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REVIEW

Coronary microvascular obstruction: the new frontier in cardioprotection

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Abstract

Cardioprotection aims at infarct size reduction and improvement of clinical outcome from myocardial infarction. The translation of cardioprotection from preclinical and promising proof-of-concept studies to clinical benefit for patients has been largely disappointing. Almost all of these studies which did not translate into clinical benefit had infarct size reduction as the primary endpoint and used protocols selected to achieve infarct size reduction. The present review puts forward the hypothesis that the coronary circulation is a so far neglected target of cardioprotection. Mechanisms of ischemia–reperfusion injury to the coronary circulation are detailed. Clinical methods and measures to assess coronary microvascular impairment in reperfused acute myocardial infarction are presented. A comparison of magnetic resonance imaging data on infarct size vs. coronary microvascular obstruction is made. Finally, the design of studies which are optimized not only for infarct size reduction but also for salvage of the coronary microcirculation is advocated.

Keywords Coronary circulation · Infarct size · Myocardial infarction · No-reflow · Reperfusion

Introduction

Cardioprotection in patients with acute myocardial infarction aims at infarct size reduction beyond that by reperfusion alone and thereby at attenuation of progression to heart failure and improvement of survival. The translation of a myriad of experimental studies on the reduction of infarct size by mechanical and pharmacological interventions, such as ischemic conditioning and drugs related to ischemic conditioning's signaling, to better clinical outcome in patients with reperfused acute myocardial infarction has been remarkably disappointing [45, 47, 56]. In fact, there is—to my best knowledge—only one single-center, randomized clinical trial which reported significantly improved clinical outcome (cardiovascular mortality and hospitalization for heart failure) as the primary endpoint after remote ischemic conditioning [36], the most promising mechanical cardioprotective intervention so far [48, 51]. Even though this trial had a positive clinical outcome, there was no evidence for infarct size reduction. More importantly, in the most recent large phase III "effect of remote ischemic conditioning on clinical outcomes in STEMI patients undergoing PPCI/effect of remote ischemic conditioning before hospital admission on myocardial salvage in patients with acute myocardial infarction" (ERIC-PPCI/CONDI 2) trial in more than 5000 ST-segment elevation myocardial infarction (STEMI) patients undergoing reperfusion by primary percutaneous coronary intervention (PPCI), remote ischemic conditioning neither reduced infarct size (by troponin release) nor improved clinical outcome (combined cardiac mortality and hospitalization for heart failure at 12 months), and this lack of effect was seen in all pre-specified subgroups independently of age, diabetes, "Thrombolysis in Myocardial Infarction" (TIMI) flow at admission and infarct location [43]. Reasons for the failure of translation have been broadly discussed, including conceptual and technical issues, such as the reductionist approach of most experimental studies in young animals without co-morbidities and co-medications [27] and the lack of adequate clinical phase II trials on dose-finding. The evidence for confounding of cardioprotection by co-morbidities

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and co-medications is relatively thin [75], whereas the lack of adequate phase II trials is quite obvious [47].

Clearly, infarct size is a major determinant of patients' prognosis, and both ventricular function and its associated clinical events and cardiovascular mortality are determined by infarct size [106]. Nevertheless, the focus on infarct size reduction for improving the long-term outcome of patients with reperfused acute myocardial infarction may have been too narrow [54]. Conversely, the injury by myocardial ischemia and reperfusion to the coronary circulation may have been neglected, both as a determinant of patients' prognosis [16] and as a target of cardioprotective interventions [42, 46, 55, 90].

The coronary circulation is not only the culprit of acute myocardial infarction through coronary occlusion by atherothrombotic debris after plaque erosion or rupture but also a victim of the ensuing myocardial ischemia with eventual reperfusion. From experimental morphology studies, the no-reflow phenomenon with severe capillary damage after myocardial ischemia and reperfusion has been known for a long time [76, 77]. The clinical reality of no-reflow became apparent with the advent of thrombolytic and interventional reperfusion, since, despite re-opening of the occluded epicardial coronary artery, there was slow or no propagation of contrast medium (i.e., reduced TIMI flow [100]), slow distribution of contrast medium in the myocardial perfusion territory (i.e., reduced myocardial blush grade (MBG) [109]), or a lack of contrast medium by echocardiography [116] or cardiac magnetic resonance imaging (CMR) [117].

