

## REVIEW

# Postconditioning: Current Controversies and Clinical Implications

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## KEYWORDS

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**Abstract Objectives:** Postconditioning of ischaemic tissue, via mechanical or pharmacological manipulation, offers an exciting avenue towards amelioration of ischaemia–reperfusion injury. Born from the concept of ischaemic preconditioning, postconditioning is advantageous in that prior knowledge of the ischaemic insult is not required, and thus clinical translation may be further reaching. This review explores the current evidence and controversies in both animal and human studies and multiple organ systems.

**Methods:** A Medline search was conducted to identify English-language articles with ‘postconditioning’ as a keyword. Two independent researchers scrutinised the literature search for potentially relevant articles. Reference lists from selected articles were manually searched for further relevant articles.

**Results and conclusions:** Postconditioning has been shown to be successful in reducing ischaemia–reperfusion injury in both animal models and clinical trials. Human studies are presently limited to cardiac studies, but there is scope for research into other organ systems with potential beneficial effects, particularly within the field of vascular surgery where ischaemia–reperfusion occurs by nature of both – the disease and the intervention.

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Postconditioning (PostC) is defined as repetitive cycles of briefly interrupted reperfusion applied at the onset of establishing reflow and has been shown to significantly improve outcome following an episode of ischaemia.<sup>1</sup> While seemingly paradoxical that interrupting blood flow should

improve outcome, the concept of PostC has arisen from the evolving understanding of ischaemia–reperfusion injury (IRI). Success at re-vascularisation has highlighted the detrimental impact of IRI in virtually every organ system in the body. Ischaemia primes the endothelium to the subsequent reperfusion insult, and the endothelial dysfunction thus induced is the harbinger of organ failure, despite restoration of blood supply. IRI has proven to be extremely challenging to protect against, because its aetiology is multifactorial. A possible breakthrough came with the

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concept of ischaemic preconditioning (IPC),<sup>2</sup> whereby short ischaemic episodes preceding the index ischaemia conferred protection from the insult. The last 2 decades have seen limited but successful use of this technique in cardiology and transplant surgery.

In 1996, Na et al. described PostC when they applied 10-min periods of intermittent reperfusion to cat myocardium following a 20-min period of index ischaemia and showed comparable benefit to IPC in reducing ventricular fibrillation.<sup>3</sup> PostC, as a concept, originated from initial work done in cardiac surgery where IRI-induced myocardial damage was noted to be improved by cardioplegic strategies aimed at slowly initiating reflow following a period of coronary vessel occlusion.<sup>4,5</sup> Zhao et al. re-ignited interest in PostC by demonstrating, for the first time, a reduction in infarct size using canine myocardium, an effect similar to that produced by IPC.<sup>1</sup>

Recently, IRI protective strategies have shown successful translation into vascular surgery for the first time. In 2007, Ali et al. successfully used IPC in reducing myocardial infarction by 22%, myocardial injury by 27% and renal impairment by 23% in elective abdominal aortic aneurysm repair.<sup>6</sup> This was achieved by two cycles of intermittent cross-clamping of one common iliac artery producing a 10-min period of ischaemia, followed by a 10-min period of reperfusion. Although PostC remains elusive from vascular surgery thus far, effective cardioprotection has been demonstrated in clinical practice.<sup>7</sup> PostC has an exciting potential advantage over its sister concept, IPC, in that PostC addresses the significant limitations of IPC in vaso-occlusive emergencies where precise information about the timing of index ischaemia is not available.

This review examines the evidence from animal and human studies for use of PostC in ameliorating IRI and its potential for application in vascular surgery.

## Methods

Two independent researchers reviewed the literature. Using Medline, articles citing 'reperfusion injury', 'preconditioning' and 'postconditioning' as keywords were identified. Of these, 204 and 538 abstracts were retrieved for preconditioning and reperfusion injury, respectively, using core clinical journals, human studies, randomised controlled studies (RCTs) and English language as filters. For PostC, no filters were used, giving a total of 356 abstracts. The abstracts were scrutinised for relevance to pathophysiology, human and animal studies and clinical application of PostC. Those not pertaining to IRI, IPC or PostC were discarded. One hundred and forty articles were short listed and analysed in detail, and 36 key papers were used for the purposes of this review. Reference lists of relevant selected articles were manually searched for further appropriate articles and to ensure that no key papers were missed.

