NO-REFLOW

Maddury Jyotsna, Nemani Lalita

DEFINITION:

The "No-reflow phenomenon" is classically defined as lack of myocardial perfusion despite opening up the Epicardial vessel in the setting of primary percutaneous coronary intervention (PCI). Broadly it refers to sudden loss of Epicardial flow i.e. abrupt onset of TIMI- zero flow after balloon dilatation or placement of a stent. Angiographic no-reflow was defined as TIMI flow grade 0, 1, and 2 after PCI. Angiographic No-Reflow is defined as the presence of TIMI 0-1 in absence of dissection, spasm, stenosis or thrombus of the epicardial vessel. Lesser degree of reduction of coronary flow (i.e.TIMI 2 flow) is defined as Slow-flow.

HISTORICAL ASPECT:

The term no-reflow was first coined by Ames et al in their experimental work on cerebral ischemia. Kloner et al. described coronary no-reflow for the first time in a canine model after prolonged (90 min) coronary occlusion followed by reperfusion. However, the same couldn't be directly extrapolated to the human situation where myocardial infarction results from occlusive superimposed coronary thrombosis. The no-reflow after AMI in humans was first described by Ito et al, who had assessed it by myocardial contrast echocardiography (MCE).

INCIDENCE:

No-reflow has a prevalence ranging from 5% up to 50%, depending on the method of assessment and the population studied. It is seen in about 10% cases of Primary PCI. It occurs with a lesser frequency in the setting of non-ST-elevation myocardial infarction (NSTEMI) or during elective PCI (1.5%); though incidence may be higher in elective saphenous venous graft interventions (4%).

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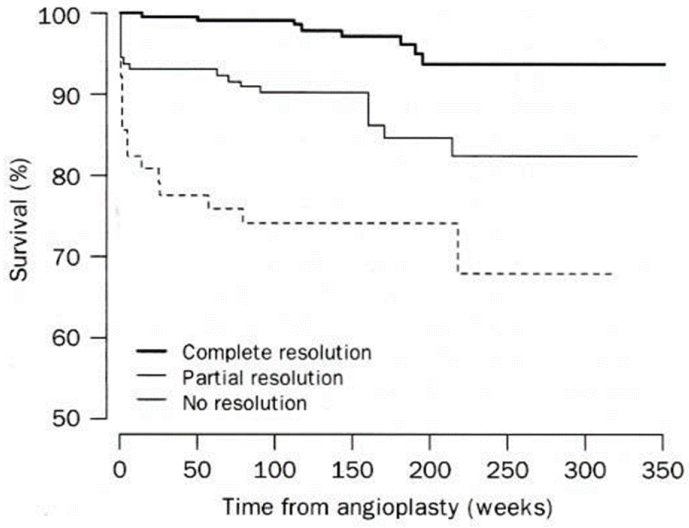
IMPORTANCE OF NO OR SLOW FLOW (Including prognosis):

No-reflow or slow-flow phenomenon has been found to be significantly associated with poor clinical and functional outcomes and prolonged hospitalization.

Prognosis: No-reflow phenomenon is associated with the poor short-term and long-term prognosis. Its negative impact on outcomes dampens the potential benefits of PPCI. The in- hospital course may be complicated with malignant arrhythmias, re- infarction, cardiac rupture and pump failure. There is an increased risk of death at 30 days. LV remodeling is absent in no-reflow resulting in LV dilation and heart failure. Five-year rates of repeated hospitalization and mortality are also high (Fig 7).

Fig 7: Survival curves showing less survival with no ECG resolution cases.



CLASSIFICATION OF NO FLOW:

Eeckhout and Kern have suggested classifying no-reflow into 1) experimental no-reflow and 2) MI reperfusion no-reflow and 3) angiographic no-reflow.

1. **Experimental no-reflow**: Refers to no-reflow induced under experimental conditions. This is due to myocardial necrosis—stunning, reperfusion injury—oxygen free radical production, α-adrenergic macro- and microvascular constriction, local increase in angiotensin II receptor density and neutrophil activation—interaction with endothelium.

2. **Myocardial infarction reperfusion no-reflow**: No-reflow in the setting of pharmacological and/or mechanical revascularization for acute myocardial infarction. The mechanism is same as experimental no Flow.

3. **Angiographic no-reflow**: No-reflow during percutaneous coronary interventions. This is due to distal embolization of plaque and/or thrombus or local release of vasoconstrictor substance). Angiographic no-reflow is again sub-classified as

    a. Reperfusion No-Reflow
    b. Interventional No-Reflow

Reperfusion No-Reflow occurs after primary PCI. May be asymptomatic or present clinically with continued chest pain and ST elevation. Characterized by preceding ischemic cell injury confined to the irreversibly damaged necrotic zone, exacerbated at the time of reperfusion. This is an independent predictor of adverse clinical outcome (heart failure, mortality).
Interventional No-Reflow follows non-infarct PCI. Typically sudden in onset, presents clinically as acute ischemia with chest pain and ECG changes. May resolve over the course of several minutes. This is common in affected myocardium that was not subjected to prolonged ischemia before the procedure. Patients with interventional no-reflow have higher rates of mortality. This interventional No-Reflow is unpredictable and uncommonly recognized in clinical practice.

Galiuto classified No reflow as sustained or reversible.
Sustained no-reflow/ structural no-reflow: Result of irreversible anatomical changes in the coronary microcirculation. Patients undergo unfavorable left ventricle (LV) remodeling.

Reversible no-reflow/ functional no-reflow: Result of functional and, thus reversible, changes of microcirculation. Patency of anatomically intact microvessels is compromised due to spasm, embolization, reperfusion injury and neurohormonal system activation Patients maintain their LV volumes unchanged over time. Similar findings were shown by Hoffman et al. by analyzing changes of myocardial blush grade (MBG) over time.

