Postconditioning: a brief review

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Abstract

Preconditioning represents the most effective form of cardioprotection that can be induced to attenuate the injury accompanying a longer lasting ischemia (=index ischemia) of sufficient duration and severity to cause myocardial necrosis. Preconditioning can be induced by short bouts of ischemia, several pharmaceuticals (e.g. adenosine), and volatile anesthetics all imposed before the index ischemia. A brief ischemia of an organ other than the heart can likewise initiate protection of the heart, which has been called "preconditioning at a distance" or "remote preconditioning". According to the more recent literature, short bouts of ischemia after an index ischemia can also initiate cardioprotection, e.g. improved post-ischemic endothelial function, reduced infarct size and less apoptosis; this protective maneuver has been called "postconditioning". Postconditioning can also be elicited at a distant organ, termed "remote postconditioning". It is the aim of this short review to (1) characterize preconditioning and in particular postconditioning, (2) describe possible mechanisms, and (3) call attention to the clinical relevance of this cardioprotective strategy.

Key words: ischemia-reperfusion, cardioprotection, remote preconditioning, remote postconditioning, reperfusion injury, reperfusion therapeutics.

Preconditioning

Ischemic preconditioning

To induce severe experimental ischemic injury, short sequences of ischemia-reperfusion preceded a long-lasting index ischemia (Figure 1) [1].

This protocol led to a surprising observation: infarct size was reduced from 30% to 7%, i.e. to about only 25% of the non-preconditioned myocardium (Figure 2, left). Analysis of the determinants of infarct size that may be effected by this cardioprotective maneuver showed that this phenomenon was independent of differences in oxygen supply during ischemia, as the regional collateral blood flow in the preconditioned and the unpreconditioned hearts was comparable (Figure 2, right).

These brief episodes of ischemia applied before a major ischemic event not only reduced infarct size but also the number of reperfusion arrhythmias

Figure 1. The schematic of preconditioning. Some short bouts of ischemia/reperfusion preceding a lasting ischemia (= index ischemia) reduce myocardial injury after the index ischemia (after Murry et al. [1])

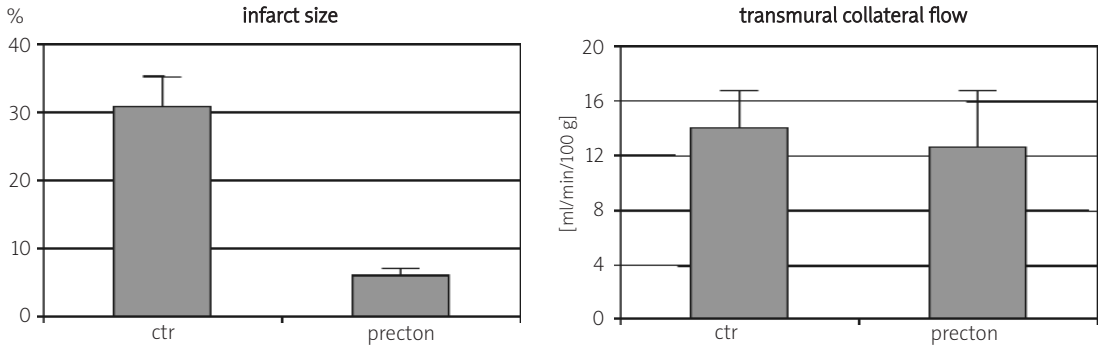

Figure 2. Preconditioning reduces the infarct size from 30% to 7%, i.e. to about 25% of the non-preconditioned myocardium (Figure 2, left). This protection does not depend on differences in oxygen supply, because regional collateral blood flow in the preconditioned and not preconditioned hearts was comparable (Figure 2, right) [1]

and myocardial apoptosis [1]. Preconditioning has been observed in virtually all species and models tested in experimental (animal) studies, as well as in humans, and is touted as the "gold standard" by which all other cardioprotective strategies are judged.

Pharmacological preconditioning

Later studies demonstrated that preconditioning can be initiated also pharmacologically, that is by drugs administered before the ischemic event, with an intervening washout period before the index ischemia (true pharmacological preconditioning) or without a washout period (more appropriately called a pharmacological pretreatment). Among others, preconditioning can be triggered by substances like adenosine, bradykinin, NO, the mitochondrial K_{ATP}-channel opener diazoxide, and also PKC activators, opioids, and prostaglandins (for review see [2]).

