Remote Ischemic Preconditioning
– Is It Time to Introduce It in Clinical Practice? –

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Ischemic Preconditioning
Ischemic preconditioning is a widely accepted concept, first introduced in 1986 by Murray et al, who showed in an animal experiment that multiple brief periods (5 min) of coronary artery occlusion dramatically reduced infarct size because of the subsequent sustained coronary occlusion. Numerous reports have followed and supported the concept. The mechanism of ischemic preconditioning has been extensively investigated and reviewed, and clinical application of ischemic preconditioning was first reported in 1993 by Yellon et al, who studied patients undergoing coronary artery bypass grafting. After putting the patients on cardiopulmonary bypass, they cross-clamped the aorta twice for 3 min with an interval of 2 min. They then performed distal bypass anastomosis with a technique of intermittent cross-clamping under electrically induced ventricular fibrillation. They showed that the myocardial ATP level after the procedure was twice as high as that of the control group.

Article p 1885

The technique of applying ischemic preconditioning, however, has inherent limitations. It requires interruption of blood flow to the target organ. Ischemic preconditioning, thus, could be only achieved in the operating room, or in a highly manipulated situation, such as coronary angioplasty. In addition, it requires additional time for the preconditioning procedure during surgery or during intervention. In some cases, ischemic preconditioning itself might cause deterioration of organ function or cause complications, such as emboli of atheroma, because of the intermittent aortic clamping or intermittent coronary balloon inflation.

Remote Ischemic Preconditioning: Concept and Clinical Application
In 1993, Przyklenk et al reported that intermittent left circumflex branch occlusion reduced infarct size by left anterior descending artery occlusion. Later, it was found that myocardial protection could be achieved by intermittent interruption of the blood flow to the kidney, small intestine or a limb. These phenomena were called remote ischemic preconditioning, and several mechanisms have been proposed. One is that some type of cardioprotective substance(s) is released from the remote organ. Major candidates are adenosine and bradykinin. The other theory is that generalized catecholamine or sympathetic nerve stimulation induced by remote organ ischemia induces cardioprotection. The exact mechanism, however, is yet to be determined. Whatever the mechanism, the idea of obtaining good myocardial protection with limb ischemia is highly intriguing to the clinician, because nothing special is required, other than a blood pressure cuff, to attain remote ischemic preconditioning. The technique has been used in pediatric cardiac surgery, and coronary artery bypass grafting.

In this issue of the Journal, Wu et al report the beneficial effect of ischemic preconditioning in patients who underwent mitral valve replacement. Despite the small number of patients, the authors demonstrated that troponin-I was significantly reduced in patients who had undergone remote ischemic preconditioning. The method of preconditioning used was similar to other previous reports; that is, simple, repeated lower limb ischemia with manchette. The report adds another successful clinical series of remote ischemic preconditioning, this time in patients undergoing mitral valve replacement with controlled myocardial ischemia using cold-blood cardioplegia.

Rahman et al have reported, however, a conflicting result in a larger series (162 patients randomly assigned) of coronary artery bypass grafting with a single center, prospective, randomized, placebo-controlled trial. With that sophisticated protocol, the authors could not show a significant difference in the primary endpoint: 48-h area-under-the-curve troponin T release. Their insignificant results raise some doubt, because the number of patient was reasonably large and the method employed was sound. Before applying the technique of remote ischemic preconditioning in various patients requiring myocardial protection, further study is warranted to clear the concern. The following unanswered questions and issues need to be addressed.

1. What is the exact mechanism of remote ischemic preconditioning?
Elucidation of the exact mechanism is important for defining the indication, limitations, and technique of remote ischemic preconditioning. By elucidating the mechanism, we may be able to demonstrate some indicator or markers for remote ischemic preconditioning. Otherwise, we will have to repeat a try-and-see-what-happens type of study. If we could find an index specifically related to preconditioning, we may be able to judge whether the preconditioning stimulus or technique is adequate or sufficient.
2. What are the limitations in the organs to be protected with remote ischemic preconditioning?

So far, remote ischemic preconditioning has been shown to be effective in protecting the heart in numerous studies. Clinical information regarding the effect on other organs, such as brain, spinal cord, kidney, or lung, is limited. It is not known whether the stimulus of preconditioning sufficient for the heart is similarly applicable for other organs. Further study is warranted to elucidate when, how, and to what extent ischemic preconditioning should be performed.

3. Is there any benefit in remote ischemic preconditioning to improve hard endpoints such as survival or major cardiovascular event?

In animal experiments, many reports have shown the effect of reducing the extent of myocardial infarction with remote ischemic preconditioning. In clinical studies, however, the benefit of preconditioning is limited to surrogate-type variables such as cardiac enzyme release or dosage of catecholamine immediately after the surgery. To show beneficial effect on hard endpoints such as survival or the incidence of peri-operative myocardial infarction, a large-scale multicenter study is needed. Because of the nature of remote ischemic preconditioning, unfortunately funding support from a pharmaceutical or medical device corporation is unlikely to occur. However, further study is warranted to elucidate the mechanism and effectiveness of remote ischemic preconditioning. If firm evidence could be obtained showing effectiveness of this non-invasive approach, it would help many sick patients suffering from cardiovascular diseases.

References