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CONTEMPORARY REVIEW

Device-Based Approaches Targeting Cardioprotection in Myocardial Infarction: The Expanding Armamentarium of Innovative Strategies

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Coronary reperfusion therapy has played a pivotal role for reducing mortality and heart failure after acute myocardial infarction. Although several adjunctive approaches have been studied for reducing infarct size further, both ischemia–reperfusion injury and microvascular obstruction are still major contributors to both early and late clinical events after acute myocardial infarction. The progress in the field of cardioprotection has found several promising proof-of-concept preclinical studies. However, translation from bench to bedside has not been very successful. This comprehensive review discusses the importance of infarct size as a driver of clinical outcomes post-acute myocardial infarction and summarizes recent novel device-based approaches for infarct size reduction. Device-based interventions including mechanical cardiac unloading, myocardial cooling, coronary sinus interventions, supersaturated oxygen therapy, and vagal stimulation are discussed. Many of these approaches can modify ischemic myocardial biology before reperfusion and offer unique opportunities to target ischemia–reperfusion injury.

Key Words: infarct size ■ ischemia–reperfusion injury ■ left ventricular unloading ■ supersaturated oxygen ■ targeted temperature management ■ vagal stimulation

Irreversible myocardial damage due to acute myocardial infarction (AMI) is a global health problem and a significant cause of chronic heart failure (HF) with an annual incidence of 805,000 in the United States alone.[1] Reperfusion of the coronary obstruction with primary percutaneous coronary intervention (PCI) has dramatically reduced mortality among patients with AMI.[2] Despite significant advances in the field of PCI for AMI, both morbidity and maladaptive left ventricular (LV) remodeling leading to HF still play a pivotal role in short- and long-term outcomes post-AMI.[3,4] Tremendous efforts have been made to develop therapeutic approaches to protect myocardial tissue during the acute ischemic insult. Despite success in both animal and clinical proof-of-concept studies, translation of adjunct cardioprotection to clinical practice has remained an unfilled gap.[5,6] Nevertheless, recent technological advances now provide a novel platform for device-based intervention to potentially fill this gap.

The purpose of this comprehensive review is to summarize cutting-edge knowledge in preclinical and clinical studies of novel device-based approaches for reducing infarct size (IS). We first cover the pathophysiological mechanisms of both ischemia–reperfusion injury (IRI) and microvascular obstruction (MVO) post AMI, which is closely linked to IS. We also discuss how these novel interventions modulate both the cardiomyocyte and noncardiomyocyte milieus, which provides clues for understanding how LV function post-AMI can be restored/preserved and leads to improved clinical outcomes.

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Nonstandard Abbreviations and Acronyms

IRI	ischemia–reperfusion injury
IS	infarct size
MVO	microvascular obstruction
PICSO	pressure-controlled intermittent coronary sinus occlusion
SSO2	supersaturated oxygen
TTM	targeted temperature management

ACUTE MYOCARDIAL INFARCTION AND PROGRESSION TO HEART FAILURE

Beginning with the "open artery theory" in the 1970s, the field of AMI management has been ruled by the fundamental principle "time is muscle," indicating that prolonged coronary occlusion leads to increased myocardial injury.[7] Of note, from the onset of coronary occlusion, the death of myocardial tissue spreads from the endocardial to the epicardial layer, the so-called "wavefront phenomenon."[8] Therefore, if reperfusion of the coronary artery is performed during the very early phase of coronary occlusion, myocardial death will be limited to the endocardial side, the IS will be small and cardiac function will be preserved. Alternatively, late reperfusion will result in a more transmural infarct with severe LV dysfunction and subsequent HF.[9] In a clinical setting, it has been established that the relationship between the total ischemic time and clinical outcomes is closely related. Most important, both clinical and preclinical studies indicate that the shorter the time to reperfusion, the less cardiomyocyte cell death.[3] Reperfusion by PCI with a door-to-balloon time within 90 minutes after hospital presentation is recommended by current guidelines.[10] However, recent data suggest that further shortening of door-to-balloon time does not reduce IS.[11] According to these findings, novel complementary cardioprotective interventions are required to maximize myocardial salvage.

ISCHEMIA–REPERFUSION INJURY DURING ACUTE MYOCARDIAL INFARCTION

In 1960, Jennings et al first presented the histological features and pathological characteristics of myocardial IRI in a canine model.[12] Despite successive demonstration of IRI in several organs in various animal models, whether it also exists in humans remains ambiguous. Although lack of efficacy in IRI-targeting pharmaceutical therapies in previous clinical trials raises doubt as to the importance of IRI in humans, there is also much supportive evidence that suggests its presence, such as myocardial edema[13] and arrhythmias[14,15] that immediately follow reperfusion. Previous research in animals has shown that reperfusion itself is a "double-edged sword" because of the paradoxical myocardial injury driven by various mechanisms including oxidative stress, inflammation, intracellular Ca^{2+} overload, and irreversible cell death.[16] The loss of equilibrium between reactive oxygen species (ROS) and endogenous antioxidant molecules leading to cardiomyocyte cellular damage defines oxidative stress. Notably, the accumulation of ROS such as oxidized glutathione or reduced nicotinamide adenine dinucleotide phosphate can modify proteins, membranes, and even DNA, leading to free radical damage.[17] ROS accumulation starts at the early phase of ischemia, uncoupling the mitochondrial respiratory chain and subsequently followed by a sudden burst in ROS generation at reperfusion, mainly driven by xanthine oxidase activation and neutrophils, which are responsible for delivering toxic agents to the myocardium.[18] To reduce ROS-induced myocardial injury during IRI, natural antioxidants such as vitamins C and E as well as other agents like resveratrol (a plant-derived polyphenol) have been studied as potential therapies.[19] Vitamins might also have effects beyond the expected antioxidative properties. For instance, a recent article published by Lee et al[20] demonstrated that vitamin D administration in a mouse IRI model reduced cardiomyocyte apoptosis and ROS, increased mitochondrial membrane potential and preserved mitochondrial structure by avoiding mitophagy (mitochondrial autophagy). However, the clinical benefit of antioxidants during AMI remains to be clarified. The IRI cascade also triggers an intense inflammatory/immune response characterized by infiltration of neutrophils, followed by macrophages and lymphocytes at both infarct core and peri-infarct myocardial areas. Interestingly, T cell lymphocyte accumulation can be seen minutes after reperfusion[21] indicating that immunity is a viable target in IRI.[22,23] These cells release various cytokines including interleukin-1 alfa and beta and promote activation of both proinflammatory and anti-inflammatory signaling pathways. Meanwhile, clinical data on immune modulatory drugs such as corticosteroids have not been able to demonstrate clear efficacy,[24] which might be partly related to the side effects.

