INVITED COMMENTARY

Remote Ischaemic Preconditioning in Vascular Surgery: Relevant Perspective or a Holy Grail?

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In their study, Kuusik *et al*. have reported the results of a randomised, double blind, single centre trial in which 111 patients who underwent digital subtraction angiography were included either in a group that received remote ischaemic preconditioning (RIPC) or in a sham group, to evaluate the effects of RIPC on arterial stiffness parameters.[1] The authors showed that RIPC did not modify the carotid-femoral pulse wave velocity (PWV), considered to be the gold standard parameter of arterial stiffness, but decreased surrogate markers of arterial stiffness, such as the augmentation index (Aix), and augmentation index corrected to heart rate (Aix@75) in cases where stenting was performed.[1] These results are of importance regarding the controversy surrounding the efficacy of RIPC in vascular surgery and contribute to opening future research; however, many confounding factors might have biased the results, such as degree of ischaemia, site of atherosclerotic lesions, type and location of stents, as well as patient comorbidities.

Stenting represents a major confounding factor because patients were randomised before angiography and not before stenting. Because it has been shown that peripheral endovascular revascularisation has a beneficial impact on pulse wave function,[2] the beneficial effects on Aix and Aix@75 observed by Kuusik *et al*. might be attributed to stent placement rather than to RIPC itself.

Diabetes may also have influenced the results. First, the authors did not quantify the extent of peripheral arterial calcifications. It is well known that there is a strong association between arterial stiffness, pressure pulsatility, wave reflection, and the presence and extent of arterial calcification.[3] Accordingly, distal arterial properties may have influenced haemodynamics and global stiffness measures, because wave reflection in the arterial system arises in regions of impedance mismatch, such as narrowing, branch point, or change in wall properties, especially in diabetic patients. Second, diabetes is an established confounding factor in most RIPC studies, often with neutral or mixed results concerning protection.[4] Because diabetes is a significant risk factor that aggravates the course and incidence of peripheral arterial disease, excluding patients with diabetes might not have represented the general population presenting with peripheral arterial disease. However, RIPC protection depends on the presence of intact neural pathways, and the peripheral and autonomic neuropathy related to diabetes might have reduced the possible effects of RIPC. As Kuusik *et al*. did not investigate the presence or stage of neuropathy in their study, it cannot be excluded that diabetes might have biased the results.

In conclusion, there is undoubtedly a sense of disappointment that proof of concept has still not been established for RIPC in vascular surgery. However, regarding the impressive magnitude of effect of RIPC in animal studies, RIPC may offer tremendous potential, even if clinical translation remains disappointing.[4] Larger clinical studies with homogeneous cohorts of patients and an optimal RIPC protocol are therefore needed to answer whether RIPC allows protection in vascular surgery.

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