The manifestations of myocardial ischemia/reperfusion injury to the coronary microcirculation range from reversible edema to capillary destruction with intramyocardial hemorrhage, and multiple mechanisms contribute to these manifestations (Fig. 1). The present review aims to characterize the coronary microvascular impairment with a particular emphasis on its relation to cardiomyocyte infarction, identify its impact on the clinical outcome of patients with reperfused acute myocardial infarction, and analyze potential protective strategies to reduce it.

Manifestations and mechanisms of coronary microvascular injury

These mechanistic studies are mostly derived from animal experiments and reductionist models.

Edema

Endothelial cells are much more resistant to hypoxic cell death than cardiomyocytes [104], but loss of pulsatile flow with resultant cell swelling and blebbing, calcium-induced contractile element activation promoting the formation of intercellular gaps [69], ischemia/reperfusion-induced shedding of the glycocalyx overlying the endothelium [110], and finally expression of adhesion molecules with release of cytokines [114] all contribute to the rapid formation of interstitial edema within minutes of myocardial ischemia. Edema is even enhanced in early reperfusion by washout of osmotically active substances from the intravascular space during reactive hyperemia [32]. The development of an edema from myocardial ischemia/reperfusion acts to compress the coronary microcirculation and to aggravate the microvascular impairment in a vicious cycle [82]. Conversely, reduction of edema by hyperosmotic reperfusion can reduce also infarct size [34]. The development of edema during reperfusion is biphasic, with an early maximum after 2 h which coincides with a beginning inflammatory response

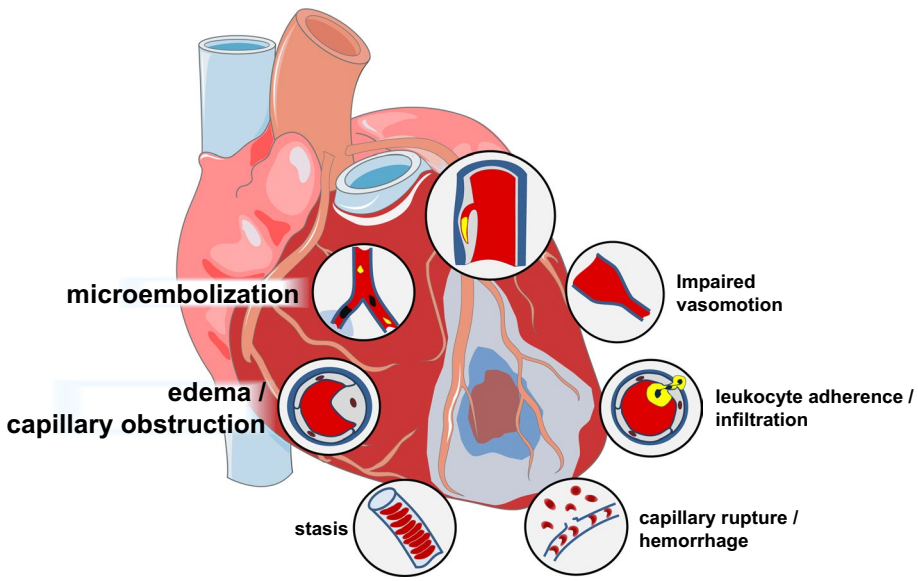

Fig. 1 Schematic diagram of mechanisms contributing to coronary microvascular injury in myocardial ischemia and reperfusion. Modified from [46]

and a second maximum after 7 days which coincides with collagen deposition and healing [29]. The biphasic pattern of edema development after reperfused acute myocardial infarction makes temporal standardization of CMR mandatory [60], in particular when the area of edema is used as a surrogate for the previously ischemic area at risk [57].

