Published in final edited form as:

J Surg Res. 2010 April ; 159(2): 660–662. doi:10.1016/j.jss.2009.04.051.

Remote Ischemic Preconditioning Reduces Myocardial Ischemia/reperfusion Injury

Jeremy L. Herrmann, M.D.¹

¹ Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana

Commentary

This study by Li and colleagues offers a direct comparison between direct myocardial ischemic preconditioning (IPC) and non-invasive hind limb remote ischemic preconditioning (RIPC) for protecting myocardium during subsequent ischemia in a rat model [1]. The authors attempt to determine whether RIPC confers late phase myocardial protection, and in contrast to previous studies that have demonstrated efficacy of these interventions separately, they aim to determine whether these interventions are equivalent in magnitude of myocardial protection during ischemia. Following 30 minutes of left anterior descending coronary artery occlusion and 120 minutes of reperfusion, they demonstrate that both direct IPC and RIPC decreased post-ischemic myocardial injury, infarct size, and incidence of ventricular arrhythmias. There were no significant differences in these parameters between the preconditioning groups suggesting that RIPC may be as efficacious as IPC in this role.

Generally speaking, IPC is the process of inducing controlled, temporary ischemic events with interval reperfusion prior to more prolonged ischemia to reduce subsequent target organ ischemia/reperfusion (I/R) injury. During direct IPC, the specific organ of interest is subjected to repeated I/R whereas in RIPC, a remote region is subjected to I/R in order to confer protection of the target organ during subsequent ischemia. Early animal studies showed that inducing ischemia in remote vascular territories or skeletal muscle could protect myocardium during subsequent ischemia [2,3]. Interestingly, brief renal and mesenteric ischemia have also been shown to confer myocardial protection during subsequent I/R [4,5]. The mechanisms of protection of RIPC are multifactorial and may include regulation of neurogenic pathways, elaboration of endogenous myocardial mediators, reduction of myocardial inflammatory cytokine production including tumor necrosis factor- α , and attenuation of I/R-induced endothelial dysfunction [6–8].

To date, a limited number of human clinical trials have been conducted to evaluate RIPC involving patients undergoing open abdominal aortic aneurysm repair [9], elective coronary artery bypass graft procedures [10], and pediatric patients undergoing congenital heart defect repair [11]. Each of these studies demonstrated the ability of RIPC to decrease myocardial injury during I/R as measured by serum cardiac markers, and renal protection was also observed in one study [9]. RIPC is clinically appealing in that it is non-pharmacologic, noninvasive, and may potentially protect multiple organs simultaneously. It may also be quickly administered

Correspondence: Jeremy L. Herrmann, M.D., 545 Barnhill Drive, Emerson Hall Room 203, Indianapolis, Indiana 46202, jlherrma@iupui.edu, Phone: 317-278-8625, Fax: 317-274-6896.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and can be timed to coincide with revascularization or other cardiac procedures in which myocardial ischemia is expected to occur. The role of IPC during acute coronary syndromes, however, is unclear.

The effects of IPC demonstrate a bimodal temporal distribution. Early phase effects occur within 3 hours of the ischemic event and are short-lived. In contrast, late phase effects begin 12–24 hours after ischemia and may last for several days [12]. In the present study, measurement of biomarkers of myocardial injury and electrocardiographic monitoring occurred during only 120 minutes of reperfusion which would coincide with the early phase of protection. Measuring infarct size at three days post-ischemia, however, provided evidence for the ability of both preconditioning techniques to confer late phase protection as well.

There are important limitations to this study. First, the markers of myocardial injury were only measured for 120 minutes after ischemia and the full duration of benefit of non-invasive hind limb RIPC in this study remains unknown. Also, as with previous studies evaluating RIPC, data comparing post-ischemic myocardial function with and without IPC are lacking. Based on these limitations, it cannot be concluded that noninvasive limb RIPC offers any clinical benefit beyond reducing myocardial injury as measured using laboratory assays. Despite these limitations, however, these results offer initial evidence that RIPC may be equivalent to direct IPC in protecting myocardium during ischemia and warrant further investigation into whether it can improve clinical outcomes.

References

1. Li SJ, Wu YN, Kang Y, et al. Noninvasive Limb Ischemic Preconditioning Protects Against Myocardial I-R Injury in Rats. *J Surg Res* 2009;x:x.
2. Przyklenk K, Bauer B, Ovize M, et al. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993;87:893. [PubMed: 7680290]
3. Birnbaum Y, Hale SL, Kloner RA. Ischemic preconditioning at a distance: reduction of myocardial infarct size by partial reduction of blood supply combined with rapid stimulation of the gastrocnemius muscle in the rabbit. *Circulation* 1997;96:1641. [PubMed: 9315559]
4. McClanahan TB, Nao BS, Wolke LJ, et al. Brief renal occlusion and reperfusion reduces myocardial infarct size in rabbits. *FASEB J* 1993;7 [abstract].
5. Gho BC, Schoemaker RG, van den Doel MA, et al. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996;94:2193. [PubMed: 8901671]
6. Meldrum DR, Dinarello CA, Shames BD, et al. Ischemic preconditioning decreases postischemic myocardial tumor necrosis factor-alpha production. Potential ultimate effector mechanism of preconditioning. *Circulation* 1998;98:II214. [PubMed: 9852905]
7. Kharbanda RK, Mortensen UM, White PA, et al. Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 2002;106:2881. [PubMed: 12460865]
8. Tapuria N, Kumar Y, Habib MM, et al. Remote ischemic preconditioning: a novel protective method from ischemia reperfusion injury--a review. *J Surg Res* 2008;150:304. [PubMed: 19040966]
9. Ali ZA, Callaghan CJ, Lim E, et al. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation* 2007;116:I98. [PubMed: 17846333]
10. Hausenloy DJ, Mwamure PK, Venugopal V, et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* 2007;370:575. [PubMed: 17707752]
11. Cheung MM, Kharbanda RK, Konstantinov IE, et al. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol* 2006;47:2277. [PubMed: 16750696]
12. Kuzuya T, Hoshida S, Yamashita N, et al. Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. *Circ Res* 1993;72:1293. [PubMed: 8495557]