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Postconditioning in Reperfusion Injury: A Status Report

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Abstract Early reperfusion after an organ ischemia is essential to salvage tissue from eventual death. However, abundant evidence suggests that reperfusion also elicits pathophysiological changes responsible for additional tissue injury after restoration of blood flow. Postconditioning (Postcon) defined as rapid sequential intermittent interruption of blood flow applied during early moments of reperfusion has successfully shown to attenuate organ injury, including the heart, spinal cord, brain, kidney, liver, muscle, lung and intestines in the experimental setting. Clinical trials have also revealed the beneficial effect of Postcon on myocardial infarction in patients undergoing percutaneous coronary intervention or coronary artery bypass graft surgery. Although there are some controversial issues regarding the efficacy of protection with Postcon in different animal models with comorbities, most preclinical studies have shown that Postcon is a potent intervention to reduce organ necrosis and apoptosis. Remote or pharmacological Postcon has emerged as alternatives in amelioration of cardiac reperfusion injury. This article will primarily discuss the existing literature regarding protection of Postcon on the heart, but there is a potential for future research into other organ systems to identify beneficial effects of Postcon on tissue reperfusion injury, particularly in patients undergoing surgical revascularization.

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Introduction

Despite considerable progress in treatment and management of ischemic heart disease in last three decades, acute myocardial infarction is still the leading cause of patient's mortality after coronary occlusion, afflicting approximately 1.5 million individuals each year in the United States. More than 30% of the patients with ventricular fibrillation die before reaching the hospital, while 5% die largely due to heart failure from myocardial infarction [1, 2]. The ultimate amount of infarct tissue after an ischemic episode primarily depends upon the severity and the duration of coronary occlusion. Therefore, initiating reperfusion to the threatened myocardium either by thrombolysis, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is the best therapeutic strategy to offer a chance of survival following acute coronary occlusion [3].

Myocardial salvage by timely reperfusion is associated with smaller infarct size, less enzyme release and better cardiac function recovery. However, there is convincing evidence that the sudden restoration of blood flow to ischemic myocardium may paradoxically exaggerate injury that is not present at the end of ischemia and could be modified by interventions given only at reperfusion [4]. Reperfusion elicits a broad range of injury pathologies depending upon the timing of restoration of blood flow and involving in a number of triggers, mediators and end-effectors responsible for vascular endothelial dysfunction, up-regulation of adhesion molecules on the endothelium, transendothelial emigration of inflammatory cells, tissue edema, infarction, and apoptosis. Many of these events

occur in the very early moments of reperfusion; however, other events trigger a cascade of responses that take place at a later phase, ultimately contributing to expansion of the infarct area, ventricular dilation, thinning of the ventricular wall and cardiac systolic or diastolic dysfunction [5]. Since reperfusion paradoxically leads to variable amounts of salvageable myocardium, the means and timing of restoring blood flow continue to be a highly debated and studied topic [6, 7].

The concept of attenuating reperfusion injury was initially introduced by Buckberg and coworkers in the late 1970s in surgical animal models and patients with acute coronary artery occlusions [8, 9]. In their studies, controlled reperfusion after ischemia with monitoring flow rate, perfusion pressure, and composition of the reperfusate have shown significant muscle salvage, less post-ischemic edema and better function recovery compared to uncontrolled reperfusion. In the mid-1980s, a phenomenon termed lethal reperfusion injury was further addressed by Braunwald and Kloner [10]. Thereafter, pharmacological interventions such as β-blocker, anti-inflammatory agents, calcium-channel blockers, free radical scavengers, sodium-hydrogen exchanger inhibitor, nitric oxide donor and adenosine have successfully reduced infarct size and improved cardiac function in animal models of ischemia and reperfusion. Although it has been more than 20 years since these protective strategies were introduced, none of the drugs that only modify reperfusion injury has gained clinical acceptance for routine treatment of infarct patients. The failure to translate these experimental therapies to the bedside has made people argue whether we still need to continually develop pharmacological agents (because the maximum protection with current conventional therapies might have already been achieved), and whether reperfusion injury truly exists in patients [11, 12]. Increasing injury seen at reperfusion likely occurs during ischemia because the time frame and boundary between ischemia and reperfusion are unknown [6]. Therefore, it is extremely valuable to explore clinically applicable and effective therapeutic strategies to address post-ischemic myocardial injury.

Postcon is defined as several repeated cycles of intermittent reperfusion/re-occlusion applied after an index ischemia, and has shown a significant reduction in infarct size [13]. The results were validated in all species studied by the investigators from different laboratories. Several clinical trials have also shown promising outcomes showing a reduction in infarct size and enzyme release in patients undergoing PCI and CABG. These experimental studies and clinical observations have demonstrated that Postcon protects the heart from reperfusion injury through altering events within the first minutes after revascularization of acute myocardial ischemia. These results have also shown that the early minutes are critical for reperfusion-induced myocardial injury. Any operating procedure aimed at modifying myocardial infarction may need to be conducted in the early minutes during restoration of coronary blood flow [14, 15]. This review article will summarize the Postcon protection reported from experimental and clinical studies, highlight unsolved issues involving the molecular signaling mechanisms underlying Postcon protection, and discuss potential new targets in treatment of reperfusion injury in different organ systems with Postcon.

Cardioprotection by Postcon: evidence from animal studies

Numerous studies including in vivo and in vitro models of dog [13, 16–18], pig [19], monkey [20], rats [21], rabbits [22] and mice [23, 24] have shown infarct-sparing effect of Postcon on ischemic/reperfused heart after it was initially reported from our laboratory in 2003 [13]. In addition, we and others have also shown that Postcon reduces hypoxia/reoxygeantion-induced cardiomyocyte necrosis and apoptosis [25–30]. This new strategy achieves cardioprotection comparable to preconditioning [17]. Although the cycles of Postcon selected in different studies are not identical, it is generally agreed upon that animals with a faster heart rate and higher metabolic rate should be postconditioned using a short duration of the algorithm. While in larger animals, the duration of alternating periods could be longer. Based on the studies updated, the duration of each alternating period of reperfusion and ischemia vary among different species. In small species (i.e., rats and mice), the algorithm of Postcon is 5–10 sec; in larger animals (i.e. dog, pig and monkey), it runs 30–60 sec; in human and cultured cardiomyocytes, alternating periods with Postcon is 1–5 min. It has been speculated that the lower metabolic rate in larger animals may decrease generation of endogenous ligand triggers of Postcon such as adenosine, thereby require a longer Postcon stimulus [31]. Some of the primary physiological endpoints of protection modulated by Postcon during reperfusion are summarized in Table 1.

