Pathophysiological aspects and management workflow of coronary microvascular obstruction in ST-segment elevation myocardial infarction

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ABSTRACT

Restoring blood flow to ischemic but viable myocardium and reducing infarct size constitute the goals of reperfusion therapy with fibrinolytic drugs or primary percutaneous intervention in patients with ST-segment elevation myocardial infarction (STEMI). However, in a sizable proportion of patients, this intervention gains to reopen the obstructed epicardial coronary artery but does not achieve myocardial reperfusion because of coronary microvascular obstruction phenomenon (CMVO). In the last years, consistent evidence has pointed out how CMVO has a negative impact on outcome in patients with acute STEMI. Of note, most of the trials in this setting, mainly targeting reperfusion damage, have failed to show beneficial effects. In this article we provide a revision of mechanisms, diagnosis and prognosis of CMVO in acute STEMI, also pointing out the need of an integrated approach in order to prevent and treat CMVO in the different time windows of the acute event.

Introduction

ST-segment elevation myocardial infarction (STEMI), usually resulted from acute thrombotic occlusion of a coronary artery, still represents one of the main causes of death.[1] In this context, restoring blood flow to ischemic but viable myocardium, as well as reducing infarct size (IS), constitute the goals of reperfusion therapy with fibrinolytic drugs or primary percutaneous intervention (PCI).[2] However, despite several efforts provided to reduce time to treatment and maximize myocardial salvage, in-hospital mortality has remained unchanged in this setting of patients.[3] In this context, it has to be taken into account that, in a sizable proportion of patients ranging from 10% to 60%, the reopening of the obstructed epicardial coronary artery is not associated with myocardial reperfusion because of coronary microvascular obstruction (CMVO).[4] Moreover, consistent evidence showed as CMVO has a negative impact on outcome, being associated with adverse left ventricular remodelling, late repeat hospital stays for heart failure, and death. In this article we point out mechanisms, diagnosis and prognosis of CMVO in acute STEMI, also emphasizing the need of an integrated approach for prevention and treatment of CMVO in different time windows.

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Mechanisms of coronary microvascular obstruction

In the past years, four interacting mechanisms have emerged as principal causes of CMVO in humans: ischemia-related injury, reperfusion-related injury, distal embolization and individual susceptibility of the microcirculation to injury (Figure 1). Recently, a pre-existing impairment of the myocardial microcirculation, principally due to cardiovascular risk factors, has been shown to yield greater vulnerability to PCI-related myocardial injury as well as a poor long-term outcome.[5,6] In particular, a pre-existing transient or permanent microcirculatory dysfunction may con-

tribute to the development and prognosis of acute coronary syndrome (ACS) via reduction of coronary blood flow, leading to an alteration of shear stress and thereby worsening of endothelial function at epicardial level as well as aggravation of thrombus formation.[7]

Ischemic and reperfusion related injuries have been translated to humans from the animal models with a first description by Kloner *et al*.[8] In particular, electron microscopic analysis after 90-min coronary occlusion followed by reperfusion, revealed severe capillary damage, endothelial protrusions and blebs blocking the capillary lumen, and endothelial gaps with extra vascular erythrocytes.[8] The most important clinical predictors of ischemia-related injury are ischemia duration and extent.[9]

When ischemia lasts more than 3 h, ischemia-associated injury is potentiated by reperfusion injury.[10] In particular, lethal reperfusion injury (myocardial necrosis due to reperfusion) and CMVO play a major role. Neutrophil-platelet aggregates, which represent a major source of oxidants, proteolytic enzymes and pro-inflammatory mediators, can cause CMVO by further obliteration of vessel lumen.[11] On the other hand, reperfusion also stimulates the production of radical oxygen species by mitochondria of cardiomyocytes that lead to the opening of mitochondrial membrane permeability transition pores, calcium overload, mitochondrial swelling and cell disruption.[11] Moreover, endothelial cells can regulate leucocyte function by the expression of adhesion molecules, *e.g.*, intercellular adhesion molecule-1 or P-selectin, and by the release of soluble factors like nitric oxide, prostacyclin, endothelin.[12]

Again, ischemia followed by reperfusion can disrupt the endothelial barrier and damage the microvasculature, facilitating extravasation of blood cells upon reperfusion and eventually causing intra-myocardial hemorrhage (IMH).[13] Of note, patients with this more severe form of CMVO seem to have a worse outcome than patients with CMVO but without IMH.[14]