Impaired vasomotion

In contrast to the traditional view, the coronary circulation is not maximally dilated during myocardial ischemia, but has, in fact, a persistent vasoconstrictor tone, which can be removed by pharmacological agents, such that regional myocardial blood flow and contractile function are improved [11]. The mechanisms underlying the persistent coronary vasoconstrictor tone in ischemic myocardium are largely unclear, but endothelial dysfunction with impaired vasodilator response to acetylcholine is quickly apparent and more pronounced in the infarct zone than the non-infarcted part of the area at risk [22]. In human coronary aspirate samples which were obtained during percutaneous coronary interventions with stent implantation, increased concentrations of serotonin, thromboxane A2 [74], and endothelin [73] have been identified. Also, an increased concentration of tumor necrosis factor α was identified, which sensitizes the coronary microcirculation to vasoconstriction by promoting endothelial dysfunction [74]. In situations of increased sympathetic activity, alpha-adrenoceptor activation also contributes to enhanced coronary vasoconstrictor tone during myocardial ischemia and early reperfusion [39, 50, 52]. In patients with reperfused acute myocardial infarction, elevated coronary sinus neuropeptide Y concentrations are associated with higher index of microvascular resistance, more edema, and microvascular obstruction [44]. Pericytes which cover the coronary capillaries also contract and contribute to the reduction of microvascular blood flow during post-ischemic reperfusion [93].

Circulating blood cells

Platelets and a number of substances which they release upon activation, e.g., adenosine diphosphate, serotonin, and thromboxane A2, can contribute to coronary microvascular constriction [95], and accordingly, inhibition of platelet activation can protect the coronary microcirculation. Myocardial ischemia/reperfusion increases the expression of adhesion molecules on the coronary vasculature and on circulating cells, such that adhesion of platelets and leukocytes to the endothelium and formation of platelet–leukocyte aggregates are promoted [78], and the adhering cells and aggregates impair coronary microvascular blood flow by physical obstruction. Also, at reduced coronary microvascular blood flow, characteristic erythrocyte aggregates obstruct the capillary circulation [20].

Coronary microembolization

The spontaneous or iatrogenic rupture of an atherosclerotic epicardial coronary lesion releases plaque debris which, together with superimposed thrombotic material, can be embolized into the coronary microcirculation if some antegrade blood flow persists [53]. The physical obstruction of the coronary microcirculation results, depending on the size of the particulate debris, in typical microinfarcts with a subsequent inflammatory reaction [19]. The importance of coronary microembolization during percutaneous coronary interventions has been questioned, because the benefit from use of protection devices has been equivocal. On the other hand, use of a mesh-covered embolic protection stent was superior to a conventional stent in patients which reperfused acute myocardial infarction with respect to TIMI blood flow and ST-segment resolution [105]. As detailed above, with rupture of an epicardial atherosclerotic plaque, not only particulate debris, but also a number of soluble substances are released which contribute to impaired microvascular perfusion, but cannot be captured with filter devices or meshes.

Capillary destruction and hemorrhage

The most severe manifestation of injury to the coronary microcirculation is structural damage to the capillaries, with massive swelling of endothelial cells, rupture of the vascular wall, and—after reperfusion—hemorrhage into the interstitial space [58, 76]. Apart from no-reflow as a consequence of capillary obstruction, hemorrhage in reperfused myocardial infarction is identified by CMR, since paramagnetic hemoglobin metabolites attenuate the T_2-weighted signal intensity in an edematous myocardial region [98]. The interstitial iron deposition from hemorrhage induces an inflammatory response to intensify the ischemia/reperfusion injury [10].