Reduction in infarct size

Reduction in infarct size is considered a “gold standard” to evaluate the efficacy of interventions tested. The first study to demonstrate the infarct-sparing effect of Postcon was performed in a canine model of 60 min coronary occlusion followed by 3 h of reperfusion [13]. The initial algorithm selected for Postcon was two cycles of 5 min reperfusion followed by 5 min reocclusion. Failure in attenuating infarct size made us to shorten the cycles from minutes to seconds, because in most canines, ventricular fibrillation occurred within the first minute after reperfusion. Surprisingly, both ventricular arrhythmia and infarct size were

Table 1 Primary physiological endpoints of protection by Postcon during reperfusion

Delay in washout of endogenous autacoids
Adenosine, opioids and bradyknin
Reduction of inflammatory response
Reactive oxygen species
TNFα, Interleukins-6 and 8
Neutrophil migration
Protection of vascular endothelium
p-selectin expression
Endothelium-dependent vasodilation
Stimulation of survival kinases and transmitter
PI-3K-AKT
p42/44 ERK MAPK
PKC-α and -ε
Hydrogen sulphide
Inhibition of death kinases
p38 MAPK
JNK MAPK
GSK-3β
PKC-δ
Preservation of mitochondrial function
Membrane potential
Permeability transition pore
K_{ATP} channels
Reduction in cardiomyocyte loss
Necrosis
Apoptosis

significantly reduced when the ischemic myocardium was reperfused with three cycles of 30-s reperfusion separated by 30-s re-occlusion. Relative to the control animals, Postcon significantly reduced the infarct size giving a compatible level in reduction of infarct size in preconditioned-animals (Fig. 1a). To determine whether there is an additive effect on reducing infarct size, in a subsequent study, preconditioning with one cycle of 5 min ischemia/10 min reperfusion before ischemia and Postcon with 30-s reperfusion/30-s ischemia at reperfusion were combined in this canine model after an index 60 min ischemia.[17] Relative to either intervention alone, combination of both protocols did not show an additive protection, whether assessed by infarct size (Fig. 1a), free radical production or vascular endothelial function. In isolated rat heart, Tsang et al. [32] did not find an additive effect with preconditioning and Postcon on infarct size. But in the in vivo rabbit model of ischemia and reperfusion, Yang et al. found that there is an additive effect of preconditioning and Postcon on infarct size [33]. Furthermore, persistent beneficial effect of Postcon against infarct size was also demonstrated in this canine model after 24 h of reperfusion (Fig. 1b) [34], and in rabbit model after 72 h reperfusion [35]. Subsequent studies in rat, rabbit, murine and monkey have also demonstrated a significant reduction in infarct size as recently reviewed by Skyschally [36] and Downey [11].

However, the infarct-sparing effect of Postcon has not been consistently reported in different species and in different pathological conditions. The first negative study with Postcon was reported by Schwartz in the in vivo pig model [37]. Three 30/30-s cycles of Postcon did not show an inhibition on infarct size at the end of 3 h of reperfusion. But in Iliodromitis's study, Postcon with eight cycles of 30-s of reperfusion separated by 30-s reocclusion did find a significant reduction in infarct size in pig [19]. Recently, there are two studies from Kloner's group showing that Postcon with a variety of cycles in rat [38] and rabbit [39] failed to reduce infarct size while these algorithms have

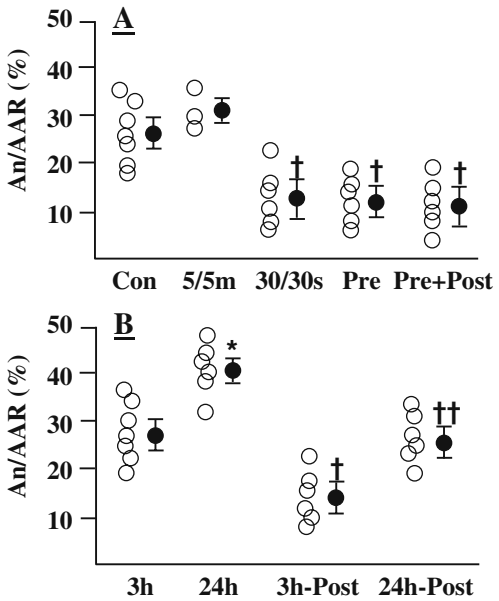

Fig. 1 Infarct size (An/AAR), expressed the area of necrosis (An) as a percentage of area at risk (AAR) in the in vivo canine model of 60 min coronary occlusion followed by 3 or 24 h of reperfusion, respectively. In figure A, Postcon was applied as three cycles 5 min reperfusion/5 min reocclusion (5/5 m) or 30 s reperfusion/30 s reocclusion (30/30 s). Algorithm of preconditioning (Precon) was selected as 5 min ischemia and 10 min of reperfusion. Pre+Post: Precon and Postcon were combined. Postcon significantly reduced An/AAR, which is equivalent cardioprotection to that of Precon. No further reduction in infarct size with Precon plus Postcon was detected. In figure B, reperfusion time was extended from 3 to 24 h. Infarct size was measured after Postcon with three cycles of 30 s reperfusion/30 s reocclusion was applied at the onset of 3 h (3 h-Post) or 24 h (24 h-Post) of reperfusion, respectively. A significant reduction in infarct size after 24 h of reperfusion was still detected in postconditioned animals. The *open circles* represent individual data points and the solid circles represent the means. *Error bars* represent standard error of the mean. †$p<0.05$ vs. control (Con); *$p<0.05$ vs. 3 h; ††$p<0.05$ vs. 24 h. Data are references [13, 17, 34]

shown to be very effective in attenuating infarct size reported from many other studies in rats [21, 40] and rabbits [41–43]. It is difficalut to explain these variations on infarct size reduction with Postcon; however, unidentified laboratory-specific variables may exist in addition to the differences of selected algorithms [44].