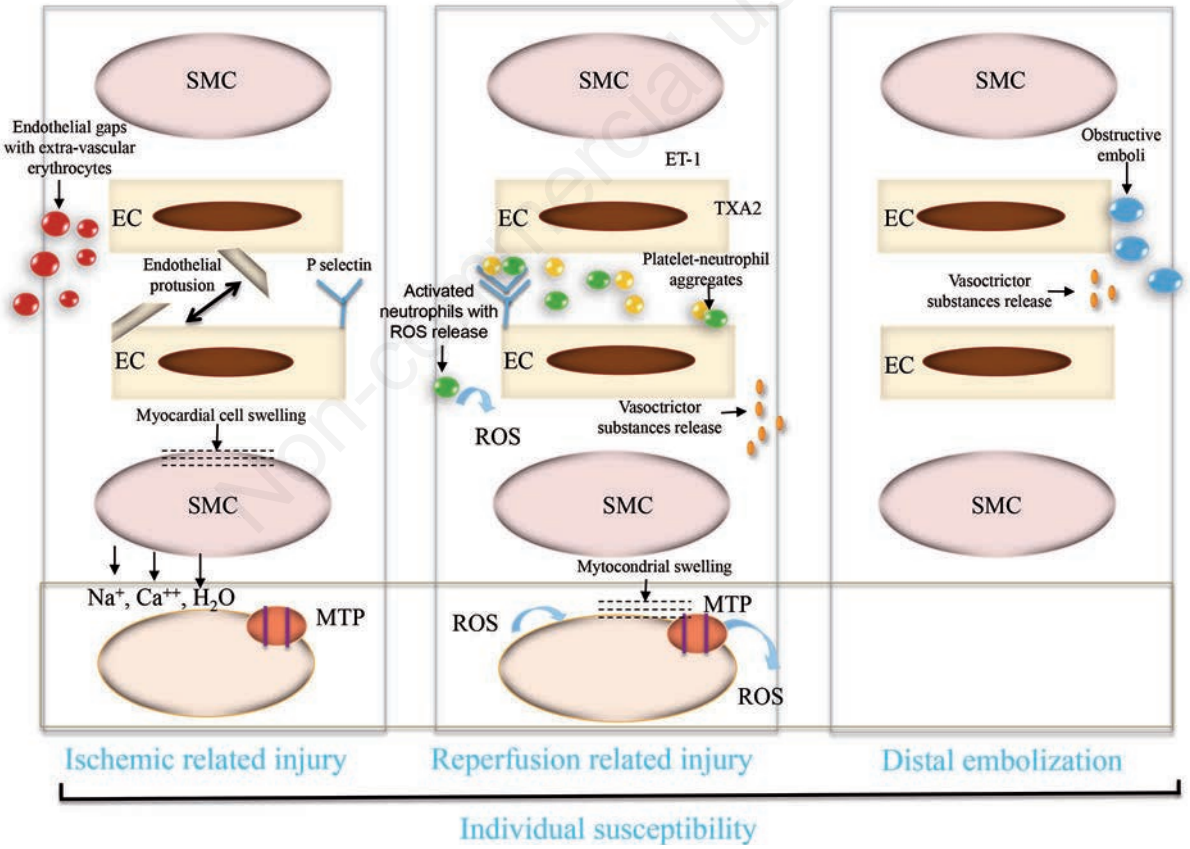

Figure 1. The 4 interacting mechanisms involved in the pathogenesis of coronary microvascular obstruction in humans: Ischemic related injury: it is characterized by severe capillary damage, endothelial protrusions, endothelial gaps with extra vascular erythrocytes (in red) and expression of P-selectin. Reperfusion related injury: the principal determinants are represented by neutrophils (in green), endothelin-1 (ET-1), thomboxane-A2 (TXA2), platelets (in yellow) and inflammatory mediators (in brown). Distal embolization: distal embolization (in blue) of plaque and thrombus material may obstruct mechanically the microcirculation, but it is also a source of vasoconstrictors and pro-coagulant substances. SMC, smooth muscle cell; EC, endothelial cell; ROS, radical oxygen species; MTP, membrane permeability transition.

A third important mechanism of CMVO is represented by distal physical and chemical substances embolization. Emboli of different sizes can originate from epicardial coronary thrombus and from fissured atherosclerotic plaques during primary PCI. However, spontaneous embolization can be suspected also before vessel manipulation. Of note, the effect of angiographically visible distal embolization on IS seems to be time-dependent.[15]

Both plaque and thrombus features are associated with risk of distal embolization. In particular, a high thrombus burden, as well as the presence of a lipid rich plaque and plaque erosion are associated with the occurrence of distal embolization.[16]

Finally, another component of CMVO is represented by the individual susceptibility to microvascular dysfunction, maybe related to the function, as well as to the structure and the density of the microcirculation.[17] Genetic factors, like 1976T.C polymorphism of the adenosine 2A receptors gene, may modulate adenosine-induced vasodilation.[18] Another element acting on the individual susceptibility to CMVO is the presence of ischemic preconditioning (IPC), which seems to protect both the myocardium and the coronary microcirculation.[17] Accordingly, pre-infarction angina might help preventing CMVO by inducing IPC. Interestingly, beneficial effect of pre-infarction angina may be blunted in humans due to risk factors or drugs therapy affecting unfavorably IPC,[19] while chronic nitrate therapy seems to stimulate IPC.[20]

Diagnosis of coronary microvascular obstruction

Based on a combination of angiographic and electrocardiographic indexes, a reasonable estimate of patients who get optimal myocardial reperfusion is approximately 35%.[17] Of note, due to its dynamic nature, in 50% of cases CMVO is irreversible, while in the remaining 50% it is reversible.[21] The diagnostic indexes may be classified as invasive or no-invasive tools (Figure 2).

Invasive indexes of coronary microvascular obstruction

The gold standard method for assessing microvascular function is the direct measurement of coronary flow reserve (CFR) using intra-coronary (IC) Doppler wire in response to a vasodilator such as adenosine. In particular, the typical CMVO pattern is characterized by: systolic retrograde flow, diminished systolic anterograde flow and rapid deceleration of diastolic flow. The attenuated CFR response post PCI seems to be associated with future cardiovascular events.[22]

Recently, several studies have tested other invasive indexes in comparison with CFR, *e.g.*, index of microvascular resistance and hyperemic microvascular resistance index, pointing out promising data about reproducibility and prognostic value.[23,24] All together, these insights from clinical pathophysiology could support therapeutic approaches beyond the primary PCI procedure itself.

