Ischemic preconditioning is a natural mechanism by which brief periods of ischemia–reperfusion initiate a complex cascade of events that culminate in the protection of the heart against a subsequent sustained ischemia, reducing infarct size, postischemic dysfunction, and the incidence of arrhythmias [1]. In essence, endogenous or exogenous triggers released during ischemic or pharmacological preconditioning activate mediators that act on end-effectors, preserving mitochondrial, cytoskeletal, and cell membrane integrity [2]. However, although much effort has been dedicated to the study of preconditioning mechanisms, these have not been clearly elucidated, and in particular the pathways involved in the protection against arrhythmias have not been as thoroughly investigated as those concerning infarct size.

One of the proposed targets of preconditioning protection is gap junctions. These intercellular structures formed by two hemichannels of connexin-43 (Cx43) mediate the exchange of small molecules and ions between two adjacent cells and play an active role in the electrical synchronization of the heart. Phosphorylation of Cx43 regulates gap junction conductance and permeability. In the normoperfused heart, most Cx43 is phosphorylated, allowing cell-to-cell coupling and the propagation of depolarization in the myocardial syncytium. During the course of ischemia, however, decreased ATP levels, increased intracellular Ca\textsuperscript{2+} concentrations, and acidosis determine gap junction closure through Cx43 dephosphorylation and internalization into the cytosol. The proportion of functional gap junctions is thus reduced, inducing cellular uncoupling manifested by enhanced tissue impedance and arrhythmogenesis [3]. Moreover, while cells are still excitable, conductance is not completely blocked, and persistence of cellular communication may allow cell-to-cell propagation of factors triggering rigor contracture [4].

There is increasing evidence indicating that these essential structures for normal cardiac function are preserved by ischemic preconditioning [5], especially since the finding that protection cannot be elicited in heterozygous Cx43-deficient mice expressing a reduced number of functional gap junctions [6]. The role of gap junctions in preconditioning has been mostly studied in the setting of protection against infarction [2,4,5], there being only two reports concerning their role in preconditioning defense against arrhythmia incidence. In a first study, Cinca et al. [7] showed that arrhythmias and the associated alterations in myocardial impedance, characterized by a steep rise in myocardial resistivity and sharp phase angle deviation, were postponed by ischemic preconditioning in open-chest pigs subjected to 4 h of coronary occlusion. These results were in agreement with other reports showing that the delayed electrical uncoupling derived from ischemic preconditioning [8] was related to a marked decrease of dephosphorylation and intracellular redistribution of Cx43 [9]. Further research is presented in this issue of Cardiovascular Research, where Papp et al. [10] demonstrate in open-chest dogs that cellular uncoupling elicited either by 5 min of ischemic preconditioning or infusion of carbenoxolone is linked to cell-to-cell coupling during the ensuing prolonged coronary occlusion, reducing instead of postponing arrhythmia incidence. However, because stronger uncoupling by the addition of carbenoxolone to the ischemic preconditioning stimulus attenuated the antiarrhythmic action, it might be speculated that only a partial gap junction closure is effective in initiating the protective pathway, possibly by establishing a balance between cell-to-cell passage of preconditioning stimuli and restriction of injury signals.
In spite of extensive research, it is yet unclear whether the protective effect of preconditioning implicates gap junction coupling or uncoupling. While gap junction closure prevents the spread of death signals reducing necrosis [11], their opening improves the transmission of the electric impulse decreasing arrhythmias [7,10]. In addition, recent studies postulate that preconditioning protection against infarction might not involve cell-to-cell coupling at all. Effectively, although ischemic preconditioning reduced infarct size in open-chest pigs and rigor contracture in isolated rat hearts, it did not produce beneficial changes in electrical impedance or action potential properties, suggesting that improved cell survival is independent of cellular communication changes [12]. Furthermore, increased ischemic redistribution of Cx43 from their position in gap junctions to other membrane locations in preconditioned rat myocardium would indicate that the protective effect takes place by an as yet undefined gap junction-unrelated pathway [13]. In contrast to the questioned role of gap junctions in preconditioning against infarction, the study of Papp et al. [10] confirms their importance in preconditioning against arrhythmias, since Cx43 dephosphorylation and impedance were reduced and gap junction permeability was increased during the sustained ischemia. This paper also shows for the first time the participation of gap junctions as triggers of the antiarrhythmic effect of preconditioning.

Although the mechanism by which preconditioning preserves cellular coupling and normal electrical conduction is still unknown, it seems to involve mitochondrial KATP channels, as shown by abrogation of the preconditioning-induced delay in uncoupling and shortening of action potential duration with the nonselective KATP inhibitor glibenclamide, and the activation of protection with the KATP channel opener cromakalin [8]. Similarly, glibenclamide or the mitochondrial-selective KATP channel inhibitor 5-hydroxydecanoate, administered prior and during the preconditioning stimulus, blocked the reduction of Cx43 translocation and dephosphorylation induced by preconditioning, whereas diazoxide, a mitochondrial KATP channel opener given instead of the mitochondrial KATP channel opener 5-hydroxydecanoate, blocked the reduction of Cx43 translocation and dephosphorylation and reduced gap junction permeability was increased during the sustained ischemia. This paper also shows for the first time the participation of gap junctions as triggers of the antiarrhythmic effect of preconditioning. Although the mechanism by which preconditioning preserves cellular coupling and normal electrical conduction is still unknown, it seems to involve mitochondrial KATP channels, as shown by abrogation of the preconditioning-induced delay in uncoupling and shortening of action potential duration. This is in accordance with the finding of Schulz et al. [11] that a delayed opening of KATP channels is critical for the protective effect of ischemic preconditioning.

In conclusion, the present data indicate the indisputable participation of gap junctions in the antiarrhythmic protection of preconditioning. However, there are still many questions that need to be answered to obtain a clearer picture of the involved underlying pathways in order to develop therapeutic strategies that might reproduce this important natural mechanism of defense.

References