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*JACC* SCIENTIFIC STATEMENT

# Reperfusion Injury in Patients With Acute Myocardial Infarction

## *JACC* Scientific Statement

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**ABSTRACT**

Despite impressive improvements in the care of patients with ST-segment elevation myocardial infarction, mortality remains high. Reperfusion is necessary for myocardial salvage, but the abrupt return of flow sets off a cascade of injurious processes that can lead to further necrosis. This has been termed myocardial ischemia-reperfusion injury and is the subject of this review. The pathologic and molecular bases for myocardial ischemia-reperfusion injury are increasingly understood and include injury from reactive oxygen species, inflammation, calcium overload, endothelial dysfunction, and impaired microvascular flow. A variety of pharmacologic strategies have been developed that have worked well in preclinical models and some have shown promise in the clinical setting. In addition, there are newer mechanical approaches including mechanical unloading of the heart prior to reperfusion that are in current clinical trials.
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Contemporary therapy for patients suffering ST-segment elevation myocardial infarction (STEMI) relies on prompt reperfusion.[1] The pathologic basis for reperfusion therapy can be traced back to the work of Reimer and Jennings who in 1977 established the concept of the "wavefront phenomenon" of myocardial necrosis in a canine model of acute myocardial infarction (AMI).[2] Their study demonstrated the relationship between the duration of coronary artery occlusion and progressive loss of salvageable myocardium. This basic concept was borne out in early trials of thrombolytic therapy and further corroborated in studies of percutaneous coronary intervention (PCI) for STEMI.[3] Yet, as necessary as reperfusion is for myocardial salvage and restoration of function, it was recognized early on that reperfusion itself could lead to acute myocardial dysfunction and necrosis. Myocardial

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## HIGHLIGHTS

- MIRI exacerbates myocardial necrosis in patients with STEMI, contributing to mortality.
- MIRI is mediated by varying combinations of ROS, inflammation, endothelial dysfunction, impaired microvascular flow, and other factors.
- A variety of pharmacologic and mechanical strategies that mitigate MIRI in preclinical models have shown promise in clinical trials.

ischemia-reperfusion injury (MIRI) is defined as the paradoxical worsening of myocardial damage following rapid restoration of blood flow in an ischemic territory. These damaging processes include lethal cardiomyocyte injury, myocardial stunning, vascular injury and dysfunction, and tissue edema. Preclinical studies have shown that cardioprotective strategies aimed at reducing MIRI can substantially increase myocardial salvage in models of ischemia-reperfusion (**Central Illustration**).

Early trials of reperfusion therapy demonstrated improvement in survival and myocardial function. Consistent with preclinical studies, time to reperfusion emerged as an important factor determining clinical efficacy. Whereas PCI has emerged as the preferred method of reperfusion, fibrinolytic therapy remains a viable alternative in settings where prompt access to a catheterization laboratory is not available. Guidelines suggest the goal for patients with STEMI should be to achieve a door-to-needle time within 30 minutes or a door-to-balloon time within 90 minutes. Systems of care that render early STEMI reperfusion feasible have been developed. For PCI, these have resulted in dramatically shorter national average door-to-balloon times.[4] Yet studies have suggested that these improvements have not been mirrored by a commensurate reduction in STEMI, suggesting that we may have reached a plateau for survival in this population.[3,5] It must be acknowledged that consistent with the recognition of the importance of time to reperfusion, prehospital delays in care are critically important in determining patient outcome in relation to total ischemic time. These include the time of onset of symptoms to medical contact, as well as time from medical contact to device (reperfusion). In turn, important issues include whether patients present through utilization of emergency medical services and whether they present to a PCI-capable hospital. Contemporary data regarding processes surrounding STEMI management have reaffirmed the critical importance of time to reperfusion in relation to mortality and suggest that there is room for improvement in both prehospital and in-hospital delays in reperfusion.[6] Despite these nuances, data suggest that alternative strategies to reduce mortality in this population are necessary and MIRI has emerged as a potential target.

The molecular underpinnings of MIRI have become better understood, and multiple therapies have shown promise in preclinical models. However, few clinical trials have proved successful in human studies. Still, several novel therapeutic agents and devices have emerged because clinically promising therapies and trials are underway (**Table 1**), suggesting that we may be on the threshold of defining a cadre of effective therapies in this arena. The purpose of this review is to describe: 1) the pathophysiologic basis of MIRI; 2) treatment strategies that are currently under investigation with an emphasis on the U.S. Food and Drug Administration–approved therapy of supersaturated oxygen ($SSO_2$), new mechanical unloading strategies, and anti-inflammatory strategies involving Nod-like receptor protein 3 (NLRP3); and 3) the future of clinical investigation in this field.

### ABBREVIATIONS AND ACRONYMS

**AMI** = acute myocardial infarction

**ASC** = apoptosis-associated speck-like protein with a carboxy-terminal CARD

**ATP** = adenosine triphosphate

**CMR** = cardiac magnetic resonance

**IABP** = intra-aortic balloon pump

**IL** = interleukin

**LV** = left ventricular

**LPS** = lipopolysaccharide

**MIRI** = myocardial ischemia-reperfusion injury

**mPTP** = mitochondrial permeability transition pores

**MVO** = microvascular obstruction

**NFκB** = nuclear factor kappa-light chain-enhancer of activated B cells

**NLRP3** = Nod-like receptor protein 3

**PCI** = percutaneous coronary intervention

**RNS** = reactive nitrogen species

**ROS** = reactive oxygen species

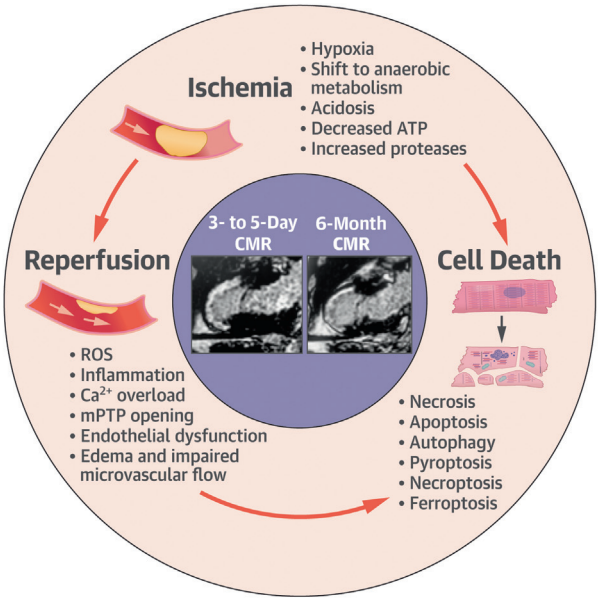
**$SSO_2$** = supersaturated oxygen

**STEMI** = ST-segment elevation myocardial infarction

## KEY PATHOPHYSIOLOGIC MECHANISMS AND FACTORS CONTRIBUTING TO MIRI

MIRI is caused by complex mechanisms involving extracellular, intracellular, and mechanical processes[7,8] that are interconnected with inflammatory aspects, and the coronary circulation is both an author and a victim in these processes. MIRI alters homeostatic processes and also influences post-STEMI left ventricular remodeling, increasing the risk of arrhythmias and potentially leading to heart failure. Here we will analyze individually some of the most promising therapeutic approaches with the understanding that a multitarget approach may be necessary.[7] Emerging evidence implicates activation of NLRP3[9] as having a pivotal role in MIRI. Indeed, histologic investigations have demonstrated the existence of NLRP3 spots in the early stages of AMI in cardiomyocytes and endothelial cells of the ischemic