SIGNALING PATHWAYS INVOLVED IN ISCHEMIA–REPERFUSION INJURY

Several signaling pathways have been studied as potential targets in cardioprotection post-AMI. However, 2 of them have been in the spotlight in recent years for

exerting their beneficial effects through downstream cascade activation (Figure 1). The reperfusion injury salvage kinase (RISK) pathway[25] confers cardioprotection when activated specifically at the time of reperfusion. The RISK pathway refers to a group of prosurvival protein kinases that include the phosphatidyl inositol-3-phosphate kinase/Akt pathway and the extracellular signal-regulated kinases-1 and -2, downstream mediators of mitogen-activated protein kinases pathway, which have been shown to limit IRI-induced cell death when activated at the onset of myocardial reperfusion.[26] Furthermore, the RISK pathway can be also activated by ischemic preconditioning and postconditioning. The survivor activating factor enhancement (SAFE) pathway is another pro-survival cascade for cardioprotection[27] and animal models have demonstrated that the activation of the SAFE pathway has been able to limit IRI through the downstream protective effects of tumor necrosis factor signaling. Interestingly, a crosstalk between RISK and SAFE pathways via signal transducers and activators of transcription-3 has been suggested in mouse models under sphingosine-1-phosphate treatment. In recent years, several reports have proposed that Janus tyrosine kinase/signal transducers and activators of transcription signaling is associated with IRI post-AMI.

Finally, the mitochondrial permeability transition pore is a critical mediator of lethal IRI,[28] whose opening at the onset of myocardial reperfusion induces cardiomyocyte death by uncoupling oxidative phosphorylation and inducing mitochondrial swelling. Preclinical studies suggest that its opening may contribute to up to 50% of the final IS. Pharmacologically inhibiting its opening by administering the mitochondrial permeability transition pore inhibitor, cyclosporine-A, at the onset of myocardial reperfusion has been demonstrated in animal studies to limit IS and prevent IRI in human myocardial tissue. However, the CIRCUS (Clinical Outcome in ST Elevation Myocardial Infarction Patients) clinical trial evaluating the role of pharmacological administration of intravenous cyclosporine-A at the time of reperfusion failed to show benefit in its primary efficacy end point, which was a composite of 1-year all-cause mortality, rehospitalization for HF or HF worsening during initial hospitalization, and LV adverse remodeling as determined by serial transthoracic echocardiography.[29] The reason for this could potentially be explained by confounders between animals and humans such as

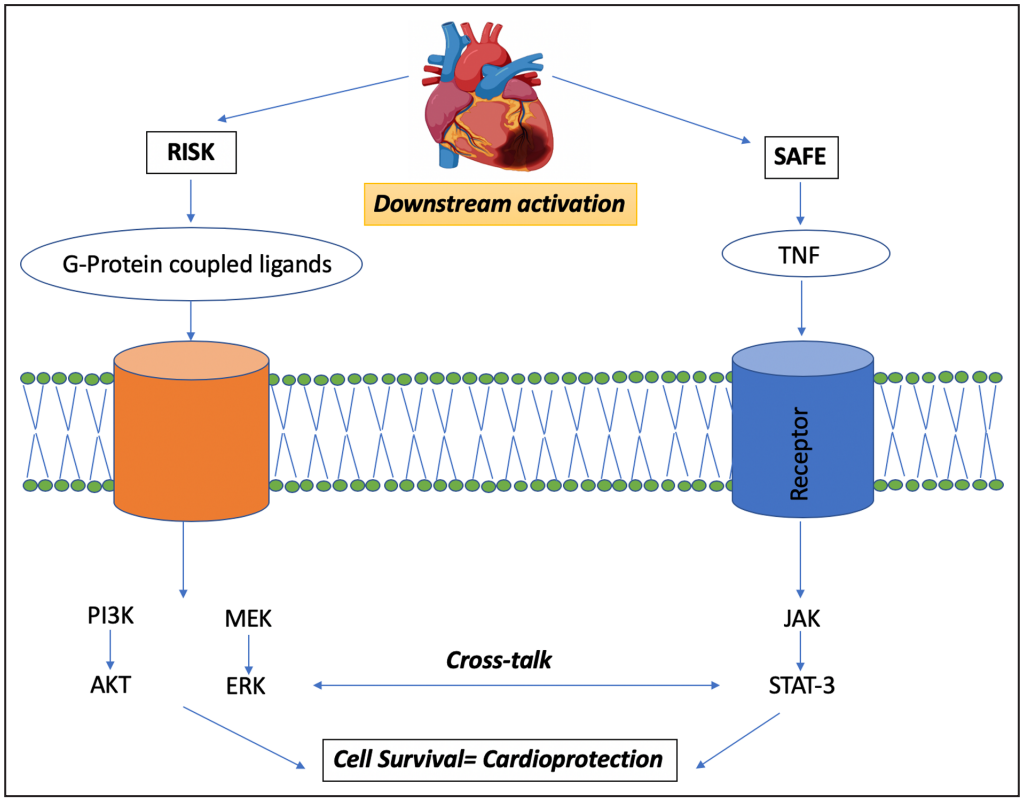

Figure 1. Schematic representation of the survivor activator factor enhancement (SAFE) and reperfusion injury salvage kinase (RISK) pathways.
Tumor necrosis factor (TNF) at low concentrations binds to its TNF receptor-2, which activates in sequence Janus kinase (JAK) and signal transducer and activator of transcription-3 (STAT-3), leading to cardioprotection via the SAFE pathway. RISK pathway involves phosphatidylinositol-3-kinase (PI3K-AKT) and/or mitogen-activated protein kinase/ERK kinase (MEK)/extracellular-signal-regulated kinase (ERK).

age, comorbidities, and comedications and issues regarding the trial design such as cyclosporine dosing, timing and selection of end points.

ROLE OF INFARCT SIZE AND MICROVASCULAR OBSTRUCTION FOR EVALUATING CARDIOPROTECTION

IS is the most frequently used endpoint in cardioprotection studies.[30] Regarding jeopardized myocardium, the total amount of myocardial tissue suffering ischemic insult is known as area at risk. Restoration of coronary blood flow, however, can paradoxically result in additional damage to the myocardium, namely IRI, as discussed previously. In order to determine the potential efficacy of innovative therapies in animal models of IRI, myocardial salvage, the ratio of IS to area at risk, is often used as an outcome variable.[31] In clinical studies, the gold standard for IS assessment is cardiac magnetic resonance imaging. The infarct can be visualized on T1-weighted imaging approximately 10 minutes after intravenous contrast administration, known as late gadolinium enhancement. In acute infarct (generally days 2–5), late gadolinium enhancement is reflected as the extravasation of gadolinium into the disrupted wall membranes. In chronic infarction (>30 days), late gadolinium enhancement results from increased gadolinium retention in the extracellular space because of collagen deposition and prolonged washout associated with reduced capillary density in the infarcted tissue.

