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Pacing Postconditioning: Recent Insights of Mechanism of Action and Probable Future Clinical Application

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Key Words
Ischemia reperfusion · Postconditioning · Pacing postconditioning

Abstract
Ischemic heart disease, also known as coronary heart disease or coronary artery disease, accounts for >50% of cardiovascular events and is a leading cause worldwide of morbidity and mortality. Hypoperfusion of the heart is the major cause of injury in ischemic heart disease, as it results in the death of cardiomyoctes due to a lack of oxygen and energy. This injury ultimately leads to a dead area in the heart called infarcted area or myocardial infarction. The formation of myocardial infarction leads to a lengthy process of remodeling which causes many changes in the architecture and the electrophysiology of the heart. These changes may eventually lead to death due to arrhythmia or heart failure. Tremendous efforts have been made over the last decades to decrease the burden of ischemic reperfusion (I/R) injury. The first salvage to the ischemic heart is reperfusion; however, this procedure is associated with a subsequent reperfusion injury. In the 1980s, a method known as preconditioning was introduced and showed great potential in combating ischemic heart disease, but this technique is limited by the difficulty of its translation to the clinic as it requires the anticipation of an occurrence of ischemic heart disease. Not long after, a new method, postconditioning, was introduced. This method showed great success, and several studies were performed to investigate its signaling cascades and the possibility of its translation to the clinic. Thereafter, several trials were made, and many methods of postconditioning were developed. One of these is intermittent dyssynchrony, pacing postconditioning (PPC), of the heart, which involves brief episodes of electrical pacing. PPC afforded a pronounced protection to the heart against I/R injury, similar to that afforded by pre- and postconditioning.

Introduction

Despite all the efforts made to decrease cardiovascular morbidity and mortality, ischemic heart disease still accounts for some of the high mortality rates [1]. After continuous efforts to decrease the mortality related to ischemic injury, researchers and clinicians were able to introduce a vitally important technique, reperfusion. They managed to open the occluded coronary artery and restore the blood supply to the affected part of the heart.

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This procedure contributed notably to decreasing the morbidity and mortality associated with ischemic heart disease [2]. However, this method of protection contributes its own injury, which is caused by the sudden reperfusion and oxygenation to the affected tissue [3, 4]. This injury is mainly a result of myocardial stunning, microvascular and endothelial injury and irreversible cell damage or necrosis [3, 5]. Although reperfusion remained the gold standard treatment for ischemic injury for some time, the search for a reasonable remedy for both ischemia and reperfusion damage continued for several years before a viable solution was obtained. In the past, manipulating the heart by conditioning showed encouraging results, which suggested that it may be a promising procedure for reducing ischemic reperfusion (I/R) injury in the near future [6]. Many methods of intervention evolved and were proposed as vital tools for decreasing I/R injury [7]. Conditioning the heart can be executed at several time points related to the time of occurrence of the I/R and can be achieved by various methods. The first method introduced was ischemic preconditioning, which is a protective method by which a brief ischemia before the major prolonged ischemia protected the heart against the subsequent lethal ischemic injury [8]. The support afforded by this method of conditioning was believed to be evoked by a brief interruption of the blood flow to the insulted area. Preconditioning afforded remarkable protection to the hearts of patients undergoing percutaneous coronary intervention [9]. Equally, this intervention was proven to be very effective in heart transplantation and open chest surgery. However, although there were numerous procedures and methods of preconditioning, it was restricted to very narrow events because of the lack of predictability of an ischemic attack in healthy individuals. This situation necessitated the search for a potent procedure that could afford optimum protection from I/R injury to the heart. Benefiting from the knowledge and experience gained in preconditioning research, Zhao et al. [10] introduced another method of conditioning lately known as ischemic postconditioning. This method involved a repetitive ischemia at the beginning of the reperfusion that followed prolonged ischemic injury. This procedure of conditioning gained enormous publicity because of its execution at reperfusion, which gave it a great chance of translation to the clinic [10]. Interestingly, this method of protection can be mimicked by drugs either before the ischemic insult (pharmacological preconditioning) or after the insult (pharmacological postconditioning) [11, 12]. Indeed, great success was achieved in the protection of the heart by this postconditioning, but its application on the affected blood vessel raised great concern which hindered its utilization in the clinic [13]. As an alternative method of avoiding the affected blood vessel, a potent intervention exploiting the same idea of pre- and postconditioning was introduced. This intervention was done on an organ or vascular bed remote from the affected blood vessel or tissue targeting the protection of the insulted organs and was accordingly called remote pre- or postconditioning, respectively [14, 15]. Recently, the group of Prinzen [16] introduced intermittent dyssynchrony, pacing postconditioning (PPC), induced by ventricular pacing to the heart, which causes a local change in the load of the ventricle . The mechanism of this protection seems to act by decreasing the stretch at the site of pacing and increasing it at a site remote from it [16]. This change in the ventricular load is believed to be the trigger of the protection PPC affords to the heart. Like all other scenarios of conditioning, PPC afforded an evident protection to the heart when applied before ischemia or at the beginning of reperfusion [17]. Both prepacing conditioning and PPC result in a protection of the myocardium similar to that attained by other methods of conditioning [18].

