IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 8 Ser.1 (August. 2021), PP 50-58
www.iosrjournals.org

No reflow phenomenon - Has it Changed in Primary Percutaneous Intervention with current use of newer dual antiplatelets -Ticagrelor plus Aspirin?

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Abstract:
Background*: No reflow after primary angioplasty (PPCI) in ST elevation myocardial infarction (STEMI) carries worse prognosis.*
Objectives: *To analyze the incidence, predictors and 30 day major adverse cardiac events (MACE) in current practice of PPCI using ticagrelor and aspirin .*
Materials and Methods*: STEMI patients undergoing PPCI within 24 hours of onset were classified into group I - with normal post procedural TIMI 3 (thrombolysis in myocardial infarction 3) flow as controls and group II - with post procedural TIMI ≤ 2 flow (no reflow) as cases and analyzed the variables and outcomes associated with no reflow.* ***Results****: 77 (23.8%) of the 324 STEMI patients had no reflow. On multivariate analysis, the predictors were creatinine kinase MB >100 IU/L (OR 7.40 : 95% confidence intervals : 3.53- 15.41: p <0.001), multivessel disease (4.55: 1-55 - 13.11: p<0.001), high thrombus score of ≥4 (3.85: 1.79 - 8.30: p<0.001), pre PPCI TIMI flow < 2 (3.11: 1.03 -9.70:p=0.44), diabetes mellitus (2.09: 1.06 - 4.14: p = 0.033), window period > 8 hours (2.5: 1.03 - 6.06: p=0.043), post dilatation (1.23:1.02 -3.43:p=0.33). 30 day MACE was higher in no reflow group than normal flow group (18.2% vs.5.7% hazard ratio 3.21: 95% confidence intervals 1.34 - 7.66: p = 0,001).*
Conclusion: *No reflow remains a significant problem despite newer antiplatelet therapy during primary . Delayed reperfusion, high thrombus burden, multi vessel disease, , diabetes mellitus, post dilatation and low initial TIMI flow (0/1) were the predictive factors for no reflow with higher short term MACE.*
Key Words*: ST elevation myocardial infarction (STEMI), Primary percutaneous intervention (PPCI), No reflow,. Prognosis*

Date of Submission: 20-07-2021 Date of Acceptance: 04-08-2021

I. Introduction

The guideline directed ST segment elevation myocardial infarction (STEMI) management emphasize early rapid re-establishment of flow in the affected coronary artery to salvage the myocardium and improve the cardiovascular outcomes.[1] No reflow phenomenon refers to myocardial tissue hypo perfusion in the presence of a patent epicardial coronary artery[2] It carries adverse outcome after primary percutaneous coronary interventions(PPCI)[3–8] It is a complex pathophysiological process associated with coronary microcirculation, reperfusion injury and distal micro embolization and thrombosis. [2,9,10] Whether the current recommendations of use of ticagrelor and aspirin as dual antiplatelets in PPCI and the reduced upfront use of thromboaspiration and glycoprotein 2b3a (GP2b3a) inhibitors in the primary angioplasty resulted in favorably altering the undesired complication of no reflow phenomenon is unclear. This study was aimed at identifying the characteristics of no reflow phenomenon in the current practice of primary PCI, its incidence, the in hospital and 30 day adverse outcomes and the predictive variables.

II. Material And Methods

Study population
This study was a prospective observational case control study conducted at a tertiary care setting involving 345 consecutive patients who satisfied the inclusion criteria.
Inclusion criteria:
All Patients with acute STEMI undergoing PPCI within 24 hours after the onset of symptoms.
Exclusion criteria
Less than 50% diameter stenosis in the infarct related artery (IRA)

Patients with coronary spasm
Emergency CABG
Thrombolytic therapy
Rescue PCI
Patient unwilling to consent for PCI
Patients who have intolerance to dual antiplatelet drugs.