Thrombolysis in myocardial infarction (TIMI) score grading system describes the rate of blood flow in the epicardial vessels, ranging between no flow at all (grade 0) to a normal flow rate (grade III). TIMI flow <3 is a marker of both CMVO and of larger IS and has been shown to affect prognosis both at short and long term follow up.[25] TIMI frame count index, defined as the number of frames required for contrast medium to reach a standardized distal landmarks, is able to stratify the prognosis of patients exhibiting TIMI flow 3 and correlate with invasive assessment of CFR.[26]

In the next years, angiographic methods based on the kinetics of dye penetration within the myocardium (myocardial *blush*), the myocardial blush grade (MBG) and TIMI myocardial perfusion grade (TMPG), shifted the attention from the epicardial flow to the microcirculatory flow by angiography.[27,28]

MBG is a densitometric method scored on a scale of 0 to 3, with higher scores indicating better perfusion. The TMPG assesses microvascular clearance of contrast medium and is scored again on a scale of 0 to 3. Both MBG and TMPG are useful to risk stratify patients having final TIMI flow 3. Thus, it is becoming common practice to define angiographic CMVO, as follows: TIMI flow grade <3 or 3 with an MBG or TMPG 0 to 1.[29]

No-invasive indexes of coronary microvascular obstruction

After primary PCI, incomplete ST resolution (STR) has been related to CMVO and worse clinical outcome.[30] However, a consensus is still lacking about which leads to analyse, the optimal timing of electrocardiogram (ECG) analysis, and whether standard ECG or continuous ECG monitoring is preferable. Assessment of single lead STR showing maximum ST elevation at baseline seems to be as accurate as the sum STR measurements,[31] whereas a recent study showed how residual ST-segment elevation can be considered as an independent marker of CMVO.[32] Of note, angiography and ECG are obtained at two different times after primary PCI and they may reflect different aspects of myocardial reperfusion, with angiography looking more at the coronary microcirculation and ECG more at myocardial cells.[17]

Myocardial contrast echography (MCE) is a method that utilizes ultrasound to visualize contrast microbubbles with a rheology similar to that of red

blood cells that freely flow within patent microcirculation. In particular, lack of intra-myocardial contrast opacification, due to CMVO, is able to predict functional recovery after STEMI.[33]

Cardiac magnetic resonance (CMR) allows an accurate quantification and localization of CMVO and IS relative to the entire left ventricle.[34] In particular, CMVO can be typified as: i) lack of gadolinium enhancement during first pass (<2 min); and ii) lack of gadolinium enhancement within a necrotic region, identified by late gadolinium hyper-enhancement (after 10-15 min). First pass (early) CMVO is more sensitive that late CMVO, as the latter underestimates the extent of CMVO. Of note, CMR may give additional hints to the presence of IMH.[13,14]

Other imaging techniques under investigation for CMVO detection include myocardial scintigraphy or hybrid positron emission tomography-computed tomography.[35]

Prognosis of coronary microvascular obstruction

Indexes of CMVO are able to predict adverse left ventricular remodelling and mortality after primary PCI (Table 1).[21,36-43] In particular, TIMI flow ≤2 is associated with an increased risk of adverse remodelling at 6 months[36] and of 5-year mortality.[37] MBG 0-1 raised the risk of adverse remodelling at 6 months[38] and of total mortality after 16 months of follow-up.[39] MCE detected CMVO was associated with an enhancement of the risk of adverse remodelling at 6 months[33] and of cardiac death after 46 months.[40] CMR detected CMVO increased the risk of adverse remodelling at 6 months[41] and of death.[42] The lack of STR