**CENTRAL ILLUSTRATION** **Schematic of Injurious Processes at Work During Both Ischemia and Reperfusion**




**Emerging Therapeutic Strategies Against MIRI**

| Process | Class | Putative mechanism | Example |
|---|---|---|---|
| Pharmacologic | NRLP3 inhibitors | Anti-inflammatory, reduced pyroptosis | Glyburide, MCC950, IFM-2427, Inzomelid, Somalix, INF4E, BAY 11-7082, OLT1177 |
| | IL inhibitors | Anti-inflammatory | GSK1070806a, anakinra, ipsum |
| | Beta-blockers | Anti-inflammatory, reduced MVO2 | Metoprolol, esmolol |
| | $SSO_2$ | Improved microvascular flow | Therox |
| | Miscellaneous | Various mechanisms | Nitrite, nitrate, metformin |
| Mechanical | Pre- or post-coronary conditioning | Multiple and various mechanisms, including the survivor activating factor enhancement, the reperfusion injury salvage kinase, and the NO/cyclic 3′:5′-guanosine monophosphate (cGMP) pathways | Intermittent coronary occlusion |
| | Remote conditioning | Multiple and various mechanisms, including intermittent peripheral ischemia leading to systemic release of cardio-protective factors | Blood pressure cuff inflation and deflation |
| | Mechanical unloading | Upregulation of cardioprotective pathways including the reperfusion injury salvage kinase pathway | Active LV unloading via the left atrium or the LV using centrifugal or transvalvular pumps respectively |

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Ischemia places energetic and hypoxic stress on cells with resultant acidosis, adenosine triphosphate (ATP) depletion, and increased protease production leading to cell death. Reperfusion reverses these processes but induces oxidative stress, ion shifts, and inflammatory stress that may also contribute to cell death. Despite timely reperfusion with primary percutaneous coronary intervention, the net effect is acute transmural injury and subsequent scar formation with maladaptive cardiac remodeling as illustrated by the 3- to 5-day and 6-month cardiac magnetic resonance (CMR) images, respectively.

**TABLE 1** List of Clinical Trials Targeting Ischemic Reperfusion Injury Listed on clinicaltrials.gov at the Time of Publication

| Trial Name (ID) | Status | Conditions | Interventions |
|---|---|---|---|
| Evolocumab in STEMI (NCT06081803) | Recruiting | • STEMI | • Drug: Repatha |
| Short and Intermediate Term Effect of Dapagliflozin on Left Ventricular Remodeling in Anterior STEMI Patients (NCT05957887) | Recruiting | • STEMI | • Drug: dapagliflozin |
| The Role of Colchicine in Reducing the Rate of Myocardial Reperfusion Injury (NCT05734612) | Enrolling by invitation | • STEMI | • Drug: colchicine<br>• Drug: placebo (lactose) |
| Effect of Colchicine on MMP-9, NOX2, and TGF-β1 in Myocardial Infarct (NCT05709509) | Recruiting | • STEMI | • Drug: colchicine<br>• Procedure: PCI<br>• Other: optimal medical treatment including statin, aspirin, $P2Y_{12}$ inhibitor, and nitrate |
| CEECSWIRI (NCT05624203) | Not yet recruiting | • STEMI | • Device: extracorporeal cardiac shock wave therapy |
| AMI-DC (NCT05554484) | Recruiting | • STEMI | • Biological: autologous peripheral-blood-derived tolerogenic dendritic cells |
| PULSE-MI (NCT05462730) | Active, not recruiting | • STEMI | • Drug: methylprednisolone<br>• Drug: isotonic saline |
| NATURE (NCT04969471) | Recruiting | • STEMI | • Device: EnVast stent<br>• Procedure: conventional treatment |
| RIP-HIGH (NCT04844931) | Recruiting | • STEMI | • Procedure: RIC + PostC + standard PCI<br>• Procedure: standard PCI |
| RIC-AFRICA (NCT04813159) | Recruiting | • STEMI | • Device: RIC<br>• Device: sham-control |
| Delivery $SSO_2$ Therapy for 60 Min in Anterior MI Patients With PCI ≤6 Hours of Symptoms Onset Compared to Standard (NCT04743245) | Enrolling by invitation | • STEMI | • Device: TherOx DownStream System<br>• Device: PCI |
| Open-label Study of Neuraminidase Inhibitor Treatment in STEMI Patients (NCT04684498) | Recruiting | • STEMI | • Drug: oseltamivir phosphate capsules |
| CLEAN (NCT04665648) | Recruiting | • STEMI | • Drug: nicorandil<br>• Drug: placebo |
| Oral Nicorandil in ST Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention (NCT04632121) | Not yet recruiting | • STEMI | • Drug: Nicorandil 20 MG |
| Early rhBNP on Myocardial Remodeling and Reperfusion in Patients With STEMI (NCT04033861) | Recruiting | • STEMI | • Drug: rhBNP<br>• Drug: control |
| DTU-STEMI (NCT03947619) | Recruiting | • STEMI, anterior | • Device: Impella CP placement prior to reperfusion with primary PCI |
| iPOST2 (NCT03787745) | Recruiting | • STEMI | • Procedure: ischemic postconditioning<br>• Procedure: conventional |
| EURO-ICE (NCT03447834) | Active, not recruiting | • STEMI | • Other: selective intracoronary hypothermia + PPCI<br>• Other: standard PPCI |
| CARIOCA (NCT03155022) | Active, not recruiting | • STEMI | • Device: RIC and intracoronary ischemic conditioning<br>• Device: patients with no RIC and no intracoronary ischemic conditioning |
| PITRI (NCT03102723) | Active, not recruiting | • STEMI | • Drug: cangrelor |

AMI-DC = AMI-DC in Patients With Anterior Wall Myocardial Infarction; CARIOCA = Combined Application of Remote and Intra-Coronary Ischemic Conditioning in Acute Myocardial Infarction; CEECSWIRI = Clinical Efficacy of Extracorporeal Cardiac Shock Wave Therapy in Patients With Ischemia-reperfusion Injury; CLEAN = Clinical Efficacy and Safety of Intravenous Infusion of Nicorandil During Primary Percutaneous Coronary Intervention; DTU-STEMI = Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction: The STEMI-DTU Trial; EURO-ICE = European Intracoronary Cooling Evaluation In Patients With ST-elevation Myocardial Infarction; iPOST2 = Ischemic Postconditioning in STEMI Patients Treated With Primary PCI; ISO-SHOCK = Incorporating Supersaturated Oxygen in Shock; NATURE = EnVast as an Adjunct PPCI in Subjects Presenting With STEMI; PCI = percutaneous coronary intervention; PITRI = Platelet Inhibition to Target Reperfusion Injury; PostC = post conditioning; PPCI = primary percutaneous coronary intervention; PULSE-MI = Pulse Glucocorticoid Therapy in Patients With ST-Segment Elevation Myocardial Infarction; rhBNP = recombinant human B-type natriuretic peptide; RIC = remote ischemic conditioning; RIC-AFRICA = Remote Ischaemic Conditioning in STEMI Patients in Sub-Saharan Africa; RIP-HIGH = Remote Ischemic Conditioning With Local Ischemic Postconditioning in High-Risk ST-elevation Myocardial Infarction; $SSO_2$ = supersaturated oxygen; STEMI = ST-segment elevation myocardial infarction.

area and border zones. Then leukocyte infiltration and fibroblast activation are observed. When inflammation subsides, NLRP3 spots become apparent in isolated cardiomyocytes and/or fibroblasts.[10,11]

Cell death modalities contributing to MIRI include, but are not limited to, pyroptosis, necrosis, apoptosis, ferroptosis, and autophagy boosting inflammation and triggering pyroptosis.[12,13] Pyroptosis, a type of controlled cell death characterized by the formation of pores in the cardiomyocyte cell membrane, release of proinflammatory cytokines, and subsequent cell lysis,[14] is a consequence of MIRI and is accompanied by sterile inflammation.[13] Pyroptosis, in particular, occurs when the immune system reacts to endogenous damage and pathogens. When cardiomyocytes are injured, NLRP3 recruits an apoptosis-associated speck-like protein with a carboxy-terminal CARD (ASC) and procaspase-1 to form inflammasome complexes that initiate the pyroptosis mechanism. This classically involves the activation of gasdermin D (GSDMD), which is the pivotal player of pyroptosis cell death.[15] Notably, physiological and functional autophagy, another type of regulated cell death, reduces NLRP3 activation and cytokine release. However, defects in autophagy pathways can lead to incomplete or ineffective autophagy and mitophagy, activating NLRP3 and exacerbating myocardial damage.[16] The primary mechanisms involved in MIRI and interconnected with NLRP3 are the production of reactive oxygen species (ROS), intracellular calcium overload, role of mitochondrial permeability transition pore (mPTP) opening, endothelial dysfunction, and inflammation.