All patients were categorised into two groups based on the post-procedural thrombolysis in myocardial infarction (TIMI) flow in Infarct Related Artery (IRA).[11]
GROUP I (Control) - Normal TIMI flow 3 (reflow)
GROUP II (Cases) - TIMI flow ≤ 2 (No reflow)

The patient was considered to exhibit no reflow phenomenon if after reopening of occluded coronary artery and successful stent placement on angiography, there is TIMI flow ≤2 despite successful dilatation and in the absence of mechanical complications such as residual severe disease, dissection, spasm or extensive angiographically evident distal embolization.

After obtaining acceptance from the hospital ethical committee, study subjects were recruited as per the inclusion criteria and evaluated for Thrombolysis in Myocardial infarction (TIMI**)** flow grade.[11] TIMI frame count (15 frames/s) immediately before and after stent insertion and after use of intracoronary drugs like nitro-glycerine, nitroprusside, tirofiban etc. at the end of the procedure.[12] Myocardial blush grading (MBG) was also performed baseline and after stent insertion.[13] Thrombus burden was estimated by using the thrombus scoring system proposed by the Gibson.[14] All patients included in study received oral loading aspirin (300 mg) and Ticagrelor (180mg), Atorvastatin 80 mg and Heparin before procedure. Detailed assessment of history, epidemiological, clinical, laboratory, angiographical and procedural characteristics were done. These patients were followed clinically and major adverse cardiovascular events (MACE) noted at discharge and at 30 days after discharge. MACE evaluated were heart failure, non-fatal re-infarction, recurrent angina, re-hospitalization for cardiovascular-related illness and all-cause mortality at 30 days. A written informed consent was obtained from all patients or relatives. The study protocol was designed in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Data collection & Statistical analysis

All the data collected were entered as per the proforma designed for the study. The acquire data were entered into Microsoft excel spread sheet and analysed using IBM SPSS statistics for windows version 21.0 (IBM Corp. Armonk. NY US). Categorical variables were expressed as frequency and percentage and continuous variables as mean ± standard deviation. Chi-square test was performed for categorical demographic, clinical and procedural characteristics and the outcomes in the two groups. Comparison between the two groups were performed using independent t test or Mann-Whitney U test. Statistically significant demographic variables and clinical, angiographic and procedural characteristics were taken as predictors of no reflow and further univariate and multivariate logistic regression analysis were performed. The predictive strength of the variables were expressed in terms of odds ratio (OR) and its 95% confidence intervals (95% CI) and the associated p value. The risk associated was assessed by hazard ratio (HR) with its 95% CI and the associated p value. P value < 0.05 was the criteria for statistical significance throughout the analysis.

III. Result

345 patients with STEMI satisfying inclusion criteria treated by PPCI were selected. Of these, 324 patients were finally included in this study (4 were intolerant to ticagrelor, 2 had less than 50% stenosis of IRA, 8 failed to give consent , 3 had severe ectasia, 4 were considered for CABG).
These 324 patients were divided into two groups (cases and controls) based on the post-procedural TIMI flow in the IRA.
Group I (Control): Normal TIMI flow 3 (reflow) group: 247(76.2%)
Group II: (Cases) TIMI flow ≤ 2 (no-reflow group: 77 (23.8%)

The demographic and baseline clinical characteristics

The baseline clinical characteristics of Cases and controls are given in Table 1.
The mean age was 58.82 ± 11.27 years. 142 (43.8%) were above 60 years of age. 246(75.9%) were males. Of the 77 cases with no reflow, 6 patients (7.7%) had no distal flow and 71 patients (92.3%) had slow flow. Mean age, gender, smoking and site of STEMI were not associated with no reflow. Diabetes mellitus, higher Killip Class at admission, and prolonged window period were significantly associated with no reflow. However though numerically higher occurrence of hypertension and dyslipidaemia were noted in the no reflow group, but not statistically significant.

