Is Aspirin Loading Before Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction Necessary?

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Translating fruitful basic research results into actual clinical application has always been difficult. Nonetheless, this palpable gap between the two fields of science medicine should be overcome by investigating and uncovering factors for the application of basic scientific research. The current study challenges this issue focusing on the field of cardioprotection afforded by ischemic preconditioning or postconditioning.

Myocardial infarct size (IS) has been recognized as a major determinant of acute and long-term prognosis in patients with acute myocardial infarction, suggesting that minimizing ischemic length through the early onset of reperfusion is the most important target for attenuating myocardial injury. Ironically, however, reperfusion per se has an adverse effect of further increasing IS, known as reperfusion injury, which explains up to 50% of the final IS [1]. Conversely, brief periods of ischemia preceding sustained ischemia can markedly decrease IS. Murry et al. first described this phenomenon as ischemic preconditioning in a canine experimental model [2], and the underlying mechanisms have been studied extensively. Until now, we have learned that the ability to undergo preconditioning is almost ubiquitous in tissues and is highly conserved across species. Although ischemic preconditioning is intrinsic and the strongest cardioprotective factor, it is not a realistic treatment approach for acute myocardial infarction in clinical practice given that it must be induced prior to the onset of myocardial infarction. Therefore, studies have investigated the effects of agents and procedures related to the mechanism of ischemic preconditioning. In 2003, Zhao et al. demonstrated that

reopening of the infarct-related artery, followed by repetitive brief interruptions of blood flow before sustained reperfusion, and reduced the myocardial infarct size by 44% in canine hearts [3]. This strategy, known as ischemic postconditioning (PostC), has been extensively shown to attenuate reperfusion injury and limit myocardial IS in various animal models, with the cardioprotective effects of PostC having been confirmed in numerous species, including humans [4, 5]. However, a recent meta-analysis of 10 randomized controlled trials showed no reduction in heart failure, all-cause mortality, or major adverse cardiac events after comparing primary percutaneous coronary intervention (PCI) in combination with PostC to traditional primary PCI over a mean follow-up of 20 months [6]. Thus, the question remains: why are the results of basic research not translated to the clinical practice? What is the cause of this apparent gap?

In this issue of the Journal, Birnbaum et al. had attempted to bridge this gap with their hypothesis suggesting that aspirin loading before reperfusion therapy could explain the discrepancy between basic research and clinical studies. Aspirin inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and therefore inhibits not only the production of thromboxane A2 (TXA2) in platelets but also the production of antiaggregatory prostaglandin I2 (PGI2) in vessel walls. This is the cause of the substantial clinical issues known as the aspirin dilemma. However, lower oral doses of aspirin are deacetylated by the liver and do not have systemic effects. COX-2 is constitutively expressed in systemic vascular endothelium, and thus COX-2-derived PGI2 exerts vasodilatory and antiplatelet properties. Low-dose aspirin is believed to be more specific for COX-1 than for COX-2, and the antiplatelet effects can be obtained with daily doses of as low as 30 mg [7]. Alternatively, The American College of Cardiology Foundation/American Heart Association guidelines for ST-elevation myocardial infarction provide a class I indication for 162–325 mg of aspirin administered as early as possible before primary PCI (Level of Evidence: B) [8], whereas the

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European Society of Cardiology guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation provides a class I indication for a loading dose of 150–300 mg orally, including chewing, or 75–250 mg of intravenous aspirin to ensure complete inhibition of thromboxane A₂-dependent platelet aggregation as soon as possible for all patients without contraindications (Level of Evidence: B) [9]. The aspirin dosages recommended in these guidelines seem excessive for simply suppressing COX-1 activity. However, no clinical trial has yet studied this, and aspirin has not been administered to the animals in basic research. In this study, the authors found that intravenous aspirin (20 mg/kg), administered during ischemia, blunted the IS-limiting effects of PostC in a rat model of ischemia–reperfusion injury. Intriguingly, the authors demonstrated that aspirin administered before reperfusion at doses comparable to those used in clinical settings attenuates the IS-limiting effect of atorvastatin that increases the production of adenosine by activating ecto-5'-nucleotidase [10] in a rat model of ischemia–reperfusion injury [11]. Furthermore, they demonstrated that a high dose of aspirin attenuated the IS-limiting effect of the P2Y₁₂-receptor antagonist ticagrelor, which prevents the uptake of adenosine into the cells administered orally for 7 days in a rat model of ischemia–reperfusion injury [12]. Atorvastatin caused marked elevation in COX-2 activity 10 min after reperfusion, and this effect was dose-dependently attenuated by aspirin (5 to 20 mg/kg). Aspirin completely blocked the effects of atorvastatin at a dose of 20 mg/kg. Similarly, ticagrelor, but not clopidogrel, dose-dependently increased COX-2 activity, and aspirin dose-dependently (5, 10, and 25 mg/kg) attenuated the IS-limiting effects of ticagrelor. Therefore, we can suggest that the dose of aspirin administered in this experiment (20 mg/kg) is similar to that used in clinical practice, which may decrease COX-2 activity. The mechanism of PostC is thought to be similar to that of ischemic preconditioning, including the activation of cell surface receptors on the cardiomyocyte and recruitment of prosurvival signaling pathways, such as the Reperfusion Injury Salvage Kinase (RISK) pathway, the Survivor Activator Factor Enhancement (SAFE) pathway, and the nitric oxide/protein kinase G pathway.

