Is 15-min Ischemia too Lethal to Be an Ischemic Preconditioning Stimulus?

To the Editor:

We would like to take this opportunity to respond to comments by Hausenloy et al1 regarding our recent study.2 In our study, we demonstrated that PTEN activity is modulated during cardiac ischemia/reperfusion, suggesting critical involvement of PTEN in both the induction and decay of ischemic preconditioning (IPC).2 Hausenloy et al appear more intent on promulgating a "standard accepted IPC protocol" than on understanding mechanisms of protection against ischemia/reperfusion injury. Without providing any supporting data, they characterize 15 minutes of ischemia as a "prolonged episode of lethal ischemia."1 In contrast, Kloner and Jennings wrote in the first sentence of their highly cited review of IPC that "total proximal coronary artery occlusions of up to 15 minutes result in reversible injury, meaning that the myocytes survive this insult."3

Our data2 show that 15 minutes of ischemia followed by 5 minutes of reperfusion induces higher levels of phosphorylated (activated) Akt in the heart, as compared with hearts subjected to 5 or 10 minutes of ischemia followed by 5 minutes of reperfusion. This ischemic stimulus protects the heart against subsequent prolonged ischemia (30 minutes) and reperfusion (thus fulfilling the criteria for IPC), as demonstrated by significantly improved recovery of left ventricular developed pressure, reduced caspase-3 activation, and reduced PARP cleavage. Finally, we demonstrated that reactive oxygen species (ROS), which are generated after hearts are subjected to 15 minutes of ischemia and then reperfused, oxidize and inactivate PTEN, thus leading to increased Akt activity. Our data provide for the first time a direct molecular mechanism for transduction of the protective IPC signal that is based on the inherent sensitivity of this phosphatase to oxidative inactivation because of the presence of a cysteine residue in the active site.4 Because ROS are produced in every IPC model and PTEN is expressed in every tissue, this pathway may underlie IPC in all organs.

Practicing scientists appreciate that every experimental model has its strengths and limitations. We have presented a paradigm-shifting hypothesis that can now be tested in other experimental models of ischemia/reperfusion injury. Whereas we recognize the potential value of comments in the editorial pages, we hope that our novel findings will stimulate research at the laboratory bench, which will advance the field beyond what is "standard" and "accepted".

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