Non-pharmaco, non-invasive management of coronary no-reflow phenomenon

Santosh Kumar Sinha¹, Mukesh Jitendra Jha², Puneet Aggarwal³, Umeshwar Pandey², Awadesh Kumar Sharma³, Mahmoodullah Razi³, Dibbendhu Khanra², Ramesh Thakur², Vinay Krishna²

¹Department of Cardiology, LPS Institute of Cardiology, Kanpur, India
²Department of Cardiology, Sri Aurobindo Institute of Cardiology, Indore, India
³Department of Cardiology, RML Institute of Medical Science, New Delhi, India

Submitted: 10 July 2020
Accepted: 30 August 2020

Arch Med Sci Atheroscler Dis 2020; 5: e271–e278
DOI: https://doi.org/10.5114/amsad.2020.102424
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Abstract

Introduction: No-reflow is an infrequent but dreaded complication of percutaneous coronary intervention (PCI), where the culprit is obstruction of the downstream microvascular bed. The aim of this study was to evaluate the efficacy and safety of forceful injection of blood (autologous blood transfusion – ABT) in reversing no-reflow during PCI because data regarding its effectiveness is not available.

Material and methods: 100–120 ml of blood was withdrawn through guiding catheter over 3 to 5 min using a 10 ml syringe and re-infused by forceful injection over 3 min through it, and its efficacy was assessed at 10 min using TIMI flow grade and quantitative corrected TIMI frame count.

Results: In total 93 patients received ABT following no-reflow. Their clinical presentation was ST-elevation myocardial infarction (STEMI) (n = 61; 65.6%), non-ST-elevation myocardial infarction (NSTEMI) (n = 23; 24.7%), and unstable angina (n = 9; 9.6%). It was observed among patients undergoing primary PCI (n = 18; 19.3%), pharmaco-invasive PCI (n = 27; 29%), rescue PCI (n = 11; 11.8%), and PCI for cardiogenic shock (n = 5; 5.3%). A mean volume of 108 ±4 ml blood was transfused. Commonest culprit vessel was left anterior descending artery (n = 51; 54.8%) followed by right coronary (n = 29; 31.7%), left circumflex (n = 19; 10.8%), and saphenous vein grafts (n = 3; 3.2%). Following ABT, TIMI 3 flow was successfully restored in 77 (82.7%) patients. TIMI flow grade improved from 1.02 to 2.52 and cTIMI frame count decreased from 60.6 ±12 to 16.1 ±6 (p < 0.001). ABT was well tolerated except transient hypotension (n = 17; 18.3%). Overall mortality was reported in 10 (10.7%) patients at 1 year.

Conclusions: In this largest and only study to date, ABT is a safe and highly effective approach to reverse no-reflow by raising driving pressure across the capillary bed.

Key words: percutaneous coronary intervention, acute coronary syndromes, TIMI frame count, TIMI flow, autologous blood transfusion, no-reflow.

Introduction

Restoration of patency of the culprit artery (infarct related artery) and re-flow of blood in the vessel occluded by thrombus by either pharmacological means using thrombolytics or mechanical means using percutaneous coronary intervention (PCI) is the gold standard of treatment in acute coronary syndrome [1, 2]. Primary PCI successfully restores TIMI 3
Material and methods

Study design and participants

This was a prospective, observational study conducted among patients who developed no-reflow following PCI for various indications between May 2017 to December 2018 at LPS Institute of Cardiology, GSVM Medical College, Kanpur, UP, India. The indication for intervention was acute coronary syndrome which included (a) ST segment elevation myocardial infarction (STEMI) incorporating primary, pharmaco-invasive, cardio-genic shock, and rescue PCI; (b) non-ST segment elevation myocardial infarction (NSTEMI); and (c) unstable angina (UA). Baseline demographics of patients, which included clinical (age, sex, clinical presentation and indication for intervention) and angiographic features and procedural data, were recorded. Lesions were classified as type A, B1/B2, or C as per American Heart Association/American College of Cardiology (AHA/ACC) criteria [12]. The presence of collaterals (either ipsilateral or contralateral) to the infarct-related artery was graded using Rentrop grading on basal angiograms [13]. All procedures were performed after obtaining written, informed consent from all patients, and the study protocol was approved by the institutional ethical committee (GSVM Medical College EC- 81/March/2017). Major exclusion criteria for PCI were intolerance to antiplatelet agents (aspirin, clopidogrel, ticagrelor, prasugrel), heparin, expected major surgery within 6 months following PCI, life expectancy < 12 months, and pregnancy.