Table 1: Baseline clinical characteristics

Clinical variables		Total N=324(100%)	Post PCI coronary flow		
			Reflow group N =247(76.2 %) Control	No reflow group N = 77(23.8%) Cases	p value
Age (mean)		58.82± 11.27	58.78 ± 11.3	58.85 ± 11.07	0.959
Age	<=60 yrs	182 (56.2)	139 (56.3)	43 (55.8)	0.947
	>60 yrs	142(43.8)	108 (43.7)	34 (44.2)	
Sex -Male		246(75.9)	189 (76.5)	57 (74)	0.655
Hypertension		140(43.2)	104 (42.1)	36 (46.8)	0.472
Diabetes mellitus		123(38.3)	82 (33.2)	41 (53.2)	0.002
Dyslipidemia		76(23.5)	54 (21.9)	21 (27.3)	0.326
Smoking		121(37.3)	92 (37.2)	29 (37.7)	0.948
Prior CAD*		33(10.2)	28 (11.3)	5 (6.5)	0.220
Site of infarction	Anterior/ Lateral	140(43.2)	101 (40.9)	39 (50.6)	0.131
	Inferior/ RV/PW†	184(56.8)	146 (59.1)	38 (49.4)	
Killip class	Grade 1 & 2	294(90.7)	234 (94.7)	60 (77.9)	0.00009
	Grade 3 & 4	30 (9.3)	13 (5.3)	17 (22.1)	
Window period(hours)		5.19± 2.92	4.43 ± 2.45	5.95 ± 3.11	p<0.0001

*CAD- *coronary artery disease* † RV/PW - *right ventricle/posterior wall*

Laboratory characteristics

The baseline laboratory characteristics are shown in Tables 2. Higher leucocyte counts, elevated blood sugar levels and elevated creatinine phosphokinase -MB fraction were significantly associated with the no reflow group.

Table 2: Comparison of laboratory variables

Laboratory variables	Reflow group N = 247 (76.2 %) control	No-reflow N = 77(23.8%) cases	p value
Total leucocyte/mm^3	9323.4 ± 2834.9	11037.7 ± 3022.7	<0.01
Lymphocyte/mm^3	60.9 ± 564.8	23 ± 9.1	0.557
Ejection Fraction(EF%)	54.80 ± 13.6	52.8 ± 16.27	0.28
Haemoglobin (Hb)gm%:	12.45 ± 1.87	12.84 ± 1.64	0.097
Creatinine(mg/dl)	1.12 ± 0.29	1.02 ± 0.35	0.082
Random Blood glucose (mg%)	119.7 ± 60.5	180.9 ± 95.7	<0.01
Total cholesterol(mg%)	188 ± 51.4	193.6 ± 52.3	0.404
Triglyceride (mg%)	121.9 ± 63.1	123.9 ± 54.5	0.807
LDL* (mg%)	119.8 ± 49.6	118.3 ± 34.5	0.807
CPKMB*IU/L	91.7 ± 90.2	163.4 ± 95.5	<0.01

*LDL- *low density lipoprotein cholesterol* ***creatine phosphokinase-myocardial fraction*

Baseline angiographic and procedural characteristics

The baseline Angiographic characteristics of no reflow and reflow groups are shown in table 3. The no reflow cohort significantly exhibited lower initial TIMI flow grade, diffuse lesions, high thrombus burden, multivessel disease and higher corrected TIMI frame count.

Table 3: Comparison of angiographic variables

Angiographic variables		Reflow N = 247(76.2 %)	No reflow N = 77(23.8%)	p value
Vessel- Infarct Related Artery	LAD/D*	99 (40.1)	38 (49.4)	0.15
	LCX/OM†	38 (15.4)	4 (5.2)	0.02
	RCA‡	110 (44.5)	35 (45.5)	0.89
Site of occlusion	Proximal	133 (53.8)	50 (64.9)	0.087
	Mid	66 (27.1)	20 (26)	0.842
	Distal	48 (19.4)	7 (9.1)	0.035
Initial TIMI flow grade	Grade 0 & 1	204 (82.6)	71 (92.2)	0.040
	Grade 2 & 3	43 (17.4)	6 (7.8)	

