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Advances in Coronary No-Reflow Phenomenon—a Contemporary Review

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Abstract

Purpose of Review Coronary artery no-reflow phenomenon is an incidental outcome of percutaneous coronary intervention in patients presenting with acute myocardial infarction. Despite advances in pharmacologic and non-pharmacologic therapies, coronary no-reflow phenomenon occurs more commonly than desired. It often results in poor clinical outcomes and remains as a relevant consideration in the cardiac catheterization laboratory. In this systematic review, we have sought to discuss the topic in detail, and to relay the most recent discoveries and data on management of this condition.

Recent Findings We discuss several pharmacologic and non-pharmacologic treatments used in the prevention and management of coronary no-reflow and microvascular obstruction. Covered topics include the understanding of pharmacologic mechanisms of current and future agents, and recent discoveries that may result in the development of future treatment options.

Summary We conclude that the pathophysiology of coronary no-reflow phenomenon and microvascular obstruction still remains incompletely understood, although several plausible theories have led to the current standard of care for its management. We also conclude that coronary no-reflow phenomenon and microvascular obstruction must be recognized as a multifactorial condition that has certain predispositions and characteristics, therefore its prevention and treatment must begin pre-procedurally and be multi-faceted including certain medications and operator techniques in the cardiac catheterization laboratory.

Keywords Coronary intervention · Acute myocardial infarction · Myocardial perfusion · Microvascular obstruction · No-reflow · Slow-reflow

Introduction

Clinical Relevance

Coronary artery no-reflow (CNR) phenomenon, often times referred to as microvascular obstruction (MVO), continues to plague outcomes in patients undergoing percutaneous coronary intervention (PCI) in the setting of acute myocardial infarction. In 1995, Morishima and colleagues revealed that approximately 30% of their patients (total $n = 93$) exhibited mild or severe CNR following PCI [1]. Other authors have cited an incidence as high as 60% [2•]. In the 1980s, Schofer et al. demonstrated, using thallium-201 and technetium-99m scintigraphy, that the size of the area of no-reflow was not significantly different after thrombolysis as compared to pre-thrombolysis, suggesting that complete reperfusion did not occur in the ischemic myocardium [3]. Regional wall motion abnormality, portion of total infarction determined by scintigraphy, incidence of myocardial rupture, and death are higher in patients who exhibit this phenomenon [1]. Clearly, the phenomenon has clinical relevance and serves as a factor in outcomes. Despite advances in our understanding of CNR pathophysiology and its prevention and treatment, the incidence of no-reflow still remains approximately 32% [4].

Definition

Coronary artery no-reflow has several definitions. Classically, it was defined as a phenomenon in which there

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is reduced myocardial flow and myocardial perfusion despite reperfusion therapy with PCI during acute myocardial infarction [7]. Normally, blood flow should resume unhindered following primary PCI, and is evaluated typically using the Thrombolysis In Myocardial Infarction risk score (TIMI) flow grading system, TIMI frame count, and myocardial blush grading [7–9]. TIMI 0 flow is defined as no antegrade flow beyond the point of occlusion; TIMI 1 flow is defined as faint antegrade flow beyond the occlusion with incomplete filling of the distal vascular bed; TIMI 2 flow is defined as delayed or sluggish antegrade flow with complete filling of the distal vascular beds; and TIMI 3 flow is defined as normal flow with complete filling of the distal vascular bed [8]. In coronary no-reflow, TIMI flow grades of 1 or 2 and high TIMI frame counts may be observed. Despite epicardial coronary TIMI 3 flow, however, MVO may occasionally persist therefore abnormal myocardial blush may also be utilized to better evaluate this phenomenon. A comparison of angiographic CNR and MVO by cardiac magnetic resonance will be discussed later. It is also important to recognize that coronary no-reflow can also occur during PCI of saphenous vein grafts [7].

Pathophysiology

Although the pathophysiology is not completely understood, several theories have been proposed. In canine models, prolonged occlusion of epicardial coronary arteries has been shown to cause damage to the endothelial lining of distal microvasculature. Such damage as seen on electron microscopy causes membrane-bound blebs and swelling of endothelial cells, which in turn reduce forward flow by physical obstruction, [5]. We have since come to understand that in humans, the etiology is more complex. In humans, distal embolization of thrombus fragments plays a large role in CNR in addition to microvascular arteriolar spasm [2•, 3, 6] (Table 1).