It is unfortunate that the present study could not elucidate which mechanism of postconditioning was inhibited by intravenous aspirin. Ischemic preconditioning has been shown to induce two distinct windows of cardioprotection known as the first and second windows. Although COX-2 has been shown to be one of the mechanisms of the second window, the results of this study suggested that it may have an acute effect. Considering the very interesting nature of this point, it is necessary to confirm whether aspirin loading blunts the IS-limiting effects of PostC in a large group of animals before clinical studies can be conducted in the near

future. Furthermore, although clopidogrel has no cardioprotective effects [12], ticagrelor [12], dipyridamole [13], and cilostazol [14] have been reported to have cardioprotective effects in a rat model ischemia–reperfusion injury. In contrast, clopidogrel has been reported to have cardioprotective effects in a rabbit model of ischemia–reperfusion injury [15]. Intriguingly, prasugrel has been reported to have cardioprotective effects in a rat model of ischemia–reperfusion injury [16]; however, prasugrel showed no cardioprotective effects in a Zucker Diabetic Fatty rat model of ischemia–reperfusion injury [17]. Nonetheless, conflicting data exist regarding the effects of P2Y₁₂-receptor antagonists as conditioning agents, which might be related to differences among species, pathogenesis of myocardial infarction (coronary ligation vs thrombus), administration schedules (oral vs intraperitoneally), and comorbidity. Now that newer antiplatelet agents are being used in clinical practice, it will be necessary to examine whether aspirin loading is actually necessary from the viewpoint of cardioprotection.

Declarations

Conflict of Interest HA have nothing to disclose. MK reports grants from Japanese government, grants from Japan Heart Foundation, grants from Japan Agency for Medical Research and Development, personal fees from Daiichi-Sankyo, personal fees from Pfizer, grants and personal fees from Ono, personal fees from Bayer, grants and personal fees from Novartis, grants and personal fees from Boehringer, grants and personal fees from Tanabe-Mitsubishi, personal fees from Japan Medical Data Center, grants and personal fees from Takeda, and grants and personal fees from AstraZeneca, outside the submitted work.

References

1. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. 2007;357(11):1121–35.
2. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5):1124–36.
3. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol*. 2003;285(2):H579–88.
4. Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, et al. Postconditioning the human heart. *Circulation*. 2005;112(14):2143–8.
5. Yang XC, Liu Y, Wang LF, Cui L, Wang T, Ge YG, et al. Reduction in myocardial infarct size by postconditioning in patients after percutaneous coronary intervention. *J Invasive Cardiol*. 2007;19(10):424–30.
6. Xing Z, Tang L, Huang J, Peng X, Hu X. Effects of ischaemic postconditioning on outcomes of patients with ST-segment elevation myocardial infarction who underwent primary percutaneous

- coronary intervention: a meta-analysis. *BMJ Open*. 2019;9(3):e022509.
7. Patrono C, Collier B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):234S–264S.
 8. O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, 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. *Circulation*. 2013;127(4):e362–425.
 9. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 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(2):119–77.
 10. Sanada S, Asanuma H, Minamino T, Node K, Takashima S, Okuda H, et al. Optimal windows of statin use for immediate infarct limitation: 5'-nucleotidase as another downstream molecule of phosphatidylinositol 3-kinase. *Circulation*. 2004;110(15):2143–9.
 11. Birnbaum Y, Lin Y, Ye Y, Martinez JD, Huang MH, Lui CY, et al. Aspirin before reperfusion blunts the infarct size limiting effect of atorvastatin. *Am J Physiol Heart Circ Physiol*. 2007;292(6):H2891–7.
 12. Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Birnbaum Y. Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect. *Arterioscler Thromb Vasc Biol*. 2014;34(9):2078–85.
 13. Allahham M, Lerman A, Atar D, Birnbaum Y. Why not dipyridamole: a review of current guidelines and re-evaluation of utility in the modern era. *Cardiovasc Drugs Ther*. 2021;10:1–8.
 14. Kherallah RY, Khawaja M, Olson M, Angiolillo D, Birnbaum Y. Cilostazol: a review of basic mechanisms and clinical uses. *Cardiovasc Drugs Ther*. 2021 Apr 16. <https://pubmed.ncbi.nlm.nih.gov/33860901/>. <https://doi.org/10.1007/s10557-021-07187-x>
 15. Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, et al. Platelet P2Y₁₂ blockers confer direct postconditioning-like protection in reperfused rabbit hearts. *J Cardiovasc Pharmacol Ther*. 2013;18(3):251–62.
 16. Dost T. Cardioprotective properties of the platelet P2Y₁₂ receptor inhibitor prasugrel on cardiac ischemia/reperfusion injury. *Pharmacol Rep*. 2020;72(3):672–9.
 17. Birnbaum Y, Birnbaum GD, Birnbaum I, Nylander S, Ye Y. Ticagrelor and rosuvastatin have additive cardioprotective effects via adenosine. *Cardiovasc Drugs Ther*. 2016;30(6):539–50.

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