TIME COURSE AND PATHOLOGY:

Traditionally, 'no reflow' phenomenon was attributed solely to microvascular obstruction caused by distal embolization of thrombi and plaque components during balloon angioplasty and stent placement. However, studies have demonstrated that it results primarily from tissue and microvascular damage during myocardial ischemia. The duration of ischemia influences no-reflow phenomenon. If the ischemic period is short (<45 min), no-reflow can be attributed to distal embolization. When coronary occlusion has lasted for >45 min, microvascular damage is more likely irrespective of distal embolization. The phenomenon typically involves first the sub endocardium and then spreads to the sub epicardium. Surrounding the no-reflow zone is a low reflow zone, which can either reverse to normality or progress to no-reflow area depending on the presence of collateral blood flow.

MECHANISM:

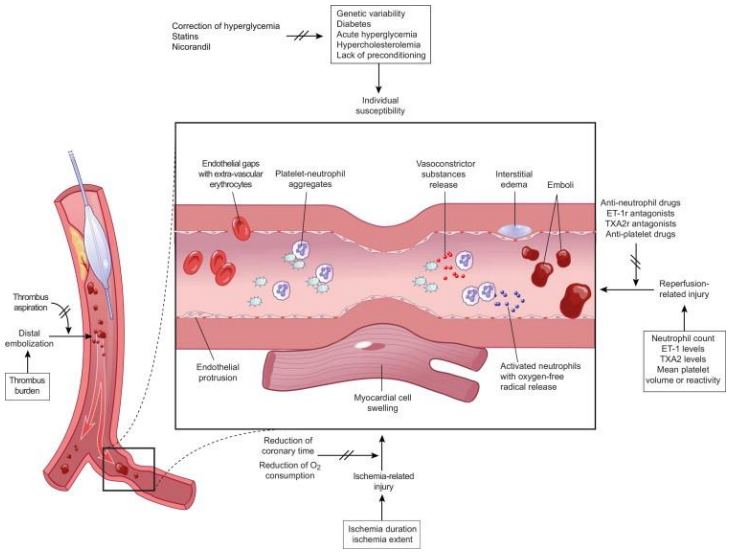
Coronary No-Reflow in humans results from a combination of 5 major pathogenic components (Niccole et al.): 1) pre-existing microvascular dysfunction 2) distal micro-embolization 3) ischemic damage 4) reperfusion injury 5) susceptibility of coronary microcirculation to injury.

a. Pre-existing microvascular dysfunction (MVO): MVO-structural and/or functional impairs coronary flow reserve (CFR) and increases the vulnerability of affected myocardium to the PCI induced injury. Pre-existing MVO is due to endothelial dysfunction and is attributed to advancing age, insulin resistance, Dyslipidemia, chronic inflammatory diseases and individual susceptibility.

b. Distal Micro-embolization: Refer to the downstream migration of thrombus debris or micro-material from fissured and ruptured atheromatous plaques during balloon dilatation or stenting. When more than 50% of the capillaries are blocked, myocardial perfusion starts falling. When the number of emboli is 25–200 or the size of micro-emboli is >200 mm, it can cause severe MVO.

c. Ischemic injury: Prolonged ischemia causes endothelial and myocardial degenerative changes. Endothelial protrusions and membrane-bound bodies contribute to capillaries luminal obliteration, the endothelial gaps allow extravascular erythrocytes migration and compression. In addition, endothelial activation promotes expression of new adhesion molecules which contributes to leucocytes accumulation. Decreased production of adenosine triphosphate resulting from ischemia impairs the sodium-potassium pump (Na+/K+-ATPase) and results in cardiac myocyte swelling. This irreversible damage leads to edema and contributes to extravascular compression (Fig 1).

Fig 1: schematic diagram showing the pathophysiology of No reflow. Courtesy of Niccoli G1.



d. Reperfusion injury: Reperfusion results in infiltration of the ischemia zone with neutrophils and platelets result in mechanical plugging of the coronary microcirculation. The resulting ROS cause mitochondrial dysfunction and cell death. They also cause direct endothelial cell death by releasing inflammatory mediators especially tumour necrosis factor alpha and interleukin-1β.Ischemia and reperfusion injuries combined result in intra-myocardial hemorrhage (IMH) which is a severe form of MVO.

e. Individual susceptibility: The combination of all the above described mechanisms contributes to the No-Reflow phenomenon but damage severity is modulated by individual predisposition of coronary microcirculation to injury.

CONDITIONS TO BE EXCLUDED BEFORE LABELLING AS NO-REFLOW:

When acute shut down of flow is noted in the target coronary artery during the intervention, certain conditions needs to excluded before labeling the condition as slow or no reflow. These are dissection, acute stent thrombosis (drug related or hypercoagulable state), plaque prolapse, multiple plaque ruptures.

a. **Dissection**: Acute stent edge dissection causes interruption of circulation in the culprit artery. Angiogram may show the flap directly before the complete interruption or if a balloon is kept across the dissection flap then flap is elevated by the balloon and flow may be established. If this "Balloon - reestablishment of the flow" is demonstrated, then a distal stent dissection is almost certain which can be tackled with another stent. Best and more certain way of demonstration of dissection is by IVUS or OCT.

b. Acute stent thrombosis: Angiogram may show the filling defects or a layered lobulated appearance, evidence of blood flow within the mass, and speckling or scintillation. Injection of the contrast to the distal coronary segment through a microcatheter and subsequent withdrawal of the catheter to the thrombus segment confirms the diagnosis. Best and more certain way of demonstration and extent of thrombus is OCT.