**PRODUCTION OF ROS.** Although controlled ROS production is necessary for cardioprotection in the pre- and postischemic phase,[17] a large amount of damaging ROS is formed during the early phases of reperfusion after ischemia. ROS can cause cell injury by disrupting cell signaling pathways, causing lipid peroxidation, and activating proinflammatory factors. High ROS levels can cause mPTP to open, resulting in the induction of ROS-induced ROS release and further mitochondrial damage.[15] ROS and reactive nitrogen species (RNS) promote tissue inflammation and NLRP3 complex activation in a variety of organs, including the heart. Furthermore, it appears that NLRP3 stimulates ROS formation at the mitochondrial level, either directly or indirectly.[18] ROS/RNS can stimulate the production of cytokines such as interleukin (IL)-18, causing tissue inflammation and promoting apoptosis and calcium overload. Thus, excessive ROS/RNS levels can cause cell death, through mechanisms such as apoptosis and pyroptosis. The ability of ROS/RNS to cause the release of inflammatory factors appears to cause ROS/RNS production as well. As a result of this vicious cycle, ROS/RNS are involved in several early and late self-damaging mechanisms.

**INTRACELLULAR CALCIUM OVERLOAD.** MIRI disrupts calcium handling, resulting in dysfunctional calcium homeostasis and an abnormal rise in intracellular calcium concentration. This calcium overload also has an effect on the mitochondria, causing a decrease in adenosine triphosphate (ATP) content, an alteration of mitochondrial membrane potential, and mPTP opening. A close relationship among calcium overload, NLRP3 expression, and pyroptosis has been observed in various tissues, including the heart.[15,19] Calcium overload in MIRI acts as an excitatory component of oxidative stress, causing the formation of inflammasomes.[15] For example, Mo et al[20] observed that calcium overload can cause pyroptosis in an adult rat cardiomyocyte hypoxia/reperfusion model by stimulating the NLRP3/caspase-1 pathway.

**ROLE OF mPTP OPENING.** Mitochondria are the core organelles of the cell that generate cellular energy via oxidative phosphorylation.[21] Both low oxygen levels after ischemia and, as previously reported, ROS formed during the early stages of reperfusion and subsequent ROS-induced ROS release harm mitochondria. Cell death caused by irreversible mPTP opening involves both of these factors.[22,23] The opening of the mPTP results in a decrease in oxidative phosphorylation activity, a decrease in mitochondrial membrane potential, and a significant decrease in ATP production. This results in mitochondrial osmotic stress and the rupture of the outer mitochondrial membrane, which leads to a variety of cardiomyocyte deaths, including pyroptosis.[13,24]

**ENDOTHELIAL DYSFUNCTION.** Endothelial dysfunction plays an important role in MIRI and is characterized by decreased NO production and increased adhesion molecule expression. Subsequent leukocyte adhesion to the endothelium leads to leukocyte infiltration. All of these phenomena are MIRI mechanisms accompanying the so-called no-reflow phenomenon. Indeed, regions with "no reflow" and microvascular obstruction (MVO) are only found in areas where the myocardium is clearly necrotic. MVO is caused by a lack of NO and paradoxical RNS production[17] and is mainly a reperfusion phenomenon that shows up as coronary no-reflow in a clinical setting. No-reflow phenomenon is brought about by vasoconstriction and microthrombus formation in the lumen of small vessels.[8,25,26] Both MVO and cardiomyocyte death are caused by intracellular and

interstitial edema, intravascular platelet and erythrocyte aggregates, and early inflammatory responses, though their relative contributions may vary. Because the causality between MVO and cardiomyocyte cell death is still unclear, the 2 phenomena should be viewed as distinct but closely related, perhaps due to similar underlying mechanisms.[27] Endothelial dysfunction is also characterized by nuclear factor kappa-B (NFκB) and other transcription factor activation, as well as increased expression of cell adhesion molecules.[8,25] It should be noted that NFκB is required for NLRP3 priming and activation.[9,28]

**INFLAMMATION.** Early reperfusion also causes inflammatory damage by stimulating mast cells and neutrophils, the products of which act as chemoattractants for other white blood cells.[29] Cathepsins, proteases with multiple pathophysiological roles, have recently piqued researchers' interest. Cathepsin G, a neutrophil chemoattractant modulator, causes morphological changes in cardiomyocytes that break focal adhesion and intracellular contacts.[29,30] Indeed, inhibiting cathepsin G with a cathepsin G and chymase inhibitor reduces MIRI lethality.[31]

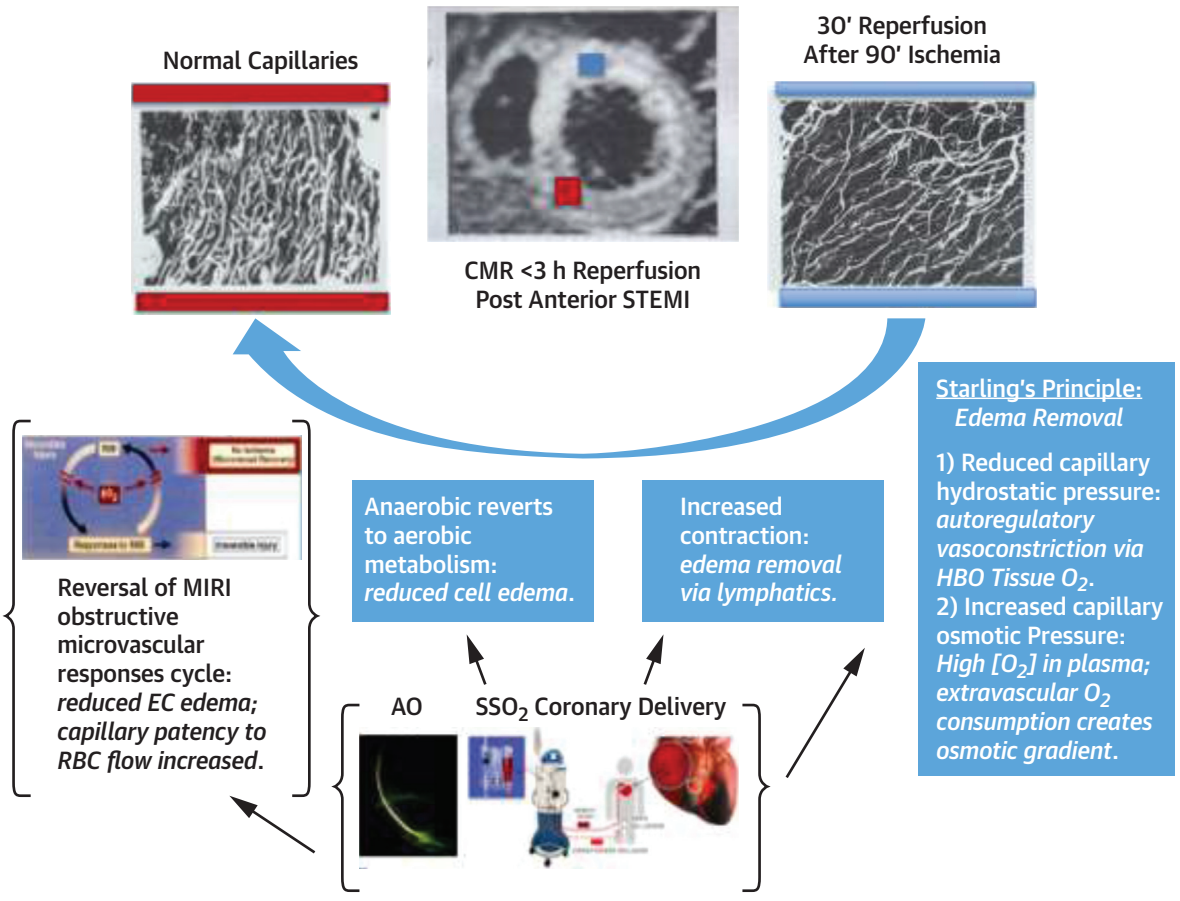
## PHARMACOLOGIC STRATEGIES TO REDUCE MIRI

