Review

Coronary Microvascular Dysfunction: A Potential Intervention Strategy against Acute Myocardial Infarction

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Abstract: Recent studies have illuminated the role of coronary microvascular dysfunction (CMD) as a pivotal contributor to acute myocardial infarction (AMI). Microvascular dysfunction may lead to severe results including microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH), which are associated with poor prognosis. This article reviews the current research on coronary microvascular dysfunction in myocardial infarction reperfusion including the mechanisms, methods and models assessing CMD. This review emphasizes the importance of CMD and proposes potential avenues for future research in this field. Interventions for CMD may pave the way for novel treatment strategies in the management of acute myocardial infarction (AMI).

Keywords: coronary microvascular dysfunction; acute myocardial infarction; therapeutic strategy

1. Introduction

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide, and its complex pathophysiology often extends beyond the traditional focus on epicardial coronary artery obstruction. A mere 25% or less of patients treated with thrombolysis achieved rapid, complete, and sustained coronary recanalization with adequate myocardial tissue perfusion [1]. The current management of ST-Elevation Myocardial Infarction (STEMI) hinges on the pivotal step of mechanical reperfusion through urgent primary percutaneous coronary intervention (PCI) [2]. However, in a significant proportion of patients, despite achieving recanalization of epicardial coronary arteries, primary PCI fails to result in myocardial reperfusion [3]. Recent advancements in cardiovascular research have illuminated the role of coronary microvascular dysfunction (CMD) as a pivotal contributor to AMI.

Coronary Microvascular Dysfunction (CMD) represents the structural and functional remodeling of the coronary microcirculation in response to various pathogenic stimuli. In 2007, Camici and Crea initially proposed a clinical and pathogenetic classification of CMD, comprising four distinct types: (i) CMD in the absence of myocardial diseases and obstructive CAD, (ii) CMD in myocardial diseases, (iii) CMD in obstructive CAD, and (iv) iatrogenic CMD [3,4]. Multiple pathogenic processes may result in the development of CMD, in this review we mainly discuss CMD in AMI. It was first recorded in the 1970s. After coronary artery bypass grafting, patients with coronary artery disease still have symptoms of ischemia [5,6]. Initial experimental studies indicated that despite adequate epicardial blood flow, impaired tissue perfusion may occur. However, subsequent studies have demonstrated that reduced microcirculatory blood flow is a localized phenomenon rather than a global one [7,8]. Over the past two decades, substantial research have

employed both invasive and non-invasive techniques to examine coronary physiology, yielding a vast repository of data that has significantly advanced our understanding of CMD. Apart from the initial report, CMD is of great importance in revascularization of AMI in recent years. More than half of the patients still have inadequate myocardial microcirculation perfusion after percutaneous coronary intervention (PCI) owing to CMD [9–11]. The severity of CMD is independently associated with adverse left ventricular remodeling and post infarction heart failure, and is also an important predictor of long-term prognosis in STEMI patients [12–14]. To date, however, no definitive therapy is available for the treatment or prevention of CMD, and the precise mechanism that triggers coronary microcirculation dysfunction in AMI remains an active area of research [6]. Understanding CMD not only enhances our comprehension of the disease but also opens avenues for novel therapeutic strategies. In this review, we summarize the pathological mechanisms of CMD in AMI, diagnostic options and experimental models for preclinical studies of CMD.

2. The Microvasculature Dysfunction: Definition, Progress

The coronary microvasculature, which includes the pre-arterioles, arterioles and capillaries, is a complex system of vessels with a diameter of less than 500 μm [15–17]. Capillaries consist of endothelial cells, pericytes, and a basement membrane. Arterioles and venules with larger diameters have a layer of smooth muscle cells and can be innervated by the sympathetic nervous system. Under physiological conditions, the microvascular system of the myocardium regulates blood flow actively to facilitate the delivery of oxygen, nutrients, and hormones to the myocardium. Also, it aids in the removal of metabolic end products from the myocardium [18]. The capacity for material exchange in micro vessels can be regulated through the permeability of endothelial cells, surface area, and blood flow [18].

