

# Ischemic postconditioning and duration of previous ischemia



## *Poscondicionamiento isquémico y duración de la isquemia previa*

José A. Barrabés<sup>a,b,c,\*</sup>

<sup>a</sup> Unidad de Críticos Cardiovasculares, Servicio de Cardiología, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>b</sup> Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain

<sup>c</sup> Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

### SEE RELATED CONTENT:

<https://doi.org/10.24875/RECICE.M22000333>

Ischemic postconditioning (iPost) was first described in 2003 as a strategy capable of reducing the size of infarction after prolonged coronary occlusion in dogs through the immediate application of reperfusion after 3 cycles of 30 seconds of coronary reocclusion followed by 30 seconds of reperfusion.<sup>1</sup> These results were soon confirmed independently, and the potential mechanisms involved described including, among others, a delayed normalization of pH levels, less accumulation of intracellular calcium, inhibition of the mitochondrial permeability transition pore, and less oxidative stress.<sup>2</sup> Compared to the robust protective effect of ischemic preconditioning, it was confirmed that iPost was only beneficial if the procedure started right after reperfusion. However, it was attenuated in elderly subjects or in the presence of comorbidities or certain drug therapies.<sup>2,3</sup>

Despite these limitations, iPost soon called the attention of interventional cardiologists because it was easy to apply during primary percutaneous coronary intervention. Back in 2005 the very first study ever conducted in humans was published. In this study, iPost reduced the size of creatine kinase release compared to the control group in patients with ST-segment elevation myocardial infarction (STEMI).<sup>4</sup> However, successive trials that estimated the size of infarction using similar methods or was more reliably measured by contrast-enhanced cardiac magnetic resonance imaging showed contradictory results. Some of these confirmed iPost protective effect while others revealed the opposite or even less myocardial salvage in patients treated with iPost compared to those who were iPost-naïve.<sup>5-7</sup> So far, no clinical trial has been able to demonstrate that iPost reduces clinical events. The largest trial ever conducted is the DANAMI-3-iPOST that included 1234 patients with STEMI treated with primary percutaneous coronary intervention within the first 12 hours of disease progression and with the culprit artery occluded at the beginning of the procedure. These patients were randomized to receive iPost or a conventional percutaneous coronary intervention.<sup>8</sup> After a median of 38 months of follow-up, the rate of the primary endpoint (death or hospitalization due to heart failure) was similar in both the iPost and the control group (10.5% vs 11.2%, respectively; non-significant *P* value) with no differences being reported in their individual components, other events, ST-segment elevation resolution or in the size of infarction measured by cardiac magnetic resonance imaging in a subgroup. A follow-up

meta-analysis confirmed the lack of tangible clinical benefits in iPost in an aggregate population of 3619 patients with STEMI.<sup>9</sup>

Given these results, clinicians have consequently lost interest in this strategy. Therefore, iPost has not joined the therapeutic arsenal for the management of patients with STEMI. However, the reason behind the contradictory results of the mentioned trials is worth analyzing to identify, if any, subgroups of patients who could benefit from the protective effect of iPost. A possible explanation could be that the benefit of iPost depends on the duration of previous ischemia.<sup>10</sup>

In an article recently published in *REC: Interventional Cardiology*, Nuche et al.<sup>11</sup> put this hypothesis to the test by comparing the effect of iPost on the size of infarction in a series of pigs undergoing left anterior descending coronary artery occlusion through 30-min balloon inflation (*N* = 19) to a different series from a previous report<sup>12</sup> where occlusion went on for 40 min (*N* = 10). Except for the duration of ischemia, the experimental protocol was identical. iPost consisted of 4 cycles of balloon reinflation and deflation (1 min each) started 1 min after reperfusion. The area at risk was measured on the contrast-enhanced multidetector computed tomography scan with contrast during ischemia while the size of infarction was measured on the contrast-enhanced cardiac magnetic resonance imaging at 7 days.

iPost did not reduce the size of infarction in animals with 30-min coronary occlusion (0.3% [0.0-3.9] vs 0.9 [0.0-2.6] of left ventricular mass in animals treated with iPost or in the control group, respectively) or 40-min coronary occlusion (31.1% [27.3-32.8] vs 27.3 [25.1-27.5], respectively; both with non-significant *P* values). Overall, T1 relaxation times were longer in animals treated with iPost. Authors conclude that iPost did not reduce the size of infarction in any of the 2 series, which goes against the possible interaction between its effect and the duration of previous ischemia. Also, longer T1 relaxation times—a marker of interstitial fibrosis—in animals with iPost suggests potential damage associated with the procedure.

The trial<sup>11</sup> comes from a group of researchers with solid experience in the area, it is technically demanding, and has been conducted following a highly sophisticated methodology, for which the authors

\* Corresponding author.

E-mail address: [jose.barrabes@vallhebron.cat](mailto:jose.barrabes@vallhebron.cat) (J.A. Barrabés)

Online 30 November 2022.