It is important to recognize, however, that CNR may be transient or sustained. Transient CNR is frequently related to functional and reversible alteration of myocardial microvasculature and tissue perfusion while sustained CNR is associated with structural and irreversible damage [10].

Invasive assessment of coronary physiology using coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve in patients undergoing primary PCI for acute myocardial infarction has been utilized to help understand the physiology. In a study of 82 patients with acute myocardial infarction, invasive assessment was performed at day 1, and at 6 months, and compared with contrast-enhanced cardiac magnetic resonance imaging to assess relationships with microvascular obstruction. MVO was present in approximately half of the patients studied, and those patients exhibited lower coronary flow reserve at primary PCI and at day 1, with higher index of microcirculatory resistance. At 6 months however, there was no significant difference between the two. Overall though, there was a significant reduction in fractional flow reserve over 6 months, specifically in patients with initial MVO [11].

Based on this information, the authors concluded that during acute myocardial infarction, microvascular dysfunction begins to recover within the first 24 h and continues for 6 months. They also concluded that the presence of MVO causes a limited response to adenosine and therefore fractional flow reserve during acute myocardial infarction underestimates the degree of culprit vessel stenosis in half of the patients.

Table 1 Risk factors and proposed etiologies of coronary no-reflow phenomenon [7, 15]

Coronary no-reflow phenomenon	
Risk factors	Age greater than 65 years
	Active tobacco use
	Previous myocardial infarction
	Higher Killip classification score
	Higher serum creatinine
	Higher C-reactive protein levels
	Greater time-to-treatment interval
	Lower ejection fraction
	Lower baseline TIMI flow grade
	Larger initial perfusion defect size
	Acute peri-procedural hyperglycemia
	Chronic hyperlipidemia and hypertension
	Low-echoic composition of lesions on IVUS
	Chronic inflammatory conditions
Etiologies	Endothelial dysfunction
	Reperfusion injury
	Distal thromboembolism with PCI
	Microvascular arterial spasm

TIMI thrombolysis in myocardial infarction, *IVUS* intravascular ultrasound, *PCI* percutaneous coronary intervention

Virtual Histology

In addition to microscopic features, the composition of a lesion as observed under intravascular ultrasound (IVUS) directly correlates with not only plaque vulnerability but also the incidence of CNR after revascularization. Low-echoic structures are described as culprits of the phenomenon and are defined as small tubular structures exterior to the media without a connection to the vessel lumen. Low-echoic structures are more prevalent in acute coronary syndromes, vulnerable plaques (thin-capped fibroatheromas), lesions with higher plaque burden, and most importantly lesions that demonstrated CNR phenomenon, as compared

to lesions without low-echoic structures [12]. This direct correlation implies that IVUS may be used to predict CNR and guide prophylactic treatment prior to PCI. Albeit, IVUS is time consuming and its use during an acute myocardial infarction may be prohibitive.

Near-infrared spectroscopy in combination with IVUS has been utilized to provide clinicians true vessel characterization by indexing the plaque lipid core burden [13••]. This information can be used to risk stratify patients undergoing coronary intervention in non-emergent settings as axial plaque shift during PCI has been identified as an acute prognostic marker for coronary no-reflow [14].

Optical coherence tomography has also been utilized to derive lipid indices in conjunction with IVUS for plaque burden and structure, concluding that lipid indices > 3500 and plaque burden > 81.5% are critical discriminators between no-reflow and normal flow [15].

Differentiating CNR from MVO

Post-intervention, cardiac magnetic resonance has been utilized for prognostication. Areas of CNR after acute myocardial infarction have been associated with MVO as seen on magnetic resonance and correlate with a greater degree of myocardial damage. Additionally, patients who exhibit MVO on magnetic resonance also experience worse short- and long-term outcomes such as adverse cardiac events and congestive heart failure [16]. However, more recent data suggests that the incidence of angiographic CNR and MVO on magnetic resonance is significantly different. In a comparison of outcomes between the two in patients with acute myocardial infarction, 36% of patients had angiographic evidence of CNR, whereas 67% had MVO on follow-up cardiac magnetic resonance 2–5 days after primary PCI. One patient with angiographic CNR did not have MVO. This may suggest that CNR and MVO may be two separate yet intimately related conditions, and microvascular obstruction may persist despite recanalization of epicardial vessels with primary PCI. Patients with MVO also had more adverse cardiac events, whereas the rate of events was similar in patients with and without angiographic coronary no-reflow. This insinuates that despite angiographic recanalization efforts, MVO has greater prognosticative value for a negative outcome [17••].