Anesthesia-induced preconditioning

After preconditioning was shown to be the most effective form of cardioprotection [2, 3], anesthetics were investigated for their potential to precondition the heart before ischemia. All halogenated, volatile substances were found to be protective, and that their action was comparable to that of ischemic preconditioning. In consequence, this form of preconditioning was introduced into the clinical setting. Indeed, studies in cardiac surgery confirmed the efficacy of this anesthetic preconditioning: postoperative Troponin I in preconditioned hearts was significantly reduced [4]. This is in distinction to conventional ischemic preconditioning, which had disparate results in clinical studies in cardiac surgery, with some studies showing benefit, but others showing no benefit or even deleterious effects [5].

Remote preconditioning; preconditioning at a distance

After preconditioning was firmly settled, an alternative mode of preconditioning was observed. Short bouts of ischemia in remote vessels or even distant organs protected the myocardium from injury that was induced by coronary artery occlusion-reperfusion. Thus, substances must have been released from the remote ischemic-reperfused tissue that protected the jeopardized myocardium. Potential protective substances for an inter organ transport are adenosine, δ_1-opioid and neurotransmitters [6]. Indeed, this list of mediators is not mutually exclusive, as adenosine may trigger the release of neurological stimuli, which then results in protection of the heart (for review see [6]).

Postconditioning

Brief interruptions (10-60 s, depending on the model) of the blood flow applied immediately after the onset of reperfusion following an index ischemia, were observed to provide cardioprotection. In the initial study in an anesthetized canine model of coronary artery occlusion-reperfusion, 3 cycles of coronary artery reperfusion alternating with 30 s of reocclusion were associated with a significant reduction in both the infarct size and the endothelial dysfunction [7] (for review see [8-11]).

This "postconditioning", so named because the stimulus was applied after the index ischemia, was later confirmed by others and in other species. For example, three sequences of reperfusion-occlusion (Figure 3) immediately after the end of an index ischemia, reduced the infarct size from 23 to 13% [9].

Postconditioning can also be induced via volatile anesthetics [12, 13]. Isoflurane, for example, reduced the infarct size by 50%, if administered early during reperfusion. Likely, this effect was mediated via the phosphatidylinositol-3-(PI3) kinase [14]. Other pharmacological agents administered at the start of reperfusion have been shown to be cardioprotective. These include adenosine, nitric oxide, cytokine and complement inhibitors, etc. However, whether this approach should be described as "pharmacological postconditioning" or as a "post-reperfusion treatment" has been argued. Since the mechanisms of