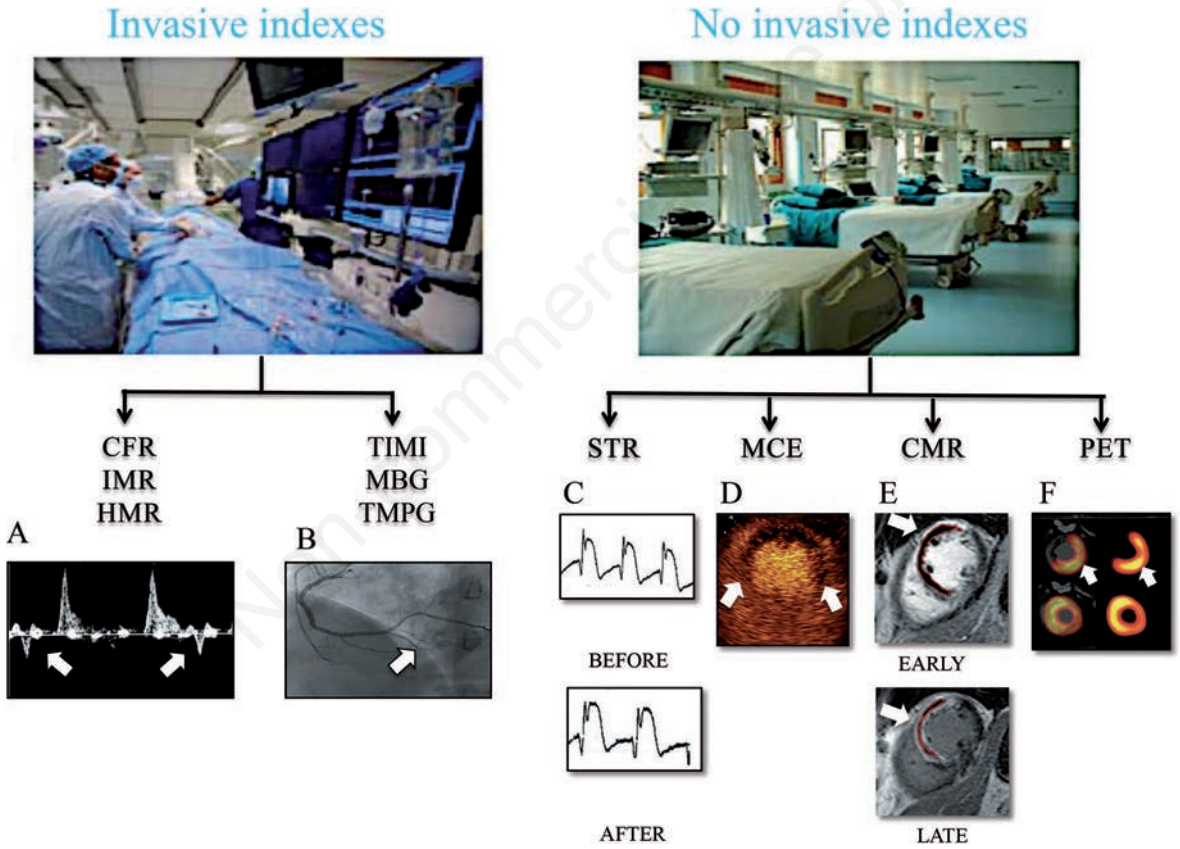

Figure 2. Invasive indexes of coronary microvascular obstruction (CMVO): coronary flow reserve (CFR) (systolic retrograde flow, panel A, indicated by white arrows); microvascular resistance (IMR) and hyperemic microvascular resistance (HMR). Thrombolysis in myocardial infarction (TIMI) flow score, myocardial blush grade (MBG) and TIMI myocardial perfusion grade (TMPG) (angiographic CMVO, panel B, indicated by white arrow in the posterior descending artery of the right coronary artery). No-invasive indexes of CMVO: ST-segment resolution (STR) (panel C, at the top, for the ST before opening infarct related artery and at the bottom for the ST after opening infarct related artery during CMVO); myocardial contrast echocardiography (MCE) (lack of intra-myocardial contrast opacification, panel D, indicated by white arrows). Cardiac magnetic resonance (CMR) (lack of gadolinium enhancement during first pass, image E, at the top, indicated by white arrow and lack of gadolinium enhancement within a necrotic region, panel E, at the bottom, indicated by white arrow). The hybrid positron emission tomography/cardiac computed tomography (PET) (panel F, indicated by white arrows).

raised the risk of total mortality after 30 days but failed to predict adverse left ventricular remodelling.[36] The combination of poor MBG (0-1) and lack of STR exhibited an additive effect on the risk of total mortality after 1 year, thus suggesting that angiographic and ECG indexes of CMVO may emblematize different pathogenetic mechanisms.[43]

Treatment strategies in different time windows

During the years, many efforts have been provided in order to detect an effective strategy to prevent and approach CMVO. Of note, currently, no treatment strategy has really proved in a randomized multicenter trial to be beneficial for the prevention or treatment of CMVO.

Hence, we will expose all therapies with an evidence and/or general agreement of possible utility in treating CMVO that need to be tested in large trials and all those that still need confirmation due to limited or conflicting evidence and/or divergence of opinion about their utility. Furthermore, we will propose a classification following the same time windows of treatment commonly utilized for STEMI patients (Table 2 and Figure 3).[44-80]

Three phases may thus be identified: the first time window extends until hospital admission for STEMI, the second time window takes place in catheterization laboratory, and the third time window unfolds in the Coronary Care Units (CCU), after catheterization laboratory.

Before catheterization laboratory

Ongoing statin therapy at the time of STEMI was associated with a lower rate of CMVO, and better functional recovery of myocardial function after 6 months of follow-up as compared to patients not on statin.[44] Moreover, the administration of high doses of statins prior to primary PCI seems to improve CMVO as compared to that of low doses.[45]

Regarding β-blockers, intravenous (IV) metoprolol administered in ambulance in patients with anterior STEMI on Killip class II or less, has shown to reduce IS, increase left ventricular ejection fraction (LVEF) and reduce the need for cardioverter-defibrillator implantation, with fewer admissions due to heart failure after 2 years.[46]

Among antiplatelet drugs commonly used in STEMI patients, pre-hospital abciximab administration seems to be useful.[47] Of note, the upstream administration of abciximab with half-dose reteplase significantly reduces IS but does not have any overall clinical benefits in primary study end point at 90 days as well as in mortality at 1 year.[48] On the other hand, a routine pre-hospital initiation of high-bolus dose tirofiban might improve STR and clinical outcome after PCI.[49]

Regarding remote ischemic conditioning (RIPC), Botker *et al.* showed that, applying three 5-min cycles of brief ischemia and reperfusion of the upper arm by using blood pressure cuff, myocardial salvage was increased in STEMI patients undergoing primary PCI, especially in those with a large area at risk.[50] Of note, morphine added to RIPC protocol was able to further improve STR.[51]

Results of studies with the glucose-insulin-potassium (GIK) in the setting of STEMI have been controversial.[52,53] Indeed, if CREATE ECLA provided neutral results with no difference in 30 days mortality with GIK as compared to placebo,[52] the recent IMME-

Table 1. Main study showing the prognostic role of coronary microvascular obstruction after primary percutaneous coronary intervention.

