholesterol	219.53	51.30	217.74	50.05	0.207	0.836
HDL	46.09	11.03	43.67	14.22	1.056	0.292
LDL	142.89	47.94	140.57	44.43	0.291	0.772
TG	118.23	55.35	128.51	73.66	0.874	0.383
DM Duration	2.96	6.70	2.95	5.19	0.010	0.992
HTN Duration	2.87	6.77	2.14	4.40	0.843	0.401
DBT	93.69	50.26	88.64	44.89	0.643	0.100

Table 2
Baseline Clinical data in the no-reflow and reflow groups − categorical variables (N = 181).

		No-reflow (N = 47)		Reflow (N = 134)		χ^2	p
		N	%	N	%		
Age	> 60	34	72.3	40	29.9	25.992	0 < 0.001
	< 60	13	27.7	94	70.1		
Gender	Male	44	93.6	117	87.3	1.407	0.236
	Female	3	6.4	17	12.7		
DM		19	40.4	54	40.3	0.0002	0.988
HTN		16	34	44	32.8	0.023	0.880
Hypercholesterolemia		31	66	83	61.9	0.241	0.624
Smoker	Current	13	27.7	61	45.5	5.181	0.075
	Ex	5	10.6	15	11.2		
	Non smoker	29	61.7	58	43.3		
Family h/o IHD		3	6.4	15	11.2	0.899	0.343
Previous MI	None	45	95.7	127	94.8	0.358	0.836
	NSTEMI	0	0	1	0.7		
	UA	2	4.3	6	4.5		
Infarct location	AWMI	24	51.1	75	56	1.478	0.687
	IWMI	12	25.5	26	19.4		
	IWMI+ RVMI	10	21.3	32	23.9		
	Others	1	2.1	1	0.7		
Reperfusion time in hours	< 3	0	0	15	11.2		
	3–6	14	29.8	106	79.1		
	> 6	33	70.2	13	9.7	68.158	0 < 0.001
Killip class	I	12	25.5	82	61.2		
	II	26	55.3	42	31.3		
	III	8	17	9	6.7	18.380	0 < 0.001
	IV	1	2.1	1	}		
					0.7		

There were no significant differences between the reflow group and the no-reflow group in terms of gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, blood pressure (both systolic and diastolic), family history of coronary artery disease, previous MI, blood urea, serum creatinine and infarct localization (P > 0.05 for all). The mean ejection fraction was 51.93 ± 9.51%; there was no statistically significant differences among no-reflow and the reflow groups [50.82 ± 9.32 vs. 53.05 ± 9.71; p = 0.182] (Fig. 2).

Compared with the reflow group, patients in the no-reflow group had a higher mean age (63.19 ± 9.62 vs.55.19 ± 10.88 years for no-reflow and reflow, respectively), a longer mean reperfusion time (6.35 ± 1.61 vs. 4.29 ± 1.25 h, respectively), a higher level of CKMB (403 ± 144.15 vs. 234.71 ±136.21 U/L, respectively) (p < 0.05 for all). Moreover, there were significant differences between the no-reflow and reflow groups with respect to a higher level of Killip class (III/IV) (19.1 vs. 7.5, respectively) (p < 0.05).

The door to balloon time was comparable in the no-reflow and the reflow group (no-reflow 93.69 ± 50.26 min vs. reflow 88.64 ± 44.89 min, p = 0.1).

14.3. Angiographic findings and primary PCI characteristics

The angiographic data and procedural features revealed that out of 181 patients, 47 had no-reflow. No-reflow was more common in patients who had a low (≤1) initial TIMI flow (91.5% vs. 47%, p < 0.001) and a low initial TMPG (≤1) (97.5% vs. 56%, p < 0.001) compared to the reflow group. Of the total cohort of the STEMI population, primary PCI was performed via femoral arterial access in 44.7% of patients and via radial access in 55.3% of patients and there was no significant difference between the two groups.

AWMI was common in both groups. There was no significant difference in the incidence of multivessel disease between the two groups. LAD as a target vessel was more common in both of the groups (Fig. 3).

The stents that were used in all of the patients were DESs (drug eluting stents). A total cut-off occlusion was more common in the no-reflow group (72.3% vs. 61.2%) but was not significantly different when compared with (p = 0.59) the reflow group. The mean reference vessel diameter was slightly lower in the no-reflow
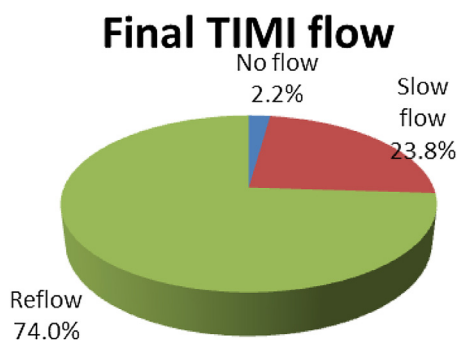

Fig. 1. The distribution of angiographic no-reflow, slow-flow and reflow in the study population.
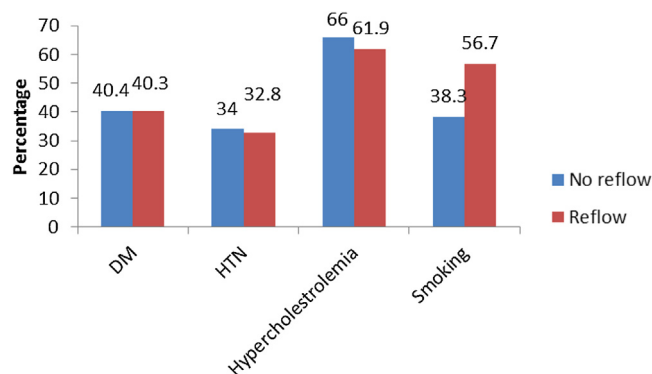