**$SSO_2$: INFARCT REDUCTION AND BEYOND.** Cardiac magnetic resonance (CMR) imaging in patients after successful primary angioplasty for acute anterior STEMI shows prominent myocardial edema that develops quickly within the ischemic "area at risk" over the first several hours of infarction,[32] with further progression over the next few days after reperfusion, presaging temporal progression of infarct expansion within the area at risk.[32-35] The importance of even low levels of edema on cardiac function is increasingly being recognized as a self-propagating cause of progressive compression of capillaries from increased interstitial hydrostatic pressure; increased intercapillary distance for $O_2$ diffusion; impairment of erythrocyte flow; and associated heart failure, both systolic and diastolic.[36-38] Myocardial contraction is necessary for lymphatic clearance of interstitial fluid, but edema per se impedes contractile recovery of the injured myocardium.[34,38,39] As interstitial pressure approaches capillary venous pressure within the edematous myocardium, bounded by the pericardial restraint and a typical high diastolic left ventricular filling pressure, local myocardial compartment pathophysiology commonly develops and compresses capillaries,[40,41] restricting erythrocyte flow.

Aqueous oxygen is a transiently (<1 second) metastable saline solution containing more dissolved oxygen by volume than the liquid carrier (>1 mL $O_2$/mL saline). Liquid mixing of aqueous oxygen with flowing arterial blood in a bubbleless manner produces $SSO_2$ with oxygen dissolved at hyperbaric partial pressures (800-1,100 mm Hg).[42] Catheter delivery of $SSO_2$ is practical in critical care settings, unlike conventional hyperbaric oxygen therapy requiring pressurized chambers. In addition, potential adverse tissue reactions at a high gas-phase ($O_2$)/tissue interface are precluded.

Results of preclinical studies provide evidence that intracoronary $SSO_2$ infusion after STEMI reperfusion shows marked reduction (>70%) in infarct size and a 24% reduction in the edematous area at risk compared to control groups.[42,43] The acute improvement (doubling) of microvascular flow observed after $SSO_2$ is likely one of the most important mechanisms for the acute normalization of left ventricular (LV) ejection fraction.[43] As discussed by Sezer et al,[44] loss of arteriolar vasoconstrictor function on early reperfusion acutely exposes capillaries to excessively high hydrostatic pressures associated with reactive hyperemia. Accordingly, in a single site randomized trial, the beneficial effects of initial gradual reperfusion at a relatively low pressure were recently reported clinically by Sezer et al[45] to reduce coronary microvascular resistance and subsequent lower troponin T release compared to conventional abrupt reperfusion. An important benefit of hyperbaric oxygen therapy for compartment syndrome is mild autoregulatory arterial/arteriolar vasoconstriction (from tissue hyperoxemia), which has been noted to occur in patients treated with $SSO_2$. A reduction of hydrostatic pressure in the capillary lumen relative to high interstitial pressures in edematous tissues, along with the hyperosmotic effect of hyperbaric dissolved oxygen in plasma,[46] enhance removal of edema fluid via the Starling principle. Increased LV contraction from hyperoxemia enhances lymphatic removal of interstitial fluid; cellular swelling associated with anaerobic metabolism is reduced with return of aerobic metabolism; and the cycle of MIRI and numerous obstructive microvascular responses may be abrogated. Corresponding to these effects, capillary patency to erythrocyte flow is improved (**Figure 1**) and LV systolic function during $SSO_2$ infusion is acutely normalized in preclinical STEMI reperfusion models.[42,43,47,48] The beneficial effects of $SSO_2$ on microvascular flow, LV function, and infarct size resolve the issue of the "oxygen paradox" or "double-edged sword" commonly ascribed to the return of oxygen with reperfusion. Acutely on reperfusion, the rapid edema formation between and within capillaries, rendered highly permeable from prior

**FIGURE 1** **Improved Microvascular Flow With $SSO_2$ Therapy**

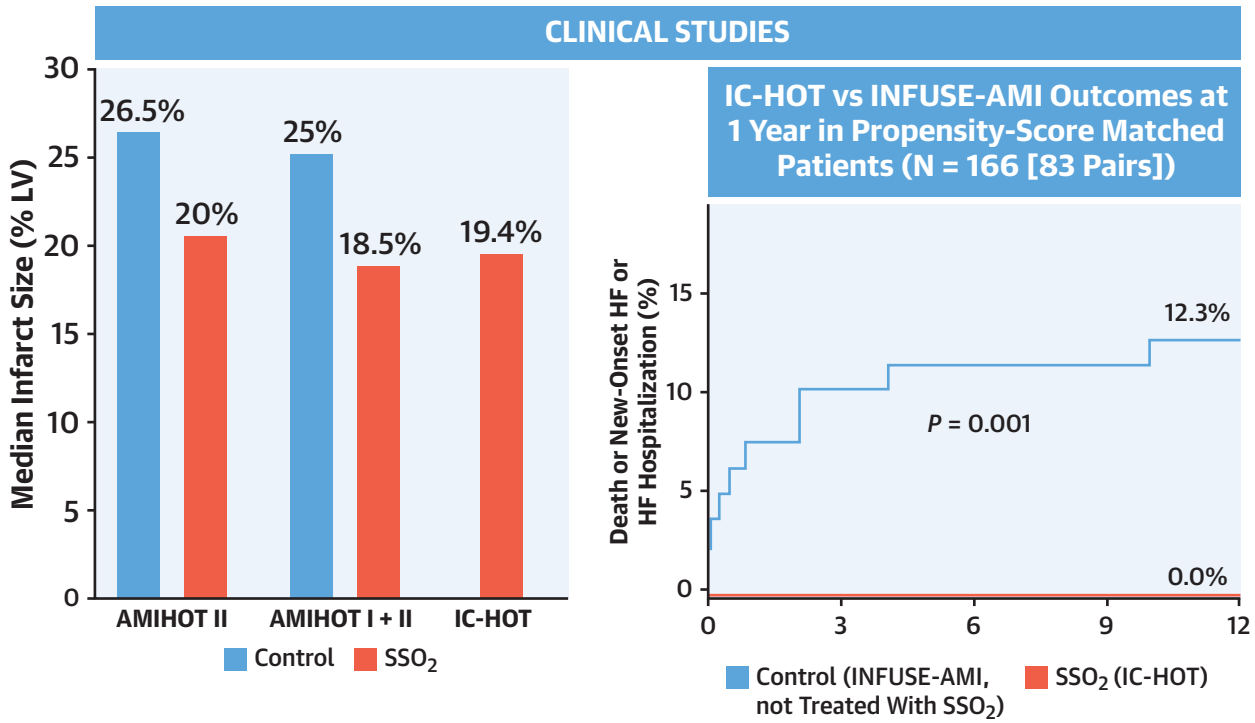



Supersaturated oxygen ($SSO_2$) edema and microvascular ischemia reduction during ST-segment elevation myocardial infarction (STEMI) reperfusion. (Top middle) Cardiac magnetic resonance (CMR) at <3 h reperfusion. Note effect of edema on myocardial thickness (blue square) compared to normal myocardium (red square). Reproduced with permission from Fernández-Jiménez et al.[32] (Top left) Normal myocardial capillaries (swine). Reproduced with permission from Pathi et al.[135] (Top right) Myocardial capillaries at 30 minutes of reperfusion post 90 minutes of ischemia (swine). Note effects of edema on thinning, pruning, and increased distance between capillaries compared to normal. Reproduced with permission from Pathi et al.[135] (Middle right) Starling principle. (Botton middle right) Increased contraction. (Botton middle left) Anaerobic reverts to aerobic metabolism. (Bottom left) Originally published by and used with permission from Dove Medical Press Ltd: Spears.[49] (Bottom middle) Coronary infusion of $SSO_2$ during post STEMI reperfusion rapidly reduces myocardial compartment edema and tissue level ischemia, resulting in marked improvement in microvascular flow. AO = aqueous oxygen; EC = endothelial cell; HBO = hyperbaric oxygen; MIRI = myocardial ischemia-reperfusion injury; RBC = red blood cells.