## Mechanisms of PostC-induced protection

Although our understanding of the precise cellular signalling events is still in evolution, similarities exist between pre- and PostC despite the fundamental differences in the timing of protection. The main theories of PostC-induced

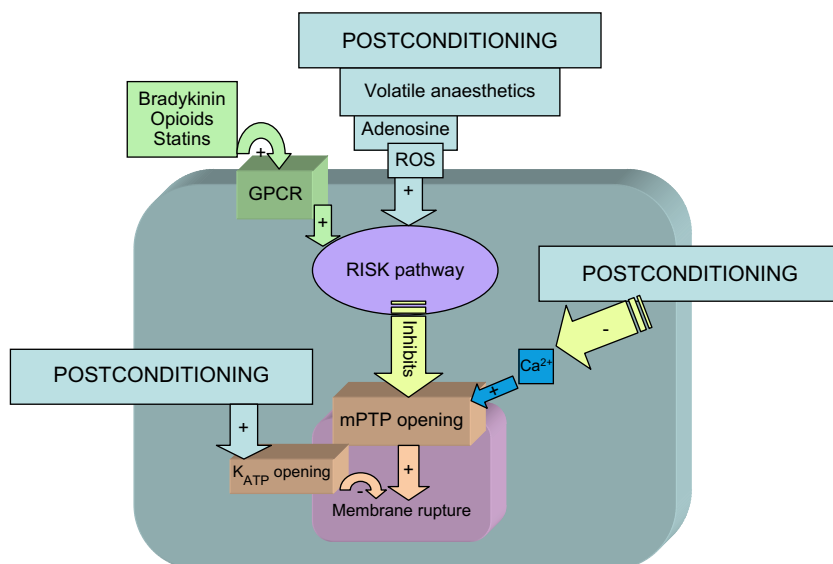
protection centre around the preservation of mitochondrial integrity via regulation of the mitochondrial permeability transition pore (mPTP), reduced sensitivity to the increased intracellular calcium ( $\text{Ca}^{2+}$ ) levels triggered by IRI, restoration of redox balance and nitric oxide (NO)-mediated vaso-relaxation.

Mitochondria are crucial in maintaining cellular function and, therefore, mechanisms of protection must involve mitochondrial survival. The mPTP is a protein pore on the mitochondrial membrane that is formed in pathological states. Opening of the mPTP allows small molecules (less than 1500 Da) to enter the mitochondrial matrix, initiating a cascade of events, including the release of apoptosis-inducing factors (AIF), such as cytochrome c, which in turn activate enzymes known as caspases, stimulating rupture of the outer membrane, apoptosis and necrosis. Argaud et al. found that inhibition of the mPTP opening by using specific mPTP inhibitors in a rabbit cardiac ischaemia model significantly limited infarct size to a comparable degree for both pre- and PostC, thereby concluding that the protective effect of PostC occurs through inhibition of the mPTP opening.<sup>8</sup> They also found that the  $\text{Ca}^{2+}$  load required to open the mPTP in postconditioned rabbits was significantly higher compared to controls, thereby demonstrating the role of PostC in preservation of cell integrity by decreasing the sensitivity of the mPTP to IRI-induced  $\text{Ca}^{2+}$  influx. PostC-induced modulation of the mPTP opening possibly occurs after 2 min of reperfusion as the pore opening is inhibited prior to this by low pH under ischaemic conditions.<sup>9</sup>

Inhibition of the mPTP opening is considered to be the final step in a complex series of cellular signalling events preventing cell death. It is thought that both pre- and PostC activate a signal transduction pathway involving the pro-survival kinases phosphatidylinositol-3-OH kinase (P13K)-Akt and the p42/p44 extracellular signal-regulated kinases (Erk1/2) which has been termed the reperfusion injury salvage kinase (RISK) pathway. The RISK pathway terminates with the inhibition of the mPTP opening at reperfusion to afford cardioprotection in both IPC and PostC.<sup>10</sup> This was demonstrated pharmacologically by inhibiting ischaemic PostC-induced phosphorylation of Akt, at the time of reperfusion, abrogating PostC-induced cardioprotection in rats.<sup>11</sup> Fig. 1 shows a simplification of the key mechanisms involved in achieving a reduction in cell death through PostC.

## Types of PostC – mechanical and pharmacological

Most of the animal studies, to date, relate to mechanical PostC whereby cardiac ischaemia is induced by coronary vessel occlusion, usually achieved by slinging the left anterior descending artery, to mimic infarction. Reperfusion is then stuttered as per protocol by releasing the vessel slings for varying time periods. Optimal protocols are much debated. In the initial description of PostC, a 44% reduction in infarct size in canine myocardium was reported, compared to the control group, using three cycles of 30 s of alternating ischaemia/reperfusion (I/R) immediately following an initial 60-min occlusion. This was consolidated by a significant reduction in creatine kinase (CK) activity and tissue oedema in the PostC group.<sup>1</sup>



**Figure 1** Simplification of the key mechanisms involved in achieving a reduction in cell death through postconditioning.