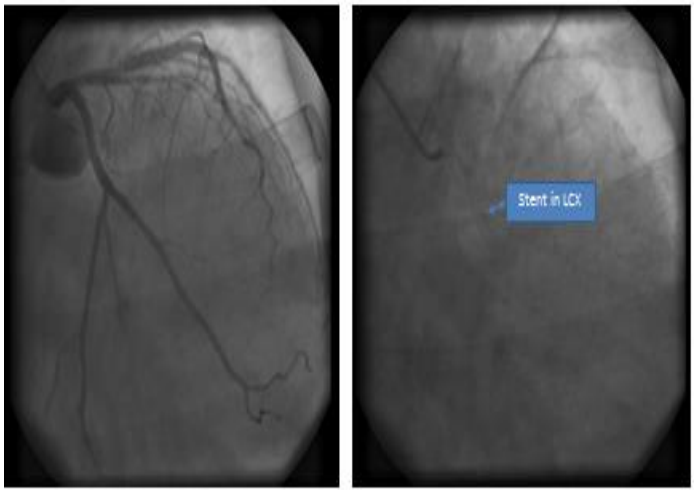
c. Plaque prolaps: Usually plaque prolapse depends on histopathology of plaque and produces more frequently slow flow than no flow. Necrotic core and fibrotic rich plaque are associated with plaque prolapse. According to Young Joon Hong et al TIMI 2 grade flow is more frequent (32 vs 16%) in plaque prolapse than non-plaque

prolapse lesions [9a]. On IVUS tissue extrusion through the stent struts will be demonstrated.

d. Multiple ruptured plaques: Angiographically it simulates thrombus but IVUS shows plaque ruptures separated by a >5-mm length of artery containing smooth lumen contours. Hong Y et al showed that IVUS-detected multiple PRs and plaque prolapse are associated with no-reflow after PCI for PR-containing culprit lesion in infarct-related arteries in AMI patients.

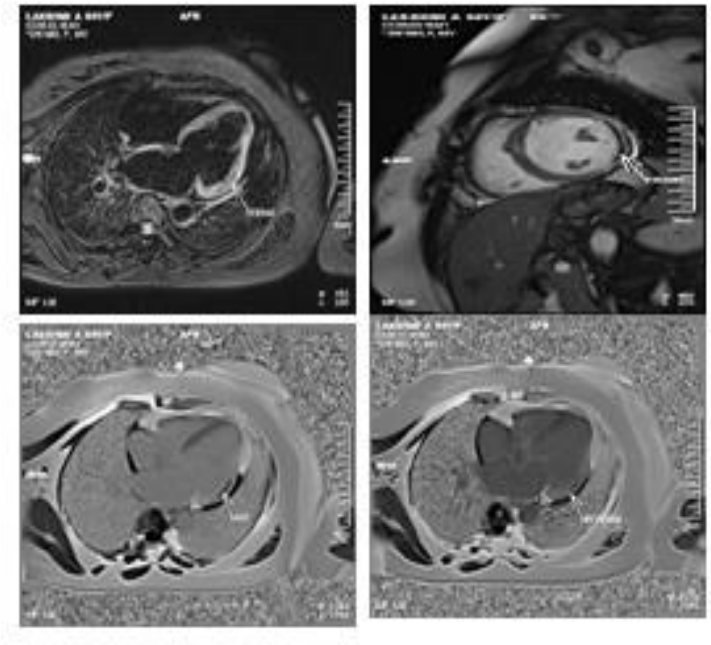
e. Arterial spasm: This is usually temporary phenomenon, most of the time relieved by intracoronary vasodilators. Here we report a case of 66 yr old female who undergone early PCI for infero-lateral MI. On day 4 of PCI patient developed VT. A check angiogram was done to rule out ischemia as the cause for VT. LCX, the culprit vessel in completely normal, but without a myocardial blush.

Fig 2: CAG showing patent PCI.



We did MRI for this patient. T2 weighted images shows myocardial oedema in the inferolateral wall. Basal & mid inferolateral wall has a transmural delayed enhancement. There was evidence of microvascular obstruction in the inferolateral wall and decrease perfusion in the in the inferolateral wall at rest. Final diagnosis given was Dilated LV/LA, RWMA in LCX territory, Moderate LV dysfunction, Myocardial edema in the LCX territory, Transmural necrosis in LCX territory (nonviable), Evidence of microvascular obstruction in LCX territory, Normal RV size & function, Moderate MR (eccentric jets) 20 to tethering of PML, No LV thrombus/ Trace posterior pericardial effusion.

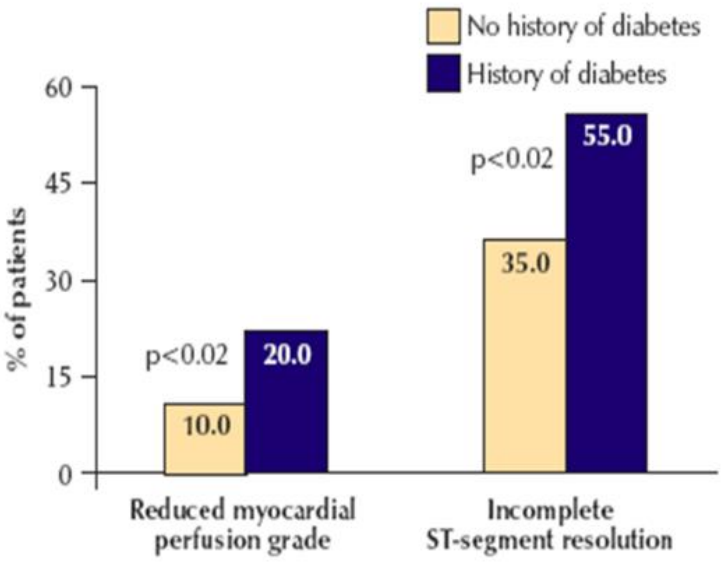
Fig 3: MRI showing microvascular obstruction in LCX territory.



