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REVIEW

Clinical update

Coronary microvascular obstruction in acute myocardial infarction

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The success of a primary percutaneous intervention (PCI) in the setting of ST elevation myocardial infarction depends on the functional and structural integrity of coronary microcirculation. Coronary microvascular dysfunction and obstruction (CMVO) occurs in up to half of patients submitted to apparently successful primary PCI and is associated to a much worse outcome. The current review summarizes the complex mechanisms responsible for CMVO, including pre-existing coronary microvascular dysfunction, and highlights the current limitations in the assessment of microvascular function. More importantly, at the light of the substantial failure of trials hitherto published on the treatment of CMVO, this review proposes a novel integrated therapeutic approach, which should overcome the limitations of previous studies.

Keywords Microvascular dysfunction • Microvascular obstruction • Acute myocardial infarction

Introduction

ST-segment elevation myocardial infarction (STEMI) usually results from acute thrombotic occlusion of a coronary artery and is a leading cause of death.[1] The goal of reperfusion therapy with fibrinolytic drugs or primary percutaneous coronary intervention (PCI) is to restore blood flow to ischaemic, but still viable, myocardium, and reduce infarct size (IS). Accordingly, reducing time to treatment and maximizing myocardial salvage—in keeping with the mantra that 'time is muscle'—represents a major challenge in the management of STEMI.[2] However, although national door-to-balloon times have improved significantly over the last years for patients undergoing primary PCI, in-hospital mortality has remained virtually unchanged.[3,4] Additional strategies are needed to reduce in-hospital mortality in this population and attention has to be turned to the development of systems addressing the continuum of STEMI care, from symptom onset through return to community. To this regard, an unmet need is to address the coronary microvascular functional and structural obstruction (CMVO), which occurs frequently even after prompt epicardial recanalization of the infarct-related artery. Coronary microvascular dysfunction has been shown to increase the risk of cardiovascular events regardless of the epicardial disease status.[5,6] Hence, at the time of reperfusion, patients with pre-existent microvascular dysfunction will benefit less from prompt reopening of the epicardial vessel, thus underscoring that, preserving a normal microvascular function before acute coronary occlusion, is a crucial target of preventive therapies for CMVO similarly to those aiming at restoring flow in the microcirculation during primary PCI and thereafter in the coronary care unit (CCU). In this article, we review mechanisms, diagnosis, and prognosis of CMVO in acute STEMI, also addressing the prevention and treatment of CMVO by highlighting the need for an integrated approach in different time windows.

Mechanisms of coronary microvascular dysfunction and obstruction

Pre-existing coronary microvascular dysfunction

Traditional and non-traditional risk factors play a role in epicardial and microvascular endothelial-dependent dysfunction, specifically in the high-risk subset with STEMI (*Figure 1*).[5,7] Furthermore, previous studies indicate that abnormal non-endothelium-dependent microvascular dilatation appears to be involved in functional and structural alterations that lead to impaired coronary flow reserve

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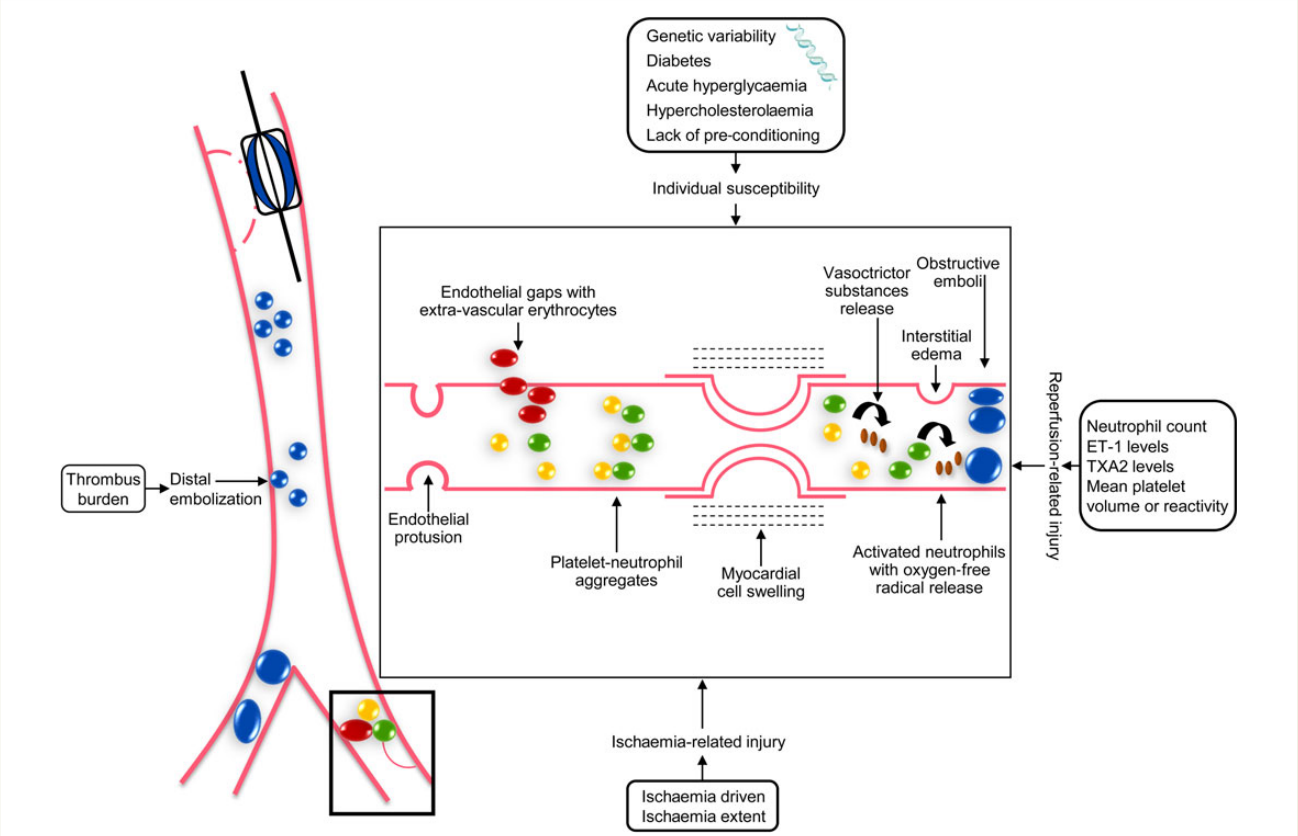

