Remote ischemic conditioning in Emergency Medicine – clinical frontiers and research opportunities

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ABSTRACT

Time-critical acute ischemic conditions such as ST-elevation myocardial infarction and acute ischemic stroke are staples in Emergency Medicine practice. While timely reperfusion therapy is a priority, the resultant acute ischemia/reperfusion injury contributes to significant mortality and morbidity. Among therapeutics targeting IRI, remote ischemic conditioning (RIC), has emerged as the most promising.

RIC, which consists of repetitive inflation and deflation of a pneumatic cuff on a limb, was first demonstrated to have protective effect on ischemia/reperfusion injury through various neural and humoral mechanisms. Its attractiveness stems from its simplicity, low-cost, safety and efficacy, while at the same time it does not impede reperfusion treatment. There is now good evidence for RIC as an effective adjunct to reperfusion in ST-elevation myocardial infarction patients for improving clinical outcomes. For other applications such as acute ischemic stroke, subarachnoid hemorrhage, traumatic brain injury, cardiac arrest and spinal injury, there is varying level of evidence.

This review aims to describe the RIC phenomenon, briefly recount its historical development, and appraise the experimental and clinical evidence for RIC in selected emergency conditions. Finally, it describes the practical issues with RIC clinical application and research in Emergency Medicine.

INTRODUCTION

Individually and collectively, acute ischemic conditions represent a tremendous global health burden. Ischemic heart disease and stroke are by far the top two leading causes of death worldwide, across all country income categories, and have remained so consistently for the past 15 years.[1] This is not to mention other acute ischemic conditions seen in Emergency Medicine (EM) such as out-of-hospital cardiac arrest (OHCA), acute ischemic stroke (AIS) and ischemic bowel, to name a few. With aging of the global population, these conditions are projected to pose an increasing public health challenge.[2–4]

Acute tissue ischemia is the crucial common pathophysiology of a number of devastating time-critical conditions that present to Emergency Departments (ED). Ischemia involves restricted blood supply to tissues, either due to arterial occlusion or a global low-flow state, and the resultant impaired tissue perfusion provides inadequate oxygen and nutrients for cellular metabolism as well as inadequate removal of metabolic waste. This activates an ischemic cascade leading to tissue necrosis and infarction, and in turn, clinical sequelae.

The mainstay of emergency treatment in these condition is to promptly restore tissue perfusion and salvage ischemic tissue, which in cases of acute thrombotic or embolic occlusion of arteries, involve reperfusion treatments. These include, in increasing order of invasiveness, injection of thrombolytics, endovascular interventions and surgical thrombectomy or bypass.[5] Indeed, the importance of timely restoration of perfusion to ischemic tissues is exemplified in oft-cited adages such as “time is myocardium”[6], “time is brain”[7] and “chain of survival”[8], as well as various time targets.[9,10]

However, with reperfusion comes ischemia/reperfusion (IR) injury (IRI), which paradoxically causes cell death in reperfused tissue[11] and contributes significantly to post-reperfusion mortality and morbidity.[12,13] For example, in a feline model of intestinal ischemia, four hours of ischemia resulted in less injury than three hours of ischemia followed by one hour of reperfusion.[11] In ST-elevation myocardial infarction (STEMI), IRI contributes up to 50% of final infarct size despite timely primary percutaneous coronary intervention (PPCI). This is a key reason for the continued high mortality and morbidity in these conditions, despite endovascular reperfusion treatments and continuous efforts to improve timeliness and access to these treatments. Hence, novel protective therapies are required to attenuate IRI alongside reperfusion in acute ischemic conditions to improve clinical outcomes. Besides organizing expeditious reperfusion therapy, Emergency Physicians could play important roles in providing therapy aimed at reducing IRI. Of treatments targeting IRI, remote ischemic conditioning (RIC)[14], is currently considered the most promising.[15]

RIC, in its most practical form, consists of repetitive inflation and deflation of a blood pressure cuff on a limb, and was first demonstrated to have a protective effect on IRI after myocardial ischemia.[16] Promising data has since emerged in other acute applications such as AIS. Its attractiveness stems from its simplicity, low-cost, safety and efficacy, while at the same time it does not impede reperfusion treatment – making it greatly appealing to the Emergency Physician.