PREDICTORS OF NO-REFLOW:

Clinical parameters: Advanced age ≥ 60 years, acute hyperglycemia, binge drinking and impaired renal function predispose to no-reflow (Fig 4). A longer time to reperfusion (duration between onset of chest pain and PCI ≥4 h) is associated with a higher prevalence and larger extent of no-reflow. Neutrophil count, mean platelet volume, platelet reactivity, TxA2, and ET-1 levels are indicators of severity of reperfusion injury and no-reflow. Higher prevalence of no-reflow is seen when the left anterior descending is the IRA artery suggesting that a larger extent of the ischemic area is an important predictor of no-reflow. Genetic susceptibility to microvascular injury and no-reflow are the 1976 T>C polymorphism of the adenosine 2A receptors gene and genetic mediated resistance to lysis.

Fig 4 : Effect of Presence of DM on No reflow. Courtesy of Timmer et al.



Wang risk score [16] based on 7 parameters:

1. Neutrophil count (≥ 8800/cm3 – 8 points);
2. Age (≥ 55 years – 5points);
3. Thrombus grade (≥ 2–5 points);
4. High blood sugar (≥_12 mmol/L – 4 points);
5. Prolonged chest pain before PCI (≥ 4 h – 2 points);
6. High Killip Class IV – 3 points and
7. Collateral circulation ≥1–2 points. The overall score for patients ranged from 0 to 29. Incidence of no-reflow may be predicted with an acceptable accuracy with score higher than 14. Platelet lymphocyte ratio (PLR) on admission was a strong predictor of no reflow in a recent study of Topark et al.

Angiographic predictors of no-reflow:

Yip et al. proposed a score to assess thrombus burden.

1. Angiographic thrombus with the greatest linear dimension more than 3 times the reference lumen diameter;
2. Cut off pattern (lesion morphology with an abrupt cut off without taper before the occlusion)
3. Presence of accumulated thrombus (≥ 5 mm of linear dimension) proximal to the occlusion
4. Presence of floating thrombus proximal to the occlusion
5. Persistent contrast medium distal to the obstruction
6. Reference lumen diameter of the infarct-related artery (IRA) ≥ 4.0 mm.

All of these features were independent predictors of no-reflow. Soeda et al showed that OCT derived lipid index <3500 and IVUS derived plaque burden >81.5% were the best morphological discriminators for no reflow.

According to Hong YJ et al in 112 patients, no-reflow was observed in 17 patients (15.2%). High-sensitivity C-reactive protein (hs-CRP) was significantly higher (6.2+/-6.0 mg/dl vs. 2.2+/-2.9 mg/dl, p=0.002) and baseline TIMI flow grade was significantly lower in no-reflow group (TIMI flow grade<3: 59% vs. 18%, p<0.001). Lesion site plaque plus media area was significantly greater (12.9+/-2.6 mm2 vs. 10.8+/-4.2 mm2, p=0.009), remodelling index was significantly higher (1.14+/-0.17 vs. 1.03+/-0.20, p=0.031), and the presence of IVUS-detected thrombus (88% vs. 56%, p=0.012), culprit lesion multiple PRs (71% vs. 37%, p=0.009), and plaque prolapse (65% vs. 34%, p=0.015) were significantly more common in no-reflow group. In the multivariate analysis, plaque prolapse (OR=33.02; 95% CI 3.38-322.75, p=0.003), hs-CRP (OR=1.03; 95% CI 1.01-1.05, p=0.013), and culprit lesion multiple PRs (OR=15.73; 95% CI 1.61-153.46, p=0.018) were independent predictors of post-PCI no-reflow in AMI patients with PR.

METHODS TO DIAGNOSE NO REFLOW:

1. CORONARY ANGIOGRAPHY: Angiogram plays a major role in the assessment of no-reflow.

a. TIMI flow refers to the intensity and extent of visualization of IRA and the speed of flow of dye. After successful PCI, the dye should flows instantaneously into the infarct related artery (IRA). TIMI flow is graded 0–3. TIMI grade 0-2 is associated with no-reflow but is of low sensitivity.

b. MBG refers to the intensity of radio-opacity of the myocardial tissue and the speed, with which the enhancement clears. The filling appears as a myocardial blush, a ground glass appearance of the myocardium on the coronary angiogram. MBG is also graded as 0–3 with higher scores indicating better perfusion. An MBG 0 to 1 is suggestive of no-reflow. It is seen in nearly 50% of patients with TIMI flow grade 3. Thus angiographic no-

reflow can be defined as a TIMI flow grade _3 or 3 with an MBG 0 to 1. In practice, TIMI flow grade and MBG are most commonly used.

c. TMPG is used to characterize the filling and clearance of the myocardial perfusion. The filling appears as myocardial blush (or ground glass appearance of the myocardium). TMPG defines the intensity of the blush and then focuses on the clearance of the contrast opacity from the myocardium. TMPG is graded 0–3.