Figure 1 There are four interacting mechanisms involved in the pathogenesis of coronary microvascular obstruction in humans: ischaemia-related injury, reperfusion-related injury, distal embolization, and individual susceptibility (both genetic and due to pre-existing coornary microvascular dysfunction) of the microcirculation to injury. *Ischaemic injury:* it depends on duration and extent of ischaemia and is characterized by severe capillary damage, endothelial protrusions, and blebs that block the capillary lumen, and endothelial gaps with extra vascular erythrocytes (in red). Interstitial myocardial oedema compresses capillaries and small arterioles, further decreasing flow through these dysfunctional vessels, whereas sodium and calcium overload explains myocardial cell swelling. *Reperfusion injury:* the principal determinants of this phenomenon are represented by neutrophils (in green), endothelin-1, thomboxane-A2, and platelets (in yellow). The obliteration of vessel lumen by neutrophil-platelet aggregates is associated with release of vasoconstrictors and inflammatory mediators (in brown). Furthermore, in cardiomyocytes, reperfusion stimulates the production of reactive oxygen species by mitochondria further aggravating microvascular function. Finally, reperfusion may increase infarct size due to mitochondria swelling and cell rupture based on opening of the mitochondrial membrane permeability transition, as well as favour intra-myocardial haemorrhage. *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 procoagulant substances. Both thrombus and plaque features modulate the effect of distal embolization on coronary microvascular obstruction. *Individual susceptibility of the microcirculation to injury:* Factors modulating individual susceptibility to coronary microvascular obstruction are presented by genetic variability, diabetes, acute hyperglicaemia, hypercholesterolaemia, and lack of pre-conditioning.

(CFR) with aging, hypertension, diabetes, dyslipidaemia, insulin resistance, and chronic inflammatory diseases.[7]

In one study among patients without obstructive coronary artery disease (CAD), future cardiovascular events were limited to those with a reduction of coronary blood flow in response to intracoronary (IC) infusion of acetylcholine.[8] Of note, endothelial dysfunction represents an independent predictor of cardiovascular events.[9] Accordingly, the presence of angina without evidence of angiographic obstructive CAD is associated with the risk of cardiovascular events, underscoring the potential role of coronary microvascular dysfunction in the pathogenesis of acute coronary syndrome (ACS).[10]

More specifically, a pre-existing impairment of the myocardial microcirculation has been shown to yield greater vulnerability to PCI-related myocardial injury as well as a poorer long-term outcome.[11,12] A pre-existing transient or permanent microvascular dysfunction may contribute to the development and prognosis of ACS via reduction of coronary blood flow, leading to an alteration of shear stress which aggravates endothelial dysfunction in epicardial arteries and might enhance thrombus formation.[5]

Ischaemic injury

Four interacting mechanisms cause CMVO in humans: ischaemia-related injury, reperfusion-related injury, distal embolization, and individual susceptibility of the microcirculation to injury (*Figure 1*).[13,14] The first two mechanisms have been translated to humans from the animal models with a first description by Kloner *et al.*[15] Electron

microscopic analysis after 90 min coronary occlusion followed by reperfusion, revealed severe capillary damage, endothelial protrusions and blebs that appeared to block the capillary lumen, and endothelial gaps with extra vascular erythrocytes.[16] Due to the loss of the glycocalix with expression of P selectin on endothelial cells adhesion of inflammatory cells to the endothelium was common. Furthermore, interstitial myocardial oedema compresses capillaries and small arterioles, further decreasing flow through these dysfunctional vessels.[15] Sodium and initial calcium overload explains myocardial cell swelling, associated to mild opening of mitochondrial membrane permeability transition pores. Importantly, in this phase collateral circulation may protect from CMVO.

The most important clinical predictor of ischaemia-related injury is ischaemia duration, but ischaemic extent also plays an important role as confirmed by the association of electrocardiographic, echocardiographic, and angiographic indices of myocardial ischaemia extent and prevalence of CMVO.[17]

Reperfusion injury

When ischaemia lasts >3 h, ischaemia-associated injury is potentiated by reperfusion injury.[18] In particular, lethal reperfusion injury (myocardial necrosis due to reperfusion) and CMVO play a major role. Coronary microvascular dysfunction and obstruction is caused by further obliteration of vessel lumen by neutrophil-platelet aggregates, which in turn produce large amount of vasoconstrictors and inflammatory mediators.[19] Furthermore, in cardiomyocytes, reperfusion stimulates the production of radical oxygen species by mitochondria that along with rapid normalization of pH lead to opening of mitochondrial membrane permeability transition pores, calcium overload, mitochondrial swelling, and cell disruption.[19] Again, neutrophils, a major source of oxidants, proteolytic enzymes, and pro-inflammatory mediators in hearts reperfused *in vivo* after prolonged ischaemia, may exacerbate CMVO in humans.[19]

Moreover, endothelial cells can modulate leucocyte function by expression of adhesion molecules, e.g. intercellular adhesion molecule-1 or P-selectin, and by release of soluble factors including nitric oxide, prostacyclin, and endothelin.[17] Finally, functional changes during CMVO can be due to release of bioactive factors from coronary plaque (e.g. endothelin-1, tissue factor, and microparticles) which have the potential to increase the severity of the functional impairment of the coronary circulation. Interestingly, one study found that IC infusion of tissue factor in a porcine model caused CMVO.[20] Moreover, oxidative stress and ischaemia *per se* reduce the bioavailability of nitric oxide, further contributing to the dysfunction of the myocardial microcirculation.[17]

Ischaemia followed by reperfusion may also favour intramyocardial haemorrhage (IMH). Indeed, hypoxia can disrupt the endothelial barrier and damage the microvasculature and facilitate blood cell extravasation upon reperfusion, thus causing IMH. It is also possible that activation of inflammation and coagulation leads to thrombosis, endothelial activation, and therefore consumption of coagulation factors aggravating the haemorrhage.[21]

Specific cardiac magnetic resonance (CMR) sequences (T2-weighted and T2*-weighted) identify iron in the tissue, thus showing IMH in up to 40% of patients with CMVO. Of note, in an *in vivo* porcine model of reperfused STEMI, IMH at T2-weighted images and at histology showed a close anatomical correlation.[22]

Importantly, patients with this more severe form of CMVO seem to have a worse outcome than patients with CMVO but without IMH.[22]

Distal embolization

A fourth important mechanism of CMVO is distal embolization. Coronary micro-embolization in experimental models causes regional contractile dysfunction due to release of tumour necrosis factor-alpha. Of note, myocardial perfusion starts falling when microspheres obstruct >50% of coronary capillaries.[23] Thus, the small number of emboli during primary PCI in the setting of STEMI, although not affecting myocardial perfusion may create a local reacting milieu with release of inflammatory and vasoactive substances such as endothelin-1.[23] Moreover, recent evidences demonstrated that, in patients with STEMI, the coronary neutrophil extracellular traps (NETs) burden correlates negatively with ST resolution (STR) and positively with IS, thus suggesting that NETs may propagate thrombosis and inflammation distally into the infarcted myocardium and contribute to myocyte death during atheroembolism.[24,25] Similarly, microparticles content of embolized material may worsen reperfusion.[26] These observations suggest that embolized material is biologically active and that may aggravate reperfusion injury beyond its mechanical obstructive effect on the microcirculation.