Good Collaterals	Yes	244 (98.8%)	75(97.4%)	0.8
Length of lesion	Discrete	160 (64.9)	31 (40.2)	0.000134
	Tubular	29 (11.7)	11 (14.2)	0.55
	Diffuse	58 (23.1)	35 (45.5)	0.000198
Thrombus score	No thrombus(0)	197 (79.8)	33 (42.9)	< 0.0001
	Low thrombus (1,2)	25 (10.1)	9 (11.7)	0.69
	High thrombus(≥3)	25 (10.1)	35 (45.5)	P<0.0001
Disease type	SVD[§]	125 (50.6)	19 (24.7)	0.0001
	DVD/TVD[‖]	122 (49.4)	58 (75.3)	0.0001
Pre Myocardial blush grade(MBG)	Grade 0	11 (4.5)	11 (14.3)	0.003
	Grade 1	79 (32)	18 (23.2)	0.14
	Grade 2	122 (49.4)	32 (41.6)	0.23
	Grade 3	35 (14.2)	16 (20.7)	0.17
Coronary Diameter (mm)		2.9+ 0.3	3.0+0.6	0.08
Corrected TIMI Frame Count		15 ± 1.81	27.4 ± 4.1	P<0.01

*****LAD/D -*left anterior descending artery/ diagonal* † LCX/OM -*left circumflex /obtuse maginal* ‡RCA- *right coronary artery* [§] SVD- *single vessel disease* [‖] DVD/TVD- *double vessel disease/ three vessel disease*

The procedural characteristics are depicted in table 4. The requirement for longer stents were significantly more in the slow flow / no reflow group than the reflow group (26.3 ± 11.9 mm vs. 22.6 ± 10.8 mm ; p=0.011) mostly due to long diffuse lesions and longer lesion indicate more extensive thrombus generation and increased possibility of no reflow.

Table 4: Comparison of procedural variables

Procedural variables		**Reflow N = 247 (76.2 %)**	**No-reflow N = 77(23.8%)**	**p value**
Procedure	Predilation	154 (62.3)	53 (68.8)	0.301
	POBA*	20 (8.1)	4 (5.2)	0.396
	Direct stenting	79 (32)	20 (26)	0.318
Pre dilation pressure		6.66 ± 4.92	6.95 ± 4.58	0.644
Post dilation pressure		8.5 ± 8.21	8.52 ± 9.09	0.984
Stent length		22.6 ± 10.8	26.3 ± 11.9	0.011
Stent diameter		2.7 ± 0.8	2.9 ± 0.7	0.090
Post stent dilatation		138 (55.9)	38 (49.4)	0.316
Glycoprotein 2b3a inhibitor use(Bailout)		4(1.6)	15(19.5)	<0.0001

*****POBA-*Percutaneous old balloon angioplasty*

Table 5: Univariate analysis of factors in No-reflow

Variables	**Odds Ratio**	**95% (CI)***
High Thrombus score	8.36	4.40 -15.72
Killip class grade III & IV	5.1	2.35-11.08
MVD (DVD/TVD) †	3.13	1.76-5.56
Initial TIMI 0 / 1	2.49	1.02-6.10
Diabetes mellitus	2.29	1.36-3.8
Window Period	1.22	1.11-1.35

*All P<0.05 † MVD (DVD/TVD) - *multi-vessel disease,(double vessel disease / three vessel disease)*

Univariate & Multiple logistic regression analysis

Univariate analysis showed that high thrombus burden, higher killip grade, multivessel disease, low initial TIMI flow 0/I, presence of Diabetes and longer reperfusion time were significant predictors of slow / no reflow and are displayed in table 5. Strong independent predictors of slow / no reflow in Multivariate analysis were elevated CK MB values (>100 U),

high thrombus burden, lower initial TIMI flow grade (i. e. ≤ 2), multivessel disease, prolonged window period, diabetes mellitus (table 6).