Interaction of cardiomyocyte injury with coronary microvascular injury

Ischemia/reperfusion injury to the coronary microcirculation has manifestations ranging in severity from reversible edema to interstitial hemorrhage. A number of mechanisms contribute to coronary microvascular injury, which may be identical (e.g., reactive oxygen species) to or different (e.g., vasoconstrictor substances) from those contributing to cardiomyocyte injury. It must be emphasized that severe coronary microvascular injury can result from ischemia/reperfusion in a previously healthy isolated, saline-perfused heart, i.e., in the absence of atherosclerosis, circulating blood cells,

vasoconstrictor substances, etc. The temporal, spatial, and causal relationship of coronary microvascular injury (no-reflow/hemorrhage as its most severe manifestation) to cardiomyocyte injury (infarction as its most severe manifestation) is not clear in detail; it appears from morphological analyses [76] that no-reflow is always within the area of infarcted tissue (Fig. 2). Interstitial and cardiomyocyte edema can compress the coronary microcirculation and contribute to microvascular injury [34, 82]. Conversely, failure to reperfuse will prolong ischemia and contribute to more cardiomyocyte injury.

The clinical diagnosis of coronary microvascular obstruction

With the advent of thrombolytic and later interventional reperfusion of an occluded coronary artery in patients with acute myocardial infarction, it became apparent that ischemia/reperfusion injury to the coronary microcirculation is a clinical reality and a problem. Sheehan et al. first reported in their TIMI trial a visual score from 0 (absent reperfusion) to three (full reperfusion) on coronary angiography [100]. The TIMI grading was developed into a more quantitative measure of counting the cine-frames which the contrast medium needed for propagation to reach a standardized distal coronary landmark [37]. The myocardial blush grade (MBG, 0–3) was also derived from coronary angiography, but did not assess the propagation of contrast medium in the visualized epicardial coronary artery but its distribution into the myocardial perfusion territory [109]. These angiography-based indices do not permit a precise localization of the microcirculatory problem. In contrast, a defect in contrast medium using echocardiography [31] or late (10–20 min after injection) gadolinium contrast CMR [117] identifies the microvascular no-reflow site and extent within the infarcted myocardium. CMR data on resting perfusion (first pass perfusion after injection) and early (1–4 min after injection) gadolinium contrast enhancement can also identify microvascular obstruction [8]. On the other hand, contrast echocardiography and CMR cannot identify lack of vasodilation or, vice versa, vasoconstriction within the previously ischemic area at risk but outside the infarcted zone.

A more hemodynamic assessment of coronary microvascular injury is derived from simultaneous measurements of coronary blood flow (velocity) and perfusion pressure during adenosine infusion and the calculation of an index of microcirculatory resistance [12]. Finally, as the most easily available non-invasive parameter, the resolution of ST-segment elevation is taken to reflect reperfusion on the microvascular level [62]. All these different parameters of coronary microvascular impairment correlate with each other. CMR is the preferred technique to diagnose the coronary microcirculatory impairment from ischemia/reperfusion; it is non-invasive and widely available and permits the localization and quantitative assessment of edema, no-reflow, and hemorrhage along with infarct size and regional contractile function (Fig. 3).

Clinical occurrence and prognostic relevance of coronary microvascular obstruction in reperfused acute myocardial infarction

The reported frequency of coronary microvascular impairment varies widely, depending to a large extent on the used diagnostic method and parameter and the time of its assessment which, in turn, depends on the method used (see above), i.e., from 5 to 70% [89]. Presence, severity, and extent of coronary microvascular impairment during reperfusion are related to advanced patients' age, hyperglycemia on admission, longer duration of coronary occlusion until reperfusion, low TIMI flow grade before reperfusion, greater area at risk, high thrombus burden, and long target lesion [63, 64, 72, 89]. In particular, evidence for hemorrhage is