Emboli of different size can originate from epicardial coronary thrombus and from fissured atherosclerotic plaques during primary PCI, but spontaneous embolization has been suspected also before vessel manipulation. In some cases, an abnormal flow after PCI could be due to the dislodgment of an obstructive thrombus distal to the culprit lesion. Of note, this phenomenon is not detectable by angiography thus requiring other methods of coronary imaging, like angioscopy and optical coherence tomography (OCT).[27,28] In this context, as suggested by a recent OCT study, the persistence of thrombus after stenting may lead to distal embolization even after stent deployment.[29] Interestingly, the effect of angiographically visible distal embolization on IS seems to be time-dependent.[30] Both plaque and thrombus features are associated to risk of distal embolization. In particular, thrombus volume is associated with the occurrence of distal embolization, as well as the presence of a lipid rich plaque.[31] Furthermore, plaque erosion is more prone to distal embolization when compared with plaque rupture in post-mortem studies, and is more frequently associated to infarctlets, thus suggesting that the thrombus type may play an important role. Hence, major predictors of distal embolization are thrombus burden as assessed by angiography or IC imaging, and plaque features as assessed by OCT.

Individual susceptibility

A fifth pathogenetic component of CMVO is represented by individual susceptibility to microvascular dysfunction, maybe related to the function, as well as to the structure and the density of the microcirculation.[13] Genetic factors may modulate adenosine-induced vasodilation. In particular, 1976T.C polymorphism of the adenosine 2A receptors gene was suspected to be related with a higher prevalence of CMVO.[32] Moreover, genetic variations within defined regions of VEGFA and CDKN2B-AS1 genes have been showed to be associated with coronary microvascular dysfunction, whereas sex-specific allelic variants within MYH15, VEGFA, and NT5E genes

seem to be related with an increased risk of coronary microvascular dysfunction in men.[33] Finally, patients with MVCO show a more compact fibrin network, possibly suggesting a genetic-mediated resistance to lysis.[34] Another factor modulating the individual susceptibility to CMVO is the presence of ischaemic pre-conditioning (IPC), which seems to protect both the myocardium and the coronary microcirculation.[13] Accordingly, pre-infarction angina might help preventing CMVO, by inducing IPC. Importantly, beneficial effect of pre-infarction angina may be blunted in humans due to risk factors or drugs therapy affecting unfavourably IPC,[35] while chronic nitrate therapy seems to stimulate IPC.[36]

Diagnosis of coronary microvascular dysfunction and obstruction

Diagnostic indices may be classified as invasive (*Figure 2A*) or non-invasive (*Figure 2B*) tools. Of note, the incidence of CMVO is variable, ranging from 10% by using angiographic assessment of thrombolysis in myocardial infarction (TIMI) flow to 60% by using CMR or myocardial contrast echocardiography (MCE).[37] Based on a combination of angiographic and electrocardiographic indices, a reasonable estimate of patients who get optimal myocardial reperfusion is ~35%.[13] Furthermore, due to its dynamic nature, in 50% of cases CMVO is irreversible, while in the remaining 50% it is reversible.[38] Of note, the majority of the studies assessing the incidence of CMVO were performed in patients with STEMI. Indeed, only few studies have assessed CMVO in patients with non-ST-segment myocardial infarction (NSTEMI). In particular, these studies included rather limited numbers of patients and their findings were controversial.[39,40] Recently, the largest study aimed at detecting the incidence of CMVO in a cohort of NSTEMI reported a frequency of 13.8%, also establishing the localization of the culprit lesion and a IS as independent predictors of CMVO.[41]

Invasive indices of coronary microvascular dysfunction and obstruction

The gold standard method for assessing microvascular function is the direct measurement of coronary blood flow velocity using an IC Doppler wire. In this context, the other tools currently employed to evaluate CMVO, such as ST elevation and biomarkers, may only to be considered as surrogate markers. The typical flow pattern associated to CMVO is characterized by: systolic retrograde flow, diminished systolic anterograde flow, and rapid deceleration of diastolic flow. The attenuated CFR response post-PCI is associated with future cardiovascular events.[42] However, the major obstacles with this method are the need for special equipment and the use of additional pharmacological interventions.

In this context, compared with CFR, the index of microvascular resistance (IMR) provides a more reproducible assessment of microcirculation, independent of haemodynamic parameters. Moreover, it has recently been shown to be a predictor of acute microvascular damage and 3-month left ventricular functional recovery after primary PCI.[43] Again, the hyperaemic microvascular resistance (HMR) index for Doppler-derived coronary flow has been shown to be associated with ventricular recovery and clinical outcome after STEMI.[44] All together, these insights from clinical pathophysiology could support therapeutic approaches beyond the primary PCI procedure itself.

Thrombolysis in myocardial infarction 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 3); 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.[45] However, CMVO may occur in nearly 50% of patients with TIMI flow 3. Gibson *et al.* described the TIMI frame count (TFC) index as the number of frames required for contrast medium to reach a standardized distal landmarks, that may stratify the prognosis of patients exhibiting TIMI flow 3 and correlate with invasive assessment of CFR.[46] 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), have been developed in order to shift the attention from the epicardial flow to the microcirculatory flow by angiography.[47,48] Myocardial blush grade is a densitometric method assessing maximum intensity of contrast medium in the microcirculation. More intensely, the myocardial blush and faster its clearance, better the microvascular perfusion. Myocardial blush grade is scored on a scale of 0–3, with higher scores indicating better perfusion. The TMPG assesses microvascular clearance of contrast medium and is scored again on a scale of 0–3. Both MBG and TMPG are able 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.[37] Angiographic methods to assess perfusion (TIMI, TFC, and MBG and TMPG) may have reproducibility concern outside core laboratory centres, thus invasive assessment of microcirculation during primary PCI are emerging including IC pressure and flow wires or their combination to detect the presence of CMVO.[37] However, no large studies have compared diagnostic accuracy of angiographic vs. wires obtained indices of CMVO so far.

