JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 10, 2023

EDITORIAL COMMENT

Ischemia Reperfusion Injury

Harder to Treat Than Cyanide Poisoning*

Gonzalo Pizarro, MD, PhD

The current treatment for acute ST-segment elevation myocardial infarction (STEMI) is early reperfusion, which was universally introduced in clinical practice after the landmark GISSI-1 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico acuto-1) trial in the late 1980s.[1] Considered one of the most successful achievements in cardiovascular medicine, timely reperfusion has drastically reduced acute post-STEMI mortality from 20% to 5%.[2] Unfortunately, many STEMI survivors go on to develop heart failure at a later stage, and this long-term sequela of successful reperfusion therapy has a major impact on patient quality of life and health care costs. One of the main predictors of progression to heart failure after STEMI is infarct size (IS), and there is therefore continued research interest in identifying ways to limit myocardial necrosis. Although one of the key determinants of IS is the myocardial ischemic event itself, there is ample experimental and clinical evidence that reperfusion therapy can extend myocardial injury through the process known as ischemia-reperfusion injury (IRI). Cardioprotective therapies are therefore focused on the prevention of IRI, with the aim of limiting IS and thus avoiding progression to heart failure.

Over the past decades, IRI has been targeted by multiple candidate therapies, most of them yielding disappointing results when translated to the clinic.[3] In experimental animal models, one of the earliest nonpharmacologic interventions shown to reduce IRI was ischemic preconditioning. In this approach, the animal's heart is "trained" through brief cycles of coronary ischemia and reperfusion before the induction of STEMI with a more prolonged coronary occlusion. However, although ischemic preconditioning considerably reduces IS, it has no direct clinical potential because of the need to start "treatment" before the STEMI event. Experimental animal models have also demonstrated IS reduction with local coronary ischemic postconditioning, applied after reperfusion; however, despite a positive proof-of-concept clinical trial, this approach showed no benefit in larger trials. Proof-of-concept trials also showed a promising clinical benefit with remote ischemic conditioning, in which brachial cuff inflations are applied during ongoing STEMI. However, once again, large clinical studies failed to confirm these findings. Promising initial results have also been reported with therapeutic hypothermia, intermittent coronary sinus occlusion, and left ventricular unloading. Preclinical models and phase II clinical trials have also tested a large number of pharmacologic strategies for IRI reduction. The tested treatments include intravenous metoprolol, cyclosporine A, adenosine, intracoronary abciximab, inhaled nitric oxide, supersaturated oxygen, glucose modulators such as glucose-insulin potassium therapy or GLP-1 analogs, intravenous sodium nitrite, the mitochondrial-targeting drugs TRO40303 and MTP-131, nicorandil, delcasertib, atrial natriuretic peptide, sodium-hydrogen exchange inhibitors, antibodies targeting inflammation, and superoxide dismutase. Regrettably, however, none of these interventions achieved a sufficient level of evidence for inclusion in the therapeutic armamentarium recommended in current clinical guidelines for IRI reduction.[4]

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Translational Laboratory for Cardiovascular Imaging and Therapy, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain; and the Cardiology Department, Hospital Ruber Juan Bravo Quironsalud Hospital Universidad Europea, Madrid, Spain.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2023.08.009

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 10, 2023
OCTOBER 2023:1295–1297

In this extremely complex scenario, the paper by de Koning et al[5] in this issue of *JACC: Basic to Translational Science* provides valuable new information. In their article, these investigators present the results of the proof-of-concept GIPS-IV (Sodium Thiosulfate to Preserve Cardiac Function in STEMI) randomized clinical trial, testing the effect of the intravenous sodium thiosulfate (STS) after STEMI. STS is a hydrogen sulfide (H_2S) donor with strong anti-inflammatory properties. Preclinical in vivo animal studies, predominantly performed in mice, demonstrated that enhancing the H_2S concentration with STS or other H_2S boosters has antioxidant and vasoactive effects, achieved through the ability of gaseous H_2S to maintain mitochondrial integrity. These properties make STS a potentially ideal preventive therapy for IRI. In GIPS-IV—an investigator-initiated trial performed in the Netherlands—373 patients were randomized to receive either STS or placebo on arrival at the hospital and 6 hours later. Patients were allocated to the treatment arm in the catheterization laboratory during primary percutaneous coronary intervention (PCI), and the first STS or placebo infusion was administered just before and during PCI. After 4 months, 226 participants (116 in the STS group and 110 in the placebo group) underwent a clinical examination and a cardiac magnetic resonance (CMR) study to assess IS as the primary endpoint. Secondary endpoints included left ventricular ejection fraction, peak creatine kinase-myocardial band, and long-term N-terminal pro-B-type natriuretic peptide. The main trial findings were that STS did not reduce IS and that there were no between-group differences in the secondary outcomes. Administration of STS was safe, and the main adverse effect was nausea and vomiting, recorded in about a third of the patients allocated to STS.