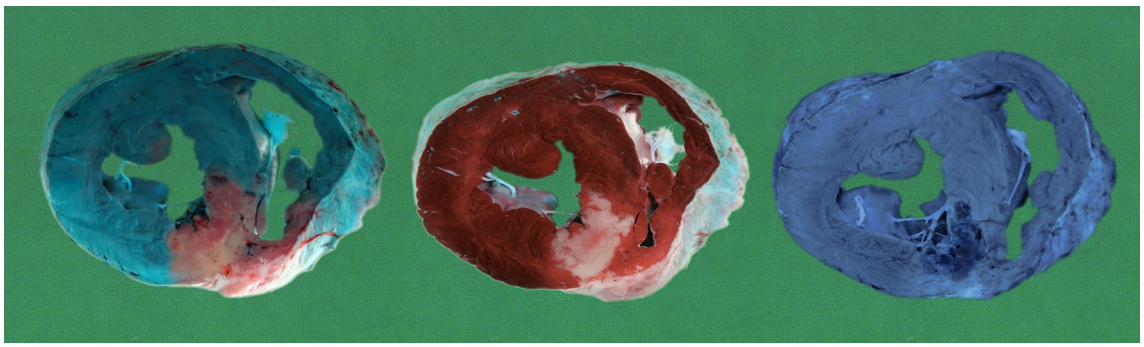

Fig. 2 Delineation of area at risk (left), infarct size (middle), and no-reflow (right) following 60 min coronary occlusion and 180 min reperfusion in a pig

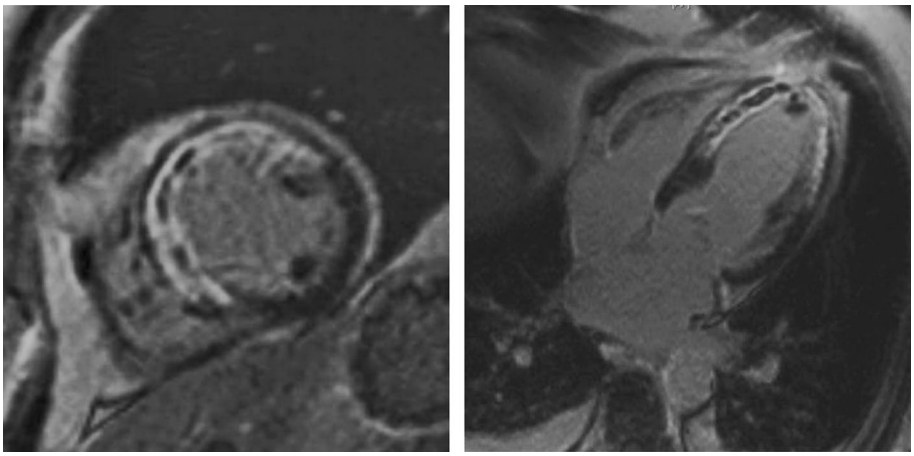

Fig. 3 Example of gadolinium contrast CMR with large anteroseptal infarction and lack of contrast (no-reflow) within the contrast-enriched infarction, in transversal and longitudinal view (with apical thrombus). Courtesy of Thomas Schlosser/University of Essen Medical School

related to larger infarct size, and hemorrhage which persists after 7 months goes along with adverse remodeling [13]. Any evidence of coronary microvascular impairment in patients with reperfused acute myocardial infarction is associated with poorer prognostic outcome than lack of it, i.e., associated with more adverse remodeling and lower ventricular function on follow-up [6, 83, 109] and with more cardiovascular events, notably higher mortality on follow-up [30, 97, 109, 111, 117]. Importantly, coronary microvascular impairment (extent of microvascular obstruction on CMR) was still significantly associated with 1 year all-cause mortality, even after adjustment for infarct size [16], thus providing additional prognostic information. In another study, only microvascular obstruction but not infarct size predicted cardiac mortality after 2 years follow-up [111].