Non-invasive indices of coronary microvascular dysfunction and obstruction

After primary PCI, incomplete STR has been related to CMVO and worse clinical outcome.[49] Different methods have been focused on the assessment of multiple leads or single leads showing maximum ST elevation at baseline.[49] Thus, 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.[50] Of note, residual ST-segment elevation was found to be an independent marker of CMVO in a recent study and approximately one-third of patients with TIMI flow Grade 3 and MBG 2–3 do not exhibit STR.[51] 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.[13]

Myocardial contrast echocardiography utilizes ultrasound to visualize contrast microbubbles with a rheology similar to that of red

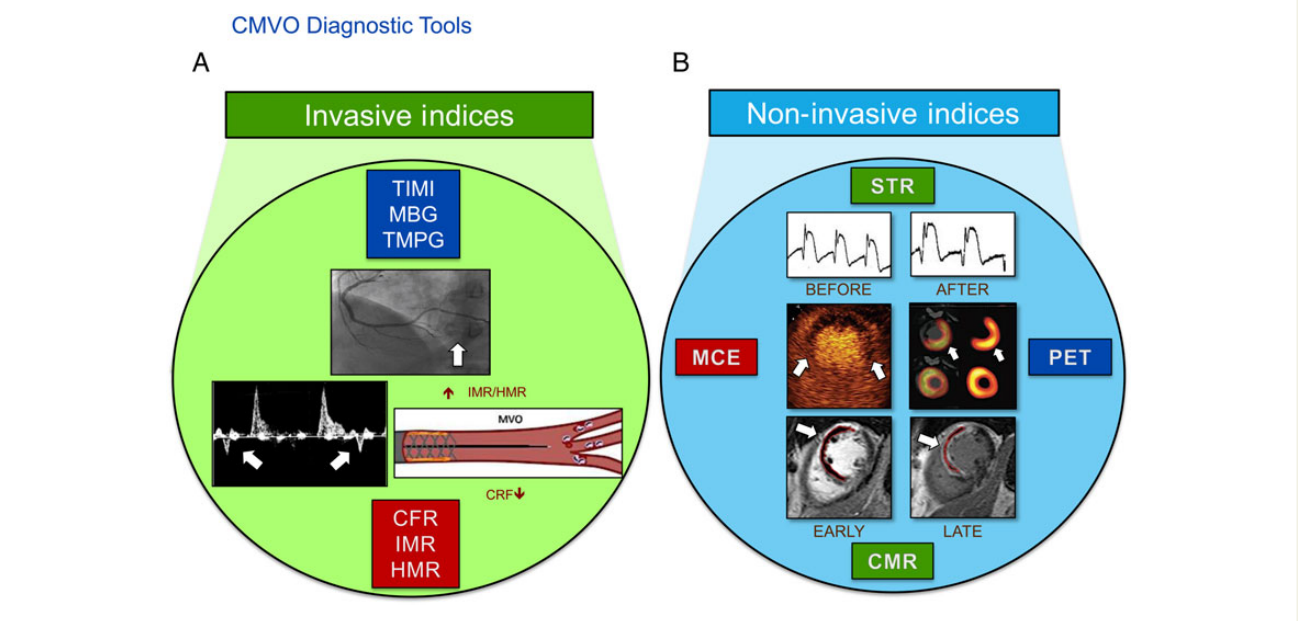

Figure 2 The diagnostic indices for coronary microvascular obstruction detection, classified as invasive (green circle) (*A*) or non-invasive tools (blue circle) (*B*). *Invasive indices*: The gold standard method for coronary microvascular dysfunction and obstruction assessment is the direct measurement of coronary flow reserve using intracoronary Doppler wire; the typical coronary microvascular dysfunction and obstruction pattern is characterized by systolic retrograde flow, diminished systolic anterograde flow, and rapid deceleration of diastolic flow. The figure at the bottom, left position, shows the systolic retrograde flow (white arrows) during intracoronary Doppler. The index of microvascular resistance provides a more reproducible assessment of microcirculation, independent of haemodynamic pertubations whereas hyperaemic microvascular resistance is associated with ventricular recovery and clinical outcome after ST-segment elevation myocardial infarction. The image at the bottom, right position, shows the typical pattern of coronary microvascular dysfunction and obstruction: reduced coronary flow reserve and increased index of microvascular resistance/hyperaemic microvascular resistance. Angiographic parameters of coronary microvascular dysfunction and obstruction are represented by thrombolysis in myocardial infarction flow score, myocardial blush grade, and thrombolysis in myocardial infarction myocardial perfusion grade. Of note, it is becoming common practice to define angiographic coronary microvascular dysfunction and obstruction as follows: thrombolysis in myocardial infarction flow grade <3 or 3 with an myocardial blush grade or thrombolysis in myocardial infarction myocardial perfusion grade 0–1. The image at the top shows a case of angiographic coronary microvascular dysfunction and obstruction (white arrow) in the posterior descending artery of the right coronary artery. *Non-invasive indices (light blue circle)*: ST-segment resolution represents an useful tool of coronary microvascular dysfunction and obstruction, also considering its prognostic value (see the image at the top, left position, for the ST before opening infarct-related artery; see the image at the top, right position, for the ST after opening infarct-related artery during coronary microvascular dysfunction and obstruction). Myocardial contrast echocardiography can be employed for coronary microvascular dysfunction and obstruction diagnosis. The typical pattern is represented by lack of intra-myocardial contrast opacification (indicated by white arrows, in the image in the centre, left position). Cardiac magnetic resonance allows multislice imaging with high tissue contrast and high spatial resolution, enabling accurate quantification, and localization of coronary microvascular dysfunction and obstruction and infarct size relative to the entire left ventricle; typical signs of coronary microvascular dysfunction and obstruction are represented by lack of gadolinium enhancement during first pass (indicated by white arrow, in the image at the bottom, on the left position) and lack of gadolinium enhancement within a necrotic region (late gadolinium hyper-enhancement) (indicated by white arrow, in the image at the bottom, on the right position). Finally, the hybrid positron emission tomography/cardiac computed tomography allows to monitor inflammatory reactions after reperfusion (indicated by white arrows, within the image in the centre, on the right position).

blood cells that freely flow within patent microcirculation while lack of intra-myocardial contrast opacification is due to microvascular obstruction that predicts functional recovery after STEMI.[52] Myocardial contrast echocardiography exhibits several limitations: moderate spatial resolution, operator dependency, and incomplete left ventricular coverage with suboptimal visualization of the lateral wall, and semi-quantitative assessment of CMVO.