There are also some controversial reports in Postcon-induced protection in models of ageing, hyperchesterolaemia, obesity and diabetes. In older rats, Yin et al. found that Postcon reduces infarct size in the in vivo model of 16 to 18-month-old rat [45]. Przyklenk et al. demonstrated that Postcon is unable to reduce infarct size in 20- to 24 old C57BL/6J mice [46]. But in aged wild-type and in C57BL/6J mice, Kerstin et al. reported that reduction in infarct size depends upon the cycles of Postcon. Significant infarct reduction was detected when the heart was postconditioned using five 5/5-s cycles, but not three 10/10-s cycles [47].

In a cholesterol supplemented diet rabbit model, Donato et al. found that Postcon reduces infarct size [48]. But Illodromitis et al. have shown that the infarct-sparing effect of Postcon is lost in rabbits with experimental hyperlipidemia and atherosclerosis [49]. The degree of hypercholesterolaemia in different models may explain the discrepancy of these studies [35].

Epidemiological studies and clinical trials have shown that obesity and diabetes are risk factors for developing acute myocardial infarction and postischemic complications. Mortality from myocardial infarction is almost doubled in obese/diabetic patients compared with nondiabetic individuals [50]. In genetically obese ob/ob murine model, Bouhidel et al. recently reported that infarct-sparing effect of Postcon is lost [51]. Wagner et al. have also found that protective effect of Postcon does not exist in rats with established metabolic syndrome, characterized by obesity, dyslipidaemia and hyperinsulinaemia, relative to the wide type rats [52]. However, in Prazyklenk's study, they demonstrated that the infarct size-limiting effect of Postcon is restored by islet cell transplantation in streptozotocin-induced diabetic mice [53]. These studies clearly demonstrated that animals with metabolic syndromes are more susceptible to ischemia/reperfusion injury. But, clinical significance from these studies is unknown since blood glucose in patients seldom reach such high concentrations because of insulin treatment [35].

Prevention of ventricular arrhythmia

The anti-arrhythmic effect of Postcon has been universally reported by different investigators. Na et al. initially reported that intermittent interruption of reperfusion with a single 5/35-s cycle of Postcon significantly reduced ventricular tachycardia and fibrillation in a cat model with 20 min of ischemia followed by 10 min of reperfusion [54]. We have also found that three 30/30-s cycles of Postcon reduces the occurrence of ventricular fibrillation at the onset of reperfusion in a canine model with 60 min ischemia [17]. Significant antiarrhythmic effect against persistent reperfusion-induced tachyarrhythmias was further demonstrated in the isolated rat heart by Galagudza et al. [56]. In the in vivo rat model of 5 min ischemia, Kloner et al. reported that four 20/20-s cycles of Postcon markedly attenuate ventricular arrhythmia. Sasaki et al. demonstrated that in isolated rat heart of 20 min global ischemia, Postcon significantly terminated reperfusion arrhythmia, but preconditioning failed to alter the incidence or duration of ventricular arrhythmia [55, 57]. In a recent report, Dow et al. demonstrated that Postcon's benefit on reperfusion ventricular arrhythmia is still maintained in 24-month-old Fischer female rats relative to younger rats [58].

Attenuation in inflammatory response and endothelial dysfunction

Data from in vivo models of ischemia and reperfusion [13] and cultured cardiomyocytes after hypoxia and reoxygenation [25] have shown that Postcon reduces the generation of reactive oxygen species as expressed by diminished dihydroethidium fluorescent staining in post-ischemic myocardium and cultured cardiomyocytes as well as plasma levels of malondialdehyde [17]. Postcon decreased the surface expression of p-selectin, adherence of neutrophils to postischemic coronary artery vascular endothelium, and accumulation of neutrophils in area-at-risk myocardium. In addition, Postcon also preserved post-ischemic coronary artery endothelial function assessed by vasodilator responses to acetylcholine [35]. However, the cause-effect relationship between inhibition of the inflammatory response and cardioprotection by Postcon is still a controversial topic in the literature. In a canine model of 60 min ischemia and 3 h of reperfusion, three 30/30-s cycles of Postcon did not alter level of superoxide radicals measured using luminal-enhanced chemiluminescence in blood taken from the anterior interventricular vein draining from the area at risk myocarium both at 3 and 24 h of reperfusion (unpublished data). In addition, reduction in infarct size and attenuation of cardiomyocyte death by Postcon have been previously demonstrated in neutrophil-free culture system [25] and isolated heart [59]. At the current time, it is not clear whether less inflammatory response after Postcon reduces myocardial injury or whether less myocardial injury by Postcon produces a smaller inflammatory response [60].

Inhibition of cytokine release and apoptosis

Reperfusion triggers pro-inflammatory cytokine release and apoptotic cell death [61]. In cultured neonatal rat cardio-

myocytes of 3 h hypoxia and 3 h reoxygenation, Sun et al. showed a reduction in generation of superoxide anion detected by lucigenin-enhanced chemiluminescence, cytochrome c release, and dihydroethidium fluorescence after three 5/5 min cycles of hypoxic Postcon [25]. Several other studies in cultured cardiomyocytes and isolated heart have also reported attenuation of apoptosis, inhibition of mPTP opening and preservation of mitochondrial integrity by hypoxic Postcon [25, 62–64]. A recent study in a rat model of 30 min ischemia and 3 h reperfusion by Kin et al. demonstrated that three 10/10-s cycles of Postcon reduce the levels of tissue necrosis factor alpha and interleukin-6, consistent with an attenuation in the number of apoptotic cells in area-at-risk myocardium [65].

