EDITORIAL

Remote Ischemic Preconditioning for Percutaneous Coronary Intervention: Waiting for Godot?

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The year 2016 marked the 30th anniversary of the discovery of the phenomenon of "ischemic conditioning," dating back to the mid-1980s when Murry, Jennings, and Reimer noted that pretreating the canine left circumflex coronary artery with 4, 5-minute cycles of occlusion and reflow before subsequent occlusion of the vessel for 40 minutes led to a 25% reduction in myocardial infarction (MI) size.[1,2] Several variations on the original concept have since evolved, and ischemic conditioning types are now known to include preconditioning, postconditioning, pharmacologic cardioprotection, and remote conditioning.[1]

Remote ischemic conditioning (RIC) was first studied around 1993 when dogs that had intermittent canine left circumflex coronary artery occlusion before left anterior descending occlusion experienced decreased infarct size.[3] Later, this expanded to encompass cycles of inflation/deflation of a sphygmomanometer placed around the upper (or lower) extremity before (preconditioning) or after (postconditioning) percutaneous coronary intervention (PCI).[4] RIC is most commonly performed by inflating a blood pressure cuff around the arm, typically for 3 or 5 minutes, and 1 to 4 cycles, with most contemporary studies using 4 5-minute cuff inflations.[1,5] Given its simplicity, RIC could readily be initiated in an ambulance during transport for primary PCI in acute MI, or could be administered before a planned coronary revascularization with either PCI or coronary artery bypass graft surgery. Ischemic conditioning has been the focus of extensive investigative efforts: a PubMed search on "ischemic preconditioning" on September 8, 2018 provided 10 301 results. While many preclinical studies have shown benefit, clinical studies have provided less consistent results.[6]

Remote ischemic preconditioning did not reduce the incidence of major adverse cardiac and cerebral events in 2 large randomized-controlled cardiac surgery trials, the RIPHeart (Remote Ischemic Preconditioning for Heart Surgery) trial[7] and the ERICCA (Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery) trial.[7,8] Although this might be related to use of propofol for sedation (which may diminish or abolish the effect of ischemia-induced cardioprotection), in ERICCA the incidence of cardiovascular death was numerically higher in the remote ischemic preconditioning group (P=0.08), suggesting possible harm.[8]

Unlike cardiac surgery, there are no completed large randomized-controlled trials assessing the effect of RIC during PCI. RIC holds the most promise for treating MI patients, with small studies showing improved salvage index by nuclear imaging, reduced infarct size and edema by magnetic resonance imaging, and improved ST-segment elevation resolution and cardiac biomarker rise.[1] The ongoing 5413 patient CONDI2/ERIC-PPCI (Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI) trial is examining the impact of RIC on the 12-month incidence of cardiac death and hospitalization for heart failure, and results are anticipated in 2019.

In the setting of elective PCI, several relatively small studies such as the CRISP Stent (Cardiac Remote Ischemic Preconditioning in Coronary Stenting) study have shown that RIC can reduce the incidence of periprocedural MI, chest pain, ischemic ECG changes, and in at least 1 study, reduce the combined end point of all-cause mortality, nonfatal MI, transient ischemic attack or stroke, and heart failure hospitalizations.[1,9] Other studies, however, were negative, with interpretation of conflicting data somewhat limited by interstudy differences in methodology and study populations.[10,11]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Yong et al examined the impact of RIC on the coronary microcirculation, as assessed by the index of microcirculatory resistance, coronary flow reserve, and hyperemic transit time.[12] In a carefully designed study, they randomized 30 patients with stable coronary artery disease, undergoing

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fractional flow reserve assessment of an intermediate coronary lesion to RIC (5-minute sphygmomanometer balloon inflation to at least 200 mm Hg and 5-minute deflation in the left arm, for a total of 3 cycles) or sham (similar cycles with sphygmomanometer inflated to 10 mm Hg).[12] As compared with sham, RIC reduced index of microcirculatory resistance and hyperemic transit time and increased coronary flow reserve, providing mechanistic insights on the potential mechanisms of RIC-associated cardioprotection.[12] However, the clinical consequences of RIC could not be assessed, because most patients did not undergo PCI and the study was not powered for clinical end points.

The authors should be congratulated for a meticulously performed clinical study which, similar to the ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial, used sham control.[13] The improvement in coronary microcirculatory function is an important mechanistic insight that may link RIC with downstream clinical effects. There are multiple other pathways that could link the remote tissue response with a protective effect at the target tissues.[14] The transfer of the cardioprotective effect itself may relate to 1 or more bloodborne humoral factors, might occur via neurohormonal stimulation transmission, or perhaps via systemic modification of circulating immune cells.[14] Potential candidates include adenosine, bradykinin, opioids, an as-yet unidentified small hydrophobic molecule isolated in studies, and STAT5, a protein involved in cytosolic signaling.[1,4] Preclinical studies have linked the ultimate cardioprotective effect to activation of adenosine, bradykinin-2, opioid, angiotensin-1, CB_2 endocannabinoid receptors, opening of K_{ATP} channels, calcitonin gene-related peptide, signaling reactive oxygen species, noradrenaline, nitric oxide, and heat shock proteins.[14]

While studies such as that of Yong et al[12] are improving our insight into the mechanisms underlying the impact of RIC, applying this therapy with the intent of improving the outcomes of PCI for patients with stable coronary artery disease will likely face significant hurdles for implementation: the incidence of periprocedural MI, as assessed by cardiac biomarker elevation, is relatively infrequent in this group, and has not consistently been linked with higher risk for subsequent major adverse clinical events.[15] Hence, even if RIC reduced the incidence of periprocedural myocardial infarction in patients with stable coronary artery disease, it is unclear whether this would translate into better long-term clinical outcomes.

