Review Article

Interventional Cardiology

Coronary microvascular obstruction and dysfunction from pathophysiology

Abstract

Although the time to coronary revascularization of patients with acute myocardial infarction with ST-Segment Elevation (STEMI) has been significantly reduced in recent years, the occurrence of Coronary Microvascular Obstruction and dysfunction (CMVO) is still a common complication associated with a worse prognosis. Currently, there are still several questions regarding CMVO, first of all, the diagnostic methods are not yet established and adequately known; the correct quantification and the attribution of a real weight in terms of prognosis are still challenging; despite the numerous therapeutic strategies proposed, by the results of some recent clinical trials are conflicting, so the clinical management of such patients is still a matter of debate. In this review, we analyse the pathophysiological mechanisms of CMVO, possible assessment methods, current pharmacological and mechanical therapeutic strategies, and propose possible future therapeutic perspectives.

Keywords: Myocardial infarction • Cardiac magnetic resonance • Heart failure • Pathophysiology • Thrombolysis • Percutaneous coronary intervention

Abbreviations: TIMI: Thrombolysis In Myocardial Infarction; HEAP: Heparin in Early Patency; TASTE: Thrombus Aspiration in ST-Elevation; SCAAR: Swedish Coronary Angiography and Angioplasty; CMVO: Coronary Microvascular Obstruction; ATLANTIC: Administration of Ticagrelor in the Ambulance to Lower Ischemic Complications; INFUSE-AMI: Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction; AIDA-STEMI: Abciximab Intracoronary versus Intravenously Drug Application in ST-Elevation Myocardial Infarction; T-TIME: Trial of Low-dose Adjunctive Alteplase during Primary PCI for STEMI; OPTIMAL: Optimal Adjunctive Thrombolysis during Primary Angioplasty; RESTORE-MI: Randomized Efficacy Study of Tissue Plasminogen Activator (TPA), Angioplasty, and Intracoronary Stenting in Acute Myocardial Infarction; STRIVE: Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction; PPCI: Primary Percutaneous Coronary Intervention; STEMI: ST-Elevation Myocardial Infarction; AMISTAD: Acute Myocardial Infarction Study of Adenosine; CICERO: Comparison of Intensive Combination Therapy and Standard Therapy for Patients with Acute Coronary Syndromes; REOPEN-AMI: Randomized Evaluation of Intracoronary Versus Intravenous Abciximab and Aspiration Thrombectomy in Patients with Anterior Myocardial Infarction; CMVO: Coronary Microvascular Obstruction; REFLO-STEMI: Randomized Evaluation of intracoronary freeWAY STent versus conventional angioplasty in ST-Elevation Myocardial Infarction; MACEs: Major Adverse Cardiovascular Events; J-WIND: Japanese Coronary Artery Disease (CAD) with Nicorandil Study; COAR: Comparison of Angioplasty and/or Rotational Atherectomy; NSTEMI: Non-ST-Elevation Myocardial Infarction; DEFER-STEMI: Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or slow-reflow in Acute ST-Segment Elevation Myocardial Infarction; DANAMI: Danish Multicenter Randomized Study on

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Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction; AMIHOT: Acute Myocardial Infarction With HyperOxemic Therapy; IC-HOT: Intracoronary Hyperoxemic Oxygen Therapy

Introduction

The past few decades have seen a significant decrease in morbidity and mortality following ST-Segment Elevation Myocardial Infarction (STEMI), primarily as a result of the establishment and widespread of intensive care units and the use of timely reperfusion techniques like urgent Primary Percutaneous Coronary Intervention (PPCI) [1]. However, mortality linked to this pathology remains high; one of the reasons is undoubtedly linked to the onset of myocardial reperfusion damage, due to Coronary Microvascular Obstruction and dysfunction (CMVO). In fact, obtaining revascularization of the epicardial coronary arteries through angioplasty is not associated with adequate myocardial reperfusion in all patients; a condition known as the no-reflow phenomenon. The no-reflow phenomenon is the angiographic manifestation of microvascular dysfunction and obstruction; the two terms are often used synonymously [2].