Table 1. Terminology of coronary microvasculature dysfunction.

| Nomenclature	Definition
IMH	Intramyocardial hemorrhage. It means erythrocytes and blood products within the myocardium or rather within the myocardial extracellular space.
MVO	Microvascular obstruction. It is the inability to reperfusion the coronary microcirculation in an earlier ischemic myocardial region, even when epicardial vessel openness is restored
Wavefront phenomenon	Myocardial infarction triggered by acute coronary occlusion progresses with increasing duration of ischemia as a transmural wavefront from the subendocardium toward the subepicardium [19].
Pericyte clamping	Pericytes constrict capillaries to reduce microvascular blood flow after ischemia.
Glycocalyx shedding	The glycocalyx is a complex polysaccharide-protein layer lining the lumen of vascular endothelial cells [20]. The loss of glycocalyx is thought to lead to vascular leak [21].

After AMI, coronary microvascular dysfunction is possible when swift re-opening of obstructed infarction-linked arteries to reinstitute coronary blood flow. Pathological processes in the small arteries, microvasculature, and interstitium do not occur simultaneously during coronary occlusion and reperfusion. Instead, the status of the infract cardiac micro vessels seems to be determined by the functional and structural outcomes of a succession of pathological changes that occur over time and space in progressive segments of the myocardial circulation [22]. In the initial stages of ischemia, there is a mild dilation of small arteries and capillaries. Prolonged ischemia damages the vessel walls, increases permeability, results in the formation of in situ thrombus, initiates cardiomyocyte ischemic necrosis, and raises various cytokines release. Despite coronary reopening at the onset of reperfusion, small arteries remain paralysis, capillaries become obstructed, and cardiomyocytes become oedematose again. Total coronary resistance is reduced, and the arteries are receiving excess blood flow. During the late stages of reperfusion, the function of small arteries is partly recovered. However, there is an increase in microvascular hemorrhage and oedema, leading to a high resistance of blood flow and "no reperfusion" phenomenon [22].

Microvascular function can be impaired after AMI, which may lead to "no reflow" phenomenon, microvascular obstruction (MVO), and intramyocardial hemorrhage (IMH) [23]. From the pathological definition, microvascular obstruction (MVO) is the inability to reperfusion the coronary microcirculation in

an earlier ischemic myocardial region, even when epicardial vessel openness is restored [24]. From the diagnostic definition, MVO is a contrast-enhanced infarct area with contrast-void infarct core observed on delayed gadolinium-enhanced cardiovascular magnetic resonance (CMR) imaging [25,26]. Intramyocardial hemorrhage (IMH) represents the more severe manifestation of CMD (Table 1.). IMH means erythrocytes and blood products within the myocardium or rather within the myocardial extracellular space [27–29]. IMH refers to the hypointense infarct core seen on T2-weighted imaging and/or T2* mapping [14,30]. T1, T2 and T2* are MRI relaxation times which are affected by the presence of oedema or hemorrhage within the tissue matrix. Hemorrhagic products in IMH act as paramagnetic centers which significantly shorten relaxation times, but the interactions are more complex and depend on the age and form of the haem iron. The conversion of hemoglobin from deoxyhemoglobin (early acute) to methemoglobin (acute) to ferritin and hemosiderin (subacute, chronic) results in a progressive shortening of T2 and T2* [31].

