Preservation of peripheral vasodilation as a surrogate of cardioprotection? The mechanistic role of ATP-dependent potassium channels and the mitochondrial permeability transition pore

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This editorial refers to ‘Postconditioning protects against human endothelial ischaemia–reperfusion injury via subtype-specific \( K_{\text{ATP}} \) channel activation and is mimicked by inhibition of the mitochondrial permeability transition pore’†, by M.I. Okorie et al., on page 1266

Myocardial infarction is almost invariably a regional event which results from occlusion of a coronary artery secondary to atherosclerotic plaque rupture. In contrast to localized infarction, atherosclerosis is a generalized process which involves the entire vascular tree, albeit to a different extent and with different manifestations. It therefore seems logical to analyse phenomena in the peripheral vasculature, which is much easier and more feasible for non-invasive access than the coronary circulation or the myocardium, with the aim of predicting the risk of a coronary event. In fact, patients with peripheral arterial disease carry a higher risk of coronary artery disease.1 Also, vascular dysfunction in specific vascular territories is associated with increased risk of coronary artery disease; erectile dysfunction is an example.2

The study by Okorie et al.3 now takes the analogy between phenomena in the peripheral vasculature and myocardial ischaemia–reperfusion one step further, i.e. to the mechanistic level. In the forearm circulation of healthy human volunteers, conduit and resistance vessel function were measured in response to reactive hyperaemia and intra-arterial acetylcholine. The study confirms impairment of vasomotor function, notably endothelium-mediated dilation, by ischaemia–reperfusion. The observed protection from such vascular dysfunction by an ischaemic postconditioning protocol is novel, thus supporting the analogy between peripheral vascular function and ischaemic–reperfused myocardium where reduction of infarct size by ischaemic postconditioning was originally reported.4 The ATP-dependent potassium (\( K_{\text{ATP}} \)) channel antagonist glibenclamide abrogated the protection, and the mitochondrial permeability transition pore (MPTP) inhibitor cyclosporine A minimized the protection, suggesting a causal involvement of \( K_{\text{ATP}} \) channels and MPTPs, again in analogy to protection of ischaemic–reperfused myocardium.4–6

Such an analogy in terms of a mechanistic involvement of \( K_{\text{ATP}} \) channels and MPTPs in protection by postconditioning between peripheral vasomotion and the ischaemic–reperfused myocardium is indeed striking, yet it involves multiple transfer steps, each of which deserves a critical consideration (Figure 1). (i) At the target organ level: brachial and coronary arteries share endothelial dysfunction as an early manifestation of atherosclerosis;7,8 however, only in some arteries, including the coronary, and usually not the brachial arteries, atherosclerosis progresses into focal luminal obstruction and/or plaque rupture. (ii) At the cellular level: brachial artery vasomotion is largely determined by only two cellular compartments, i.e. the endothelial and vascular smooth muscle cells, along with an inflammatory component even at early stages of atherosclerosis. In contrast, in the setting of myocardial ischaemia–reperfusion, there are—in addition to endothelial and vascular smooth muscle cells—interstitial/inflammatory cells and platelets at the site of atherosclerotic plaque rupture and thrombosis which release a number of potent mediators for both vasomotion and cardioprotection. Importantly, cardiomyocytes are the target of ischaemia–reperfusion, again in interaction with endothelial and interstitial/inflammatory cells, and they are exposed to all these mediators.5 (iii) At the subcellular level: the study by Okorie et al.3 addresses \( K_{\text{ATP}} \) channels and MPTPs in the observed protection of vasomotor function. MPTPs are still elusive, on both the structural and the molecular level, but are fairly well characterized on the functional level,6 and as such they are probably germane to mitochondrial
all cell types which have mitochondria. $K_{\text{ATP}}$ channels are expressed and functional in the sarcolemma and in the inner mitochondrial membrane of cardiomyocytes,\textsuperscript{9,10} in vascular smooth muscle cells,\textsuperscript{11} and possibly also in endothelial cells.\textsuperscript{12} Mitochondrial $K_{\text{ATP}}$ channels are still not fully identified, on both the structural and the molecular level, but again are fairly well characterized on the functional level.\textsuperscript{9} A causal role for mitochondrial $K_{\text{ATP}}$ channels in cardioprotection\textsuperscript{5} and intense interaction with cardioprotective signalling in cardiomyocytes\textsuperscript{13} are well established.

The study by Okorie \textit{et al.}\textsuperscript{3} addresses $K_{\text{ATP}}$ channels and MPTPs using an antagonist approach. However, glibenclamide is not selective for either sarcolemmal or mitochondrial $K_{\text{ATP}}$ channels, and we do not know whether glibenclamide antagonizes the protective effects of postconditioning on brachial artery vasomotion through an action on endothelial or vascular smooth muscle cells, or both. Likewise, cyclosporine A could antagonize MPTP channels in endothelial and/or vascular smooth muscle cells. Moreover, cyclosporine A not only inhibits MPTP opening, but also inhibits the phosphatase calcineurin, and it increases calcium influx into vascular smooth muscle cells\textsuperscript{14} and could thus interfere with endothelial function and/or vascular smooth muscle function through effects other than inhibition of MPTP opening.\textsuperscript{15} Such uncertainty on the cellular (endothelial vs. vascular smooth muscle cells) and subcellular (sarcolemmal vs. mitochondrial $K_{\text{ATP}}$ channels, MPTP vs. calcineurin) targets of the tool drugs in this study obviously challenges all potential extrapolation to ischaemic–reperfused cardiomyocytes.

In conclusion, a closer look at the mechanistic background of the study by Okorie \textit{et al.}\textsuperscript{3} opens up a Pandora’s box of fundamental questions. Yet the idea to extrapolate from peripheral vasodilation to cardioprotection remains attractive, and the study clearly supports such an approach on the phenomenological level by demonstrating preservation of peripheral vasodilation by ischaemic postconditioning. Whether or not such extrapolation from preservation of peripheral vasodilation to cardioprotection or its potential failure with co-morbidities and/or co-medications\textsuperscript{4} also holds on the mechanistic level remains to be seen.

\textbf{Conflict of interest:} none declared.

\textbf{References}
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