2604-7322 / © 2022 Sociedad Española de Cardiología. Published by Permanyer Publications. This is an open access journal under the CC BY-NC-ND 4.0 license.

should be credited. Results go against an interaction between the benefit of iPost and the duration of previous ischemia. However, before this becomes the definitive conclusion, some methodological considerations should be made. In the first place, to assess the effect of any protective procedures, the size of infarction in the control group should have certain variability and, on average, should not be too large or too small.<sup>13</sup> However, in this trial, after 30 min of ischemia barely any infarction was reported (3.8% [0.0-8.5] of the area at risk) while after 40 min infarctions were massive (98.2% [70.7-98.8] of the area at risk). Although these ischemia times were selected because they had caused medium-sized infarctions in former trials,<sup>14</sup> homogeneity of the infarction size seen in both series and the almost non-existent infarctions in the 30 min series complicate discarding a possible beneficial effect of iPost in the results reported. Secondly, and on this regard too, it was surprising to see that by increasing ischemia time in just 10 min we went from almost non-existent infarctions to infarctions that occupy the entire area at risk. Although the experimental protocol was the same, as both series were conducted in different moments in time, variations in the conditions of the experiment such as animal breed, room temperature, materials used, etc, may have impacted the results and, therefore, cannot be ruled out. In this sense, results stress out the possible setback associated with the use of historic series. Finally, for the lack of a targeted anatomopathological study, a possible explanation for the massive infarctions reported in the 40 min series is that maybe some animals had coronary reocclusions between the end of the experiment and when the size of infarction was estimated 7 days later. Reocclusion is a common occurrence in this experimental model, especially when ischemia has been prolonged, and although the risk of ischemia drops with antiplatelet therapy (3 doses of clopidogrel were used in this trial) it does not go away completely.<sup>15</sup>

Despite these considerations, the truth is that the results of this study<sup>11</sup> do not offer any signs of a potential cardioprotective effect of iPost by changing the ischemia times in this experimental model. This, added to the lack of clinical benefits reported in the previously mentioned trials confirms that, currently, iPost should not be used in patients with STEMI. This anticipates that it will be difficult to find a population of target patients in whom this procedure might be beneficial.

## FUNDING

J.A. Barrabés received research funds from *Instituto de Salud Carlos III* (PI20/01681 project) and *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares* (CIBERCV) co-financed by the European Regional Development Fund.

## CONFLICTS OF INTEREST

None reported.

## REFERENCES

- Zhao ZQ, Corvera JS, Halkos ME, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol.* 2003;285:H579-H588.
- Hausenloy DJ, Barrabés JA, Botker HE, et al. Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery. *Basic Res Cardiol.* 2016;111:70.
- Kin H, Zhao ZQ, Sun HY, et al. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. *Cardiovasc Res.* 2004;62:74-85.
- Staat P, Rioufol G, Piot C, et al. Postconditioning the human heart. *Circulation.* 2005;112:2143-2148.
- Khan AR, Binabduhah AA, Alastal Y, et al. Cardioprotective role of ischemic postconditioning in acute myocardial infarction: a systematic review and meta-analysis. *Am Heart J.* 2014;168:512-521.e4.
- Khalili H, Patel VG, Mayo HG, et al. Surrogate and clinical outcomes following ischemic postconditioning during primary percutaneous coronary intervention of ST-segment elevation myocardial infarction: a meta-analysis of 15 randomized trials. *Catheter Cardiovasc Interv.* 2014;84:978-986.
- Freixa X, Bellera N, Ortiz-Pérez JT, et al. Ischaemic postconditioning revisited: lack of effects on infarct size following primary percutaneous coronary intervention. *Eur Heart J.* 2012;33:103-112.
- Engström T, Kelbæk H, Helqvist S, et al. Effect of ischemic postconditioning during primary percutaneous coronary intervention for patients with ST-segment elevation myocardial infarction: a randomized clinical trial. *JAMA Cardiol.* 2017;2:490-497.
- Mentias A, Mahmoud AN, Elgendy IY, et al. Ischemic postconditioning during primary percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2017;90:1059-1067.
- Manintveld OC, Te Lintel Hekkert M, van den Bos EJ, et al. Cardiac effects of postconditioning depend critically on the duration of index ischemia. *Am J Physiol Heart Circ Physiol.* 2007;292:H1551-H1560.
- Nuche J, Galán-Arriola C, Fernández-Jiménez R, et al. Ischemic postconditioning fails to reduce infarct size in pig models of intermediate and prolonged ischemia. *REC Interv Cardiol.* 2022. <https://doi.org/10.24875/RECICE.M22000333>.
- 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.
- García-Dorado D, Théroux P, Elizaga J, et al. Myocardial reperfusion in the pig heart model: infarct size and duration of coronary occlusion. *Cardiovasc Res.* 1987;21:537-544.
- Lobo-Gonzalez M, Galán-Arriola C, Rossello X, et al. Metoprolol blunts the time-dependent progression of infarct size. *Basic Res Cardiol.* 2020;115:55.
- Barrabés JA, García-Dorado D, Oliveras J, et al. Intimal injury in a transiently occluded coronary artery increases myocardial necrosis. Effect of aspirin. *Pflugers Arch.* 1996;432:663-670.