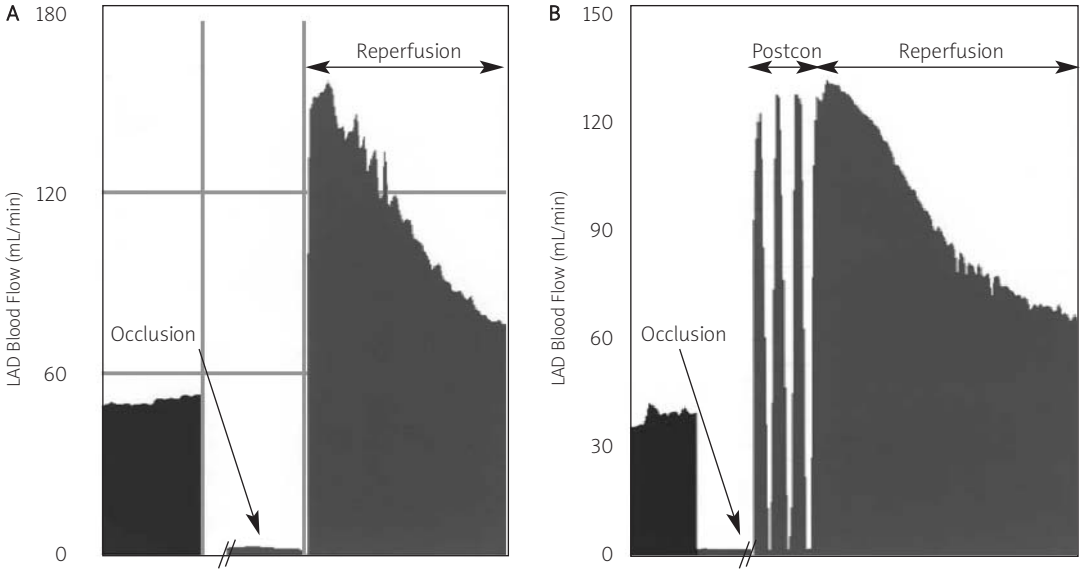

Figure 3. Protocol of postconditioning. left: Reperfusion is started without interruption after the occlusion. right: Following occlusion, postconditioning is initiated via three short sequences of reperfusion/occlusion before the long lasting reperfusion [9]

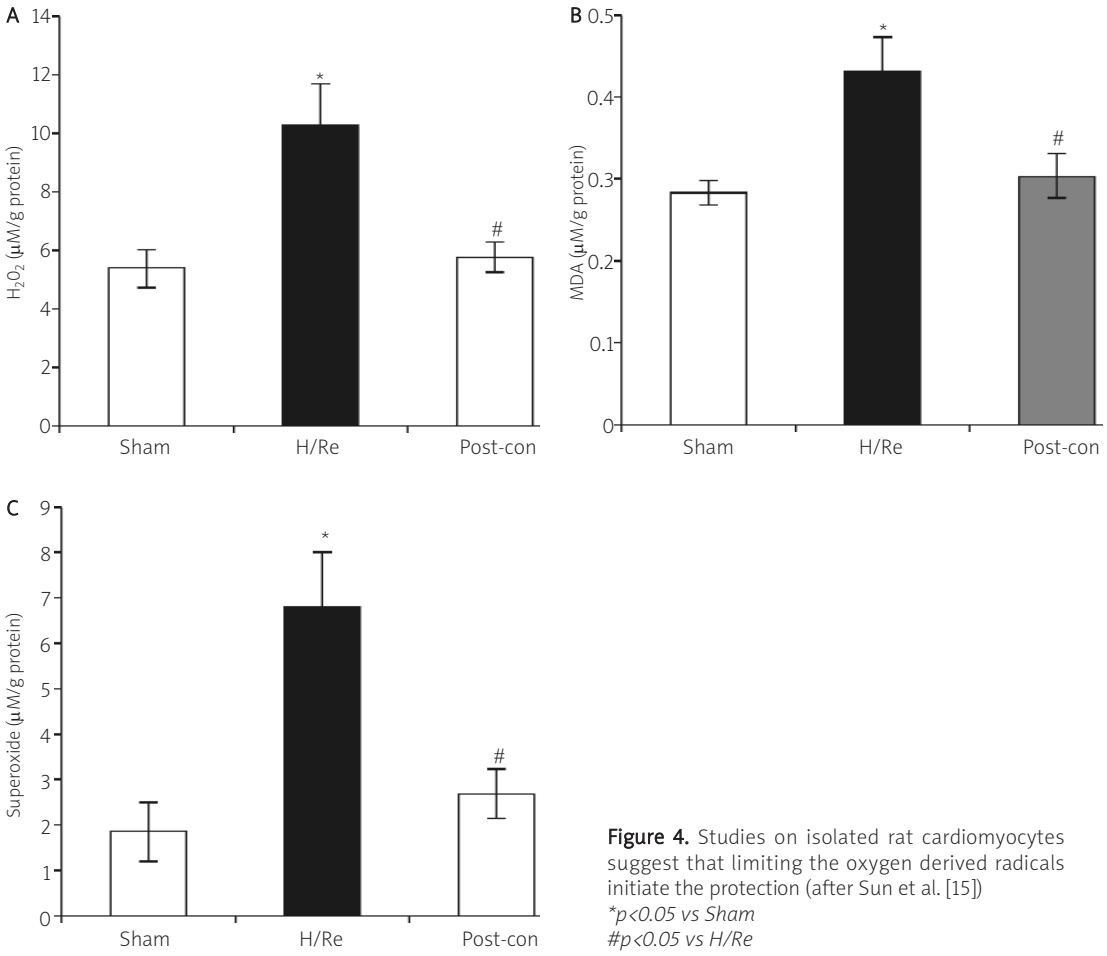

Figure 4. Studies on isolated rat cardiomyocytes suggest that limiting the oxygen derived radicals initiate the protection (after Sun et al. [15])
**p<0.05 vs Sham*
#p<0.05 vs H/Re