Protection from coronary microvascular injury by ischemia/reperfusion

There are many experimental studies which demonstrate reduced edema, improved coronary vasomotion, less leukocyte adherence, and reduced extent of no-reflow in response to ischemic conditioning maneuvers or cardioprotective drugs (for review, see: [46]). In many of these studies, the primary interest was directed at reduction of infarct size. Of note, reduction of cardiomyocyte injury (infarct size) and reduction of coronary microvascular injury did not always go along. Ischemic pre- and postconditioning reduced both infarct size and edema in dogs with 60 min coronary occlusion and subsequent reperfusion [120]. In pigs, ischemic postconditioning has been reported to reduce infarct size and no-reflow [119], to not reduce infarct size and no-reflow [5, 28] or to reduce infarct size, but not no-reflow [101]. In one study in pigs with 60 min coronary occlusion and subsequent reperfusion, pre-, post-, and remote ischemic conditioning all reduced infarct size but not no-reflow [101]. In another study in pigs with 90 min coronary occlusion and subsequent reperfusion, preconditioning reduced both infarct size and no-reflow, postconditioning reduced no-reflow, but not infarct size, and remote ischemic conditioning did neither reduce infarct size nor no-reflow [3]. Disparate effects on infarct size and no-reflow were also observed in rats undergoing coronary occlusion with subsequent reperfusion where topical hypothermia, when started before reperfusion, reduced infarct size and no-reflow, and hypothermia still reduced no-reflow but not infarct size when initiated at 30 min reperfusion [41]. When interpreting these equivocal effects on infarct size and coronary microvascular injury, it is important to realize that no systematic studies on stimulus strength/dose–response relationships for ischemic conditioning strategies exist and that most studies just used a single algorithm of ischemic conditioning which was selected to reduce infarct size in the given experimental setting. Other than the above hypothermia study [41], I am not aware of any experimental study which measured infarct size and no-reflow with a protocol selected for the reduction of no-reflow.

Ischemic preconditioning can be intentionally used only in patients undergoing elective interventions and, therefore, is not relevant for acute myocardial infarction. However, spontaneous ischemic preconditioning can occur in the form of pre-infarction angina, and patients with pre-infarction angina have not only reduced infarct size [56] but also less microvascular obstruction, as assessed by angiography and reduction of ST-segment elevation [91] or CMR [66]. Ischemic postconditioning and remote ischemic conditioning have been used in patients with acute myocardial infarction. I am focusing here on those studies which have both infarct size (by CMR) and coronary microvascular impairment (edema or no-reflow by CMR) as endpoints [1, 2, 4, 5, 9, 14, 17, 18, 21, 23, 24, 26, 33, 35, 38, 40, 59, 65, 67, 68, 70, 71, 79, 80, 84–87, 92, 94, 99, 107, 108, 115, 118] (Fig. 4). In most of these studies, infarct size was the primary endpoint and in only a few was edema [107, 115] or no-reflow [4, 5, 17, 79, 86] the primary endpoint. In most of these

