Infarct Size Reduction by Targeting Ischemic Injury

Back to Square One

Xavier Rossello, Borja Ibanez

Timely reperfusion is needed to salvage viable myocardium in patients with ST-segment–elevation myocardial infarction.[1] The concept that the fate of the ischemic myocardium depends on subsequent spontaneous or interventional coronary reperfusion was established in experimental large animal models >4 decades ago.[2] Further research identified that the process of restoring blood flow to the ischemic myocardium comes at a cost, as induces additional myocardial damage, known as myocardial ischemia/reperfusion injury.[2] For a long time, it has been assumed that although ischemic injury can only be reduced by faster blood flow restoration, reperfusion-related myocardial injury can be ameliorated by interventions applied anytime before (or at the latest at) reperfusion. The possibility of reducing infarct size by a strategy applied soon before reperfusion (eg, in the cath lab) is logistically attractive and for this reason has gained lots of interest. Unlike reperfusion itself, whose translation is one of the most successful stories of medicine ever, cardioprotective therapies targeting reperfusion-related injury have not yet been successful and remain one of the top 10 unmet clinical needs in cardiology.[1,3]

Article, see p 1102

One of the major determinants of (long-term) mortality and morbidity in patients with ST-segment–elevation myocardial infarction is the extent of myocardial necrosis, known as infarct size, resulting from both ischemic- and reperfusion-related injuries.[4,5] Therapies able to reduce infarct size have been historically tested under the hypothesis that smaller infarctions will result in fewer adverse clinical events in the long term.[4,6] Among them, ischemic conditioning deserves special attention. In 1986, Murry et al[7] published a seminal study demonstrating that several brief (5 minutes) cycles of noninjurious ischemia and reperfusion render the myocardium significantly protection from a subsequent sustained ischemic insult. This phenomenon whereby the myocardium can endogenously be protected from lethal ischemia/reperfusion injury was defined as ischemic preconditioning and has been subsequently replicated in numerous preclinical studies,[8] as well as in other organs.[9] Brief episodes of ischemia and reperfusion in one organ render remote tissues and organs resistant to ischemia/reperfusion injury, something known as remote ischemic conditioning.[9] Interestingly, remote ischemic conditioning has been shown to exert cardioprotection even when it is initiated during ongoing myocardial infarction,[10] a maneuver known as remote ischemic perconditioning (perRIC). All different variants of conditioning (pre, per, post, local, or remote) are thought to reduce infarct size by targeting reperfusion-related injury.

In this issue of *Circulation Research*, Kleinbongard et al[11] studied the electrocardiographic changes occurring during perRIC in a swine model of myocardial ischemia/reperfusion injury. Isoflurane-anesthetized Göttingen minipigs underwent open-chest temporary (60 minutes) coronary occlusion followed by reperfusion. At minute 20 of ischemia, pigs were randomized to perRIC (4 cycles of 5-minute occlusion/5-minute reperfusion of the hindlimb) or control (no perRIC). ST-segment elevation was analyzed in a V_2-like electrocardiography lead at baseline, at 5- and 55-minute coronary occlusion, and at 10-, 30-, 60-, and 120-minute reperfusion. Hundred and eighty minutes after reperfusion, animals were euthanized, and hearts processed for pathology-based infarct size and no-reflow quantifications. perRIC was associated with significantly smaller infarct sizes. There was a nonsignificant trend for smaller areas of no-reflow in the perRIC group. perRIC increased phosphorylation of STAT3 (signal transducer and activator of transcription 3). These results are in agreement with many previous studies and validate the authors' model of perRIC. The main novelty of the article relates to the serial electrocardiographic findings: at 5-minute ischemia (ie, before perRIC was initiated), ST-segment deviations were not different, but ST-segment deviation at 55-minute ischemia significantly recovered in perRIC pigs compared with matched controls. This observation has 2 main clinical implications: (1) ischemic perconditioning has a clear impact on the ischemic bit of the overall ischemia/reperfusion injury and (2) electrocardiography can be used for real-time monitoring of the impact of cardioprotective therapies over myocardial ischemic injury and, maybe, can be used to roughly identify a subset of patients with a high underlying risk of developing large infarcts who can actually benefit from cardioprotective interventions.

The study by Kleinbongard et al[11] challenges the paradigm that perRIC mostly attenuates reperfusion-related injury because the reduction in ST-segment elevation observed during ongoing ischemia points toward an impact on ischemic injury. The mechanism by which perRIC can ameliorate ischemic damage is unknown and was beyond the scope of this article. Given the virtual absence of residual blood flow into the ischemic region, it seems implausible that a humoral signal released

From the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Translational Laboratory for Cardiovascular Imaging and Therapy, Madrid, Spain (X.R., B.I.); CIBER de enfermedades CardioVasculares (CIBERCV), Madrid, Spain (X.R., B.I.); and Cardiology Department, IIS-Fundación Jiménez Díaz University Hospital, Madrid, Spain (B.I.).

