Predictors and outcome of no-reflow post primary percutaneous coronary intervention for ST elevation myocardial infarction

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ABSTRACT

Background: No-reflow (TIMI <3) during primary PCI (PCI) for STEMI occurs in 11–41% of cases, indicates poor myocardial tissue perfusion, and is associated with a poor outcome. We aimed to determine predictors and 12 month outcomes of patients who developed no-reflow.
Methods: We analysed the PCI database of The Canberra Hospital and identified 781 patients who underwent primary PCI during 2008–2012. Follow-up at 12 months was with letter, phone call and review of hospital records.
Results: No-reflow was observed in 189 patients (25%) at the end of the procedure. Patients with no-reflow were older (64 vs. 61 years, p = 0.03). No-reflow patients were more likely to have initial TIMI flow <3 (89% vs. 79%, p = 0.001), thrombus score ≥ 4 (83% vs. 69%, p = 0.0001), higher use of glycoprotein IIb/IIIa inhibitors (57% vs. 48%, p = 0.03) and longer median symptom to balloon time (223 min vs. 192 min, p = 0.004). No-reflow was an independent predictor of mortality (HR 1.95, CI 1.04-3.59, p = 0.037) during 12 month follow-up. On multivariate analysis, age > 60 years, thrombus score ≥ 4 and symptom to balloon time > 360 min were independent predictors of no-reflow. In 17% of cases of no reflow, it occurred only after stent insertion.
Conclusions: No-reflow occurred in 25% of STEMI patients undergoing primary PCI and was more likely with older age, high thrombus burden and delayed presentation. No-reflow was associated with a higher risk of death at 12 month follow-up.

1. Introduction

Primary percutaneous coronary intervention (PCI) is the reperfusion strategy of choice in restoring blood flow to the occluded coronary artery in patients with ST elevation myocardial infarction (STEMI) [1]. Impaired coronary flow (Thrombolysis in Myocardial infarction grade < 3) despite restoration of epicardial coronary artery patency in the absence of any spasm or dissection is known as no-reflow [2]. It is thought to be caused by a combination of ischemic endothelial injury that obstructs the capillary lumen, neutrophil accumulation, reactive oxygen species and distal embolization of atherothrombotic debris [2,3]. No-reflow occurs in 11–41% of STEMI patients treated by primary PCI and is associated with poor left ventricular function, adverse clinical events and death [2,3]. A number of clinical, serologic and angiographic parameters have been shown to be associated with no-reflow [3].

The results of clinical trials testing a number of treatment strategies for no-reflow have been conflicting and there is no definitive treatment of no-reflow once it has occurred [4–8]. In the absence of an effective treatment strategy, it is crucial to prevent no-reflow by knowing the predictors or risk factors of no-reflow. Previous studies have identified various predictors of no-reflow, which are different between studies, likely due to the differences in the populations being studied [2,3,9, 10]. We aimed to identify the clinical and angiographic factors that predicted no-reflow in our contemporary cohort of consecutive patients with STEMI treated with primary PCI, and to determine the impact of no-reflow on mortality.

2. Methods

2.1. Study population

We reviewed the PCI database of The Canberra Hospital and identified 781 patients who presented as acute ST elevation myocardial infarction during 2008 to 2012. The creation and maintenance of the PCI registry was approved by the ACT Health Human Research Ethics Committee and all patients provided written consent for inclusion in the registry and follow-up. Demographic and procedural characteristics and the indication for the procedure were prospectively recorded and entered into the database. TIMI flow was measured retrospectively by a single experienced cardiologist who was blinded to the clinical data.

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The Canberra Hospital is the region's major public hospital, providing specialist and acute care to more than 700,000 people. We perform approximately 2000 diagnostic angiograms, 800 PCI and 150 primary PCI procedures per year.

2.2. Procedure

PCI procedures were performed through the femoral or radial artery using 6 Fr sheaths. All patients were treated with dual antiplatelet therapy including aspirin and either clopidogrel or prasugrel prior to the procedure. Aspirin was continued indefinitely and clopidogrel or prasugrel was recommended for 12 months. Intravenous heparin was administered to achieve an activated clotting time of 300 s. Adjunctive pharmacotherapy including the use of glycoprotein IIb/IIIa inhibitors and the type of stent were at the discretion of the interventional cardiologist. All patients underwent pre and post intervention ECG.

