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EDITORIAL

Remote Ischaemic Preconditioning in Vascular Surgery: Is it Worth the Effort?

Kepler et al. reported the results of a randomised, sham controlled, double blind, single centre trial in which 90 patients who underwent vascular surgery were included in a group that received remote ischaemic preconditioning (RIPC) or into a sham group.[1] In the RIPC group, four cycles of five minutes of ischaemia and five minutes of reperfusion were administered using a blood pressure cuff placed on one arm, before open abdominal aortic aneurysm repair, surgical lower limb revascularisation surgery, or carotid endarterectomy. As compared with the sham group, RIPC had no effect on primary outcomes, defined as augmentation index and aortic pulse wave velocity, both measured pre-operatively and 20–28 h after surgery. These results are of importance regarding the controversy surrounding the efficacy of RIPC in vascular surgery.

The results of Kepler et al. focusing on the effect of RIPC on arterial stiffness are very interesting.[1] It is based on an "all comers" approach leading to the randomisation of a relatively large population over a short period of time. This "all comers" design may have facilitated recruitment of a larger cohort than would have been possible if it focused on one type of procedure. However, the heterogeneity of the population probably introduced bias, as patients with aneurysm disease, and also patients with chronic arterial occlusive disease, were included. Four other clinical trials have also used this "all comers" approach to investigate RIPC in vascular surgery.[2–5] None of these studies found surrogate evidence for organ protection and influence of RIPC on clinical outcomes. It is therefore reasonable to speculate that RIPC would offer no additional protection to vascular patients because of advanced systemic atherosclerosis and the possibility that occlusive disease may induce preconditioning through limb claudication.

Kepler et al. also discussed the possible effects of confounders that could abrogate the effects of RIPC, such as anaesthesia, diabetes, or the RIPC protocol itself. Indeed, the most widely discussed confounder in human studies believed to lessen the effects of RIPC is propofol. To date, trials assessing the effect of RIPC in vascular surgery have used either propofol anaesthesia,[4–11] or provided no information about the anaesthetic protocol.[2,3,12] However, no clinical trial has been conducted that was specifically designed to investigate the influence of an anaesthetic regimen with propofol on the effectiveness of RIPC. Consequently, the evidence from experimental studies remains the closest estimation and a recent experimental study directly designed to investigate the adverse effects of the anaesthetic regimen on RIPC demonstrated that the use of propofol reserved the protective effect of RIPC, while protective effects were observed in animal groups receiving pentobarbital or sevoflurane/remifentanil for the induction and maintenance of anaesthesia.[13] Diabetes is also an important confounder, and evidence suggests that the benefit of conditioning strategies is abrogated in the diabetic state. Impaired activation of the protective signalling pathway, decreased generation and release of nitric oxide, dysfunction of adenosine triphosphate (ATP) sensitive potassium channels, and elevated oxidative stress due to mitochondrial function are highly integrated in the diabetic state and may account for the lack of benefit of conditioning strategies in diabetes.[14] Another important confounder, whether the RIPC protocol itself is the optimal RIPC modality still remains unclear. To date, no study has addressed the optimal site and duration of the RIPC stimulus, or the optimal number of repetitions. Moreover, the temporal aspect of RIPC effectiveness has not been addressed. It is unclear how effectively RIPC might convey organ protection with increasing time periods between preconditioning and injury, as well as with the strength of injury.

Moreover, the underlying mechanistic pathways underlying RIPC remain to be elucidated. Ischaemic conditioning strategies confer organ protection by inducing a cascade of intracellular kinases, opening of ATP sensitive potassium channels, and maintaining mitochondrial permeability transition pores in a closed state. However, the underlying mode of action of RIPC explaining how protection is conferred to distant organs is still not fully understood but can be considered to be the result of a complex neurohumoral interaction. The protective signal conveyed from the remote organ comprises a blood borne humoral factor that is carried from the remote organ to the distant organs and/or the activation of a neurogenic pathway. The neurogenic pathway requires the release of chemical mediators from the remote organ, which activate the sensory nerve endings to convey signals to the brain. The latter consequently stimulates the efferent nerve, innervating distant organs to induce protection. In support of a humoral pathway, RIPC requires a period of reperfusion of the remote organ or tissue, suggesting that protection requires washout of

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protective factors into the circulation, while RIPC can be abolished by pre-treatment with ganglion blockers, supporting the neurogenic pathway. Finally, a systemic pathway might also be involved, as RIPC has been shown to have a systemic anti-inflammatory influence through suppression of the expression of pro-inflammatory genes in leucocytes and reduced neutrophilic adhesion.[5,15]

Undoubtedly, there is a sense of disappointment that proof of concept has still not been established for RIPC in vascular surgery. However, regarding the high complication rates following major vascular interventions and the impressive magnitude of effect of RIPC in animal studies, RIPC obviously offers tremendous potential, even if clinical translation remains disappointing. Future clinical studies on homogenous cohorts of patients with standardised non-propofol anaesthesia are mandatory. Moreover, subgroups of patients, or subgroups of vascular procedures, may be less likely to benefit from RIPC. Finally, the RIPC protocol itself might be adapted to the main organ to protect, as all organs do probably not need the same number or intensity of ischaemia—reperfusion cycles to be protected. Identifying patients that would benefit from RIPC, as well as the optimal RIPC protocol and the mechanism through which RIPC may exert organ protection, may therefore be the key to confirming that RIPC holds promise in vascular surgery. The editors of *EJVES* are looking forward to the submission of high quality translational research on the potential effects of RIPC in patients with vascular diseases.[16]

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Anne Lejay*
Department of Vascular Surgery and Kidney Transplantation, University Hospital of Strasbourg, France
EA3072 Mitochondria, Oxidative Stress and Muscular Protection, University Hospital of Strasbourg, France
Department of Physiology, University Hospital of Strasbourg, Strasbourg, France

Bernard Geny
EA3072 Mitochondria, Oxidative Stress and Muscular Protection, University Hospital of Strasbourg, France
Department of Physiology, University Hospital of Strasbourg, Strasbourg, France

Philippe Kolh
Department of Biomedical and Preclinical Sciences, University Hospital of Liège, Liège, Belgium

Nabil Chakfe
Department of Vascular Surgery and Kidney Transplantation, University Hospital of Strasbourg, France
EA3072 Mitochondria, Oxidative Stress and Muscular Protection, University Hospital of Strasbourg, France

*Corresponding author. Department of Vascular Surgery and Kidney Transplantation, Nouvel Hôpital Civil, 1 Place de l'hôpital, 67091 Strasbourg, France.
Email-address: anne.lejay@chru-strasbourg.fr (Anne Lejay)