postconditioning have not been fully elucidated, and the importance of the alternating cycles of ischemia-reperfusion has not been appreciated nor determined to be critical to protection, direct association to "postconditioning" (whatever "conditioning" means at reperfusion) should be debated.

Additional studies support the cardioprotective potency of postconditioning to reduce the infarct size, endothelial dysfunction, and neutrophil accumulation in the jeopardized area. These results are suggestive that within the first minutes of reperfusion, endogenous processes are initiated that help reduce reperfusion injury after a limited duration of ischemia. The multiplicity of cell types that are effected by postconditioning, i.e. cardiomyocytes, vascular endothelial cells and inflammatory cells, reflects the complexity of reperfusion injury, and suggests a wide network of effects within this complex interactive web of responses. This wider view of reperfusion injury is in contradistinction to the focus on the myocyte as the primary victim and player in responses to reperfusion.

In the meantime, it is well established that the observed cardioprotective effects of postconditioning were not the accidental result of one particular laboratory, experimental model or one particular species, because postconditioning was shown to be effective in isolated cardiomyocytes [15], in isolated-perfused hearts [16], and in situ hearts of mice [17], rats [18], rabbits [19], pigs [20] and dogs [21]. Moreover, in a study of 30 patients with acute myocardial infarction who were clinically destined for angioplasty with stent deployment, short sequences of coronary artery occlusion-reperfusion applied using the angioplasty catheter apparently reduced post-ischemic infarct size [22].

Mechanisms of postconditioning

Reperfusion injury is a complex response that involves many of the cells in the integrated structure of the myocardium, notably the cardiomyocytes, vascular endothelial cells, and resident or "localized" inflammatory cells. The effects of postconditioning on each of these cells types alone, and then their interaction, must still be described. The underlying mechanisms of postconditioning on cardiomyocytes were elucidated by thorough studies in isolated rat cardiomyocytes [15].

These studies suggest that limitation of oxygen radicals (Figure 4) or of Ca^{2+}-overload (Figure 5) is involved in the protection. Postconditioning seems to reduce the oxidative stress, in particular by reduction of the superoxide load that is generated, and in mitochondrial peroxide production and the depletion of glutathione [23]. Other mechanisms to induce postconditioning are guanylyl cyclase activation, opening of the mitochondrial KATP channels, and inhibiting opening of mitochondrial permeability transition pores (mPTPs) [12]. Activation of protective pathways (eNOS and NO; ERK1/2; PI3-kinase – Akt) is also discussed [9] as well as activation of adenosine receptors [18] and opioid receptors [24]. Regarding the modulation of these endogenous autacoids, ischemia has been shown to increase the generation of each of these substances. Reperfusion may wash out (adenosine) or reduce the generation (opioids) of these autacoids so that they are no longer available to exert their endogenous cardioprotection. By mechanisms that have not yet been elucidated, postconditioning delays the washout of adenosine, and may thereby increase its exposure to the vascular space in which adenosine may exert potent cardioprotection [25,