Conditioning as a Strategy for Heart Protection

To target ischemic injury, reperfusion is the most effective intervention, and its ultimate injury can be antagonized by postconditioning [10]. Combining reperfusion and postconditioning further decreases I/R injury; however, it does not eliminate it completely. Since the introduction of postconditioning, many studies have been done on animals and in the clinic [10, 19, 20]. Quite excellent achievements were attained in the animal and small clinical studies; however, the results of the largest clinical studies were disappointing [21, 22] (table 1). Similarly, many of the drugs used to target I/R injury showed positive results in animals and small clinical studies [23], but their use in large clinical studies gave a disappointing outcome [24] (table 1). Some other methods of protection were executed during ischemia, such as remote pre- and postconditioning; however, the failure of the large-scale trial also compromised their translation to the clinic [25, 26]. Surprisingly, to date there is no drug which has been proven to afford optimum protection to the heart or to make outstanding progress in the protection of the heart against I/R injury (table 1). PPC is done 'remotely' from the occluded blood vessel; however, on the same organ, it

could be a promising method of protection of the heart. Interestingly, PPC can be performed at reperfusion or simultaneously during ischemia to decrease ischemic injury and completely abrogate the reperfusion injury. This review focused on PPC to the heart, as it has the potential of in the future being a leading method in the protection of the heart against I/R injury in the clinical setting.

PPC: The New Potentials of Protection

In PPC, myocardial protection was proven to be triggered by brief periods of intermittent mechanical dyssynchrony induced by ventricular pacing at normal heart rate during the early moments of reperfusion [17]. Pacing preconditioning was induced by 3 episodes of 5-min duration of left ventricular pacing interspersed with 3 episodes of 5-min right atrium pacing prior to the index ischemia. In 2006, Vanagt et al. [16] reported a reduction in the myocardial infarct size by brief periods of PPC for the first time. Based on their findings, in 2007 the same group investigated the possibility of protection if the same protocol of pacing preconditioning was applied at reperfusion [17]. They used isolated rabbit hearts which were subjected to 30-min regional ischemia followed by 3 cycles of 5-min left ventricular pacing alternated with 3 cycles of 5-min right atrium pacing [17]. This study reported a significant reduction in the infarct size comparable to that produced by pacing preconditioning [17]. Interestingly, PPC was translated successfully to rat and pig hearts after its success in the rabbit [18, 27]. The protection of PPC was attained in isolated, buffer-perfused as well as blood-perfused hearts in vivo [18]. It is worth noting that the infarct size reduction by PPC was proven to be sustained over the long term. The abnormal mechanical loading of the myocardium is believed to be the trigger of this PPC-induced protection [18]. These findings were also supported by another study which proved the protection of the myocardium by mechanical stretch [28]. Stretch was also proven to be effective in the protection of the heart as shown by Gysembergh et al. [29]. Previous studies have shown that myocardial blood flow or lactate release did not change during the switching from the right atrium to left ventricular pacing in the early reperfusion phase of PPC [16, 17]. This finding provides solid proof that ischemia and graded reperfusion are not likely to be triggers of PPC protection [18]. The notion that the abnormal stretch of the myocytes leads to a release of angiotensin, which is known to induce a hypertrophic response in the myocyte, had not been validated in the previous PPC studies. Our recent studies did not show a role for angiotensin II in the protection of the heart by PPC. The angiotensin receptor 1 blocker candesartan does not affect the protective role of PPC, which excludes angiotensin receptor 1 as a candidate in PPC-induced protection [18]. This suggests the presence of intermediate candidates that might be important in the upstream protective pathways of PPC.