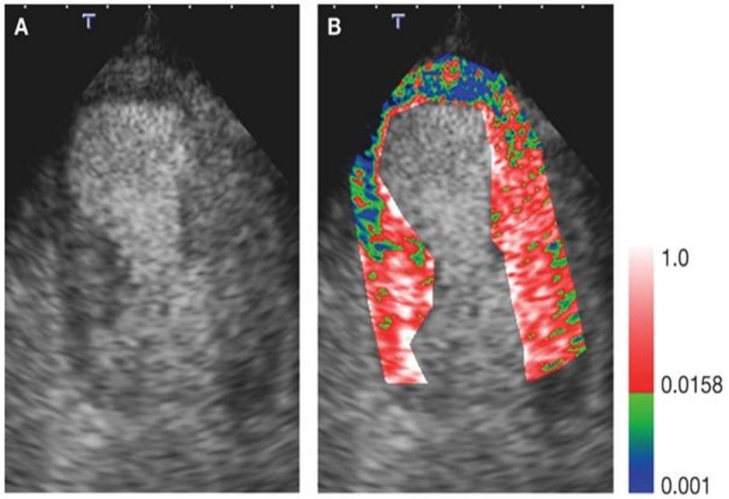
d. Corrected TIMI frame count (cTFC) is defined as the number of cine frames required for dye to reach standardized distal markers of the coronary tree. Lower cTFC after PPCI have been associated with more favorable prognosis. Thus TIMI flow grading and CTFC evaluate the Epicardial flow, while MBG and TMPG evaluate the microvascular flow.

4. **ELECTROCARDIOGRAPHY**: Study of ST resolution (STR) in serial ECGs is a bedside method of assessing myocardial perfusion following PCI. A rapid decrease of ST elevation is highly suggestive of reperfusion. STR at 60 min after PCI should exceed 70%. STR <70% at 60 min is a marker of no reflow. A rapid decrease of ST segment is highly specific (91%) and fairly sensitive (77%) parameter of myocardial reperfusion.

3. **MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY (MCE):**

MCE is one of the best methods to predict no reflow. Intra-myocardial contrast opacification is visualized and recorded after injecting intravenously an ultrasound contrast agent containing small micro bubbles. Absence of opacification detects no reflow/dysfunctional microvascular circulation. MCE is best recorded after 24–48 h after PPCI since MCE performed immediately after PPCI may underestimate the size and extent of no reflow (Fig 5).

Fig 5: Myocardial contrast echo demonstrating opacification on defects due to No reflow.



5. **CORONARY MAGNETIC RESONANCE IMAGING (CMRI)**: CMRI is the most sensitive and specific method to assess the extent of no reflows. The ideal time is 1 week after myocardial infarction although it can be done at 48–72 h after PCI. Necrotic or fibrotic myocardium enhances gadolinium distribution into the interstitium, which appears as a bright signal: hyperenhancement. The severe microvascular damage in the context of MVO prevents gadolinium from entering the injured myocardium which appears dark and hypo enhanced, surrounded by the hyper-enhanced infarcted myocardium This a non-invasive Gadolinium based technique performed in two steps (i) Early MVO is performed soon after injecting gadolinium and recorded during the first pass of the contrast agent and (ii) late or delayed contrast enhanced MVO is performed 10–20 min after the injection of contrast. The early phase represents no reflow, while the delayed phase depicts the extent of myocardial necrosis.

6. **CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY (CCTA):** Kinohira et al. showed in a small study on 26 patients that low-attenuation plaque in CCTA can predict PCI complications, mainly slow-flow. In the small study of Nakazawa et al. MDCT images of the culprit lesion were assessed in 51 patients who underwent PCI. In patients in whom no-reflow occurred after PCI

there was significantly lower culprit plaque density and signet-ring sign was found more frequently. Rafał Wolny et al in a case report also showed the similar complication in CCTA proved vulnerable plaque.

6. INTRAVASCULAR IMAGING: They have a role in investigating the potential predictors of No-Reflow phenomenon.

a. Intravascular ultrasound (IVUS) - Echo-attenuated plaque, containing more fibrofatty tissue and necrotic core strongly correlated with No-reflow (HORIZONS-AMI trial). other IVUS findings associated with higher risk of slow-flow are intraluminal thrombus, thin-capped fibro-atheroma morphology (TCFA) and large plaque burden.

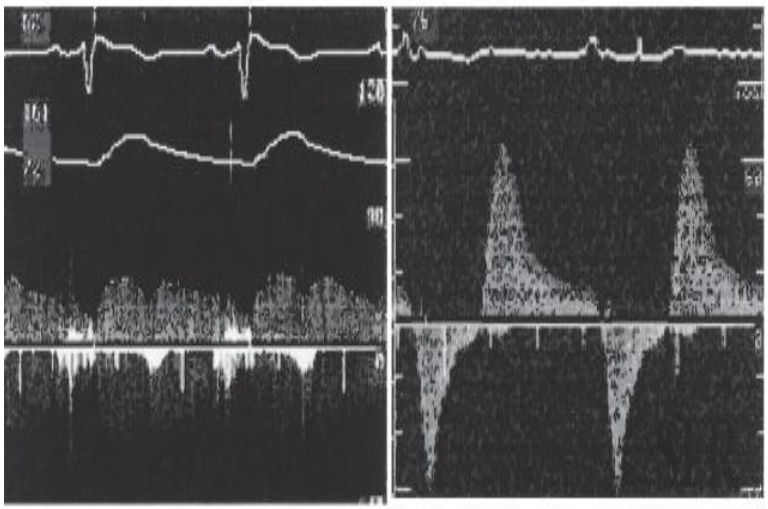
b. Optical Coherence Tomography (OCT) – The thin-cap fibro atheroma (TCFA), identified by OCT, have been more frequently associated with no-reflow.