Infarct healing is the repair process where collagenous scar tissue is produced to provide stability and tensile strength to necrotic myocardium. The greater infarct relative to total myocardial mass results in an inability to maintain LV geometry in light of mechanical stresses post-AMI, leading to adverse LV remodeling and increased sphericity.[32] Of note, cardiac magnetic resonance can also assess MVO, which occurs when capillaries become obstructed by cellular debris and thrombus, resulting in nonperfusion of the infarct core despite culprit vessel reperfusion.[33] Angiographically called no-reflow, and electrocardiographically manifested as persisting ST-elevation in the infarcted myocardial area, MVO leads to worse outcomes including larger IS and maladaptive remodeling.[34] Importantly, the presence of severe myocardial edema on T2-weighted imaging has been associated with worse MVO/IS and presence of intramyocardial hemorrhage.[35] Of note, intramyocardial hemorrhage has been recently associated with a 4-fold greater loss in salvageable myocardium within 72 hours of AMI reperfusion and known to worsen clinical outcomes including HF hospitalizations and cardiac death. From the time perspective, for every 30-minute delay from symptom onset to myocardial reperfusion, IS increases by nearly 30% and 1-year mortality increases by 5% to 7%.[36] Finally, the relationship between IS and clinical outcomes was evaluated in a meta-analysis of 10 randomized clinical trials involving 2632 patients with ST-elevation AMI in whom IS was measured by cardiac magnetic resonance imaging or technetium(tc)-99m sestamibi single-photon emission computed tomography. IS measured within the first month of PCI was strongly associated with all-cause mortality and HF hospitalization during 1 year of follow-up,[37] reinforcing the importance of this parameter in preclinical and clinical studies.

CARDIOPROTECTION FOR INFARCT SIZE REDUCTION: READY FOR PRIMETIME?

The majority of adjunct therapies for AMI cardioprotection have failed so far to translate from bench to bedside.[5,6] Novel targets such as noncardiomyocyte cells, coronary circulation, innate immunity, circulating hematopoietic cells, extracellular vesicles, and cardiac innervation still have promise in future translation to the clinical arena. Moreover, addressing confounders between preclinical and clinical cardioprotective trials such as collateral coronary circulation, IS, infarct location, risk factors (aging, sex, obesity), comorbidities (hypertension, diabetes) and comedications[38] as well as establishing consortium groups for rigorous and standardized study designs are among the ongoing efforts to translate promising preclinical results to patient care.[39] From the mechanistic perspective, Davidson et al[40] divided adjunct cardioprotection according to the protective modality, time of application, cellular target, and intracellular target. Briefly, they classified protective modalities into 3 areas of active research: ischemic conditioning, pharmacologic cardioprotection, and physical interventions. Ischemic conditioning, which refers to application of brief episodes of ischemia, can be further divided into preconditioning, before ischemic insult; post conditioning, after ischemia; and remote ischemic conditioning, for remote application such as in the limbs. Remote postconditioning is unique in that it can be applied to patients with AMI and extensive research has been in place both in clinical and preclinical areas.[41] Pharmacologic cardioprotection involves chemical substances administered to exert beneficial effects during ischemia or reperfusion including antiplatelet agents, antidiabetic drugs among others.[42] Finally, device-based approaches include targeted temperature management (TTM), vagal stimulation as well as other device-based interventions,[43] which are the main focus of this review.

DEVICE-BASED APPROACHES FOR MINIMIZING INFARCT SIZE

The vast majority of previous studies focused on pharmacological approaches to target IRI, either with or without ischemic postconditioning therapies.[42] Despite improving long-term clinical outcomes, the P2Y12 inhibitors do not provide substantial IS reduction.[44] None of the other pharmacological approaches translated to clinical practice since the introduction of PCI. There are several possible explanations regarding lack of success in pharmacological interventions including delayed drug delivery to the jeopardized myocardium until coronary artery reperfusion, insufficient drug gastric absorption, hepatic drug biotransformation (affected by age, sex, liver perfusion, drug–drug interactions, cytochrome P450 polymorphisms), and reduced renal clearance. Importantly, deleterious effects of reperfusion are expected to cause myocardial damage within a few minutes with subsequent rapid cell swelling and electrolyte accumulation within 2 minutes after reperfusion.[45] In contrast to pharmacological approaches that require coronary reperfusion for the drugs to exert effects in the ischemic myocardium, device-based approaches have the potential ability to alter myocardial biology by directly affecting the myocardium from the endocardial side, coronary sinus side, or through the nervous system. In this review we will dissect the mechanistic pathways and the rationale of why these device-based interventions may in fact add substantial benefit for reduction in IS during the ischemic insult in patients presenting with AMI.

CONCEPT OF LV UNLOADING

A contributing factor of myocardial necrosis burden during AMI is the shift toward increased myocardial metabolic demands with concomitant wasting of residual supply of oxygen to the injured myocardium. Once a coronary artery becomes occluded, both myocardial chronotropic and inotropic responses increase to compensate for reduced stroke volume, which results in impaired myocardial oxygen supply-to-demand ratio reducing the potential for myocardial salvage. This concept was first introduced by Maroko et al[46] in 1971 identifying oxygen supply and demand as main determinants of IS in the setting of AMI. Following this dogma, the term LV unloading has been employed to describe approaches that are aimed to reduce cardiac workload. Recently, Burkhoff et al[47,48] defined acute LV unloading as any maneuver, therapy, or intervention aiming to reduce the total mechanical power expenditure of the LV, which correlates with reductions in myocardial oxygen consumption and hemodynamic forces that lead to adverse LV remodeling. In this sense, the objective of cardiac unloading is two-fold during AMI: to achieve myocardial salvage and to avert adverse ventricular remodeling and HF development. In addition, it has been demonstrated in multiple preclinical models that IS correlates directly with oxygen consumption during AMI[49]: in other words, less oxygen consumption is associated with smaller IS.

MECHANICAL LV UNLOADING

Understanding the interplay of LV hemodynamics and myocardial oxygen consumption has been of paramount importance for the development of cardiac unloading devices in the recent years. Upon development of percutaneous ventricular assist devices like the Impella (Abiomed, Inc., Danvers, MA), rapid and effective ventricular unloading became clinically possible. The rationale for LV unloading with Impella before reperfusion during AMI and subsequent cardioprotection has been demonstrated in several large animal models. Initial research by Meyns et al[50] in 2003, demonstrated that LV unloading using Impella reduced myocardial oxygen consumption resulting in correlated IS reduction in a sheep model of AMI. In addition, sustained mechanical LV unloading during the acute myocardial ischemia has been demonstrated to improve both myocardial perfusion and collateral flow index which inversely correlated with IS.[51] We also demonstrated the relationship between increased microvascular perfusion in the infarct tissue and decreased LV end-diastolic wall stress during mechanical LV unloading using microsphere injection.[52] Kapur et al dissected the signaling pathways underlying the beneficial effects of mechanical LV unloading on myocardial tissue during AMI, including activation of the endogenous RISK pathway within the infarct zone, augmentation of stromal cell-derived factor-1α (SDF-1α) levels, activation of antiapoptotic pathways with inhibition of B-cell lymphoma-2 (BCL-2) and B-cell lymphoma associated X (BAX)[53] as well as maintenance of both myocardial energetics and mitochondrial integrity[54] (Figure 2).