Fig. 2. The distribution of risk factors in the no-reflow and reflow groups.
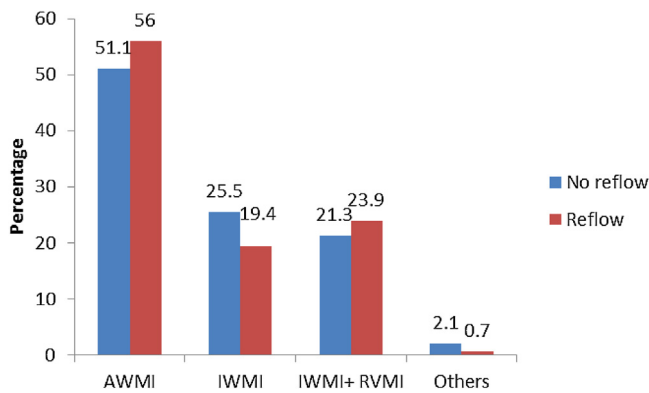
Fig. 3. Myocardial infarction types in the no-reflow and the reflow groups.

group, but was not statistically significant (no-reflow 2.90 ± 1.11 vs. 3.07 ± 0.61, p = 0.18). The number of target lesions was significantly higher in the no-reflow group (28.17 ± 14.08 vs. 21.07 ± 9.73 mm, $p < 0.001$).

It was also observed that the no-reflow group mainly consisted of patients with delayed reperfusion of ≥ 6 h (70.2% vs. 9.7%, $p < 0.001$) and a high thrombus burden (66% vs. 14.9%, $p < 0.001$).

However, the presence of multivessel disease, the IRA, the target lesion locations, the percentage of stenosis, and the type of lesion were not different between the 2 groups (p > 0.05 for all).

The number of patients with an ST resolution of <70% was significantly lower in the no-reflow group (87.2% vs. 26.9%. $p < 0.001$).

The amount of contrast volume that was used for the primary PCI was slightly higher in the no-reflow group, but was not statistically significantly different (163.47 ± 57.7 ml vs. 167.03 ± 76.11 ml; p = 0.51). The mean fluoroscopic time required for the completion of the primary PCI was slightly higher for the no-reflow group, but this difference was not statistically significant (12.28 ± 8.17 min vs. 11.47 ± 13.8 min; p = 0.7) (Table 3 and 4).

Among the procedural features, the incidence of no-reflow was significantly lower in the direct stenting group than in the group with stenting with pre-dilatation or with balloon angioplasty (6/96 (8.6%), 22/75 (29.3%), 5/8 (62.5%), respectively).

There was a significant difference in the use of aspiration thrombectomy between the no-reflow and the reflow groups (61.7% vs. 31.3%; $p < 0.001$) but this association is by chance because of the high thrombus burden that led to the no-reflow phenomenon.

Tirofiban use was also significantly associated with no-reflow (34% vs. 9.7%; $p < 0.001$) but the association is by chance because the high thrombus burden led to the no-reflow phenomenon in spite of pharmacological treatment and treatment with aspiration thrombectomy.

There was no significant difference in the use of repeated balloon dilatation and post-dilatation between the two groups.
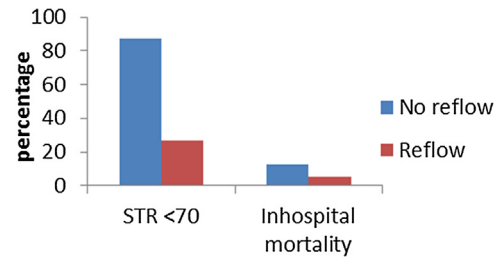

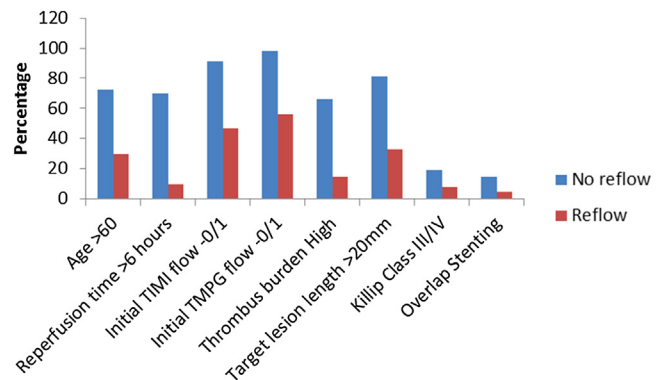Fig. 4. STR and in-hospital mortality in the reflow and no-reflow groups.

Fig. 5. Independent predictors of the no-reflow phenomenon.

15. Complications and no-reflow

There was one case of sustained ventricular tachycardia (VT) in the no-reflow group and none in the reflow group (NS, 2.1% vs. 0; p = 0.09).

Cardiogenic shock was slightly higher in the no-reflow group but was not statistically significant (6.4% vs. 2.2%; p = 0.172).

