Bringing preconditioning and postconditioning into focus

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After many years of debate during which the preponderance of opinion was skeptical about the experimental and clinical existence of reperfusion injury (with attitudes ranging between polite condescendence and overt denial), it can be said that the controversy has been now largely resolved, and that the death of cardiomyocytes during reperfusion is now generally admitted as a fact. Perhaps this agreement is still more firm in the experimental literature than in clinical cardiology. The discovery of the phenomenon of postconditioning [1] has undoubtedly contributed to this change of opinion. The first reports of postconditioning the human heart by Laskey et al. and Ovize et al. certainly support the concept of reperfusion injury as a clinical entity that can be measured even in a small group of patients [2,3]. The report by Zhao et al. [1] has aroused a renewed interest in the mechanisms of cell death during ischemia–reperfusion, and of endogenous protection against it [4]. Postconditioning is as powerful as preconditioning and has the potential of being clinically applicable in the most common situation of unexpected coronary occlusion and acute myocardial infarction [3]. Yet, the mechanisms by which postconditioning limits reperfusion-induced cell death and the relationship between the mechanisms in pre- and postconditioning are far from being completely understood.

The present Spotlight Issue presents a series of review articles with the aim of providing an up-to-date overview of the state of the art in the rapidly moving field of research on endogenous protection against myocardial cell death secondary to ischemia–reperfusion.

The reason for the resurrection of this field of research is that it is necessary to gain an adequate understanding of the mechanisms of reperfusion injury. Originally considered the major and virtually unique effectors of reperfusion injury, free radicals and the oxidative stress imposed by them were then progressively relegated to marginal roles after (1) experimental studies failed to draw consensus on the efficacy of free radical scavengers, (2) failure to identify the molecular targets of free radicals responsible for cell death during the initial minutes of reperfusion, and (3) the emergence of a newer paradigm of lethal reperfusion injury that gave a central position to alterations of Ca2+ homeostasis and excessive contractile activation [5].

The review article by Zweier and Talukder in this issue [6] analyzes how different factors have reshaped and redefined the importance of free radicals and oxidative stress in reperfusion. Prominent among these factors are the role of nitrosative stress and its interplay with oxidative stress, the role of free radicals in protective signaling cascades (as opposed to their previously held deleterious effects), and, probably more importantly, the identification of a molecular target for oxidative stress that can link free radicals with cell death, in particular via the mitochondrial permeability transition pore (MPTP). Since the original description of the potential role of this pore in lethal reperfusion injury by the group of Halestrap et al. [7], evidence on the importance of this role has rapidly accumulated, as reviewed in this issue by Di Lisa and Bernardi [8].

Our understanding of the mechanisms of reperfusion-induced cell death relies to a large extent on the analysis of the effects of interventions applied at the time of reperfusion, among which postconditioning occupies a very prominent role due to its simplicity, effectiveness, and applicability. The article by Zhao and Vinten-Johansen in this issue [9] reviews the mechanisms by which postconditioning reduces reperfusion injury, with focus on those mechanisms requiring activation of endogenous protective
signaling cascades. An attempt is made to provide a panoramic view of both intracellular and extracellular responses in postconditioning cardioprotection. A striking feature of these endogenous protective mechanisms, reviewed in this issue by Gross and Gross [10], is that many of the ligand triggers and intracellular pathways involved are shared by pre-and postconditioning. This seems to be particularly true in the case of PKC epsilon, as reviewed by Inagaki et al. [11], but is also true for NO. In this issue Cohen et al. [12] analyze the role of NO as a mediator of endogenous cardioprotection, as well as the therapeutic value of pharmacological NO stimulation in the prevention of lethal reperfusion injury. PKC and PKG are included in the group of kinases known as survival kinases, which also includes members of the MAPK family (ERK1/2) and the PI3K-Akt and JAK-STAT pathways, whose role in pre- and postconditioning is reviewed by Hausenloy and Yellon [13]. Since the discovery of “late preconditioning”, it has also been revealed that reprogramming of cardiac genes can provide substantial endogenous protection of the heart against ischemia/reperfusion injury. Of the many genes triggered by an ischemic preconditioning protocol, only a few have been fully analyzed with respect to a role in sustained protection, as described by Das and Maulik [14].

The wealth of information on triggers and mediators of pre- and postconditioning is in contrast to the paucity of data on the end-effectors of protection. Evidence supporting the hypothesis that protection is mediated by an inhibitory effect on MPTP is reviewed by Gateau-Roesch et al. [15], while Garcia-Dorado et al. [16] and Piper et al. [17] analyze this evidence in the context of other proposed end-effectors leading to improved Ca\(^{2+}\) handling, or attenuated calpain activation and cytoskeletal fragility leading to reduced reperfusion-induced hypercontracture. The issue includes also a review by Diaz and Wilson [18] of the once denied and now widely admitted value of isolated cardiomyocyte models in the study of endogenous cardioprotection. There are also contemporary discussions of the potential clinical value of pre- and postconditioning in myocardial protection, first from the cardiologist’s perspective in the setting of acute coronary syndrome by Kloner and Rezkalla [19], and second from the cardiac surgeon’s perspective by Ramzy et al. [20].

Finally, but most importantly, the issue includes a series of original articles describing some of the most recent advances in the field of cardioprotection. Three papers provide new information on the role of PKC, including the interaction of PKC with the adenosine A2b receptor in postconditioning [21] or the important role of PKC delta, in particular in the aged heart [22] and its relation with GSK-3\(\beta\), a key molecule in endogenous protection signaling [23]. Five papers deal with the end-effector mechanisms of protection, and two of them stress the importance of phospholamban phosphorylation in this process. The phosphorylation of Ser\(^{16}\) and Thr\(^{17}\) sites of phospholamban is shown to improve cytosolic Ca\(^{2+}\) handling in an elegant study using genetically manipulated animals in which these sites have been mutated [24]. In the other study, increased Ca\(^{2+}\) uptake by the SR during reperfusion secondary to phospholamban phosphorylation is identified as an end-effector mechanism of protection mediated by pro-survival kinases involving PI 3-kinase and eNOS in response to insulin administration [25]. Two studies identify attenuated cytoskeletal degradation as end-effectors of protection. In one of these studies, relocation of fodrin to the sarcolemma is investigated [26], and in the other, attenuated calpain-dependent degradation of alpha-fodrin and ankyrin is found to result in attenuated detachment of Na\(^{+}/K\)^{-} ATPase from the sarcolemma and preserved Na\(^{+}\) pump activity during reperfusion in preconditioned hearts [27]. Finally, a paper describes reduced gap junction permeability and attenuated cell-to-cell propagation of necrosis as an end-effector mechanism of protection induced by MitoK\(_{\text{ATP}}\) channel activation [28], a protective pathway that has been recently described to involve the mitochondrial localization of Cx43 [29]. The role of reduced peroxynitrite formation and increased NO availability in cardioprotection [30], and the effects of increased NO availability on myocardial oxygen consumption in late preconditioning [31], are also analyzed.

This issue may bring into focus some new insights into the well-known myocardial protective strategy of preconditioning. In addition, it offers further insight into the endogenous protection exerted by postconditioning, and begs the question of what events are occurring at reperfusion that are common between the two strategies. The clinical perspectives in this Spotlight Issue are crucial because translation of any strategy into the clinical arena is a validation of its ultimate importance as a therapy in humans.

References