Cardioprotection by Postcon: evidence from clinical trials

Recently, Hansen et al. performed a systemic review and meta-analysis from six studies with a total of 123 patients who underwent PCI with or without Postcon in multiple centers. These studies were randomized based on the age, gender and comorbidity on admission. The results revealed that STEMI patients undergoing primary PCI greatly benefitted from Postcon over standard care for reduction of infarct size, peak CK release and left ventricular ejection fraction [66]. In addition, at the time of writing this article, there are 24 clinical trials of Postcon or remote Postcon either enrolling patients or ready for launch, and three on "pharmacological" Postcon with sevoflurane and adenosine for STEMI patients undergoing PCI or CABG procedures (search from ClinicalTrials.gov).

Resolution in ST-segment elevation

In a pilot study in 2005, Laskey [67] first reported that two 90/90-s cycles of repeated balloon inflation and deflation separated by 3–5 min of reperfusion during angioplasty reduced the magnitude of ST-segment elevation compared to controls. The rate of ST-segment resolution was faster at the end of the PCI procedure. Furthermore, coronary flow velocity reserve was significantly improved in "conditioned" hearts compared to the standard-of-care cohort. In 2008, the authors further demonstrated the beneficial effects of Postcon during PCI for STEMI patients on measures of myocardial perfusion and microcirculatory function. They found that ST segment resolution is faster and hyperemic coronary vasodilator response is greater in postconditioned patients. In addition, a peak of serum CK activity was significantly lower when compared with controls. Although there is a concern regarding embolism of atherosclerotic debris in distal coronary arteries by repetitive inflation and deflation during PCI, distal perfusion was significantly improved by this maneuver in this study. No angiographic or clinical complications were found [68].

Reduction in creatine kinase release and inflammatory response

The first study to demonstrate reduction in infarct size by Postcon in patients was reported by Ovize and his colleagues in a multi-center randomized clinical trial [69]. The patients that achieved a TIMI flow grade of 2–3 at completion of the angioplasty/stent procedure were randomized to receive either standard of care treatment or four 60/60-s cycles of Postcon. Infarct size estimated from the area under the CK curve at 72 h of reperfusion was significantly less, and greater coronary blood flow was achieved in patients with Postcon. The results of this study were intriguing because it is a "proof of concept" study to demonstrate reperfusion injury in patients. This observation was extended by Ma et al. in 2006 [70]. They showed that Postcon significantly reduces the levels of CK, CK-MB and malondialdehyde, and increases the velocity of coronary blood relative to patients who underwent conventional PCI. After 8 weeks, the wall motion score index (WMSI) calculated by DeltaWMSI was significantly improved and endothelium-dependent vasodilation was enhanced. In a retrospective study, Darling et al. reported a similar result that reduced CK release was seen in STEMI patients who underwent more than 4 cycles with inflations of the angioplasty balloon at the time of reperfusion compared with those who received less than 3 inflations [71]. Coincidental results were also reported in another recent retrospective study from 433 STEMI patients by Wang et al. [72]. Significant reduction in peak CK release, faster resolution in ST-segment and improvement in left ventricular ejection fraction were observed in postconditioned patients with more than 3 cycles repetitive low-pressure balloon inflations within 10 min of reflow during primary PCI.

Persistent attenuation in infarct size and apoptosis

Emerging experimental evidence suggests that post-ischemic injury is an on-going process that continues up to delayed phases of reperfusion, as evidenced by the extent of myocardial necrosis and progressive induction of apoptosis over reperfusion time [5, 73]. Although experimental studies have shown that Postcon reduces infarct size after 24 h of reperfusion in canine [13, 16–18, 35] and 72 h of reperfusion in rabbit [41], little is known whether application of Postcon at the onset of reperfusion permanently reduces infarct size after a prolonged reperfusion in patients.

Reduction in infarct size after a prolonged reperfusion was initially reported by Yang and his colleagues in 2007 [74]. In 23 patients, three 30/30-s cycles of Postcon reduced the area under the CK activity curve during the first 72 h of reperfusion, consistent with the previous report from Ovize's group. Importantly, at 7-d of reperfusion, infarct size expressed as percent left ventricle, detected by single-photo emission computed tomography (SPECT) was 27% less than in the control patients, suggesting a long-term protection of Postcon.

Soon thereafter, another study was reported by Ovize and his colleagues in 2008, consisting of two groups of patients randomized for area-at-risk myocardium, collateral flow and duration of ischemia [75]. The authors found that infarct size, also determined using the SPECT method, was 39% less than the control group at 6 months when the patients were postconditioned using four 60/60-s cycles of repeated deflation and inflation. At one year after this intervention, left ventricular ejection fraction in postconditioned patients exhibited a 7% increase compared with controls.

After Yang and his colleagues published their first study to show a reduction in infarct size in patients [74], in a subsequent clinical trial, they further compared the efficacy between three 30/30-s cycles and three 60/60-s cycles of Postcon on infarct size. Although they found no significant difference in reduction in infarct size using these two Postcon algorithms (personal communication, unpublished data), in their follow-up analysis reported by Zhao et al. in 2009, three 60/60-s cycles of Postcon significantly reduced soluble plasma Fas/APO-1 and Fas ligand, the surrogate markers for myocardial apoptosis. These beneficial effects were accompanied by an improvement in left ventricular function 7 days after stenting [76]. Along with long-term attenuation in infarct size with four 60/60-s cycles of Postcon [74, 75], it is clear from this observation and others that 60/60-s cycles of Postcon provide better recovery from injury in patients with acute myocardial infarction with regards to tissue necrosis, cardiac dysfunction and myocardial apoptosis.

Protection of Postcon in cardiac surgery

Cardiac surgery (i.e. coronary artery revascularization, congenital lesion repair and valve replacement) is associated with ischemia/reperfusion injury for most of the operations performed. During the last decades, much progress has been made to reduce myocardial injury during aortic clamping by the induction of electromechanical arrest and profound cardiac cooling with cold crystalloid solutions or protection with blood cardioplegia. However, rapid restoration of coronary blood during aortic declamping induces further reperfusion damage. Despite a great number of experimentally-developed therapeutic strategies and clinical studies to address reperfusion injury, a significant portion of the surgical population may still experience substantial morbidity related to adverse cardiovascular events after cardiac surgery. Very few interventions have been incorporated in routine clinical practice. Postcon can be applied by declamping and reclamping the aorta when surgical procedure is completed or intermittently delivering blood through the cardioplegia line to mimic the perfusion pattern of Postcon at the onset of aortic clamp release.