This review article hopes to engage the EM clinical and research community on the three-decade-long body of work surrounding RIC, with specific focus on applications relevant to EM (both ED and prehospital settings). This review will describe the RIC phenomenon, give a brief historical account of the scientific work leading to the current understanding, appraise the preclinical and clinical evidence for RIC in various emergency conditions, and finally, describe the practical issues with its clinical application and research in EM.

Remote ischemic conditioning – an introduction

Remote ischemic conditioning is the mechanism whereby repetitive, brief, sub-lethal episodes of ischemia/reperfusion in various effector organs activates powerful endogenous protection against IRI after acute ischemia and reperfusion of distant target organs. In its most practical form, this means that repetitive inflation and deflation of a pneumatic cuff on a limb in patients with acute organ ischemic would be beneficial.

Remote ischemic conditioning has three temporal variants, defined in relation to the onset time of the ischemic insult and reperfusion: remote ischemic preconditioning (RIPreC), perconditioning (RIPerC), and postconditioning (RIPost) (Figure 1). In acute clinical settings, RIPreC is not practicable because it must be commenced even before ischemia, whereas RIPerC, and to a much smaller extent, RIPost, are highly relevant as they be applied after the onset of ischemia and at reperfusion, respectively. Figure 1 shows how in a patient with a stereotypical acute ischemic condition navigating through an emergency care system could benefit from these temporal variants, of which the time spent in the ambulance and the ED has the strongest evidence and highest relevance to EMs. This review aims to review clinical applications in EM, and so will focus on RIPerC. Unless otherwise stated, RIC will refer to RIPerC.

The mechanism of RIC is incompletely understood, in terms of signal release, signal transfer to the target organ as well as signal transduction within the target organ. The current understanding is that the conditioning stimulus is effected through complementary humoral and neural pathways.[17] The humoral pathway has been studied more extensively, with studies have demonstrating the transport of blood-borne humoral factors, including an unidentified hydrophobic molecule sized 3.5-15kDa.[18] A systemic inflammatory response due to immune cell

mobilization and infiltration have also been implicated.[19,20] The neural pathway are demonstrated in experiments showing the reduction of, but not complete abolishment of the protective effect of RIC with transection of the femoral nerve, as well as in human experiments showing abrogated protection in subjects with diabetic neuropathy.[21] A summary of known effector organs, methods of eliciting protection, mechanisms and target organs is presented in Figure 2.

The mechanism of RIC in specific clinical applications like STEMI and AIS are beyond the scope of this review, and the interested reader is referred to relevant reviews.[22–24]

Bench to bedside – a historical perspective

The predecessor of RIC is ischemic preconditioning. This was demonstrated by landmark experiments in 1986 by Murry et al which found that brief, intermittent ischemia and reperfusion of myocardium, followed by prolonged occlusion, reduced infarct size when compared to unconditioned controls.[25] In an open-chest dog model, four cycles of 5 minute / 5 minute IR of the left circumflex artery (LCx) prior to a 40 minute LCx occlusion reduced infarct size by 75%.

Pryzklenck et al then illustrated the "remote" aspect of RIC by demonstrating that conditioning the LCx reduced infarct size from left anterior descending occlusion in dogs.[26] Since then, this laboratory curiosity has sparked off countless experiments that established RIC as a robust phenomenon with a variety of effector and target organs.[14]

It was the finding that this cardioprotective stimulus can be effected by skeletal muscle[27] and hence simply inflating and deflating a blood pressure cuff placed on the arm or leg[28] that facilitated its translation into the clinical setting. The first human proof-of-concept study was on elective coronary artery bypass graft surgery where RIC reduced myocardial injury after ischemic cardioplegia.[29]

Clinical emergency applications

The role of RIC in the treatment of a range of conditions have been investigated in preclinical studies, clinical trials and meta-analyses.[30] The following conditions are chosen for their relevance to EM practice and are discussed in this section (Table 1).