Cardiac magnetic resonance allows multislice imaging with high tissue contrast and high spatial resolution, enabling accurate quantification and localization of CMVO and IS relative to the entire left ventricle. Cardiac magnetic resonance-defined CMVO correlates with MCE, angiographic, and invasive indices used for the assessment of CMVO.[53] In particular, it can be diagnosed 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 than late CMVO, as the latter underestimates the extent of CMVO. Cardiac magnetic resonance may give additional hints to the presence of IMH that appears to be consequence of microvascular injury in humans.[21,22] Indeed, a clinical study using CMR imaging for detection of IMH and MCE for detection of perfusion defects, demonstrated that IMH occurred in

patients with sizable contrast defects only.[54] Other imaging techniques have been utilized or are under investigation for CMVO detection including myocardial scintigraphy or hybrid positron emission tomography-computed tomography, with promising results as they may allow to monitor inflammatory reactions after reperfusion.[55]

Prognosis of coronary microvascular dysfunction and obstruction

Indices of CMVO predict adverse left ventricular remodelling and mortality after primary PCI (*Figure 3*; Supplementary material online, *Table S1*). In particular, TIMI flow ≤2 is associated with an increased risk of adverse remodelling at 6 months[58] and of 5-year mortality.[59] Myocardial blush grade 0–1 increases the risk of adverse remodelling at 6 months[60] and of total mortality after 16 months of follow-up.[61] Myocardial contrast echocardiography detected CMVO increases the risk of adverse remodelling at 6 months[52] and of cardiac death after 46 months.[57] Cardiac magnetic resonance detected CMVO increases the risk of adverse remodelling at 6 months[62] and of death.[63] The lack of STR increase the risk of total mortality after 30 days but failed to consistently predict adverse left ventricular remodelling.[58] The combination of poor MBG (0 to 1) and lack of STR showed an additive effect on the risk of total mortality after 1 year, thus suggesting that angiographic and ECG indices of CMVO may reflect different pathogenetic mechanisms.[56] Finally, CMR markers of myocardial damage (IS and especially CMVO) provided independent and incremental prognostic