Novel Discoveries

Recently, pro-inflammatory Matrix metalloproteinase-9 (MMP-9) levels have been associated with CNR. Local intra-coronary MMP-9 levels distal to lesions in 65 patients presenting with acute myocardial infarction were measured and noted that local MMP-9 levels as compared to systemic levels has a positive predictive value for CNR by TIMI flow grading [18]. The involvement of MMP in inflammatory pathways has been long known, therefore it is difficult to determine its role in CNR in regard to causation vs. association.

The relationship between CNR and fibrin clot permeability and susceptibility to lysis in assays using exogenous thrombin has also been described. A 2007 study concluded that patients who demonstrated no-reflow after PCI had more compact fibrin networks and resistance to lysis. Given our current understanding of the role of genetics involved in fibrinogen levels and fibrin clot structure and function, the conclusion was made that perhaps some patients may have a genetic predisposition to CNR [19]. Similarly, serum levels of SCUBE1 [signal peptide-CUB (complement C1r/C1 s)-EGF-like domain-containing protein 1] in patients with CNR have been compared to normal human subjects and an almost threefold increase in serum levels has been noted in patients who exhibit CNR. Therefore, it is suspected that SCUBE1, a cell surface glycoprotein encoded by the SCUBE1 gene, is expressed in platelets and endothelial cells, and may contribute to thrombus activation, aggregation, and development of CNR [20].

Oxidative stress has also been linked to development of microvascular obstruction. Specifically, sustained levels of NOX2, the catalytic subunit of NADPH oxidase that is released by platelet activation, results in a vicious cycle of platelet aggregate stabilization and thrombus growth that contributes to CNR [21]. Although the clinical implication of these findings is yet to be determined, such discoveries continue to pave the way for novel therapies.

Risk Factors and Prevention

As with all diseases, CNR has been associated with several risk factors, therefore management of CNR begins with prevention through avoidance of certain substances such as tobacco, caffeine, and alcohol and control of other risk factors [22]. Detailed below, some of these risk factors are modifiable, and others are non-modifiable. Interestingly, the majority of such risk factors overlap with well-established risk factors for coronary atherosclerosis itself, such as hyperlipidemia, hypertension, tobacco use, renal disease, and chronic inflammatory processes [7].

In a logistics regression model of 10 variables in 1140 patients of which 108 demonstrated CNR age, smoking, previous myocardial infarction, Killip classification, serum creatinine, C-reactive protein levels, prolonged ischemia related to delayed treatment, LV ejection fraction, baseline TIMI flow grade, and initial perfusion defect were all identified as predictors of CNR [23] (Table 1).

Hyperglycemia

Although the link between diabetes mellitus and coronary atherosclerosis is well accepted, acute hyperglycemia specifically has been associated with higher incidence of CNR. In a study of 146 patients in which approximately 33% demonstrated CNR on intracoronary myocardial contrast echocardiography, higher admission glucose levels were documented as compared to those that did not demonstrate CNR (209 vs 159 mg/dL) [24]. It is important to note that there was no difference in glycosylated hemoglobin levels or incidence of diabetes in the two groups, suggesting that acute hyperglycemia regardless of presence or severity of diabetes mellitus is a predictive and prognostic factor in CNR [24, 25]. Therefore, management of acute hyperglycemia peri-procedurally is important for prevention and improving long-term outcomes in patients who suffer CNR.

Hyperlipidemia

Similarly, the indications of statin therapy for prevention and treatment of atherosclerosis are well established. However, a large meta-analysis of 3086 patients treated with statins pre-procedurally concluded that *acute* intensive statin therapy significantly reduces post-procedural risk of CNR. The incidence of post-procedural CNR was reduced by 4.2% in all patients who underwent PCI, and also there was attenuation of CNR by 5% in non-ST-elevation myocardial infarction patients [26].

