Published in final edited form as:

Transl Stroke Res. 2013 February ; 4(1): 19–24. doi:10.1007/s12975-012-0224-3.

Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection

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Abstract

Ischemic conditioning is a form of endogenous protection induced by transient, subcritical ischemia in a tissue. Organs with high sensitivity to ischemia, such as the heart, the brain, and spinal cord represent the most critical and potentially promising targets for potential therapeutic applications of ischemic conditioning. Numerous preclinical investigations have systematically studied the molecular pathways and potential benefits of both pre- and post-conditioning with promising results. The purpose of this review is to summarize the present knowledge on cerebral pre- and post-conditioning, with an emphasis in the clinical application of these forms of neuroprotection.

Methods—A systematic Medline search for the terms preconditioning and postconditioning was performed. Publications related to the nervous system and to human applications were selected and analyzed.

Findings—Pre- and post-conditioning appear to provide similar levels of neuroprotection. The preconditioning window of benefit can be subdivided into early and late effects, depending on whether the effect appears immediately after the sublethal stress or with a delay of days. In general early effects have been associated post-translational modification of critical proteins (membrane receptors, mitochondrial respiratory chain) while late effects are the result of gene up- or down-regulation. Transient ischemic attacks appear to represent a form of clinically relevant preconditioning by inducing ischemic tolerance in the brain and reducing the severity of subsequent strokes. Remote forms of ischemic pre- and post-conditioning have been more commonly used in clinical studies, as the remote application reduces the risk of injuring the target tissue for which protection is pursued. Limb transient ischemia is the preferred method of induction of remote conditioning with evidence supporting its safety. Clinical studies in a variety of populations at risk of central nervous damage including carotid disease, cervical myelopathy and subarachnoid hemorrhage have shown improvement in surrogate markers of injury.

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Disclosures:

CD Supported by NINDS K08 NS069817

NRG Research sponsored by the Ruth and Raymond Stotter Chair Endowment in Neurosurgery.

Conclusions—Promising preclinical and early clinical studies noting improvement in surrogate markers of central nervous injury after the use of remote pre- and post-conditioning treatments demand follow-up systematic investigations to address effectiveness. Challenges in the application of these techniques to pressing clinical cerebrovascular disease ought to be overcome through careful, well-designed, translational investigations.

Keywords

Preconditioning; Postconditioning; Ischemia; Reperfusion Injury; Neuroprotection; Brain injury

Defining Preconditioning, Postconditioning and Variations

Preconditioning (PC) has classically been described as exposure of an organ to a sub-lethal physiologic stress which confers subsequent protection from lethal injury, generally by a more prolonged exposure to the same stressor. Ischemic preconditioning (IPC) was first described in 1986 as the use of four 5 min cycles of coronary occlusion, each individually insufficient to cause myocardial necrosis, resulting in a substantial reduction (75%) in the area of infarction after a subsequent, prolonged (40 min) coronary occlusion and reperfusion which caused infarction [1]. Cerebral IPC was described 4 years later [2] and achieved using brief (2 min) bilateral carotid occlusions to protect against subsequent neuronal death resulting from 5 min bilateral carotid occlusion in gerbils.

Numerous labs have now demonstrated neuroprotection using IPC in preclinical models of focal and global brain injury[3]. Subsequent work has divided the cerebral protection after IPC into two windows [3]: an early, acute phase where protection is present within minutes of IPC but fades after a few hours; and a late window of protection occurring generally >24 h after IPC, in many studies more effective, that lasts about a week. Additionally, it has been demonstrated that short bursts of ischemia *after* reperfusion is also protective in brain, a phenomenon referred to as postconditioning (PostC) [4]. Similar to IPC, ischemic postconditioning (IPostC) was initially shown to be protective in heart [5] and subsequently brain [6]. Numerous animal and clinical trials of IPost have been conducted primarily in the last decade and have been the subject of recent reviews [7–9]. Overall IPostC appears to provide the same degree of cardioprotection and neuroprotection as IPC though the requirements for execution immediately at reperfusion are stricter.

Several additional methods to induce ischemic tolerance have emerged as modifications of classic IPC and IPostC. Remote ischemic preconditioning (RIPC) and postconditioning (RIPostC) refer to ischemic tolerance induced by brief ischemia at a site distant to the brain, most commonly the extremities. Given the practical ability to access the extremities and the substantially diminished concern for patient safety with brief limb ischemia compared to brain ischemia of any duration, it should be no surprise that this method is most commonly employed in clinical trials. Pharmacological preconditioning refers to the use of certain drugs such as volatile anesthetics (eg isoflurane, desflurane) to induce ischemic tolerance and is likewise more popular for clinical applications than the use of brief brain ischemia. Akin to pharmacologic PC, cross tolerance refers to other forms of physiologic stress (eg heat, hyperoxia, lipopolysaccharide) which induce ischemic tolerance in brain. Clinical trials of cross tolerance in the brain have not been reported.