2.3. Assessment of coronary angiograms

All angiograms were reviewed by an experienced cardiologist blinded to the patients' outcome and follow-up status. Epicardial coronary blood flow was quantified visually using the Thrombolysis in Myocardial infarction (TIMI) flow grade classification [11]. Initial TIMI flow was assessed at the beginning of the procedure prior to wire insertion and final TIMI flow was assessed at the end of the procedure. No-reflow was defined as TIMI grade <3 at the end of the procedure in the absence of any coronary dissection or spasm. In the sub-group of patients that developed no-reflow, coronary flow was also assessed immediately before and after stent insertion in order to assess the influence of stent deployment on no-reflow. Coronary flow immediately before and after stent insertion was quantified by TIMI frame count in order to objectively determine any change in flow after stent insertion [11]. For this purpose, TIMI frame count (TFC) of >20 was defined as no-reflow. All angiograms were recorded at 15 frames/s.

Myocardial blush grading was not performed as most angiogram films were not acquired long enough to estimate the myocardial blush grade. Thrombus burden was estimated by using the thrombus scoring system proposed by the TIMI group [12].

2.4. Definitions and endpoints

The primary clinical endpoint for the study was all-cause mortality at 12 months. Other outcomes measured were re-infarction, stent thrombosis, transient ischemic attack (TIA) or cerebrovascular event (CVA), target lesion PCI, and coronary artery bypass grafting (CABG). MACE was defined as the composite of death, stent thrombosis, target vessel revascularization, re-infarction and stroke. Stent thrombosis was defined as definite stent thrombosis by angiography. MI was defined according to the third universal definition of MI [13]. Stroke was defined as a new focal neurological deficit following catheterisation or intervention lasting more than 24 h and confirmed by imaging. Cardiogenic shock was defined as a systolic BP <90 mm Hg or a requirement for inotropic therapy.

Symptom onset time was the time recalled by the patient as the onset of symptoms. First medical contact (FMC) was defined as the time of arrival of ambulance at the scene or patient arrival time at the first emergency department. Balloon time was defined as the time of first device used for reperfusion.

2.5. Data collection and follow-up

In-hospital clinical events were recorded by a research nurse prior to discharge. Long term follow-up was conducted by letter, phone calls and review of hospital records at 12 months. In case of adverse events, further details were obtained from the patient's medical records, physician or from other hospitals. We also obtained approval to access the

Australian Institute of Health and Welfare National Death Index to obtain accurate data on vital status and date of death for our patients. We supplied the patients' name, date of birth and residential address and these parameters were matched with data on the national death index. We accepted a match when a patient on the national death index had the same name and date of birth as a patient in our registry.

2.6. Statistical analysis

Patients were categorised as having "normal flow" or "no-reflow" based on the final TIMI flow at the end of the procedure. The baseline clinical characteristics and procedural characteristics of the two groups were compared using the Student's t test for continuous variables and the chi-square test for categorical variables. Cox proportional hazard multivariate analysis was performed to determine predictors of death during follow-up. We also performed a multivariate analysis to determine predictors of no-reflow. Variables in the model included age > 60 years, gender, smoking status, diabetes mellitus, hypertension, cardiogenic shock, anterior MI, culprit vessel, thrombus score, three vessel disease, glycoprotein IIb/IIIa inhibitor use, use of >1 stent, total stent length, type B2/C lesion, symptom to first medical contact and symptom to balloon time. A p value <0.05 was considered significant. All statistical analyses were performed using SPSS Statistics for Windows, Version 22.0.

3. Results

Primary PCI was performed in 781 patients during 2008–2012. Seventeen patients were excluded for the following reasons; 1 patient had intravascular ultrasound (IVUS) and percutaneous coronary intervention (PCI) was not required, 12 patients had unsuccessful PCI, 4 patients did not have long term follow-up although they had no in-hospital adverse events. Therefore we had 764 patients with long-term follow-up for analysis. No-reflow was seen in 189 (25%) patients at the end of the procedure. The clinical characteristics of patients with final no-reflow or normal flow are shown in Table 1. Patients with no-reflow were older (64 ± 12 years vs. 61 ± 13 years, p = 0.02) and there was a trend for them to be less likely to be smokers (22% vs. 29%, p = 0.052).