ST-elevation myocardial infarction

Evident from the above account of the historical development of RIC, STEMI is the classical application in which RIC is most tested and has the most robust evidence base. Despite timely reperfusion by PPCI, mortality and morbidity after STEMI remain significant, with 7% death and 22% heart failure at 1-year.[31] Further, the reduction of mortality since the advent of PPCI is accompanied by increasing chronic heart failure incidence.[32] There is therefore an urgent need to develop cardioprotective therapies in order to prevent heart failure after STEMI.

Therapeutic strategies that have potential to improve clinical outcomes in reperfused STEMI patients include RIC, IPost, exenatide, and metoprolol. These have emerged amongst a multitude of cardioprotective interventions investigated with largely neutral clinical data.[15]

Botker et al conducted a landmark randomized controlled trial (RCT) on STEMI patients using RIC on the ambulance.[33] This study demonstrated a 36% increase in myocardial salvage on SPECT imaging. On 3.8 year follow up, the RIC group had 35% fewer MACE and 52% reduction in all-cause mortality.[34] Furthermore, cumulative cardiovascular medical costs were 18% lower, mainly contributed by reduced readmissions.[35] Since then, several trials showed benefit in surrogate outcomes of myocardial injury such as biomarkers or ST-segment resolution.[36–40]

A 2017 meta-analysis of nine RCTs with 1220 patients examined RIC in patients with STEMI who received PPCI.[41] Myocardial salvage index was higher in the RIC group compared with control group (mean difference [MD]: 0.08; 95% CI, 0.02–0.14; four trials included, total 636 patients). Infarct size was reduced in the RIC group compared with the control group (MD: -2.46; 95% CI, -4.66 to -0.26), with moderate statistical heterogeneity among studies (five trials, 848 patients). Finally, MACE was lower in the RIC group (9.5%) compared with the control group (17.0%; RR: 0.57; 95% CI, 0.40–0.82; four trials, 928 patients).

Most recently, the RIC-STEMI trial reported in 2018.[42] This was the largest trial to date with 500 patients randomized to RIC versus sham RIC in the catheterization laboratory 10 minutes before PPCI, which found a reduction in the primary endpoint of combined cardiac death and hospitalization for heart failure, as well as each individually. This was the first trial powered to demonstrate improved clinical outcome as the primary endpoint.

In summary, there is robust evidence for RIC as an effective adjunct to PPCI in STEMI patients for reducing infarct size and MACE. Whether it can improve long-term clinical outcomes is unclear and is currently being investigated in the European multicenter CONDI-2/ERIC-PPCI trial (NCT02342522) which has completed recruitment of 5200 STEMI patients and will report it results in Summer 2019.[43] Notably, these completed and ongoing trials excluded patients with STEMI complicated by cardiogenic shock or cardiac arrest, a group which will be discussed in the section on cardiac arrest.

Acute ischemic stroke

Recanalization in AIS has traditionally been achieved using systemic thrombolysis[44], but in recent years have seen a rapid increase with current use of endovascular techniques.[45,46] With recanalization, cerebral reperfusion injury occurs, and manifests as deterioration of penumbra, disruption of the blood–brain barrier, cerebral edema, and intracerebral hemorrhage.[13] Perhaps analogous to STEMI, pharmacological targeting of neuroprotection has been largely disappointing.[47]

The potential for RIC in human AIS was initially suggested by observations of natural RIPreC in that preceding transient ischemic attack attenuated subsequent stroke with smaller infarct size and less clinical deficits compared with patients without a preceding transient event.[44,48,49] Furthermore, patients who had untreated peripheral vascular disease prior to stroke (presumably preconditioned) similarly had lower disability and mortality.[50]

Experiments using embolic middle cerebral artery occlusion mice models showed that with or without thrombolysis at 4 hours, RIC similarly reduced cerebral infarct sizes, with greater benefit seen in thrombolyzed mice.[51]

The first human proof-of-concept RCT was conducted by Hougaard at el in 2009, randomizing 443 suspected stroke patients on the ambulance to RIC or standard care.[52] Only patients who were subsequently thrombolyzed were analyzed. The outcome was neutral in terms of infarct size but showed increased tissue survival at one month with RIC. The study was not powered to detect differences in clinical outcomes.