These preclinical studies led to the STEMI-DTU (ST-Elevation Myocardial Infarction-Door to Unload) pilot trial in humans initiated by Kapur and colleagues assessing the safety and feasibility of mechanical LV unloading with Impella followed by delayed reperfusion in patients with AMI.[55] Recent results of the study confirmed the safety and feasibility of LV unloading before reperfusion and showed that primary LV unloading and delayed reperfusion for 30 minutes did not increase IS. Moreover, in the subgroup of patients with ST elevation ≥6 mm, IS normalized to the area at risk was significantly smaller in patients who underwent 30 minutes of LV unloading before reperfusion compared with immediate reperfusion despite a longer total ischemic time. The trial is currently in the second phase, which aims to

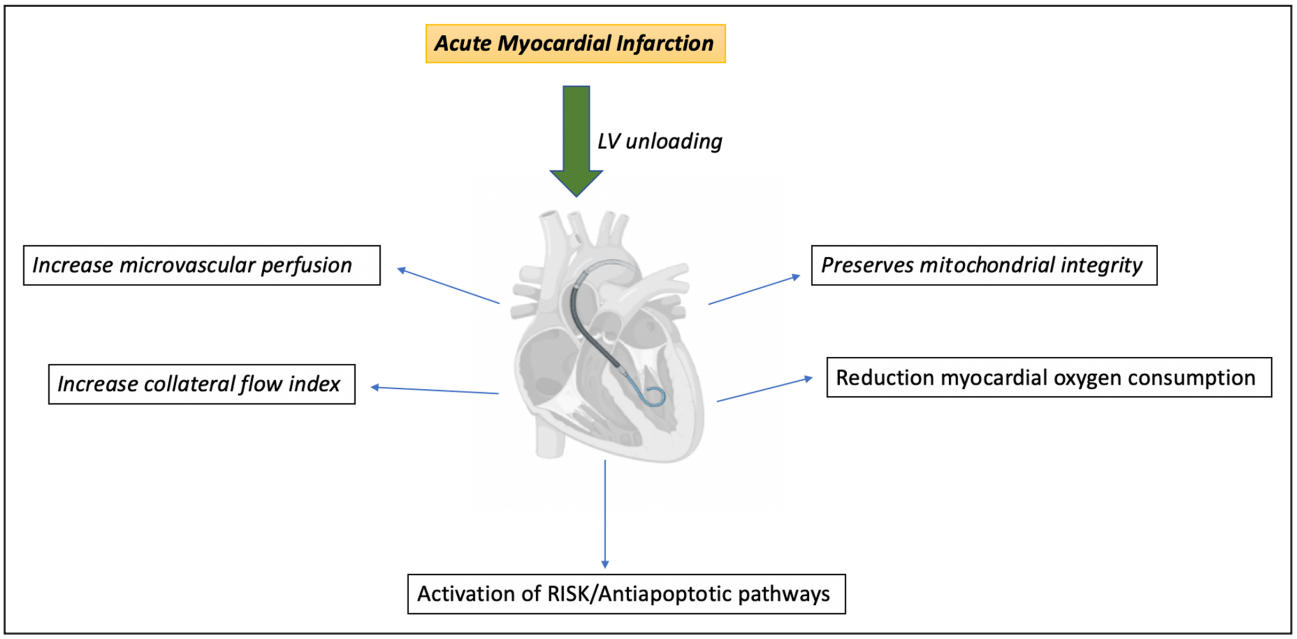

Figure 2. Schematic representation of Impella-assisted mechanical left ventricular (LV) unloading.
LV unloading improves myocardial perfusion in the infarct zone, preserves mitochondrial structure, and augments collateral coronary circulation driving to reduction in final infarct size (IS). Created using Biorender.com. RISK indicates reperfusion injury salvage kinase.

test the efficacy of Impella-mediated LV unloading for reducing IS and improving clinical outcomes in a prospective, multicenter, randomized control trial involving up to 60 centers in the United States and additional international sites (NCT03947619). The estimated study end date is October 2027.

MYOCARDIAL COOLING

TTM as a strategy of tissue protection has been studied for decades in several diseases such as stroke and is an approved treatment for brain protection after recovery of spontaneous circulation in patients suffering out-of-hospital cardiac arrest.[56] In the ischemic heart, TTM has shown IS reduction in several preclinical models with a variety of animal species, ischemia duration, cooling methods, cooling duration, magnitude of cooling, and timing of cooling initiation.[57,58] Most of these studies used target temperature between 32 °C and 35 °C. Meanwhile, experimental data suggest that even small changes of temperature within normothermic range can affect IS significantly. In fact, one rabbit study demonstrated linear relationship between IS and temperature in the 35 °C to 42 °C range with controlled heart rate.[59] Importantly, IS reduction may be achieved only when cooling is initiated during the ischemic phase with lack of benefit once reperfusion has started.[60] Of note, some studies postulated reduction in MVO with no impact on IS reduction, pointing to TTM's unique salutary effects at the myocardial microvasculature level.[61]

When translating TTM to clinical application, several approaches and devices for achieving targeted temperature have been employed. However, none of them has fulfilled the ideal features for rapid enough cooling for AMI with minimal side effects.[62] In contrast to strong evidence in preclinical studies, a recent patient level pooled analysis of 6 published randomized clinical trials including a total of 629 patients treated with endovascular TTM found that the IS reduction is limited to patients with anterior wall involvement and those cooled below 35 °C.[63]

