LETTERS TO THE EDITOR

Regarding "Remote and local ischemic preconditioning equivalently protects rat skeletal muscle mitochondrial function during experimental aortic cross-clamping"

Mansour et al[1] showed that local and remote ischemic preconditioning (LIPC and RIPC) protect skeletal muscle against ischemia reperfusion-induced mitochondrial dysfunction during aortic cross-clamping. Based on these results, the authors advocate a broader use of RIPC in the setting of vascular surgery. Recently, we performed a systematic review and meta-analysis of animal studies investigating the effects of ischemic preconditioning on ischemia-reperfusion injury (IRI) of the kidney.[2] Our analysis showed that LIPC and RIPC are equally effective in the protection against renal IRI and therefore support the conclusion by Mansour et al[1] that LIPC and RIPC equivalently protects against skeletal muscle IRI.

To date, no studies (animal or human) have investigated the effect of aging, medication, and comorbidities such as diabetes, hypertension, or obesity on RIPC in skeletal muscle or renal IRI. For the heart, it has been shown that aging, medication, and comorbidities influence ischemic preconditioning efficacy.[3] In the study by Mansour et al,[1] and also in the majority of other animal studies investigating the effects of ischemic preconditioning, healthy young adult animals have been used. Therefore, the question arises whether the efficacy of RIPC holds for patients with cardiovascular (co)-morbidity. In our view, testing of suboptimal RIPC protocols in large clinical trials could unnecessarily delay implementation into routine clinical practice, due to marginal or negative results.

Interestingly, our meta-analysis also revealed that the "late window of protection" (RIPC >24 hours before index ischemia) was more effective as compared to the "early window of protection" (RIPC ≤24 hours). Therefore, activation of both (early and late) windows of protection by RIPC might also result in improved protection against IRI of human skeletal muscle and other target organs. Because patients undergoing major vascular surgery are exposed to a significant risk of myocardial and renal IRI, we believe that the RIPC protocol should be optimized for different target organs in vascular patients. Almost all clinical trials currently registered at http://Clinicaltrials.gov investigating the effects of RIPC use the early window of protection. To our knowledge, data on the efficacy of combined activation of the early and late window in humans are lacking. Therefore, we believe that further (pre)clinical research is required to optimize the RIPC protocol in cardiovascular patients before a broader implementation in vascular surgery.

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Reply

We appreciate Dr Menting and colleague's comments and agreement on the fact that local and remote ischemic preconditioning (IPC and rIPC) proved equivalent protection on skeletal muscle and kidneys during ischemia-reperfusion. A similar protection was also observed on other target organs.[1-3] Further, unlike postconditioning,[4] IPC and rIPC have not been demonstrated to be deleterious on skeletal muscle.

Nevertheless, whether efficacy of IPC and rIPC holds true in vascular patients characterized by comorbidities remains a significant issue because conditioning-related cardioprotective properties appeared reduced in presence of diabetes, hypercholesterolemia, or older age. Additionally, specific organ sensitivity to ischemia-reperfusion, oxidative stress, and inflammation might also be key limiting factors of IPC and rIPC protective effects. Thus, a protocol algorithm might well protect one organ and not the others.

Should we therefore wait until all light to be made on the mechanisms involved in IPC and rIPC beneficial effects and on eventual ischemic preconditioning drawbacks? As suggested by Menting et al, a way to overcome such potential limitations might be combination use of both early and late windows of protection. Combined ischemic conditioning and pharmacologic approaches might also be useful to optimize conditioning protocols.

In the clinical setting, Ali et al[5] proved in a randomized controlled trial that rIPC reduced myocardial and renal injury after abdominal aortic cross-clamping for elective abdominal aortic aneurysm repair. Despite comorbidities, preconditioned patients presented with better outcomes than not conditioned patients.

Acknowledging that experimental data are still needed and that, based on current evidence from small pilot trials, there are too few data to be able to say whether IPC has consistent beneficial effects,[6] we nevertheless believe that implementation of personalized IPC protocols should not be delayed into clinical practice. Large scale controlled studies should be performed to determine whether IPC will protect patients during their hospital stay, therefore improving their surgical overall outcomes.

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