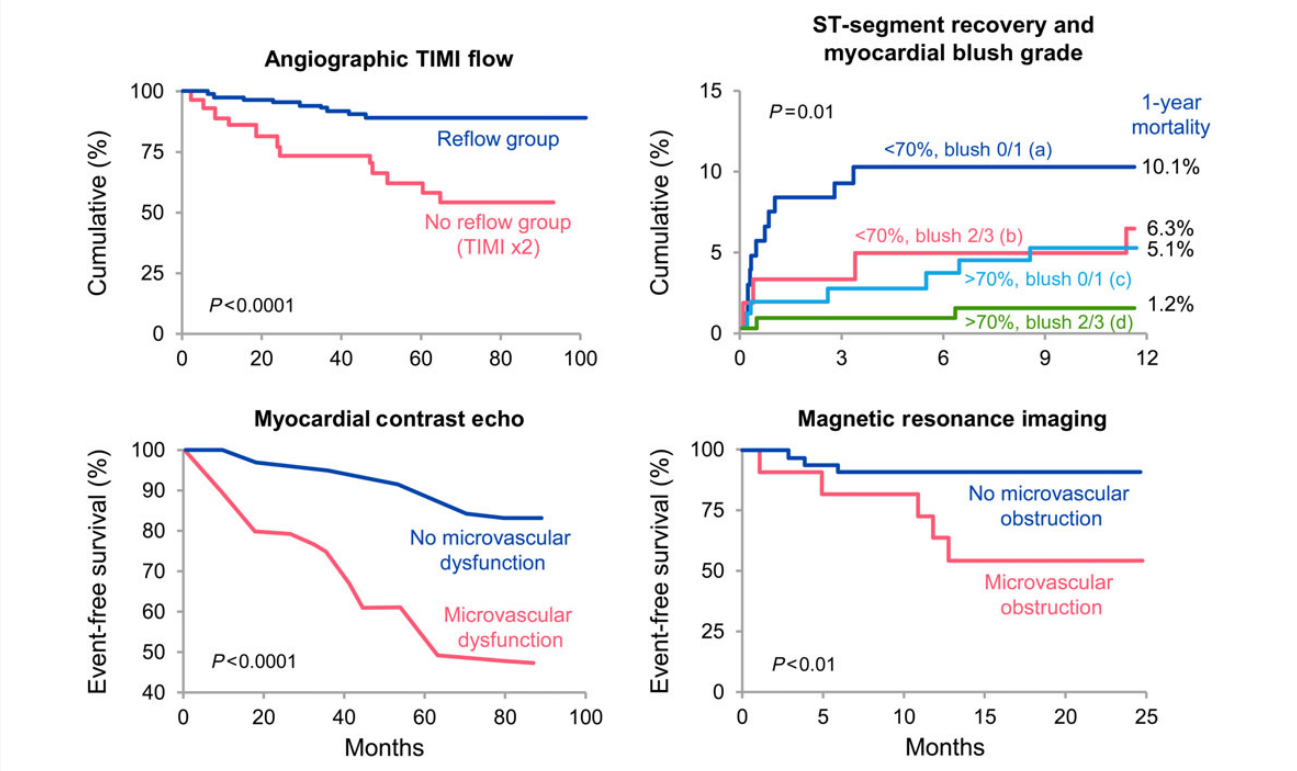

Figure 3 The prognostic role of coronary microvascular obstruction: at the top left, Kaplan–Meier survival curve showing, at long-term follow-up (100 months), that patients in the coronary microvascular obstruction group, evaluated by angiographic thrombolysis in myocardial infarction flow, had a significantly higher incidence of cardiac death (%), compared with those without coronary microvascular obstruction (log-rank $P < 0.0001$).[45] At the top right, Kaplan–Meier survival curve showing cumulative adverse event rates (%), according to myocardial blush grade, among patients with and without ST-segment resolution, during 1 year follow-up (log-rank $P = 0.01$). In particular, among patients with ST-segment resolution < 70%, the cumulative adverse event rate was 10.1% for myocardial blush grade 0/1, and 6.3% for myocardial blush grade 2/3. Among patients with ST-segment resolution > 70%, the cumulative event rate was 5.1% for myocardial blush grade 0/1, and 1.2% for myocardial blush grade 2/3.[56] At the bottom left, Kaplan–Meier survival curve showing combined event free survival (%) in patients with and without microvascular reperfusion, after perfused acute myocardial infarction, evaluated by myocardial contrast echocardiography. In particular, patients without microvascular reperfusion exhibit a higher cumulative 5-year combined event rate (long-rank test $P < 0.0001$), than those without microvascular dysfunction.[57] At the bottom right, Kaplan–Meier survival curve showing combined event free survival (%) in patients with and without microvascular obstruction, after perfused acute myocardial infarction, evaluated by magnetic resonance imaging. In particular, patients with microvascular obstruction exhibit a higher cumulative 2-year combined event rate (long-rank test $P = 0.001$) than those without microvascular obstruction.[22]

information in addition to clinical risk score and left ventricular ejection fraction (LVEF) in a recent large study in patients with STEMI.[64]

Treatment strategies in different time windows

During the years, many efforts have been made in order to detect an effective strategy to prevent and approach CMVO. In this context, management of CMVO should follow the same time windows of treatment commonly utilized for STEMI patients (*Figure 4*). Three phases may thus be identified. The first time window is broad and extends until hospital admission for STEMI. The second time window is in catheterization laboratory which provides the unique opportunity to target directly the coronary microcirculation supplied by the infarct-related artery. The third time window is, after catheterization laboratory, in the coronary care unit where both mechanical and pharmacological interventions may be implemented to reverse CMVO.

It has to be highlighted that currently no treatment has convincingly been proved to be beneficial for the prevention or treatment of CMVO in a multicenter controlled randomized trial with clinical endpoints. For this reason, in each time window, we have arbitrarily divided therapies into three groups: (i) therapies with evidence and/or general agreement of possible utility and that need to be tested in large trials with clinical endpoints, (ii) therapies that still need confirmation due to limited or conflicting evidence and/or divergence of opinion about their utility (controversial therapies), and (iii) therapies for which the general agreement is that they are ineffective (inadequate therapies) (Supplementary material online, *Table S2*, *Figure 4*). We hope that this approach might provide a comprehensive framework for setting up a coordinated therapeutic approach to the management of CMVO, which spans from prevention to treatment.

Before the catheterization laboratory

Therapies to be tested in large trials with clinical endpoints

Ongoing statin therapy at the time of STEMI was associated to a lower rate of CMVO, and better functional recovery of myocardial function after 6 months of follow-up when compared with patients not on statin.[65] Recently, the administration of high doses of statins prior to primary PCI has been found to improve CMVO when compared with that of low doses.[66]

Regarding β-blockers, pre-clinical studies showed that the third-generation β-blockers like carvedilol and nebivolol are able to

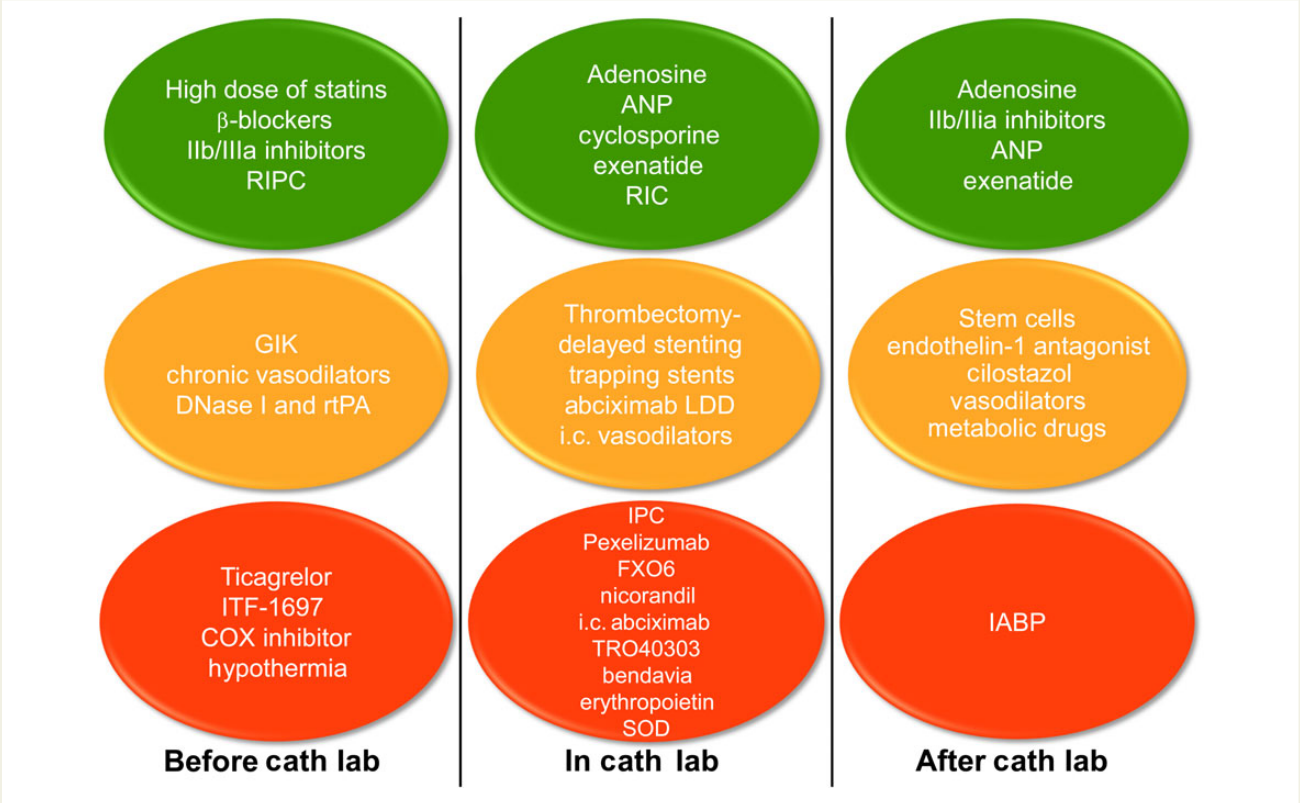

Figure 4 The current treatments of coronary microvascular dysfunction and obstruction in different time windows: before catheterization laboratory, in the catheterization laboratory, and after catheterization laboratory. In particular, the green circles show the therapies to be tested in large trials with clinical endpoints, the green circles report the controversial therapies and the ochre circles show the inadequate treatments. ANP, atrial natriuretic peptide; COX, cyclooxygenase; GIK, glucose–insulin–potassium; IABP, intra-aortic balloon pumping; IC, intracoronary; IPC, ischaemic post-conditioning; LDD, local drug delivery; RIC, remote ischaemic conditioning; RIPC, remote ischaemic pre-conditioning; rt-PA, recombinant tissue-type plasminogen activator; SOD, superoxide dismutase.