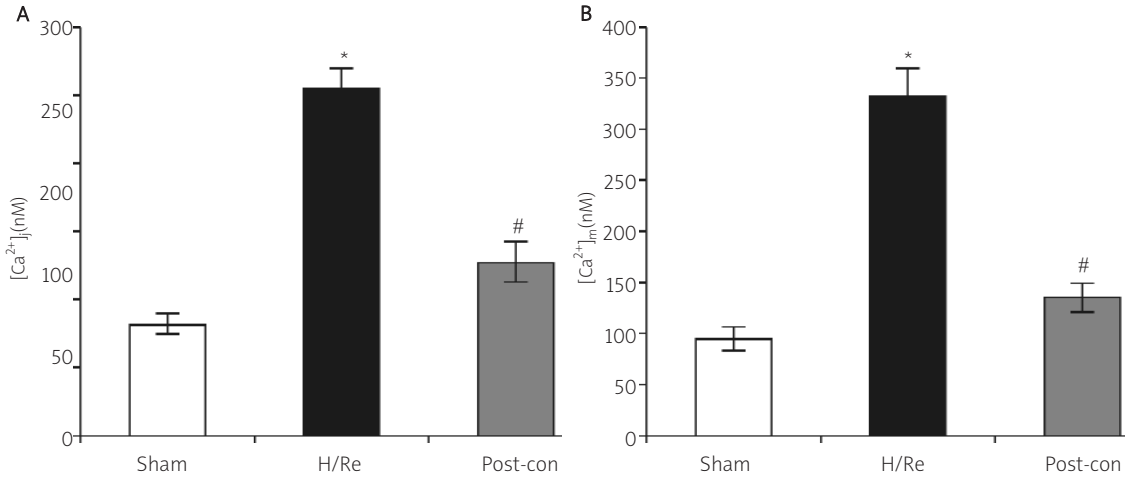

Figure 5. Both the intracellular (A) and the mitochondrial (B) Ca^{2+}-concentrations are increased during reperfusion after hypoxia (H/Re). These increases can be largely reduced with the help of postconditioning [15]
**p<0.05 vs Sham; #p<0.05 vs H/Re*

26]. For opioids, postconditioning may promote generation of precursor molecules by unclear mechanisms.

Tsang et al. [16] have proposed that there are "passive" and "active" phases to the mechanisms of postconditioning. The "passive" portion is initiated via stepwise reperfusion that reduces oxygen radicals (presumably the delivery), mitochondrial Ca^{2+} overload, and neutrophils. By the "active" portion, the "reperfusion injury salvage" kinases (RISK) pathway is activated by endogenous stimulators, e.g. adenosine, opioids or other as yet unidentified endogenous substances, and stressors such as ischemia-reperfusion. Here, two interactive pathways might be responsible at least for protection in cardiomyocytes (Figure 6). (1) Activation of PI3 kinase, Akt, and eNOS to inhibit opening of the mPTPs. (2) Activation of MEK1/2 and ERK1/2. In turn, Akt together with ERK1/2 activate p70s6K, which finally initiates protein translation. In vivo studies to clarify which of the survival kinases are important for postconditioning, suggest that the cardioprotection is likely mediated via the ERK1/2 pathway, rather than via the PI3 kinase/Akt pathway [27]. An even more recent study comes to the conclusion that in postconditioning both Akt and ERK are activated, but that their activation does not protect from reperfusion injury [28]. Hence, these early and partially contradictory results need future investigations in models which isolate the various cell types, and in the integrated organ and organism. In addition, whether there is an active and passive division merits further thought. For example, the "passive" inhibition of neutrophils may be derived from "active" processes of augmenting endogenous signals such as adenosine and opioids, and activation of protein kinase C isoforms that converge on the mPTP, oxidative enzymes, and other "effector" targets.

Remote postconditioning

After having established remote preconditioning, remote postconditioning was demonstrated, as well: occlusion of the renal artery immediately before the onset of reperfusion of a coronary artery clearly reduced the myocardial infarct size [29]. These investigations provided some results of interest: (1) The benefit is likely initiated within the first minutes of the reperfusion of the coronary artery, (2) the inter-organ remote postconditioning is likely mediated via adenosine liberated from the ischemic-reperfused kidney since cardioprotection was abrogated by an adenosine receptor blocker (8-p-sulfophenyl theophylline). It is not known whether the adenosine receptors were localized in the heart or in a remote organ, and whether neurological mediation of the adenosine stimulus is involved [29].