3. Pathophysiological Mechanisms of Coronary Microvascular Dysfunction

The timely restoration of continuous epicardial patency represents the most crucial action for rescuing ischemic myocardium from imminent infarction. Nonetheless, the swift re-opening of obstructed infarction-linked arteries to reinstitute coronary blood flow is likely to raise the possibility of coronary microvascular dysfunction. Firstly, alterations in endothelial cell permeability can influence vascular permeability. Secondly, after ischemia reperfusion, pericytes and glycocalyx may result in microvascular obstruction. Additionally, distal blockage and oedema may also contribute to microvascular obstruction. (Figure 1.)
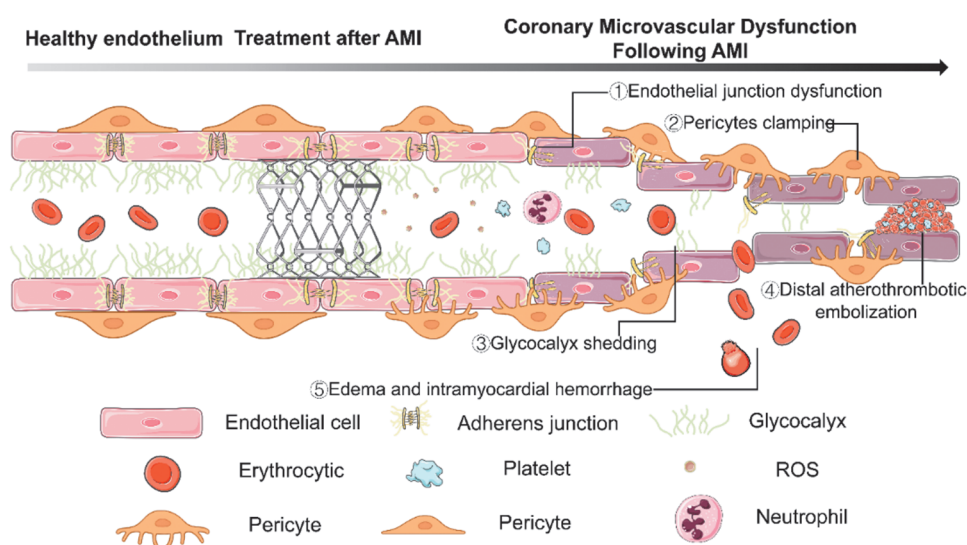
Figure 1. Pathophysiological mechanisms of coronary microvascular dysfunction in AMI. Coronary microvascular dysfunction is reflected by a sequel of pathophysiological changes, including the loss permeability of intercellular junctions of endothelial cells, pericytes clamping, glycocalyx shedding, distal atherothrombotic embolization and oedema of tissue. AMI, acute myocardial infarction; ROS, reactive oxygen species. (This schematic was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https:// smart.servier.com(accessed on 9-10-2024)) [32].

3.1. The Permeability of Intercellular Junctions of Endothelial Cells

Capillary of healthy myocardium composes endothelial cells, basement membrane, pinocytotic vesicles, attached pericytes and inter-endothelial cell junction [25]. Endothelial cells have crucial functions in regulating vascular tone, macromolecule and fluid permeability, coagulation, and angiogenesis. The dysfunction of endothelial cells is an important cause of many cardiovascular diseases [33]. Under in vitro conditions, coronary artery endothelial cells are tolerant to hypoxia and can survive for several days. However, in vivo, during myocardial infarction, vascular endothelial cells swell due to hypoxia and a concomitant loss of blood flow shear stress. This leads to a decreased density of microvascular cells,

compromised structural integrity and reduced vasodilatory response [23,30]. Due to the lack of oxygen, vasoactive substances decrease, and vasoconstrictors increase [25]. It makes it harder to restore the flow. In the first hour after ischemic infarction, hypoxia leads to the production of reactive oxygen species, along with increased production of cytokines such as thrombin and histamine [34,35]. Endothelial-type nitric oxide synthase (eNOS) vasodilator release is reduced and endothelin-1 vasoconstrictor release is increased [24]. In response to cytokines and growth factors, cell membrane invagination to form vesicles leads to increased transcellular transport; cleavage of adhesion and tight junction proteins leads to increased paracellular transport and increased vascular permeability [35].

3.2. Pericytes Clamping

Pericytes are cells wrapped around the endothelial cells in the micro circulation. They are the second most common cell type in the heart, even more numerous than cardiomyocytes. More than 80% of coronary capillaries have pericytes on their surface [36]. Pericytes can supporting micro vessels and control the blood flow [30]. In the brain, the no-reflow phenomenon is mainly due to the irreversible contraction of capillaries because of Pericytes [36]. Intracellular calcium concentration plays a crucial role in pericyte tone. Pericytes shrink under high concentration of Ca^{2+} in cells. However, their roles in reperfusion in heart still remain unknown [37]. After AMI, pericardial cells may constrict coronary capillaries and reduce microvascular blood flow [36,37]. Cardiac pericytes may represent an innovative therapeutic target for coronary no-reflow phenomenon after myocardial infarction.

3.3. Glycocalyx Shedding

The glycocalyx is gel-like layers of proteoglycans and glycosaminoglycans that covers endothelial cells and pericytes [37,38]. The functions of the glycocalyx are classified into mechanical and biochemical functions. The mechanical functions maintain the vascular tone, transduce extracellular signals, and preserve vascular integrity. Biochemical functions, on the other hand, require interaction with plasma proteins and plasma cells [38]. An animal model of cardiac IRI shows that the thickness of the glycocalyx decreases after reperfusion [38]. Shedding of the glycocalyx has been shown to cause a reduction in NO-dependent endothelium-mediated vasodilation. This degradation may also lead to a loss of interaction with complement regulatory proteins in the plasma, resulting in enhanced complement deposition and tissue damage [38]. Thus, regenerating and protecting the glycocalyx may present a pioneering goal for protecting the coronary vasculature.