prolonged hypoxia, impedes erythrocyte flow, causing a well-described cycle of microvascular hypoxia and inflammatory microvascular responses.[42,46,49] The marked reduction of myocardial myeloperoxidase acutely after $SSO_2$ in 2 different animal models[48,50] is consistent with the concept that $SSO_2$ reduces MIRI-induced inflammatory responses.[49,51]

In the AMIHOT (Acute Myocardial Infarction With Hyperoxemic Therapy) I and II trials,[52,53] patients with anterior STEMI who were successfully reperfused by PCI within 6 hours of symptom onset were randomized to intracoronary $SSO_2$ perfusion for 90 minutes or standard care alone. Mean infarct size by myocardial perfusion imaging at 2 weeks post procedure was 26% lower in the $SSO_2$ group compared with the control group ($P < 0.01$).[53] For patients treated within 3 hours of symptom onset, the median infarct reduction in the $SSO_2$ group (n = 112) vs control (n =57) was 41%. For the groups treated at 3-6 hours from symptom onset, the median infarct reduction associated with $SSO_2$ (n = 146) vs control (n = 67) was 9%. The single arm, multicenter IC-HOT (Evaluation of Intracoronary Hyperoxemic Oxygen Therapy in Anterior Acute Myocardial Infarction Patients)

**FIGURE 2** Clinical Data Relevant to $SSO_2$ Infusion




Infarct size at 2 weeks (myocardial perfusion imaging, AMIHOT [Acute Myocardial Infarction With Hyperoxemic Therapy] I and II trials) and 1 month (cardiac magnetic resonance, IC-HOT [Evaluation of Intracoronary Hyperoxemic Oxygen Therapy in Anterior Acute Myocardial Infarction Patients] trial) in supersaturated oxygen ($SSO_2$)-treated anterior ST-segment elevation myocardial infarction after successful percutaneous coronary intervention reperfusion vs control subjects. Complication rate in the IC-HOT trial was significantly lower than a matched cohort from the INFUSE-AMI[128] trial. Figure provided by Therox/Zoll. HF = heart failure; LV = left ventricular; pts = patients.

study[54] demonstrated the safety of $SSO_2$ therapy selectively delivered to the left main coronary artery for 60 minutes after PCI in 100 patients with anterior STEMI using an optimized delivery system. In addition, the therapy was associated with the same relatively low left ventricular mean infarct size by CMR at 1 month (**Figure 2**). The 0% mortality and 1% new onset heart failure at 1-year follow-up in the trial, in contrast to the mortality rate and new onset heart failure in a matched cohort,[55] provide compelling evidence of clinical efficacy, leading to U.S. Food and Drug Administration approval of $SSO_2$ in 2019. The low microvascular occlusion (0.3%) by CMR in the trial is consistent with improved microvascular flow as the basis of beneficial LV remodeling at 30 days in prior $SSO_2$ studies.[56,57]

The postapproval $SSO_2$ study AMI-HOT III (Delivery $SSO_2$ Therapy for 60 Minutes in Anterior MI Patients With PCI ≤6 Hours of Symptoms Onset Compared to Standard; NCT04743245) is currently underway to further define clinical efficacy in larger groups of patients with anterior STEMI.

**INHIBITORS OF NLRP3.** A number of substances have been studied as anti-inflammatory compounds in the cardiovascular area; some have failed and have been discontinued (losmapimod, atreleuton, setileuton, methotrexate, varespladib, canakinumab, darapladib, PF-04191834, and veliflapon), others are still under investigation (eg, anakinra, colchicine, allopurinol, everolimus, IFM-2427, montelukast, Somalix, Inzomelid, tocilizumab, ziltivekimab, to name a few).[16,58]

Nicorandil is a niacinamide derivative that opens ATP-sensitive $K^+$ channels and donates NO. It protects the myocardium, nervous system, and coronary circulation during STEMI. Nicorandil reduces pyroptosis in rats after a myocardial infarction by inhibiting the TLR4/MyD88/NF-B/NLRP3 inflammatory pathway.[59] Panaxynol is a naturally occurring minor component found in Umbelliferae plants. Many clinical investigations have revealed that panaxynol

has nutritional value as well as anti-inflammatory and other pharmacologic properties. Panaxynol administration significantly reduces apoptosis and myocardial injury, suppresses cell pyroptosis, and inhibits proinflammatory cytokines and neutrophil infiltration via an NLRP3 inhibitor, thus reducing myocardial infarct size.[60]

Colchicine is a well-known anti-inflammatory medication that has recently been shown to inhibit NLRP3 assembly and activation. A better understanding of the mechanism of action has made it possible to conduct research in a variety of cardiac settings.[61] Colchicine suppresses P2X7 activation by extracellular ATP as well as inflammasome aggregation (ASC and NLRP3 polymerization via the pyrin domain).[62] In a rodent model of "non-reperfused" AMI, a high dose of colchicine significantly inhibited the increase in inflammasome activity 24 hours after AMI.[63] Colchicine reduces inflammation at the cellular level by blocking leukocytes as well as the expression of E-selectin by endothelial cells, smooth muscle cell proliferation, macrophage adhesion, and platelet activation. However, in the context of AMI, there are no experimental studies that have analyzed which cells are involved in the beneficial effects of colchicine that have also been demonstrated in some clinical studies,[64,65] but not in others.[66]

Glyburide inhibits IL-1 release in vitro. In contrast, glyburide inhibits the NLRP3 inflammasome and causes lethal hypoglycemia in mice.[67] A glyburide derivative lacking the moiety responsible for inducing insulin secretion, 4-[2-[2-(5-chloro-2-methoxybenzamido)ethyl] benzene sulfonamide, was developed. This preserves the inflammasome inhibitory effect while removing the hypoglycemic effect of glyburide.[68] In a mouse model of MIRI, glyburide analogs reduced caspase-1 activity and ASC macromolecular aggregation. This was accompanied by a decrease in cardiac troponin I plasma levels as well as by an infarct size reduction.[68] MCC950 is a potent NLRP3 inhibitor,[69] which resulted successfully in an encephalomyelitis model of a constitutively active NLRP3 mutant. A month of MCC950 treatment successfully rescued these mice.[70] In a swine model of coronary artery ligation and reperfusion, MCC950 infusion 15 minutes before 75-minute ischemia and treatment once a day after ischemia/reperfusion decreased myocardial IL-1 levels, reduced infarct size, blunted neutrophil infiltration into the myocardium, and preserved LV ejection fraction.[71] IFM-2427 is one of the NLRP3 inhibitors being investigated. It, too, contains a sulfonamide, but unlike MCC950, the urea and tricyclic part is replaced with an acetamide attached to a substituted phenyl. On the other side of the molecule, the pyrrolic ring is replaced by several aromatic heterocycles, with a strong preference for thiophenes and thiazoles. In 2019, IFM-2427 was approved for a phase I clinical trial in Crohn disease, gout, and coronary artery disease.[72] Somalix and Inzomelid are 2 NLRP3 inhibitors that have been developed. In 2019, 24 patent applications were published for both compounds, and all patents were compared to the MCC950 sulfonylureas series. Both substances are currently being studied in clinical trials. Somalix is being investigated as an oral treatment for inflammatory conditions such as cardiovascular disease and arthritis.[69] Cocco et al[73] designed INF4E, which is an acrylamide derivative. Somalix and INF4E are covalent inhibitors of NLRP3 and its ATPase activity, both of which are usually required for NLRP3 inflammasome activation. In a rodent model of MIRI, infusion of INF4E just before ischemia resulted in a significant recovery in LV developed pressure 60 minutes after ischemia and a significant reduction in infarct size.[74] Recently, INF200, a novel NLRP3 inhibitor, has been synthetized by the same group. It has shown promising results in preventing pyroptosis triggered by lipopolysaccharide (LPS)/ATP and LPS/monosodium urate crystals and reducing IL-1β release in human macrophages. In an in vivo rat model of high-fat diet-induced metaflammation (a condition of chronic low-grade inflammation), INF200 counteracted high-fat diet-dependent changes, ameliorated lipid and glucose profiles, blunted systemic inflammation and cardiac dysfunction biomarkers, and limited MIRI.[75] It also decreased IRI-dependent NLRP3 activation, oxidative stress and inflammation, highlighting the potential of INF200 as a novel NLRP3 inhibitor to reverse cardiometabolic dysfunction linked to obesity.[75] BAY 11-7082, an NFκB inhibitor, inhibits NLRP3 ATPase activity directly. Pretreatment with BAY 11-7082 significantly reduced infarct size; it also decreased cardiac fibrosis and improved LV fractional shortening in a rat model of MIRI.[74] OLT1177 is an active sulfonyl nitrile molecule that was found to be safe when administered orally to humans. It has been examined in murine models of coronary artery occlusion. In 1 study, OLT1177 administration resulted in a significant decrease in infarct size and plasma troponin I, with the preservation of LV fractional shortening after coronary ligation without reperfusion.[76] In another murine study using both 30-minute and 75-minute ischemic times, OLT1177 treatment at reperfusion showed significant dose-dependent reduction in infarct size.[77] Marchetti et al[78] found that inhibiting NLRP3 ATPase activity resulted in decreased NLRP-ASC oligomerization; yet, no effects on absent in