The procedural characteristics are shown in Table 2. The normal flow and no-reflow groups were similar in terms of the culprit vessels involved, proportion of patients with three vessel disease (21% vs. 20%, p = 0.77) and total stent length per patient (24 ± 12 vs. 22.1 ± 11 mm, p = 0.06). Use of prasugrel (23% vs. 24%, p = 0.95) and drug eluting stents (22% vs. 22%, p = 0.96) was similar between the two groups. Balloon angioplasty alone was used more often in no-reflow group (10.6% vs. 2.6%, p = <0.0001). Patients with no-reflow were more likely to have initial TIMI flow of 0–1 (77% vs. 64%, p = 0.0007) and thrombus score ≥4 (83% vs. 69%, p = 0.0001). Glycoprotein IIb/

Table 1
Clinical characteristics of patients with normal flow and no-reflow.

	No-reflow n = 189 (25%)	Normal flow n = 575 (75%)	p value
Mean age (years)	64 ± 13	61.4 ± 13	0.023
Female sex	43 (23%)	131 (23%)	0.98
Diabetes	38 (20%)	97 (17%)	0.32
Hypertension	79 (42%)	236 (41%)	0.85
Smoker	42 (22%)	169 (29%)	0.052
Ex-smoker	36 (19%)	100 (17%)	0.61
Hyperlipidaemia	60 (32%)	171 (30%)	0.60
Family history of IHD	43 (23%)	154 (27%)	0.27
BMI	27.7 ± 5.4	27.2 ± 4.6	0.91
Prior PCI	27 (15%)	96 (17%)	0.42
Prior CABG	12 (6%)	22 (4%)	0.16

BMI = body mass index, CABG = coronary artery bypass graft, IHD = ischemic heart disease,
PCI = percutaneous coronary intervention.

Table 2
Procedural characteristics of patients with normal flow and no-reflow.

	No-reflow n = 189 (25%)	Normal flow n = 575 (75%)	p value
Radial access	10 (5%)	23 (4%)	0.46
Culprit vessel:			
LAD/diagonal	77 (41%)	249 (43%)	0.49
LCx/marginal	28 (15%)	85 (15%)	
RCA	78 (41%)	233 (41%	
Bypass graft	6 (3.2%)	8 (1.4%)	
Initial TIMI flow 0–1	146 (77%)	369 (64%)	0.0007
Thrombus score ≥4	156 (83%)	391 (69%)	0.0001
3 Vessel disease	39 (21%)	112 (20%)	0.77
Prasugrel	44 (23%)	135 (24%)	0.95
Glycoprotein IIb/IIIa	107 (57%)	273 (48%)	0.03
DES use	38 (22%)	124 (22%)	0.96
>1 Stent used	50 (30%)	147 (27%)	0.40
Balloon angioplasty only	20 (10.6)	15 (2.6%)	<0.0001
Total stent length (mm)	24.0 ± 12	22.1 ± 11	0.06
Cardiac arrest	6 (3%)	6 (1%)	0.06
Cardiogenic shock	11 (6%)	21 (4%)	0.21
Type B2/C lesion	159 (84%)	478 (83%)	0.71
Median symptom to FMC, (IQR)	105 (53–199)	81 (45–146)	0.004
Median FMC to balloon time, (IQR)	97 (70–140)	93 (72–135)	0.12
Median symptom to balloon time, (IQR)	223 (156–406)	192 (135–291)	0.004

FMC = first medical contact, IQR = interquartile range reported as 25% to 75% range, LAD = left anterior descending artery (if diagonal artery was culprit artery it was included in LAD group), LCx = left circumflex artery (if obtuse marginal artery was culprit artery it was included in LCx group), RCA = right coronary artery, DES = drug eluting stent.

IIIa inhibitors were used more often in patients with no-reflow (57% vs. 48%, p = 0.03). Patients who experienced no-reflow had a longer median symptom to first medical contact time (105 min vs. 81 min, p = 0.004) and symptom to balloon time (223 min vs. 192 min, p = 0.004). Out of the 189 patients with no-reflow, an analysis of TIMI flow before and after stent deployment was performed in 150 patients with suitable images. In 25 of these 150 patients (17%), no-reflow occurred immediately after stent implantation.

Clinical outcomes are shown in Table 3. Patients with no-reflow had a higher 12 month mortality (13% vs. 6%, p = 0.004). There was no difference in target lesion PCI, re-infarction, stent thrombosis, TIA/CVA and CABG at 12 months. There was a higher MACE at 12 months in patients with no-reflow (18% vs. 11.5%, p = 0.025).