Currently one of the main aims in the treatment of patients with STEMI is to achieve a reduction in the infarcted myocardial area; in fact, infarct size is a major determinant of ventricular function and clinical ischemic complications, so by reducing it; it's possible to reach lower mortality rate and an improvement in prognosis. Considering the significant role of microvascular impairment as another determinant of the patient's prognosis; precise knowledge of the mechanisms responsible for microvascular obstruction, the implementation of techniques aimed at preventing the latter, its early identification, and the implementation of effective therapeutic measures could help to achieve these objectives.

Literature Review

Mechanisms

It is known that obtaining adequate blood flow at the level of the epicardial coronary arteries, by angioplasty with eventual coronary stent implantation, does not correspond in all cases to achieving an effective degree of myocardial reperfusion [3]. From an angiographic point of view, once coronary angioplasty has been completed, it is possible to state the quality of the flow obtained, by means of the "Thrombolysis in Myocardial Infarction (TIMI) flow grade" score, according to which a grade lower than 3 corresponds to poor flow or even no-reflow [4]. Electrocardiographically, a failure to reduce ST-segment elevation by at least 70% at one hour after primary coronary angioplasty is likely to be associated with poor regional microvascular flow [5]. However, the imaging diagnostic test that currently represents the gold standard in identifying microvascular obstruction is Cardiac Magnetic Resonance (CMR); which in sequences sampled after contrast agents' injection, detects CMVO as a strongly hypointense area (black zone), within the area of late gadolinium enhancement (hyperintense zone) which represents the infarcted myocardium.

The pathophysiology of the no-reflow phenomenon is markedly complex; there are several mechanisms that have been described and thought to be responsible for the failure to restore flow at the microvascular level in a previously ischemic area despite the re-opening of epicardial vessels.

Ischemic damage, especially if prolonged over time, inevitably leads to cardiomyocyte death. The death of cardiomyocytes in the context of oxygen deprivation occurs by necrosis, a process that involves cellular and mitochondrial swelling, formation of numerous reactive oxygen species, disruption of the cell membrane, and release of pro-inflammatory substances (including toxic substances contained in lysosomes) into the circulation. The release of various catabolites (ammonium, lactates, ions, glycogen derived substances) alters the chemical-physical characteristics of the interstitial space; in particular, it modifies its pH and osmotic power, so as to cause cellular swelling and interstitial edema; furthermore, a real inflammatory cascade is activated [6-8].

Predictive significance and prognosis

The no-reflow phenomenon is an independent predictor of short-term and long-term mortality, but also of hospitalization for Heart Failure (HF) [9,10].

Many risk factors have also been shown to be associated with the development of the no-reflow event; such as diabetes, hypertension, dyslipidaemia, and smoking [11,12].

Other possible prognostic factors appear to be advanced age, high thrombotic burden, and delayed presentation to the emergency department [13]. For this purpose, a risk score has been created, which takes into account clinical characteristics, angiographic and coronary physiology-derived parameters [14,15].

Moreover, according to imaging studies, individuals with MVO develop higher left ventricular end-systolic volumes and adverse left ventricular remodelling, despite optimal medical treatment [16,17]. In particular, it appears that MVO may result in extravasation of red blood cells, which causes intramyocardial haemorrhage and consequently a reduction in the ejection fraction and an increase in infarct size. It is also linked to a prolonged filtered QRS, a sign of arrhythmic risk [18].

Lastly, another potential imaging prognostic factor is the presence of late gadolinium MVO and its extension in the myocardial wall [19].

Diagnostic methods

For the detection of MVO, invasive and non-invasive methods can be used. Regarding invasive methods, the standard for MVO identification is the measurement of Coronary Flow Velocity (CFV) pattern using a Doppler guidewire. In this context, the presence of systolic retrograde flow or the reduction of systolic anterograde flow associated with a rapid deceleration of diastolic flow represents the characteristic pattern of MVO; and this one could be a possible predictor of complications and in-hospital survival after AMI [20].

Moreover, Coronary Flow Reserve (CFR) offers details regarding microcirculation (obviously in the absence of epicardial coronary stenosis) by calculating the ratio of coronary flow during peak hyperaemia to coronary flow at rest. An estimate<2 is related to the presence of MVO [21,22].

