



REVIEW

# The application of remote ischemic conditioning in cardiac surgery [version 1; referees: 3 approved]

Zeljko J. Bosnjak <sup>1,2</sup>, Zhi-Dong Ge<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA

<sup>2</sup>Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI, 53226, USA

**v1** **First published:** 16 Jun 2017, 6(F1000 Faculty Rev):928 (doi: 10.12688/f1000research.11018.1)




**Latest published:** 16 Jun 2017, 6(F1000 Faculty Rev):928 (doi: 10.12688/f1000research.11018.1)

**Abstract**

Perioperative myocardial ischemia and infarction are the leading causes of morbidity and mortality following anesthesia and surgery. The discovery of endogenous cardioprotective mechanisms has led to testing of new methods to protect the human heart. These approaches have included ischemic pre-conditioning, per-conditioning, post-conditioning, and remote conditioning of the myocardium. Pre-conditioning and per-conditioning include brief and repetitive periods of sub-lethal ischemia before and during prolonged ischemia, respectively; and post-conditioning is applied at the onset of reperfusion. Remote ischemic conditioning involves transient, repetitive, non-lethal ischemia and reperfusion in one organ or tissue (remote from the heart) that renders myocardium more resistant to lethal ischemia/reperfusion injury. In healthy, young hearts, many conditioning maneuvers can significantly increase the resistance of the heart against ischemia/reperfusion injury. The large multicenter clinical trials with ischemic remote conditioning have not been proven successful in cardiac surgery thus far. The lack of clinical success is due to underlying risk factors that interfere with remote ischemic conditioning and the use of cardioprotective agents that have activated the endogenous cardioprotective mechanisms prior to remote ischemic conditioning. Future preclinical research using remote ischemic conditioning will need to be conducted using comorbid models.

**Open Peer Review**

**Referee Status:** 

|  | Invited Referees  |   |   |
|--|---|---|---|
|  | 1   | 2   | 3   |
| <b>version 1</b><br>published<br>16 Jun 2017 |  |  |  |

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 **Pasquale Pagliaro** , University of Torino, Italy
- 2 **James M. Downey** , University of South Alabama, USA
- 3 **Karin Przyklenk** , Wayne State University School of Medicine, USA

**Discuss this article**

Comments (0)

**Corresponding author:** Zeljko J. Bosnjak ([zbosnjak@mcw.edu](mailto:zbosnjak@mcw.edu))

**Competing interests:** The authors declare that they have no competing interests.

**How to cite this article:** Bosnjak ZJ and Ge ZD. **The application of remote ischemic conditioning in cardiac surgery [version 1; referees: 3 approved]** *F1000Research* 2017, **6**(F1000 Faculty Rev):928 (doi: [10.12688/f1000research.11018.1](https://doi.org/10.12688/f1000research.11018.1))

**Copyright:** © 2017 Bosnjak ZJ and Ge ZD. This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Grant information:** This work was supported by grant P01GM066730 from the National Institutes of Health (Bethesda, MD, USA) (to ZJB). *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**First published:** 16 Jun 2017, **6**(F1000 Faculty Rev):928 (doi: [10.12688/f1000research.11018.1](https://doi.org/10.12688/f1000research.11018.1))

## Introduction

When the coronary arterial blood flow is blocked, it is critical to re-establish the blood flow to the ischemic area of the heart as soon as possible. During the return of blood supply to the ischemic myocardium, there is paradoxical myocardial damage; the excess oxygen may trigger further myocardial cell death and greater cardiac injury, termed myocardial reperfusion injury<sup>1</sup>. Although medical advances in cardiac treatment have been significant, there is very little that can be done pharmacologically or mechanically to prevent the injury of the reperfused myocardium, which can lead to heart failure and death. The development of novel cardioprotective strategies that would mitigate further myocardial injury, secondary to ischemia/reperfusion (I/R) injury, is required and is the focus of many preclinical and clinical investigations<sup>2,3</sup>. The endogenous cardioprotection—mediated via ischemic pre-conditioning, ischemic per-conditioning, and ischemic post-conditioning—has some clear drawbacks because it has to be administered to the compromised myocardium. On the other hand, the maneuvers implemented with remote ischemic conditioning (RIC) (pre-, per-, and post-conditioning) have the advantage of applying the protective ischemia to an organ distant from the heart<sup>4</sup>. Therefore, in this short review article, we focus mostly on RIC because of its popularity, non-invasive nature, and relative safety.

## Potential mechanisms underlying cardioprotection by remote ischemic conditioning

RIC is the phenomenon in which transient, repetitive, non-lethal ischemia and reperfusion in one organ or tissue (remote from the heart) render myocardium resistant to lethal I/R injury<sup>4</sup>. It represents a strategy for harnessing the body's endogenous, protective capabilities against the myocardial injury incurred by I/R. In experimental animals, brief episodes of ischemia and reperfusion in an arm or a leg dramatically reduce myocardial infarct size when applied prior to lethal myocardial ischemia (remote ischemic pre-conditioning), during lethal myocardial ischemia (remote ischemic per-conditioning), or at the onset of reperfusion (remote ischemic post-conditioning)<sup>5-10</sup>. Remote ischemic pre-conditioning and post-conditioning produce similar efficacy of cardioprotection against I/R injury<sup>11</sup>.