On multivariate analysis (Table 4), independent predictors of mortality were cardiogenic shock, age >60, initial TIMI flow 0–1 and no-reflow. Surprisingly, smoking status was associated with a lower risk of death. In our cohort smokers were on average 11 years younger than non-smokers (65 ± 13 vs. 54 ± 9, p = <0.0001). The other baseline characteristics were similar between the two groups.

We performed a further multivariate analysis to determine independent predictors of no-reflow (Table 5). We found that thrombus score

Table 3
Clinical outcomes of patients with normal flow and no-reflow at 12 months.

	No-reflow n = 189 (25%)	Normal flow n = 575 (75%)	p value
Mean days follow-up	321 ± 208	325 ± 211	0.80
Death	24 (13%)	34 (6%)	0.004
Stent thrombosis	3 (1.6%)	8 (1.4%)	0.85
Re-infarction	8 (4.2%)	20 (3.5%)	0.64
Target lesion PCI	7 (3.7%)	20 (3.5)%	0.88
CABG	4 (2.1%)	8 (1.4%)	0.50
TIA/CVA	1 (0.5%)	2 (0.35%)	0.76
MACE	34 (18.0%)	66 (11.5%)	0.025

CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, TIA = transient ischemic attack, CVA = cerebrovascular accident, MACE = major adverse cardiovascular events.

Table 4
Independent predictors of death on multivariate cox regression analysis.

Variable	Hazard ratio	Confidence interval	p value
Cardiogenic shock	11.1	5.9–19.9	<0.0001
Age > 60 years	2.87	1.54–5.88	<0.0005
Initial TIMI flow 0–1	2.29	1.12–5.31	0.021
No-reflow	1.79	1.04–3.04	0.037
Smoker	0.34	0.12–0.80	0.011

≥4, symptom to balloon time >360 min, and age >60 years were significant predictors of no reflow in STEMI patients.

4. Discussion

In our cohort no-reflow was seen in 25% of patients with STEMI undergoing primary PCI. The reported incidence of no-reflow varies depending upon the population being studied. When including all patients undergoing PCI for any indication, the incidence has been reported to be around 2.3–4.8% [2,9]. The reported incidence is higher in patients with STEMI and ranges from 11 to 41% [2].

No-reflow is a strong prognostic marker and has been shown to be associated with worse short and long term mortality [10,14]. The poor prognosis with no-reflow is due to larger infarct sizes, adverse left ventricular remodelling and reduced left ventricular systolic function [14]. In our study no-reflow was one of the independent predictors of death at 12 months. Interestingly, smoking status was associated with a lower risk of death. We believe that this is mainly because smokers were on average 11 years younger than non-smokers, even though we tried to correct for this in our multivariate analysis.

Several studies have tested various treatments for no-reflow after it has occurred, but these therapies have been unsuccessful. A recent Cochrane review of 10 randomised studies showed no benefit from adenosine or verapamil in reducing no-reflow, non-fatal myocardial infarction or all-cause mortality and there was some evidence of increase in side effects with adenosine [5]. Use of distal embolic protection devices in native coronary arteries has also failed to show an improvement in myocardial perfusion or reduction in infarct size in patients with STEMI [6–8]. It is therefore crucial to try and prevent no-reflow from occurring in the first place. In our cohort, there were three risk factors predictive of no-reflow. Firstly older patients (age > 60 years) were more likely to have no-reflow which has also been shown in other studies [2,9,10]. Intravascular ultrasound (IVUS) studies have shown that high burden of mixed atheromatous plaque is associated with a higher likelihood of no-reflow [15]. It is also known that elderly patients have a higher plaque burden with high necrotic core on IVUS [16]. It is possible that this high plaque burden predisposes elderly patients to no-reflow.

Secondly delayed presentation was a significant predictor of no-reflow and this is a potentially preventable factor. Delayed presentation is associated with greater ischaemic injury which leads to oedema of capillary bed, swelling of myocardial cells and neutrophil plugging [3]. It is well known from animal studies that longer duration of occlusion of coronary artery is associated with no-reflow after reopening the artery [3]. In our study delayed presentation with a pain to balloon time >360 min was associated with no-reflow. Previous studies have shown that delayed presentation >6 h from symptom onset to be independently associated with no-reflow [2,17]. However, studies using a shorter cut-off of delayed presentation (<6 h from symptom onset) do

Table 5
Independent predictors of no-reflow on multivariate analysis.