melanoma 2 (AIM2) or NLR family CARD domain containing 4 (NLRC4) inflammasomes were observed.

A study on spirulina maxima extract investigated its effect on innate immunity. Spirulina maxima extract suppressed LPS-induced augmentation of proinflammatory cytokines, attenuated NLRP3 inflammasome activation, and inhibited LPS-induced phosphorylation of extracellular signal-regulated kinase. This suggests that spirulina maxima extract limits the activation of the NLRP3 inflammasome by blocking extracellular signal-regulated kinase signaling.[79] Vinpocetine, a vincamine derivative, is used for ischemic stroke prevention and treatment. It reduces infarct volume and promotes behavioral function recovery in stroke mice. It inhibits peri-infarct neuron apoptosis, promotes B-cell leukemia/lymphoma (Bcl)-2 expression, inhibits BCL2-associated X protein (Bax) and cleaved caspase-3 (Casp3) expression, and reduces microglia proliferation. Vinpocetine suppresses the NLRP3 inflammasome expression, reducing brain IRI in mice.[80] Whether vinpocetine protects against MIRI damage remains to be studied.[81]

**BLOCKADE OF IL-18, IL-1α, AND IL-1β IN CARDIOVASCULAR DISEASE.** After myocardial reperfusion, tissue expression of IL messenger RNA and circulating concentrations of IL proteins increase. The role of IL-18 in MIRI and experimental heart transplantation models has been investigated. An antibody that neutralizes IL-18 reduced the infarcted area significantly 1 hour before ischemia/reperfusion.[82] Gu et al[83] investigated the cardioprotective effects of GSK1070806a, an IL-18 monoclonal antibody. It has also been studied in individuals suffering from inflammatory bowel disease or diabetes.[84,85] In subsequent studies in mice subjected to acute infarction, an $IgG_{2a}$ monoclonal antibody directed against IL-1β was used to investigate selective inhibition of this IL. This antibody is a murine analog of canakinumab, a human monoclonal antibody that blocks IL-1 β.[86,87] Also, anakinra, a widely used recombinant IL-1 receptor antagonist, improved left ventricular contractile function and reduced the rate of myocardial apoptosis after an acute infarction. Anakinra is approved for the treatment of rheumatoid arthritis in Europe and the United States, and it has been tested in clinical trials against MIRI (VCU-ART3 [Interleukin-1 (IL-1) Blockade in Acute Myocardial Infarction]; NCT01950299). Pilot clinical trials of anakinra in patients with reperfused STEMI subjected to primary PCI displayed that IL-1 blockade reduced C-reactive protein levels at 72 hours, and reduced the rate of new onset cardiac failure after STEMI infarction and, importantly, was safe and nontoxic.[88-90] A similar decrease in acute inflammatory response has been observed in the MRC-ILA phase II clinical cardiac trial with anakinra in subjects with non-STEMI.[91] In this trial, there were no differences in adverse clinical events at 30 days or 3 months, but at 12 months, anakinra-treated patients had fewer ischemic events than placebo-treated subjects did. Moreover, phase II clinical trials with anakinra in individuals with heart failure suggested the beneficial effects of IL-1 inhibition.[71,92]

All of the compounds mentioned in the previous paragraphs need larger trials to validate their clinical utility. Moreover, several questions remain unanswered. For instance, we do not know if and when it is necessary to inhibit inflammasome activity and whether the inflammasome is central to the process leading to heart failure. In a nutshell, we do not know with precision what mediators or inflammasome products to target. This is critical to focus the therapeutic goal maintaining physiological homeostatic status. Data from the BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure) cohort have revealed some putative therapeutic targets, including the inhibition of inducible T-cell costimulator ligand (ICOSLG), CD28, and CD70, tumor necrosis factor superfamily member-14 (TNFSF14), as well as the augmentation of interferon production.[93] In summary, inflammation in MIRI leading to heart failure is a complex process involving many unknown factors. Understanding the relationship among inflammation, MIRI, and heart failure may lead to potential therapeutic targets. Nevertheless, we should be aware that, whereas a better understanding of inflammatory processes in cardiomyocyte injury is needed, it may overlook the real enemy: the malfunctioning of homeostatic properties. Therefore, we must also consider other pharmacologic approaches from a multitarget perspective.

**β-BLOCKERS.** Most of the evidence supporting the clinical benefit associated with acute administration of β-blockers during STEMI come from the pre-reperfusion era.[94,95] In the era of PCI-based reperfusion, the METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial[96] tested the infarct-size-limiting effect of the β1 selective blocker metoprolol in 270 anterior wall STEMI patients. Infarct size, evaluated by CMR imaging 5 days after reperfusion was significantly smaller in patients who received intravenous metoprolol during ongoing ischemia. LV ejection fraction 6 months after MI was significantly higher in

metoprolol-treated patients.[97] Another trial (BEAT-AMI [Beta-Blocker Therapy in Acute Myocardial Infarction]), tested another β-blocker (esmolol) and also showed an infarct-limiting effect of the β-blocker.[98] Of note, in the EARLY-BAMI (Early-Beta-Blocker Administration Before Reperfusion Primary PCI in Patients With ST-Elevation Myocardial Infarction) trial,[99] infarct size (evaluated 1 month after reperfusion) was not smaller in patients receiving metoprolol before reperfusion. Differences in the timing of metoprolol administration in the METOCARD-CNIC and EARLY BAMI trials (immediately on STEMI diagnosis in the former, and very close to reperfusion in the latter) seem to explain the disparate infarct-limiting effects of metoprolol in both trials. In this regard, it has been demonstrated both in experimental models and in patients that the sooner metoprolol is injected in the course of a STEMI, the larger the infarct-limiting effects.[100-102] A recent meta-analysis of trials performed in the reperfusion era showed that the administration of intravenous β-blockers in the acute phase of STEMI is safe (ie, no increase in cardiogenic shock) and even reduces the incidence of cardiac arrest.[103]

Reduction in MI size is not a class effect of β-blockers. A recent experimental study showed that not all β1-selective blockers exert the same effect against IRI.[104] Metoprolol, but not atenolol or propranolol, was associated with smaller infarct size in murine models of MIRI. Esmolol is another β-blocker that could be associated with infarct size reduction when administered before reperfusion.[105] The spatial interaction between the β-blocker agent and the β1 receptor seems to be responsible for this variable effect against IRI.[104]

The mechanism of metoproloĺs cardioprotective capacities involve a direct effect on neutrophils in the context of the infarct-associated exacerbated inflammatory state.[106] Metoprolol acts during early phases of neutrophil recruitment on reperfusion and impairs its structural and functional rearrangements resulting in a blunted inflammatory reaction. In the clinical setting, metoprolol inhibits neutrophil-platelet interactions in acute coronary syndrome patients.[106] This biological effect of metoprolol extends to other conditions where neutrophil-mediated exacerbated inflammation plays a central pathophysiological role. In a recent pilot trial in patients with COVID-associated acute respiratory distress syndrome, intravenous metoprolol administration was associated with a massive reduction in neutrophil infiltration in the bronchoalveolar lavage, and this translated into a very rapid improvement in ventilatory mechanics and oxygenation.[107]

Overall, cumulative evidence show that metoprolol has a unique effect against MIRI through an inhibition of the neutrophil-mediated exacerbated inflammation taking place during reperfusion. The fact that metoprolol targets circulating cells to protect the heart makes this pharmacologic strategy very appealing to be tested in combination with other interventions targeting the myocardium.