Hypertension

Hypertension is also no exception though its direct relationship with CNR has not been studied in human models. In a porcine model during which the ascending aorta was partially clamped to produce the effect of increased afterload, areas of infarction and no-reflow were both independently and significantly increased [27]. The benefits of angiotensin receptor blockers in patients at risk for CNR have been demonstrated in 51 patients on chronic therapy, during which the incidence of CNR was significantly less (8 vs. 26.7%). The results were attributed to the favorable effects of angiotensin receptor blockers on microvascular integrity rather than its blood pressure-lowering properties [28]. Beta-blockers have also been studied in diabetic patients with CNR; the study revealed that the incidence of CNR was 12 vs. 28% in patients treated pre-procedurally with beta-blockers as compared to those who were not [29]. However, given the lack of further data for the use of the above-mentioned agents and the complex interplay of hemodynamics in a patient suffering from an acute myocardial infarction with myocardial dysfunction, the use of such agents should be with great caution.

Mechanical Considerations

Role of Aspiration Thrombectomy

As mentioned earlier, distal embolization of thrombus particles in microvasculature is one of the proposed etiologies of CNR. Distal embolization is affected by two variables: mechanical disruption of the thrombus during ballooning, and the initial burden or volume of thrombus present. In order to reduce the risk of distal embolization of thrombus fragments, techniques such as thrombus aspiration have previously been studied with improved clinical outcomes. One thousand patients with acute myocardial infarction who received thrombus aspiration prior to PCI as compared to PCI alone experienced less adverse cardiovascular events, greater resolution of ST-segments, and overall decreased number of deaths [30]. This was also the case in a meta-analysis of 11 studies evaluating aspiration thrombectomy [31]. Both such studies suggested that pre-PCI thrombus aspiration results in improved clinical outcomes and angiographic characteristics irrespective of the baseline condition of the patient [30]. As a result, thrombus aspiration was frequently utilized until a meta-analysis of 21 trials revealed that despite improvement in surrogate markers of enhanced reperfusion, 30-day post-infarction mortality, risk of re-infarction, and stroke did not improve with aspiration thrombectomy [32]. Nonetheless, it was noted that there was substantially less CNR in patients who received aspiration thrombectomy and this was confirmed in a 2016 meta-analysis of close to 20,000 patients from 18 studies [33]. However, given these inconsistencies in benefits of thrombus aspiration in primary PCI for acute myocardial infarction and the suggested risks involved, notably stroke, routine aspiration thrombectomy has been downgraded to a class III recommendation by ACC/AHA/SCAI guidelines [34].

Rheolytic thrombectomy and its utility in CNR has also been studied and concluded that it did not improve the risk of CNR, though the results were not statistically significant [35]. Overall, this data suggests that aspiration thrombectomy may be beneficial in reducing incidence of CNR especially when there is a large thrombus burden, although clinical outcomes are inconsistent. It should also be recognized that different techniques and operator experience may yield different results, and that it is not without risk.

Role of Balloon Angioplasty

Intuitively, balloon inflation pressures and stent deployment seem to have a correlation with CNR. However, the number of implanted stents, maximal inflation pressures, and repeat balloon dilatations did not affect the incidence of CNR during primary PCI for acute myocardial infarction [36]. Still, barotrauma and distal embolization may be

minimized by limiting the number, diameter, and pressure of balloon inflations since the exact mechanism of CNR is yet to be fully understood [37].

Deferred stenting in patients with acute myocardial infarction has been studied in several trials involving minimalist immediate mechanical intervention with variable results. A recent meta-analysis of these trials however revealed that a deferred stenting strategy did not reduce the occurrence of CNR, death, myocardial infarction, or repeat revascularization as compared with immediate stenting though it did result in improved LV function long term [38].

Ischemic Post-Conditioning

As the proposed mechanism of CNR is founded in microvascular dysfunction and reperfusion injury, the benefits of ischemic post-conditioning with serial interval balloon dilatations has come into question [39].

A study of 25 patients with acute myocardial infarction who underwent 1-min cycles of ischemic post-conditioning and revealed that MVO was significantly reduced as seen on contrasted cardiac magnetic resonance imaging [40].

Furthermore, ischemic post-conditioning improves global and regional contractility, reduces infarct size, and even results in increases in ventricular ejection fraction [41]. This was later refuted by two randomized trials that failed to show short- or long-term improvement in myocardial function. In-fact, myocardial salvage was reduced in post-conditioning [42, 43]. Thus, ischemic post-conditioning may play a role in prevention and treatment of angiographic CNR at a vascular level; however, its overall effect on myocardial function and clinical outcomes is still in debate.

Role of Mechanical Circulatory Support

Intra-aortic balloon pump counterpulsation (IABP) is typically utilized for afterload reduction in cardiogenic shock, but has been used to enhance diastolic coronary perfusion despite the controversies that surround its benefit [44].