Several limitations may account for the lack of benefit of TTM. First, previously used systemic cooling methods cannot guarantee that ischemic myocardium be cooled in a timely manner before reperfusion. Optimization of delivery systems will likely reduce the time for achieving sufficient myocardial cooling. Second, hypothermia might have confounded the platelet inhibition. Both oral (clopidogrel, ticagrelor, and prasugrel) as well as intravenous (cangrelor) P2Y12 inhibitors exert efficient platelet inhibition in patients who are normothermic, but the efficacy is reduced in patients undergoing therapeutic hypothermia.[64,65] Third, systemic delivery of hypothermia can induce shivering in patients, which can increase systemic oxygen demand and enhance the adrenergic state. Fourth, addition of any device including TTM requires extra time, which prolongs symptom-to-reperfusion time. Fifth, when cold fluid infusion is used, large amount of fluids to cool the whole body can potentially induce pulmonary edema in patients who are hemodynamically

compromised. For example, the COOL-AMI EU trial (prospective, open-label, multicenter randomized trial) evaluated cooling as an adjunctive therapy to PCI in patients with AMI.[66] In total, 111 patients were randomized to endovascular hypothermia (33.3 °C) (Zoll Proteus Intravascular Cooling System) versus control (standard of care). No differences were seen in the primary end point of IS at 4 to 6 days post AMI or in 30-day major adverse cardiac events. Moreover, the hypothermia strategy resulted in a 44-minute increase in total ischemic time due to complexities in delivery system logistics. The EURO-ICE (European Intracoronary Cooling Evaluation in Patients With ST-Elevation Myocardial Infarction) trial[67] is currently ongoing and will clarify whether selective intracoronary hypothermia (Figure 3)[68] (normal saline infusion at room temperature for 10 minutes through balloon catheter followed by normal saline at 4 °C infused for 10 minutes during the reperfusion phase) can reduce IS in a safe and timely manner (NCT03447834). This is an elegant approach differentiated from previous trials by limiting the cooling to the infarcted region without inducing systemic hypothermia, being more aligned with PCI with the option of therapy through radial access, no requirement for antishivering medications, less cold saline for infusion (147 mL versus 1028 mL for systemic hypothermia), and rapid onset of cooling with only 6-minute cooling-related delay in total door-to-balloon time.[69] The first 50 enrolled patients revealed promising results with no in-hospital mortality.[70] The estimated study completion date is December 2022.

CORONARY SINUS INTERVENTIONS

The purpose of intervening in coronary venous circulation relies on a fundamental principle: a controlled pressure increase of the coronary sinus is able to induce a retrograde perfusion gradient in ischemic myocardium with improvement in myocardial tissue perfusion.[71] Overall, 3 main classes of coronary sinus interventions have been proposed and tested: (1) retroperfusion technique, (2) retroinfusion technique, and (3) coronary sinus occlusion techniques. The retroperfusion technique, which refers to active blood pumping into the coronary sinus, has demonstrated efficacy in improving myocardial metabolism and reducing IS in animal models.[72] The retroinfusion technique, which refers to active pumping of substances into the coronary sinus with or without blood, has shown to be safe to deliver cell therapy in preclinical models. However, these retroperfusion/infusion techniques have been mainly designed for investigational purposes as well as for delivering cardioplegia during heart surgery and so are technically not feasible for providing cardioprotection in AMI. Coronary sinus occlusion techniques include both intermittent and pressure-controlled intermittent coronary sinus occlusion (PICSO). Both of them use a balloon-tipped catheter equipped with a

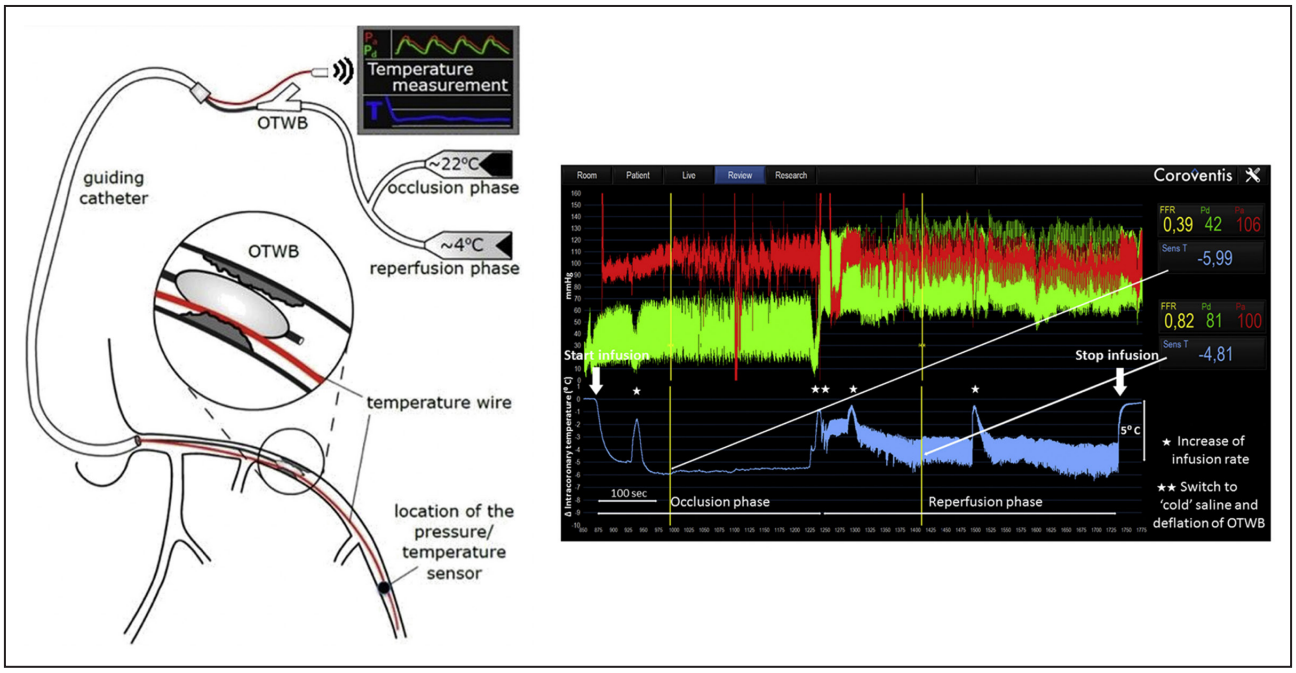

Figure 3. Intracoronary hypothermia for infarct size reduction.
This local cardiac cooling method is currently tested in a clinical trial. Aortic pressure (Pa) in red, distal coronary pressure (Pd) in green, and intracoronary temperature in blue. Note that during the reperfusion phase, Pd rises (balloon is deflated) and coronary flow is (partially) restored. Numeric values of Pa, Pd, and temperature during both phases are displayed on the right. Reproduced with permission from El Farissi et al.[68] Copyright © [2022], [Mary Ann Liebert, Inc.].

sensor for coronary sinus pressure monitoring placed at the ostium of the coronary sinus. During balloon inflation, a pulsatile and progressive increase in coronary sinus pressure is observed at each cardiac cycle until a pressure plateau is achieved. Then, the balloon is deflated allowing systolic venous drainage (Figure 4).[73] The capacity of these techniques to provide cardioprotection relies on several aspects. First, canine models have shown that increasing coronary sinus pressure allows redistribution of blood flow to the endocardial layers.[74] Moreover, PICSO has been recognized also in a canine model for its ability to reduce myocardial edema and hasten the clearance of deleterious molecule buildup during the acute ischemic phase,[75] likely by plasma skimming into the venous microcirculation.