The rate of post-interventional bleeding complications (TIMI minor) was higher in the reflow group but was not statistically significant (no TIMI minor bleed in the no-reflow group vs. 2.2% in the reflow group, p = 0.301). There were no cases of TIMI major bleeding in this cohort.

There were 6 cases of in-hospital deaths in the no-reflow group and 7 cases in the reflow group. This difference was not statistically significant (p = 0.0848) (Figs. 4 and 5).

16. Independent predictors of the no-reflow phenomenon

Univariate analyses identified that age >60 years (OR = 6.146, 95%CI 2.937–12.86, $p < 0.001$), reperfusion time >6 h (OR = 21.94, 95%CI 9.402–51.2, $p < 0.001$), low initial TIMI flow (≤ 1) (OR = 12.12, 95%CI 4.117–35.65, $p < 0.001$), low initial TMPG flow (≤ 1) (OR = 36.19, 95%CI 4.847–270.2, $p < 0.001$), a high thrombus burden (OR = 11.04,95%CI 5.124–23.8, $p < 0.001$), a long target lesion

Table 3
Angiographic data in the no-reflow and reflow groups – continuous variables (N = 181).

	No-reflow (N = 47)		Reflow (N = 134)		t	p
	mean	sd	mean	sd		
Target lesion length	28.17	14.08	21.05	9.73	3.807	<0.001
Reference diameter	2.90	1.11	3.07	0.61	1.346	0.180
STR	53.74	17.85	79.17	14.79	9.597	<0.001
Reperfusion time (hrs)	6.35	1.61	4.29	1.25	8.989	<0.001
Fluoro Time	12.28	8.17	11.47	13.80	0.379	0.705
Pre-dilatation inflation pressure	11.27	3.06	11.33	3.24	0.068	0.946
Post-dilatation inflation pressure	17.69	3.25	17.51	1.98	0.242	0.810
Contrast volume	113.47	27.7	117.03	26.11	0.651	0.510

Table 4
Angiographic data in the no-reflow and reflow groups – categorical variables (N = 181).

		No-reflow (N = 47)		Reflow (N = 134)		χ^2	p
		N	%	N	%		
IRA	LAD	24	51.1	75	55.9		
	LCX	3	6.4	11	8.3		
	Ramus	0	0	1	0.7		
	RCA	20	42.6	48	35.8		
Initial TIMI flow	0/1	43	91.5	63	47	28.362	0 < 0.001
	2/3	4	8.5	71	53		
Initial TMPG	0/1	46	97.9	75	56	27.569	0 < 0.001
	2/3	1	2.1	59	44		
Target lesion location	Proximal	31	66	72	53.7	2.122	0.346
	Mid	14	29.8	54	40.3		
	Distal	2	4.3	8	6		
Percentage stenosis	100	34	72.3	82	61.2	7.458	0.059
	90–99	8	17	13	9.7		
	80–89	5	10.6	35	26.1		
	70–79	0	0	4	3		
Type of lesion	Eccentric	43	91.5	123	91.8	0.004	0.949
	Concentric	4	8.5	11	8.2		
Multivessel disease	Yes	25	53.2	66	49.3	0.216	0.642
Thrombus burden	Nil (grade 0)	14	29.8	72	53.7	46.909	0 < 0.001
	Low (grade 1/2)	2	4.3	38	28.4		
	Moderate (grade 3)	0	0	4	3		
	High (grade 4/5)	31	66	20	14.9		
Thrombus aspiration alone		1	2.1	1	0.7	0.608	0.436
Stenting after thrombus aspiration without pre-dilatation		16	34	26	19.4	4.185	0.041
Stenting after pre-dilatation and thrombus aspiration		12	25.5	15	11.2	5.636	0.018
Balloon angioplasty		5	10.6	3	2.2	5.811	0.016
Direct stenting alone		6	12.8	41	30.6	5.755	0.016
Pre-dilatation		22	46.8	53	39.6	0.755	0.385
Post-dilatation		21	44.6	41	30.6	3.064	0.080
Repeated balloon dilatation	≥2	8	17	16	11.9	0.781	0.377
	< 2	39	83	118	88.1		
Multiple stents		7	14.9	6	4.5	5.663	0.017
Aspiration thrombectomy		29	61.7	42	31.3	13.452	0 < 0.001
Tirofiban use		16	34	13	9.7	15.322	0 < 0.001
Bleeding	TIMI minor	0	0	3	2.2	1.070	0.301
	None	47	100	131	97.8		
Overlap stenting		7	14.9	6	4.5	5.663	0.017
Cardiogenic shock		3	6.4	3	2.2	1.865	0.172
Sustained VT		1	2.1	0	0	2.867	0.090
Pharmacological treatment given for no-reflow/slow-flow	Inj NTG	5	10.6	14	10.4	7.703	0.053
	Inj Adenosine	1	2.1	2	1.5		
	NTG + Adenosine	12	25.5	13	9.7		
	Not given	29	61.7	105	78.4		
Target lesion length	>20	38	80.9	44	33.1	31.949	0 < 0.001
	<20	9	19.1	89	66.9		
STR	<70	41	87.2	36	26.9	51.877	0 < 0.001
	>70	6	12.8	98	73.1		
In-hospital mortality	Dead	6	12.7	7	5.2	2.969	0.0848
	Alive	41	87.3	127	94.8		
Reperfusion time	>6 h	33	70.2	13	9.7	67.214	0 < 0.001
	<6 h	14	29.8	121	90.3		
Thrombus burden	High	31	66	20	14.9	44.777	0 < 0.001
	Low	16	34	114	85.1		
Access	Femoral	21	44.7	60	44.8	1.551	0.213
	Radial	26	55.3	74	55.2		

(OR = 8.54, 95%CI 3.794–19.23, p < 0.001), Killip Class III/IV (OR = 2.937,95%CI 1.112–7.756,p = 0.025) and overlap stenting (OR = 3.733,95%CI 1.186–11.75,p = 0.017) were the independent predictors of no-reflow (Table 5). CPK MB was not included as a predictor as it was a consequence of no-reflow and not a predictor (it occurred after the no-reflow) (Fig. 6).