The mechanisms of cardioprotection by RIC are complex and have not been fully elucidated. However, it has been established that the signaling pathways from the tissue/organ subject to transient, repetitive I/R to the heart consist of three entities: remote stimulus to generate protective signal, the transfer of the signal to the heart, and myocardial responses to the transferred signal resulting in cardioprotection<sup>12,13</sup>. In experimental animals, if the sensory nerve to the ischemic limb, spinal cord, or the vagus nerve is transected or silenced, the cardioprotective effects of RIC are lost<sup>14-17</sup>. These studies reveal the importance of neural pathways in transmitting the signal for cardioprotection in RIC. Over the past few years, many humoral factors have also been implicated, including nitric oxide, adenosine, bradykinin, opioid peptides, prostaglandins, natriuretic peptides, endocannabinoids, angiotensin I and calcitonin gene-related peptide, hypoxia-inducible factor 1 $\alpha$ , erythropoietin, stromal-derived factor 1 $\alpha$ , hypoxia-inducible factor prolyl hydroxylase 2 (encoded by *EGLN1* gene), and microRNAs<sup>18-24</sup>. Currently, it is believed that the stimulus of remote ischemic pre-conditioning activates afferent C fiber sensory nerves by locally released

autacoids to transmit cardioprotective signal<sup>25</sup>. In the meantime, the aforementioned humoral factors released by the tissue undergoing transient I/R are relayed in the blood to the heart, where they trigger cardioprotection. Humoral pathways may be more prominent in remote ischemic post-conditioning relative to remote ischemic pre-conditioning<sup>11,14</sup>.

The intracellular signaling pathways of RIC in myocardium are thought to have much in common with local ischemic pre- and post-conditioning<sup>26</sup>. Autacoids, neurohormones, and humoral factors generated by remote stimulus bind to G protein-coupled receptors in myocardium or activate intracellular signal pathways in a receptor-independent manner or do both<sup>25</sup>. Three main intracellular signaling pathways may be critical in RIC-elicited cardioprotection against I/R injury: the endothelial nitric oxide synthase/protein kinase G pathway, the reperfusion injury salvage kinase pathway, and the survivor activating factor enhancement pathway<sup>13,27</sup>. Ultimately, these signaling pathways converge on the mitochondria and the cytoskeleton, resulting in inhibition of opening of the mitochondria permeability transition pore (mPTP), preservation of mitochondrial integrity and function, and reduction of cytoskeleton damage<sup>28,29</sup>.

It is worth noting that there is considerable similarity between remote conditioning and exercise. Exercise appears to act as a physiological stress leading to similar accumulation of metabolic mediators such as adenosine, bradykinin, and calcitonin gene-related peptide along with baroreflex responses that induce beneficial myocardial adaptive responses at a cellular level<sup>30</sup>. Moreover, it was shown that individuals with cardiovascular disease who participate in vigorous exercise prior to their cardiac event have improved ejection fraction and may obtain a protective benefit similar to that of RIC<sup>31</sup>.

## Clinical trials of remote ischemic conditioning for cardiac surgery

RIC was shown to reduce cardiac injury in patients undergoing revascularization and other cardiac surgeries, as seen by reduction of cardiac biomarker release<sup>32-36</sup>. Notwithstanding more recent clinical outcome studies (for example, ERICCA and RIPHeart), most of the clinical studies were conducted on small cohorts of selected patients and in controlled conditions. These smaller trials on the effectiveness of RIC during elective interventional revascularization, other forms of cardiac surgeries, non-cardiac vascular surgeries, and others have shown various degrees of beneficial effects of RIC<sup>37,38</sup>.

One of the larger trials, which involved 1,280 patients and used both remote ischemic pre- and post-conditioning, did not show a reduction in the number of major adverse outcomes<sup>39</sup>. Some additional negative studies on RIC in humans were attributed mostly to underlying risk factors or medications that interfere with different cardioprotective interventions. One recent review covered the cardioprotection by ischemic pre-conditioning, ischemic post-conditioning, and remote conditioning in various clinical settings<sup>40</sup>. In addition to comorbidities and medications, the negative results may be due to the anesthetics used during the surgeries, which have been proven to prevent the protection by RIC. For instance, propofol has been shown to eliminate the benefits of RIC. It is of interest that

most of the negative studies on the protection of RIC so far have used propofol as anesthetic<sup>41</sup>.

Owing to both positive and negative results from various clinical trials, the results from large multicenter randomized controlled trials (such as ERICCA and RIPHeart) were meant to close that gap<sup>42</sup>. In the ERICCA study, with 1,612 patients undergoing elective on-pump coronary artery bypass grafting with or without valve surgery and without standardization of the anesthetic regimen, remote ischemic pre-conditioning using transient-arm I/R did not improve clinical outcomes<sup>43</sup>. Similarly, the RIPHeart study, in which the upper-limb remote ischemic pre-conditioning was performed while 1,385 patients were under propofol-induced anesthesia, did not show a relevant benefit among patients undergoing elective cardiac surgery<sup>44</sup>. The trials also failed to confirm the presence of initial cardioprotection by RIC-induced reduction of cardiac troponin release. Both of these studies are a clear disappointment in the cardioprotection efforts<sup>45</sup>. These large trials (ERICCA and RIPHeart) during cardiac surgery contradict previous smaller trials on the role of RIC<sup>34,36</sup>. Taken together, the recent large multicenter trials using RIC have not proven successful in cardiac surgery.

The lack of success in cardiac surgery using RIC is multifactorial. One cause is that cardiovascular risk factors can interfere with RIC. Most of the risk factors responsible for human ischemic heart disease in the first place include hypertension, chronic obstructive pulmonary disease, heart failure, atherosclerosis, diabetes and other metabolic diseases, age, and routine drug therapies<sup>40,46-48</sup>. Another cause is the utility of cardioprotective agents that have activated the endogenous cardioprotective mechanisms prior to RIC<sup>49</sup>. Potential cardioprotective agents that would mitigate/interfere with cardioprotective interventions may include volatile anesthetics, propofol, P2Y12 blocking agents, beta blockers, morphine, nicorandil, sulfonyleureas, statins, angiotensin-converting enzyme inhibitors, and nitrates<sup>49-53</sup>. In addition, the beneficial effect of ischemic conditioning is not detectable in patients with the small extent of myocardial injury<sup>54</sup>.

ST segment elevation myocardial infarction is one of the leading causes of mortalities and morbidities worldwide<sup>55,56</sup>, and infarct size is the main determinant of prognosis. Reduction of infarct size is a main goal of treatment and can be achieved efficiently with primary angioplasty. Successful and timely reperfusion with percutaneous coronary intervention (PCI) or primary angioplasty attenuates infarct size and improves cardiac function and clinical outcomes<sup>57,58</sup>. However, sudden reperfusion can cause fatal myocardial injury<sup>2,3,59</sup>, which may limit therapeutic benefits. Thus, supplementary cardioprotection such as RIC may be considered in elective and emergent PCI<sup>60</sup>. Clinical trials using small cohorts of selected patients generally suggest that RIC can provide cardioprotection by lowering peak troponin I or reducing infarct size (or both) in patients undergoing elective PCI<sup>60-64</sup>.