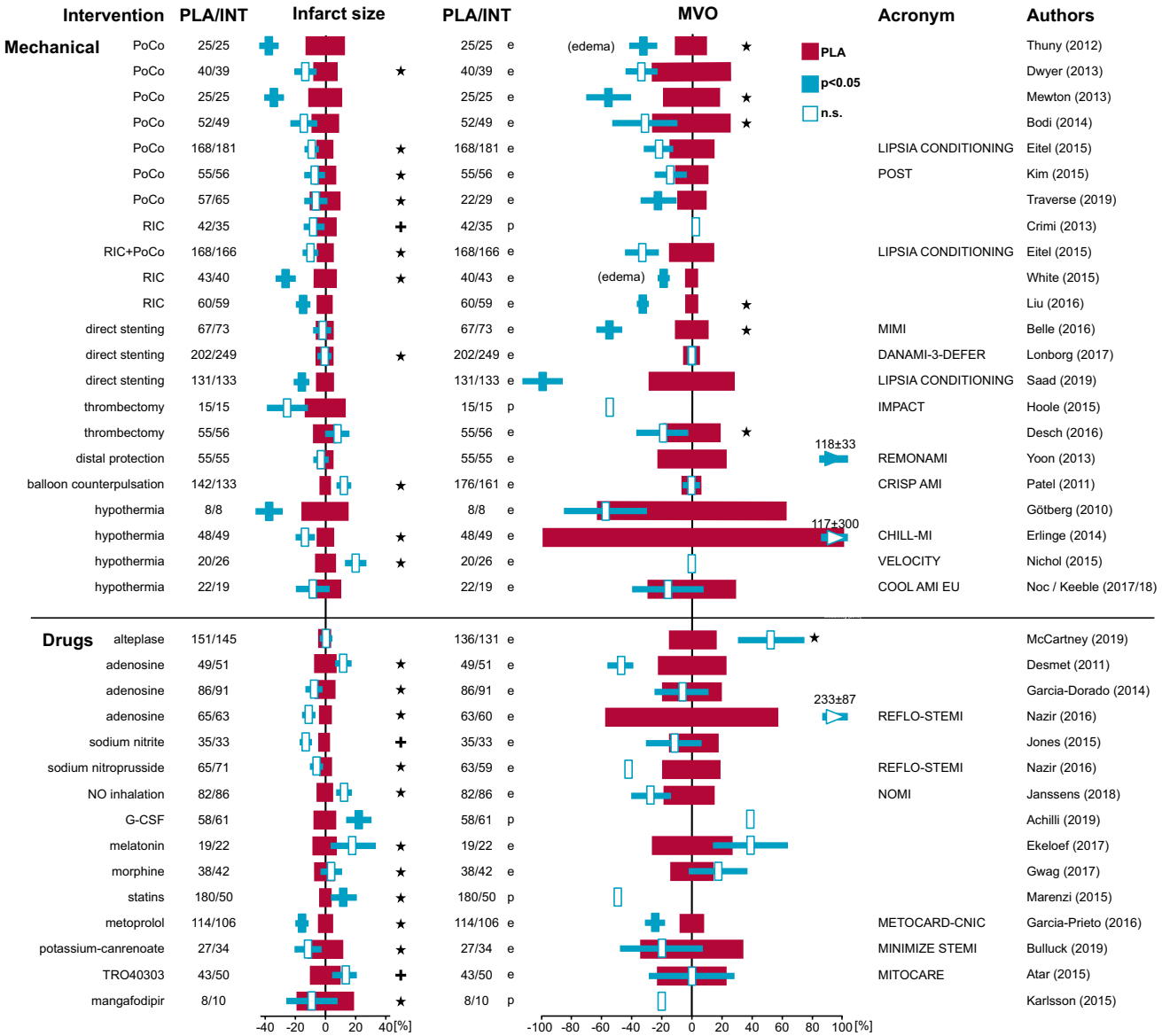

Fig. 4 Forest plot of studies using magnetic resonance imaging to assess infarct size and coronary microvascular obstruction (MVO) in response to mechanical or pharmacological cardioprotective interventions. The red bars represent the standard error of the mean (set as zero) in the placebo group. Blue bars represent the standard error of the mean (filled when significant) in the intervention group. *denotes primary endpoint. $^{+}$denotes infarct size using biomarkers as primary endpoint. *PoCo* ischemic postconditioning, *RIC* remote ischemic conditioning, *NO* nitric oxide, *G-CSF* granulocyte colony stimulating factor, *PLA* placebo, *INT* intervention

studies, the single conditioning algorithm used was selected for infarct size reduction, and it is, therefore, not surprising that edema or no-reflow, respectively, were significantly reduced in only few studies [4, 79, 86, 99, 107, 108, 115]. Of note, however, there is the recent NIHLBI-sponsored trial where infarct size was not reduced by ischemic postconditioning but no-reflow was, and this was associated with improved left-ventricular function at 1 year follow-up [108]. Other than in a very small safety study [38], hypothermia neither reduced infarct size nor no-reflow [26, 92]. Direct stenting in the "effect of conditioning on myocardial damage in STEMI" (LIPSIA) trial was associated with reduced infarct size and microvascular obstruction [99] and with reduced microvascular obstruction in the "minimal invasive procedure for myocardial infarction" (MIMI) trial [4]. Thrombectomy [17, 59], distal protection [118], and balloon counterpulsation [94] neither reduced infarct size nor microvascular obstruction. Studies using drugs rather than mechanical interventions also mostly aimed for infarct size reduction [1, 2, 9, 18, 24, 33, 35, 40, 65, 67, 68, 84, 87], except for one study using alteplase which aimed for microvascular obstruction and found neither reduced infarct size

nor reduced microvascular obstruction [85]. All drug studies were disappointingly neutral, except for metoprolol which reduced infarct size [61] and microvascular obstruction significantly [35] and erythropoietin which tended to increase infarct size and even doubled the incidence of microvascular obstruction significantly [81].