The concept of remote postconditioning is not merely a laboratory curiosity; it may have clinical application. One may have significant trepidation in applying cyclical angioplasty balloon inflations in the target coronary artery as done by Laskey et al. [30] and Staat et al. [22]. An alternative approach is to

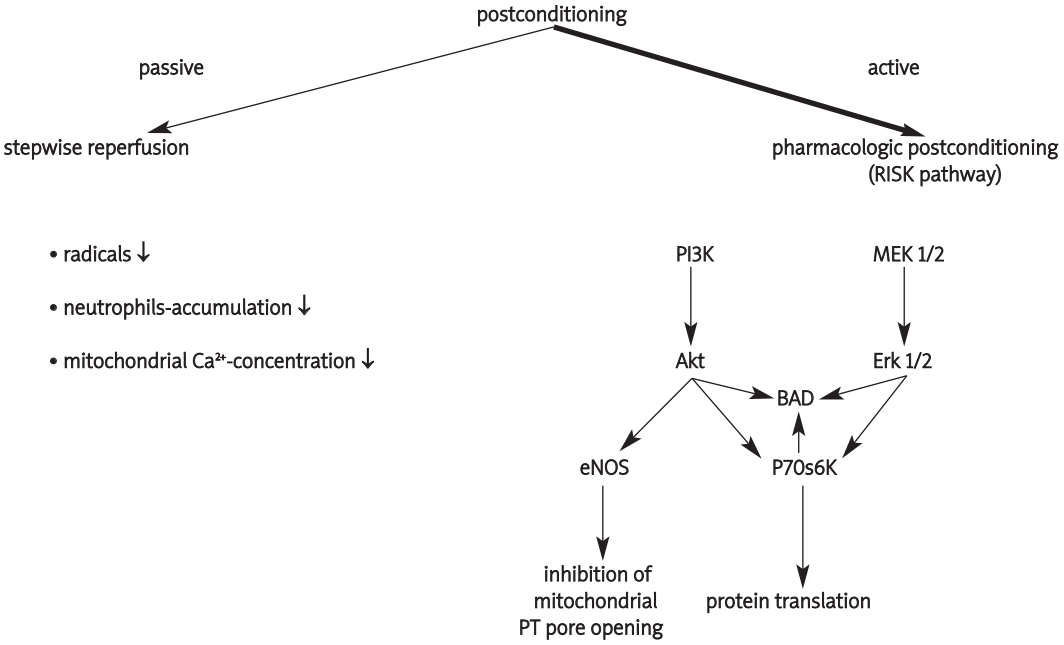

Figure 6. The schematic of postconditioning. A "passive" route could be activated by interruption of the reperfusion leading to reduced oxygen derived radicals, neutrophil accumulation, and mitochondrial Ca^{2+}-concentration. In turn, an "active" route – by using the RISK pathway – finally inhibits the mitochondrial permeability transition pores and induces protein translation (after Tsang et al. [16])

"stimulate" postconditioning via another organ, such as the leg. This "organ" is much more accessible than the kidney as used in the original study introducing this concept [29]. A tourniquet could be applied to the leg during transport to the emergency room or to the cath-lab to set up a strong postconditioning signal. The tourniquet could then be removed just before completion of the angioplasty procedure and in advance of the onset of reperfusion, being certain not to miss the window of cardioprotection afforded in the first minutes of reperfusion [18].

Postconditioning vs preconditioning

Postconditioning provides cardioprotective effects similar to ischemic preconditioning [7]. Comparison of postconditioning and preconditioning exhibits relatively many similarities (Table I). Studies on different species demonstrated that both phenomena reduced the infarct area to similar degrees (with one notable exception [19]) and protected coronary vascular endothelial function (Figure 7) [9].

Already in the "preconditioning era", the question was asked whether or not multiple triggers can enhance cardioprotection. Appropriate studies had disproved such additive effects (for review see [2]).

Nevertheless, an additive effect could exist for preconditioning plus postconditioning. Yet, in a study on anesthetized dogs, postconditioning did not amplify protection beyond the preceding preconditioning [21]. This finding suggests that the injury due to reperfusion can be reduced. It is still not clear whether the two cardioprotective strategies are additive under certain circumstances, such as prolonged ischemia in which the protection of one or the other maneuver drops out [31]. If the two maneuvers do indeed share identical mechanisms, then they may not be additive unless two "bouts" are better than one. Certainly, it is not known whether multiple episodes of postconditioning spread out over the early and later phases of reperfusion are cardioprotective, although the number of cycles within each episode does not seem important. On the other hand, if there are differences in the molecular mechanisms (i.e. ERK1/2 vs PI3-kinase) or the timing of effect (ischemia vs reperfusion) then the two maneuvers may be additive under the correct circumstances.