An additional parameter to recognize MVO could be represented by the microvascular resistance index, which is based on the distal coronary pressure and the mean transit time of a bolus of saline solution during maximum hyperaemia (using the thermodilution method). In particular, the Index of Microcirculatory Resistance (IMR)>25 indicates the presence of MVO, while an IMR>40 correlates with a higher rate of mortality and rehospitalization for heart failure at 1 year [8,23,24].

On the other hand, new methods have been developed for the evaluation of the coronary microcirculation, such as Angiography-derived index of microcirculatory resistance (IMRangio), a pressure-wire-free index which with a higher reproducibility calculates the assessment of coronary microvascular function [25], and CorFlow Therapy™, a modern device that assesses transitory coronary occlusion by inflating balloons, gradually introducing crystalloids while simultaneously measuring the pressure distal to the balloon [26].

As written before, TIMI<3 is a possible marker of larger infarct size as well as MVO, and it has been demonstrated that it could influence long and short-term prognosis [27]. Through this well-known method it is also possible to quantify the number of frames necessary for the contrast agent to fill the totality of coronary arteries, and in this way to verify the physiology of the microcirculation [28].

To focus more on the microcirculatory flow, angiographic techniques based on the diffusion of the dye into the myocardium have been developed, determining what is defined as Myocardial Blush Grade (MBG). MBG values range from 0 to 3, where higher values correspond to better perfusion; while values of 0 or 1, even in the presence of a TIMI 3, could indicate MVO and could be a strong angiographic predictor of mortality [29-31].

Instead, as regards non-invasive diagnostic, gadolinium-enhanced cardiac MRI is considered the gold standard for the diagnosis of no reflow, allowing the quantification of MVO and Infarct Size (IS) [32]. By using various techniques, cardiac MRI permits viewing myocardial damage; in particular, through T1, T2, and T2* mapping, it is feasible to quantify the entity of myocardial injury and to evaluate the extracellular volume. Additionally, T2 sequences could detect the presence of myocardial oedema (i.e. hyperintense core) and/or myocardial haemorrhage (i.e. hypointense core), the latter as an independent predictor of adverse LV remodeling [33-35].

During first-pass perfusion sequences, MVO usually manifests as a perfusion defect; while after administration of contrast agent, MVO can be identified as a hypointense necrotic core surrounded by the hyperintensity of necrotic myocardium, visible in the first minutes (early gadolinium enhancement) and after 10-15 minutes (late gadolinium enhancement). Compared to late MVO, which could understate the amount of MVO, early MVO is more sensitive, and for this reason, mostly used in the evaluation of this pathological process [36-38].

Similarly, areas of MVO can be also identified as regions of hypoperfusion on contrast-enhanced echocardiography, nuclear imaging with positron emission tomography, and single-photon emission computed tomography [39-42].

Finally, among the non-invasive methods, residual ST-elevation on the post-procedural ECG and/or the presence of Q waves provide important additional data on the prognosis and microvascular status [43,44].

How to treat

Although no-reflow has been a recognized phenomenon for many years, there is currently no strong evidence regarding its treatment; clinical trials conducted on different treatment strategies have resulted in improvements on several surrogate endpoints, but few have had real impacts on cardiovascular mortality [45]. Currently, the primary therapy for no-reflow involves intracoronary drugs responsible for coronary arteries dilatation; in fact, several studies suggest that vasodilator medications (e.g. adenosine, calcium channel blockers, sodium nitroprusside) and antiplatelet therapies (e.g. glycoprotein IIB/IIIA inhibitors) may be effective, either alone or in combination. Alongside these strategies, other non-pharmacological approaches have been investigated in different trials; these treatment options include coronary post-conditioning,

remote ischemia conditioning, and instruments to prevent thrombotic material embolization.

Below we review the available pharmacological and nonpharmacological therapies and the most promising ones for the future.

Pharmacological treatment

Among the various pharmacological therapies suggested to reduce microvascular obstruction in patients with STEMI, those recognized as having the greatest clinical benefits are therapies with antithrombotic agents and those with vasodilators.

Antithrombotic agents: Different classes of antithrombotic drugs have been employed in this clinical setting: Antiplatelet, anticoagulant, and thrombolytic agents.

Antithrombotic molecules could reduce CMVO by a dual action: Promoting its dissolution and reducing the risk of formation of other thrombotic material at the level of the lesion itself. Time plays a key role; the earlier these drugs are administered, the greater the chances of achieving a significant benefit in terms of reducing atherosclerotic burden [46].

