Ischaemic preconditioning and mitochondrial permeability transition: a long-lasting relationship

EXPERT’S PERSPECTIVE

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This editorial refers to an article by D.J. Hausenloy et al.25 published in Cardiovascular Research in 2002. It is accompanied by a retrospective editorial by the authors of that original article, D.J. Hausenloy et al., pp. 160–164, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

Since its first description 25 years ago,1 ischaemic preconditioning has become one of the most studied protective interventions in the cardiovascular field, in part due to its universality (it is effective in all animal species tested, including humans, and in different organs) and reproducibility (it has only a weak dependence on the ischaemic protocol applied before sustained ischaemia or on the duration and severity of the ischaemic insult). The identification of the involved signalling pathways and end-effectors was expected to have important therapeutic implications. However, despite the enormous amount of experimental data, our understanding of the cellular mechanisms responsible for preconditioning protection remains incomplete and at some points controversial. The reason for this failure is demonstrated by the large number of publications describing different molecular pathways involved in protection, some of them acting in parallel or being redundant or dispensable, whereas others appear to be additive or to operate in series, making it very difficult to integrate them into a comprehensive survival pathway. No less important was the lack of understanding of the ultimate mechanisms (end-effectors) by which these signalling pathways reduce cell death. End-effectors of preconditioning have to be molecules downstream the signalling pathway directly involved in cell death. They have the greatest therapeutic interest for obvious reasons; however, their identification has proved not to be a trivial task, and multiple candidates have been proposed.

Often, the triggers, mediators, and end-effectors of preconditioning protection have been difficult to differentiate. An example of this confusion is the mitochondrial K$_{ATP}$ channels. During the past decade, the idea that mitochondrial K$_{ATP}$ channels could be important players in preconditioning protection emerged as a dominant concept. They were proposed to trigger the ischaemic preconditioning cascade,2 to participate in the ROS-dependent signalling pathways,3,4 and also to act as the end-effectors of cardioprotection,5 presumably by improving energy transfer efficiency or by attenuating mitochondrial Ca$^{2+}$ overload during reperfusion.6 However, experimental evidence could not definitely prove that mitochondrial K$_{ATP}$ channels may be the end-effectors of cardioprotection, their molecular identity remains largely unknown, and even their existence is debated.5

Cell death induced by an ischaemic episode occurs mainly in the first minutes of reperfusion. Excessive contractile activation (hypercontracture) and proteolytic activation secondary to elevated cytosolic Ca$^{2+}$ concentration have been shown to play a causative role in necrotic cell death.10–12 and contractile inhibition has been proposed to be an end-effector of ischaemic preconditioning.13,14 Ischaemic preconditioning preserves cGMP-PKG signalling, which, in turn, improves Ca$^{2+}$ handling and cell survival by targeting intracellular molecules known to attenuate sarcoplasmic reticulum-driven Ca$^{2+}$ oscillations and hypercontracture15–17 and to reduce the sensitivity of myofilaments to Ca$^{2+}$.18 Proteolysis mediated by Ca$^{2+}$-dependent calpain activation has also been proposed to be reduced by previous ischaemic preconditioning,19 which results in attenuated sarcosomal Na$^{+}$ pump dysfunction, reduced Ca$^{2+}$ overload secondary to reverse Na$^{+}$-Ca$^{2+}$ exchange, preserved sarcosomal integrity, and less hypercontracture.20 Other potential end-effectors of ischaemic preconditioning are gap junction channels—involved in the propagation of cell death during reperfusion21 membrane hemichannels—whose uncontrolled opening may trigger massive cell swelling and death,22 and connexin43—recently described to participate in cardioprotection by mechanisms not related to intercellular communication but to its mitochondrial localization.23,24

In 2002, Hausenloy et al.25 published the first experimental evidence of the involvement of mitochondrial permeability transition in the protection afforded by ischaemic and pharmacological preconditioning. In that study, isolated perfused rat hearts were subjected to 35 min regional ischaemia and 120 min reperfusion with or without...
questions remain unsolved. Whether or not mitochondrial permeability transition is a multiprotein channel or merely reflects an increased permeability stage of otherwise damaged mitochondria has not yet been clarified, nor has the molecular mechanism responsible for its causative role in acute sarcolemmal rupture been defined. Also, its potential modulation by other factors, like age, diabetes, and other comorbidities that clearly reduce the effectiveness of preconditioning cardioprotection, is far from well characterized and is the object of much scientific interest. The paper from Hausenloy et al.25 was not free of limitations. Many would have said that the most important aspect was that the authors relied exclusively on pharmacological interventions and did not take advantage of genetically modified animals. However, it was an important paper because it opened a new area of research and helped to set up a new paradigm in cardiovascular science.

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References