3.4. Distal Atherothrombotic Embolization

Distal coronary microembolization is a key mechanism of vascular injury. Spontaneous or medically induced rupture of atherosclerotic epicardial plaques leads to the release of particulate debris, which embolizes distally into the coronary microcirculation along with superimposed microthrombi. The inflamed plaque fragments cause microvascular occlusion, leading to MVO [24]. Both the medical rupture of atherosclerotic plaques through angioplasty and distal embolization resulting from spontaneous plaque erosion during ACS cause the discharge of particulate debris, along with soluble factors which hamper microvascular perfusion [39, 40]. The activation of neutrophils in susceptible coronary plaques partly mediates this process, coupled with the escalated release of mediators derived from neutrophils, such as neutrophil extracellular traps (NETs) and particles. The described mechanisms contribute to the prothrombotic and proinflammatory cascade by forming neutrophil-platelet aggregates, activating the complement cascade, releasing inflammatory cytokines by activated endothelial cells, generating ROS that lead to oxidative damage, and causing local tissue degradation [41]. Furthermore, angioplasty-induced plaque rupture and tissue factor exposure can exacerbate this cascade response, resulting in the promotion of thrombosis and subsequent MVO [14].

3.5. Oedema

Cardiomyocytes contain over 75% of water. During ischemia, cardiomyocytes become oedematose

due to the loss of energy function of cell membrane ion pumps and increased interstitial osmolarity resulting from metabolite accumulation. Upon reperfusion, the normal osmotic pressure of blood exacerbates cardiomyocyte oedema. After a few hours, the oedema of the cardiomyocytes begins to diminish as fresh blood continues to dilute the metabolites [23,25]. However, it is possible that due to increased vascular permeability following ischemia-reperfusion, cardiomyocytes may become oedematose once again. The oedema may cause rupture of the myocardial membrane and result in cell death. Myocardial oedema may increase extravascular pressure on the coronary microcirculation, causing disturbances in microvascular coronary perfusion upon reperfusion [23,25].

4. Role of the Coronary Microvasculature Dysfunction in Ischemic-Reperfusion Injury

CMD may cause microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH), which are associated with adverse LV remodeling and poor prognosis. Inflammatory activation also plays an important role in poor LV remodeling and increased cardiovascular events. Furthermore, vascular integrity is associated with impaired cardiac function and increased early mortality.

4.1. Hemorrhage Leads to More Myocardial Cell Death

Prolonged hypoxia time would decrease the inter-endothelial cell junctions [25,42]. The destruction of cellar junctions probably prompt the destruction of endothelial cells after the reperfusion [30]. Besides, the alleviated Ca^{2+} concentration of microenvironment shrinks the endothelial cells, makes the permeability of large molecules across the cells more easily [37]. Following a 90-min coronary artery ischemia reperfusion procedure in a dog model, significant capillary damage is observed [26]. This includes the formation of endothelial protrusions and blebs that obstruct the capillary lumen, the emergence of endothelial gaps that enhance endothelial permeability, and the presence of extravascular erythrocytes, which may ultimately result in intramyocardial hemorrhage [43].