In the past few years, the approach of facilitated primary angioplasty using Glycoprotein IIb/IIIa Inhibitor (GPI) or thrombolytics was attempted, however, the results obtained were not appreciably satisfactory, so this strategy was almost completely abandoned [47].

Parenteral anticoagulants: The role of intravenous anticoagulants not only counterbalances the pro-coagulant effect of catheters inserted for coronary angioplasty but also in the mechanism of thrombus dissolution; this is supported by some trials that have tested the ability to improve TIMI-flow, infarct area and 30-days mortality reducing of heparin or aspirin administration before primary angioplasty [48,49]. The HEAP trial that compared the administration of heparin at different dosages versus placebo before angioplasty showed no significant benefits obtained from administration of that drug [50]. Different results come from the TASTE trial [51], and the SCAAR registry, which state that unfractionated heparin injection before primary angioplasty leads to better coronary flow; therefore, heparin should be used alone or in combination with glycoproteins inhibitors, under no-reflow conditions after the angioplasty procedure.

Oral antiplatelet agents: Potent oral P2Y12 inhibitors have been demonstrated to have direct cardioprotective effects in animal trials, lowering the infarct size [52]; this is in addition to the possible decrease of CMVO and infarct size *via* diminishing the thrombus load and distal embolization. Data from the ATLANTIC trial suggest that there are no significant differences in terms of ST-segment resolution and post-procedural TIMI flow between those taking ticagrelor prior to hospital admission and those taking it in hospital [53]. Observational studies have shown that high doses of clopidogrel are able to reduce CMVO detected by CMR [54,55]. In addition, the use of ticagrelor compared to clopidogrel has been shown to reduce microvascular obstruction in patients with acute coronary syndrome [56,57].

Parenteral antiplatelet agents: Prior to the widespread use of dual antiplatelet medication, glycoprotein IIB/IIIA inhibitors were effective antiplatelet medicines that prevented platelet aggregation [51]. Studies demonstrating the clear advantages of glycoprotein IIB/IIIA inhibitors in addition to conventional treatment have not been conducted to yet [58]. Moreover, there is still conflicting data in the literature regarding the best way to administer these molecules: Intravenous or intracoronary. The CICERO trial [59], and the INFUSE-AMI [60], study showed the clear benefits of intracoronary infusion of these drugs in reducing the extent of the infarcted myocardial area; on the other hand, the AIDA-STEMI trial [61], did not show clear differences in outcomes between the two modes of administration. According to the last international guidelines, if angiographic evidence of a big thrombus, sluggish or no reflow, or other thrombotic complications is present, using a GPI as a bailout treatment is advised. Current international guidelines do not suggest the routine use of these drugs, but only if the angiography shows a large thrombus, slow-reflow or no-reflow, or other thrombotic complications [62]. Several clinical trials (such as the NCT04957719 that's testing Selatogrel that's a P2Y12i; and CT04825743 that's testing Zalunfiban which is a GPIs) are underway, and they are investigating different new formulations of antithrombotic drugs that could be used at the time of diagnosis. For patients with STEMI undergoing PPCI, Cangrelor offers quick and strong P2Y12 inhibition, which may minimize the extent of the infarct and CMVO. Further data on the efficacy of cangrelor, as opposed to placebo, in lowering infarct size and CMVO in STEMI patients receiving pre-PPCI (pre-Primary Percutaneous Coronary Intervention) or during PPCI is to be obtained from the ongoing PITRI-trial (Platelet Inhibition to Target Reperfusion Injury) [63].

Intracoronary fibrinolysis: The role of fibrinolytic therapy is not yet fully defined; some early studies have shown great benefits in terms of myocardial perfusion, but subsequent studies have obtained conflicting data. The recent randomized clinical trial T-TIME [64], showed that low-dose of intracoronary alteplase

didn't improve MVO. The OPTIMAL [65], RESTORE-MI [66], and STRIVE [67], studies will yield additional data about the security and effectiveness of low-dose thrombolytics during PPCI in STEMI patients.