The study by de Koning et al[5] has notable strengths. First, the decision to perform this phase 2 clinical trial was supported by consistent experimental data from small and large animal models together with positive preclinical meta-analyses and an apparently good safety profile in humans. Second, the investigators showed courage in conducting the first clinical test of STS in the context of STEMI. The negative results of the trial in no way detract from their commitment to bench-to-bedside science. The incorporation of new drugs and the introduction of new uses for established drugs require the demonstration of a clear clinical benefit in large clinical trials, and this must be preceded by well-designed small pilot trials like this one. Sadly, in the current climate, it seems that only publicly funded, investigator-driven trials can take these necessary risks. A third strength of the study was the selection of IS measured by CMR as the primary endpoint. IS is widely accepted as a surrogate of hard clinical endpoints, such as mortality or admission for heart failure. CMR is without question the best noninvasive technique for the characterization of the postinfarcted myocardium and, additionally, has unparalleled capacity for the calculation of left ventricular volumes and ejection fraction.

The key study limitations that may in part explain the neutral results are related to timing and the inclusion criteria. Infusion of the first STS dose began on arrival at the catheterization laboratory and was likely incomplete until long after reperfusion in most patients. For protection against IRI, the sooner a drug is administered, the bigger the benefit seems to be, and the "intrareperfusion" infusion of STS in GIPS-IV may have resulted in an insufficient blood concentration at the time of PCI. Another timing issue is the 4-month CMR follow-up examination; post-STEMI remodeling is an active process lasting more than a year, and the 4-month follow-up imaging thus appears to be somewhat premature. The study would also have benefitted from an additional acute CMR study to identify potential effects of STS on relevant pathophysiologic processes, such as edema, microvascular obstruction, and intramyocardial hemorrhage. In the case of edema, although several CMR edema sequences have been used in the past to measure area at risk, there is evidence that this approach is inappropriate, and it is no longer recommended. In their study, de Koning et al[5] assessed area at risk from indirect but convincing angiographic data showing a similar distribution of proximal vessel occlusion in both study arms. Also related to the timing, a longer clinical follow-up would be required to confirm the trial's efficacy and safety results.

Regarding the inclusion criteria, it is remarkable that 147 patients (39% of the total) did not undergo the 4-month CMR study, which determined the primary endpoint of the trial. Even considering the effect of the COVID-19 pandemic, this dropout rate is higher than expected and threatens the internal validity of the study. The outcome measures may also have been influenced by the pretreatment of all trial participants with antiplatelet drugs, as recommended by current clinical guidelines, because platelet inhibitors have a cardioprotective action that can dilute the effect of any other therapy. Finally, it is important to note that the trial examined a low-risk STEMI population, with hemodynamic stability (97% in Killip class I) and small infarctions (~8% of left

ventricular mass). More restrictive inclusion criteria, such as the selection of only anterior infarctions with a larger myocardial area at risk, would have helped to clarify more precisely the potential cardioprotective benefit of STS.

The term inflammation derives from the Latin *inflammare*, meaning "to cause to catch fire." One of the main approved clinical indications for STS is as the antidote to cyanide poisoning, a relatively common consequence of breathing in smoke from a fire. Extending this metaphor, and contrary to the hypothesis that motivated the GIPS-IV trial, STS does not appear to be the antidote for the acute inflammatory process following STEMI and its resolution by PCI. Although the GIPS-IV trial results do not totally discard the possibility of any potential benefit of STS therapy in STEMI patients, they do suggest that this approach is yet another example of a false start in the clinical application of a promising preclinical cardioprotective therapy.

ACKNOWLEDGMENT Simon Bartlett (Centro Nacional de Investigaciones Cardiovasculares Carlos III) provided English editing.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Pizarro holds the grant RED2022-134467-I (ImBio4Net) from the Unique Scientific and Technical Infrastructure Red Distribuida de Imagen Biomédica, Ministry of Science and Innovation of Spain. The Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is supported by the Instituto de Salud Carlos III, the Ministry of Science and Innovation and the Pro CNIC Foundation and is a Severo Ochoa Center of Excellence (CEX2020-001041-S).

ADDRESS FOR CORRESPONDENCE: Dr Gonzalo Pizarro Sánchez, Melchor Fernández Almagro, 28029 Madrid, Spain. E-mail: gonzalo.pizarro@cnic.es.

REFERENCES

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet*. 1986;1:397–402.

2. Jollis JG, Granger CB, Zègre-Hemsey JK, et al. Treatment time and in-hospital mortality among patients with ST-segment elevation myocardial infarction, 2018-2021. *JAMA*. 2022;328:2033–2040.

3. Ibanez B, Heusch G, Ovize M, Van De Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol*. 2015;65:1454–1471.

4. O'Gara PT, Fushner FG, Ascheim AD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78–e140.

5. de Koning M-SLY, van Dorp P, Assa S, et al. Sodium thiosulfate in acute myocardial infarction: a randomized clinical trial. *J Am Coll Cardiol Basic Trans Science*. 2023;8(10):1285–1294.

KEY WORDS hydrogen sulfide, ischemia-reperfusion injury, myocardial infarction, randomized controlled trial, thiosulfates