### Effects of anesthetic cardioprotection on remote ischemic conditioning in cardiac surgery

One could speculate that the lack of protection in these two phase III clinical trials is because of the use of propofol anesthesia in most of the patients in the ERICCA trial and all patients in the RIPHeart trial. Attenuation of RIC in the presence of propofol anesthesia

has been reported<sup>65</sup>, and the use of propofol, rather than volatile anesthesia, appears to be a common denominator of studies that failed to protect with RIC<sup>66,67</sup>. It is likely that the use of volatile anesthetics would have made the ERICCA and RIPHeart trials more complete. Indeed, the successful cardioprotection by RIC was also documented in acute myocardial infarction, where the type of anesthesia was not an issue<sup>60,68,69</sup>.

Parallel to the most powerful endogenous cardioprotective mechanism of ischemic pre-conditioning<sup>70</sup>, pharmacologic cardioprotection with volatile anesthetics emerged as a considerably less risk-bearing and equally effective intervention<sup>71</sup>. The American College of Cardiology Foundation and the American Heart Association Task Force on Practice Guidelines adopted a recommendation for the use of volatile anesthetics in surgical patients at risk for myocardial ischemia<sup>72</sup>. Since anesthetic cardioprotection was discovered, experimental and clinical research has focused on elucidating the mechanisms of anesthetic cardioprotection with the anticipation of finding an anesthetic agent or approach that would be the most beneficial for patients with coronary artery disease. Clinical studies with sufficient power to detect differences between process variables and outcome among anesthetic agents or techniques have confirmed the relevance of anesthetic cardioprotection for patients<sup>73-79</sup>. The loss of cardioprotection is strongly associated with the risk of death/non-fatal myocardial infarction within the year after determining the absence of pre-conditioning with the PCI model of coronary occlusion<sup>80</sup>. At one year, the risks of death were reduced by 85% in patients who manifested pre-conditioning as compared with patients who did not. The ability for cardioprotection to remain significantly, and inversely, associated with the risk of death/non-fatal myocardial infarction in one year affirms the clinical significance of this phenomenon.

Every year, volatile anesthetics are used in millions of patients undergoing cardiac surgery. Whether RIC provides more cardioprotection to the myocardium of the volatile anesthetic-anesthetized patients undergoing cardiac surgery has been examined, yet the clinical outcomes remain uncertain. Some clinical studies show that the cardioprotective effect of RIC is unable to be detected in isoflurane-anesthetized patients undergoing coronary artery bypass grafting<sup>50,51</sup>. In contrast, other small-scale clinical trials indicate that RIC can provide additional protective effects in isoflurane-anesthetized patients undergoing cardiac surgery<sup>41,67</sup>. However, recent studies from two large-scale, multicenter, clinical trials of RIC show negative results in cardiac surgery<sup>43,44</sup>. The reasons for the differences among these studies are complex and have not been fully understood. To use better RIC and lessen myocardial I/R injury in human cardiac surgery, a greater understanding of the interaction between RIC and volatile anesthetic conditioning is necessary.

### Challenges of remote ischemic conditioning in diabetic cardiovascular disease

Diabetes is a significant predictor of increased perioperative risk due to a greater susceptibility to I/R injury. Both preclinical and clinical results indicate that the cardioprotective effect of ischemic and pharmacologic conditioning is impaired in the presence of diabetes. Type 2 diabetes occurs in 9.3% of the US population, affecting 29.1 million individuals<sup>81</sup>; and the prevalence of this

disease is expected to increase by over 200% in the next several decades. Impaired glucose tolerance currently affects 20% to 35% of all middle-aged and elderly Americans, and hyperglycemia alone is a significant independent predictor of cardiovascular morbidity and mortality in patients undergoing cardiac surgery<sup>82–85</sup>. The mechanisms that contribute to increased risk in diabetes and hyperglycemia are poorly understood but likely are related to insufficient activation of pro-survival signaling pathways, elevated nitrosative stress, activation of the PI3K/Akt/mTOR (phosphatidylinositol 3-kinase, serine/threonine kinase also known as protein kinase B, and mammalian target of rapamycin) pathway, and autophagy<sup>46</sup>. Aggressive control of blood glucose concentration using insulin is one approach, but it is unlikely that insulin alone can substantially improve cardiovascular outcomes in patients with diabetes.

Patients with diabetes have a significantly higher incidence of coronary heart disease compared with non-diabetic individuals<sup>55,86</sup>. At present, 15% to 30% of the patients who undergo coronary artery surgery are diabetic<sup>87–89</sup>. During cardiac surgery, the heart is inevitably subjected to I/R injury due to pre-existing coronary occlusion and heart arrest subsequent to aortic artery cross-clamp. After cardiac surgery, patients with diabetes have an increased mortality and poorer clinical recovery than non-obese, non-diabetic patients<sup>55,90</sup>. Therefore, diabetic populations may obtain a greater benefit from therapies shown to be effective in treating ischemic heart disease.

The cardioprotective effect of single-dose RIC in diabetes is often disappointing<sup>46,91–93</sup>. The mechanisms underlying the impaired cardioprotective effect of RIC by diabetes are not fully elucidated. About 60% to 70% of people with diabetes mellitus eventually develop diabetic peripheral neuropathy<sup>94</sup>. In many of these patients, peripheral neuropathy, including sensory C fibers which are required by the cardioprotective effect of RIC, is damaged<sup>95</sup>. This damage may be an important contributor to the reduction of RIC cardioprotection during diabetes<sup>96,97</sup>. In future clinical trials, selection of patients with functional sensory C fibers may help to improve the clinical outcome of RIC. In addition, diabetes impairs the PI3K/Akt/glycogen synthase kinase 3 beta (PI3K/Akt/GSK3- $\beta$ ) signaling pathway and phosphorylation of ERK1/2 (extracellular signal-regulated protein kinases 1 and 2), decreases generation and release of nitric oxide, inactivates ATP-sensitive potassium channels, and elevates oxidative stress<sup>98–100</sup>. These intracellular signaling pathways are crucial for endogenous cardioprotection. Diabetes-elicited impairments in these signaling pathways may critically contribute to the attenuation of RIC cardioprotection<sup>92</sup>.