A comprehensive discussion of pharmacologic PC in the brain is beyond the scope of this review but has been reviewed recently elsewhere [10]. Inhaled volatile anesthetics such as sevoflurane, isoflurane, enflurane, desflurane and rarely halothane have most commonly been employed to achieve PC effects. A meta-analysis of trials of inhaled anesthetics in cardiopulmonary bypass [11] demonstrated reductions in myocardial injury (troponin extrusion) with use of desflurane and sevoflurane and a trend to mortality benefit. In most studies the anesthetic is used for anesthesia and thus given before and after ischemia so its effect may be as a PC or PostC agent. A more convincing trial of pharmacologic PC gave nitroglycerine 24–28 hours prior to an exercise stress test improved exercise performance in patients with coronary artery disease [12]. Pharmacologic PostC is essentially indistinguishable from pharmacotherapy after an ischemic event and will also not be addressed in this review.

Evidence for Clinical Relevance of IPC from TIA and Stroke

Transient ischemic accidents (TIA) are brief, self-limited focal neurological deficits believed to be caused by arterial thrombosis and endogenous thrombolysis with no resultant permanent injury. In most IPC studies these TIAs are defined as episodes lasting <60 min since longer episodes have been associated with CT evidence of infarction in 80% [13]. Thus a TIA lasting <60 min mirrors the sublethal IR given to induce IPC or IPostC. Patients who have TIAs are at increased risk for subsequent stroke. Several studies [14–20] have sought to test the hypothesis that an antecedent history of TIA induces ischemic tolerance with subsequent reduction in stroke severity in a manner analogous to IPC (Table 1). In general these reports have confirmed this hypothesis though one notable exception was a study which considered longer durations of TIA (median 120 minutes) demonstrating no protection [20].

The studies summarized in Table 1 are suggestive of an induced ischemic tolerance in the brain resulting from TIA which reduces the severity of subsequent strokes. TIA is a clinical diagnosis made on the basis of history and physical exam and in many studies the diagnosis is made after stroke has occurred presenting a risk for recall bias. Nonetheless the results of these studies is fairly consistent in supporting the clinical existence of IPC with only one notable exception [20]. Furthermore these studies mirror similar comparisons done in patients suffering myocardial infarction which show that preceding angina reduces myocardial injury [21, 22].

TIA within these reports appear to be neuroprotective when they are recent (within a week), multiple (2–3 but not more) and of brief duration (<20 min). This replicates experimental IPC findings. TIA is not effective in protecting against lacunar strokes which are smaller and tend to differ in etiology. TIA also do not appear to protect in the elderly brain [15] consistent with human results in angina-MI [23] and animal IPC data in brain [24]. The nature of this protection is both direct (smaller infarct with similar perfusion defect) and an indirect by facilitating faster thrombolysis [16, 17], again consistent with cardiac studies [21].

Timing Preconditioning and Postconditioning

The molecular mechanisms whereby IPC and PostC operate against cerebral ischemia are discussed elsewhere within this issue and have been reviewed extensively in other publications [3, 10]. There appears to be significant overlap between the protective mechanisms of these two therapies involving activation of reperfusion injury salvage kinases (RISK) pathways [25, 26] such as Akt, ERK 1/2 and MAPK or through modification of key mitochondrial targets [27]. Acute protection from IPC likely results from post-translational protein modifications (eg phosphorylation) within cell energetic or survival systems which are immediate. Delayed IPC likely results from protein synthesis of previously dormant genes involved in angiogenesis, energy metabolism, vasomotor control, inflammation and cell survival (eg growth factors). This mechanistic hypothesis explains the delayed nature of this protective window as well as its more long lasting effects, in some cases up to a week.

The early and late windows of IPC have been extensively studied and validated in animal models but it's less clear whether these findings are mirrored in humans. The TIA-stroke data cited in the preceding section supports the hypothesis that IPC is more effective within a week of the anticipated insult. Loukogeorgakis and colleagues used a model of upper limb vascular occlusion with a blood pressure cuff and release after 20 min to demonstrate that this form of ischemia-reperfusion (IR) resulted in reductions in flow mediated dilation. RIPC applied to the opposite arm in 5 min IR intervals prevented reductions in flow mediated dilation when applied immediately, 24h or 48h before the more prolonged IR, but not 4h before IR [28]. These clinical results replicate the immediate and delayed windows of IPC and corroborate the improvement in endothelial function seen using immediate RIPC by Kharbanda and colleagues [29]. Loukogeorgakis subsequently demonstrated that RIPostC was effective in preventing similar reduction in flow mediated dilation when delivered immediately after reperfusion but that protection was lost with only a 1 min delay [30].