In hemorrhagic myocardial infarction, hemolysis of erythrocytes leaking into the extracellular environment releases hemoglobin, and degradants of hemoglobin are converted into iron crystals, which may have adverse effects on cardiomyocytes [30,44]. Intracardiac iron levels in hemorrhagic myocardial infarction peak in the acute phase of MI and remain constant in the chronic phase. Moreover, hemorrhagic MI is accompanied by fat deposition, with iron content in the infarct zone showing a strong correlation with fat deposition from week 8 to month 6 after MI, with the amount of iron in the infarct zone determining the extent of fat deposition. Iron-induced physiological responses of macrophage recruitment, lipid peroxidation, foam cell formation, steroidogenesis, foam cell apoptosis and iron cycling were activated in the area of hemorrhagic MI compared to non-hemorrhagic MI [45]. There is other literature that shows a significant association between the presence of IMH and the time to peak of neutrophils in the blood [46]. The use of FDA-approved trivalent iron chelators can reduce lipomatosis in the region of MI and improve recovery of cardiac function after MI [45,47]. However, without differentiating between hemorrhagic and non-hemorrhagic myocardial infarction, the direct use of iron chelators does not necessarily lead to a good outcome [47]. After engulfing oxidized red blood cells, iron-containing macrophages oxidize the surrounding low-density lipoprotein (LDL), accumulate cholesterol, and produce waxy material, leading to the transformation of macrophages into foam cells. Foam cells release cytokines that promote macrophage entry and create a vicious cycle [45,48]. It has also been shown that hemorrhage can cause a wide range of tissue reactions independent of coronary occlusion. It can lead to greater inflammation, cell death and MVO [49].

4.2. Microvascular Damage Leads to Inflammation

Intramyocardial hemorrhage is significantly associated with systemic inflammation and is strongly associated with pro-inflammatory markers (IL-6, fibrinogen, neutrophil count, CRP); persistent MVO is also associated with these inflammatory markers, but the correlation is much weaker [46]. Also, in hemorrhagic MI, macrophage populations fail to convert from a pro-inflammatory M1 state to a pro-healing M2 state [45]. Persistent and excessive inflammation is thought to contribute to poor LV remodeling and increased cardiovascular events after MI [50].

In animal reperfusion experiments, there was an influx of neutrophils into the intima and medial layers

of the coronary arteries. The reperfused neutrophils tended to be located between the endothelium and the elastic lamina [25]. Neutrophil extravasation and the release of matrix metalloproteinases lead to active rupture of the basement membrane, allowing leakage of red blood cells from the microvasculature leading to IMH [51]. Reperfusion stimulates mitochondrial production of reactive oxygen species (ROS), leading to increased membrane permeability, calcium overload, endothelial swelling and cell rupture [24]. During post-ischemic reperfusion, the pericapillary cells covering the coronary arteries also contract, leading to reduced coronary microvascular blood flow [24]. There is a variable increase in inflammatory biomarkers after revascularization compared to pre-PCI, and different inflammatory markers have different times to peak. Neutrophils peaked at four hours after PCI, IL-6 at 24 h, C-reactive protein (CRP) at 48 h and fibrinogen at 1 week [46]. Persistent and excessive inflammation is thought to contribute to poor LV remodeling and increased cardiovascular events after MI [50]. Immune cell aggregates or forms of neutrophil extracellular traps can directly obstruct blood flow. The degree of MVO has been shown to correlate with the neutrophil/lymphocyte ratio on admission. In addition, the presence of MVO correlates with levels of inflammatory cytokines. However, treatment regimens targeting inflammatory factors have not shown efficacy [25].

4.3. Coronary Microvasculature Dysfunction Leads to Anomalies of Vascular Tone

The endothelium can play a crucial role in regulating vascular tone, as evidenced by the molecules it produces. A series of anomalies have been identified in coronary microvasculature dysfunction, leading to a decline in NO production and an impairment of NO signaling cascade activity, which is dependent on the activity of soluble guanylate cyclase [52,53]. Furthermore, the intracellular accumulation of ROS produced in AMI facilitates the transformation of NO into peroxynitrite radicals and uncouples the endothelial NO synthase (eNOS), thereby switching its activity from a NO- to a ROS-producing enzyme and impairing NO-mediated vasodilation [54,55]. Besides, it is implicated in the modulation of calcium sensitivity and rho-kinase-induced myosin light chain dephosphorylation, which may results in anomalies of vascular tone [54].

5. Methods for Assessing Microvasculature Dysfunction

Microvascular dysfunction is complex and heterogeneous, so accessing CMD is important. The diagnosis of CMD may be achieved through the utilization of invasive (coronary angiography and catheter-based coronary physiology measurements) and non-invasive (myocardial contrast echocardiography, electrocardiogram and cardiovascular magnetic resonance imaging) methodologies [56].