Vasodilators: Vasoconstriction is a major contributor to CMVO, mediated by receptors in epicardial conduit arteries and micro vessels, and several signaling molecules (such as endothelin, serotonin, and thromboxane).

- ***Calcium Channels Blockers (CCBs):*** CCBs (verapamil, diltiazem, nicardipine) are used to treat no-reflow through various mechanisms; they act through smooth muscle relaxation and coronary vasodilatation. Analyzing the literature, we find that some studies have shown that the use of verapamil and diltiazem leads to significant benefits relative to the no-reflow phenomenon [44,68,69].
- ***B-Blockers (BBs):*** This category of drugs as long known, implements a protective action against the heart muscle and limits the extent of ischemic damage. Some molecules, such as carvedilol and nebivolol, have shown efficacy in protecting microcirculation during acute myocardial infarction in pre-clinical studies [30]. According to current ESC guidelines intravenous beta-blockers (preferably metoprolol) should be considered (IIa) at the time of presentation in patients undergoing PPCI with no signs of acute heart failure, an SBP>120 mmHg, and no other contraindications [62].
- ***Adenosine:*** It's a purine nucleoside with a short half-life (<2 s), it has different synergic actions such as vasodilating the coronary microcirculation and relaxing smooth muscle; it has also anti-inflammatory and anti-platelets effects. Its contribution to vasodilation is mediated by the activation of the A2A receptor on endothelial cells. Numerous RCTs tested the administration of different dosages of adenosine with different results. According to the results of a small RCT [70], administration of an intracoronary high dose of adenosine (4 mg) before PPCI could result in a lower incidence of the no-reflow phenomenon, and could improve clinical outcomes. The AMISTAD I and AMISTAD II trials [71,72], investigated the effects of different doses of intracoronary adenosine during thrombolysis or PPCI; only the highest dose (70 μg/kg/min for 3 h) of adenosine administrated within the first 3 hours from symptoms onset, led to an improvement in strong clinical outcomes such as heart failure occurrence and mortality. REOPEN-AMI trial [73,74], showed that higher dosages (120 μg as a fast bolus, followed by 2 mg as a slow bolus) of intracoronary adenosine after thrombus aspiration, allowed to improve CMVO, identified as ST-segment resolution, as well as reduction of enzymatic values; this strategy was compared to placebo and sodium nitroprusside. By contrast, in the REFLO-STEMI trial [75], patients with STEMI who received a high dose of intracoronary adenosine (2 mg-3 mg total) immediately after thrombectomy and after stenting had an increase in infarct size and MACEs, with a greater degree of reduction of left ventricle ejection fraction. A meta-analysis found that intracoronary adenosine in patients with acute coronary syndrome and long ischemic time was associated with an increased number of atrio-ventricular blocks, and ventricular arrhythmias, without offering clinical benefits [76]. These studies imply that intracoronary adenosine may reduce CMVO. However, further study is needed to determine a standardized dosage and timing for optimal clinical outcomes.
- ***Sodium nitroprusside:*** The REOPEN-AMI trial [74], and REFLO-STEMI [75], agreed that intracoronary sodium nitroprusside administration at the time of PPCI was of little use in terms of reducing CMVO. Ultimately, these findings imply that nitroprusside should not be administered regularly during PPCI in patients with STEMI, since its effectiveness and dosage finding require additional exploration.
- ***Nicorandil:*** Nicorandil stimulates coronary artery vasodilation by donating nitric oxide and opening ATP-sensitive K^+ channels. This reduces cardiomyocyte death and mimics ischemic preconditioning. According to the results of J-WIND trial [77], intravenous administration of nicorandil didn't significantly modify enzymatic infarct size. The CHANGE trial [78], which studied 238 patients with STEMI, found that nicorandil (6 mg bolus followed by continuous infusion at a rate of 6 mg/h) before PPCI, improved CMVO and infarct size assessed by CMR, both short-term and long-term. Patients of the CHANGE trial were at higher risk due to long ischemia time, which was responsible for higher incidence of no-reflow and larger infarct size, if compared to patients of the J-WIND trial. Moreover, a meta-analysis of 2055 patients with STEMI, showed that intracoronary administration of nicorandil during PPCI improved coronary blood flow and preserved LVEF, with reduced occurrence of MACE [79]. Overall, intravenous treatment with nicorandil before or before PPCI in patients with STEMI might be considered to reduce CMVO, but stronger data from bigger trials are still needed.
- ***Adrenaline:*** It is responsible for vasodilation through B2

adrenergic receptors agonism. An observational study showed that intracoronary adrenaline during PPCI in patients with STEMI and coronary no-reflow led to improve both TIMI flow and clinical outcomes (composite of death or heart failure) [80]. The COAR trial [81], compared intracoronary adrenaline and adenosine in patients with ACS, no-reflow and normotension; the group with adrenaline had on average improved TIMI flow but not significantly lesser adverse clinical events.