protect microcirculation and reduce the IS.[67,68] Of note, β-blockers given early after chest pain onset may be of utility. Intravenous (IV) metoprolol, administered in ambulance in patients with anterior STEMI on Killip class II or less, has been shown to reduce IS, increase LVEF, and reduce the need for implantable cardioverter-defibrillator implantation, with fewer admissions due to heart failure after 2 years.[69] Among antiplatelet drugs commonly used in STEMI patients, pre-hospital abciximab administration may be useful.[70] Of note, the FINESSE trial demonstrated that upstream administration of abciximab with half-dose reteplase significantly reduces IS but does not have any overall clinical benefit in primary study endpoint at 90 days as well as in mortality at 1 year.[71] On the other hand, the On-TIME-2 trial showed as a routine pre-hospital initiation of high-bolus dose tirofiban might improve STR and clinical outcome after PCI.[72]

Conditioning strategies can be implemented after chest pain onset only. Accordingly, Botker *et al.* showed that, applying three 5-min cycles of brief ischaemia 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.[73] Of note, adding morphine to remote ischaemic preconditioning (RIPC) protocol further improved of STR.[74] This form of protection is called RIPC, as ischaemia of an organ may lead to protection of a distant organ.

Controversial therapies

Results of studies with the glucose–insulin–potassium (GIK) in the setting of STEMI have been controversial.[75,76] The CREATE ECLA provided indeed neutral results with no difference in 30 days mortality with GIK when compared with placebo.[75] Conversely, the recent IMMEDIATE trial showed reduction in IS and lower rate of in-hospital mortality and cardiac arrest in patients randomized GIK than in controls, with trial treatment started in the ambulance by paramedics suggesting to start treatments very early after chest pain onset.[76] 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.[36,77]

Finally, evidence from a new experimental study proposed a therapeutic potential role of NET-targeted intervention in myocardial injury-reperfusion injury and CMVO.[78] Indeed, DNase I, which targets NETs, in combination with recombinant tissue-type plasminogen activator (rt-PA), which targets fibrin, should be an ideal option to disrupt the NET- and fibrin-provided mesh like backbone structure of thrombus.

Inadequate therapies

Apart from IIb–IIIa inhibitors, new oral antiplatelet drugs have provided conflicting results. In particular, a sub-analysis of PLATO trial, failed to find differences with regard to myocardial perfusion between clopidogrel and ticagrelor[79] and in large ATLANTIC study, pre-hospital administration of ticagrelor, in patients with acute STEMI, did not improve pre-PCI coronary reperfusion as assessed by STR.[80] Of note, among thienopyridines, ticagrelor only was tested in large clinical trials in order to evaluate its effect on pre-PCI coronary reperfusion. A small study using CMR to assess CMVO showed that clopidogrel pre-treatment in STEMI may improve reperfusion.[81] Finally, no data are available regarding the efficacy of prasugrel on CMVO.

ITF-1697, a C-reactive protein-derived tetrapeptide, was tested in a multicentre randomized double-blind study. In particular, IV infusion of four dosages of ITF-1697 or placebo was started before PCI and continued for 24 h. Post-procedure perfusion, assessed by TIMI flow, corrected TFC, MBG, and STR was similar for the placebo. Furthermore, the results showed no differences between the treatment regimes in enzymatic IS or clinical outcome up to 30 days.[82]

On the other hand, starting from previous consistent evidences,[83,84] a new theoretical basis for the clinical application of COX inhibitors in the prevention and treatment of CMVO has been recently provided,[85] although their thrombogenic action is likely to be an insurmountable limitation.

Finally, in the CHILL-MI study, hypothermia induced by cold saline and endovascular cooling failed to show a reduction of IS and CMVO.[86]

In the catheterization laboratory

Therapies to be tested in large trials with clinical endpoints

Adenosine can prevent CMVO through several mechanisms. The AMISTAD trial suggested that IV adenosine started before reperfusion might improve the outcome when given early (<3.2 h from chest pain onset) when compared with placebo.[87,88] In the last few years, other reports have provided mixed results regarding the role of IC adenosine.[89–93] Differences in way of administration, timing and dosages may explain these discrepancies. 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 when compared with 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.[94,95]

Atrial natriuretic peptide (ANP), cyclosporine, and exenatide, known to have cardioprotective effects, have shown beneficial effects on IS while the effect on indices of CMVO is neutral or not reported.[96–98]

In the J-Wind trial, ANP, which activates the RISK cardioprotective pathways, reduced enzymatic IS, and improved LVEF.[96]

Exenatide, a glucagon-like peptide-1 agonist, has been shown to reduce IS when administered at time of reperfusion in animal models. Exenatide, started 15 min before primary PCI and given intravenously for 6 h post-procedure, increased salvage index but 30-day clinical events were similar when compared with placebo.[98]

Cardioprotection by mechanical remote conditioning may be given during primary PCI. Indeed, a recent study showed that remote conditioning (3 cycles of ischaemia/reperfusion of the lower limb) at the time of primary PCI reduced enzymatic IS, and was associated with an improvement of T2-weighted oedema volume assessed by CMR and STR when compared with conventional primary PCI.[99]