The clinical relevance of this intervention to protect the ischemic myocardium against IRI has been evaluated in both preclinical and clinical studies. For example, Khattab et al[76] found in a closed-chest swine MI model that PICSO was safe and effective in improving coronary perfusion pressure with subsequent amelioration in myocardial oxygen consumption. In the clinical field, small studies using PICSO showed feasibility, safety, and increased coronary wedge pressure through coronary sinus pressure augmentation.[77]

In 2015, the Prepare RAMSES study evaluated this technique in addition to primary PCI in patients with anterior AMI.[78] In total, 30 patients were randomized to coronary sinus occlusion versus standard of care. PICSO was initiated in 19 patients (63%); however, it could be maintained for 90 (±2) minutes in only 12 patients (40%). Comparing all patients treated with PICSO to matched controls, no significant differences in IS or LV function were found. However, IS reduction from 2–5 days to 4 months was greater for patients successfully treated with PICSO compared with matched controls (41.6±8.2% versus 27.7±9.9%, P=0.04). Although this trial showed PICSO was safe as an adjunct therapy for reducing IRI and IS during AMI, logistic aspects required further troubleshooting. A recent propensity score-matched population of patients with AMI in 5 UK hospitals showed that PICSO is associated with reduced IS at 5 days post AMI.[79] The benefits of PICSO during AMI are not only directed to IS reduction but also salutary on the myocardial microcirculation. As shown recently by De Maria et al, applying PICSO to patients with AMI and an index of microvasculature resistance >40 before PCI demonstrated microvascular function improvement in addition to IS reduction. Currently, the PICSO-AMI-I trial is ongoing and will shed light on whether PICSO started after coronary flow restoration can reduce IS in AMI (NCT03625869). The estimated study completion date is July 2025.

Figure 4. Coronary sinus intervention for retrograde perfusion.
Example of continuous coronary sinus pressure measured during pressure-controlled intermittent coronary sinus occlusion (PICSO) balloon deflation and inflation. A balloon-tipped catheter is introduced in the coronary sinus. The catheter, which is connected to a console, is able to monitor coronary sinus pressure and automatically repeat inflations and deflations. Reproduced from Vidal-Calés et al[73] under the terms and conditions of the Creative Commons Attribution (CC-BY) license (https://creativecommons.org/licenses/by/4.0/).

SUPERSATURATED OXYGEN THERAPY

Experimental studies have shown focal patchy areas of microvascular ischemia during reperfusion in the area at risk, reducing capillary density and creating arteriovenous shunts that can potentially affect final IS and myocardial recovery. In order to improve myocardial oxygen delivery and enhance coronary microvascular function, higher oxygen concentrations are required because of low plasma solubility.[81] In fact, the recent randomized trial DETO2X-AMI[82] (Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction) showed that routine administration of standard oxygen therapy in patients with suspected AMI without hypoxemia had no clinical benefit on all-cause mortality at 1-year follow-up. Although this trial did not evaluate IS, the lack of benefit can potentially be related to limited oxygen delivery to the ischemic myocardium. The rationale for investigating the benefit of increasing plasma oxygen tension during myocardial ischemia has been provided by experiments that revealed both increase in coronary blood flow and ischemia alleviation during hyperoxia.[83,84] Hyperbaric oxygen therapy can provide oxygen with an atmospheric pressure 2 to 3 times higher than normal air pressure resulting in an increase in oxygen tension above 10 to 15 times normal plasma concentration.[85] Initial experimental studies with hyperbaric oxygen therapy in the prereperfusion era demonstrated a reduction in ventricular arrhythmias and survival improvement.[86] Moreover, a Cochrane Systematic Review noted that in acute coronary syndrome, individual small trials suggested the addition of

hyperbaric oxygen therapy reduces the risk of major adverse cardiac events, dysrhythmias, and the time to relief from ischemic pain but does not reduce mortality.[87] Although hyperbaric oxygen therapy incorporated new data about the benefits of highly concentrated oxygen for the postreperfusion ischemic myocardium, this treatment is not technically feasible during AMI. Local infusion of blood hyperbarically oxygenated with aqueous oxygen is termed supersaturated oxygen (SSO2) delivery. Aqueous oxygen is an infusible physiological solution (usually normal saline) containing oxygen dissolved at high partial pressures, on the order of 40 bars or greater, yielding an oxygen concentration of >1.1.[88] The delivery of SSO2 with a partial pressure of oxygen (PaO2) of 760 to 1000 mm Hg in the affected artery immediately after successful reperfusion has markedly reduced IS in both canine and swine coronary occlusion models (Figure 5)[89,90] by decreasing capillary endothelial cell swelling, reducing myeloperoxidase levels (a marker of free radical oxygen tissue damage), altering nitric oxide synthase expression, and inhibiting leukocyte activation and adherence as well as endothelial preservation.[91] Following promising pilot study results,[92] 269 patients with anterior or large inferior AMI undergoing successful PCI within 24 hours of symptom onset were randomly assigned to SSO2 or control treatment in the AMIHOT-I (Acute Myocardial Infarction With Hyperoxemic Therapy-I) trial.[93] In this study, IS measured by technetium (tc)-99m- sestamibi single photon emission computed tomography imaging at 14 days was not significantly different between the 2 treatment groups. However, the 105 patients with anterior AMI reperfused within 6 hours in the SSO2 group had a smaller IS, less post-PCI residual ischemic burden measured by ST-segment Holter monitoring, and improved echocardiographic regional wall motion at 3 months (P=0.04, by intent-to-treat analysis). These findings motivated a second, prospective, randomized trial of SSO2 therapy, the AMIHOT-II trial,[94] randomizing a total of 304 patients. This time the trial targeted only the patients with large anterior AMI undergoing PCI within 6 hours of symptom onset. The trial followed a Bayesian statistical design, where the results of the Phase II study were incorporated into those of the follow-up trial, with weighting of the Phase II data according to degree of similarity between trials. A statistically significant smaller median IS, measured at 2 weeks by single photon emission computed tomography, was noted in the treatment group compared with the control group (18.5% versus 25% of LV mass, or a relative IS reduction of 26%). Moreover, in patients with a baseline LV ejection fraction <40%, even greater myocardial salvage was noted with an absolute IS of 33.5% in controls and 23.5% in patients treated with SSO2. Regarding clinical outcomes, SSO2 was noninferior to the control group in terms of 30-day major advanced cardiac events, but increased risk of bleeding was observed (SSO2 delivery requires 7–8 Fr femoral access). These results need to be taken with caution however, because the AMIHOT-II was an underpowered trial in terms of IS reduction at 14 days but was positive only