Pharmacological treatment

Mechanical treatment: The scientific evidence relating distal embolization to CMVO during PPCI in STEMI patients has led to the need for supplementary devices that might reduce this risk. Devices that collect embolic material distal to the culprit lesion or minimize thrombus load at the level of the thrombotic plaque are currently under development to handle distal embolization during PPCI. Despite its considerable theoretical utility, the use of distal filter protection in the coronary branches was marred by numerous practical difficulties (for example the risk of passing through the culprit lesion and causing embolization and the risk of device entrapment), and there were few real clinical benefits; Therefore, this technique has been almost completely abandoned.

On the other hand, more encouraging outcomes have been seen with the development of mechanical devices to lessen the thrombus load, the procedure is known as "thrombectomy") [82]. Thrombectomy may be performed manually or mechanically.

During manual thrombectomy, also known as "manual thrombus aspiration", the vacuum is produced.

The use of such devices has spread rapidly due to the relative ease of use, and potential data from early randomized clinical trials [83,84]. Several RCTs have followed over the years with mixed results regarding the true efficacy of this method. Two multicenter trials have supported the absence of clinical benefit in the systematic use of manual thrombectomy. A subsequent meta-analysis confirmed the efficacy of the use of thrombo-aspiration in terms of reducing cardiovascular mortality, in the face of an increased incidence of cerebrovascular events [85]. Other more recent studies highlight the possible greater utility of the method in the clinical setting of NSTEMI rather than STEMI [86]. Thrombo-aspiration, to date is a method to be used by experienced operators during PPCI, only under specific clinical conditions, especially if a high atherosclerotic burden is present.

Among the most potential mechanical mechanisms of thrombus removal are retrieval stent systems that are able to be expanded at the level of the lesion and snare the thrombotic material [87].

Excimer laser thrombectomy is believed to reduce thrombotic material by debulking and vaporizing plaque; this method has never been studied in RCTs.

Another method is that of PiCSO (Pressure-controlled intermittent Coronary Sinus Occlusion), which involves transfemoral venous insertion at the level of the coronary sinus of a catheter with a balloon at the tip, which according to specific algorithms is inflated and deflated, to create a redistribution of blood flow by increasing the amount of blood flowing to the ischemic myocardium through activation [88-90]. The ongoing PiCSO-AMI-Trial study will offer additional data regarding the usefulness of this method in patients with CMVO.

Procedure-induced distal embolism of thrombus or friable atheromatous debris is one of the main reasons for CMVO in PPCI. In recent years, several types of coronary stents have been developed in order to reduce the risk of distal embolization of thrombotic material; among them there are balloon-expandable, bare-metal stents with Polyethylene Terephthalate (PET) micronet mesh covering (MGuard; Inspire MD), their purpose was to capture and remove materials that are prone to embolism, so avoiding distant embolization. These devices have not been widely used because subsequent clinical studies have shown their reduced durability over time, linked to a higher rate of intra-stent restenosis [91]. Self-expanding stents have also been experimented within patients with STEMI, which have the characteristic of growing autonomously in volume gradually, in the hours following implantation so as to reduce peri-procedural trauma, which may be responsible for plaque rupture and embolization of thrombotic material; they also failed to easily enter clinical practice, as their use was burdened with a greater risk of stent misplacement and ischemic events; to support this, we have data from APPOSITION III (a post-market registry to assess the Stentys self-expanding coronary stent in acute myocardial infarction) register [92].