The downstream pathways of PPC resemble those of the ischemic pre- and postconditioning, but its upstream pathways showed a clear variation (fig. 1). It was shown that protein kinase C activation, which is important in ischemic postconditioning, is involved in PPC protection

Table 1. Clinical trials with remote preconditioning, pharmacological conditioning, preconditioning and postconditioning that did not show protection of the heart against I/R injury

Treatment methods
Remote preconditioning
Lavi et al. [26], 2014
Rentoukas et al. [49], 2010
Karuppasamy et al. [50], 2011
Carrasco-Chinchilla et al. [25], 2013
Pavione et al. [51], 2012
Lucchinetti et al. [52], 2012
Rahman et al. [53], 2010
Hong et al. [54], 2010
Li et al. [55], 2010
Munk et al. [56], 2010
Pharmacological conditioning
Landoni et al. [47], 2008
Bates et al. [57], 2008
Liem et al. [58], 2009
Desmet et al. [59], 2011
Kitakaze et al. [60], 2007
Ott [61], 2010
Najjar et al. [62], 2011
Ross et al. [46], 2005
Fokkema et al. [63], 2009
Preconditioning
Ghosh et al. [64], 2003
Wu et al. [65], 2001
Cremer et al. [66], 1997
Postconditioning
Limalanathan et al. [22], 2014
Freixa et al. [21], 2012
Sorensson et al. [67], 2010

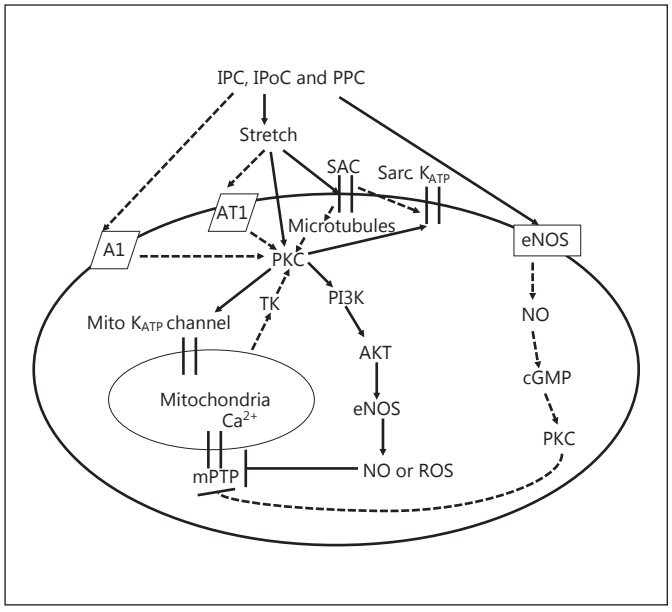

Fig. 1. Schematic representation showing the potential pathways for preconditioning, postconditioning and PPC. The dashed lines show pathways which are not known in PPC protection. A1 = Adenosine receptor 1; AKT = protein kinase B; At1 = angiotensin receptor 1; cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; IPC = ischemic postconditioning; IPoC = ischemic postconditioning; Mito K_{ATP} = mitochondrial ATP-sensitive K^+ channel; mPTP = mitochondria permeability transition pore; NO = nitric oxide; PKC = protein kinase C; ROS = reactive oxygen species; SAC = stretch activated channel; Sarc K_{ATP} = sarcolemmal ATP-sensitive K^+ channel; TK = tyrosine kinase.