In surgical repair of Tetrology of Fallot in children, Luo et al. first reported that three 30/30-s cycles of Postcon (i.e. aortic declamping and reclamping) at the onset of aortic clamp release significantly reduces plasma troponin I and lactate levels compared with the control patients during reperfusion [77]. In a progress report, they found that the rate of morbidity, the time of ventilation and ICU stay, the dose of inotropic agents were significantly less in the postconditioned patients. In adult patients undergoing valve replacement using cardiopulmonary bypass and standard crystalloid cardioplegia solution, Luo et al. further analyzed the change of plasma CK-MB over time in patients with and without Postcon. Plasma CK-MB was significantly lower in the postconditioned patients relative to the control group with identical cardiopulmonary resuscitation protocols at 4 and 8 h after reperfusion. There is a concern regarding repetitive aortic clamping, particularly for elderly patients who have some degree of atheromatous plaques in the aorta, which may cause emboli in the distal coronary artery or induce stroke and focal ischemia. However, no adverse effects were reported from their studies [78].

Protective mechanisms targeted by Postcon

There are a number of intrinsic reperfusion processes that contribute to reperfusion-induced myocardial injury. These consequences include the generation of free oxygen radicals, neutrophil accumulation, endothelial dysfunction, rapid recovery of tissue acidosis, loss of calcium homeostasis, myocardial stunning and necrosis, all of which have the ability to cause greater tissue damage within a few minutes after restoration of blood flow. Although understanding of the precise cellular signaling pathways with Postcon is still evolving, based on the reports from different experimental settings, diverse signaling mechanisms by targeting on these events have been proposed. As depicted in Fig. 2, Postcon reduces superoxide free radical generation and lipid peroxidaion, attenuates inflammatory and endothelial cell-cell interactions [13], preserves actions of endogenous autacoids such as adenosine, opioids, bradykinin via G-protein-coupled receptor (GPCR) [79–82], stimulates survival kinases such as the p42/44 ERK MAPK,

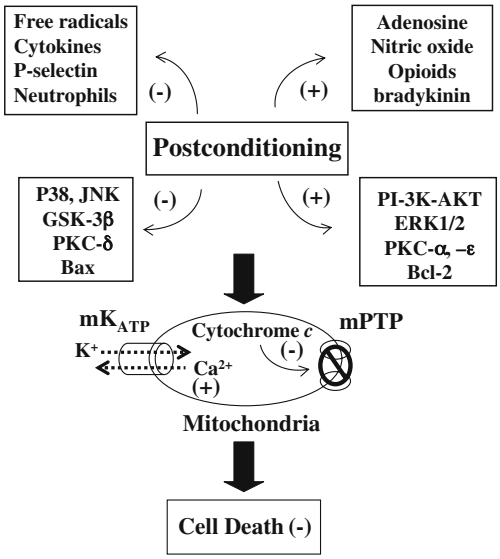

Fig. 2 Simplified schematic diagrams of reperfusion salvage by Postcon. Protection with Postcon may be derived from its parallel, up- or down-stream direct or indirect effects on inflammatory responses, endogenous autacoids, survival and death protein kinases, mitochondrial K_{ATP} channel (mK_{ATP}) and mitochondrial permeability transition pore (mPTP). The current theory regarding signalling mechanisms underlying protection is that Postcon activates G protein-coupled receptors on the cell membrane via endogenous autacoids followed by modulation of protein kinase pathways, which has been proposed to inhibit p38, JNK MAPK, PKCδ, GSK-3β and stimulate PI-3K-AKT, ERK MAPK and PKCε. The rebalance among these death and survival protein kinases by Postcon may initiate a down-stream opening of mK_{ATP} and closing of mPTP responsible for inhibition of necrosis and apoptosis

PI-3K-Akt and protein kinase C-ε [32, 79, 83], reduces activity of death kinases including the JNK MAPK and the p38 MAPKs, inhibits phosphorylation of inducible transcription factor (i.e., NF-κB) [65] and glycogen synthase kinase-3β [84], slows down recovery of tissue pH [85], activates mitochondrial K_{ATP} channels [33, 86], and inhibits mitochondrial permeability transition pore (mPTP) opening [41, 86]. Delay in application of Postcon, even for a few minutes, eliminates these cellular events, suggesting that these signaling cascades are quickly activated during early periods of reperfusion, and work as causative mechanisms for protection [21].

However, it is not clear from previous studies how these signaling cascades are linked. For example, administration of different receptor antagonists either for adenosine, opioid, or bradykinin alone at the onset of reperfusion abrogated infarct reduction by Postcon [79, 82, 87]. Blockade of survival kinases or reactivation of death kinases also eliminated protection by Postcon. It is possible that, in response to oxidant stimulation, the endogenous autacoids, survival and death protein kinases could be altered in a parallel manner at certain time points during reperfusion. On the other hand, the activation of some protein kinases may also depend on the status of other isoforms of protein kinases. For example, the PKC activation relies upon PI-3K-Akt phosphorylation, and the PKCε translocation inhibitor blocks ERK1/2 activation [88, 89]. These data suggest that there is cross-talk among protein kinases. At the current time, however, we do not know exactly whether survival or death protein kinase-mediated signaling mechanisms occur simultaneously, and how they are balanced in modulation of infarct size by Postcon.