## MECHANICAL STRATEGIES TO REDUCE MIRI

In this section we focus on novel mechanical strategies to mitigate MIRI. However, it merits emphasis that there is an abundant literature regarding the effects of ischemic pre- and postconditioning both directly in the coronary arteries as well as remotely. These data are beyond the scope of our review but have been reviewed extensively in current literature.[25,108,109]

**MECHANICAL UNLOADING.** A critical barrier to pharmacologic strategies to reduce reperfusion injury is the mandate for rapid coronary reperfusion and, therefore, insufficient time for any drug efficacy prior to reperfusion especially if administered systemically. There exists a need for improved strategies to limit myocardial damage by broadly promoting cardioprotective physiological and molecular mechanisms before reperfusion of an infarct-related artery. Preclinical studies dating back to the 1990s employed intra-aortic balloon pump (IABP) or rotodynamic flow pump in models of AMI and determined that mechanically reducing LV work and oxygen consumption, known as LV unloading, before the onset of ischemia or immediately before reperfusion reduces infarct size.[110-112]

In 2003, Meyns et al[113] reported that activation of a transvalvular axial flow pump during ischemia or after reperfusion significantly reduced myocardial oxygen consumption, metabolic demand, and subsequent infarct size. These early observations were further supported by LeDoux et al[114] who described that activation of either a transvalvular axial flow pump or IABP before, but not after reperfusion reduces infarct size. In 2013, Kapur et al[115] reported for the first time that compared to reperfusion alone, unloading the LV using an extracorporeal, centrifugal pump and left atrial drainage and intentionally delaying coronary reperfusion for 30 minutes (primary unloading) reduces myocardial infarct size in a preclinical model of AMI. In 2015, extending the transvalvular unloading time to 60 minutes before reperfusion also reduces infarct size and activates cardioprotective signaling via stromal derived factor-1α and the reperfusion injury salvage kinase

pathway.[116] Multiple laboratories worldwide have confirmed reduced infarct size and decreased subsequent heart failure with LV unloading before reperfusion in preclinical models of AMI.[117,118] Subsequent reports identified that LV unloading for 30 minutes is necessary and sufficient to reduce infarct size, increase coronary collateral blood flow, limit myocardial inflammation, activate cardioprotective signaling, preserve myocardial energy substrate utilization, and stabilize mitochondrial structural and functional integrity (**Figure 3**).[119-122] LV unloading was also associated with reduced expression and activity of hypoxia-inducible factor 1-alpha (HIF1A) within the area at risk before reperfusion, suggesting that LV unloading itself reduces myocardial ischemia.[120] Collectively, these preclinical data identify that LV unloading before reperfusion may reduce reperfusion injury and support the need for further clinical testing.

In 2011, the CRISP-AMI (Counterpulsation to Reduce Infarct Size in Patients With Anterior Myocardial Infarction) trial randomized patients with anterior STEMI to reperfusion alone or IABP activation immediately before reperfusion.[123] The primary endpoint of myocardial infarct size normalized to total LV mass quantified by CMR 3 to 5 days after presentation was not significantly different between the 2 arms (IABP + PCI vs PCI alone: 42.1% vs 37.5%; $P = 0.06$). The degree of MVO was similar in both arms (IABP+PCI vs PCI alone: 6.8% vs 5.7%; $P = 0.34$). Notably, 8.5% of patients in the PCI-alone arm crossed over to requiring an IABP after reperfusion in this study. These data suggest that prophylactic IABP use does not promote myocardial salvage and supports that significant myocardial damage occurs during an anterior STEMI.

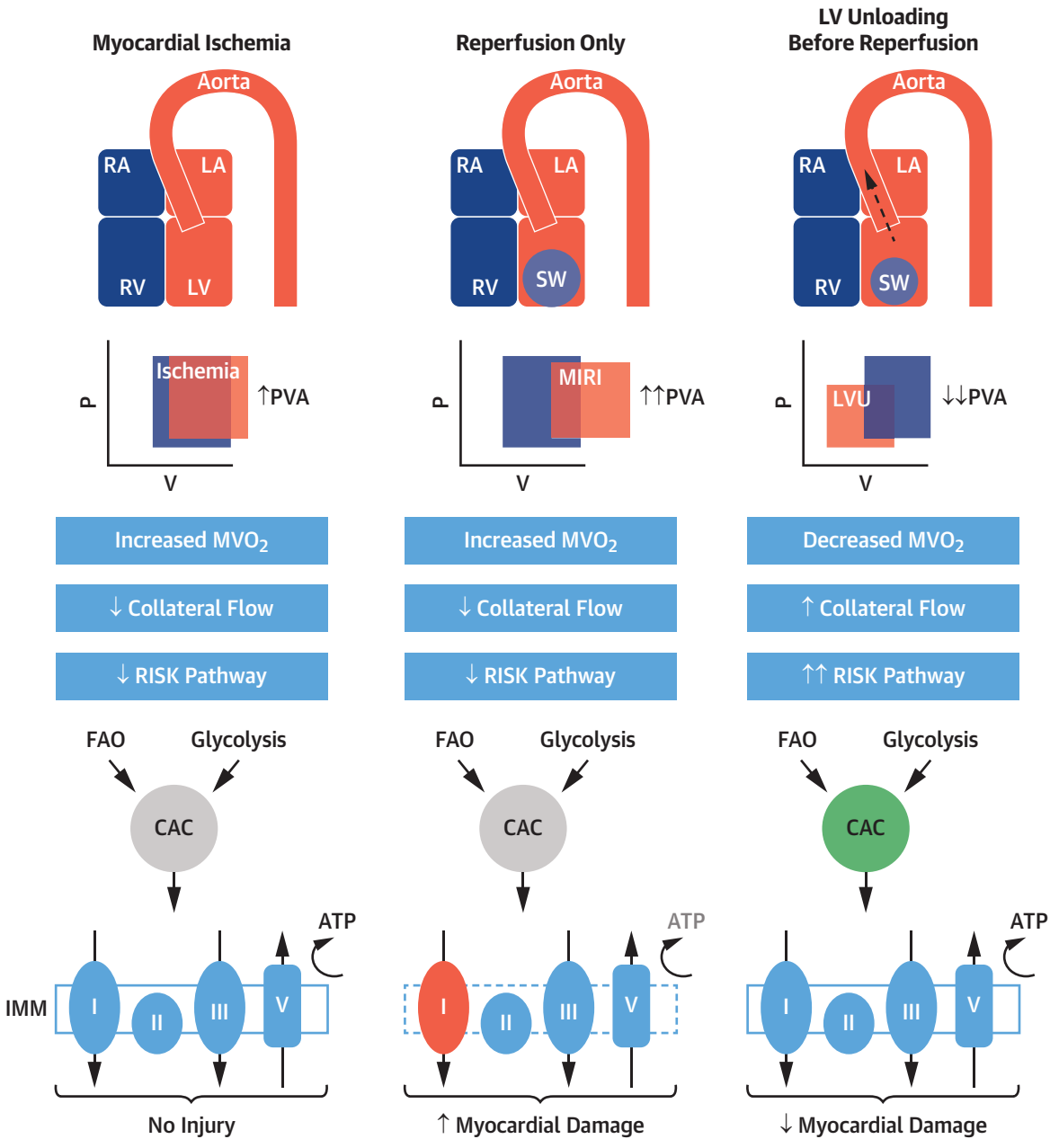
In 2019, the STEMI-DTU (Door to Unload) pilot tested the feasibility and safety of deploying a transvalvular pump in anterior STEMI and explored whether 30 minutes of delay to reperfusion is necessary to reduce infarct size.[124] The pilot study randomized 50 patients with anterior STEMI to LV unloading and immediate reperfusion or unloading for 30 minutes before reperfusion. The study demonstrated 100% compliance with the 30 minutes of LV unloading in anterior STEMI and established the feasibility of LV unloading with an Impella CP before PCI. No statistically significant difference was observed in infarct size normalized to total LV mass at 3 to 5 days (unloading and immediate vs delayed reperfusion: 19.1% vs 16.7%; $P = 0.58$) or MVO (2.7% vs 1.3%; $P = 0.22$). Among patients with the largest estimated myocardial area at risk as determined by the sum of precordial STEs (>6 mm), unloading and delayed reperfusion significantly reduced infarct size compared to unloading and immediate reperfusion, suggesting that the 30 minutes of myocardial conditioning may be necessary and sufficient to optimize myocardial salvage with LV unloading. Although the pilot study did not include a control arm with PCI alone, the results of the study suggest potential for improved myocardial salvage when compared to the PCI alone arm of the CRISP-AMI trial. For these reasons, the STEMI-DTU pivotal trial was launched in late 2019 and is currently randomizing 668 subjects with anterior STEMI to LV unloading for 30 minutes before reperfusion or reperfusion alone.[125] The primary endpoint is 3-5 day infarct size normalized to total LV mass with secondary 1-year endpoints of cardiovascular mortality, cardiogenic shock after PCI, LV assist device or heart transplant, heart failure, and intracardiac defibrillator or cardiac resynchronization therapy placement.

