Editorial

Myocardial preservation during primary percutaneous intervention: It's time to rethink?

Primary Percutaneous Coronary Intervention (PPCI) plays the most important role in the management of ST Segment elevation myocardial infarction (STEMI). It is more effective than thrombolytic therapy (TT) for the treatment of STEMI. Timely reperfusion either by TT or PPCI is the key factor for limiting infarct size, preserving left ventricular ejection fraction (LVEF) and decreasing mortality. To achieve maximum myocardial salvage it is important to restore the full patency of large epicardial coronary arteries, but it is also necessary to maintain blood flow in microcirculation of the reperfused bed. Myocardial damage during STEMI is primarily due to ischemia, but paradoxically, reperfusion also play an important role. A clear understanding of ischemic and reperfusion injury may help to improve myocardial protection during PPCI. The ischemic injury can be minimized by early revascularization, however limiting reperfusion injury require more insight into its pathophysiology. Reperfusion injury can lead to reperfusion arrhythmias, myocardial stunning, microvascular obstruction (MVO) leading to no-flow and sometime lethal cellular injury. Usually every effort was made by interventionist to maintain the epicardial patency, they often forget that in spite of fully open epicardial artery, effective reperfusion may not have reached to the myocardial tissue and restoration of blood flow to ischemic tissue is incomplete. This often mitigate the full benefit of PPCI. Treatments for MVO that were shown to be effective in pre-clinical research have often failed to translate into effective clinical therapies. Current review will emphasize the importance of myocardial preservation during PPCI.

1. No-flow

During PPCI successful opening of epicardial infarction related artery, but incomplete restoration of blood flow to ischemic myocardial tissue is called no-flow. This is because of severe MVO. No-flow because of procedure failure (i.e. incomplete lesion dilatation, coronary spasm, dissection or in situ thrombosis) should be carefully excluded from true no-flow. No-flow phenomenon is dynamic by nature and may spontaneously resolve itself over time. The phenomenon of no-flow was first confirmed in animal models of brain ischaemia, then in canine ischemic heart. It was first demonstrated in human heart with use of myocardial contrast echocardiography (MCE) and changes of myocardial blush grade (MBG).

The reported incidence of no-flow during PPCI is quite variable. In some series it is between 1 and 3% cases. However higher incidence has been reported 5–25 %. This depend upon the definition which was used in various studies. Some define TIMI grade ≤2 and some included patients with TIMI grade ≤ 1 as no-flow. When MVO was assessed within 7 days after reperfusion by PPCI using cardiac magnetic resonance imaging (CMR) microvascular obstruction was present in up to 56.9 % of patients. Early detection, preventive measures and treatment of no-flow may alter the final outcome of PPCI.

2. Mechanism of No-flow

No flow during PPCI is caused by a combination of multiple mechanisms. The four important mechanism is describes below.

1 Microembolization:

Microembolization from erosion or rupture of atherosclerotic plaque occurs in approximately 25 % of all PCIs. Its incidence ranges from 0 % to 70 %, in part depending on the method of its assessment and it seems to be predominating cause of no-flow. It occurs frequently with preexisting kidney disease, acute coronary syndrome, complex and lengthy lesions, increased number and duration of balloon inflations, use of rotablation and use of stent rather than POBA. Plateau erosion is more prone to distal embolization when compared with plaque rupture. A study done with doppler guide wire had shown that average PCI generates approximately 25 emboli particles which are not sufficient to cause MVO in human. When the number increases to > 25–200 or the size of micro-emboli is > 200 μm, it can lead to severe MVO and no-flow. Although this is more common in venous graft, but can occur in native coronary arteries. Microparticles content of embolized material are also important. Embolized material are found to be biologically active and may aggravate reperfusion injury beyond its mechanical obstructive effect on the microcirculation. During PPCI generation of micro emboli is strongly associated with thrombus burden, increased myocardial damage, MVO and no-flow.

2 Ischemia mediated injury:
Complete absence of blood supply to the myocardium leads to depletion of residual oxygen of the myocardium within seconds. Anaerobic metabolism is activated which is to produce sufficient ATP for basal cell activity for a short time. As the duration of ischemia increase there is accumulation of many inflammatory and bioactive products which further slows down ATP production. Further ion pumps in the sarcosome and sarcoplasmic reticulum cease to function, leading to calcium overload into the cell which further damage mitochondria and cell in the ischemic zone. Once ATP is completely depleted, cardiomyocytes undergo ischemic contracture and death through a process of oncosis and necrosis. However, even before this step, programmed cell death pathways may be activated which include apoptosis, necroptosis or pyroptosis.  

