

# Correspondence

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## Transient Limb Ischemia Induces Remote Ischemic Preconditioning In Vivo

To the Editor:

Kharbanda et al<sup>1</sup> recently published experimental evidence for remote myocardial preconditioning (RMP)<sup>1,2</sup> in swine. In addition, they provided evidence for remote skeletal preconditioning (RSP) in humans by showing protection against endothelial dysfunction produced by sustained ischemia and reperfusion in an arm after brief ischemia in the contralateral arm of healthy subjects.<sup>1</sup> The authors did not determine the mechanisms of RSP and RMP in their study but pointed out the many similarities between classical myocardial preconditioning (CMP) and RMP and equated RMP produced by skeletal muscle ischemia with RSP. However, this appears to be an oversimplification.

Firstly, the type of stimulus required to elicit RMP differs from that of CMP. Thus, three periods of 3-minute coronary artery occlusion (3×3-minute CAO) interspersed by 5 minutes of reperfusion elicits cardioprotection in rats that is superior to that of a single 15-minute CAO.<sup>3</sup> In contrast, whereas a single 15-minute mesenteric artery occlusion affords similar protection as a 15-minute CAO, a 3×3-minute mesenteric artery occlusion protocol fails to elicit RMP.<sup>3</sup> Secondly, while CMP does not involve an autonomic neurogenic pathway,<sup>2</sup> we have shown that adenosine released in the small intestine during mesenteric artery occlusion stimulates afferent nerves within the mesenteric bed on reperfusion, which via a neurogenic pathway leads to activation of myocardial adenosine receptors and cardioprotection.<sup>3</sup> Thirdly, while RMP by mesenteric and renal ischemia clearly involves an autonomic neurogenic pathway (as the ganglion blocker hexamethonium abolishes cardioprotection),<sup>2,3</sup> RSP and RMP by skeletal muscle ischemia was not amenable to ganglion blockade, indicating that either a circulating substance or that a nonautonomic neurogenic pathway must be involved.<sup>4,5</sup>

Involvement of a neurogenic pathway may be of importance for mediators such as adenosine that are currently under clinical investigation for their ischemia-reperfusion damage-limiting effects. The mechanism by which these mediators exert their actions has been questioned, as circulating substances may not reach the jeopardized myocardium when a coronary artery is occluded. The neurogenic pathway offers an alternative explanation for the protection by these mediators, as they can reach remote tissues, where they activate a neurogenic pathway that leads to cardioprotection.<sup>3</sup> However, as stated above, the pathway likely depends on the type and locus of the ischemic stimulus. In view of these considerations, it is unfortunate that Kharbanda et al<sup>1</sup> did not study the mechanisms of RSP and RMP, although we can understand that the authors may have some reservations in using hexamethonium in clinical studies.

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## Response

The points made by Liem et al illustrate the complexity of the phenomenon of remote preconditioning and highlight the potential differences between species and models used to study the process. While pointing out similarities between remote and classical myocardial preconditioning, we do not equate the two. Indeed, we would caution against any assumption of mechanistic concordance in terms of either end-organ or interspecies responses. For example, although short intermittent periods of mesenteric ischemia fail to induce remote ischemic preconditioning (rIPC) in rats, our data show that short intermittent periods of skeletal muscle ischemia do induce rIPC in swine.<sup>1</sup> Furthermore, our human study demonstrates that this stimulus also induces remote endothelial preconditioning—we did not measure markers of skeletal muscle injury. This stimulus has also been shown by others to reduce systemic inflammation and lung injury in a swine model of hindlimb ischemia-reperfusion.<sup>2</sup>

As we discussed in our paper, neurogenic mechanisms may be involved in remote preconditioning.<sup>3</sup> Mesenteric and renal ischemia appear to induce rIPC through an autonomic pathway in rats.<sup>4</sup> Liem et al question whether a neuronal mechanism is also involved when the stimulus for remote preconditioning is limb ischemia. They correctly point out that in the rat, skeletal muscle ischemia leads to skeletal muscle and myocardial preconditioning in the presence of hexamethonium-induced ganglion blockade. However, in the same model, rIPC induced by limb ischemia is partially abolished by reserpine, suggesting a role for adrenergic nerves.<sup>5</sup>

A detailed investigation of the mechanisms involved in our models is important and is underway. Understanding the nature of the stimuli and the mechanisms through which rIPC is mediated may allow novel strategies for tissue protection in humans. We would reemphasize that these may differ between species and experimental models.

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