Coronary angiography is a standard procedure for diagnosing CMD following PCI. At least four angiographic metrics have been employed for the diagnosis of CMD: thrombolysis in myocardial infarction (TIMI) flow grade, corrected TIMI frame count, myocardial blush grade and TIMI myocardial perfusion grade. The TIMI flow grade is a method of estimating blood flow in the epicardial coronary arteries. The degree of blood flow is quantified on a scale of 0 to 3, with a TIMI flow grade of less than 3 serving as the diagnostic criterion for MVO [57]. The utilization of invasive catheter-based techniques enables the acquisition of a range of physiological indices that characterize coronary microcirculation. These include, but are not limited to, indices such as coronary flow velocity patterns, coronary flow reserve, the index of microvascular resistance, hyperemic microvascular resistance, resistive reserve ratio, the instantaneous hyperemic diastolic flow velocity-pressure slope and coronary zero flow pressure [25]. In summary, CMD is characterized by a reduction in diastolic deceleration time and the appearance of systolic retrograde flow, a decline in coronary flow reserve, an increase in the hyperemic microvascular resistance index, and an elevation in the index of microcirculatory resistance [25,56].

Non-invasive cardiac magnetic resonance (CMR) is the gold standard for the assessment of MVO and IMH [43,51]. T2* is the standard approach for diagnosing IMH. The products of the degradation of erythrocyte-oxygenated hemoglobin that infiltrates into the cardiomyocytes are mainly paramagnetic and can shorten T2 values and be detected as low signal. T2* mapping is the most sensitive sequence in CMR and detects myocardial iron deposition. Thus, Days 3 to 10 after reperfusion are currently the best time to detect IMH [44,58,59] (Figure 2). The most common technique used to diagnose and quantify MVO is late gadolinium enhancement analysis in CMR [51,60]. In this analysis, the infarct area is an enhanced high signal region and the low signal region in the infarcted region of MVO [60].
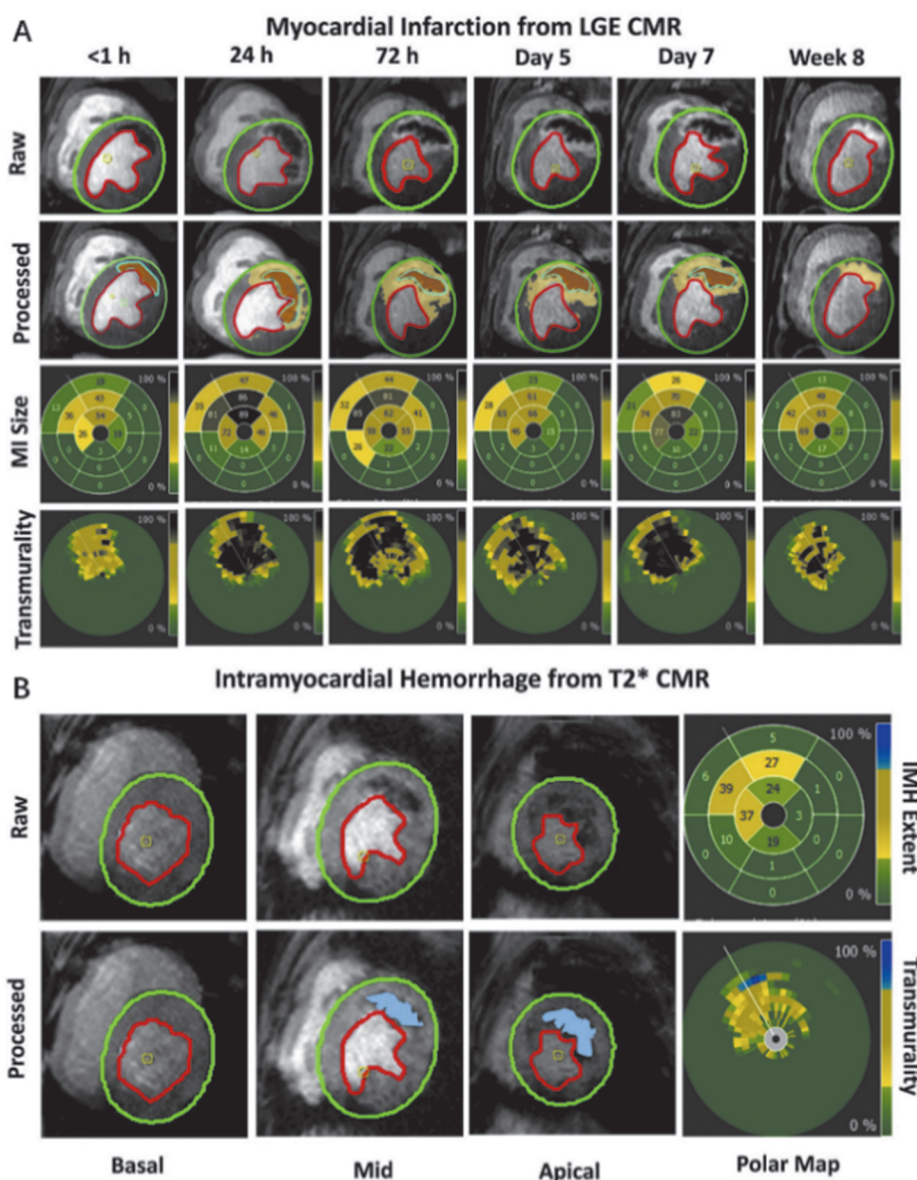
Figure 2. CMR is the gold standard for the assessment of MVO and IMH. (**A**) Unprocessed late gadolinium (LGE) enhancement and processed LGE. The figures displayed above represent data obtained from post-reperfusion assessments conducted at 1, 24, and 72 h, as well as at 5 and 7 days. MVO is brown shaded, and infarcted region is yellow shaded. The bottom 2 rows show the fraction of the myocardium infarcted, and polar plot showing cerebral infarction transmittance map. (**B**) The presence of intramyocardial hemorrhage within the MI zone was identified based on T2* cardiac magnetic resonance imaging in the short-axis views with segmental representation on the right. MI size at 24 h and day 7 has substantially increased. The red outlines endocardial border and the green outlines epicardial border [44].