The clinical implication of these studies is that IPC, or at least RIPC, permits for two windows where protection can be delivered assuming foreknowledge of the ischemic event. This may be relevant in preventing possible brain IR injury that can be anticipated such as in surgery requiring cardiopulmonary bypass or carotid endarterectomies. Successful RIPostC may require application immediately at the time of reperfusion and without delay. This still could be of clinical relevance as RIPostC could be given at the time of thrombolysis in the case of stroke or during cardiopulmonary resuscitation in the case of cardiac arrest.

It is important to note that these studies have both used a model of endothelial, not brain injury. Furthermore they investigated *remote* IPC and IPostC, not ischemia delivered directly to the brain. However since RIPC and RIPostC are likely the most practical and safe forms of delivering ischemic tolerance clinically, these findings are important to appreciate. Within the field of brain injury, there is some preclinical data which contradicts these findings. IPostC has been demonstrated to be neuroprotective against focal IR when delayed as late as 6h after reperfusion [31] and against global IR with delays of up to 2d [32, 33]. Thus it remains to be established clinically when IPC and IPostC can be effectively delivered in clinical practice.

Practical Clinical Considerations

The delivery of brief ischemia in IPC and IPostC can be technically challenging and is not without at least a theoretical risk. Clinical trials of IPC in patients on cardiopulmonary bypass involve brief aortic clamping pre-procedure [26] but this is only feasible with an open chest. When therapies are intravascular, such as catheter directed thrombolysis of stroke or coiling of aneurysms, clinicians have the opportunity to create focal ischemia with inflation/deflation of a balloon for brief periods. Such a strategy has been utilized in the heart to deliver IPC and PostC with some evidence of a therapeutic benefit [34, 35].

However the heart can tolerate brief ischemia without necrosis better than the brain so it remains unclear that such a therapy in humans is justifiable on a risk basis. MRI has demonstrated that some TIAs previously dubbed “benign” actually result in infarction [36]. Indeed experimental “sublethal” ischemia when examined using more sensitive injury detection methodologies or longer durations of follow up, clearly shows the hallmarks of injury [37]. Animal studies demonstrate that some combinations of brief ischemia can yield more severe, rather than less severe, subsequent ischemic injury [38]. These concerns have resulted in a growing interest in the application of remote PC and PostC, where the therapeutic risk is minimal, becoming the preferred method of inducing cerebral ischemic tolerance [39]. This review will therefore primarily summarize trials of RIPC and PIPostC.

Application of PC and PostC also requires some consideration of therapeutic heterogeneity in population subgroups which may be more sensitive to injury during brief ischemia or may benefit less from its protections. These subpopulations include the elderly [15, 24] and females [40, 41] where both animal and clinical data have called into questions the effectiveness of IPC. Medication use by patients is another important consideration. A recent interventional cardiology trial of RIPC excluded 93/336 patients screened due to their use of glibenclamide or nicorandil which antagonize and mimic IPC protection, respectively [42]. Ironically, >95% of patients enrolled in this trial were on statins, also considered pharmacological preconditioning agents [43, 44]. Where to draw the line on inclusion and exclusion of patients based on their medication profiles becomes increasingly problematic as ever more drugs are implicated as PPC agents and makes the need for empiric clinical data greater.

Remote Preconditioning and Postconditioning

Remote ischemia as it's applied to PC and PostC is achieved by inflation of a blood pressure cuff to produce limb ischemia by occluding blood flow to an arm or leg for 5–10 minutes in 2–4 cycles prior to (RIPC) or after (RIPostC) the potentially injurious ischemia. To achieve ischemia cuff pressures of >200 mm Hg or 30 mm Hg above the patient's systolic blood pressure are often used. In a study of RIPC using this protocol Bilgin-Freiert and colleagues {Bilgin-Freiert, 2012 #99} evaluated limb transient ischemia with muscle microdialysis measuring lactate, lactate/pyruvate ratio, and glycerol. An average follow up of 29 days demonstrated no complications associated with the procedure and muscle microdialysis during RIPC sessions showed a significant increase in lactate/pyruvate ratio and lactate, indicating muscle ischemia, with no significant variation in glycerol, indicating no

permanent cell damage. In a recent phase I trial in patients with subarachnoid hemorrhage [39], these inflation pressures created some pain but were generally well tolerated and safe. RIPC and RIPC have been most extensively tested in recent randomized controlled trials aimed at producing cardioprotection and most of this work has been nicely summarized in recent reviews [26, 45].