Repeated RIC, where short periods of limb ischemia are repeatedly applied over days or weeks, is the extension of RIC. Recent studies have identified repeated RIC as a newer strategy for cardioprotection<sup>27,93,101,102</sup>. Compared with clinical single-dose RIC and local ischemic conditioning, repeated RIC appeared to have more consistently yielded significantly beneficial results against remodeling in both preclinical and clinical studies of RIC<sup>101–103</sup>. It has been demonstrated that repeated RIC reduces adverse cardiac remodeling after myocardial infarction, elevates survival of animals in a dose-dependent fashion, improves endothelial function and skin microcirculation, and modulates the systemic

inflammatory responses<sup>101,104,105</sup>. Intriguingly, repeated RIC is beneficial for healing in lower-extremity diabetic ulcers<sup>106</sup>. Whether repeated RIC is effective in I/R protection of diabetic hearts remains elusive. The efficacy, potential, and safety of repeated RIC in protection of diabetic hearts need to be tested in future experimental studies and clinical trials.

Restoring myocardial sensitivity to RIC in the setting of diabetes is of primary importance. Since diabetes impairs multiple signal transduction pathways of RIC, it is reasonable to believe that a therapy that targets one pathway may not completely restore the sensitivity of the myocardium to RIC. In the various signal transduction pathways, GSK3- $\beta$  is the intervention point of convergence, and the mPTP is thought to be the final effector of cardioprotection<sup>107,108</sup>. The studies to restore myocardial sensitivity to local ischemic conditioning in diabetes have focused on GSK3- $\beta$  and the mPTP. Pharmacological inhibition of either GSK3- $\beta$  or the mPTP restores the protective potential of local ischemic conditioning in the diabetic heart<sup>109,110</sup>. Whether pharmacological interventions also are effective in restoring the cardioprotective potential of RIC in diabetes has not been investigated. Given that intact neural pathway is required for the cardioprotective effect of RIC<sup>13</sup>, it is likely that a combination of approaches that target both neural integrity and the final common signaling molecules and effectors would be the best strategy for restoring the myocardial response to RIC in diabetes.

## Summary

It is fair to say that owing to underlying risk factors that interfere with different cardioprotective interventions and the use of cardioprotective agents, most of the clinical trials with cardioprotective drugs have not been very successful. The results of various ischemic conditioning in humans appear to follow the same unsuccessful path, although RIC is a potent form of endogenous cardioprotection in healthy animals. In future research endeavors, the validation of drug targets and various cardiac conditioning needs to be conducted in comorbid animal models to have a successful clinical translation.

## Abbreviations

ERICCA, Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery; GSK3- $\beta$ , glycogen synthase kinase 3 beta; I/R, ischemia/reperfusion; mPTP, mitochondria permeability transition pore; PCI, percutaneous coronary intervention; PI3K/Akt, phosphatidylinositol 3-kinase, serine/threonine kinase also known as protein kinase B; RIC, remote ischemic conditioning; RIPHeart, Remote Ischemic Preconditioning for Heart Surgery.

## Competing interests

The authors declare that they have no competing interests.

## Grant information

This work was supported by grant P01GM066730 from the National Institutes of Health (Bethesda, MD, USA) (to ZJB).