CMVO diagnostic index	Year of publication	Author	Patients (n)	Risk measure
Risk of adverse remodeling				
TIMI flow	2004	Bax *et al.*[36]	73	OR 5.6, 95% CI 1.40-22
MBG	2006	Araszkiewicz *et al.*[38]	145	OR 3.15, 95% CI 1.35-7.31
MCE	2008	Galiuto *et al.*[21]	110	OR 12.7, 95% CI 2.65-61.2
CMR	2012	Lombardo *et al.*[41]	41	OR 3.1, 95% CI 1.45-6.64
Risk of death				
TIMI flow	2010	Ndrepepa *et al.*[37]	1406	OR 1.66, 95% CI 1.17-2.36
MBG	2003	Henriques *et al.*[39]	294	OR 4.2, 95% CI 2.1-8.5
MCE	2004	Bolognese *et al.*[40]	124	OR 10.7, 95% CI 2.4-47
CMR	2010	De Waha *et al.*[42]	438	HR 5.12, 95% CI 1.09-24.06
ECG	2005	Sorajja *et al.*[43]	456	OR 2.5, 95% CI 1.02-6.3

CMVO, coronary microvascular obstruction; TIMI, thrombolysis in myocardial infarction; OR, odds ratio; CI, confidence interval; MBG, myocardial blush grade; MCE, myocardial contrast echocardiography; CMR, cardiac magnetic resonance; HR, hazard ratio; ECG, electrocardiogram.

DIATE trial showed reduction in IS and lower rate of in-hospital mortality and cardiac arrest in patients randomized GIK than in controls.[53] Similarly, the role of chronic treatment and early re-administration of ACE inhibitors or nitrates, both associated with better reperfusion in small retrospective studies, should be tested on a large scale.[54,81]

In the catheterization laboratory

Adenosine can prevent CMVO through several mechanisms. Differences in way of administration, timing and dosages may explain the discrepancies observed in the studies. Indeed, if IV adenosine started before reperfusion might improve the outcome when given early (<3.2 h from chest pain onset) as compared to placebo,[55] other reports have provided mixed results regarding the role of IC adenosine.[56,57] In the REOPEN-AMI trial, we found high dosages of IC adenosine, given after thrombus aspiration through the aspiration catheter, improved STR and enzymatic IS as compared to placebo or sodium nitroprusside, which translated in a reduction of major adverse cardiac events (MACEs) and a better left ventricular remodelling at 1-year follow-up.[58,59]

Moreover, atrial natriuretic peptide (ANP), cyclosporine and exenatide, known to have cardioprotective effects, have shown beneficial effects on IS while the effect on indexes of CMVO is neutral or not reported.[60-62]

In particular, ANP, which activates the RISK cardioprotective pathways, limited enzymatic IS and improved LVEF.[60]

Again, exenatide, a glucagon-like peptide-1 agonist started 15 min before primary PCI and given intravenously for 6 h post procedure, increased salvage index but 30-day clinical events were similar as compared to placebo.[62]

Cardioprotection by mechanical remote conditioning (3 cycles of ischemia/reperfusion of the lower limb) at the time of primary PCI reduced enzymatic IS, and was associated with an improvement of T2-weighted edema volume assessed by CMR and STR as compared to conventional primary PCI.[63]

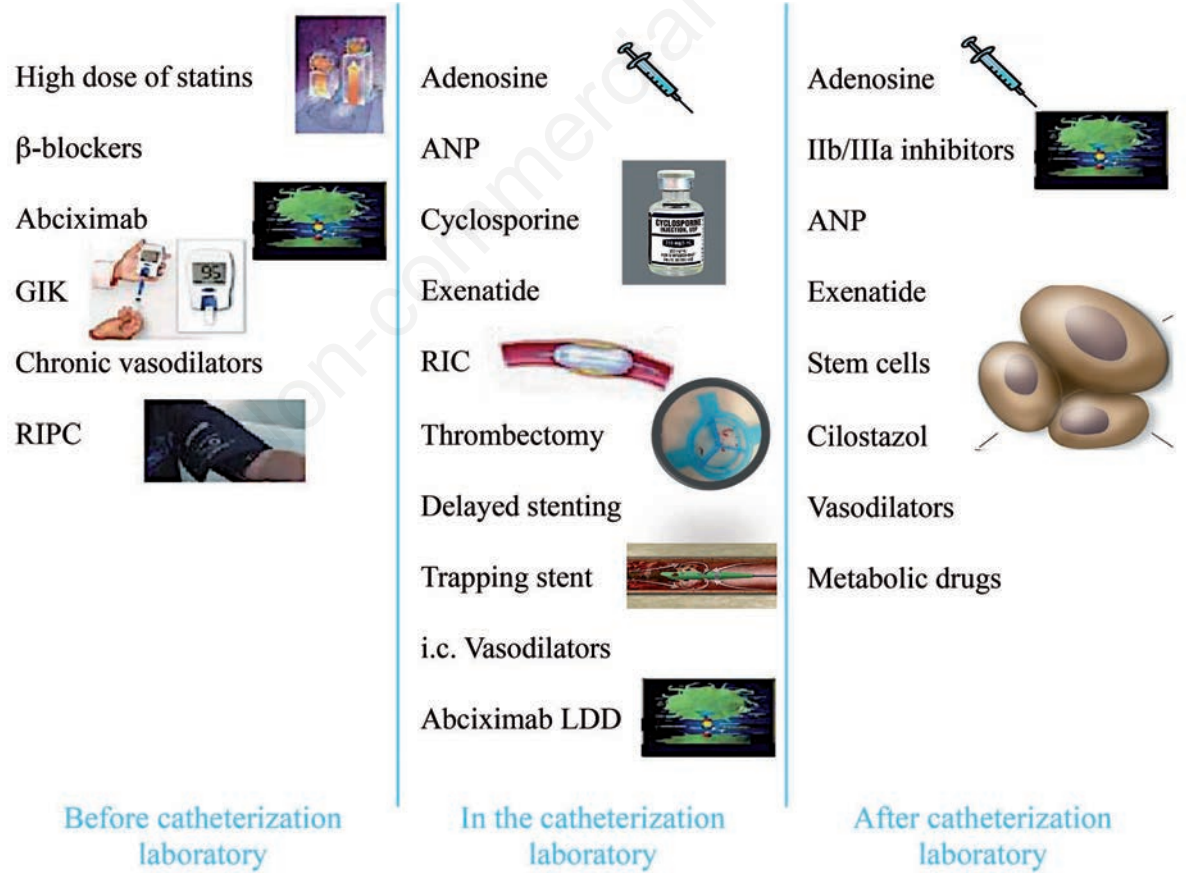

Figure 3. Current treatments of coronary microvascular obstruction in different time windows: before catheterization laboratory, in the catheterization laboratory and after catheterization laboratory. ANP, atrial natriuretic peptide; GIK, glucose insulin potassium; RIC, remote ischemic conditioning; RIPC, remote ischemic pre-conditioning; i.c., intra-coronary; LDD, local drug delivery.