Multiple stepwise logistic regression analysis identified that reperfusion time >6 h (OR = 13.844, 95%CI 3.214–59.636, p < 0.001), age >60 years (OR = 8.886, 95%CI 2.145–36.80, p = 0.003), a long target lesion (OR = 8.637, 95%CI 1.975–37.768, p = 0.004), low initial TIMI flow (≤1) (OR = 20.861, 95%CI 1.739–250.290, p = 0.017) were found to be significantly associated with no-reflow and were the independent predictors of the no-flow phenomenon (Table 6) in our study (7).

We also included 30-day mortality. The 30 day mortality in the no-reflow group was 6% and in the reflow group was 7% (NS).

17. Discussion

17.1. Historical overview of no re-flow

The term no-reflow was first used by Majno and colleagues in the setting of cerebral ischaemia in 1967.[15] This phenomenon was initially described by Krug et al.[10] during the induction of myocardial infarction in the canine model in 1966 and again by Kloner et al.[7] in 1974, at which time it occurred for 90 min after temporary epicardial coronary artery occlusion. Myocardial tracers, such as carbon black or thioflavin S (a fluorescent stain

Table 5
Univariate analysis.

		NO REFLOW		REFLOW		χ^2	P	OR	95% CI FOR OR	
		N	%	N	%				LOWER	UPPER
Age	>60	34	72.3	40	29.9	25.992	0 < 0.001	6.146	2.937	12.86
Reperfusion time	>6 h	33	70.2	13	9.7	67.214	0 < 0.001	21.94	9.402	51.2
Initial TIMI flow	0/1	43	91.5	63	47	28.362	0 < 0.001	12.12	4.117	35.65
Initial TMPG flow	0/1	46	97.9	75	56	27.569	0 < 0.001	36.19	4.847	270.2
Thrombus burden	High	31	66	20	14.9	44.777	0 < 0.001	11.04	5.124	23.8
Target lesion length	> 20 mm	38	80.9	44	33.1	31.949	0 < 0.001	8.54	3.794	19.23
Killip Class III/IV	Yes	9	19.1	10	7.5	5.058	0.025	2.937	1.112	7.756
Overlap stenting	Yes	7	14.9	6	4.5	5.663	0.017	3.733	1.186	11.75

for the endothelium), were injected to document uniform flow distribution across the myocardial tissue after 40 min of occlusion. After 90 min, persistent subendocardial perfusion defects were seen with no-reflow.

17.2. Electron microscopic findings in no-reflow

Electron microscopic examination shows severe myocardial capillary damage with a loss of pinocytotic vesicles in the endothelial cells, endothelial blisters or blebs and endothelial gaps with neutrophil infiltration. Intraluminal capillary plugging by neutrophils and/or micro –thrombi with myocardial cell swelling was also noted.

Kloner et al.[7] added the concept of 'coronary' no-reflow, in accordance with the descriptions of this phenomenon in the brain, kidney and skin tissues.[15,16]

17.3. The first clinical observation of no-reflow

The first clinical observation of coronary no-reflow was reported by Schofer et al.[11] in 1985 in 16 patients who had experienced a first anterior myocardial infarction. These patients were evaluated with dual scintigraphic studies using thallium-201 (myocardial uptake) and technecium–99 m microalbumin aggregates (myocardial perfusion). Amongst 11 patients who were studied prior to and immediately after thrombolysis, one patient who had identical defects according to both techniques prior to thrombolysis developed a further extension of the perfusion defect after thrombolysis with technecium–99 m without a change in the size of the thallium-201 uptake defect. Therefore, Schofer et al.[11] concluded that no-reflow also occurred in humans during the reperfusion of acute myocardial infarction.[11]

One year later, Bates et al. reported the angiographic correlation of no-reflow as an abnormally slow antegrade contrast filling in the infarct-related artery.[17] In 1991, Pomerantz et al. reported five more cases of no-reflow that were successfully treated by intracoronary verapamil.[18] The first clinical case of no-reflow during PTCA for acute myocardial infarction was reported by Feld et al. in 1992.[19]

Table 6
Multivariate analysis (binary logistic regression).

	p	OR	95% C.I. for OR	
			Lower	Upper
Reperfusion time	<0.001	13.844	3.214	59.636
Age	0.003	8.886	2.145	36.800
Target lesion length	0.004	8.637	1.975	37.768
Initial TIMI flow	0.017	20.861	1.739	250.290
Initial TMPG	0.920	0.851	0.036	20.116
Thrombus burden	0.109	3.262	0.769	13.831
Killip class III/IV	0.698	1.468	0.210	10.249
Overlap stenting	0.487	0.456	0.050	4.181

17.4. Pathophysiology of no-reflow

The longer the ischemia, the more severe the no-reflow.[7]