Correspondence to Borja Ibáñez, MD, PhD, Translational Laboratory for Cardiovascular Imaging and Therapy, Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Melchor Fernández Almagro, 3, 28029, Madrid, Spain. E-mail bibanez@cnic.es

(*Circ Res*. 2018;122:1041-1043.
DOI: 10.1161/CIRCRESAHA.118.312939.)

***Circulation Research* is available at http://circres.ahajournals.org**
DOI: 10.1161/CIRCRESAHA.118.312939

from the distant organ undergoing brief episodes of ischemia/reperfusion is the source of ischemic injury attenuation. It is intuitive to argue that a neural pathway is involved in this protection, but we are far from understanding the actual mechanism. This study is landmark not only from the conditioning perspective but also for the entire cardioprotection field because it places ischemic injury back in the arena of relevant targets for infarct size reduction, something ignored for many years. This study also provides explanation for a finding identified in the CONDI trial (Effect of RIC on Clinical Outcomes in STEMI Patients Undergoing pPCI),[10] where perRIC seemed to offer stronger protection when applied long before reperfusion.[12] In this line, another strategy that has been shown to reduce infarct size (ie, intravenous metoprolol) exerts stronger cardioprotection when applied long before reperfusion.[13] Altogether, these evidences suggest that therapies effectively reducing infarct size exert an important effect on ischemic injury. Beyond the conceptual change of this finding, there is a practical consequence: these therapies should be applied as soon as possible on myocardial infarction diagnosis, and this is many times in the out-of-hospital setting. The identification of the anti-ischemic effect of perRIC and metoprolol (and probably other strategies) does not mean that they do not ameliorate reperfusion-related injury as well. In this sense, recently it has been shown that metoprolol has a direct effect on neutrophils, and this results in a potent effect against reperfusion-related injury.[14] In fact, ischemic- and reperfusion-related injuries are indissoluble from each other, and, thus, any therapy reducing ischemic-related injury will also impact reperfusion-related injury.

The electrocardiography is a tool routinely used in patients with suspected AMI to establish a diagnosis.[1] The identification of ST-segment elevation in ≥2 contiguous leads provides information about the affected location, the need for reperfusion, and even about its prognosis. Taking into account recent disappointing results in randomized clinical trials assessing cardioprotective therapies, there is a need to find early markers that can provide valuable information to identify patients at high risk, who can actually benefit from cardioprotective therapies, as well as patients already protected who cannot benefit at all of them. Despite being used worldwide for >100 years, electrocardiography is still the cornerstone of the diagnosis of AMI and can emerge as a new test to select which patients should and should not be included in randomized clinical trials evaluating cardioprotective interventions.

In the past decades, ST-segment, T-wave, and QRS changes have been incorporated into electrocardiography scoring systems to assess the severity and acuteness of ischemia. For instance, Birnbaum et al[15] demonstrated that the distortion in the terminal portion of the QRS complex in admission electrocardiography in patients presenting with ST-segment–elevation myocardial infarction was associated with poor prognosis when present in ≥2 contiguous leads. More recently, this electrocardiographic pattern has been independently associated with larger myocardium at risk and infarct size in patients with anterior AMI.[16] Therefore, QRS distortion might be used to select those patients with larger myocardial risk, who can greatly benefit from a cardioprotective intervention.

There is currently great expectation for the outcome of the combination of 2 large ongoing randomized, controlled, clinical trials, namely, the CONDI2 (NCT01857414) and ERIC-PPCI (Effect of Remote Ischaemic Conditioning on Clinical Outcomes in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention; NCT02342522) studies,[17] which is a European endeavor (Denmark, Spain, Serbia, and United Kingdom, respectively) involving together >5300 patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention. These trials aim to evaluate the effect of perRIC on long-term clinical outcomes. These trials enroll patients at a wide range of time to reperfusion (ie, some patients are recruited and put on perRIC long before reperfusion [in the ambulance], whereas others are recruited in the cath lab soon before reperfusion). According to the results from Kleinbongard et al motivating this editorial,[11] it seems imperative to design a secondary analysis of the trials in which only patients recruited in the out-of-hospital setting are analyzed. If ischemic injury reduction was the main driver of protection on perRIC, applying this intervention soon before reperfusion (ie, in the cath lab or emergency department), when ischemic damage is almost ended, would significantly reduce the infarct-limiting effects of this maneuver.