In animal models, IABP support before, during, and after reperfusion has been shown to improve coronary and myocardial perfusion caused by microvascular obstruction [45, 46].

However, in a study of 17 human subjects who underwent PCI of the left anterior descending artery, IABP did not provide a substantial benefit in coronary flow velocity pattern in those who exhibited angiographic CNR vs. those who did not. Diastolic deceleration time was smaller and systolic retrograde flow was greater in the no-reflow group, but the utilization of IABP did not change either parameter [47].

The role of Impella mechanical support devices in treatment of coronary no-reflow has not yet been studied.

Role of Therapeutic Hypothermia

Again, in animal studies, therapeutic hypothermia initiated before and after coronary artery reperfusion reduces coronary no-reflow through its protective mechanisms on reperfusion injury pathophysiology [48, 49]. Its routine use solely for CNR prevention and treatment is not feasible in human subjects.

Pharmacological Considerations

Role of Anti-Platelet Therapy

Given the multifactorial etiology of CNR, one of which includes distal embolization of thrombus fragments, anti-platelet therapy has been evaluated and commonly used when thrombus burden is noted to be high angiographically. Arachidonic acid-induced platelet aggregation and serum thromboxane B_2 levels before and after PCI have been studied and have illustrated that arachidonic acid-induced aggregation > 100 (AUC*min) before PCI predicted CNR in diabetic patients with a 96.2% sensitivity and 38.5% specificity [50].

In a 2010 study of 91 patients who presented with their first acute myocardial infarction and underwent coronary angiography, it was noted that patients who were not on chronic aspirin therapy prior to the event had on average a higher thrombus grade. This concludes that aspirin therapy alone, as assessed using multivariate analysis, results in a decrease in angiographic thrombus grade in patients with first-time acute myocardial infarction treated with PCI [51].

Owing to the similar mechanism of platelet aggregation inhibition, P2Y12 inhibitors may have similar benefits. A 600 mg loading dose of clopidogrel during an acute myocardial infarction, as compared to a 300 mg load, resulted in a decreased incidence of angiographic CNR [52].

In addition to anti-platelet activity, ticagrelor specifically increases endogenous adenosine levels that result in vasodilatation. Cellular injury results in production of adenosine via metabolism of adenosine triphosphate and adenosine diphosphate through activation of nucleotidases CD39 and CD73 [53]. This adenosine however is up-taken by cells via the adenosine transporter ENT-1 and metabolized, which results in decreased concentrations of adenosine. Ticagrelor inhibits ENT-1 which in turn results in increased extracellular concentration of adenosine [54]. Adenosine then exerts its vasodilatory effect via $A_{2A}R$ and $A_{2B}R$ adenosine receptors that mediate vasodilation through nitric oxide-dependent and -independent pathways, [55].

Cangrelor is a reversible P2Y12 inhibitor with high affinity and short half-life that permits its use in infusion form peri-

procedurally as it does not require metabolite conversion [56]. Cangrelor does not inhibit ENT-1, although its main metabolite does inhibit ENT-1, giving it weak inhibition of adenosine uptake overall [57].

Glycoprotein IIb/IIIa inhibitors have been associated with improvements in microcirculation by relieving thrombus burden and minimizing distal embolization [58, 59]. Abciximab has been studied extensively and found to improve myocardial perfusion when used periprocedurally and up to several hours after PCI [60]. The use of intravenous vs. intracoronary abciximab has come into question however, with equivocal data supporting both intracoronary and intravenous use as assessed by different methods such as ST-segment resolution, enzymatic infarct size, and myocardial blush grade [61, 62]. Intracoronary abciximab has been associated with improved myocardial reperfusion as assessed by myocardial blush grade [62].

Role of Vasodilator Therapy

As described earlier, adenosine is a potent arterial vasodilator and has the ability to reverse the effect of other endogenous vasoconstrictors [63]. Additionally, it is an endogenous nucleoside that activates extracellular receptors, which result in the inhibition of platelet aggregation involved in formation of thromboembolic and its propagation [64, 65].

It is known that intracoronary adenosine administered throughout PCI significantly reduces CNR during acute myocardial infarctions in both native coronaries and bypass grafts [66–68]. Adenosine employs its properties on microvasculature while PCI or thrombolysis induces patency within the epicardial coronary artery [7].