Table 2. Main clinical studies about coronary microvascular obstruction management.

Therapeutic option	Year	SD	Pts (n)	Dose	Primary end-point	Notes	Ref
Before the catheterization laboratory							
Statins	2006	OS	293	Chronic statin pre-treatment	CMVO (assessed by MCE)	↓ CMVO and LV dimensions ↑ wall motion and LVEF	Iwakura *et al.*[44]
	2010	OL-RCT	171	Pre PCI: 80 mg *vs* 10 mg of atorvastatin; 10 mg of atorvastatin before PCI continued for 30 days	Clinical outcome: MACE at 30-days (death, nonfatal MI, and TVR)	↑ MBG and STR, no differences in clinical outcome	Kim *et al.*[45]
β-blockers	2014	SB-RCT	270	IV metoprolol (up to three 5 mg bolus)	Clinical outcome: composite of death, HF admission, re-MI and malignant ventricular arrhythmias	↑ LVEF and HF admission ↓ ICD indication	Pizarro *et al.*[46]
GpIIB/IIIa	2012	OL-RCT	110	IV bolus of 0.25 mg/kg Abciximab during transportation *vs* before PCI	IS (assessed by CMR at 6 months)	↓ IS (only if longer transportation time)	Petronio *et al.*[47]
	2009	DB-RCT	2452	IV bolus (2.5 mg/kg) of Abciximab + 12 h infusion before PCI *vs* IV bolus abciximab +12 h infusion after randomization *vs* IV bolus of abciximab +12 h infusion + reteplase	Clinical outcome: composite of all-cause mortality or complications of MI at 90 days	↓ IS (assessed by myocardial necrosis markers), no differences in primary end-point and mortality	Ellis *et al.*[48]
	2008	DB-RCT	936	25 μg/kg IV bolus of tirofiban and 0.15 μg/kg/min infusion of tirofiban *vs* placebo	CMVO (assessed by ST segment Deviation >3 mm at 1 h after PCI)	↓ CMVO before and 1 h after PCI	Van't Hof *et al.*[49]
Intermittent arm ischemia	2010	SB-RCT	251	Four cycles of 5-min inflation and 5-min deflation of a blood pressure cuff	IS (assessed by myocardial salvage Index through SPECT at 30 days)	↑ IS	Botker *et al.*[50]
	2010	OL-RCT	96	Three-4 min inflations/deflations of arm cuff (RIPC) delivered in ambulance and morphine *vs* RIPC only *vs* control	CMVO (assessed by STR)	↓ CMVO in group RIPC and morphine	Rentoukas *et al.*[51]
GIK	2005	OL/DB-RCT*	20,201	IV 1000 mL 25% glucose, 50 UI insulin, 80 mm KCl (1.5 mL/kg/h during 24 h) *vs* standard care	Clinical outcome: all cause of mortality at 30 days	No differences in mortality	Mehta *et al.*[52]
	2012	DB-RCT	871	In ambulance IV 30% glucose, 50 UI/L insulin, 80 mEq of KCl/L (1.5 mL/kg/h during 12 h)	Clinical outcome: shift away from ACS to MI within 24 h	↓ Cardiac arrest, in-hospital mortality and IS s (assessed by SPECT) at 30 days	Selker *et al.*[53]
Nitrates	2010	OS	52,693	Chronic nitrates pre-treatment	Clinical outcome: incidence of acute ischemic events	Shift away from STEMI to NSTEMI ↓ IS (assessed by myocardial necrosis markers)	Ambrosio *et al.*[54]
In the catheterization laboratory							
Adenosine	2006	DB-RCT	2118	50 or 70 μg/kg/min for 3 h starting within 15 min of reperfusion	Clinical outcome: composite of new onset in-hospital HF, and HF admission, or all cause	↓ 1-and 6 month mortality, primary 6-month clinical endpoint if reperfusion <3.17 h	Kloner *et al.*[55]

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Table 2. Continued from previous page.