Procedural details

The procedures were performed through either transfemoral or transradial route following standard techniques using unfractionated heparin on a weight-based regime (70–100 U/kg) as an anticoagulant. Lesion modification was done except in cases of direct stenting where the lesion appeared very soft (thrombus laden) and post dilatation was performed accordingly. In the case of multi-vessel involvement in a patient with acute coronary syndrome (ACS), only the infarct-related artery was intervened during index hospitalisation. All patients were pre-treated with aspirin (325 mg) and P2Y12 inhibitors (ticagrelor, prasugrel, or clopidogrel), and dual antiplatelet (DAPT) agents were continued for at least 12 months followed by aspirin alone indefinitely. The preferred antiplatelet agent was ticagrelor, followed by prasugrel and clopidogrel depending on economy and drug availability. All patients were followed up clinically (history, electrocardiogram, and echocardiogram) at 1 week, 1 month, 6 months, and 12 months, and check angiogram was performed only if symptomatic or when they presented with acute coronary syndrome. Target vessel-related myocardial infarction (MI) was attributed to the target vessel or could not be related to another vessel on the basis of clinical presentation, laboratory data, and electrocardiogram and angiograph-
ic findings [14]. Revascularisation was performed when the diameter of stenosis was $\geq 70\%$ along with subjective evidence of ischaemia.

**Assessment of coronary flow in the catheterisation laboratory**

All angiograms were reviewed and graded independently by two interventional cardiologists to assess TIMI flow grade in accordance with the TIMI before intervention, at the onset of no-reflow, and at the end of the procedure [15]. Vasospasm, edge dissection, or thrombus were ruled out before labelling as no-reflow phenomena. Angiographic flow was assessed using corrected TIMI frame count method (cTFC) [16]. All cine angiograms were recorded at 30 frames/s with a field size that enabled visualisation of both entry of contrast into the culprit artery and its runoff from a distal landmark. It was analysed by another independent investigator in random order, who was unaware of the sequence of injections. The initial frame used for the TFC was the first frame in which contrast fully enters the artery, whereas last frame was defined as the frame when contrast first entered the branch most distal to the culprit lesion. The number of cine frames between the first and last frames was measured to determine the TFC. Intra-observer variability was assessed with two separate readings, which was $\pm 5$ frames. The cTFC was compared before and after autologous blood transfusion.

**Protocol of autologous transfusion**

In case of coronary no reflow, 100–120 ml of blood was withdrawn from the side port of a small extension tube attached to side arm of a Y-connector using multiple 10 ml syringes over a 3- to 5-minute period with the guidewire kept in situ. All syringes were carefully de-aired and then blood was forcefully injected from the side port of Y-connector over a 3- to 4-minute period using handheld syringes. The force of injection is subjective, but it should be little more forceful than what one uses for routine contrast injection and should be enough to finish infusion of blood over 3–4 min. The amount of blood required to be infused was decided based mainly on the calibre of vessel and site of stent placement. In a medium sized vessel ($> 3$ mm) with proximal stent, nearly 120 ml of blood was infused while in a medium to smaller size vessel with shorter stent at mid segment of the artery, 80 ml was infused. Electrocardiogram and vitals were closely monitored. In the case of transient hypotension, intravenous fluid was infused. TIMI flow and cTFC were finally re-assessed after 10 min. Procedural success was defined as attainment of TIMI 3 flow. In the case of no response from ABT, standard measures like intracoronary verapamil, sodium nitroprusside, adenosine, and nicorandil were used after 15 min.

**Statistical analysis**

Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were presented as the mean $\pm$ standard deviation (SD). Categorical data were recorded as percentages. Differences in cTFC before and after ABT were analysed using the $\chi^2$ test. A probability level of $p < 0.05$ was considered statistically significant.