Prolonged ischemia is known to cause specific changes in endothelium, ischemia followed by reperfusion lead to endothelial cell and microvascular damage. Endothelial cells showed large intraluminal protrusions, decreased pinocytic vesicles, large endothelial gaps with extra vascular erythrocytes and fibrin deposit, which leads to endothelial and capillary dysfunction leading to MVO. Myocardial cell swelling with marked interstitial edema is one of the early morphologic changes which compresses capillaries and small arterioles leading to MVO. The most important clinical predictor of ischemia related injury is ischemia duration and ischemic extent. 

3 Reperfusion injury: 

After prolong ischemia when reperfusion starts, ischemia mediated injury is potentiated by reperfusion injury which may lead to further myocardial necrosis. Calcium paradox, i.e. the readmission of calcium after a short period of calcium-free or low-calcium (ischemic) plays important role in immediate damage to the myocyte. Calcium overload lead to damage to the sarcosome and the sarcoplasmic reticulum, mitochondria and subsequently myocytes. Platelets leukocyte aggregates in microvasculature produces large amount of vasoconstrictors, oxidants, proteolytic enzymes and pro inflammatory mediators. Abrupt pH restoration (pH Paradox) during reperfusion and production of radical oxygen species (Oxygen Paradox and Oxidative Stress) lead to opening of mitochondrial membrane permeability transition pores, calcium overload of cells, mitochondrial swelling, and cell membrane disruption results in further coronary vascular dysfunction and MVO. Release and accumulation of many bioactive factors from endothelium and coronary plaque e.g. neutrophils, proteolytic enzymes, prostacyclin, endothelin-1, tissue factors, and microparticles may further increase functional impairment of coronary microvascular. Reperfusion after ischemia often lead to intramyocardial haemorrhage. Endothelial damage, activation of inflammation and coagulation pathway further aggravate the haemorrhage. 

4 Susceptibility of coronary microcirculation to injury: 

Traditional and non-traditional risk factors play a role in epicardial and microvascular endothelial dysfunction. Aging, hypertension, diabetes, dyslipidaemia, insulin resistance, and chronic inflammatory diseases has shown to impaired coronary flow reserve. Diabetes and hypercholesterolemia may precipitate no-flow. Individual genetic susceptibility may also plays role in the modulation of no-flow. Hyperglycemia may contribute to no-flow irrespective of previous glycemic control and lead to larger infarct size and worse functional recovery in STEMI patients with successful reperfusion. Pre-infarction angina is associated with reduced no-flow leading to preservation of the microvasculature. 

3. Predictors of no flow 

Longer time to reperfusion and thrombus burden at a lesion site is a major predictor for distal embolization and no-flow. Another risk factor for no-flow is Saphenous vein graft intervention. A positive relationship between acute increase myocardial wall thickness and occurrence of no-flow was proposed. Several studies have demonstrated that platelets play an important role in no-flow. Platelet reactivity on admission, mean platelet volume on admission and plasma levels of thromboxane-A2 might be associated with the no-flow. Depletion of antioxidants, Endothelin-1 levels on admission, and increase neutrophil count may be associated with the no-flow phenomenon and MVO in STEMI. SYN-TAX score can identify patients at risk for developing no-flow. Soluble suppression of tumorigenicity (sST2) was found to be one of the independent predictors of the no-flow phenomenon in STEMI patients undergoing PPCI. 