Therapeutic option	Year	SD	Pts (n)	Dose	Primary end-point	Notes	Ref
	2010	SB-RCT	54	4 mg IC	Clinical outcome: feasibility, safety in MI (assessed by adverse clinical events) and CMVO (assessed by TIMI flow grade)	↓ CMVO and composite end-point ↑ LVEF	Marzilli *et al.*[56]
	2011	DB-RCT	110	4 mg IC	IS (assessed by CMR at 2-3 days)	No differences in IS	Desmet *et al.*[57]
	2013	OL-RCT	240	120 µg of adenosine (fast bolus) followed by 2 mg in 2 min, *vs* 60 µg of nitroprussiate (fast bolus) followed by 100 µg in 2 min, *vs* placebo	CMVO (assessed by STR ≥70% at 90 min after PCI)	↑ CMVO in patients treated with adenosine *vs* placebo, no differences in MACE (composite of cardiac death, MI, TLR, and hospitalization due to HF)	Niccoli *et al.*[58]
	2014	OL-RCT	240	120 µg of adenosine (fast bolus) followed by 2 mg in 2 min, *vs* 60 µg of nitroprussiate (fast bolus) followed by 100 µg in 2 min, *vs* placebo	CMVO (assessed by STR ≥70% at 90 min after PCI)	↑ Clinical outcome at 1 year ↓ LV remodelling and CMVO	Niccoli *et al.*[59]
ANP	2007	SB-RCT	569	IV 0-0.25 µg/kg/min of ANP after reperfusion, during 3 days *vs* IV 5% glucose solution during 3 days	IS (assessed by myocardial necrosis markers)	↓ IS ↑ of LVEF at 6 and 12 month follow-up	Kitakaze *et al.*[60]
Cyclosporine	2008	SB-RCT	58	IV bolus 2.5 mg cyclosporine (25 mg/mL) *vs* placebo, before reperfusion	IS (assessed by myocardial necrosis markers)	↓ IS and CK values	Piot *et al.*[61]
Exenatide	2012	DB-RCT	172	Bolus dose before 15 min of reperfusion: 0.12 µg/min during 15 min; Infusion dose: IV 0.043 µg/min during 6 h	IS (assessed by CMR at 3 months)	↑ Myocardial salvage index, no differences in clinical events at 30 days	Lonborg *et al.*[62]
RIC	2013	SB-RCT	100	3 cycles of 5 min/5 min ischemia/reperfusion by cuff inflation/deflation of the lower limb	IS (assessed by myocardial necrosis markers)	↓ IS ↑ Of T2-weighted edema volume and STR >50%	Crimi *et al.*[63]
Manual thrombus aspiration	2005	OL-RCT	99	Diver	CMVO (assessed by MBG and STR ≥70% after PCI)	↓ CMVO	Burzotta *et al.*[64]
	2008	OL-RCT	1071	Export catheter	Clinical outcome: cardiac death or non-fatal re-MI at 1 year	↑ MBG, STR and clinical outcome	Svilaas *et al.*[65]
	2008	OL-RCT	1071	Export catheter	Clinical outcome: cardiac death or non-fatal re-MI at 1 year	↓ 1-year cardiac death or non-fatal re-MI	Vlaar *et al.*[66]
	2013	SB-RCT	7244	Eliminate, Pronto and Export catheter	Clinical outcome: all-cause mortality at 30 days	No differences in 30 days mortality	Frobert *et al.*[67]
	2014	SB-RCT	7244	Eliminate, Pronto and Export catheter	Clinical outcome: all-cause mortality at 30 days	No differences in mortality, rehospitalization or MI, or stent thrombosis at 1 year	Lagerqvist *et al.*[68]

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Therapeutic option	Year	SD	Pts (n)	Dose	Primary end-point	Notes	Ref
	2015	OL-RCT	10,732	Export catheter	Clinical outcome: CV death, recurrent MI, cardiogenic shock or NYHA class IV HF within 180 days	No difference in clinical outcome	Jolly *et al.*[69]
AngioJet rheolytic thrombectomy	2010	OL-RCT	51	AngioJet rheolytic thrombectomy system	CMVO (assessed by early STR) and IS (assessed by SPECT)	↓ CMVO and MACE at 6-month follow-up; no differences in IS	Migliorini *et al.*[70]
Local-plaque trapping devices	2012	SB-RCT	433	MGuard stent system *vs* commercially available BMS and DES	CMVO (assessed by STR≥70% at 60 to 90 min after PCI)	↓ CMVO ↑ TIMI flow grade; no differences in mortality and MACE at 30 days	Stone *et al.*[71]
Local-delivery of abciximab	2010	OL-RCT	50	0.25 mg/kg of abciximab given by local delivery catheter before PCI	Clinical outcome: changes in thrombus score after PCI by OCT	↑ Changes of thrombus ↓ cTFC, MI and MACE at 1 year	Prati *et al.*[72]
Delayed stent	2014	SB-RCT	101	Intention-to-stent 4 to 16 h later or conventional treatment with immediate stenting	CMVO (assessed by TIMI flow-grade)	↓ CMVO ↑ Myocardial salvage index at 6 months	Carrick *et al.*[73]
Verapamil and diltiazem	2012	SB-RCT	102	*Verapamil:* Infusion dose: 100 µg/mL; bolus dose: 200 µg (up to 2000 µg) *Diltiazem:* Infusion dose: 400 µg/mL; bolus dose: 400 µg (up to 1000 µg); *vs* nitroglycerin	CMVO (assessed by cTFC)	↑ Complete STR at 3 h ↓ Peak Tn levels, and NT-proBNP levels at 1 and 30 days after PCI; no difference in cTFC	Huang *et al.*[74]
Nitroprusside	2006	DB-RCT	98	60 µg IC	CMVO (assessed by cTFC and STR≥70%)	No differences in CMVO and TLR, MI, or death	Amit *et al.*[75]
After the catheterization laboratory							
Abciximab	2005	OL-RCT	90	IV bolus dose: 0.25 mg/kg IV bolus; Infusion dose; 0.125 µg/min during 12 h	LV remodelling at 6 months (assessed by TTE)	↓LV remodelling ↑ STR rate	Petronio *et al.*[76]
Stem cells	2013	DB-RCT	42	IC stem cell therapy	IS (assessed by CMR at 3 years)	Blunted improvement of LVEF associated with stem cell treatment	Wohrle *et al.*[77]
Cilostazol	2013	OS	727	Loading dose: 200 mg Maintenance dose: 100 mg twice daily	Composite MACE (composite of all-cause death, MI, and repeated PCI or CABG), during 12 month follow-up	↓ Cardiac mortality, and MACE	Lee *et al.*[78]
Calcium antagonist and dypiridamole	2010	SB-RCT	46	*Dipyridamole dose*: IC 0.56 mg/kg; *Verapamil dose:* IC 1 mg	CMVO (assessed by TIMI flow grade, cTFC, TMPG)	↓ CMVO	Tanzilli *et al.*[79]
Ranolazine	2012	DB-RCT	70	1000 mg for ranolazine twice daily *vs* placebo	IS (assessed by myocardial necrosis markers)	↓ Of peri-procedural MI and IS	Pelliccia *et al.*[80]