Studies of RIPC in the human brain are limited but provocative. Walsh and colleagues randomized adults undergoing carotid endarterectomy to RIPC delivered by sequential compression of each thigh for 10 min with cuff pressures sufficient to obliterate the foot pulses by Doppler [46]. This pretreatment resulted in significant reductions in deterioration of patients' saccadic latency, used as a surrogate for mild brain injury. In a randomized trial of forty patients with cervical spondylotic myelopathy requiring decompression, Hu and colleagues demonstrated that three 5 min upper right limb ischemia-reperfusion to 200 mm Hg right after anesthesia induction resulted in reductions in neuron specific enolase and S100B release and a more rapid clinical recovery [47]. Though not in humans, Jensen and colleagues studied RIPC in a very clinically relevant model of deep hypothermic circulatory arrest in Yorkshire pigs. Providing 4 cycles of 5 min each hind limb ischemia-reperfusion immediately before 1 h circulatory arrest resulting in reductions in brain lactate and more rapid EEG recovery and behavioral scores [48]. RIPC in this model was not only neuroprotective but also cardioprotective. These three trials clearly demonstrate the promise of RIPC which coupled to its non-invasive nature and safety makes this the most feasible form of delivering IPC to the brain.

Gonzalez and colleagues recently reported the hemodynamic and brain metabolic effects of remote conditioning in patients with subarachnoid hemorrhage during the initial 2 weeks after the event [49] when vasospasm risk is highest. Depending on whether the injurious event is considered the subarachnoid hemorrhage or the subsequent vasospasm, this treatment may be interpreted as RIPC or RIPC. Patients were treated with 3–4 sessions of RIPC in the 2–12 days after a subarachnoid hemorrhage. In this investigation, RIPC produced cerebrovascular effects characterized by transient vasodilation and brain metabolic effects, as measured by microdialysis, suggestive of ischemia protection and cell membrane preservation that lasted 25–54 hours after RIPC. These findings are consistent with others' observations of improved endothelial function using RIPC [29, 28].

Considerable uncertainty exists regarding the role of RIPC in humans. The narrow window of opportunity to provide therapy in regards to reperfusion observed by Loukogeorgakis [30] makes it challenging to apply in clinical practice. In the cases of stroke before the thrombolysis or endovascular intervention window, a rapid application of RIPC could theoretically reduce the injury induced by reperfusion. In the case of strokes past the thrombolysis window, reperfusion, if it occurs at all, is variable and the timing of this is not apparent. In the case of cardiac arrest, the timing of return of spontaneous circulation (ie reperfusion) is better documented but the surrounding chaos makes immediate application of RIPC practically challenging though clearly possible. These two disease entities, non-reperfused stroke and cardiac arrest, represent well over a million cases annually in the US with considerable morbidity and mortality [50]. Thus the promise of RIPC certainly warrants consideration within these patients.

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Table 1

Clinical studies of stroke outcomes in patients with and without antecedent TIA.

Study Reference	Patient/TIA Characteristics	Major Outcomes	Subgroup Analysis
Weih et al. 1999	Case: control (1:3) of patients with/without TIA in same vascular territory as stroke	Antecedent TIA was associated with less severe stroke presentation, better mRS and GCS. mRS and GCS were not significant in multivariate analysis.	TIA to stroke interval ranged from 6h to 2y
Moncayo et al. 2000	Anterior circulation stroke with ipsilateral TIA (<60 min)	Favourable outcomes (No or mild disability; independent scale) observed in patients with 1–3 antecedent TIAs lasting 10–20 min within 1 wk of stroke (reduced benefit in 1–4 wks)	TIAs protective in large artery, cardioembolic strokes
Wegener et al. 2004	Nonlacunar stroke with TIA in any vascular territory	Reduced infarcts by MRI in patients with antecedent TIA despite similar perfusion deficits. Faster recanalization (TIMI flow) of lesions and better admission and discharge NIHSS and mRS in patients with prior TIA.	TIA <4 wks before stroke had better outcomes than TIA 4 wks
Schaller et al. 2004	Stroke due to cerebral artery thrombosis treated with urokinase	TIA pre-stroke improved recanalization (TIMI flow), mRS and NIHSS at mean 13 month follow up; follow up NIHSS unavailable on 41% patients without TIA	1–3 TIAs lasting 0–20 min within 1 week of stroke best result
Arboix et al. 2004	Nonlacunar and lacunar stroke with or without prior TIA	Prior TIA improved mRS in nonlacunar but not lacunar strokes	
Johnston. 2004	TIA with subsequent stroke based on TIA characteristics	Failed to confirm that TIA <1 d, 1–7d or >7 d before stroke alters the occurrence of disability (mRS 2).	TIA duration 20–270 min (120 min median)
Della Morte et al. 2008	Nonlacunar stroke with prior TIA in patients >65 yo	No change in NIHSS or mRS at the time of discharge based on prior TIA	No change if TIA < or = 72h after stroke

Abbreviations: NIHSS, NIH Stroke Scale; mRS, modified Rankin scale; GCS, Glasgow coma scale; TIMI, thrombolysis in myocardial infarction grade