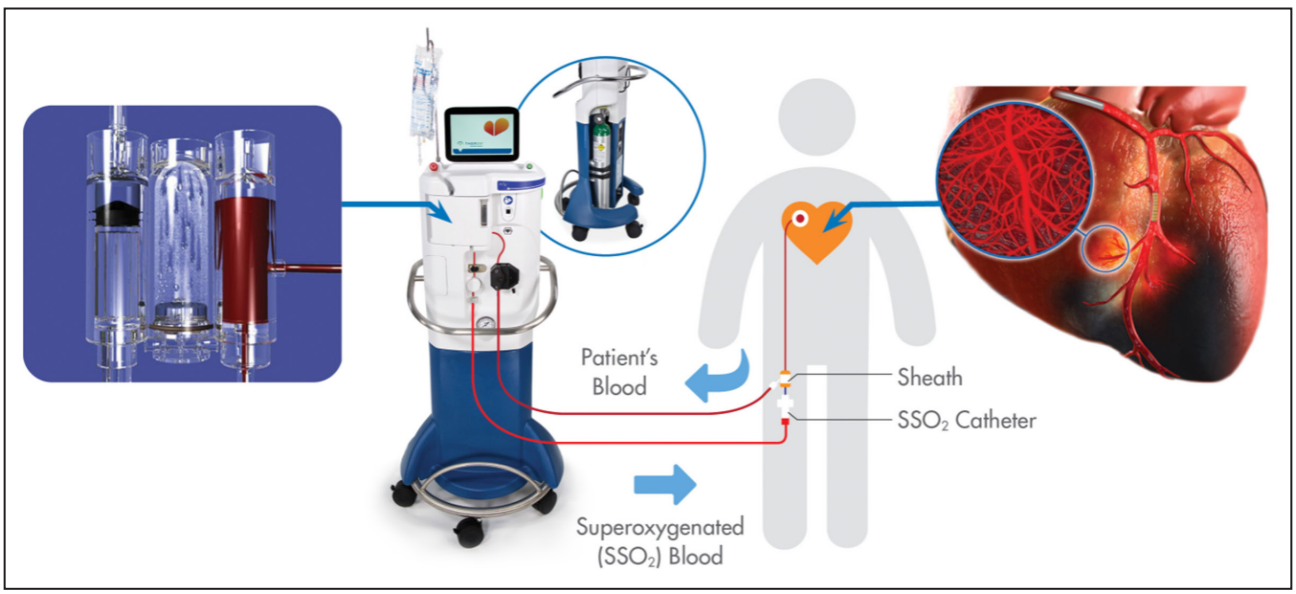

Figure 5. Supersaturated oxygen therapy. Blood is directed towards an oxygenation polycarbonate chamber to achieve a partial pressure of oxygen (PO_2) of 760–1000 mm Hg.
Hyperoxemic blood is then returned at 100 mL/min for 60 minutes through a dedicated 5 French (Fr) intracoronary infusion catheter placed at the ostium of the left coronary artery, providing supersaturated oxygen to the whole left coronary artery. Images courtesy of Zoll Medical Corporation (Zoll.com).

when pooling the positive subgroup from AMIHOT-I cohort.

Although nonsignificant, the SSO2 arm showed a trend for increased stent thrombosis in these studies. The safety of SSO2 therapy was later confirmed in 100 patients with anterior AMI treated with 60 minutes of intracoronary SSO2 post PCI (IC-HOT [Evaluation of Intracoronary Hyperoxemic Oxygen Therapy in Anterior Acute Myocardial Infarction Patients] single arm trial). This study demonstrated smaller IS in SSO2 group by cardiac magnetic resonance at 30 days. It also showed logistical improvement in the SSO2 delivery technique through infusion via a guide catheter into the left main coronary artery using either 5-Fr radial access or 7-Fr femoral access and increased rate of 60-minute SSO2 infusion (100 mL/min). Infarct size reduction was comparable to the AMIHOT-II trial and total 30-day net adverse cardiac events were 7.8% versus 13.1% (AMIHOT-II) and 10.7% set as performance goal. At 1-year follow-up, there were lower rates of both all-cause mortality and new-onset HF/HF hospitalizations.[95] In light of these results, SSO2 is the first Food and Drug Administration-approved device-based therapy for AMI cardioprotection.

In 2021, the ISO-SHOCK (Incorporating Supersaturated Oxygen in Shock) trial started patient recruitment and will improve the gap of knowledge through a multicenter, prospective randomized (1:1) study to evaluate the safety and feasibility of SSO2 therapy delivered for 60 minutes selectively into the affected coronary artery of patients presenting with AMI and cardiogenic shock (NCT04876040). The estimated study completion date is June 2025.

VAGAL STIMULATION

The activation of efferent vagal nerves by electrical stimulation or by reflexes (baroreflex, chemoreflex) reduces heart rate as well as increases coronary blood flow through a nitric oxide-dependent mechanism.[96] Moreover, the interplay between IRI and autonomic balance enhances sympathetic activity with consequent decreased vagal activity, worsening IRI.[97] Several mechanisms have been related to cardioprotection through efferent vagal stimulation including improved mitochondrial function, attenuation of ROS formation, antiapoptotic cardiomyocyte signaling, and reduction of systemic and local inflammatory responses.[97] For instance, in a canine model of IRI, Zhang et al[98]