4. Diagnosis of no flow 

Galiuto proposed a pathological classification of no-flow, based upon pathophysiology and therapeutic options of no-flow. Structural no-flow which is largely irreversible and caused by prolonged ischemia leading to damage and loss of capillary integrity with endothelial swelling and edema thus causing severe MVO. The extent of lesion depends upon the severity and duration of ischemia. Functional no-flow which is largely reversible and in which patency of microvascularity is compromised due to spasm, micro embolization and reperfusion injury etc. The patient with no-flow has persistent chest pain, tachycardia, and hypotension. Although MVO is reversible in about 50% of patients, persistent no-flow and MVO should be considered with persistent chest pain post PCI. Surface ECG gives clue to diagnosis. Lack of ST Segment resolution (complete resolution defined as a 50–70 % decrease of sum of ST segment) is considered as an established marker of no-flow. Assessment of no-flow in catheterization laboratory is a common practice. During PCI no flow phenomenon is define by Thrombolysis In Myocardial Infarction (TIMI) flow grade. TIMI flow grade 0 to 2, is associated with no-flow. The TIMI Flow is widely used for acute success and short or long term clinical outcomes after PPCI and thrombolysis. However newer technique has shown than epicardial TIMI flow grade 3 may be an incomplete measure of reperfusion success and still MVO and poor outcome is seen. Corrected TIMI frame Count (CTFC) more objectively assess coronary circulation. However has not reached wide acceptance in assessing MVO. An alternative method to assess micro vascular perfusion is the TIMI myocardial perfusion grade (TIMI-MPG), graded on a scale of 0–3. TIMI myocardial perfusion grades, flow grades, frame count all has shown to predict outcome in PPCI. Myocardial Blush Grade (MBG) measures the relative “blush” or intensity of the contrast reaching in the myocardial tissue and the rapidity by which it clears. Intensity of the myocardial blush and faster clearance is suggestive of better microvascular perfusion. Its scale is described as 0,1,2, 3 with higher scores means better perfusion. MBG is mainly influenced by microvascular patency and is less dependent on the amount of muscle necrosis. After PPCI significant number of patients with TIMI 3 flow has MBG of R. Yadav, S. Yadav, K.C. Goswami et al. Indian Heart Journal 73 (2021) 395–403
0—1, which is suggestive of no-flow. MBG can better describe the effectiveness of myocardial reperfusion and is an independent predictor of long-term mortality, independent of Killip class, TIMI grade flow, LVEF and other clinical variables.65,66 Patients treated by either PPCI68 or thrombolysis57 integration of MBG and STR, not only MBG, was found to be of greater prognostic utility. A very good outcomes in patients with an MBG 2 to 3 and STR >70 %, very poor outcomes in patients with MBG 0 to 1 and STR<70 %.

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flow.69 No-flow at MCE was found to be the better predictor of adverse LV remodeling than MBG, TIMI grade flow and STR.70

CMR at present it is a gold standard for assessment and diagnosis of no-flow. It can accurately characterize the presence and spatial extent of no-flow regions. It is useful in discriminating areas of necrosis with and without no-flow. It can also predict left ventricular remodeling and patient outcome in STEMI.77,78

5. Consequences of No-flow

Clinically it is important because no-flow predicts poor outcomes after PPCI.131,14,77,78 It is associated with nonresolving chest pain and persistent ST-T changes. Major consequences of no-flow are larger infarct size, poor LVEF, LV dilatation, ventricular arrhythmia75–77 and adverse LV remodeling.78 No-flow phenomena after PPCI predicts an increased risk of death and reinfarction,14,75,76 even after 5 years.77 No-flow is a progressive phenomenon and its presentation may be delayed.

6. Prevention and treatment strategies

Well controlled blood sugar levels improve long term prognosis in STEMI.79 Chronic hyperglycemia plays a key role in coronary vascular endothelium dysfunction.80 The no-flow phenomenon was found more in patients with hyperglycemia leading to larger infarct size and worse functional recovery.77 So control diabetes was found more in patients with hyperglycemia leading to larger spatial extent of no-

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interventions in vein grafts with minimal myocardial depressant effect.

Nitroprusside and nitroglycerin are nitric oxide donors that vasodilate conductance vessels >200 μm. Microvessels are unable to metabolize nitroglycerin to nitric oxide; in contrast, nitroprusside does not require metabolism. Nitroprusside has been extensively studied and found to be useful for management of no-flow phenomenon and also as an adjunct therapy during PCI for prevention of no-flow. Nitroprusside has been also studied and in small trials and case reports shown benefit in preventing no-flow and coronary perfusion during PCI. But not been studied in large randomized trials. It is less effective that verapamil and diltiazem.

Intravenous nicorandil as adjuvant therapy during PCI improved myocardial perfusion, prevent no-flow and cardiac function and also long term clinical outcome. However, a randomized trial found no reduction in infarct size with nicorandil versus placebo but intravenous atrial natriuretic peptide had shown to lower infarct size, fewer reperfusion injuries, and better clinical outcomes than controls. Pharmacological post-conditioning by intravenous administration of cyclosporine, a direct MPTP blocker has also been studied for preventing reperfusion injury and reduce myocardial infarct size but was not found to be better than those with placebo. Niu X et al performed a network meta-analysis to assess the effect of 7 intracoronary agents (adenosine, anisodamine, diltiazem, nicorandil, nitroprusside, urapidil, and verapamil) on the no-flow phenomenon in patients with STEMI undergoing PCI. They found that only addition of anisodamine was associated with improved post-procedural TIMI flow grade, more occurrences of STR, and improvement of LVEF. The cardioprotective effect of anisodamine conferred a MACE-free survival benefit. Additionally, nitroprusside was shown to improve coronary flow and clinical outcomes. Compared with standard care, adenosine, nicorandil, and verapamil improved coronary flow but not shown to improve cardiac function and clinical outcomes. Intracoronary administration of anisodamine appears to improve myocardial reperfusion, cardiac function, and clinical outcomes in patients with STEMI undergoing PCI.