A second RCT was the ReCAST which was a pilot for a larger ongoing ReCAST-2 trial (NCT02779712).[53] 26 patients with AIS onset within 24 hours were randomized to RIC or sham

RIC in a stroke unit. There was no difference in the primary outcome of patient tolerability. There was a significant decrease in day-90 NIHSS score in the RIC group: median NIHSS score 1 versus 3. None of the patients appeared to have been thrombolyzed.

A 2018 Cochrane review was performed on the topic but is less applicable to EM because the above two trials on AIS were aggregated with two trials on small vessel cerebral disease.[6] Relevant ongoing trials on the topic include the ReCAST-2 trial and the RESCUE-BRAIN trial (NCT02189928). There are currently no published trials on RIC in patients who receive thrombectomy. The use of RIPreC in stroke prevention, while exciting, will not be discussed in this review.

Aneurysmal subarachnoid hemorrhage

Spontaneously ruptured aneurysms account for 80% of subarachnoid hemorrhage (SAH). Of those who survive the early brain injury, even with successful embolization of the ruptured aneurysm, delayed brain ischemia occur in 30% of patients and contributes to substantial long-term physical and cognitive disability.[54,55]

Preconditioning before inducing SAH in rats was shown to improve vasospasm, reduce cerebral inflammatory cytokines, reduce tissue hypoxia, and reduce neurological deterioration.[56–58] While preconditioning need to occur before SAH, these studies serve to demonstrate that innate protective systems are present and can be activated through conditioning.[56]

Two Phase I clinical trials tested RIC after SAH.[59,60] In one study, 33 patients underwent RIC every 24-48 hours for 14 days.[60] In the second study, 20 patients underwent RIC on non-

consecutive days for four sessions.[59] As intended, these two studies demonstrated both safety and feasibility of RIC in SAH. However, they were not designed to test effect on delayed brain ischemia. A post-hoc matched cohort analysis of the Gonzalez study[59] showed RIC to be independently associated with good functional outcome on discharge (modified Rankin Scale 0-2).[61]

Traumatic brain injury

Separate experiments on closed-skull TBI mouse models found that RIC two hours after injury preserved cognitive functions and motor coordination compared to sham RIC.[62,63] A proof-of-concept RCT randomized 40 severe TBI patients to RIC within one-hour and found RIC to reduce levels of the brain injury biomarkers S-100B and neuron-specific enolase.[64]

Cardiac arrest

RIC during cardiopulmonary resuscitation (CPR) in porcine models of prolonged cardiac arrest (untreated ventricular fibrillation, VF) improved left ventricular ejection fracture at one and four hours as well as neurological function at 24 and 48 hours.[65,66] This was achieved using four cycles of 20-second/20-second no-CPR/CPR started within three minute of starting CPR after 15 minutes of untreated VF. The same research group later showed that RIC was synergistic with other enhancements in CPR including active compression/decompression CPR, abdominal binding and impedance threshold device[66]. Another group approached RIC differently, using four cycles of five minute femoral artery occlusion, and found reduced cardiac biomarkers and trend towards improved neurological outcomes.[67] Whether RIC would be beneficial in the clinical setting of cardiac arrest remains to be tested.

Spinal cord injury

The possibility of a role for RIC in emergency treatment of spinal cord injury is suggested by findings that IPost in rabbit models of spinal cord ischemia improved neuronal survival[68,69] and neurological function[68,70].

Practical issues

Unknown Optimal RIC Protocol

The optimal RIC protocol has yet to be fully defined. If RIC were considered as one would a drug, its dosing, pharmacokinetics, and pharmacodynamics are poorly characterized. The most commonly employed technique is three to four repetitions of 5 minute inflation/ 5 minute deflation using a standard blood pressure cuff on the arm. These are however empirically chosen and not guided by human studies investigating protocol aspects such as the optimal number of cycles, duration of inflation/deflation and arm versus leg.

Clinical studies have predominantly applied the cuff on the upper arm, although a few used the thigh. In mice, RIC on one or both hind-limbs did not differ in cardioprotection, implying that muscle mass is inconsequential.[71] While there are practical advantages to using the leg and leaving both arms unencumbered for intravenous access and blood pressure monitoring, it has been suggested that it is less tolerable by patients due to discomfort (cite). In a real-life clinical setting, there are also unproven safety concerns in preexisting lower limb peripheral arterial disease.