As potential executors, the opening of mitochondrial K_{ATP} channels and the closing of mPTP have been reported to be cardioprotective during reperfusion [33, 86]. Several recent studies have confirmed that the infarct-sparing effect of Postcon is abrogated by the mitochondrial K_{ATP} channel blocker, 5-hydroxydecanoate, but not by the sarcolemmal K_{ATP} channel blocker, HMR1098 [33]. The collapse of mitochondrial membrane potential and the opening of mPTP in the inner mitochondrial membrane, which occur in the early minutes of reperfusion, have been linked to the pathogenesis of both necrosis and apoptosis [90, 91]. This opening of mPTP, associated with intracellular Ca^{2+} overload [91], has been proposed to disrupt permeability characteristics of the membrane, resulting in an influx of normally impermeable proteins with subsequent mitochondrial swelling, breakdown in protein gradient and collapse of oxidative phosporylation [92]. The releasing of cytochrome c from mitochondria activates downstream "execution response" via caspases that stimulates rupture of the outer membrane, apoptosis and necrosis [93–95]. It has been suggested that inhibition of mPTP depends upon activation of mitochondrial K_{ATP} channels [96]. The possible link between the K_{ATP} channel and the mPTP indicates that mitochondrial K_{ATP} channels may be considered more of a mediator than its previous role as an end-effector organelle [97]. However, it is unknown how opening of the mitochondrial K_{ATP} channel by Postcon is associated with inhibition of mPTP. In addition, it will be important to know whether there is a functional link among survival kinases, mitochondrial K_{ATP} channel and mPTP to explain the molecular mechanisms responsible for protection by Postcon.

It is generally agreed upon that inhibition of mPTP with Postcon is a final step in a complex series of cellular events responsible for cell protection [33, 41, 86]. The mPTP remains in a largely closed state during ischemia and increases its open probability during early reperfusion. Opening of the mPTP is considered as key event in reperfusion-induced cell death. Argaud et al. first reported that Postcon reduces calcium-induced opening of the mPTP in mitochondria isolated from the area-at-risk myocardium [41]. In cultured cardiac muscle cells, Mykytenko et al. also found that hypoxic Postcon maintains mitochondrial mem-

brane potential and inhibits opening of the mPTP [86]. Accordingly, pharmacological inhibition of the mPTP with cyclosporine A during reperfusion has shown a reduction in infarct size similar to that in postconditioned animals [98]. Piot et al. has recently reported that administration of cyclosporine A at the time of reperfusion reduces infarct size evidenced by less creatine kinase release and delayed hyperenhancement on MRI in patients [99]. This is the first study to show that patients who undergo PCI can be pharmacologically postconditioned. Due to a lack of clinical evidence to show infarct-sparing effect by pharmacological interventions, these results are promising although it is a "proof of concept" small clinical trial.

Remote Postcon

The first study to demonstrate infarct-sparing effect with remote Postcon was reported by Kerendi et al. in a rat model of ischemia and reperfusion in 2005 [100]. In that study, a renal artery was ligated for 5 min and then released at the onset of coronary artery reperfusion. Compared to the control animals with abrupt reperfusion, infarct size was reduced by nearly 50%. This remote protection was abrogated by an adenosine receptor antagonist. In a subsequent study with a swine model of acute myocardial infarction, Andreka et al. also found that four 5/5 min cycles of blood pressure cuff inflation/deflation applied to the lower limb at the onset of balloon deflation after 90 min coronary occlusion reduce infarct size and creatine kinase release at 72 h after reperfusion [101]. These observations suggest that remote Postcon releases soluble and circulating mediators such as adenosine that can sustain the transit time between a remote organ and an ischemic/reperfused heart.

The first human study to demonstrate the protective effect of remote Postcon on endothelial function after 20 min ischemia followed by reperfusion was performed by Loukogeorgakis in 2006 [102]. They found that remote Postcon applied in an arm or leg at the onset of reperfusion significantly preserves flow-mediated vasodilatation. Protection was blocked by a non-selective K_{ATP} channel blocker, glibenclamide [103]. A recent clinical observation reported by Bøtker et al. at the American College of Cardiology 58th Annual Scientific Session in 2009 demonstrated that upper-limb ischemia with four 5/5 min inflation/deflation using a standard blood pressure cuff initiated during ambulance transfer (named as remote perconditioning) reduces myocardial infarct size measured by SPECT imaging after 30 days of standard PCI in STEMI patients. Although the protective mechanisms underlying remote Postcon are unknown, these data have clearly demonstrated the feasibility and safety in application of remote Postcon as an adjunct to current reperfusion strategies.

Attenuation of reperfusion injury by Postcon in other organs

The role of Postcon in attenuation of reperfusion injury in other organ systems including the spinal cord, brain, kidney, muscle, liver, lung and intestine has been recently studied and summarized in Table 2.

Reduction of spinal cord and brain injury

In spinal cord with infrarenal aorta occlusion-induced ischemia, Jiang et al. demonstrated that four 60/60-s cycles of Postcon significantly increased the Tarlov score and number of intact motor neurons in rabbit [104]. Protection was still preserved when application of Postcon was delayed 5 min after reperfusion, but with no protection after 10 min. Also, they found that additive neuroprotective effects on the spinal cord when preconditioning and Postcon were combined [105]. Song et al. found that attenuation in spinal cord injury during 48 h of reperfusion with three 30/30 s cycles of Postcon is associated with up-regulation of endogenous antioxidant enzymes activities [106]. Wang et al. demonstrated that several different algorithms of Postcon from 15/15-s to 60/60-s protect neuronal loss and cytochrome c release at 7 d of reperfusion after 10 min global cerebral ischemia in rats [107]. In addition, neuroprotection with Postcon has been associated with preservation of endogenous antioxidant enzymes[108] and down-regulation of cytochromec c release and caspase 3 activity [109]. Interestingly, Burda et al. [110] showed that Postcon performed 2 days after reperfusion in a rat model of global ischemia still robustly reduces hippocampal injury. Zhao and his colleagues recently reported that 3 or 6 h of delay in application of Postcon after focal ischemia significantly reduces infarct size and improves behavioral outcomes, showing there is a wide window in application of Postcon after stroke [111–113].