Table 6: Multiple logistic regression analysis (independent predictors)

Predictors	OR	95% CI	p value
Window period (> 8 hours)	2.5	1.03 - 6.06	0.043
Hypertension	1.26	0.76 - 1.62	0.261
Diabetes mellitus	2.09	1.06 - 4.15	0.033
Smoking	1.012	0.47-2.70	0.476
Killip class III& IV	2.87	0.95- 8.65	0.061
CK MB* (> 100 U)	7.40	3.53- 15.41	<0.001
Pre PCI TIMI flow (0-1) †	3.11	1.03-9.70	0.044
High thrombus score	3.85	1.79-8.30	<0.001
Multivessel disease	4.55	1.55-13.11	<0.001
Post Stenting dilatation	1.23	1.02- 3.43	0.033
Lesion length >20 mm	1.39	0.93 - 5.43	0.066

*CK MB - creatinine kinase MB fraction † pre PCI TIMI flow - pre-percutaneous intervention TIMI flow

The association of advanced age (>60 years) with slow flow/ no reflow was not significant whereas post dilation after stenting were significantly associated with no reflow in multiple regression analysis. The longer lesion length showed a trend towards positive association with no-reflow, but did not reach statistical significance.

Major adverse cardiovascular events (MACE)

Significantly higher in-hospital mortality was observed in the no reflow group as well as prolonged hospital stay. In hospital mortality was 5 (6.5%) in no-reflow group and 5(2%) in reflow group which was statistically significant ($p < 0.05$). Duration of hospital stay was also high 6.5 ± 2.6 days in no-reflow group compared to 4.6 ± 0.9 days in reflow group which was also statistically significant ($p < 0.001$).

30 day Major adverse cardiovascular events (MACE) (table 7) were significantly higher in no reflow group than reflow group (HR: 3.21; 95% confidence interval 1.34 - 7.66; p =0.001). There was significant difference in the left ventricular ejection fraction as assessed by echocardiography between the two groups at 30days (56.66 ± 13.22 % in reflow group vs 52.7 ± 16.23% in no-reflow group; P=0.037). The elevated MACE was mostly driven by recurrent angina (10.4% vs 2.06% ; HR:5.13 95%CI 1.43- 18.41; p=0.001). Though numerically higher occurrence of heart failure (7.8% vs 3.7%: HR 2.14 95% CI 0.65 - 7.02; p=0.14), Re-infarction (1.3%vs 0.4%), Stroke (1.3% vs 0.4%) occurred in the no reflow group but were not statistically significant. All-cause mortality was higher 7(9.1%) in no-reflow group and 6 (2.4%) in the re flow group (HR 3.74; 95% CI 1.04 - 13.42 ; p=0.01) at 30 days.

IV. Discussion

This study was performed to look into the characteristics of no-reflow phenomenon in the contemporary guideline recommended practice of primary PCI using ticagrelor and aspirin as dual antiplatelets (DAPT) combined with low usage of pre / peri PCI glycoprotein 2 b 3a inhibitors and thromboaspiration, the predisposing factors for no-reflow and the associated 30 day major adverse cardiovascular events. No reflow phenomenon was seen in 23.8% of primary angioplasty patients, associated with higher in hospital mortality, longer hospital stay and higher 30 day composite MACE. No-reflow phenomenon is a feared complication after percutaneous coronary interventions which is associated with worse prognosis.[4–8]. Krug et al [15] in 1966 reported flow disturbances in distal coronary artery after temporary occlusion of the coronary in cat models, attributing this to raised intraventricular pressure though we identify this as "no reflow " now, he probably was the first to recognise this curious phenomenon in laboratory. The concept of "No reflow" was first clinically introduced more than 50 years ago, on September 9,1967 by Majno and colleagues following reperfusion of ischemic brain experiments. [16] . The no-reflow phenomenon in the myocardium was later originally described in 1974 by Kloner et al in a series of dog experiments on temporary

Table 7: Major adverse cardiovascular events (MACE) at 30day Comparison between Reflow and No reflow groups