7. INTRACORONARY DOPPLER : Intracoronary Doppler guidewire is used to assess micro vascular function by measuring coronary flow velocity (CFV) and coronary flow reserve (CFR) from which microcirculatory index can be calculated. The three characteristic components seen in no reflow are (a) systolic flow reversal, (b) reduced systolic antegrade flow and (c) forward diastolic flow with rapid deceleration slope.

Intracoronary pressure measurement: A double lumen catheter with a side hole is employed to measure intracoronary pressure gradient in IRA. Absence of pressure gradient indicates absence of obstruction in IRA. By using pressure/thermostat guidewire placed distally in IRA, index of micro-circulatory resistance (IMR) can be calculated which is related to acute microvascular damage in no-reflow.

In a case of microemboli to coronary resistance vessels, coronary flow velocity falls during the cardiac cycle. In a case of capillary obstruction, the myocardial blood volume decreases significantly, and thus coronary flow rapidly fulfills the unstressed volume of coronary microcirculation to cause rapid deceleration of diastolic flow velocity. Due to the obstruction of capillaries and venues, an increase in systolic myocardial stress causes the reverse flow, called systolic flow reversal (Fig 6).

Fig 6: Coronary blood flow velocity patterns in a case of microemboli and in a case of capillary obstruction.



Different investigative modalities and finding in a case of No reflow are represented in Table 1.

Table 1: Imaging modalities used to detect the No reflow

Pathogenic Mechanism of No-Flow	Predictor	Therapeutic implication
Distal embolization	Thrombus burden	Thrombus aspiration
Ischaemia	Ischaemia duration	Reduction of coronary time
	Ischaemia extent	Reduction of oxygen consumption
Reperfusion	Neutrophil count	Specific anti-neutrophil drug
	ET-1 levels	ET-1 r antagonist
	TXA2 levels	TXA2 r antagonist
	Mean platelet volume or reactivity	Antiplatelet drugs
Individual susceptibility	Diabetes	Correction of hyperglycemia
	Acute hyperglycemia	Correction of hyperglycemia
	Hypercholesterolemia	Statin therapy
	Lack of pre conditioning	Nicorandil

PHARMACOLOGICALAPPROACH:

Local vasodilator therapy and local antiplatelet therapy form the sheet anchor of treatment in the cath lab for no-reflow. The 2011 ACC PCI guidelines give a class IIa recommendation for administration of an intracoronary vasodilator (adenosine, calcium channel blocker, or nitroprusside) to treat PCI-related no-reflow that occurs during primary or elective PCI. Current guidelines recommend use of GpIIb/IIIa only as a bailout procedure in no-reflow patients.

1. Adenosine: It is a short acting endogenous nucleoside that increases microvascular flow owing to its vasodilator properties. It inhibits neutrophils adhesion and migration, exerts antiplatelet effects, and inhibits oxygen free radical formation. Adenosine has shown to be beneficial for both intravenous and intracoronary administration.

    a. The AMISTAD trial showed that I.V adenosine infused before initiation of thrombolytic therapy resulted in 33% relative reduction in infarct size (67% RR in patients with anterior MI).

    b. AMISTAD-II trial aimed to assess the benefit of adenosine routine use in 2118 patients presenting with STEMI - No significant difference in clinical outcome but a significant reduction in infarct size with I.V high dose of 70mcg/kg/min).
    c. REOPEN TRIAL proved that intracoronary adenosine 120 mg bolus followed by 2 mg in 33 ml saline slow infusion over 2 min, was more beneficial than nitroprusside in treating no-reflow. STR >70% at 90 min was found in 71% adenosine vs. 54% in nitroprusside vs. 51% in saline placebo group. 30 days MACE (heart failure and recurrent MI) was 10% in adenosine group vs. 14% in nitroprusside group and 20% in saline group.
    d. In Su et al. Analysis of 11 RCTs involving 1027 STEMI patients, there was no evidence that adenosine reduces short term or long term all cause mortality or recurrent myocardial infarction. However adenosine as treatment did reduce angiographic no-reflow.
    e. e.Gao et al. - PRISMA COMPLAINT meta-analysis of 15 RCTs with 1736 patients revealed better STR and improved TIMI flow grade after adenosine but no definite improvement in LVEF or mortality.
    f. f.REFLOW STEMI is an ongoing trial to compare the effects of adenosine, nitroprusside and placebo. Primary end point is the measurement of infarct size at the end of 48–72 h by CMRI. The results are awaited.

Yetgin et al howed that no-reflow and infarct size depended on dose of adenosine. The optimal IC bolus dose of adenosine was 100 mg in right coronary artery (RCA) and 200 mg in left coronary artery (LCA) to induce maximum hyperemia and with minimal side effects (Adjedj et al .

2. Calcium channel blockers: These drugs act by blocking L-type channels in the cell membrane of myocardium and cause endothelial dependent relaxation of micro-vessels. These also reduce oxygen demand by the myocardium and minimize the damage caused by oxygen free radicals.

    a. Verapamil- 100-250 mg intracoronary bolus followed by 100 mg/min (max 1000mg) in STEMI patients with no-reflow improved TIMI flow with reduction of corrected TIMI frame count (CTFC)
    b. In a randomized study of 150 STEMI patients, verapamil and adenosine were equally effective for prevention of no-reflow and improving TIMI frame count.
    c. In the RECOVER-AMI trial, both verapamil and diltiazem were equally effective in no-reflow. Diltiazem was administered 400 mg (diluted in NS) intracoronary followed by 90 mg BD orally.
    d. Wang et.al's [11] meta-analysis of 8 RCTs showed that both verapamil and diltiazem equally reduced no-reflow but no improvement in LVEF at 6months.
    e. Nicardepine 360-460 mg intracoronary improved TIMI flow grade and reduced CTFC in 72 patients with no-reflow. Prophylactic intra-graft Nicardepine followed immediately by direct stenting of SVGs without mechanical distal protection in a series of 68 elective

patients dramatically reduced the incidence of no-reflow.

f. All the three calcium channel blockers (Verapamil, Diltiazem and Nicardepine) are well tolerated and have produced good results in the treatment of no reflow.