Table I. Comparison between preconditioning and postconditioning (after Vinten-Johansen et al. [9])

			pre-con	post-con
physiological effects	reduces	infarct size	+	+
		stunning	±	+ (?)
		apoptosis	+	+
		tissue edema	+	+
		vascular injury		
		endothelial dysfunction	+	+
		perfusion injury	+	+
	delays	adenosine washout	–	+
cellular and subcellular effects	inhibits	neutrophil accumulation	+	+
		neutrophil-attachment on endothelial cells	+	+
		endothelial cell activation	+	+
		O_2-generation by endothelial cells	+	+
		O_2-generation by myocytes	+	+
		generation of cytokines	+	?
	activates	K_{ATP} channel	+	+
	closes	mitochon. permeability transition pores	+	+
	mediated via	adenosine	+	+
	mediated via	opioids	+	?
molecular effects	pathways	PI3 kinase/pAkt	+	±
		GSK3β	+	?
		ERK 1/2 – MEK	–	+
		P70S6K	+	+
		eNOS	+	+

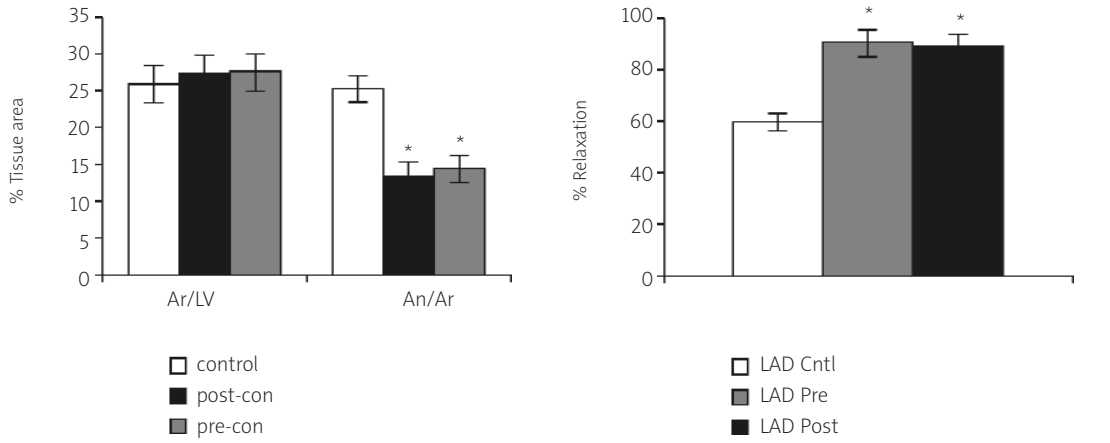

Figure 7. Postconditioning and preconditioning to a similar extent reduce the infarct size (left) and prevent from endothelial dysfunction (preserved relaxation; right) [9]; *left: *p<0.05 vs control; right: *p<0.05 vs LAD Cntl*

Summary

Depending on the point in time and location, an almost symmetrical schematic of myocardial "conditioning" can be drawn (Figure 8). A protective intervention before the prolonged ischemia initiates preconditioning of the heart. This intervention can alternatively be performed on the heart or in the periphery. A protective intervention after a lasting ischemia induces postconditioning. Again, the intervention can be performed on the heart or in the periphery. The question of timing is not a moot point, since there is the question of when does preconditioning exert protection among its various mechanisms. There is some data to suggest that the role of the RISK pathway induced by preconditioning may actually be exerted during reperfusion. Similar observations have been made for protein kinase C involvement (Zatta, unpublished observations).