MACE at 4week	Reflow Group (N=247)		No reflow Group (N=77)				
Item	Count	%	Count	%	Hazard ratio	95%C.I	P value
Overall MACE	14	5.7	14	18.2	3.21	1.34 -7.66	0.001
Angina	5	2.1	8	10.4	5.13	1.43 -18.41	0.001
Heart failure	9	3.7	6	7.8	2.14	0.65-7.02	0.13
Reinfarction	1	0.4	1	1.3	3.21	0.12-83.23	0.38
Readmission	1	0.4	2	2.6	6.41	0.45-91.58	0.08
Stent thrombosis	1	0.4	1	1.3	3.21	0.12-83.23	0.38
Stroke	1	0.4	1	1.3	3.21	0.12-83.23	0.38
All-cause mortality	6	2.4	7	9.1	3.74	1.04-13.42	0.01

coronary occlusion and reperfusion. [17] Percutaneous coronary interventions brought the no-reflow phenomenon to light as it could be seen with the naked eye in human hearts in the setting of acute myocardial infarction. No-reflow with impaired myocardial perfusion can be diagnosed angiographically (TIMI blood flow grades, the corrected TIMI frame count (TFC), and the myocardial blush grade (MBG)) or by using imaging modalities that can quantify myocardial perfusion, such as myocardial contrast echocardiography. [12–14,18]Higher thrombus burden, higher Killips class at presentation, lower TIMI flow scores, presence of multivessel disease, diabetes mellitus and prolonged window period were associated with no reflow in univariate analysis in this study. However the independent predictors of no reflow were total ischemic time (i.e. window period >8 hours), diabetes mellitus, elevated CK-MB >100IU, low initial TIMI flow grade ≤ 2, presence of MVD and post dilatation after stenting.

Older Age has been portended as a predictor in prior studies[19–23,] however age was not a predictor in this study. In a large recent meta-analysis, Fajar et al 2018 reported, older age as a predisposing factor for no-reflow in 24 studies (OR 1.894 CI 1.520-2.359; $p < 0.0001$)[19]. Only six studies of the 24 included in the meta-analysis showed no such relation with age. Age related increase in coronary medial calcification and multi vessel disease and hypercoagulability due to elevate activated factors VII, IX and X , increased platelet activity , age related endothelial dysfunction and increased stiffness of the elastic arteries- all may contribute to increased thrombus formation and contribute to higher no reflow phenomenon. [24] The lack of effect of age in this study is unclear and probably related to overall younger population (mean age 58 years) or the interplay of both identified or unidentified confounding risk variables.

There was no gender propensity for no reflow phenomenon in this study. Similarly, we did not find any association of smoking, hypertension or site of infarction with no reflow. Diabetes mellitus increased independently the risk of no reflow by two fold in this study. Iwakura et al 2003 investigated hyperglycaemia and no reflow phenomenon in patients with AMI.[25.] Blood glucose level was found to be an independent predictor of no reflow.[25] Similarly the recent large meta analysis, Fajir et al also observed that diabetes mellitus increased (1.45 times) risk than the non diabetic for development of no-reflow (OR 1.45 95% CI 1.16 - 1.81; P=0.001).[19] Ashraf et al in a recent large trial quoted diabetes as an important independent variable in prediction of no-reflow, (OR was 1.66 ; 95% CI : 1.14-2.42 : P=0.009)[20.]

Prolonged window period (>8 hours) increased the risk of no reflow 2.5 times in this study on multivariate analysis as reported in previous studies. [19–21] Prolonged window period indicates long ischemic period and more extensive myocardial damage, more thrombus formation at the site of occlusion and more myocardial cellular necrosis, distal micro vascular endothelial cell damage, dysfunction and swelling and luminal protrusion of endothelial cells as well as extraneous compression by myocardial oedema all contributing to no reflow once circulation is re-established[.2,9,10,21] This stresses the very basic and important fact that the public should be educated regarding early accomplishment of revascularization in acute myocardial infarction by seeking medical aid at the earliest in acute chest pain.