After the prolonged cessation of coronary occlusion and the restoration of blood flow to the epicardial coronary arteries, there is sufficient structural damage to the microvasculature to prevent the restoration of normal blood flow to the cardiac myocytes.[20] The structural damage is more pronounced with longer periods of coronary occlusion.[7] No-reflow appears to be a process rather than an immediate event that occurs at the moment of reperfusion. Experimental studies showed that the no-reflow area increases with time after reperfusion.[21,22]

17.5. Microscopic examination in no-reflow

Microscopic examination showed that myocardial cells within the no-reflow area were swollen. The capillary endothelium was damaged and had areas of regional swelling with large intra-luminal protrusions that, in some cases, appeared to plug the capillary lumen.[7]

Intravascular plugging by fibrin or platelets may also contribute to the no-reflow phenomenon.[23,24] Treatment with the following
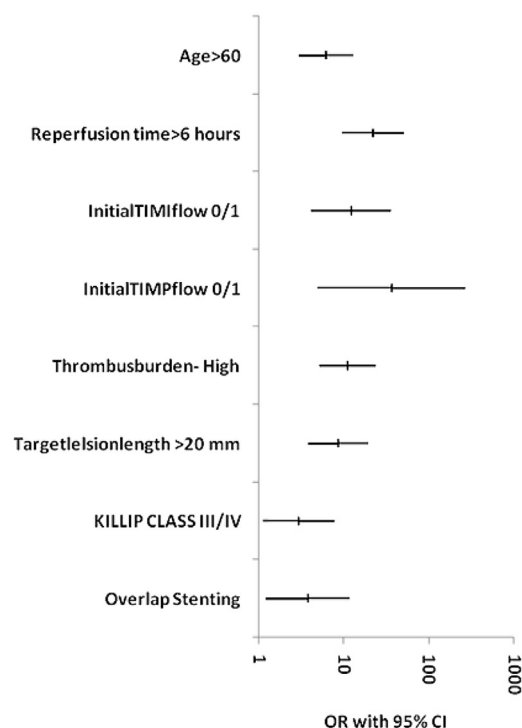

Fig. 6. The forest plot for factors associated with no-reflow derived from univariate analysis of binary logistic regression.
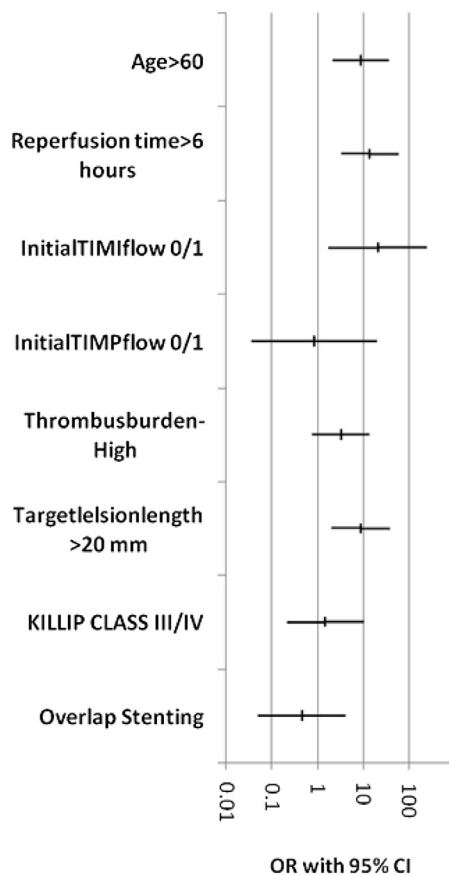
Fig. 7. The forest plot for factors associated with no-reflow derived from multivariate analysis of binary logistic regression.

drugs improves no-reflow: ibuprofen[25], prostaglandin E1[26], and vascular washout with heparinized saline.[27]

Leukocyte intravascular plugging appears to play an important role in the pathophysiology of no-reflow. Researchers[28] showed that the no-reflow areas had evidence of capillary leukocyte plugging.[28] Neutropenic animals do not develop no-reflow.[29]

Diminished flow through the microvasculature compared with normal zones is usually referred to as 'low reflow.'[30] No-reflow can also occur in vein grafts or even in native coronaries. Distal protection devices may prevent no-reflow.

17.6. The definition of no-reflow

The no-reflow phenomenon was originally observed in experimental models of acute myocardial infarction (MI) and was described as a failure to restore normal myocardial blood flow despite the removal of the coronary obstruction.[7,31] Since that time, no-reflow has been shown to complicate thrombolytic therapy and percutaneous revascularization with PTCA.[32,18]

Defined angiographically, no-reflow manifests as an acute reduction in coronary flow (TIMI grade 0–1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion. A lesser degree of flow impairment (TIMI grade 2) is generally referred to as "slow-flow".

17.7. Classes of patients who may develop no-reflow

No-reflow has been observed after systemic thrombolysis for myocardial infarction, after primary angioplasty and after PTCA to vein grafts. It also occurs after rotablation atherectomy. (2–9%). No-reflow has been found to correlate with the total burr activation

time[33,34] and has been found to be reversible in 60% of the cases. Intracoronary calcium antagonists prevent or restore flow and so microvascular spasm has been believed to be a cause of no-reflow. Long lesions, recent unstable angina and the use of beta-blockers within 24 h can also cause no-reflow during rotablation.[35–37]

No-reflow after TEC atherectomy is usually irreversible.[38] No-reflow can also occur after rescue PCI.