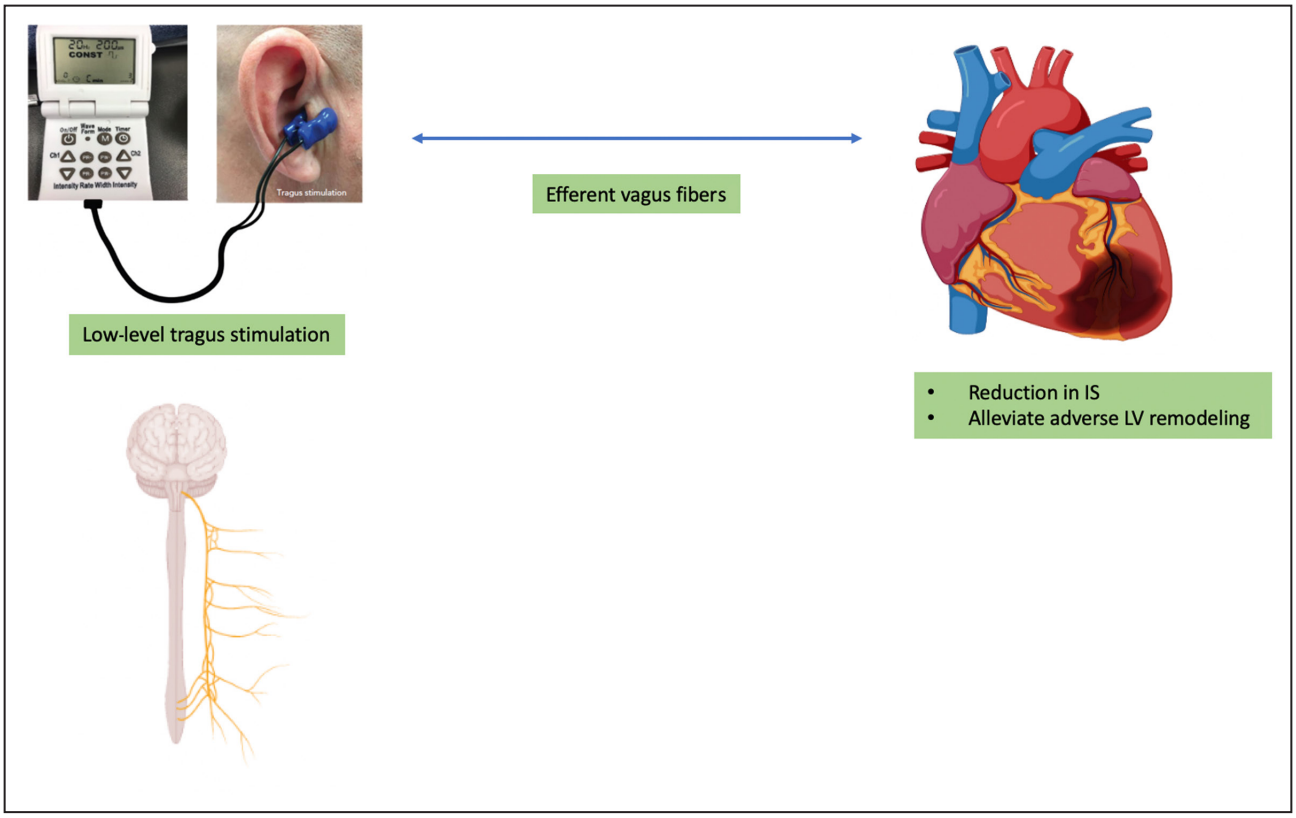

Figure 6. Vagus nerve stimulation. Electrical signal delivered to the tragus stimulate the auricular branch of the vagus nerve (afferent fibers).
The excitation then enters the medulla oblongata at the brainstem, which excites the vagus efferent fibers to modulate cardiac function. Low-level tragus stimulation reduces infarct size (IS) and relieves left ventricular (LV) remodeling after myocardial infarction. Figures created using Biorender.com and tragus stimulation image reproduced from Jiang et al[104] under the terms and conditions of the Creative Commons Attribution (CC-BY) license (https://creativecommons.org/licenses/by/4.0/).

demonstrated the capacity of averting IRI through cholinergic anti-inflammatory pathway activation. Moreover, a rat model evaluating vagal activation during remote ischemic conditioning has shown to provide cardioprotection through the release of a humoral factor, possibly glucagon-like peptide 1 from the gut.[99] Vagal stimulation in preclinical models has been shown to both reduce IS and preserve LV function and performance. Uemura et al[100] demonstrated that vagal stimulation attenuated myocardial IRI by inducing TIMP-1 (tissue inhibitor matrix metalloproteinase 1) expression and reducing active MMP-9 (matrix metallopeptidase 9). In addition, Arimura et al[101] demonstrated in a canine MI model that bradycardia induction by transvenous superior vena cava pacing for a total of 60 minutes starting before coronary reperfusion not only reduced IS but also preserved LV function at 1-month follow-up. Interestingly, electrical stimulation of efferent vagal nerves has been shown to reduce IS and MVO in experimental models,[102] even in the absence of heart rate reduction.[103] In patients with AMI, a proof-of-concept study using vagal stimulation by low-electrical transcutaneous stimulation at the right auricular tragus (Figure 6),[104] starting at catheterization room arrival to 2 hours post-reperfusion, reduced IS ($P<0.05$), reduced ventricular arrhythmias and improved LV ejection fraction ($P=0.01$) compared with sham procedure.[105] Unfortunately, the TREATMI trial (2017) aiming to evaluate the impact of transcutaneous vagal stimulation and autonomic modulation of inflammation in AMI failed to enroll the expected number of patients (NCT03284281).

FUTURE APPLICATIONS AND PERSPECTIVES

The details of each device-based therapy and ongoing clinical trials are summarized in the Table. Understanding the pathophysiology and molecular mechanisms of IRI and myocardial repair after AMI will promote the development of new cardioprotective strategies. Regarding the techniques highlighted here, the combination of these interventions seems to be a reasonable path in the upcoming years. For example, our laboratory is exploring the cardioprotective effects in swine MI models by application of both mechanical LV unloading and TTM[106] for maximum myocardial salvage. Currently, the most important barrier to overcome is related to logistic issues as previously described, including standardized access in underserved populations, improving delivery feasibility, lowering the total time of application, and reducing risk of perioperative complications.

CONCLUSIONS

This review summarizes key concepts in the field of device-based approaches for cardioprotection. The armamentarium of novel therapeutics for tackling IS to prevent future clinical events is promising but still faces complex logistic challenges and requires adequately powered clinical trials. The near future will need these interventions in order to change the prognosis of the growing population with HF after AMI.

Table. Device-Based Therapies for ST-Elevation Myocardial Infarction

Approach	Clinical evidence	Target	Time of application	Treatment duration	Extravascular access requirement	Ongoing studies	Regulatory status
Myocardial cooling	RCT studies	IRI/MVO	Before and after reperfusion	Median time 3 h across studies	Yes, for endovascular cooling (venous, 8–9F)	Euro-ICE (European Intracoronary Cooling Evaluation in Patients With ST-Elevation Myocardial Infarction) RCT	FDA approved in cardiac arrest
Left ventricular unloading	Non-RCT studies	IRI	Before and after reperfusion	30 min before and continues after reperfusion (more than 3 h)	Yes, large bore arterial (13–14 F)	STEMI-DTU (ST-Elevation Myocardial Infarction-Door to Unload) pivotal RCT	FDA approved and CE market for cardiogenic shock and high-risk PCI
PICSO	Non-RCT studies	IRI/MVO	After reperfusion but before PCI	50 min (10 min for coronary sinus cannulation)	Venous (8–9 F)	PICSO-AMI-I	FDA breakthrough designation (investigational)
SSO2	RCT studies	MVO	After reperfusion	60 min	Yes, PCI access can be used	ISO-Shock (Incorporating Supersaturated Oxygen in Shock) RCT	Both FDA and CE market approval in AMI
Vagal	RCT	IRI	Before PCI	2 h	No	None	None
Stimulation	Proof-of-concept					TREATMI failed to enroll patients	

AMI indicates acute myocardial infarction; CE, Conformité Européenne; F, French; FDA, Food and Drug Administration; IRI, ischemia–reperfusion injury; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; PICSO, pressure-controlled intermittent coronary sinus occlusion; RCT, randomized controlled trial; and SSO_2, supersatured oxygen.

ARTICLE INFORMATION

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