Controversial therapies

Initial small single centre studies about thrombus aspiration showed promising results with regard to functional or structural indices of CMVO,[100] whereas clinical efficacy was then confirmed in the larger TAPAS[101]; indeed, at 1-year follow-up mortality was lower in patients randomized to manual thrombus aspiration than in those

randomized to conventional primary PCI.[102] Later, the TASTE trial randomized 7244 patients with STEMI to manual thrombus aspiration or to conventional primary PCI. Death from any cause after 30 days occurred in 2.8% and in 3.0% of patients, respectively.[103] After 1 year, no mortality benefit was associated with manual thrombus aspiration.[104] Eventually, the TOTAL trial has recently clarified as, in patients with STEMI undergoing primary PCI, routine manual thrombectomy when compared with PCI alone did not reduce the risk of cardiovascular death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days.[105] On the other hand, the Angiojet mechanical thrombectomy device in the JETSTENT study, that included patients with acute MI and angiographic evidence of large thrombus burden, showed improvement in STR in the treatment group. Importantly, after 1 year, MACEs rate were 14.9% in the Angiojet group vs. 22.7% in the direct stenting group.[106] Nevertheless, thrombus aspiration may have some limitations. In particular, one recent OCT study failed to show larger lumen area after thrombus aspiration when compared with that observed after conventional primary PCI.[29] Thus, other approaches including stent with trapping capabilities[107] and local delivery of abciximab at culprit lesion level through special porous balloon[108] failed to improve clinical outcome. Interestingly, in recent a study, patients with STEMI and at least 1 risk factors for CMVO were randomized to a strategy of immediate stenting vs. delayed stenting (the vessel was initially recanalized by thrombus aspiration or minimal balloon dilatation followed by IIb–IIIa infusion).[109] The authors showed 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.

Vasodilators may be given in the catheterization laboratory, including verapamil, diltiazem, and nitroprusside.[110,111] While all have been associated with improvement of flow by angiography, clinical outcome data are lacking for calcium-antagonists,[110] or controversial for nitroprusside.[111]

Inadequate therapies

Intracoronary administration of abciximab failed to improve MACEs (all-cause mortality, recurrent MI, and new heart failure) and CMVO rate at 3 months when compared with its IV administration.[112] Similarly, nicorandil, a hybrid drug of ATP-sensitive K-channel opener and nicotinamide nitrate, in the large J-WIND trial failed to improve clinical outcome.[96]

While RIPC given early before reperfusion is a promising therapy, post-conditioning that refers to stuttering or interrupted reperfusion with a series of brief coronary artery re-occlusion-reperfusion cycles before full and final reperfusion, had disappointing results.[113,114] Most but not all studies on post-conditioning have shown a beneficial effect on IS and CMVO.[113] However, the largest study so far published which randomized 700 patients to post-conditioning vs.. conventional primary PCI failed to show improvement of STR and clinical outcome at 30 days follow-up.[114] An appropriately sized study on post-conditioning with clinical endpoints and 3 years of follow-up is ongoing (DANAMI-3).

Opening of mitochondrial permeability transition pores has a central role in reperfusion injury, leading to mitochondria swelling and cell death. Thus, new area of investigation is focus on protecting the mitochondria during STEMI. Of note, IV infusion of TRO40303, an inhibitor of the mitochondrial permeability transition pores, failed to reduce IS or improve LVEF in patients with STEMI randomized vs. placebo in the MITOCARE study.[115]

The recent data emerged from EMBRACE study showed as Bendavia, another potential mitochondria-targeted peptide able to cross cell membranes and reduce ischaemia-reperfusion injury in animal models, did not reduce myocardial damage in STEMI patients.[116]

Drugs able to reduce lethal reperfusion injury have shown negative results. In particular, the APEX-AMI aimed at assessing the efficacy of pexelizumab, a humanized monoclonal antibody that binds the C5 component of complement, failed to improved 30-days mortality as well as TIMI-3 flow rate when compared with placebo.[117] On the other hand, the FIRE trial conducted to test the FX06, a peptide derived from human fibrin, failed to reduce IS or CMVO as assessed by CMR.[118] Of note, FX06 is able to compete with E1 fragments of fibrin for binding to an endothelial specific molecule, VEcadherin, thereby acting as an anti-inflammatory.

Finally, most of the studies on erythropoietin have shown no effect on IS,[119] and supersaturated oxygen therapy showed controversial results.[120]

After the catheterization laboratory

Therapies to be tested in large trials with clinical endpoints

The aggressive risk factors modifications, guidelines-based therapy, and rehabilitation all were proven to have a significant impact on the recurrence of ACS and re-hospitalization. This therapeutic approach may exert its effect at least in part by improving coronary microvascular dysfunction. Furthermore, as shown above, some drug infusions started in the catheterization laboratory may be continued in CCU. In particular, beneficial effects have been shown for IV IIb–IIIa inhibitors,[121] adenosine,[88] ANP,[96] and more recently exenatide.[98] The duration of IV infusion for such therapies in CCU should be matter of future studies, as currently tested drugs have been given for variable times from 3 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.[122]

Controversial therapies

The effect of stem cells on CMVO has provided mixed results.[123–125] Indeed, improvement of CFR after cell therapy has not consistently been shown in all trials,[123] conversely in the presence of CMVO, the improvement of LVEF associated to stem cell treatment seems to be blunted.[124] Finally, 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.[126]

The use of vasodilators (calcium-channel antagonist, dypiridamole) or metabolic drugs (ranolazine) at discharge needs future research having as endpoint reversion of CMVO, improved remodelling, and clinical outcome.[127,128] Finally, endothelin-1 may be another promising therapeutic target of.[129,130]

Inadequate therapies

Intra-aortic balloon pumping (IABP) is able to reduce myocardial oxygen demand due to systolic left ventricular unloading and increases myocardial perfusion.[131,132] However, Maekawa *et al.* failed to show an increase of mean diastolic flow velocity and peak diastolic flow velocity in left anterior descending by IABP in patients with angiographic CMVO.[131] Moreover, IABP failed to reduce IS in high-risk PCI.[132]

Conclusions

The role of the microcirculation in determining short- and long-term outcome following ACS continues to emerge. In this context, over the past decades many studies have focused on the potential mechanisms by which reperfusion damage contributes to the microvascular abnormalities. The current review highlights a novel aspects of the complex role of coronary microcirculation in ACS and promotes the notion that pre-existing coronary microvascular dysfunction may play a major role in determining CMVO and outcome of reperfusion strategies following primary PCI. Future trials should explore the effects of integrated treatments aimed at prevention and treatment of coronary microvascular dysfunction in this setting.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

A.L., F.C.: handled funding and supervision. G.N., G.S., A.L., F.C.: conceived and designed the research. G.N., G.S.: drafted the manuscript. A.L., F.C.: Made critical revision of the manuscript for key intellectual content. G.S., G.N.: the names of the authors who did anything else on the manuscript other than what we have listed.

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