[18]. Another important pathway of PI3K-Akt, which is also referred to as RISK pathway [18, 30, 31], was proven to be effective in PPC [18]. Furthermore, the blockade of the mitochondrial ATP-sensitive K^+ channel by 5-hydroxydecanoate eliminates the cardioprotective effect of PPC [18]. Accordingly, the opening of the mitochondrial ATP-sensitive K^+ channel is considered to be an important candidate in the cardioprotection mediated by PPC (fig. 1). To attain the optimum beneficial effects, PPC should be applied during the first 5 min of reperfusion. It can be applied clinically in heart transplants, cardiac surgery and percutaneous coronary intervention [18]. Recently, a role for tumor necrosis factor α, brain natriuretic peptide and nitric oxide in PPC was reported by Babiker et al. [27]. PPC, however, was proven not to be effective in diabetic animals, but it was similarly effective in male and female hearts with no remarkable gender differences [32]. Microtubules were also proven to be involved in the protection afforded by PPC [18].

Future of Heart Protection and PPC

Despite the success of all the methods of conditioning in animal studies, the translation to the clinic is rather limited and compromised by the lack of an optimum protective effect. Recently, the negative results reported by three big trials in ischemia and remote conditioning have caused an obstacle for the future of conditioning research. Ischemic preconditioning was proven to be effective in salvaging the heart [8], but its translation to the clinic was limited by the lack of a predictable time of occurrence of the ischemic insult [33]. However, it is still beneficial in patients undergoing percutaneous coronary intervention or opening side branch occlusion [34, 35]. Indeed, both preconditioning and postconditioning techniques accommodate the risk of injury as they are applied on the occluded blood vessel [36, 37]. In contrast, remote pre- and postconditioning are done with no risk away from the insulted organ with promising results in the protection of the heart. Preconditioning done on the same vascular bed [15], on a remote vascular bed in a remote organ [38] or in small clinical trials [39, 40] showed a considerable protection. Unfortunately, the translation of this method to the clinic is jeopardized by the unpredictable occurrence of ischemia. Postconditioning that can be applied after the onset of ischemia at the beginning of reperfusion afforded effective and successful protection to the heart in animals [10] and humans [20]. Remote postconditioning was applied to avoid the anticipated injury of the blood vessels. A strong body of evidence has shown that remote postconditioning is effective in animal studies [41, 42] and in ST elevation myocardial infarction [14, 43]. Recently, this method of protection has been put on hold because of the disappointing results of the last few large-scale studies [25, 26] (table 1). The use of the drugs in preconditioning and postconditioning [44, 45] protection showed great success in animals and small clinical experiments [23], but the application in large experiments did not produce the required optimum protection [24, 46] (table 1). Furthermore, the protective effects of anesthetics shown in animal studies did not show the required protection in the clinic [47]. To date, PPC seems to be the best candidate for the application in the clinic. Interestingly, however, not applied directly to the heart, recurrent electroconvulsive therapy did not impose harmful effects on the heart [48]. PPC is applied on the same organ away from any capillary bed, and it is void of the vascular damage of the other methods [18]. PPC can be performed during the occlusion (sustained ischemia). It has the potential of being applied as precondition-

ing before starting reperfusion or as a postconditioning method at the onset of reperfusion. Interestingly, preconditioning pacing and PPC can easily be combined to produce additive protection, which may be beneficial for the protection of diabetic and hypertrophied hearts.

The only important limitation of PPC is its invasive nature. This shortcoming can be extenuated by the fact that invasion is unavoidable in the treatment of ischemia as the catheter will be inserted anyway in order to open the occlusion or to place the stent. Interestingly, the same catheter can be used for pacing the heart. Furthermore, the PPC technique is easy and inexpensive and can be applied in ordinary clinical settings.

Conclusion

PPC is one of the various methods of postconditioning. It implies an abnormal stretch of the heart induced by electrical pacing in the protection of the heart against I/R injury. It is applied remotely from the affected coronary artery; however, it is applied on the same organ. While it shares the downstream pathways of protection with the other postconditioning methods,, its downstream pathways are different. These characteristics give it potential for adding to the protection gained by other methods of protection. Furthermore, being easy and safe to apply suggests it as a future method for the protection of the heart; however, its beneficial effects are to be confirmed beforehand by pilot studies on the human heart.

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Disclosure Statement

The author has no conflicts of interest to reveal.

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