In terms of number of cycles, Johnsen et al compared two, four, six and eight cycles on an isolated perfused mouse heart model, and found that four and six cycles are superior to two cycles.[71] There are also suggestions that excessive conditioning may be deleterious.

Equipment

Practically any tourniquet capable of applying pressure on the proximal aspect of a limb above systolic blood pressure would achieve arterial occlusion and can be used for RIC. This is most

commonly done with a manual blood pressure cuff, sphygmomanometer and stopwatch, although some studies employed automatic cuff systems (eg autoRIC®, modified FB-270 oscillometric monitor; Fukuda Denshi)[72] or a normal cuff connected to an automatic device (PeriVasc Cuff Unit;EBIDA)[73]. An automatic device can be left on and a pre-programmed protocol will run, hence relieving resources (both manpower and cognitive) in a busy resuscitation room or ambulance. These nontangible benefits are as difficult to demonstrate as those with mechanical chest compression devices in out-of-hospital cardiac arrest.[74] In addition, in a trial setting, a sham control RIC protocol can be programmed into the device.

Setting

RIC has been applied successfully in emergency settings including in the ambulance[33,75], during air medical transport[76], in the ED, as well as in the catheterization lab. When using a manual cuff, RIC requires a dedicated personnel to administer, which is a practical limitation in the prehospital setting. A decision whether to implement RIC on the ambulance is clearly dependent on the average prehospital transport times of the system. In one system, 18% of patients had a transportation time too short to complete four cycles of RIC.[52]

DISCUSSION

Emergency Physicians are uniquely positioned to impact outcomes in acute time-critical conditions. While advances in reperfusion has reduced early mortality and advances in rehabilitation mitigate the consequences of the ischemic insult in those who survive the acute event, it is preferable to optimize treatment in the initial treatment window to reduce disability in the first place. After reperfusion, reperfusion injury is the most viable treatment target. In this regard, RIC presents a practical and cheap intervention that is emerging as efficacious for several indications. There is solid evidence from experimental and clinical studies to support the ability of RIC to protect against IRI. In terms of translation, the efficacy is most concretely shown for STEMI, which has been subjected to a longer history of and more numerous trials. One remarkable feature is that of all the clinical studies that tested RIC, including one study that performed RIC twice daily on both arms for 300 consecutive days, no safety issues were found.[77]

While enthusiasm for RIC has sometimes been tempered by a number of neutral clinical studies, the reasons for this are complex and have been discussed extensively in the literature. They have been attributed to design issues of both experimental and clinical studies used to test novel cardioprotective therapies.[15] Some of these design limitations included testing in clinical trials without prior experimentation on large animals, pre-clinical experiments in healthy adults without co-morbidities and concomitant medications usually received by patients, and trials including patients with too small infarct sizes to benefit significantly. These limitations mean that neutral trials need to be interpreted carefully, and highlight the challenges of translating experimental studies into the clinics.[78] A lesson can be learnt from how it took almost a decade between the first proof-of-concept RIC trial in STEMI and the first RIC trial showing improved clinical outcome.[33,42]

This review also reveals opportunities for acute care research. As described above, IRI is an unwanted effect of reperfusion and is culpable for profound mortality and morbidity in a variety of acute ischemic conditions, and is therefore a high-yield target to develop therapeutics for. These therapeutics are however, understandably unattractive for the pharmaceutical industry because these protective agents are given only once and not as continuous therapy.

From a pathophysiologic point of view, RIC would have limited benefit if intended to replace reperfusion therapy, as it mainly works to salvage reperfused ischemic tissue. Hence, efforts to apply RIC to resource-limited EM settings such as tactical, wilderness and rural settings would have limited impact. Further, from a systems point of view, there is no replacement for developing emergency care systems and regionalization of care to improve access to and timeliness of reperfusion.[43]

Increased awareness of this body of work may stimulate clinical and experimental investigations of this phenomenon for Emergency Physicians and EM researchers. The practical nature of this treatment and time window makes it attractive for the EM setting. In the Emergency Physician's task to lead in the organization and optimization of care for time-critical diseases, RIC adds to the armamentarium and is a clinical and research frontier for EM.