Higher Killips class (>2) at presentation with STEMI and baseline higher CK-MB which reflects more extensive myocardial damage also independently predicted no reflow in multivariate analysis in this study. Similarly high thrombus score (4or5), low pre PCI TIMI flow score (<2), multivessel disease, longer lesion length (>20 mm) , and post dilatation after stenting - all of which were risk predictors in our study as has been shown in previous studies.[.20,21,26,27] Mortality had been reported higher in myocardial perfusion grades 0/1 than in grades 2/3.[13]. It has been reported that no reflow with large infarct size was more frequent in patients with high thrombus burden, reduced TIMI flow and collateral flow. The major contributor of no reflow is micro vascular obstruction caused by the embolization of thrombus originating from unstable plaque during PCI.[2] Sky Schally et al reported that distal coronary embolization was associated with severe regional contractile dysfunction in animal models.[28]

Multi vessel disease also increased the risk of no-reflow in this study (OR 4.5 (95% CI: 1.5-3.1; P<0.001). This has been observed also in previous studies. [4,26,27,29–31] . In the study by Magro et al to predict no reflow after PPCI in STEMI based on the SYNTAX score, it was reported that a SYNTAX score >21 was an independent predictor of No reflow (OR 1.29 95% CI 1.02 -1.63, p< 0.001).[5] SYNTAX score is contributed by many factors such as number and location of coronary lesions, chronic total occlusions, bifurcation lesions and calcifications which indicated severe atherosclerotic vascular disease. Magro et al stated that collateral circulation which is protective, would be poorly developed and insufficient if contributing artery is diseased.[5] Previously it is also commented that diffuse disease often signified an impaired microcirculatory index.[5,32] The study by Padmajan et al from Trivandrum[21]and Ashraf et al from Karachi[20] showed dissonant results of the association of MVD and no reflow whereas the meta-analysis in 2018[19] (9 of the 27 studies showed that MVD was associated with no reflow phenomenon. Goldstein et al. reported that the presence of multiple complex plaques (increased atherosclerotic burden) was associated with a poor prognosis in MI patients. [24.] MVD reflects higher atherosclerotic burden and probably add additional risk of more severe micro vascular dysfunction and embolization.[24] On similar note, longer and diffuse lesions also showed significantly high no reflow (45.5% vs.

23.1% ; P = 0.0001) as they have higher plaque burden and plays a similar role in causing distal micro vascular dysfunction. [32]

Post dilatation after stenting is likely to lead to more prolapse of thrombus and atherosclerotic plaque debri from the underlying plaque, further micro emboli distally, micro vascular occlusion and dysfunction facilitating no reflow phenomenon. A higher rate of distal embolization was found in patients with advanced Killip class, and hence the no reflow observed in these patients in a study by De Luca et al.[33]

A linear association between initial Killip class and post procedural TIMI 3 flow was also observed in the Shock Trial Registry by Hochman JS et al.[34] More aggressive supportive management for patents with high killip class is needed to reduce the occurrence of no-reflow phenomenon.

The laboratory variables associated with no- reflow phenomenon in the present study were elevated leucocyte count, elevated blood sugar values and CK-MB. High leukocyte count was a poor prognostic predictor in a study by Danesh Sani et al. [35] The exact role of leucocytes in the genesis of no reflow is unclear and the relationship with inflammation needs more research. Wang et al showed that on admission plasma glucose >13 mmol/L was one of the no reflow predictors.[36] Creatinine kinase (CK) function as a channel for high-energy phosphoryl groups and lead to sequential phosphotransferase that is responsible for transmission of adenosine triphosphate (ATP) from mitochondria to ATP-consuming sites.[37]. In ATP-consuming site, CK rapidly regenerates ATP from creatine- phosphate. Therefore, CK may facilitate highly energy-demanding functions for vascular contractility that may contribute for the development of no reflow.[37]

In Hospital events

In hospital mortality (6.5% vs. 2%; p=0.05) and duration of hospitalization (6.5 ± 2.6 days vs. 4.6 ± 1.9 days : P<0.001) were significantly higher in the no reflow group in our study and align with the observations made by Ashraf et al who reported higher in hospital mortality in patients who had no reflow (6.8% vs. 2.9% ; P=0.01).[20] Higher in hospital events in those exhibiting no reflow during PPCI had also been described in multiple earlier studies[4,6–8,20,27,30,31,38,39]