**Results**

**Patient and lesion characteristics**

During the index period 93 patients experienced no-reflow phenomenon, who were treated using ABT, among 1982 interventions performed. Baseline clinical and angiographic characteristics are shown in Table I. The patient population consisted of 66 (71%) men and 27 (29%) women, with a mean age of $53.4 \pm 17.9$ years. The commonest risk factor was smoking ($n = 228; 31.9\%$) in the form of either cigarette or bidi ($n = 29; 31.2\%$) followed diabetes ($n = 24; 25.8\%$) and hypertension ($n = 23; 24.7\%$). Indications for PCI were STEMI ($n = 61; 65.6\%$), NSTEMI ($n = 20; 21.5\%$), UA ($n = 9; 9.6\%$), and graft vessel ($n = 03; 3.2\%$). The left ventricular ejection fraction was severely impaired in 18 (19.3%) patients, while it was relatively preserved in 55 (59.1%) patients. The culprit vessel was left anterior descending artery in 51 (54.8%) patients, left circumflex artery in 10 (10.8%), right coronary artery in 29 (31.2%), and saphenous vein grafts in 3 (3.2%) patients. All grafts were degenerated (mean vein graft age: 13.3 $\pm 2.1$ years). Target lesions were typically high risk (ACC/AHA class B2 or C lesions) in 78 (83.9%) patients and mostly complex, and thrombotic (Table II).

**Procedural details**

The average delay from the beginning of symptoms to start of intervention was $6.2 \pm 3.5$ h in patients with primary PCI, NSTEMI, and UA and 32.4 $\pm 12.6$ h and 24.6 h in patients with rescue and pharmaco-invasive PCI, respectively. Collaterals to the culprit artery were observed in 23 (24.7%) patients, who were labelled as grade 3 in 10 (10%), grade 2 in 11 (12%), and grade 1 in 2 (2.7%) patients. Thrombus aspiration was performed using a Thrombuster II (Kaneka Medical; Japan) aspiration catheter in 10 (20.4%) patients who had acute total occlusion. Partial restoration of flow (TIMI 1/ TIMI 2) was observed in all 38 patients who had total occlusion at baseline (Figure 1). All lesions...
Table I. Baseline, clinical, and angiographic characteristics of patients (n = 93)

| Characteristics                          | N (%)     |
|-----------------------------------------|-----------|
| Age [years]                             | 53.4 ± 17.9 |
| Male                                    | 66 (71)   |
| Female                                  | 27 (29)   |
| CAD risk factors:                       |           |
| Hypertension                            | 23 (24.7) |
| Diabetes mellitus                       | 24 (25.8) |
| Smokers (cigarette/bidi/smokeless tobacco) | 29 (31.2) |
| Family history of CAD                   | 4 (4.3)   |
| Dyslipidaemia                           | 20 (21.5) |
| Clinical presentation:                  |           |
| STEMI                                   | 61 (65.6) |
| Primary                                 | 27 (29)   |
| Pharmaco-invasive                       | 18 (19.3) |
| Cardiogenic shock                       | 5 (5.3)   |
| Rescue PTCA                             | 11 (11.8) |
| NSTEMI                                  | 20 (21.5) |
| UA                                      | 9 (9.6)   |
| Graft Vessel PCI                        | 3 (3.2)   |
| LVEF:                                   |           |
| > 45%                                   | 55 (59.1) |
| 35–45%                                  | 20 (21.5) |
| < 35%                                   | 18 (19.3) |
| Medications:                            |           |
| Aspirin                                 | 90 (96.8) |
| Clopidogrel                             | 54 (58.1) |
| Prasugrel                               | 24 (25.8) |
| Ticagrel                                | 15 (16.1) |
| Statin                                  | 90 (96.8) |
| β-blocker                               | 67 (72)   |
| ACEI/ARB                                | 74 (79.6) |
| Ivabradine                              | 6 (6.4)   |
| Aldosterone antagonist                  | 22 (33.7) |
| Angiographic severity of CAD (Target vessel location): | |
| SVD                                     | 49 (52.7) |
| DVD                                     | 23 (24.7) |
| TVD                                     | 21 (22.5) |
| Culprit lesion location:                |           |
| LAD                                     | 51 (54.8) |
| RCA                                     | 29 (31.2) |
| LCx                                     | 10 (10.8) |
| SVG                                     | 3 (3.2)   |

Data presented as mean ± standard deviation or number (percentage). CAD – coronary artery disease, DM – diabetes mellitus, PCI – percutaneous coronary intervention, STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST segment elevation myocardial infarction, UA – unstable angina, LVEF – left ventricular ejection fraction, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin-receptor blocker, SVD – single-vessel disease, DVD – double-vessel disease, TVD – triple-vessel disease, LAD – left anterior descending coronary artery, LCx – left circumflex coronary artery, RCA – right coronary artery, SVG – saphenous vein grafts.