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

## References



1. Yellon DM, Hausenloy DJ: **Myocardial reperfusion injury.** *N Engl J Med.* 2007; **357**(11): 1121–35.  
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Hausenloy DJ, Yellon DM: **Targeting Myocardial Reperfusion Injury--The Search Continues.** *N Engl J Med.* 2015; **373**(11): 1073–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Fröhlich GM, Meier P, White SK, *et al.*: **Myocardial reperfusion injury: looking beyond primary PCI.** *Eur Heart J.* 2013; **34**(23): 1714–22.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
4. Hausenloy DJ, Yellon DM: **Ischaemic conditioning and reperfusion injury.** *Nat Rev Cardiol.* 2016; **13**(4): 193–209.  
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Giricz Z, Varga ZV, Baranyai T, *et al.*: **Cardioprotection by remote ischemic preconditioning of the rat heart is mediated by extracellular vesicles.** *J Mol Cell Cardiol.* 2014; **68**: 75–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Skyschally A, Gent S, Amanakis G, *et al.*: **Across-Species Transfer of Protection by Remote Ischemic Preconditioning With Species-Specific Myocardial Signal Transduction by Reperfusion Injury Salvage Kinase and Survival Activating Factor Enhancement Pathways.** *Circ Res.* 2015; **117**(3): 279–88.  
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Bromage DI, Pickard JM, Rossello X, *et al.*: **Remote ischaemic conditioning reduces infarct size in animal in vivo models of ischaemia-reperfusion injury: a systematic review and meta-analysis.** *Cardiovasc Res.* 2017; **113**(3): 288–97.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
8. Randhawa PK, Jaggi AS: **Investigating the involvement of TRPV1, ion channels in remote hind limb preconditioning-induced cardioprotection in rats.** *Naunyn Schmiedeberg Arch Pharmacol.* 2017; **390**(2): 117–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
9. Schmidt MR, Smerup M, Konstantinov IE, *et al.*: **Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a  $K_{ATP}$ -dependent mechanism: first demonstration of remote ischemic preconditioning.** *Am J Physiol Heart Circ Physiol.* 2007; **292**(4): H1883–90.  
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Sziártó A, Czígány Z, Turóczy Z, *et al.*: **Remote ischemic preconditioning—a simple, low-risk method to decrease ischemic reperfusion injury: models, protocols and mechanistic background. A review.** *J Surg Res.* 2012; **178**(2): 797–806.  
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Basalay M, Barsukevich V, Mastitskaya S, *et al.*: **Remote ischaemic pre- and delayed postconditioning - similar degree of cardioprotection but distinct mechanisms.** *Exp Physiol.* 2012; **97**(8): 908–17.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Hausenloy DJ, Yellon DM: **Remote ischaemic preconditioning: underlying mechanisms and clinical application.** *Cardiovasc Res.* 2008; **79**(3): 377–86.  
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Kleinbongard P, Skyschally A, Heusch G: **Cardioprotection by remote ischemic conditioning and its signal transduction.** *Pflugers Arch.* 2017; **469**(2): 159–81.  
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Mastitskaya S, Marina N, Gourine A, *et al.*: **Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal preganglionic neurones.** *Cardiovasc Res.* 2012; **95**(4): 487–94.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Donato M, Buchholz B, Rodríguez M, *et al.*: **Role of the parasympathetic nervous system in cardioprotection by remote hindlimb ischaemic preconditioning.** *Exp Physiol.* 2013; **98**(2): 425–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Pickard JM, Davidson SM, Hausenloy DJ, *et al.*: **Co-dependence of the neural and humoral pathways in the mechanism of remote ischemic conditioning.** *Basic Res Cardiol.* 2016; **111**(4): 50.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
17. Basalay MV, Mastitskaya S, Mrochek A, *et al.*: **Glucagon-like peptide-1 (GLP-1) mediates cardioprotection by remote ischaemic conditioning.** *Cardiovasc Res.* 2016; **112**(3): 669–76.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
18. Surendra H, Diaz RJ, Harvey K, *et al.*: **Interaction of  $\delta$  and  $\kappa$  opioid receptors with adenosine  $A_1$  receptors mediates cardioprotection by remote ischemic preconditioning.** *J Mol Cell Cardiol.* 2013; **60**: 142–50.  
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Rassaf T, Totzeck M, Hendgen-Cotta UB, *et al.*: **Circulating nitrite contributes to cardioprotection by remote ischemic preconditioning.** *Circ Res.* 2014; **114**(10): 1601–10.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
20. Randhawa PK, Jaggi AS: **Unraveling the role of adenosine in remote ischemic preconditioning-induced cardioprotection.** *Life Sci.* 2016; **155**: 140–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
21. Hu Q, Luo W, Huang L, *et al.*: **Apoptosis-related microRNA changes in the right atrium induced by remote ischemic preconditioning during valve replacement surgery.** *Sci Rep.* 2016; **6**: 18959.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
22. Mastitskaya S, Basalay M, Hosford PS, *et al.*: **Identifying the Source of a Humoral Factor of Remote (Pre)Conditioning Cardioprotection.** *PLoS One.* 2016; **11**(2): e0150108.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
23. Randhawa PK, Jaggi AS: **Opioids in Remote Ischemic Preconditioning-Induced Cardioprotection.** *J Cardiovasc Pharmacol Ther.* 2016; **22**(2): pii: 1074248416660621.  
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Olenchok BA, Moslehi J, Baik AH, *et al.*: **EGLN1 Inhibition and Retouring of  $\alpha$ -Ketoglutarate Suffice for Remote Ischemic Protection.** *Cell.* 2016; **165**(2): 497.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
25. Heusch G, Botker HE, Przyklenk K, *et al.*: **Remote ischemic conditioning.** *J Am Coll Cardiol.* 2015; **65**(2): 177–95.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Heusch G: **Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning.** *Circ Res.* 2015; **116**(4): 674–99.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
27. Vanezis AP, Rodrigo GC, Squire IB, *et al.*: **Remote ischaemic conditioning and remodelling following myocardial infarction: current evidence and future perspectives.** *Heart Fail Rev.* 2016; **21**(5): 635–43.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Turrell HE, Thaitirarot C, Crumie H, *et al.*: **Remote ischemic preconditioning of cardiomyocytes inhibits the mitochondrial permeability transition pore independently of reduced calcium-loading or  $\text{sarck}_{ATP}$  channel activation.** *Physiol Rep.* 2014; **2**(11): pii: e12231.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Leung CH, Wang L, Nielsen JM, *et al.*: **Remote cardioprotection by transfer of coronary effluent from ischemic preconditioned rabbit heart preserves mitochondrial integrity and function via adenosine receptor activation.** *Cardiovasc Drugs Ther.* 2014; **28**(1): 7–17.  
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Marongiu E, Crisafulli A: **Cardioprotection acquired through exercise: the role of ischemic preconditioning.** *Curr Cardiol Rev.* 2014; **10**(4): 336–48.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Rock-Willoughby J, Boardley D, Badenhop DT, *et al.*: **Vigorous exercise mimics remote ischemic preconditioning and provides benefit in cardiac rehabilitation patients.** *J Clin Exp Cardiol.* 2013; **4**(8): 1000261.  
[Publisher Full Text](#)
32. Candilio L, Malik A, Ariti C, *et al.*: **Effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomised controlled clinical trial.** *Heart.* 2015; **101**(3): 185–92.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
33. Davies WR, Brown AJ, Watson W, *et al.*: **Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up.** *Circ Cardiovasc Interv.* 2013; **6**(3): 246–51.  
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Hausenloy DJ, Mwamure PK, Venugopal V, *et al.*: **Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial.** *Lancet.* 2007; **370**(9587): 575–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
35. Hoole SP, Heck PM, Sharples L, *et al.*: **Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial.** *Circulation.* 2009; **119**(6): 820–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
36. Thielmann M, Kottenberg E, Kleinbongard P, *et al.*: **Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial.** *Lancet.* 2013; **382**(9892): 597–604.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
37. Sivaraman V, Pickard JM, Hausenloy DJ: **Remote ischaemic conditioning: cardiac protection from afar.** *Anaesthesia.* 2015; **70**(6): 732–48.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Wu Q, Wang T, Chen S, *et al.*: **Cardiac protective effects of remote ischaemic preconditioning in children undergoing tetralogy of fallot repair surgery: a randomized controlled trial.** *Eur Heart J.* 2017; 01–11.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
39. Hong DM, Lee EH, Kim HJ, *et al.*: **Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic Preconditioning with Postconditioning Outcome Trial.** *Eur Heart J.* 2014; **35**(3): 176–83.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
40. Ferdinandy P, Hausenloy DJ, Heusch G, *et al.*: **Interaction of risk factors,**

- comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. *Pharmacol Rev.* 2014; **66**(4): 1142–74.  
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Kottenberg E, Thielmann M, Bergmann L, *et al.*: Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol - a clinical trial. *Acta Anaesthesiol Scand.* 2012; **56**(1): 30–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Heusch G, Gersh BJ: ERICCA and RIPHeart: two nails in the coffin for cardioprotection by remote ischemic conditioning? Probably not! *Eur Heart J.* 2016; **37**(2): 200–2.  
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Hausenloy DJ, Candillo L, Evans R, *et al.*: Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *N Engl J Med.* 2015; **373**(15): 1408–17.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
44. Meybohm P, Bein B, Brosteanu O, *et al.*: A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. *N Engl J Med.* 2015; **373**(15): 1397–407.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
45. Cung TT, Morel O, Cayla G, *et al.*: Cyclosporine before PCI in Patients with Acute Myocardial Infarction. *N Engl J Med.* 2015; **373**(11): 1021–31.  
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Baranyai T, Nagy CT, Kocsos G, *et al.*: Acute hyperglycemia abolishes cardioprotection by remote ischemic preconditioning. *Cardiovasc Diabetol.* 2015; **14**: 151.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
47. Kleinbongard P, Neuhäuser M, Thielmann M, *et al.*: Confounders of Cardioprotection by Remote Ischemic Preconditioning in Patients Undergoing Coronary Artery Bypass Grafting. *Cardiology.* 2016; **133**(2): 128–33.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
48. Zhou C, Bulluck H, Fang N, *et al.*: Age and Surgical Complexity impact on Renoprotection by Remote Ischemic Preconditioning during Adult Cardiac Surgery: A Meta analysis. *Sci Rep.* 2017; **7**(1): 215.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. Yang XM, Liu Y, Cui L, *et al.*: Platelet P2Y<sub>12</sub> blockers confer direct postconditioning-like protection in reperfused rabbit hearts. *J Cardiovasc Pharmacol Ther.* 2013; **18**(3): 251–62.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Lucchinetti E, Bestmann L, Feng J, *et al.*: Remote ischemic preconditioning applied during isoflurane inhalation provides no benefit to the myocardium of patients undergoing on-pump coronary artery bypass graft surgery: lack of synergy or evidence of antagonism in cardioprotection? *Anesthesiology.* 2012; **116**(2): 296–310.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. Zhou C, Liu Y, Yao Y, *et al.*:  $\beta$ -blockers and volatile anesthetics may attenuate cardioprotection by remote preconditioning in adult cardiac surgery: a meta-analysis of 15 randomized trials. *J Cardiothorac Vasc Anesth.* 2013; **27**(2): 305–11.  
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Iliodromitis EK, Cohen MV, Dagres N, *et al.*: What is Wrong With Cardiac Conditioning? We May be Shooting at Moving Targets. *J Cardiovasc Pharmacol Ther.* 2015; **20**(4): 357–69.  
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Andreadou I, Iliodromitis EK, Rassaf T, *et al.*: The role of gasotransmitters NO, H<sub>2</sub>S and CO in myocardial ischaemia/reperfusion injury and cardioprotection by preconditioning, postconditioning and remote conditioning. *Br J Pharmacol.* 2015; **172**(6): 1587–606.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Sörensson P, Saleh N, Bouvier F, *et al.*: Effect of postconditioning on infarct size in patients with ST elevation myocardial infarction. *Heart.* 2010; **96**(21): 1710–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Mozaffarian D, Benjamin EJ, Go AS, *et al.*: Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation.* 2015; **131**(4): e29–322.  
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Reed GW, Rossi JE, Cannon CP: Acute myocardial infarction. *Lancet.* 2017; **389**(10065): 197–210.  
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Grines CL, Browne KF, Marco J, *et al.*: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med.* 1993; **328**(10): 673–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
58. Zijlstra F, Hoorntje JC, de Boer MJ, *et al.*: Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1999; **341**(19): 1413–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Hausenloy DJ, Botker HE, Engstrom T, *et al.*: Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. *Eur Heart J.* 2017; **38**(13): 935–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Botker HE, Kharbada R, Schmidt MR, *et al.*: Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010; **375**(9716): 727–34.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. Rentoukas I, Giannopoulos G, Kaoukis A, *et al.*: Cardioprotective role of remote ischemic preconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv.* 2010; **3**(1): 49–55.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
62. Munk K, Andersen NH, Schmidt MR, *et al.*: Remote Ischemic Conditioning in Patients With Myocardial Infarction Treated With Primary Angioplasty: Impact on Left Ventricular Function Assessed by Comprehensive Echocardiography and Gated Single-Photon Emission CT. *Circ Cardiovasc Imaging.* 2010; **3**(6): 656–62.  
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Jimenez-Navarro MF, Carrasco-Chinchilla F, Munoz-Garcia AJ, *et al.*: Remote ischemic postconditioning: does it protect against ischemic damage in percutaneous coronary revascularization? justification and design of a randomized placebo-controlled clinical trial. *Cardiology.* 2011; **119**(3): 164–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Crimi G, Pica S, Raineri C, *et al.*: Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc Interv.* 2013; **6**(10): 1055–63.  
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Bautin AE, Galagudza MM, Datsenko SV, *et al.*: [Effects of remote ischemic preconditioning on perioperative period in elective aortic valve replacement] *Anesteziol Reanimatol.* 2014; **3**(3): 11–7.  
[PubMed Abstract](#)
66. Heusch G: Cardioprotection: chances and challenges of its translation to the clinic. *Lancet.* 2013; **381**(9861): 166–75.  
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Zangrillo A, Musu M, Greco T, *et al.*: Additive Effect on Survival of Anaesthetic Cardiac Protection and Remote Ischemic Preconditioning in Cardiac Surgery: A Bayesian Network Meta-Analysis of Randomized Trials. *PLoS One.* 2015; **10**(7): e0134264.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
68. Eitel I, Stiermaier T, Rommel KP, *et al.*: Cardioprotection by combined intrahospital remote ischaemic preconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial. *Eur Heart J.* 2015; **36**(44): 3049–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
69. Yellon DM, Ackbarkhan AK, Balgobin V, *et al.*: Remote Ischemic Conditioning Reduces Myocardial Infarct Size in STEMI Patients Treated by Thrombolysis. *J Am Coll Cardiol.* 2015; **65**(25): 2764–5.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
70. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation.* 1986; **74**(5): 1124–36.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
71. Wartier DC, al-Wathiqui MH, Kampine JP, *et al.*: Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology.* 1988; **69**(4): 552–65.  
[PubMed Abstract](#)
72. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery), American Society of Echocardiography, American Society of Nuclear Cardiology: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth Analg.* 2008; **106**(3): 685–712.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
73. Belhomme D, Peynet J, Louzy M, *et al.*: Evidence for preconditioning by isoflurane in coronary artery bypass graft surgery. *Circulation.* 1999; **100**(19 Suppl): I1340–4.  
[PubMed Abstract](#) | [Publisher Full Text](#)
74. De Hert SG, Turani F, Mathur S, *et al.*: Cardioprotection with volatile anesthetics: mechanisms and clinical implications. *Anesth Analg.* 2005; **100**(6): 1584–93.  
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Hanouz JL, Yvon A, Massetti M, *et al.*: Mechanisms of desflurane-induced preconditioning in isolated human right atria *in vitro*. *Anesthesiology.* 2002; **97**(1): 33–41.  
[PubMed Abstract](#)
76. Yvon A, Hanouz JL, Haelewyn B, *et al.*: Mechanisms of sevoflurane-induced myocardial preconditioning in isolated human right atria *in vitro*. *Anesthesiology.* 2003; **99**(1): 27–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
77. Zaugg M, Lucchinetti E, Garcia C, *et al.*: Anaesthetics and cardiac preconditioning. Part II. Clinical implications. *Br J Anaesth.* 2003; **91**(4): 566–76.  
[PubMed Abstract](#) | [Publisher Full Text](#)
78. Zaugg M, Lucchinetti E, Spahn DR, *et al.*: Volatile anesthetics mimic cardiac