*The CREATE trial utilizes a partial 2×2 factorial design comparing reviparin to placebo given for 7 days or until discharge [if discharge is earlier than 7 days (double blind)], and GIK *vs* control (open label) given for 24 h. ACS, acute coronary syndrome; ANP, atrial natriuretic peptide; APEX-AMI, assessment of pexelizumab in acute myocardial infarction; BMS, bar metal stent; CABG, coronary artery bypass grafts; CK, creatine kinase; CMR, cardiac magnetic resonance; CMVO, coronary microvascular obstruction; cTFC, corrected TIMI frame count; CV, cardiovascular; DB, double-blind; DES, drug eluting stent; EF, ejection fraction; GIK, glucose-insulin-potassium; HF, heart failure; IABP, intra-aortic balloon pump; IC, intracoronary; ICD, implantable cardioverter defibrillator; IPC, ischemic-post-conditioning; IS, infarct size; IU, International Unit; IV, intravenous; LAD, left anterior descending artery; LV, left ventricular; MACE, major adverse cardiac event; MBG, myocardial blush grade; MCE, myocardial contrast echocardiography; MI, myocardial infarction; min, minutes; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NSTEMI, non-ST elevation myocardial infarction; OL, open-label; OS, observational study; PCI, percutaneous coronary intervention; Pts, patients; RCT, randomized controlled trial; RIC, remote ischemic conditioning; RIPC, remote-ischemic preconditioning; RT, randomized trial; SB, single-blind; SD, study design; SPECT, single photon emission computed tomography; STEMI, ST-elevation myocardial infarction; STR, ST-resolution; TIMI, thrombolysis in myocardial infarction; TLR, target lesion revascularization; TMPG, thrombolysis in myocardial infarction myocardial perfusion grade; Tn, troponin; TTE, transthoracic echocardiography; TVR, target vessel revascularization.

If the TAPAS trial[65,66] confirmed the clinical efficacy of the initial promising data about the functional or structural indexes of CMVO,[64] the TASTE trial failed to show any mortality benefit at 1 year.[67,68] Eventually, the TOTAL trial has recently clarified as, in patients with STEMI undergoing primary PCI, routine manual thrombectomy as compared to PCI alone did not reduce the risk of cardiovascular death, recurrent MI, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days.[69]

The Angiojet mechanical thrombectomy device in the JETSTENT study showed an improvement in STR and a lower 1-year MACEs rate in the treatment group, compared to the direct stenting group.[70] Other approaches including stent with trapping capabilities[71] and local delivery of abciximab at culprit lesion level through special porous balloon[72] failed to improve clinical outcome. Interestingly, in a recent randomized study aimed at comparing a strategy of immediate stenting *vs* delayed stenting, the authors showed a lower rate of CMVO and greater myocardial salvage index at 6 months in the deferred group, thus suggesting that leaving time form residual thrombus dissolution before stenting may play an important role in the prevention of CMVO.[73]

Finally, the use of vasodilators, including verapamil, diltiazem, and nitroprusside[74,75] have been associated with improvement of flow by angiography, although clinical outcome data are lacking in calcium-antagonists[74] or controversial for nitroprusside.[75]

After catheterization laboratory

The aggressive risk factors modifications, guidelines based therapy and rehabilitation were all proven to have a significant impact on the recurrence of ACS and re-hospitalization and may exert their effect at least in part by improving coronary microvascular function. Furthermore, some drug infusion started in the catheterization laboratory may be continued in CCU. In particular, beneficial effects have been shown for IV IIb-IIIa inhibitors,[76] adenosine,[55] ANP[60] and more recently exenatide.[62] The duration of IV infusion for such therapies in CCU should be matter of future studies, as currently tested drugs have been administered for variable times from 3 h to 12 h. More prolonged therapies (up to 24 h) may possibly increase the rate of reversible CMVO, that has been described to occur spontaneously in nearly half of patients after 1 month.[82]

The utility of stem cells in CMVO has provided mixed results.[77,83] Indeed, improvement of CFR after cell therapy has not consistently been shown in all trials,[83] conversely in the presence of CMVO, the improvement of LVEF associated with stem cell treatment seems to be dampened.[77]

In a recent study, the addition of cilostazol (for 1 month) to double antiplatelet therapy with aspirin and clopidogrel in patients with angiographic CMVO improved the clinical outcome after 1 year.[78]

The use of vasodilators (calcium-channel antagonist, dypiridamole) or metabolic drugs (ranolazine) at discharge needs future research having as end-point reversion of CMVO.[79,80]

Finally, a continuous effort in improvement of coronary microvascular dysfunction is mandatory as it may predict a worse outcome even when the acute coronary occlusion has been solved by coronary stenting.

Conclusions

In the last years, several evidences have pointed out that CMVO may negate the benefit of PCI in the context of STEMI. Yet, most of the trials in this setting, mainly targeting reperfusion damage, have failed to show beneficial effects. This review article revises the mechanisms, diagnosis and prognosis of CMVO in acute STEMI, also proposing the notion of an integrated approach finalized to prevent and treat CMVO in different time windows of the acute event.

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