6. Models for Investigating CMD

The dearth of research models has resulted in a paucity of knowledge regarding the mechanism of CMD in AMI. Furthermore, there is an urgent need for research into the development of drugs and therapeutic treatments for microvascular injury, which also requires the use of research models. The currently available models are described in the following section.

6.1. In Vivo Models

The search for drugs to alleviate microvascular injury requires the establishment of relevant animal

models. The quantity of intramyocardial hemorrhage varies depending on the animal model species and the duration of ischemia. In the canine model, a partial canine IMH resulted from 3 h of ligation followed by 1 h of reperfusion but did not result in MVO only and no IMH [45]. In the porcine model, IMH was present at 90 min of ligation and not at 45 min of ligation, but there was some mortality during the procedure in both dogs and pigs. In the rat model, the duration of ischemia before reperfusion is critical in determining whether the myocardial infarction model is a bleeding or non-bleeding type [58]. A 30-min ischemia followed by reperfusion ensures that the rat myocardial infarction model is non-hemorrhagic, while a 90-min ischemia followed by reperfusion ensures that the infarction model is hemorrhagic [60]. No differences in IMH between sexes have been reported. In medium-sized animals, female specimens were preferred for experimentation due to their relatively docile temperament [45].

In animal experiments, the commonly used assay is similar to the clinical one, using CMR to detect IMH [45,61–63]. Currently, vascular endothelial barrier function is also observed by FITC-dextran permeation, where FITC-dextran is unable to pass through the endothelium under normal conditions because it is too large and can pass through when the endothelial barrier is compromised. The higher the endothelial permeability, the greater the accumulation of FITC-dextran in the extracellular spaces of the vessel and the higher the fluorescence intensity. This provides a new idea for detecting the vascular endothelial barrier. However, it remains to be conclusively proven whether endothelial barrier dysfunction necessarily means IMH. Also this approach must be sacrificed to animals and does not allow for the completion of a continuous evaluation in the same animal [64]. In animal model, the cardiac microvascular perfusion can also be detected by TRITC-lectin assay [65,66]. Mice were euthanized 10min after the injection of 100 μL TRITC-lectin (0.1 mg/mL) iv. The heart samples were cryosectioned and immunofluorescence stained for CD31. The lectin/CD31 counterstained sections can be observed under a confocal microscope. The ratio of lectin-positive capillaries to CD31-positive capillaries shows the ratio of microvascular reperfusion [65,66].