Renal protection

The mortality rate after reperfusion of the ischemic kidney after renal transplantation is associated with delayed graft dysfunction due to increased necrosis of renal tubules. Szwarc et al. reported that three 30/30 s cycles of Postcon reduce the level of serum creatinine and improve kidney function 8 days after grafting [114]. Liu et al. demonstrated that Postcon-exerted protection is evidenced by increase in nitric oxide release and NO synthase expression [115]. Recently, Serviddio et al. found that Postcon with a

Table 2 Protection by Postcon on different organ systems

References	Species	Organs	Postcon protocols			Protection endpoints and mechanisms
			Index ischemic duration (min)	Number of cycles	Ischemia/reperfusion per cycle	
Jiang et al. [104]	Rabbit	Spinal cord	25	6	5/5 or 10/10 s	Tarlow score, intact motor neuron No.
Jiang et al. [105]	Rabbit	Spinal cord	30	4	60/60 s	Histology, amyloid precursor protein
Song et al. [106]	Rabbit	Spinal cord	20	3	30/30 s	SOD, CAT activity
Wang et al. [107]	Rat	Spinal cord	10	3	15/15, 30/30. 60/60 s	Cytochrome c, neuronal damage
Zhao et al. [111]	Rat	Brain	15,30,60	3	10/10 s	Infarct size, apoptotic index, free radicals
Xing et al. [109]	Rat	Brain	60	3	30/30 s	Cytochrome c, Bax, caspase-3 activity
Burda et al. [110]	Rat	Brain	15	1	5 min/n/a	Neuronal population in cortex, striatum
Ren et al. [113]	Rat	Brain	30	10	10/10 s	FDG uptake, edema, infarct size
Szwarc et al. [114]	Mice	Kidney	30	3	30/30 s	Creatinine level, wet/dry ratio
Liu et al. [115]	Rat	Kidney	45	6	10/10 s	eNOS, iNOS, endothelin-1, NO
Serviddio et al. [116]	Rat	Kidney	90	3	180/5, 360/5, 720/5 s	BUN, creatinine, mitochondrial function
Chen et al. [117]	Rat	Kidney	45	n/a	n/a	AKT, ERK activity
Yun et al. [118]	Rat	Kidney	45	6, 10	10/10 s	SOD, AKT, GSH-Px, MDA activity
Eldaif et al. [119]	Rat	Kidney	45	4	45/45	BUN, creatinine, histology, TUNEL
Sivaraman et al. [120]	Human	Atrial muscle	90	4	30/30 s	Contractile function
McAllister et al. [121]	Pig	Skeletal muscle	240	4, 6	30/30 s	Infarction, ATP content
Sun et al. [123]	Rat	Liver	60	4	2/2,3/2,5/2,7/2 s	TUNEL staining, Bcl-2
Wang et al. [124]	Rat	Liver	Graft	n/a	n/a	TNFa, MIP-2 expression
Wu et al. [125]	Rat	Liver	n/a	n/a	n/a	MDA, GSH, SOD, GSH-Px, MPO
Wang et al. [126]	Rat	Liver	30	3	30/30 s	Apoptotic index, glucose, GGT
Xia et al. [127]	Rat	Lung	40	3	30/30 s	Haeme oxygenase-1, MDA activity
Liu et al. [128]	Rat	Lung	60	3	30/30 s	Wet/dry ratio, TNFα, IL-6, MDA activity
Santos et al. [129]	Rat	Intestine	30	3	30/30 s	Chu's score, wet/dry ratio
Liu et al. [130]	Rat	Intestine	60	3	30/30 s	Chu's score, wet/dry ratio, TNFα, IL-6

Data presented in this table are obtained from a combination search using a key word in each category plus Postcon in Medline. The results only show the protection with mechanical Postcon and do not include studies of pharmacological, remote and delayed Postcon

n/a means that data are not available in Medline

consecutive sequence of 3, 6 and 12 min of reperfusion, separated by 5 min of reocclusion reduces creatinine and BUN levels. Protection was associated with preservation of mitochondrial function after 24 and 48 h of reperfusion [116]. Furthermore, attenuation of reperfusion injury with Postcon in kidney has been also associated with phosphorylation of Akt and ERK1/2 by Chen et al. [117] and preservation of antioxidant enzymes such as superoxide dismutase, catalase and glutathione perokidase by Yun et al. [118]. We have recently reported that attenuation of renal ischemia/reperfusion injury by Postcon involves adenosine receptor and PKC activation [119].

Muscle preservation

The first study using human atrial appendages was reported by Sivaraman et al. [120]. Atrial trabecula were isolated and mounted on a superperfusion apparatus and subjected to 90 min of hypoxia followed by 120 min of reoxygenation. Four 30/30-s cycles of hypoxic Postcon improved the recovery of contractile function relative to the baseline values. Protection was abolished in the presence of either LY294002, a PI3K inhibitor or UO126, a MEK1/2 inhibitor. In an elegant study by McAllister et al. [121], reperfusion of latissimus dorsi muscle flaps after 4 h ischemia showed a time-dependent expansion of muscle infarction with a peak at 24 h. Four 30/30 s cycles of Postcon applied at onset of reperfusion reduces muscle infarction significantly at 48 h of reperfusion. Protection was mimicked by the mPTP inhibitor cyclosporine A or NIM-811, and abolished by mPTP opener atractyloside. Furthermore, protection was associated with a decrease in muscle myeloperoxidase activity and mitochondrial calcium concentration. In a rat model of 4 h limb ischemia induced by infrarenal cross-clamping of the abdominal aorta followed by 4 h of reperfusion, Szijarto et al. demonstrated that six 10/10-s cycles of aortic Postcon induce a significant reduction in systemic inflammatory response and preservation in microcirculatory flow character [122].

Protection in hepatic reperfusion injury

The first study to demonstrate protection of Postcon on liver injury was reported by Sun et al. in a rat model of ischemia and reperfusion. The authors found that Postcon reduces hepatocellular apoptosis and preserves mitochondrial ultrastructure. Protection was accompanied by up-regulation of Bcl-2 and inhibition of superoxide free radical generation [123]. In a rat model of liver transplantation, Wang et al. demonstrated that lower cytokine levels and preserved antioxidase contents as well as reduced TNFα and MIP-2 expression are seen at 6 h of liver graft in postconditioned animals [124]. Similar findings were also observed by Wu et al. [125]. They found that Postcon preserves the endogenous antioxidant enzyme activity and inhibits inflammatory response, giving a level of protection comparable to preconditioning. A comparative study between preconditioning and Postcon was recently reported by Wang et al. using a rat model of liver ischemia/reperfusion during transplantation. Mortality rate and hepatocellular apoptosis were equally inhibited either by preconditioning or Postcon, reflected by preserved hepatocyte function and reduced Fas gene expression [126].