Acknowledgments

Dr Rossello has received support from SEC-CNIC CARDIOJOVEN Program. Dr Ibanez holds grants related to this topic from the Spanish Ministry of Economy and Competitiveness (MINECO) through the Carlos III Institute of Health-Fondo de Investigación Sanitaria (PI16/02110) and the Fondo Europeo de Desarrolo Regional (FEDER, RD: SAF2013-49663-EXP). The Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is supported by the Ministry of Economy, Industry and Competitiveness (MEIC) and the Pro CNIC Foundation and is a Severo Ochoa Center of Excellence (SEV-2015-0505).

Disclosures

None.

References

1. Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393.
2. Ibáñez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol*. 2015;65:1454–1471. doi: 10.1016/j.jacc.2015.02.032.
3. Fuster V. Top 10 cardiovascular therapies and interventions for the next decade. *Nat Rev Cardiol*. 2014;11:671–683. doi: 10.1038/nrcardio.2014.137.
4. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol*. 2016;67:1674–1683. doi: 10.1016/j.jacc.2016.01.069.
5. Rossello X, Hall AR, Bell RM, Yellon DM. Characterization of the Langendorff perfused isolated mouse heart model of global ischemia-reperfusion injury: impact of ischemia and reperfusion length on infarct size and LDH release. *J Cardiovasc Pharmacol Ther*. 2016;21:286–295. doi: 10.1177/1074248415604462.
6. Bolli R, Becker L, Gross G, Mentzer R Jr, Balshaw D, Lathrop DA; NHLBI Working Group on the Translation of Therapies for Protecting

the Heart from Ischemia. Myocardial protection at a crossroads: the need for translation into clinical therapy. *Circ Res*. 2004;95:125–134. doi: 10.1161/01.RES.0000137171.97172.d7.
7. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74:1124–1136.
8. Fernández-Jiménez R, Galán-Arriola C, Sánchez-González J, et al. Effect of ischemia duration and protective interventions on the temporal dynamics of tissue composition after myocardial infarction. *Circ Res*. 2017;121:439–450. doi: 10.1161/CIRCRESAHA.117.310901.
9. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol*. 2015;65:177–195. doi: 10.1016/j.jacc.2014.10.031.
10. Bøtker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet*. 2010;375:727–734. doi: 10.1016/S0140-6736(09)62001-8.
11. Kleinbongard P, Amanakis G, Skyschally A, Heusch G. Reflection of cardioprotection by remote ischemic perconditioning in attenuated ST-segment elevation during ongoing coronary occlusion in pigs: evidence for cardioprotection from ischemic injury. *Circ Res*. 2018;122:1102–1108. doi: 10.1161/CIRCRESAHA.118.312784
12. Pryds K, Terkelsen CJ, Sloth AD, Munk K, Nielsen SS, Schmidt MR, Bøtker HE; CONDI Investigators. Remote ischaemic conditioning and healthcare system delay in patients with ST-segment elevation myocardial infarction. *Heart*. 2016;102:1023–1028. doi: 10.1136/heartjnl-2015-308980.
13. García-Ruiz JM, Fernández-Jiménez R, García-Alvarez A, et al. Impact of the timing of metoprolol administration during STEMI on infarct size and ventricular function. *J Am Coll Cardiol*. 2016;67:2093–2104. doi: 10.1016/j.jacc.2016.02.050.
14. García-Prieto J, Villena-Gutiérrez R, Gómez M, et al. Neutrophil stunning by metoprolol reduces infarct size. *Nat Commun*. 2017;8:14780. doi: 10.1038/ncomms14780.
15. Birnbaum Y, Hale SL, Kloner RA. Differences in reperfusion length following 30 minutes of ischemia in the rabbit influence infarct size, as measured by triphenyltetrazolium chloride staining. *J Mol Cell Cardiol*. 1997;29:657–666.
16. Valle-Caballero MJ, Fernández-Jiménez R, Díaz-Munoz R, Mateos A, Rodríguez-Álvarez M, Iglesias-Vázquez JA, Saborido C, Navarro C, Dominguez ML, Gorjón L, Fontoira JC, Fuster V, García-Rubira JC, Ibanez B. QRS distortion in pre-reperfusion electrocardiogram is a bedside predictor of large myocardium at risk and infarct size (a METOCARD-CNIC trial substudy). *Int J Cardiol*. 2016;202:666–673. doi: 10.1016/j.ijcard.2015.09.117.
17. Hausenloy DJ, Kharbanda R, Rahbek Schmidt M, et al. Effect of remote ischaemic conditioning on clinical outcomes in patients presenting with an ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J*. 2015;36:1846–1848.

KEY WORDS: Editorials ■ ischemia ■ ischemic preconditioning ■ myocardium ■ reperfusion injury

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Infarct Size Reduction by Targeting Ischemic Injury: Back to Square One

Xavier Rossello and Borja Ibanez

Circ Res. 2018;122:1041-1043
doi: 10.1161/CIRCRESAHA.118.312939
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571