6.2. In Vitro Models

Cell lines like Human cardiac microvascular endothelial cells (HCMECs) can be chose to investigate microvascular injury [66]. Primary MCMECs can be extracted from the LV of C57BL/6 mice [65,67]. To be succinct, left ventricles were minced and digested by Liberase. The cell suspensions were incubated with CD31-coupled microbeads for 30 min at 4 °C and collected by using a magnetic separator. Cells can be cultured in fibronectin-coated dishes with complete endothelial culture medium [65,66].

To introduce OGD/R injury, HCMECs or primary MCMECs can be maintained in a hypoxic chamber (5% CO_2 and 95% N_2, 37 °C). A few hours later, the cells were restored to normal atmosphere to induce reoxygenation injury [65].

7. Conclusions and Prospects

CMD have been widely reported in the clinical practices and have been shown to have a significant impact on cardiac function and ultimate prognosis [68]. MVO is an independent predictor of LV remodeling and patient outcome. The prognostic impact of IMH in reperfused AMI has been demonstrated an additional adverse prognostic effect beyond MVO, which has been investigated in several independent CMR-based studies [59]. IMH can be a third determinant of infarct size [44], in addition to the size of the vascular bed (or the number of cardiomyocytes downstream of the criminal lesion) and the duration of ischemia in the region [69]. After reperfusion therapy, IMH undergoes a second wave of wavefront-like infarct expansion (Figure 2), leading to an approximately twofold increase in infarct size. Severe CMD, like IMH and MVO, substantially diminishes the benefits of reperfusion therapy [44]. Therefore, it is important to be aware of CMD after AMI.

To date, no recognized risk factors or predictors of CMD after AMI have been identified in clinical practice [32]. The presence and extent of IMH are associated with glycoprotein IIb/IIIa inhibitor therapy and anterior infarction [70]. But it remains unclear why CMD presents in only a portion of patients after AMI. Admission hyperglycemia level is related to CMD, while having diabetes or lowering blood glucose concentration did not affect the incidence of CMD [70–73].

Moreover, the necessity for more precise instruments to detect microvascular status is also apparent. In addition to severe pathological states in CMD such as IMH and MVO, existing clinical methods encounter

difficulties in imaging myocardial microvascular structure and blood flow in vivo. Ultrasound localization microscopy (ULM) is a technique that enables the imaging of deep microvasculature with resolution beyond the diffraction limit. This is achieved by accurately localizing microbubbles (MBs) from contrast-enhanced ultrasound (CEUS) images. Furthermore, ULM allows for the measurement of hemodynamics in microvasculature by tracking the movements of super-localized MBs [74]. Two-photon microscopy has reported to be employed in the detection of cerebral microvascular abnormalities in animal models, and it seem be a potential method to detect CMD [75–77].

Currently, there is no clinical treatment available to limit infarct size caused by reperfusion injury. Previous studies have aimed to reduce reperfusion injury by focusing on platelet aggregation, oxidative stress, and endothelial dysfunction. However, the efficacy of these drugs has been limited [44]. The lack of clarity surrounding the pathological mechanism, the reproducibility of preclinical research design, and the absence of comorbidities and combination drugs in animals have all contributed to the failure of the transformation of relevant drugs from preclinical research and development to clinical practice [32]. Also, most of the current studies on CMD still rely on medium-sized animals, such as dogs and pigs. There are very few relevant models for small animals available [45,58,60,61,63]. While pigs provide relevant data to translate experimental findings to the clinic because of their proximity anatomically and hemodynamically to humans [78], it is essential to develop small animal models from an economic and animal welfare standpoint. The degree of microvascular dysfunction varies with time in AMI. It is crucial to identify drug therapy targets and the optimal time window for administration. There is a limited amount of literature regarding the stage of MI in small animals, and the question of whether drugs have varying efficacy for different levels of CMD warrants future investigation.

In conclusion, the recognition of coronary microvascular dysfunction as a critical factor in acute myocardial infarction necessitates a paradigm shift in therapeutic strategies. Microvascular barrier function depends upon the presence of an intact glycocalyx, endothelium, pericytes and a basement membrane. Damage to any one of these components, which is a common occurrence in AMI, can result in IMH, oedema formation, MVO, and impaired ventricular function. By focusing on the microvascular landscape, clinicians can develop tailored interventions that not only address the immediate consequences of coronary artery obstruction but also enhance overall myocardial resilience. As research continues to unveil the complexities of CMD, it is imperative that novel therapies evolve to integrate both microvascular and macrovascular considerations in the holistic management of AMI.

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