CONCLUSION

RIC is a practical, low-cost and safe intervention to ameliorate IRI. Its efficacy is proven in STEMI, and evidence is emerging for other acute ischemic conditions including AIS.

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CONFLICTS OF INTEREST

The authors do not have any conflict of interests to declare.

REFERENCES

1. World Health Organization. The top 10 causes of death. http://www.who.int/mediacentre/factsheets/fs310/en/. Published 2017. Accessed March 14, 2017.

2. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement From the American Heart Association. *Circulation*. 2011;123(8):933-944. doi:10.1161/CIR.0b013e31820a55f5.

3. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the Impact of Heart Failure in the United States: A Policy Statement From the American Heart Association. *Circ Hear Fail*. 2013;6(3):606-619. doi:10.1161/HHF.0b013e318291329a.

4. Ovbiagele B, Goldstein LB, Higashida RT, et al. Forecasting the Future of Stroke in the United States: A Policy Statement From the American Heart Association and American Stroke Association. *Stroke*. 2013;44(8):2361-2375. doi:10.1161/STR.0b013e31829734f2.

5. Santistevan JR. Acute Limb Ischemia: An Emergency Medicine Approach. *Emerg Med Clin North Am*. 2017;35(4):889-909. doi:10.1016/j.emc.2017.07.006.

6. Gibson CM. Time is myocardium and time is outcomes. *Circulation*. 2001;104(22):2632-2634. doi:10.1161/01.cir.0000147778.05979.e6.

7. Saver JL. Time is brain - Quantified. *Stroke*. 2006;37(1):263-266. doi:10.1161/01.STR.0000196957.55928.ab.

8. Cummins R, Ornato JP, Thies WH, et al. Improving Survival From Sudden Cardiac Arrest : The " Chain of Survival " Concept. *Circulation*. 1991;Vol 83, No:1832-1847. doi:10.1161/01.CIR.83.5.1832.

9. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-2619. doi:10.1093/eurheartj/ehs215.

10. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-425. doi:10.1161/CIR.0b013e3182742cf6.

11. Grace PA. Ischaemia-reperfusion injury. *Br J Surg*. 1994;81(5):637-647. http://www.ncbi.nlm.nih.gov/pubmed/8044536. Accessed September 11, 2018.

12. Yellon DM, Hausenloy DJ. Myocardial Reperfusion Injury. *N Engl J Med*. 2007;357(11):1121-1135. doi:10.1056/NEJMra071667.

13. Bai J, Lyden PD. Revisiting cerebral postischemic reperfusion injury: New insights in understanding reperfusion failure, hemorrhage, and edema. *Int J Stroke*. 2015;10(2):143-152. doi:10.1111/ijs.12434.

14. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol*. 2015;65(2):177-195. doi:10.1016/j.jacc.2014.10.031.

15. 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):935-941d. doi:10.1093/eurheartj/ehw145.

16. Cheung MMH, Kharbanda RK, Konstantinov IE, et al. Randomized Controlled Trial of the Effects of Remote Ischemic Preconditioning on Children Undergoing Cardiac Surgery. *J Am Coll Cardiol*. 2006;47(11):2277-2282. doi:10.1016/j.jacc.2006.01.066.

17. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: Underlying mechanisms and clinical application. *Cardiovasc Res*. 2008;79(3):377-386. doi:10.1093/cvr/cvn114.

18. Serejo FC, Rodrigues LF, da Silva Tavares KC, de Carvalho ACC, Nascimento JHM. Cardioprotective Properties of Humoral Factors Released From Rat Hearts Subject to Ischemic Preconditioning. *J Cardiovasc Pharmacol*. 2007;49(4):214-220. doi:10.1097/FJC.0b013e3180325ad9.

19. Weber C. Far from the heart: Receptor cross-talk in remote conditioning. *Nat Med*. 2010;16(7):760-762. doi:10.1038/nm0710-760.

