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Review Article

No reflow phenomenon in percutaneous coronary interventions in ST-segment elevation myocardial infarction

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ABSTRACT

Percutaneous coronary intervention (PCI) is effective in opening the infarct related artery and restoring thrombolysis in myocardial infarction flow 3 (TIMI-flow 3) in large majority of ST-elevation myocardial infarction (STEMI). However there remain a small but significant proportion of patients, who continue to manifest diminished myocardial reperfusion despite successful opening of the obstructed epicardial artery. This phenomenon is called no-reflow. Clinically it manifests with recurrence of chest pain and dyspnea and may progress to cardiogenic shock, cardiac arrest, serious arrhythmias and acute heart failure. No reflow is regarded as independent predictor of death or recurrent myocardial infarction. No reflow is a multi-factorial phenomenon. However micro embolization of atherothrombotic debris during PCI remains the principal mechanism responsible for microvascular obstruction. This review summarizes the pathogenesis, diagnostic methods and the results of various recent randomized trials and studies on the prevention and management of no-reflow.

1. Introduction

Primary percutaneous coronary intervention (PPCI) is the gold standard of treatment of ST segment elevation myocardial infarction (STEMI).[1] PPCI restores thrombolysis in myocardial infarction flow 3 (TIMI 3) in over 90% of patients. However there remain a small proportion of patients, who continue to exhibit overt impairment of myocardial reperfusion despite successful opening of infarct related epicardial artery (IRA). This phenomenon is called no-reflow, which is largely because of severe microvascular obstruction (MVO). Sudden loss of epicardial flow following ballooning or stenting may also occur in incomplete lesion dilation, epicardial vascular spasm, epicardial dissection or in situ thrombosis. These procedural failures are totally different clinical events and need careful exclusion. No reflow in human has a negative effect on the clinical outcome negating the potential benefit of PPCI in STEMI.[2–4] Indeed no reflow is regarded as an independent predictor of death and myocardial infarction.[5–7]

No reflow may set in soon after completion of PCI (within 1–2 h). Recognition of no reflow is essential if it occurs in the catheterization laboratory (cath lab).[8] Ideally the patient should not leave the cath lab unless no reflow has been satisfactorily managed. Clinically no reflow may present with the recurrence of chest pain, cardiogenic shock with hypotension, malignant arrhythmias or acute dyspnea due to pulmonary edema secondary to heart failure. No reflow is a progressive phenomenon and its presentation may be delayed. Angiographic no reflow after PCI is associated with reduced myocardial salvage, larger infarct size and increased long term 5 year mortality.[9] Early detection, preventive measures and treatment of no reflow may alter the final outcome of PCI.

2. Classification

Galiuto[10] proposed a pathological classification of no reflow, which is defined as inability to reperfuse a region of myocardium under prolonged ischemia despite re-opening of infarct related

Abbreviations: CFR, coronary flow reserve; CFV, coronary flow velocity; CMRI, cardiac magnetic resonance imaging; CTFC, corrected TIMI frame count; ICCU, intensive coronary care unit; IMH, intra myocardial/mural hemorrhage; IPC, ischemic pre-conditioning; IRA, infarct related artery; IS, infarct size; IVUS, intravascular ultrasound; LV, left ventricle; MACE, major adverse cardiovascular event; MBG, myocardial blush grade; MCE, myocardial contrast echocardiography; MPV, mean platelet volume; MVO, microvascular obstruction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PET, positron emission tomography; PLR, platelet lymphocyte ratio; PPCI, primary percutaneous coronary intervention; ROC, receiver operating characteristics/curve; STEMI, ST-elevation myocardial infarction; STR, ST-segment resolution; TIMI, thrombolysis in myocardial infarction; TMPG, TIMI myocardial perfusion grade.

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artery (IRA). The classification is based upon pathophysiology and therapeutic options of no reflow.

2.1. Structural no reflow

Microvessels within the necrotic myocardium region under prolonged ischemia exhibit (a) damage and loss of capillary integrity with endothelial swelling and odema and (b) microvascular obstruction. Structural no reflow is largely irreversible. The extent of lesion depends upon the severity and duration of ischemia.

2.2. Functional no reflow

Patency of microvasculature is compromised due to spasm, microthrombotic embolization and reperfusion injury, with accumulation of neutrophils and platelets with activation of neurohumoral system. Functional no reflow may be reversible to a varying degree.