17.8. The clinical presentation of no-reflow

The clinical presentation of the no-reflow phenomenon varies greatly and depends on the clinical setting, despite often being related to the moment of reperfusion.[39] In the catheterization laboratory, the clinical presentation of no-reflow during short-term intervention in myocardial infarction patients is often sudden and dramatic. The dye stagnates in the coronary artery, the patient complains of chest pain, and hemodynamic compromise soon follows. The sudden hemodynamic deterioration may also be related to athero-embolism and the slowing of blood flow in the non-culprit arteries.[40,41]

In the coronary care unit, the presentation is usually less dramatic. After thrombolytic therapy, the patient will experience chest pain and ST-segment elevation and may have hemodynamic deterioration.[32] New Q waves may appear[42] and some of those patients may be diagnosed as having infarct extensions. Older patients with a lower incidence of preinfarction angina had no-reflow more often.[43] This may be because ischemic preconditioning permits the development of collaterals that may prevent no-reflow.[44] The no-reflow phenomenon was also found in patients with ventricular arrhythmias.[45]

No-reflow can also be associated with early congestive heart failure, and even cardiac rupture.[7,46] To determine the prognosis of the no-reflow phenomenon, researchers followed up 30 patients with no-reflow for a mean period of 1.2 years.[47] They compared this group to a control group of 90 patients, and no-reflow was associated with more malignant arrhythmias, a lower ejection fraction, and more cardiac death.

17.9. How to diagnose no-reflow and slow-flow

Slow flow and no-reflow with impaired myocardial perfusion can be diagnosed angiographically or by using adjunctive imaging modalities that can quantify myocardial perfusion, such as myocardial contrast echocardiography.

17.10. Myocardial contrast echocardiography

Myocardial contrast echocardiography can be used to assess microvascular function and has become the gold standard for the non- invasive investigation of the no-reflow phenomenon. Myocardial contrast echocardiography was first performed during coronary angiography after the injection of microbubbles into infarct related arteries after angioplasty. No-reflow zones were seen in 25–30% of patients with acute myocardial infarction (AMI) despite the detection of open arteries on angiography.[8]

Myocardial contrast echocardiography can be performed at the bedside with the intravenous injection of commercially available contrast agents. The perfusion defects that are observed on contrast echocardiography will reflect the regions of microvascular obstruction, but the infarct size is underestimated. After a vasodilator stress, the defects should match the infarct size.[48]

17.11. Coronary angiography

Thrombolysis in myocardial infarction (TIMI) blood flow grades are used to evaluate the quality of coronary flow during coronary

angiography.[49] Historically, a TIMI 0/I flow was considered a failure of reperfusion and a TIMI II/III flow identified patients with successful reperfusion.[50]

17.12. Myocardial blush (beyond TIMI 3 flow)

In patients with TIMI blush Grade 3, the myocardial blush clears within three cardiac cycles of washout. Among patients with TIMI III flow, the assessment of myocardial blush thus permits further risk stratification; only patients with normal epicardial flow and normal tissue-level perfusion have an extremely low risk of dying. A poor TIMI perfusion grade is a marker of poor prognosis after primary angioplasty.

17.13. Coronary doppler imaging in no-reflow

The no-reflow phenomenon has a characteristic coronary blood flow pattern with three main components: systolic flow reversal; reduced antegrade systolic flow; and forward diastolic flow with a rapid deceleration slope. This to-and-fro nature of blood flow causes coronary forward flow to be reduced. If TIMI II flow is noted after PCI, the to-and-fro flow velocity pattern implies no-reflow, and further stenting will not help.[51]

The coronary blood flow velocity pattern helps to differentiate between individuals with micro-emboli and those without. Patients with coronary micro- emboli have a slow forward flow, an increase in diastolic-to-systolic flow ratio and an increased coronary arterial resistance.[52]

17.14. Other imaging modalities

Nuclear imaging, single-photon emission CT, the use of thallium or technetium-99m, and PET have been used to study no-reflow. Contrast-enhanced MRI can also be used. The first pass of the contrast agent and delayed contrast-enhanced MRI 20 min after contrast injection can be used to detect myocardial necrosis.[53,54]

Thrombus aspiration to prevent no-reflow: the role of mechanical thrombectomy and aspiration thrombectomy.

It is believed that the mechanical removal of the thrombus or the performance of aspiration thrombectomy will prevent no-reflow. We generally perform aspiration thrombectomy with a Pronto V4 catheter or a Nipro TVAC catheter. Although the guidelines say not to perform aspiration thrombectomy, we obtained good results. Our institutional policy is if the patient has a totally occluded coronary artery after passing a guide- wire we do 2 or 3 runs of aspiration thrombectomy. We have not had any case of stroke in the last 3 years. Prior to this we had 3 strokes. We are therefore careful in

1) making sure we open the aspiration catheter only in the area of the blocked vessel;
2) closing the aspiration catheter (which is connected to a syringe that is kept at negative pressure) before entering the previously normal part of the vessel, and we especially close it before withdrawing the catheter near a large branch (say near the mouth of the circumflex coronary artery) to prevent embolization to normal vessels;
3) removing the aspiration catheter completely from the artery and guide, even in a radial route before giving any check injection and allowing a back bleed;
4) performing injections after just withdrawing the aspiration catheter or balloon into the aorta in the guide catheter, which can cause embolization into the cerebral vessels;
5) withdrawing balloons, and not performing an injection with the balloon in the guide catheter (especially in radial angioplasty). Ideally, the guide catheter should be steady and engaged while

withdrawing the aspiration catheter, again to prevent embolization.