Another possible approach to reduce MCVO could be to defer stent implantation, so as to wait for a reduction in thrombotic burden and a restoration of microcirculation function. Two major clinical trials support this approach, the DEFER-STEMI trial [93], and the DANAMI 3-Defer study [94]; according to their results, patients who received delayed stent implantation had lower slow-reflow and no-reflow rate, and a greater amount of myocardial saved from ischemia. Importantly, this method is not suitable for all patients and more data to ensure its safety and efficacy are still needed.

Strategy to reduce reperfusion damage: In order to save as much of the vital myocardium as possible, rapid restoration of coronary blood flow is essential; but it is known the risk of developing Ischemia-Reperfusion Injury (IRI); several molecular mechanisms are recognized to underlie this damage, such as increased oxidative stress, complement activation, increased intracellular calcium, migration of pro-inflammatory cells, mitochondrial dysfunction. Numerous approaches have been tested to minimize reperfusion injury, among them we recognize local and remote ischemic pre- and- post-conditioning methods, which principle is to apply cycles of ischemia and reperfusion. Ischemic post-conditioning is one of the most promising, it involves short cycles of reperfusion interrupted by ischemia applied at the onset of reperfusion, and it's linked to a reduction in infarct size. According to systematic reviews and meta-analyses, ischemic post conditioning following PPCI in STEMI patients may be cardioprotective, lowering myocardial enzyme levels and improving Left Ventricular Ejection Fraction (LVEF) [95,96]. Another ambitious technique is that of remote ischemic post-conditioning, according to which a blood pressure cuff attached to an upper or lower limb during brief ischemia and reperfusion causes the release of anti-inflammatory and cardioprotective chemicals into the system, which may lessen CMVO. Similar effects can also be achieved by performing pharmacological post-conditioning through for example high doses of statins, which act as anti-inflammatory and antithrombotic agents, improve endothelial function, and lead to coronary vasodilatation; in METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial [97], administration of metoprolol before PPCI was associated with a reduction of infarct size at CMR.

Future perspectives

Among the possible strategies to be used in the no reflow phenomenon, still under study, hypothermia should be mentioned as a potential cardioprotective therapy. However, although it has had promising results in animals, in humans, particularly in inferior wall infarction, has resulted in transient conduction abnormalities [98]. Consequently, several studies are being conducted, such as the EURO-ICE study, which recruited patients with anterior STEMI and TIMI flow grade 0 and examined the reduction in infarct size in subjects who underwent Selective Intracoronary Hypothermia (SIH) [99].

Additionally, hypothermia could be considered in conjunction with other cardioprotective treatments like the intracoronary application of super-saturated oxygen or left ventricular unloading prior to reperfusion. Particularly, the AMIHOT I and II trials, have demonstrated a possible advantage of hyperoxemic therapy in reducing infarct size in patients with anterior MI who received early reperfusion (<6 hours from the onset of symptoms) and impaired LV function [100,101]. The IC-HOT study contributed to confirming the feasibility as well as security of supersaturated oxygen therapy [102].

In order to enhance microvascular perfusion, the use of a microaxial pump, as Impella®, unloads the left ventricle potentially improving blood flow by lowering microvascular resistances [103].

Moreover, several drugs are being studied for acute coronary syndrome and even if they are not specific to MVO (Microvascular Obstruction), they could reduce infarct size; in this context, a peptide called MTP-131 (Mitochondrial Targeting Peptide) enhances myocyte survival following reperfusion and its safety has been verified, although its effectiveness compared to placebo has not been proven [104].

The use of stem cells could replace injured cardiac myocytes and through paracrine signaling could release growth factors, improving left ventricular function in patients at risk for adverse remodeling [105-107]. Particularly, stem cells might be stimulated by low-level laser therapy, and according to a recent study, it appears to be a safe and feasible method [108].

Finally, another possible emerging therapeutic target is pericytes, as their constriction may result in microvascular obstruction, which might increase patient morbidity [109].

Conclusion

In patients with myocardial infarction, coronary microvascular obstruction is becoming increasingly important as it is associated with higher morbidity and mortality. Several mechanisms are involved in this process, among these many are known, others are unknown. Therefore, there is still no effective treatment in reducing the adverse events related to this phenomenon. Owing to its complex mechanisms, a multimodal strategy may enhance prognosis in patients with MVO and reduce adverse events. However, further studies are needed to examine the results of combined therapies in the prevention and treatment of this condition.

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