Is This Truly Ischemic Preconditioning?

To the Editor:

In a recent article, Cai and Semenza\(^1\) claim to have demonstrated a role for modulation of PTEN activity in the setting of ischemic preconditioning (IPC), using an isolated perfused rat heart. We believe the findings of this study are potentially of great significance as this study is the first to implicate PTEN in myocardial ischemia–reperfusion injury. However, we question the model of IPC used in this study. Specifically we question whether 15 minutes of myocardial ischemia followed by 30 minutes of myocardial reperfusion actually qualifies as an IPC protocol in the isolated perfused rat heart. Ischemic preconditioning as initially described by Murry and colleagues\(^2\) comprised 5 minute episodes of myocardial ischemia and reperfusion in the in vivo dog heart. The standard accepted IPC protocol in the isolated perfused rat heart comprises either 1 or 2 cycles of 5 minutes of ischemia followed by either 5 or 10 minutes of reperfusion before a 30-minute sustained lethal episode of ischemia and 120 minutes of reperfusion. Importantly, the preconditioning ischemia is short-lived and non-lethal.

In their study, Cai and Semenza\(^1\) used an IPC protocol comprising 15 minutes of myocardial ischemia, which in this model may be expected to induce lethal myocardial ischemia or severe reperfusion-induced arrhythmias. The authors remark that in most species a preconditioning ischemic episode of 15 minutes followed by reperfusion is sufficient for protection, but we are unaware of any studies using such an IPC protocol. In addition, they cite articles by Barbosa and colleagues\(^3\) and Schulz and colleagues\(^4\) as justification for using such a long preconditioning ischemic stimulus, but even these studies did not use more than 10 minutes of preconditioning ischemia.

We believe that the distinction between a nonlethal and lethal preconditioning ischemic episode is crucial as events occurring doing a standard IPC protocol would be expected to differ from that induced by a prolonged episode of lethal ischemia as used in the study by Cai and Semenza.\(^1\) This is particularly pertinent when investigating PTEN, whose activity is determined by phosphorylation (an ATP-dependent process) and oxidation, when the modulation in activity would be expected to vary with the length of the preconditioning ischemic episode.

Because of the relatively prolonged preconditioning ischemic stimulus used in the study by Cai and Semenza,\(^1\) we have to question whether the phenomenon of IPC was actually investigated. It would be important to establish whether a standard IPC protocol comprising 5 minutes of myocardial ischemia and reperfusion for the isolated perfused rat heart would have had the same effects on PTEN activity observed with the prolonged 15 minutes of ischemia used in this study.

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