Variable	Hazard ratio	Confidence interval	p value
Thrombus score ≥4	2.28	1.50–3.55	< 0.0001
Symptom to balloon time >360 min	1.72	1.21–2.44	0.0024
Age > 60 years	1.53	1.08–2.18	0.018

not show delayed presentation as an independent predictor of no-reflow [9,18]. Measures to educate the public in recognition of heart attack symptoms and early presentation by ambulance to hospital may be beneficial. Continued efforts to minimise delays within the health system due to diagnosis, transfer and intervention in STEMI patients may also reduce the overall risk of no-reflow [19].

Thirdly, in our study thrombus score ≥4 was an independent predictor of no-reflow. A high thrombus burden commonly occurs in the setting of an occluded infarct artery and both features have been found to increase the risk of no reflow [17,20–22]. Distal embolization of thrombotic debris can lead to poor myocardial perfusion, larger infarct size and poor prognosis [23]. Another interesting observation was that 17% of patients developed no-reflow immediately after stent implantation. This can occur as stent implantation can dislodge athero-thrombotic debris and cause distal embolization [24]. The observation of this phenomenon has led several groups to develop a strategy of deferred stenting in selected STEMI cases [25–27]. In this strategy, flow is restored using thrombectomy and possibly balloon inflations and stenting are deferred to allow the thrombus burden to decrease over a period of hours to days. At the same time, this allows the microvasculature to recover [25]. A meta-analysis of five non-randomised studies comparing immediate versus deferred stenting showed that deferred stenting reduced the occurrence of no-reflow and distal embolization without an increase in major bleeding or major adverse cardiac events [26]. Recently, a small proof of concept trial randomised 101 STEMI patients with risk factors for no-reflow such as age >65 years, occluded infarct artery, high thrombus burden or presentation after 6 h to immediate stenting or deferred stenting after a median time of 9 h [25]. There was a reduction in the incidence of no-reflow and a follow-up cardiac MRI at 6 months showed greater myocardial salvage in the deferred group which may have prognostic significance. There was no increase in bleeding in the deferred group with prolonged antithrombotic treatment [25].

Considering that there is no evidence based treatment for no-reflow once it has occurred, it is important to identify patients with the above mentioned three risk factors of no-reflow, who may benefit from more targeted therapies such as deferred stenting or more intensive anticoagulant therapy. Larger randomised studies are needed to test the strategy of deferred stenting.

5. Limitations

This is a single centre observational study, but the data apart from flow assessment was collected prospectively and the research staff collecting data on clinical events was not aware of the occurrence of no-reflow in patients. The assessment of coronary flow was performed by the TIMI flow method which can be subjective, but this was performed by a single experienced cardiologist in order to maintain consistency. Also most previous studies have used TIMI flow as the method for assessing no-reflow [3]. Assessment of myocardial blush grade (MBG) was not performed as most angiogram films were not acquired long enough to visualise the myocardial blush. Although TIMI flow is less accurate than MBG in measuring myocardial perfusion, it has been shown to be a predictor of mortality in numerous studies and so remains a useful marker that is practical and easy to measure in clinical practice [3]. Ejection fraction is a strong predictor of prognosis but was not included in the multivariate analysis as this information was not known at the time of presentation. It may be difficult to assess the independent effect of no-reflow in the absence of ejection fraction. However, these two parameters are associated with each other, as no-reflow leads to poor ejection fraction due to distal embolization and myocardial infarction [3]. As ejection fraction is usually not known at the time of presentation, no-reflow serves as a useful alternative marker to predict prognosis. Finally, in our multivariate model, we did not include serologic markers such as blood glucose, C-reactive protein (CRP) or brain natriuretic peptide (BNP) that have been shown to be predictors of no-reflow in other studies, as this information was not routinely recorded in our database [3].

However, we included clinical and angiographic variables that are available to the operator at the time of primary PCI. The three risk factors identified in this study can be readily used to identify a patient at high risk for no-reflow.

6. Conclusions

No-reflow occurred in 25% of STEMI patients undergoing primary PCI and was more likely with older age, high thrombus burden and delayed presentation. No-reflow was associated with a higher risk of death at 12 month follow-up. As there is no effective treatment for no-reflow once it has occurred, it is important to try and predict and prevent no-reflow from occurring. In patients at high risk of no-reflow such as those with older age, high thrombus burden or delayed presentation, a strategy of deferred stenting and longer antithrombotic therapy may be considered. These strategies require further confirmation in clinical trials.

Conflict of interest

Nil.

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