As understanding of the mechanisms of PostC have been unravelled, pharmacological PostC has arisen. Pharmacological PostC mimetics have the potential advantage of reducing the requirement for invasive therapy associated with unavoidable endothelial trauma and possible embolic events, and some of them already have FDA approval facilitating their usage in trials. Furthermore, they may cater to a subset of patients too frail for invasive procedures, or too far from specialised centres. FDA-approved drugs such as adenosine<sup>12</sup> and volatile anaesthetic agents such as isoflurane<sup>13,14</sup> and sevoflurane<sup>15</sup> have already been considered to improve outcome in animal studies.

Similar reductions in infarct size have been demonstrated with isoflurane and mechanical or ischaemic PostC in rabbit myocardium.<sup>16,17</sup> In combination with mechanical PostC, a cumulative beneficial effect has been shown.<sup>15</sup> Anaesthetic-induced PostC appears to result from similar mechanisms to ischaemic PostC, and the effect of both can be abrogated by inhibition of the RISK pathway.<sup>17</sup>

Adenosine receptor stimulation has been implicated in cardioprotection for some time, and its concentrations have been found to be increased in the presence of damaged tissue, suggesting a role for cellular protection. For example, the results of the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial I, prospectively recruiting 236 patients, concluded that the addition of adenosine to the treatment of acute myocardial infarction (AMI) with thrombolysis resulted in a 33% reduction in infarct size.<sup>18</sup> Kin et al. found strong evidence to support the involvement of some adenosine receptor subtypes in PostC.<sup>19</sup> They further demonstrated that PostC delays washout of adenosine at 2 min, supporting the notion that PostC is time related and significant delay results in loss of this protective window. Adenosine has also been suggested to be a trigger in the pathways involving survival kinases, NO and  $K_{ATP}$  channels. Hausenloy and Yellon reviewed in detail the host of other agents including cytokines; G-protein-coupled receptor ligands, including bradykinin and opioids, and statins such as atorvastatin<sup>20</sup> thought to confer

cardioprotection in a similar manner, particularly through activation of the RISK pathway.

### Mechanical PostC – controversies from animal studies

Since the initial description in canine models PostC has been effective in multiple species and organ systems, but debate still exists as to the optimal I/R cycle. The initial assumption that more cycles of I/R would provide more robust protection has now been discarded. Extending the cumulative occlusion time not only causes aggravation of the ischaemic insult, but multiple occlusive cycles may also give rise to poor results due to vasospasm. For the same reason, cycle duration is clearly important in influencing the degree of PostC-induced protection. This logic did not prevail in two studies on rabbits where three cycles of 20-s I/Rs produced a reduction in the infarct size compared to three cycles of 10-s I/Rs.<sup>16,17</sup> Thus the implication arises that there may be a minimum time threshold of ischaemia in order to stimulate cardioprotection. This minimum time threshold has so far not been reproducible between species or even within species.

A similar predicament also exists regarding the time of application of PostC after index ischaemia. A delay of 10 min before commencing PostC in rabbits resulted in infarct sizes comparable with controls.<sup>21</sup> A delay of just 1 min prior to onset of the cycle has been shown to reduce the cardioprotection in rats.<sup>22</sup> These findings suggest that PostC acts to modulate IRI in the initial moments of reperfusion.

The total duration of the index ischaemia also gives variable results within the same species. Differing experimental coronary occlusion times to produce index ischaemia using the same PostC protocols have been found to have different results. In some cases, just 30 min of index ischaemia could be ameliorated, suggesting that PostC is protective only after shorter episodes of index ischaemia.<sup>23</sup> A gender difference has been demonstrated in

postconditioned rats, with female rat hearts not protected after longer periods of index ischaemia in comparison to their male counterparts.<sup>24</sup> This may translate into humans, driving a different optimal protocol for men and women. Perhaps of most concern is the finding that PostC was ineffective in hypercholesterolaemic rabbits.<sup>25</sup> Whether this study means that hypercholesterolaemic animals are not protected by PostC or just that an effective protocol was not trialled, this does potentially pose a problem for clinical studies.

These controversies have obvious implications for translation of this concept into human studies. A protocol enrolling patients must be effective and safe for all patients; multiple large trials may be required to identify the optimum protocol for human studies and further for individual organ systems.