Table II. Procedural characteristics and outcome of patients (n = 93)

| Variables                          | Values, n (%)     |
|-----------------------------------|-------------------|
| AHA/ACC lesion class:             |                   |
| A                                 | 2 (2.1)           |
| B1                                | 13 (13.9)         |
| B2                                | 68 (73.1)         |
| C                                 | 10 (10.8)         |
| Lesion characteristics:           |                   |
| Ulcerated                         | 13 (13.9)         |
| Thrombus                          | 68 (73.1)         |
| Acute total occlusion             | 38 (40.8)         |
| Dissection                        | 5 (5.3)           |
| Collaterals present (grade 1–3)   | 23 (24.7)         |
| Size of vessels [mm]:             |                   |
| 2.25–2.5                          | 21 (22.5)         |
| 2.5–3                             | 30 (32.3)         |
| 3–3.5                             | 33 (35.4)         |
| 3.5–4 mm                          | 9 (9.8)           |
| TIMI flow pre procedure:          |                   |
| Grade 0                           | 39 (41.9)         |
| Grade 1                           | 25 (26.8)         |
| Grade 2                           | 17 (18.4)         |
| Grade 3                           | 12 (12.9)         |
| Median length of stent per patient [mm] | 36 ±12           |
| Procedural details:               |                   |
| Lesion modification:              |                   |
| Direct stenting                   | 10 (10.8)         |
| Thrombosuction                    | 19 (20.4)         |
| Predilatation (semi/noncompliant balloon) | 83 (89.2)     |
| GP IIb/IIIa antagonist             | 21 (22.5)         |
| Post-dilation                     | 80 (86)           |
| Amount of blood used for autologous transfusion [ml] | 98 (80–130)    |
| Transient hypotension             | 17 (18.3)         |
| Dissection, air embolism          | 0 (0)             |
| CV end points:                    |                   |
| Cardiac death                     | 9 (9.7)           |
| ACS                               | 2 (2.1)           |
| Stroke                            | 0 (0)             |
| MACCE                             | 12 (12.9)         |
| TLR                               | 2 (2.1)           |
| Stent thrombosis                  | 4 (4.2)           |
| Corrected TIMI frame count (Pre ABT) | 53.6            |
| Corrected TIMI frame count (Post ABT) | 16.9             |
| TIMI flow post procedure:         |                   |
| Grade 0                           | 0 (0)             |
| Grade 1                           | 3 (3.2)           |
| Grade 2                           | 13 (14)           |
| Grade 3                           | 77 (82.8)         |

CV end points – cardiovascular end points, MACCE – major acute cardio cerebrovascular events – composite of CV events and all deaths, TLR – target lesion revascularisation.
were predilated except in 10 patients (10.7%) who had a discrete ulcerated lesion where direct stenting was performed (Table II). GP IIb/IIIa antagonist (Tirofiban) was used after balloon dilatation in 10 (10.8%) patients, while 14 (12.5%) patients received it after stent deployment in 66 patients, and post-stenting balloon dilatation in 37 patients, of whom 56 (60.2%) had TIMI 1 flow while 37 (39.8%) patients had TIMI 2 flow (Figure 1).

A mean dosage of 96 ml of blood was forcefully injected (median: 112 ml, range: 80–130 ml). TIMI flow grade and cTFC after no-reflow and following ABT is shown in Figures 2 and 3. A significant improvement in TIMI flow grade was observed after ABT ($p < 0.01$). TIMI flow grade improved from 1.02 to 2.52 after ABT with successful restoration of TIMI 3 flow in 77 (82.8%) patients while TIMI 2 flow was restored in 16 (17.8%) patients. Therefore, the overall success rate of ABT was 86%. No-reflow was successfully reversed in all 3 (100%) patients with vein graft, and 74 of 90 patients (82.2%) among native vessel intervention. Patients with the lowest TIMI flow grade after PTCA showed the most extensive improvement of coronary flow (Figure 1). Similarly, TIMI frame count decreased from 62 ±12 at the time of no-reflow to 18 ±6 after ABT ($p < 0.001$), with an improvement of 44 ±7. In native vessels it decreased from 60 ±10 to 17 ±5 following ABT ($p < 0.001$), while in venous bypass grafts the TIMI frame count decreased from 64 ±16 to 22 ±8 after ABT ($p < 0.01$). A typical no-reflow situation of totally occluded RCA in a patient presenting with acute IWMI and its successful reversal with ABT is shown in Figure 4.