Adenosine has been shown in the AMISTAD and AMISTAD-II trials to reduce infarct size, but failed to show improvements in clinical outcomes unless patients achieved early reperfusion [69–71]. Several meta-analyses have been performed which suggest the benefit of adenosine; however, it is important to recognize that adenosine has a very short half-life and therefore its benefit may be limited if given in boluses. In a pig model in which mid-LAD occlusion was induced, intracoronary bolus dosing as compared to infusion dosing of adenosine revealed that infusion protocols resulted in significant reductions in infarct size and risk of CNR [72]. However, it is difficult to recreate this in human subjects without risk, as intracoronary infusion of adenosine may cause atrioventricular conduction blocks and other side effects. In a meta-analysis comparing adenosine to verapamil, adverse events with adenosine such as bradycardia, hypotension, and atrioventricular conduction block were significantly increased [73]. Overall, a meta-analysis of 1487 patients in 13 randomized trials comparing intracoronary adenosine to placebo during acute myocardial infarction revealed a higher incidence of ST resolution, lower mean ischemic time, larger increase in LV ejection fraction, lower rate of heart failure, and lower incidence of major adverse cardiac events in the short and long term in the intracoronary adenosine group as compared to placebo [74].

Currently, a multicenter, prospective, randomized, controlled open label trial on the comparison of intracoronary adenosine and sodium nitroprusside vs. standard therapy, entitled REFLO-STEMI trial, is being conducted [75].

A drug with a more sustained and perhaps greater vasodilatory effect is sodium nitroprusside. Intracoronary sodium nitroprusside and adenosine have been studied in normal coronary arteries and noted that sodium nitroprusside resulted in a more prolonged coronary hyperemic response as compared to adenosine [76]. Also, intracoronary sodium nitroprusside in addition to adenosine results in much greater improvement in coronary flow as compared to adenosine alone and placebo [77]. Overall, two separate meta-analyses of 11 total randomized clinical trials conclude that sodium nitroprusside is effective in preventing CNR [78, 79].

Calcium channel blockers have been studied in CNR given the nature of their mechanism of action in vasodilatation. An analysis of eight randomized controlled trials of nondihydropyridine calcium channel blockers verapamil and diltiazem in patients with CNR demonstrated that intracoronary verapamil and diltiazem decreased the occurrence of CNR and reduced corrected TIMI frame count. Additionally, there was a significant reduction in 6-month major adverse cardiovascular events in the diltiazem/verapamil group as compared to control groups [80].

Nevertheless, nondihydropyridine calcium channel blockers may pose a cardiac depressant effect through negative ionotropy which could have severe implications in a patient with acute myocardial infarction and systolic dysfunction. Consequently, nicardipine, a dihydropyridine calcium channel blocker, was been studied in a large retrospective analysis of CNR patients and showed that CNR was successfully reversed with complete restoration of TIMI 3 flow in 98.6% of patients [81]. Most importantly, nicardipine has less adverse hemodynamic side effects [82] that allows for repeat dosing until resolution of coronary no reflow [81].

Nicorandil is an agent that causes coronary vasodilatation by serving as a nicotamide nitrate and also by opening mitochondrial potassium channels that result in the reduction of intracellular calcium [83]. This mechanism may be cardioprotective, hence its benefits during acute coronary syndromes, as the opening of ATP-sensitive K+ channels is an innate protective mechanism of cardiac myocytes when insulted with ischemia [84]. Additionally, nicorandil

modulates neutrophil activation and thus has anti-inflammatory properties that impact the pathophysiology of acute coronary syndrome [83]. Nicorandil, when given as a single injection, has been proven to mitigate CNR [85] and when given as an infusion, has been shown to improve myocardial viability, function, and clinical outcomes [86, 87]. In a meta-analysis of 17 studies, nicorandil prevented CNR and also was associated with greater LV ejection fraction and lower LV end-diastolic volume indices suggesting its continued effect on functional recovery after acute myocardial infarction [88]. Unfortunately, nicorandil is not available in the USA.

Other Therapies

Several other adjunctive therapies have been studied, as discussed below, with variable results, and are therefore not recommended for routine use. Nonetheless, large randomized clinical trials are warranted to investigate their potential benefits in CNR.

Cyclosporine-A is a powerful inhibitor of mitochondrial permeability transition pores that play a large role in cellular death during reperfusion injury [89]. Cyclosporine-A was shown to have a positive impact in rat skin-graft models and the prevention of no-reflow [90], and a reduction in myocardial infarct size in a small trial of human subjects, although the TIMI grade flow was similar as compared to the control group [91]. In a study of 395 patients who received intravenous cyclosporine-A prior to PCI for acute myocardial infarction did not result in better clinical outcomes as compared to placebo, and did not prevent left ventricular remodeling at 1 year [92].