Deciding on whether to apply a medical intervention should always be based on the risk/benefit ratio, as well as its cost-effectiveness. The major appeal of RIC has been its low risk (although there were some concerns with higher cardiovascular mortality in the ERICCA trial as described above[8]), low cost, and ease of implementation. Whether RIC provides clinical benefit during PCI remains controversial and may be hard to prove in low-risk patients with stable coronary artery disease. Patients presenting with MI may have more to gain, but whether the study findings will also apply to those patients is unknown: "pre"conditioning cannot be performed in such patients and the microcirculation may be irreversibly injured by the time RIC is initiated. Also mechanical means, such as embolic protection devices, may be more efficacious in protecting the coronary microcirculation from additional damage, as shown in the VAMPIRE (Vacuum Aspiration Thrombus Removal) 3 trial.[16] On the other hand, with increasing data supporting the use of multivessel revascularization during ST-segment–elevation myocardial infarction, there may be opportunity for preventing injury caused by distal embolization or side branch compromise of those initially "unharmed" myocardial territories.

"Waiting for Godot" describes the current status of the field of cardioprotection. Whether CONDI2/ERIC-PPCI will bring Godot remains to be seen.

Disclosures

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References

1. Hausenloy DJ, Yellon DM. Ischaemic conditioning and reperfusion injury. *Nat Rev Cardiol*. 2016;13:193–209.
2. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74:1124–1136.
3. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*. 1993;87:893–899.
4. Przyklenk K. Reduction of myocardial infarct size with ischemic "conditioning": physiologic and technical considerations. *Anesth Analg*. 2013;117:891–901.
5. Kanoria S, Jalan R, Seifalian AM, Williams R, Davidson BR. Protocols and mechanisms for remote ischemic preconditioning: a novel method for reducing ischemia reperfusion injury. *Transplantation*. 2007;84:445–458.
6. Rossello X, Yellon DM. A critical review on the translational journey of cardioprotective therapies!. *Int J Cardiol*. 2016;220:176–184.
7. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaelte G, Boning A, Niemann B, Roesner J, Kletzin F, Strouhal U, Reyher C, Laufenberg-Feldmann R, Ferner M, Brandes IF, Bauer M, Stehr SN, Kortgen A, Wittmann M, Baumgarten G, Meyer-Treschan T, Kienbaum P, Heringlake M, Schon J, Sander M, Treskatsch S, Smul T, Wolwender E, Schilling T, Fuernau G, Hasenclever D, Zacharowski K; RIPHeart Study Collaborators. A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med*. 2015;373:1397–1407.
8. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM; ERICCA Trial Investigators. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med*. 2015;373:1408–1417.
9. Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, Clarke SC, Shapiro LM, Schofield PM, O'Sullivan M, Dutka DP. Cardiac remote ischemic preconditioning in coronary stenting (CRISP Stent) study: a prospective, randomized control trial. *Circulation*. 2009;119:820–827.

10. Prasad A, Gossl M, Hoyt J, Lennon RJ, Polk L, Simari R, Holmes DR Jr, Rihal CS, Lerman A. Remote ischemic preconditioning immediately before percutaneous coronary intervention does not impact myocardial necrosis, inflammatory response, and circulating endothelial progenitor cell counts: a single center randomized sham controlled trial. *Catheter Cardiovasc Interv*. 2013;81:930–936.

11. Moretti C, Cerrato E, Cavallero E, Lin S, Rossi ML, Picchi A, Sanguineti F, Ugo F, Palazzuoli A, Bertaina M, Presbitero P, Shao-Liang C, Pozzi R, Giammaria M, Limbruno U, Lefevre T, Gasparetto V, Garbo R, Omede P, Sheiban I, Escaned J, Biondi-Zoccai G, Gaita F, Perl L, D'Ascenzo F. The European and Chinese cardiac and renal remote ischemic preconditioning study (EURO-CRIPS CardioGroup I): a randomized controlled trial. *Int J Cardiol*. 2018;257:1–6.

12. Lau JK, Roy P, Javadzadegan A, Moshfegh A, Fearon WF, Ng M, Lowe H, Brieger D, Kritharides L, Yong AS. Remote ischemic preconditioning acutely improves coronary microcirculatory function. *J Am Heart Assoc*. 2018;7:e009058. DOI: 10.1161/JAHA.118.009058.

13. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP; ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391:31–40.

14. Lim SY, Hausenloy DJ. Remote ischemic conditioning: from bench to bedside. *Front Physiol*. 2012;3:27.

15. Yang X, Tamez H, Lai C, Ho K, Cutlip D. Type 4a myocardial infarction: incidence, risk factors, and long-term outcomes. *Catheter Cardiovasc Interv*. 2017;89:849–856.

16. Hibi K, Kozuma K, Sonoda S, Endo T, Tanaka H, Kyono H, Koshida R, Ishihara T, Awata M, Kume T, Tanabe K, Morino Y, Tsukahara K, Ikari Y, Fujii K, Yamasaki M, Yamanaka T, Kimura K, Isshiki T; VAMPIRE 3 Investigators. A randomized study of distal filter protection versus conventional treatment during percutaneous coronary intervention in patients with attenuated plaque identified by intravascular ultrasound. *JACC Cardiovasc Interv*. 2018;11:1545–1555.

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