It can be stated that the efficacy of postconditioning can readily be compared with ischemic preconditioning. This strategy should start as early as possible after the onset of reperfusion to assure protection, lest the endogenous cardioprotective "window" be closed. In this regard, strategies to

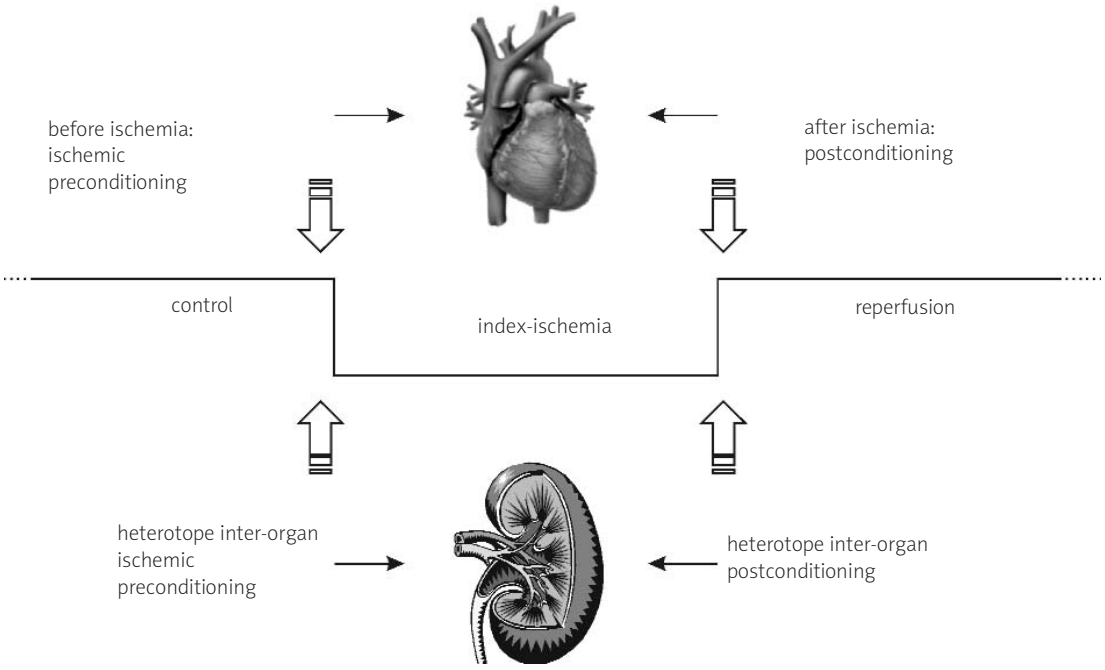

Figure 8. The schematic of preconditioning and postconditioning of the heart. Independent of the time, the protective intervention can be performed either on the heart or in the periphery (= remote) (after Kerendi et al. [29])

increase the open duration of this window would be important. The limitation to the first minutes after the onset of reperfusion speaks for the participation of oxygen radicals [18, 32]. On the other hand, Ca^{2+}-overload and subsequent Ca^{2+}-dependent contracture are being discussed [15]. Both superoxide anions and intracellular calcium are purported triggers of mitochondrial permeability channel opening. In addition, the participation of other triggers relevant to reperfusion injury, such as complement-induced injuries, [33], the cytokines (IL-6, IL-8, TNFα) and other inflammatory mediators (tissue factor, thrombin, protease activated receptors) should not be excluded from the menu of mechanisms to interrogate in preconditioning and postconditioning.

Future prospects

Postconditioning: open questions

Previous studies described considerable species depending differences. On the other hand, preconditioning and postconditioning induced comparable protection but to different genomic responses. Thus, for longer periods, beneficial effects could be different [34]. Since the underlying mechanisms of postconditioning remain unclear, much room is left for future studies.

Postconditioning: clinical application

Parallel with a certain euphoria, criticism about the relatively young phenomenon "postconditioning" exists. E.g. postconditioning could simply be a form of stepwise/controlled reperfusion [35], which is used already in the clinical cath-lab [32]. On the other hand, this form of reperfusion could present a valuable strategy in coronary artery bypass surgery (off-pump-surgery) to reduce myocardial injury. However, it is not clear at this early point how postconditioning differs from other forms of modified reperfusion such as "gradual reperfusion", if at all. There are some interesting differences between the two modes of reperfusion. This in itself is a potential field of investigation.

Before any routine use in the clinic, one should keep in mind that hearts might be preconditioned already via repeat anginal episodes or by anesthetics. Thus, additional protection may not be expected. If required, postconditioning could be initiated via appropriate anesthetics [4, 14]. After all, postconditioning will be superior to preconditioning as protective interventions after acute myocardial infarction can easily be performed [19].

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