- preconditioning by priming the activation of mitochondrial K<sup>ATP</sup> channels via multiple signaling pathways.** *Anesthesiology*. 2002; 97(1): 4–14.  
[PubMed Abstract](#) | [Publisher Full Text](#)
79. Zaugg M, Lucchinetti E, Uecker M, *et al.*: **Anaesthetics and cardiac preconditioning. Part I. Signalling and cytoprotective mechanisms.** *Br J Anaesth*. 2003; 91(4): 551–65.  
[PubMed Abstract](#) | [Publisher Full Text](#)
80. Laskey WK, Beach D: **Frequency and clinical significance of ischemic preconditioning during percutaneous coronary intervention.** *J Am Coll Cardiol*. 2003; 42(6): 998–1003.  
[PubMed Abstract](#) | [Publisher Full Text](#)
81. NDFS CfDCaP: **National diabetes statistics report.** 2014.  
[Reference Source](#)
82. Doenst T, Wijeyesundera D, Karkouti K, *et al.*: **Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery.** *J Thorac Cardiovasc Surg*. 2005; 130(4): 1144.  
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Mulnier HE, Seaman HE, Raleigh VS, *et al.*: **Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database.** *Diabetologia*. 2008; 51(9): 1639–45.  
[PubMed Abstract](#) | [Publisher Full Text](#)
84. van der Horst IC, Nijsten MW, Vogelzang M, *et al.*: **Persistent hyperglycemia is an independent predictor of outcome in acute myocardial infarction.** *Cardiovasc Diabetol*. 2007; 6: 2.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Wahab NN, Cowden EA, Pearce NJ, *et al.*: **Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era?** *J Am Coll Cardiol*. 2002; 40(10): 1748–54.  
[PubMed Abstract](#) | [Publisher Full Text](#)
86. Poddar KL, Modi DK, Wayangankar S, *et al.*: **Two-Decade Trends in the Prevalence of Atherosclerotic Risk Factors, Coronary Plaque Morphology, and Outcomes in Adults Aged  $\leq 45$  Years Undergoing Percutaneous Coronary Intervention.** *Am J Cardiol*. 2016; 118(7): 939–43.  
[PubMed Abstract](#) | [Publisher Full Text](#)
87. Benedetto U, Caputo M, Vohra H, *et al.*: **Off-pump versus on-pump coronary artery bypass surgery in patients with actively treated diabetes and multivessel coronary disease.** *J Thorac Cardiovasc Surg*. 2016; 152(5): 1321–1330.e12.  
[PubMed Abstract](#) | [Publisher Full Text](#)
88. Ndumele CE, Matsushita K, Lazo M, *et al.*: **Obesity and Subtypes of Incident Cardiovascular Disease.** *J Am Heart Assoc*. 2016; 5(8): pii: e003921.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
89. Sardarina M, Akbarpour S, Lotfaliani M, *et al.*: **Risk Factors for Incidence of Cardiovascular Diseases and All-Cause Mortality in a Middle Eastern Population over a Decade Follow-up: Tehran Lipid and Glucose Study.** *PLoS One*. 2016; 11(12): e0167623.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
90. **F** Holzmann MJ, Rathsmann B, Eliasson B, *et al.*: **Long-term prognosis in patients with type 1 and 2 diabetes mellitus after coronary artery bypass grafting.** *J Am Coll Cardiol*. 2015; 65(16): 1644–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
91. Xu X, Zhou Y, Luo S, *et al.*: **Effect of remote ischemic preconditioning in the elderly patients with coronary artery disease with diabetes mellitus undergoing elective drug-eluting stent implantation.** *Angiology*. 2014; 65(8): 660–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
92. Lejay A, Fang F, John R, *et al.*: **Ischemia reperfusion injury, ischemic conditioning and diabetes mellitus.** *J Mol Cell Cardiol*. 2016; 91: 11–22.  
[PubMed Abstract](#) | [Publisher Full Text](#)
93. Epps JA, Smart NA: **Remote ischaemic conditioning in the context of type 2 diabetes and neuropathy: the case for repeat application as a novel therapy for lower extremity ulceration.** *Cardiovasc Diabetol*. 2016; 15(1): 130.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
94. Boulton AJ, Vinik AI, Arezzo JC, *et al.*: **Diabetic neuropathies: a statement by the American Diabetes Association.** *Diabetes Care*. 2005; 28(4): 956–62.  
[PubMed Abstract](#) | [Publisher Full Text](#)
95. Green AQ, Krishnan S, Finucane FM, *et al.*: **Altered C-fiber function as an indicator of early peripheral neuropathy in individuals with impaired glucose tolerance.** *Diabetes Care*. 2010; 33(1): 174–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
96. Jensen RV, Stottrup NB, Kristiansen SB, *et al.*: **Release of a humoral circulating cardioprotective factor by remote ischemic preconditioning is dependent on preserved neural pathways in diabetic patients.** *Basic Res Cardiol*. 2012; 107(5): 285.  
[PubMed Abstract](#) | [Publisher Full Text](#)