Collectively these preclinical and clinical observations identify several key novel directions for the field of myocardial salvage and reperfusion injury. First, LV unloading directly decreases cardiac workload, thereby reducing myocardial oxygen demand while improving coronary blood flow and myocardial perfusion, thereby reducing the burden of myocardial ischemia before reperfusion is performed. Second, LV unloading activates a cardioprotective signaling cascade that protects against reperfusion injury and preserves mitochondrial function, thereby enabling myocardial recovery. Third, if LV unloading reduces myocardial ischemia and a "window of time" is introduced before reperfusion, then adjunct pharmacotherapy can be delivered to optimize hemodynamic conditions and further protect against reperfusion injury. Finally, if LV unloading translates into reduced infarct size, then subsequent heart failure over 1 to 5 years should be significantly reduced, which has potentially significant implications for patients, health care systems, and emerging technologies that can unload the LV.[126,127] At this stage, the burden of proof is on LV unloading, and the emerging clinical trials testing these concepts are critically important.

## SUMMARY, GAPS, AND FUTURE DIRECTIONS

The main goal in the management of MI is to reestablish blood flow to the heart as quickly as possible to diminish the extent of MI. Despite this inherent benefit, prompt reperfusion may also directly result in myocardial damage through MIRI. With the exception of $SSO_2$, the MIRI field, in general, has had difficulties translating promising preclinical results to benefit in randomized clinical human trials

**FIGURE 3** Mechanisms of Cardioprotection With Mechanical LVU




Under ischemic conditions, left ventricular (LV) pressure volume area (PVA) and myocardial oxygen consumption ($MVO_2$) increases, coronary collateral blood flow decreases and cardioprotective signaling via the reperfusion injury salvage kinase (RISK) pathway is impaired. This leads to increased anaerobic glycolysis and reduced energy production that contributes to myocardial damage. Myocardial reperfusion exacerbates this injury by further impairing mitochondrial complex I activity that disrupts mitochondrial structural integrity and accelerates myocardial damage. Left ventricular unloading (LVU) reduces PVA and $MVO_2$ and improves coronary collateral flow thereby reducing ischemic injury. LVU further activates the RISK pathway, improves myocardial energetics, and preserves mitochondrial integrity thereby reducing myocardial damage due to reperfusion injury. ATP = adenosine triphosphate; CAC = citric acid cycle; FAO = fatty acid oxidation; IMM = inner mitochondrial membrane; LA = left atrium; LV = left ventricle; MIRI = myocardial ischemia-reperfusion injury; RA = right atrium; RV = right ventricle; SW = stroke work.

because there are several limitations. Some of these limitations include trouble diagnosing IRI early, lack of effective pharmacologic therapies, and minimal alternatives for repairing the injured myocardium. Thus, innovative cardioprotective strategies are still required to lessen the deleterious effects of AMI. Within this review we have focused on several relevant and emerging pharmacologic and mechanical therapies to minimize reperfusion injury.

To launch this field forward and translate basic science to commercially available products, adequately powered clinical trials designed to demonstrate safety, efficacy, and mechanism of benefit are much needed. One potential shortcoming for the development of applicable therapies within the MIRI field is the lack of an experimental model that closely recapitulates the myocardial injury seen from reperfusion injury in humans. Hence, caution should be taken regarding the appropriate models (including large animal models) and timing of ischemia and reperfusion for in vitro, in vivo, and ex vivo experiments.

An exception to the failed efforts to translate promising preclinical applications to effective clinical therapies is the success of $SSO_2$ in reducing infarct size in anterior STEMI patients treated within 6 hours of symptom onset.[128] Rapid interruption and reversal of a cycle of myocardial edema and microvascular ischemia associated with reperfusion by multiple mechanisms observed in animal models portended the excellent functional and clinical results observed to date with the current U.S. Food and Drug Administration-approved system. Rapid development of reperfusion edema and microvascular ischemia causing microvascular compartment pathophysiology may be key components of the "wavefront phenomenon" of myocardial injury. With the advent of $SSO_2$, there is now a means to mitigate these problems. Moreover, recognition of compartment pathophysiology reinforces the importance of LV diastolic unloading, beyond reduction of myocardial $O_2$ demand, to reduce capillary compression by edema. Reduction of input capillary hydrostatic pressure may reduce edema associated with the hyperemic response to prior ischemia. Strategies such as gradual reperfusion and variations of postconditioning may be helpful in this regard.

Many pharmacologic therapies showing promise may be more efficacious when increased microvascular flow allows their delivery to postischemic myocardium. This last point merits emphasis because future solutions to MIRI may include the use of combination therapies. MIRI influences several physiological pathways within the heart, such as inflammation,[28] oxidative stress,[129] and impaired substrate use.[130] Therefore, future pharmacologic therapies should be optimized for timing of maximum cardioprotection and then combined to potentially amplify effectiveness. Therapeutic combinations could include the use of anti-inflammatories, free-radical scavengers/antioxidants, renin-angiotensin-aldosterone inhibitors, calcium channel blockers, sodium-glucose cotransporter inhibitors, and targeted mitochondrial therapies. These interventions warrant further investigation.

Device-based therapies such as mechanical unloading and preconditioning have shown promise in reducing MIRI following AMI. Some reports have proposed that mechanical unloading may decrease the severity of MIRI by reducing myocardial oxygen demand and preventing oxidative stress, but more research is needed to fully understand the proper timing for unloading and the specific molecular mechanisms involved in cardioprotection.[121,131] It has also been suggested that ischemic preconditioning (direct or remote) can activate cardioprotective pathways in the heart; however, it remains uncertain whether exposing the heart or other organs to this type of mild stress is warranted or practical.[132-134]

In summary, MIRI remains an important contributor to myocardial damage in the setting of AMI. In the absence of a widely adopted and accepted intervention to prevent MIRI, clinical investigations to define the most effective strategies, including combination therapies, are much needed and will continue well into the future.

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