30 day major adverse cardiac events

Significant higher MACE at 30days (HR 3.21 95% CI ; 1.3 -7.6 : P =0.001) and a decline in left ventricular ejection fraction by echocardiography at 30days (52.7 ± 16.2 % in no reflow vs. 56. 1 ± 13.8 % in control) were seen. The higher MACE at 30 days was contributed largely by the recurrent angina in patients who exhibited no reflow(HR 5.1; 95% CI : 1.4 - 18.5: P=0.001). There was a trend towards higher occurrence of heart failure in no reflow group than the normal group. The all cause mortality was significantly higher in no-reflow group compared to the normal flow group 7 (9.1%) vs 6(2.4%) [HR 3.74 95% CI 1.04 - 13.42 ; P=0.01] at 30 days. Ndreppa et al reported higher 30 day MACE at one year in patients with no reflow 37% vs. 25.7% P= 0.011) and higher one year mortality 16.7% vs. 5.5%, hazard ratio, 3.35 (95% CI, 1.97 to 5.69, *P*=0.001).[6] Choo et al who made a time dependent analysis of mortality in no reflow phenomenon in a study and observed that the 30 day mortality was higher in no reflow group compared to the normal group (28/262 (10.7%) vs. 47/1755 (2.5%) : P<0.001) (adjusted HR 3.11 95% CI 1.91 - 5.05 P<0.001).[4] Mortality and MACE were also reported to be high in 30 days in the no reflow group compared to the normal flow group in reports by others as well. [5,26]

This study is unique in that all the STEMI patients who underwent primary PCI included in this study received the newer dual antiplatelets - ticagrelor and aspirin and additionally had lower usage of glycoprotein 2b 3 a inhibitors pre / peri PCI as well as lower application of thromboaspiration techniques. Despite this newer antiplatelet regimen and advancement in stent designs, the incidence of no reflow phenomenon in this study was 23.8% similar to that has been reported in previous studies. However a direct comparison between newer dual antiplatelet regimen and conventional regimen such as clopidogrel and aspirin was not done and the change it would have made to the outcome is uncertain. Any factor which encouraged the formation of thrombus in the IRA and hence further distal embolization during PCI aggravated no reflow. Thus interventions should be targeted to reduce the occurrence of no reflow during primary PCI by modifying the interventional strategies and implement appropriate steps to reduce no reflow.

V. Conclusions

No reflow remains as a significant problem even in the current guideline based PPCI protocol with newer DAPT i.e. with ticagrelor and asprirn. Patients with delayed reperfusion, diabetes mellitus, low initial TIMI flow, high thrombus burden, multivessel disease, larger infarcts and post stent dilatation were at an increased risk for no reflow development and portends adverse early cardiovascular outcomes. Our results may contribute to develop better understanding regarding the risk factors of no reflow in management of acute coronary syndrome and points to adoption of early revascularization strategy for STEMI.

VI. Limitations

This was an observational single centre study involving a Southeast Asian ethnic group and can't be generalized to all ethnic groups. Neither was this a randomized nor a large trial. The assessment of coronary flow was performed by the TIMI flow method which could be subjective, but this had been minimized, as this was evaluated by experienced cardiologist. TIMI frame count was also used in order to maintain accuracy. We have not analysed no-reflow using myocardial contrast echocardiography or nuclear scintigraphy which would have added additional specificity. But this study is unique in that all the STEMI patients included in the study received new dual antiplatelet regimen with ticagrelor and aspirin and low usage of glycoprotein 2 b 3 a inhibitors and thromboaspiration techniques align with the current guideline based management and reflects the real world scenario.

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Ashis Ranjan. "No reflow phenomenon - Has it Changed in Primary Percutaneous Intervention with current use of newer dual antiplatelets -Ticagrelor plus Aspirin?." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(08), 2021, pp. 50-58.