**In-hospital and follow-up outcome**

In three patients with no-reflow, two patients had partial restoration of flow (TIMI 2) following intracoronary administration of sodium nitroprusside. They were discharged after 10.2 ±2.2 days. The remaining patient with no-reflow was later mechanically ventilated because of progressive heart failure, and he later succumbed on the fifth day. However, no re-infarct or stent thrombosis were reported during index hospitalisation. On follow-up, CV events were reported in 11 (11.8%) patients, which was primarily driven by cardiac death ($n = 9$; 9.7%). Overall death was 9.7%, while death among patients who had presented with cardiogenic shock was 20% ($n = 1$). Two patients presented with STEMI as a result of late stent thrombosis, who underwent successful revascularisation. Malignant arrhythmia ($n = 4$; 44%) and progressive pump dysfunction ($n = 5$; 56%) were reasons for all cardiac death. MACCE was reported among 12 (12.9%) patients.
In our study, the success rate of ABT (82.8%) was comparable to other pharmacological measures like intracoronary administration of the combination of adenosine and nitroprusside, adenosine alone, calcium channel blockers (nicardipine, diltiazem, verapamil), vasodilators (nicorandil, sodium nitroprusside), and epinephrine, the success rate of which varies from 65% to 95% [17]. The various side effects with these agents are atrio-ventricular block, ST elevation or ST depression, need of temporary pacing wire, or atropine occurring in various proportions.

Adenosine, a purine nucleoside, although effective for no-reflow, has very rapid clearance because it has a half-life of 6 s and therefore may require multiple administration, which is time-consuming. Microvascular dysfunction, thrombus burden, and retrograde perfusion by collaterals, diabetes, and dyslipidaemia are among the exacerbating factors.
consuming and costly. Also, it causes bronchospasm, chest pain, hypotension, and transient atrioventricular block [18, 19]. ABT, in contrast to adenosine, is a one-time affair and is not associated with these side effects.

Nicorandil has the dual property of nitrate donor and ATP-sensitive potassium channel-opener, which acts on the micro-resistance vessel causing vasodilatation. It is helpful in combating no-reflow but has no action on aorto-coronary vein grafts, which might be a disadvantage, while our study has shown the effectiveness of ABT in this substrate of patients, as well [20–22].

Similarly, calcium channel blockers (nicardipine, diltiazem, verapamil) are also effective, but a major concern is the various degree of atrioventricular block and hypotension. In this regard, ABT is superior and safer because no rhythm disturbance was noted [23–25].

Overall mortality over 12-month follow-up was concordant with Werner et al. [23], who reported it to be around 10%. Our finding was also similar to results among patients who had presented with cardiogenic shock.

In our study, ABT was quite safe, although transient hypotension was reported in 18%, which was reversible. The possible reason for its beneficial effect is increased driving pressure across the capillary bed, which helps clear the microvascular bed of debris, thus restoring the flow. As the density of erythrocytes and neutrophils decreases across the capillary bed, reactive oxygen species-mediated endothelial damage, inflammation, and interstitial oedema does not happen, which helps to achieve TIMI 3 flow. As the spiral of multiple factors culminate into the final phenomena of no-reflow, its treatment is multiple. As the clogging of microvascular bed is quickly cleared, the chain reaction of inflammatory cascade turning into endothelial injury and intramural haemorrhage does not occur. Or study has a complex substrate of patients, although graft vessel intervention was less, but even in this small group it was 100% successful. Therefore, we speculate that it may show its benefit in a larger cohort, as well. In our study, 22.5% of patients received GP IIb/IIIa antagonists, and they benefitted from this therapy.

Although this was a prospective study of consecutive patients in whom no-reflow was observed, this was a nonrandomised study (lack of control group), had small number of patients, was observed in background of acute myocardial infarction only, and had no long-term follow-up. Moreover, acute gain in TIMI flow following forceful injection of blood confirmed its efficacy. However, one might opine about spontaneous resolution of no-reflow after prolonged observation over an extended period of time, but considering the background of AMI where the earliest attainment of TIMI 3 flow is the gold standard, it was not considered. Because this is the first study to be reported, it warrants further evaluation in larger randomised controlled trials.

In conclusion, the phenomenon of no-reflow is not uncommon, especially in the setting of primary percutaneous coronary intervention or intervention of bypass graft. Our study, the first ever to be reported, demonstrated the efficacy and safety of forceful injection of blood in reversing no-reflow. This modality will be newer therapeutic option in the armamentarium for the treatment of no-reflow in the catheterisation laboratory.

**Conflict of interest**

The authors declare no conflict of interest.

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