Perspective

Clinical studies using ischemic conditioning and related drugs with the aim to reduce infarct size have been largely unsuccessful, and therefore, coronary microvascular impairment as a target of adjunct cardioprotection comes into focus, as it is, beyond infarct size, a determinant of patients' prognosis in terms of LV function and mortality. Indeed, the single-phase III trial on remote ischemic conditioning which demonstrated improved clinical outcome provided no evidence for infarct size reduction [36]; was there possibly an attenuation of coronary microvascular injury? In contrast, remote ischemic conditioning in the CONDI (effect of remote ischemic conditioning before hospital admission on myocardial salvage in patients with acute myocardial infarction) trial increased myocardial salvage on scintigraphy at 30 days reperfusion, but did not improve ST-segment resolution or TIMI frame count at early reperfusion [7], consistent with the results of a study in pigs where infarct size but not no-reflow was reduced by remote ischemic conditioning [101]. However, on retrospective analysis, there was better patients' outcome in the CONDI trial [103]. Ischemic postconditioning in a recent single-center RCT reduced no-reflow but not infarct size, and there was a better outcome in LV function on 1 year follow-up [108]. In the "Danish study of optimal treatment of patients with ST-elevation myocardial infarction" (DANAMI-3-iPOST) trial, ischemic postconditioning in STEMI patients undergoing PPCI tended to improve left-ventricular function but not reduce mortality or hospitalization for heart failure over 3 year follow-up [25]. On retrospective analysis, however, thrombectomy per se improved the clinical endpoints but abrogated the protection by ischemic postconditioning which was seen in patients without thrombectomy, and this interaction was attributed to a delay of the postconditioning intervention or to coronary microembolization [88], as seen previously in a pig model of myocardial infarction [102].

Thus, the effects of conditioning interventions on cardiomyocyte injury and coronary microvascular injury can be very disparate, and it is not clear what effect ultimately determines prognosis. It appears therefore prudent: (1) to better understand the mechanisms which underlie coronary microvascular impairment from ischemia/reperfusion and to identify novel targets for adjunct cardioprotection. Such novel targets would not be mutually exclusive from targets of cardiomyocyte protection, but hopefully additive in the sense of a multi-target strategy of cardioprotection [15]. (2) To systematically study the algorithms of ischemic postconditioning and remote ischemic conditioning for stimulus strength-effect relationships not only in infarct size reduction, but also in reduction of coronary microvascular impairment. There is a promising experimental study in rats with myocardial infarction demonstrating protection in terms of reduced adverse remodeling and reduced mortality by repeated remote ischemic conditioning for 28 days following reperfusion [113]. Along this line, there are promising preliminary clinical data in patients with chronic ischemic heart failure in whom repeated remote ischemic conditioning over 4 weeks reduced blood pressure and NT-pro BNP plasma levels [96]. In contrast, daily remote ischemic conditioning starting 3 days after PPCI in STEMI patients and continued for 4 weeks did neither reduce infarct size nor improve left-ventricular function—the protective intervention was probably started too late [112]. To systematically develop better ischemic conditioning and other protective strategies, experimental studies will have to leave the "comfort zone" of looking at the acute reperfusion phase where cardiomyocyte injury prevails in short-term protocols and they will have to look at more long-term processes, such as restoration of coronary microvascular perfusion, infarct healing, remodeling, LV function, and mortality in long-term protocols [49]. Unless we have robust preclinical data on clinically relevant, long-term endpoints from clinically relevant large animal models, we cannot really expect successful translation of preclinical cardioprotection studies to patient benefit.

Despite the prevailing disappointment on the poor translation of cardioprotection to patient benefit, we cannot give up on adjunct cardioprotection, given the persistently high 1 year mortality from acute myocardial infarction and the increasing incidence of post-infarction heart failure [54]. Apart from and in addition to infarct size reduction, the attenuation of coronary microvascular ischemia/reperfusion injury appears a worthwhile target of protection with prognostic relevance—a new frontier of cardioprotection.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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