Platelet inhibition with glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) may reduce downstream embolization and generation of thrombus thus reduce release of vasoactive and chemotactic mediators from platelets. Role of GPIIb/IIIa platelet receptor antagonists have some promise but are not currently routinely used in clinical practice for the prevention or treatment of no-reflow.

However glycoprotein IIb/IIIa receptor antagonist in combination with other therapy during PCI has shown better outcome and decrease the incidence of no-flow. By contrast, glycoprotein IIb/IIIa receptor antagonists have failed to mitigate the impact of distal embolization in SVG intervention. Intracoronary thrombolysis in a small randomized trial, immediately following PCI improved microvascular integrity and tissue perfusion. The role of oral anticoagulant has also been studied in animal model which failed to show a benefit of intravenous dabigatran treatment for no-flow. Administration of Glucagon-like peptide (GLP)-1 agonist liraglutide 30 min before PCI is found to reduce no-flow. At present administration of an intracoronary vaso dilator (adenosine, calcium channel blockers, nitroprusside not nitroglycerin, nicorandil or epinephrine) is reasonable to treat PCI related no-flow or MVO but not as adjuvant therapy for the prevention of no-flow.

Use of intermittent low-pressure balloon inflations in the infarct-related artery after direct stenting (Myocardial post-conditioning) decreases infarct size and improves microvascular perfusion. Remote ischemic preconditioning by intermittent inflations of a blood pressure cuff on the upper limb before reperfusion improved ST-segment resolution, myocardial edema levels, myocardial salvage index and incidence of major adverse cardiac and cerebrovascular events but non-significant beneficial effect on infarct size, TIMI flow grade III or LVEF following PCI. Pharmacological pre- and postconditioning may be achieved by administration of exenatide, an antiapoptotic glucagonlike peptide-1 analogue, which also activates prosurvival kinases and found beneficial in reducing infarct size. Aqueous oxygen hyperoxemic intracoronary perfusion was found to improve microvascular blood flow and decrease infarct size in canine model. Intracoronary delivery of supersaturated oxygen in patients undergoing PCI results in a significant reduction in infarct size with non-inferior rates of major adverse cardiovascular events at 30 days. Induced hypothermia may have cardioprotective effect in STEMI and has shown to decrease no-flow.

Glucose-insulin-potassium has shown mixed results. It was not found to be beneficial in STEMI however it reduce infarct size and serious arrhythmias when administered in the ambulance to patients with STEMI that will receive PCI.

7. Conclusion

Despite improvements in treatment strategies and awareness STEMI remains an important cause of morbidity and mortality and its incidence is rising. Early reperfusion, is the most effective strategy and only proven strategy for reducing infarct size and improving clinical outcome. The process of myocardial reperfusion itself, however, can lead to severe injury to the myocardium, thereby reducing the beneficial effects of reperfusion. Despite the convincing experimental evidence of many strategies to minimize the reperfusion injury, it has not translated in improving clinical outcome. Reduction of reperfusion injury remains a neglected therapeutic target by interventionist, even though it is highly needed. Today, the only realistic strategy to reduce reperfusion injury in STEMI patients remains early reperfusion. No-flow and MVO following PCI is a multifactorial phenomenon with variable etiologies in different clinical settings and is quite frequent during PCI. This is associated with poor both acute and long term outcome. Prevention of no-flow and MVO following PCI is beneficial in reducing cardiac injury and improving clinical outcome. Prevention and treatment are of prime importance because maximum gain of revascularization occurs with normal epicardial coronary flow with no microvascular damage. Several preventive measures in animal model and small studies have effectively decrease the degree of MVO and improve clinical outcome in the setting of PCI. Unfortunately, there is limited data comparing the efficacy of various strategies. There is also no large randomized trials to guide selection of various therapies for prevention of no-flow in clinical setting. Key strategies for prevention of no-flow is early revascularization, short door-to-balloon times, keep stent length minimal, deployment of stent at nominal pressures, direct stenting, high dose statin and proper antiplatelet and anticoagulation therapy. Manual thrombus aspiration can be used when there is angiographic evidence of large thrombus burden. Distal/proximal protection devices have not been proved beneficial.

Treatment of no-reflow have not been studied in large randomized trials so there are no definite recommendation. However in absence of alternative proven therapy administration of vasodilators should be considered mainly adenosine, verapamil, nicorandil, nitroprusside and epinephrine. Distal intracoronary infusion via infusion catheter is better than over guiding catheter injection because it causes less systemic hemodynamic effects. Although other may be beneficial in individual patients, we do not currently recommend the routine use of other pharmacological and mechanical interventions.
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