The Tapas trial was a positive trial that showed that aspiration thrombectomy reduces mortality during primary angioplasty.[55] However, the Total trial and the Taste trial both showed that there were more strokes in the control arm.[56,57] Jolly et al. evaluated the benefits of thrombus aspiration in STEMI patients at a one-year follow-up. It was found that routine thrombus aspiration did not reduce longer-term clinical outcomes in STEMI patients within one year, and the mortality was 4 percent in both of the groups. Thrombus aspiration may also lead to embolic stroke.

Finally, the ACC and ESC guidelines have also downgraded their recommendation for thrombus aspiration.

17.15. The treatment of no-reflow

Since no-reflow has been associated with coronary spasm, calcium channel antagonists, such as verapamil, have been shown to improve no-reflow.[18] Since no-reflow has been associated with increased coronary resistance, it is possible that this is how both sodium nitroprusside and intracoronary nitroglycerin act to reduce coronary resistance.

Embryonic haemangioblasts have been used experimentally.[58] Bone marrow derived angioblasts prevent the apoptosis of the myocytes and improve cardiac function.

Intracoronary but not intravenous adenosine has been shown to improve no-reflow.[5]

Intracoronary adrenaline has also been shown to be useful in no-reflow[59] Authors have reported that the localized installation of adenosine through custom made balloons can successfully reduce no-reflow.[60]

Glycoprotein 2b/3a inhibitors appear to help in some cases. However, neither distal protection or proximal protection devices help.[61,62]

17.16. Prevention of no-reflow

The prevention of no-reflow would improve cardiac mortality after primary angioplasty. Thrombus aspiration followed by direct stenting, to enable the prevention of embolization of the thrombus debris, is believed to be helpful.

17.17. How does adenosine help?

Adenosine lowers the neutrophil counts in the infarct zones, maintains endothelial integrity and may exert a cardioprotective effect. In patients with acute MI, intracoronary administration of 24–48 µg of adenosine reduces no-reflow after PCI.[63]

Nicorandil is a hybrid between a mitochondrial potassium-channel opener and NO, and has shown promising results in patients with acute MI when given before reperfusion. This drug reduces preload and afterload, dilates coronary resistance vessels, reduces the Ca2+ overload of myocytes, and attenuates neutrophil activation.[64,65] These actions are apparent even when nicorandil is given intravenously.

Treatment with intracoronary nitroprusside or verapamil was associated with a significant improvement in coronary flow and an increase in TIMI flow grade.[66]

Sodium–hydrogen pump inhibitors have the potential to reduce reperfusion injury by attenuating intracellular Ca2+ overload. In an experimental study, the use of such an agent improved microvascular function and myocardial blood flow, and reduced infarct size. Large-scale multicentre trials did not show any benefit of cariporide or eniporide on functional and clinical outcomes in patients with a wide range of ischemic risks.[67–69]

Other adjunctive agents, including monoclonal antibodies against leukocytes, complement receptor inhibitors, adhesion molecule antibodies, endothelin-A selective antagonists, and erythropoietin have been tried.

Post-conditioning has been associated with reduced no-reflow.[70] The mechanism of protection involves the activation of extracellular-signal-regulated kinase, the production of nitric oxide, the opening of mitochondrial potassium channels, and the inhibition of the opening of the mitochondrial permeability transition pore. Staat et al.[71] performed post-conditioning during PCI for acute MI in humans, starting within 1 min of reflow, and achieved reflow by inflating an angioplasty balloon for 1 min followed by deflation for 1 min 4 times.[71]

17.18. Predictors of no-reflow in other studies

Studies have been undertaken to identify clinical factors, angiographic findings and procedural features that can predict the no-reflow phenomenon in patients with AMI after primary PCI.

In the study conducted by Hua Zhou et al.[72] in 312 consecutive patients with AMI who had been treated from January 2008 to December 2010 at the Cardiology Department of East Hospital, Tongji University School of Medicine, fifty-four (17.3%) of the patients developed NR phenomenon after primary PCI.

Univariate analysis showed that age, time from onset to reperfusion, systolic blood pressure (SBP) on admission, Killip class of myocardial infarction, intra-aortic balloon pump (IABP) use before primary PCI, TIMI flow grade before primary PCI, type of occlusion, thrombus burden on baseline angiography, target lesion length, reference luminal diameter and method of reperfusion were correlated with no-reflow (p<0.05 for all). Multiple logistic regression analysis identified that age >65 years (OR = 1.470, 95% confidence interval (CI) 1.460–1.490, p = 0.007), >6 h from the time of onset to reperfusion (OR = 1.270, 95%CI 1.160–1.400, p = 0.001), low SBP on admission (< 100 mmHg, OR = 1.910, 95%CI 1.018–3.896, p = 0.004), IABP use before PCI (OR = 1.949, 95%CI 1.168–3.253, p = 0.011), low (1) TIMI flow grade before primary PCI (OR = 1.100, 95%CI 1.080–1.250, p < 0.001), high thrombus burden (OR = 1.600, 95%CI 1.470–2.760, p = 0.030), and long target lesion (OR = 1.948, 95%CI 1.908–1.990, p = 0.019) on angiography were independent predictors of no-reflow.