### Role of PostC in brain and spinal cord ischaemia

The protective effect of PostC in carotid artery occlusion has been studied. Using anaesthetised rats, the middle cerebral artery was cauterised and common carotid arteries (CCAs) were occluded every 30 s for 10 s for a total of three cycles. An 80%, 51% and 17% reductions in mean infarct size were reported, with 15, 30 and 60 min of CCA occlusions (index ischaemia), respectively, thereby indicating the dependency of degree of protection afforded in relation to the duration of index ischaemia.<sup>26</sup> Unlike cardiac tissue, the beneficial effect of PostC in the brain tissue can be seen up to 2 days after the initial ischaemic event. Danielisova et al. demonstrated the use of delayed PostC to reverse impending neuronal death and reported that it was effective when performed 2 days after the index ischaemia with a staggering 90% reduction in neuronal death.<sup>27</sup> This delayed neuroprotection was, however, not found in the spinal cord. Jiang et al. induced spinal cord ischaemia in anaesthetised rabbits by cross-clamping the abdominal aorta just distal to the renal arteries for 25 min. They found that PostC initiated immediately after reperfusion produced significantly reduced neurological impairment with improved hind limb motor function with less protection at 5 min and no protection at 10 min.<sup>28</sup> Although the significance of PostC as a potential adjuvant treatment in stroke, carotid endarterectomy and thoracic aortic interventions cannot be underestimated, there is a paucity of human data to propagate clinical relevance at this stage.

### Human clinical trials

In 2005, Staat et al. published the first multicentre RCT demonstrating that PostC is effective in humans. Thirty patients with AMI underwent primary coronary angioplasty and stenting, with 16 of 30 patients assigned to the PostC arm of the trial. The protocol commenced within 1 min of coronary stent insertion and comprised four cycles of 1-min coronary artery I/R by angioplasty balloon. At 48 h post-angioplasty, a significant reduction in mean ST-segment elevation ( $P = 0.09$ ) and improved myocardial perfusion ( $P < 0.02$ ) were seen, followed by a significant reduction in CK release ( $P < 0.05$ ) during the first 72 h.<sup>7</sup> Prolonged protection by PostC has been demonstrated with

PostC-induced reduction in infarct size in AMI remaining apparent after 7 days of reperfusion.<sup>29</sup> Ma et al., in 2006, studied reactive oxygen species (ROS) production and endothelial function in association with PostC in addition to myocardial enzymes and cardiac function. They randomised 94 patients with AMI undergoing primary coronary angioplasty to control or PostC groups using three cycles of 30-s I/R. The postconditioned patients had a faster time to normal blood flow in the infarct-related coronary artery with a significantly ( $P < 0.05$ ) lower CK and creatine kinase isoenzyme (CK-MB) peaks. Wall motion score index was significantly larger in the postconditioned group ( $P < 0.05$ ), corresponding with improved ventricular wall movement post-angioplasty. Malondialdehyde (MDA) levels were significantly lower in the postconditioned group ( $P < 0.05$ ). Brachial arterial endothelial function studied by echo Doppler technique showed that endothelium-dependent vasodilatory function was improved in the PostC group, but there was no difference between the two groups with regards to endothelium-independent function, thereby indicating that PostC ameliorates endothelial dysfunction probably via increased NO availability.<sup>30,31</sup> Preservation of endothelial function has also been demonstrated in a separate study where this effect was lost even with a 1-min delay post-reperfusion.<sup>32</sup>

In 2007, Luo et al. published the first RCT evaluating PostC in surgical patients. They studied 24 children with tetralogy of Fallot undergoing cardiac surgery. The PostC group required significantly less inotropes during the first 24 h ( $P = 0.017$ ) and showed 50% lower troponin I ( $P = 0.05$ ) and 34% lower CK-MB ( $P = 0.034$ ) levels than controls.<sup>33</sup> In 2008, they have reported a similar success in adult valve replacement surgery randomising 50 patients between control and PostC arms using three cycles of 30-s aortic I/R.<sup>34</sup>

Successful pharmacological PostC in humans in the surgical setting has been reported by Jin et al. using  $1.5 \text{ mg kg}^{-1}$  adenosine given within 1 min of aortic cross-clamp removal. A significant reduction in troponin and reduced inotrope scores in patients undergoing valve replacement surgery were noted.<sup>35</sup> An improvement in post-occlusive hyperaemic reaction of forearm endothelium in the presence of sevoflurane has been shown.<sup>36</sup>

### Conclusion

PostC offers an exciting avenue for reducing the magnitude of IRI, and its translation into clinical practice has been demonstrated in the clinical setting. Further work is clearly required to assess the potential benefit of PostC in humans, particularly with respect to vascular surgery, and to standardise the protocols in relation to each organ system. It does have an advantage over IPC in that forewarning of the episode of index ischaemia is not required, although the benefit of PostC may be limited by a delay in application after reperfusion. The human data thus far are reported only from myocardial studies, and there is clearly heterogeneity in the protocols used to gain this effect. PostC is still very much limited to specialised centres and research groups, and, until larger studies confirm its benefit, the clinical results need to be scrutinised, and patients should

be subjected to these treatments only after formal ethical approval has been obtained.

## Conflict of Interest/Funding

None.

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