FX06 is a human fibrin peptide that may improve the necrotic core zone. In the FIRE trial, it was shown to improve MVO as assessed by cardiac magnetic resonance, although it failed to reduce the infarct size compared to placebo [93].

Pexelizumab is a humanized monoclonal antibody that binds the C5 component of complement and failed to show an improvement in 30-day mortality and rate of TIMI 3 flow in the APEX-AMI trial [94].

Dabigatran, as studied in a rabbit model, concluded that it did not prevent or mitigate CNR suggesting that fibrin does not play a major role in microvascular obstruction [95]. This however contradicts the results of the FIRE trial and the findings on fibrin [14, 95].

Administration of liraglutide versus placebo during acute myocardial infarction revealed a significantly lower incidence of CNR as compared to placebo [96]. The effect of GLP-1 analogs may be attributed to improvement in glucose levels and reduction in inflammation that ultimately result in

Table 2 Suggested peri-procedural therapies for prevention and treatment of coronary no-reflow phenomenon, and their respective benefits [40–82]

Suggested therapies			
	Agent	Indication	Benefit
Peri-procedural	Insulin	Acute hyperglycemia	+
	Aspirin	CVD prophylaxis	++
	P2Y12 Inhibitors	PCI	+++
	Statins	CVD prophylaxis	++
	ARBs or Beta-blockers	Hypertension/Remodeling	+
During PCI	IC Abciximab	High thrombus burden	+++
	IC Adenosine	Vasospasm/No-reflow	+++
	IC Sodium Nitroprusside	Vasospasm/No-reflow	+++
	IC Nicardipine	Vasospasm/No-reflow	++++
	IC Diltiazem/Verapamil	Vasospasm/No-reflow	+++
	Aspiration Thrombectomy	High thrombus burden	−
	Ischemic Post-conditioning	No-reflow phenomenon	+/−
	MCS	No-reflow phenomenon	?
Experimental	Cyclosporine-A		−
	FX06		−
	Pexelizumab		−
	Dabigatran		−
	Liraglutide		++
	Erythropoietin		−
	Nicorandil	(Approved in Europe only)	++++

CVD cardiovascular disease, *ARB* angiotensin II receptor blocker, *IC* intracoronary, *MCS* mechanical circulatory support

improved endothelial function, as both methods have been known to contribute to CNR [7, 96].

Erythropoietin, administered in studies of ischemic animal models, has been found to attenuate vascular injury through reduced apoptosis, suppressed inflammation, and increased nitric oxide availability [97]. Endogenous erythropoietin levels were found to be inversely related to angiographic and ECG coronary no-reflow following PCI in acute myocardial infarctions [98]. Further human trials are necessary to study and justify exogenous administration of erythropoietin in coronary no-reflow phenomenon.

Conclusion

Coronary artery no-reflow phenomenon and microvascular obstruction are known complications of primary PCI in patients presenting with acute myocardial infarction. Although the pathophysiology is not completely understood, several proposed mechanisms have led to scientific investigation of potential preventive and treatment measures as discussed in this review. Cardiac magnetic resonance suggests that microvascular obstruction and angiographic CNR may be two separate yet intimately related entities as it relates to clinical outcomes. Given the multifactorial nature of CNR phenomenon and the intricate interplay of hemodynamics observed in a patient with acute coronary syndrome, several pharmacologic and non-pharmacologic therapies have become the standard of care. Nevertheless, all of these interventions either individually or in conjunction with one-another should focus on prevention by improving pre-procedural medical optimization, door-to-balloon time, reperfusion techniques, and consideration of aspiration thrombectomy in the presence of a large thrombus burden. Once CNR is recognized, pharmacologic therapy with adenosine, sodium nitroprusside, and calcium channel-blockers should be considered as they have proven benefit. Table 2 summarizes our recommendations in peri-procedural combination therapy for the prevention and treatment of CNR (Table 2). Despite our current understanding and technologic advancements in PCI, such as newer generations of drug eluting stents, CNR and MVO remain as a persistent problem with limited treatment options.

Compliance with Ethical Standards

Conflict of Interest Ahmadreza Karimianpour and Anbukarasi Maran declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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