Attenuation of reperfusion injury in lung and intestine

Protection of Postcon on reperfusion-initiated lung and intestine injury has been recently reported. Xia et al. demonstrated that three 30/30-s cycles of Postcon reduces lung wet/dry weight ratio and malondiadehyde content. Protection was abolished using a heme oxygenase-1 inhibitor [127]. Similar findings were also demonstrated by Liu et al. using the same algorithm of Postcon in rat. Ischemia/reperfusion-induced damage in lung evidenced by increased wet/dry weight ratio, pulmonary permeability index and inflammatory responses were significantly inhibited by Postcon similar to levels in preconditioned animals [128]. In rat model of mesenteric ischemia and reperfusion, Santos et al. found that intestinal mucosa injury evidenced by significantly-increased Chu's score and wet/dry weight ratio was abolished by Postcon [129]. Liu et al. reported similar findings that either preconditioning or Postcon alone provides significant protection; additive effects on attenuation of intestinal injury, cytokines generation and neutrophil infiltration were detected when both interventions were applied in a same animal [130].

Unsolved issues

Many fundamental questions regarding protection by Postcon remaine unanswered. Although the majority of published experimental studies and clinical observations have demonstrated a protective effect of Postcon on different organ systems, there is variability in attenuation of the infarct size with different cycles of Postcon, particularly in the heart. The optimal cycle length to be applied is unknown at the present time. Differences in species, ischemic time and pathological states may underlie these inconsistent observations [31, 36]. Therefore, it is necessary to further explore these signaling pathways by matching different algorithms to study protocols.

Pharmacological Postcon has been proposed as a future direction in treatment of ischemic heart disease based on the investigation of Postcon. As stated above, multiple

signal-transduction pathways have been demonstrated to participate in infarct reduction by Postcon. Although drugs such as adenosine, nitric oxide, opioids or bradykinin when administered at reperfusion have shown to be effective in reducing infarct size in animal studies, no drug has been approved for limiting infarct size in patients with acute coronary syndrome [11]. Therefore, the design strategy of reperfusion therapeutics to salvage tissue injury will be a challenging task because mechanical Postcon may adjust the balance among multiple death and survival signals to exert its protection, which cannot be mimicked by treatment with a single drug.

The duration of ischemia beyond which Postcon can salvage tissue injury has not been well defined. Many randomized clinical trials have shown beneficial effects of early reperfusion within 12 h and possibly up to 24 h after acute myocardial infarction. Although studies have shown that the infarct-sparing effect of Postcon is lost after 45 min of coronary occlusion in animal models [131], the benefits of Postcon applied during late reperfusion, particularly in asymptomatic patients with ongoing ischemia in ischemic border regions that are prone to arrhythmias and necrosis, have yet to be determined in clinical studies. In these cases, reperfusion is warranted to preserve the border areas that may be underperfused even if the interventions occur many hours or days after the initial infarction. It is possible that application of Postcon after prolonged ischemia may improve blood supply and reduce the work demand without clearly salvageable myocardium. It was previously reported that the infarct zone expands during reperfusion and infarct-sparing effect of Postcon is abolished when it is applied a few minutes after reperfusion [35]. However, a recent animal study has provided experimental evidence that six 15/15 min cycles of Postcon applied at 3 or 6 h of reperfusion after focal ischemia significantly reduce infarct size and tissue edema for up to 2 months, suggesting a long-term protection. Therefore, it is necessary to investigate whether a delay in application of Postcon either after prolonged ischemia or reperfusion has a significant impact on in-hospital mortality and long-term survival.

We have previously shown that there is a comparable reduction in infarct size by Postcon and preconditioning [13, 17]. However, it is generally agreed upon that preconditioning is more potent than Postcon in initiating endogenous protective mechanisms [11]. Preconditioning is applied before coronary occlusion and Postcon is applied after irreversible ischemic damage. Preconditioning may increase “damage threshold” of the myocardium during ischemia, but Postcon may increase tolerance of the myocardium for reperfusion-initiated injury. A recent study reported by Cohen’s group helps differentiate this relationship. These investigators studied cynomolgus monkeys with 90 min coronary occlusion followed by 4 h of reperfusion [20]. They found that two 10/10 min cycles of preconditioning reduced infarct size by 95%, but six 30/30-s cycles of Postcon only decreased the infarct size by 38%, which is equal to level of protection by Postcon in human. It is generally accepted that Postcon protects against the cause of cell death occurring during reperfusion, making it applicable as a therapeutic intervention for patients with acute myocardial infarction. Therefore, obtaining such a beneficial effect by simple manipulation of reperfusion has garnered much clinical interest [69]. Multiple-center clinical trials are needed to further demonstrate whether Postcon should be selected as a conventional intervention for the treatment of infarct patients.

Concluding summary

At the current time, Postcon intervention in case of acute myocardial infarction is still in its infancy. Skepticism exists with this treatment method especially when it is applied in different models with comorbities. Although human studies have shown its sustained clinical benefit by reducing tissue injury after acute myocardial infarction, large double-blinded, randomized clinical trials with conventional therapeutic endpoints are imperative to clarify the role of Postcon in treatment of myocardial infarction. Since no drug has shown clinical benefit in treatment of infarct patients in the last 20 years, pharmacological Postcon through identifying a single mechanism to mimic mechanical Postcon should be cautiously considered. Remote Postcon has shown clinical efficacy and safety in mitigating myocardial injury in patients. However, to derive meaningful efficacy data for improving immediate and long-term prognosis after myocardial injury requires more mechanistic investigations. It remains to be determined whether animal data showing protection with Postcon on other organ systems can be incorporated into future clinical trials. Thus, Postcon as a simple mechanical intervention that can be selectively applied during reperfusion may have a broad prospect in treatment of different organ systems after ischemia and reperfusion [132].

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