3. Nitroprusside: It is a nitric oxide donor with vaso-dilatators, antiplatelet, and anti-inflammatory properties; the potential benefits of this agent should be weighed against the possible harm of systemic hypotension. Doses of 50-100 mcg have been studied in various trials but results proved inferior to CCBs and Adenosine.

4. Nicorandil: It is an ATP-sensitive potassium channel opener and a nitric oxide (NO) donor and is a potent vasodilator. It also modulates neutrophil activation and suppresses formation of oxygen free radicals. Chen et.al showed that it reduces reperfusion injury and improved LV function in patients with no reflow. Nicorandil at a dose of 2 mg intracoronary bolus and/or 8 mg/h infusion is beneficial in the prevention and treatment of no reflow and reducing major cardiac adverse events (MACE) at 5 years. Intracoronary nicorandil was more effective than IC verapamil in preventing no-reflow in 61 patients (63 lesions) undergoing rotational atherectomy.

5. Glycoprotein IIB/IIIA inhibitors: Abciximab, tirofiban and eptifibatide have been used for the prevention and treatment of no reflow. Though theoretically these drugs appear as attractive options for no-reflow, their efficacy has not been proven in randomized trials.

   a. In a study of 90 STEMI [18] patients, no reflow occurred less frequently in abciximab group (7%) compared with control group (17%). A recent randomized trial of intracoronary abciximab demonstrated a significantly smaller infarct size when assessed by CMRI. In the AIDA-STEMI , intracoronary or intravenous abciximab did not result in any difference in the combined end point of death, re-infarction or congestive heart failure.

   b. Tirofiban given as upstream intravenous infusion achieved better STR and MBG following PCI in ON TIME TRIAL.

   c. Eptifibatide improved reperfusion by TIMI flow grading in PROTECT TIMI trial.

The COCTAIL TRIAL to assess the safety and efficacy of IC cocktail injection combined with thrombus aspiration in STEMI patients treated with primary PCI are under study. The cocktail includes bivalirudin, tirofiban and tenectaplase. The trial is sponsored and conducted at Xijing Hospital, China. The trial is currently recruiting participants and the results are still awaited. COCTAIL II study has compared standard vs CLEARWAY infused abciximab in myocardial infarction.

6. Nitroglycerine: Intracoronary nitroglycerin failed to show any benefit in treatment of no-reflow. This is due to the fact that nitroglycerin is predominantly a venodilator and has little impact on arteriolar tone. Nitroglycerine needs to be metabolized by the vascular wall to derive its nitric oxide, which the micro vascular resistance arterioles are unable to.

Mechanical therapies: There is no data to treat no reflow with any of the mechanical therapies.

PREVENTION OF NO-REFLOW:

The aim should be to counteract the various mechanisms of no-reflow. Prevention of No-reflow.

a. BEFORE THE ONSET OF INFARCTION PAIN

b. **BEFORE REPERFUSION:** by decreasing the ischemic time with minimum door to balloon time no flow can be decreased. By reducing the severity of ischemia and improving myocardial perfusion with drugs that reduce myocardial oxygen consumption can also be tried. The beneficial effects of Carvedilol, Fosinopril, and Valsartan on coronary no-reflow have indeed been recently demonstrated.

c. **IN THE CATH LAB:** Patients at high risk of No-Reflow on the basis of the presence of reperfusion-related injury can be treated with drugs like Glycoprotein IIb/IIIa antagonists, Adenosine, Nicorandil aimed at counteracting endothelial platelet and neutrophil activation. Selective ET-1 or TxA2 antagonism might represent novel therapeutic approaches (25).

Abciximab: Among glycoprotein IIb/IIIa antagonists, abciximab has been found to improve myocardial perfusion when started during PPCI and infused for 12 h thereafter, as assessed by a higher rate of STR 50% at 60 min after PCI (73% vs.57%, $p < 0.05$). Intracoronary abciximab has been proven to be superior to intravenous abciximab in patients treated by primary PPCI approaches (26, 27). Ellis and colleagues analysed 102 vein graft stenosis from the EPIC and EPILOG trials and failed to demonstrate any clinical benefit with the active drug treatment with an 18•6% incidence of death, myocardial infarction and urgent revascularization at 30 days compared to 16•3% for placebo. They hypothesized that distal embolization of athermomatous plaque from the vein graft wall is less sensitive to the antiplatelet effect of abciximab. But this is not true in the case saphenous vein graft PCI.

A. PREVENTION OF DISTAL EMBOLISM:

1. Direct stenting- Placement of a stent without prior balloon predilation has been advocated as a means to reduce no-reflow. Direct stent implantation, by entrapping athero-thrombotic debris, reduces the risk of distal embolization, but unfortunately only a few subsets of patients are suitable for direct stenting. In elective cases direct stenting has shown no benefit, where as in primary PCI, a small randomized trial showed decrease rates of slow flow or no-reflow as compared to placebo.

2. Aspiration Thrombectomy: Thrombectomy devices have initially shown promising results, especially in the subset of patients with large thrombus burden. More than 20 randomized trials have investigated the benefits of manual thrombectomy over conventional PCI. Three landmarks that have influenced the present role of this strategy are the TAPAS, TASTE and TOTAL studies.

    a. TAPAS trial - Manual thrombus aspiration group fare better in angiographic outcomes and reduction in cardiac death.
    b. TASTE trial - Failed to demonstrate any difference in mortality, recurrent myocardial infarction and stent thrombosis at 30 days in the two groups.
    c. TOTAL trial - No statistical difference in the primary outcome of recurrent MI, heart failure stent thrombosis or mortality between the two groups. There was an increase in the incidence of stroke at 48 h and 30 days in the thrombus aspiration.