97. Saxena P, Newman MA, Shehatha JS, *et al.*: **Remote ischemic conditioning: evolution of the concept, mechanisms, and clinical application.** *J Card Surg*. 2010; 25(1): 127–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
98. Baumgardt SL, Paterson M, Leucker TM, *et al.*: **Chronic Co-Administration of Sepiapterin and L-Citrulline Ameliorates Diabetic Cardiomyopathy and Myocardial Ischemia/Reperfusion Injury in Obese Type 2 Diabetic Mice.** *Circ Heart Fail*. 2016; 9(1): e002424.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
99. Wang X, Zhao L: **Calycosin ameliorates diabetes-induced cognitive impairments in rats by reducing oxidative stress via the PI3K/Akt/GSK-3 $\beta$  signaling pathway.** *Biochem Biophys Res Commun*. 2016; 473(2): 428–34.  
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Chen ZC, Cheng YZ, Chen LJ, *et al.*: **Increase of ATP-sensitive potassium (K<sub>ATP</sub>) channels in the heart of type-1 diabetic rats.** *Cardiovasc Diabetol*. 2012; 11: 8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
101. Wei M, Xin P, Li S, *et al.*: **Repeated remote ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model of myocardial infarction.** *Circ Res*. 2011; 108(10): 1220–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
102. **F** Yamaguchi T, Izumi Y, Nakamura Y, *et al.*: **Repeated remote ischemic conditioning attenuates left ventricular remodeling via exosome-mediated intercellular communication on chronic heart failure after myocardial infarction.** *Int J Cardiol*. 2015; 178: 239–46.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
103. **F** Sardar P, Chatterjee S, Kundu A, *et al.*: **Remote ischemic preconditioning in patients undergoing cardiovascular surgery: Evidence from a meta-analysis of randomized controlled trials.** *Int J Cardiol*. 2016; 221: 34–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
104. Shimizu M, Saxena P, Konstantinov IE, *et al.*: **Remote ischemic preconditioning decreases adhesion and selectively modifies functional responses of human neutrophils.** *J Surg Res*. 2010; 158(1): 155–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)
105. Jones H, Hopkins N, Bailey TG, *et al.*: **Seven-day remote ischemic preconditioning improves local and systemic endothelial function and microcirculation in healthy humans.** *Am J Hypertens*. 2014; 27(7): 918–25.  
[PubMed Abstract](#) | [Publisher Full Text](#)
106. **F** Shaked G, Czeiger D, Abu Arar A, *et al.*: **Intermittent cycles of remote ischemic preconditioning augment diabetic foot ulcer healing.** *Wound Repair Regen*. 2015; 23(2): 191–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
107. Murphy E: **Primary and secondary signaling pathways in early preconditioning that converge on the mitochondria to produce cardioprotection.** *Circ Res*. 2004; 94(1): 7–16.  
[PubMed Abstract](#) | [Publisher Full Text](#)
108. Juhaszova M, Zorov DB, Yaniv Y, *et al.*: **Role of glycogen synthase kinase-3 $\beta$  in cardioprotection.** *Circ Res*. 2009; 104(11): 1240–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
109. **F** Jamwal S, Kumar K, Reddy BV: **Beneficial effect of zinc chloride and zinc ionophore pyrithione on attenuated cardioprotective potential of preconditioning phenomenon in STZ-induced diabetic rat heart.** *Perfusion*. 2016; 31(4): 334–42.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
110. **F** Najafi M, Farajnia S, Mohammadi M, *et al.*: **Inhibition of mitochondrial permeability transition pore restores the cardioprotection by postconditioning in diabetic hearts.** *J Diabetes Metab Disord*. 2014; 13(1): 106.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)



# Open Peer Review

Current Referee Status:



---

## Editorial Note on the Review Process

**F1000 Faculty Reviews** are commissioned from members of the prestigious **F1000 Faculty** and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

---

## The referees who approved this article are:

### Version 1

- 1 **Karin Przyklenk** Cardiovascular Research Institute and Departments of Physiology and Emergency Medicine, Wayne State University School of Medicine, Detroit, MI, USA  
**Competing Interests:** No competing interests were disclosed.
- 1 **James M. Downey** Department of Physiology and Cell Biology, College of Medicine, University of South Alabama, AL, USA  
**Competing Interests:** No competing interests were disclosed.
- 1 **Pasquale Pagliaro** Department of Clinical and Biological Sciences, University of Torino, Orbassano, Turin, Italy  
**Competing Interests:** No competing interests were disclosed.