17.19. Delay in treatment and no-reflow

Delayed presentation to the hospital causes delayed treatment. This is directly related to an increase in no-reflow and mortality. Wide campaigns to bring the patient to the hospital earlier will prevent no-reflow.

Delayed reperfusion (a long duration from onset to reperfusion) is related to no-reflow. The above study showed that patients with a long duration before reperfusion (>6 h) had a significantly greater thrombus burden and a 1.3-fold increase in the no-reflow rate than patients with a short duration of reperfusion.[73]

Yip et al.[70] demonstrated that in patients with AMI who had a high thrombus burden, the rate of no-reflow was lower than in those with reperfusion in less than 4 h. This indicates the possible correlation of a thrombus burden with the duration of reperfusion.[70]

Patients who had a low TIMI flow in the IRA prior to PCI had a higher rate of no-reflow than those with a good (2) TIMI flow according to baseline angiography. De Luca et al. found that a pre-PCI good TIMI flow was strongly related to the post-procedural TIMI 3 flow, myocardial blush grade 2–3 and lower enzymatic infarct size.[71] A good patency of the IRA prior to PCI suggests a lower thrombus burden, a spontaneous endogenous lysis of the thrombus, the resolution of vasospasm and a smaller infarct size.

An IVUS sub-study of no-reflow has shown that a soft lipid rich plaque is associated with no-reflow more so than a hard atherosclerotic plaque.[72]

Tanaka et al. used IVUS to examine plaque burden and identified that a higher lipid content in the inner plaque core and the width of the external elastic membrane were independent markers for the no-reflow phenomenon.[73]

Our study demonstrates that the presence of large lesioned vessels, especially those with an IRA diameter above 4 mm, was associated with the occurrence of no-reflow. Patients with lesions that were larger than 20 mm in size were more likely to develop no-reflow after primary PCI than those with lesions that were smaller than 20 mm in size. Large vessels are able to contain large amounts of plaque lipid or thrombi. The larger the lesioned vessels, the slower the flow velocity. The longer the target lesion, the larger the amount of thrombus and plaque burden. This would explain the high risk for slow/no-reflow that was observed in these patients after primary PCI.[74,75]

Kirma et al. reported their findings in a series of 382 consecutive patients with AMI who underwent primary PCI within 12 h of symptom onset.[46] Patients with ischemic symptoms that had persisted for more than 12 h were also included. Clinical, angiographic and procedural data were collected for each subject. Ninety-three (24.3%) of the patients developed no-reflow, and their findings were compared with those of the reflow group. Univariate analysis showed that advanced age (> 60 years), delayed reperfusion (≥4 h), low (≤1) TIMI flow prior to PCI, cut-off type total occlusion, high thrombus burden according to baseline angiography, the presence of a long target lesion (>13.5 mm) and large vessel diameter all correlated with no-reflow (p < 0.05 for all). Multiple logistic regression analysis identified that advanced age (odds ratio (OR) 1.04, p = 0.001), delayed reperfusion (OR 1.4, p = 0.0004), low TIMI flow before primary PCI (OR 1.1, p = 0.0002), target lesion length (OR 5.1, p = 0.0003) and high thrombus burden (OR 1.6, p = 0.03) on angiography as independent predictors of the no-reflow phenomenon.[76]

18. Limitations of this study

- A small sample size. We only included 181 patients in this 6-month period as this was a post-graduate thesis that could be started only after clearance from the ethical committee and the research committee. Furthermore, we had only one catheterization lab at the time of the study (presently we have almost finished installing a second catheterization lab so we will soon be able to evaluate more patients. In addition, very often when a patient with primary angioplasty arrived at the lab, they would exhibit CTO (chronic total occlusion). We did not make the patient wait, we generally asked for thrombolysis with streptokinase.
- We have not analysed the microvascular function and no-reflow using myocardial contrast echocardiography or nuclear scintigraphy.
- This is an observational study and not a prospective randomized trial. The higher number of patients in the no-reflow group who received GpIIb/IIIa inhibitors and who underwent thrombus aspiration was most likely related to their initial large thrombus burden.
- We appear to have a relatively higher rate of no-reflow. This is probably because of the reasons given below.
- Recently we have changed to treating loading primary angioplasty patients with Ticagrelor. Since then we appear to have fewer no-reflow patients in spite of some of the patients presenting after nine hours. So it is possible that since we were using clopidogrel there was a higher rate of no-reflow. Of course we now aggressively give intra coronary adenosine two or three

times. We are also using shorter stents (18 mm rather than 23 mm) and our no-reflow rate has come down. Prior to performing this research we did not really understand the risk factors of no-reflow.

19. Conclusions of the study

In conclusion, pathogenesis of the no-reflow phenomenon is complex and multifactorial. In light of our recent study, patients who are likely to develop no-reflow after primary PCI can be identified by simple clinical and angiographic features.

Patients with advanced age, delayed reperfusion, low TIMI flow and/or a long target lesion according to baseline angiography are at increased risk for no-reflow development. In our study, we achieved a TIMI 3 flow in the IRA after pre-dilatation, yet the same patients developed no-reflow after stent implantation.

It is therefore important to avoid or minimize trauma to the vessel, avoid repetitive balloon dilatations and use the shortest stent if possible. In recent years, it has been shown that coronary stent implantation without pre-dilatation is feasible and can be performed safely in selected patients with AMI. Because most patients with AMI have a combination of these factors, combined treatment strategies should be preferred.

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