Base on the recent evidence, ACC/AHA/SCAI have modified their earlier recommendation. Manual aspiration thrombectomy is reasonable for patients undergoing primary PCI is now class IIb recommendation (level of evidence C-LD). There is no role for Routine aspiration thrombectomy before primary PCI –Class III (level of evidence- A).

3. Rheolytic thrombectomy: Rheolytic thrombectomy (ANGIOJET/X-SIZER) has shown no benefit in primary PCI.

4. **Distal Filters**: Distal protection with filters has not shown to have any benefit in preventing no reflow in the setting of ST elevation MI whereas it has been shown to be beneficial in preventing no reflow in elective saphenous vein PCI.

    a. SAFER trial tested the Percusurge in patients undergoing stent placement in saphenous vein grafts. In comparison to patients who were randomized to no device, Percusurge reduced MACE by 42% at 1 month (9.6% vs. 16.5%), with most of the reduction being in post-procedure MI (8.6% vs. 14.7%) and no-reflow phenomenon (3%vs.9%).
    b. Filter wire Ex device was assessed in 230 saphenous vein graft patients and its use was associated with reduced MACE (11.3%) and TIMI O/1 flow rate and reduced distal micro-embolization. Filter wire EX reduced distal embolization and was associated with improved TIMI 3 myocardial blush and ST segment resolution post PCI in 53 patients treated for acute MI.

5. Deferred stenting: Deferred stenting (6-12 hrs) in selected high risk patients may reduce the incidence of no reflow during which the patient receives supportive therapy. In a recent randomized study of STEMI patients, deferred stenting reduced the incidence of no

reflow as judged by TIMI flow grade and cardiac MRI in high risk patients.

6. **M-guard stent:** M guard was a technology, designed to prevent distal embolization and no reflow following PCI. It consists of a bare metal stent with cobalt chromium strut and polyethylene theraphthalate mesh (micronet) covering anchored to the external surface of the strut. Three non-randomized and two randomized trials (Piscione Trial, MAGICAL trial, REWARD and MASTER-I and II) have shown it to be beneficial in STEMI patients with large thrombus burden, restoring myocardial reperfusion and reducing no-reflow. However, M-guard stent has exhibited three drawbacks: (i) high rates of instant restenosis(ii) difficulty in negotiation (4.1%) and (iii) stent dislodgement (0.9%). Hence, the stent has been recalled and the MASTER II Trial cancelled. The manufacturers are now trying to develop a new drug eluting version of M-guard stent.

B.REDUCTION OF ISCHEMIA: Measures to reduce time interval from onset of chest pain to PPCI are probably the best measure to improve myocardial salvage and reduce risk of no reflow. The use of the intra-aortic balloon pump is probably the last measure. It may be beneficial when hemodynamic instability is present by improving flow but only after the epi-cardial occlusion is successfully relieved.

C.PREVENTION OF REPERFUSION INJURY:

a. **Hyperoxemic reperfusion**: Intracoronary hyperoxemic reperfusion has been advocated for prevention of reperfusion injury. Hyperoxemic reperfusion improved microvascular blood flow and decreased infarct size in a canine model of ischemia reperfusion. In the AMIHOT-II (Acute Myocardial Infarction With Hyperoxemic Therapy II) trial this approach reduced infarct size but was not associated with improved tissue perfusion as assessed by ST-segment resolution. Because the clinical benefit of hyperoxemic reperfusion has yet to be shown, the routine use of this invasive strategy in the current era of routine thrombectomy cannot be recommended at present.
b. **Myocardial post-conditioning**: by use of intermittent low-pressure balloon inflations in the infarct-related artery reduced infarct size and improved microvascular perfusion as assessed by myocardial blush, and long-term functional recovery. Pharmacological post-conditioning by intravenous administration of cyclosporine, a direct MPTP blocker, versus placebo , at the time of primary PCI decreased infarct size. Remote post-conditioning by intermittent inflations of a blood pressure cuff on the upper limb before reperfusion improved ST-segment resolution following primary PCI, an effect that was enhanced by administration of morphine. These preliminary studies suggest a beneficial role for conditioning strategies in the setting of primary infarct PCI. However, their efficacy in patients undergoing thrombectomy and receiving glycoprotein IIb/IIIa inhibitors remains to be defined.
c. It might be reasonable for patients with multiple vulnerable plaques (detected by any imaging modality) to be scheduled for coronary artery bypass grafting (CABG) rather than PCI. If PCI is chosen, avoiding balloon pre-dilation and performing direct stenting should be encouraged. The use of distal protection devices should be considered. Its significant impact on reduction of major adverse cardiac events after PCI in saphenous vein grafts was shown in the SAFER trial ; however, there was no such relationship in the setting of primary PCI of native coronary arteries in the EMERALD trial . On the other hand, when only patients with angio-scopically-detected ruptured plaque were analysed, distal protection reduced microcirculation damage and left ventricular dysfunction. Another concern is the potential use of additional antiplatelet drugs. Pre-procedural glycoprotein IIb/IIIa receptor inhibitor administration may be beneficial in some high-risk patients undergoing saphenous graft angioplasty.

In conclusion, prevention of No reflow is better than the treatment. So, we have to indentify the conditions which are likely to develop No reflow before PCI itself and target them to have good long term results.

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