3. Incidence

No reflow is an under-reported complication. A low incidence of 1–3% has been recorded in large registries based on TIMI flow grade, myocardial blush grade and ST resolution.[11] Modern more sensitive methods of assessing no reflow and microcirculatory dysfunction include myocardial contrast echocardiography (MCE) and cardiac magnetic resonance imaging (CMRI), which have recorded a higher incidence (10–30%). Fortunately no reflow may resolve in due course of time in as many as 50% patients.[10] However, the immediate prognosis of no reflow often remains uncertain and grave especially in cath lab.

4. Pathogenesis

The goal of reperfusion therapy by percutaneous coronary intervention in acute myocardial infarction is to restore optimal blood flow in the infarct related artery (IRA) in order to ensure adequate blood supply to the ischemic but yet viable myocardium and to reduce infarct size and mortality. In no reflow, myocardial reperfusion is not achieved inspite of patent IRA. No reflow is a multifactorial phenomenon and five mechanisms have been recognized (Niccoli et al.)[12]: (i) pre-existing microvascular dysfunction, (ii) distal micro-thrombo-embolization, (iii) ischemic injury, (iv) reperfusion injury and (v) individual susceptibility. All these factors are inter-related in a complex manner (Fig. 1).

4.1. Pre-existing microvascular dysfunction

MVO may be either structural or functional or both. MVO impairs coronary flow reserve (CFR) and increases the vulnerability of affected myocardium to the PCI induced injury. Thus the benefits of re-opening of the obstructed epicardial artery are greatly compromised by pre-existing microvascular dysfunction. Pre-existing MVO may be related to advancing age, abnormal insulin resistance and lipid metabolism (diabetes and hyperlipidemia), chronic inflammatory diseases and individual susceptibility.[12] Endothelial dysfunction is regarded as an independent predictor of adverse cardiac events.[13–15]

4.2. Distal micro-thrombo-embolization

Micro-embolism during PCI is a predominant cause of no-reflow in humans. Micro-thrombo-emboli refer to thrombus debris or micro-material from fissured and ruptured atheromatous plaques from the infarct related artery (IRA) going downstream during balloon dilatation or stenting. Myocardial perfusion starts falling, when embolic microspheres block >50% of coronary capillaries (Niccoli et al.).[12] During PCI, 0–25 microspheres may travel downstream without causing MVO. The number and size of micro-emboli may vary in different individuals. When the number >25–200 or the size of micro-emboli is >200 μm, it can cause severe MVO. Thrombus burden and plaque erosions can be assessed by intra-vascular ultrasound (IVUS) and optical coherence tomography (OCT).

4.3. Ischemic injury

Kloner et al.[16] demonstrated that temporary ligation of coronary artery in dogs for a period of >90 min resulted in ischemic anatomical changes in the capillaries of ischemic zone. These were seen by electron microscopy, which revealed significant capillary damage in the form of swollen endothelial cells with intra-luminal protrusions and platelet and fibrin thrombi. These changes were followed by occurrence of endothelial gaps and loss of integrity of capillary wall with extravascular collection of erythrocytes.

4.4. Reperfusion injury

The purpose of reperfusion is to reverse the ill-effects of ischemia. However, when ischemia >3 h, reperfusion may aggravate endothelial injury. Reperfusion leads to massive infiltration of

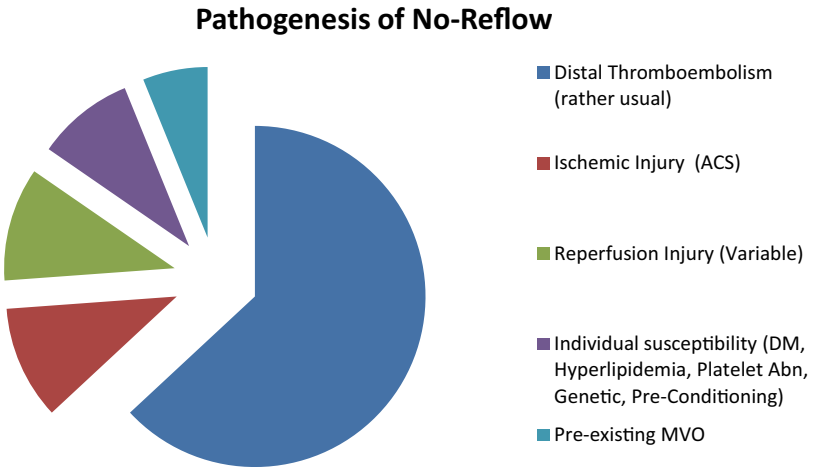

Fig. 1. Pathogenesis of no reflow.
ACS, acute coronary syndrome; DM, diabetes mellitus; MVO, microvascular obstruction.
(Adapted from Niccoli et al.[12,22])