20. Saxena P, Newman MAJ, Shehatha JS, Redington AN, Konstantinov IE. Remote ischemic conditioning: evolution of the concept, mechanisms, and clinical application. *J Card Surg*. 2010;25(1):127-134. doi:10.1111/j.1540-8191.2009.00820.x.

21. Jensen RV, Støttrup NB, Kristiansen SB, Bøtker HE. 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):1-9. doi:10.1007/s00395-012-0285-1.

22. Zhou G, Li MH, Tudor G, Lu HT, Kadirvel R, Kallmes D. Remote ischemic conditioning in cerebral diseases and neurointerventional procedures: Recent research progress. *Front Neurol*. 2018;9(MAY). doi:10.3389/fneur.2018.00339.

23. Chong J, Bulluck H, Yap EP, Ho AFW, Hausenloy DJ. Remote ischemic conditioning in ST-segment elevation myocardial infarction: an update. *Cond Med*. 2018;1(5):213-222.

24. Chen G, Thakkar M, Robinson C, Doré S. Limb remote ischemic conditioning: Mechanisms, anesthetics, and the potential for expanding therapeutic options. *Front Neurol*. 2018;9(FEB). doi:10.3389/fneur.2018.00040.

25. Murry CE, Jennings RB, Reimer K a. Preconditioning with ischemia : injury delay of lethal cell ischemic myocardium. *Circulation*. 1986;74(5):1224-1136. doi:10.1161/01.CIR.74.5.1124.

26. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic "preconditioning" protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation*. 1993;87(3):893-899. doi:10.1161/01.CIR.87.3.893.

27. Birnbaum Y, Hale SL, Kloner RA. Ischemic preconditioning at a distance: reduction of myocardial infarct size by partial reduction of blood supply combined with rapid stimulation of the gastrocnemius muscle in the rabbit. *Circulation*. 1997;96(5):1641-1646. http://www.ncbi.nlm.nih.gov/pubmed/9315559. Accessed May 28, 2018.

28. Oxman T, Arad M, Klein R, Avazov N, Rabinowitz B. Limb ischemia preconditions the heart against reperfusion tachyarrhythmia. *Am J Physiol*. 1997;273(4 Pt 2):H1707-12. http://www.ncbi.nlm.nih.gov/pubmed/9362234. Accessed May 28, 2018.

29. 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 (London, England)*. 2007;370(9587):575-579. doi:10.1016/S0140-6736(07)61296-3.

30. Sprick JD, Mallet RT, Przyklenk K, Rickards CA. Ischemic and hypoxic conditioning: Potential for protection of vital organs. *Exp Physiol*. 2018:1-40. doi:10.1113/EP087122.

31. Cung T-T, Morel O, Cayla G, et al. Cyclosporine before PCI in Patients with Acute Myocardial Infarction. *N Engl J Med*. 2015;373(11):1021-1031. doi:10.1056/NEJMoa1505489.

32. Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining In-Hospital Mortality and Increasing Heart Failure Incidence in Elderly Patients With First Myocardial Infarction. *J Am Coll Cardiol*. 2009;53(1):13-20. doi:10.1016/j.jacc.2008.08.067.

33. Bøtker HE, Kharbanda 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):727-734. doi:10.1016/S0140-6736(09)62001-8.

34. Sloth AD, Schmidt MR, Munk K, et al. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *Eur Heart J*. 2014;35(3):168-175. doi:10.1093/eurheartj/eht369.

35. Sloth AD, Schmidt MR, Munk K, et al. Cost-effectiveness of remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. *Eur Hear J Acute Cardiovasc Care*. 2017;6(3):244-253. doi:10.1177/2048872615626657.

36. White SK, Frohlich GM, Sado DM, et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2015;8(1):178-188. doi:10.1016/j.jcin.2014.05.015.

37. Prunier F, Angoulvant D, Saint Etienne C, et al. The RIPOST-MI study, assessing remote ischemic perconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction. *Basic Res Cardiol*. 2014;109(2). doi:10.1007/s00395-013-0400-y.

38. 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):1055-1063. doi:10.1016/j.jcin.2013.05.011.

39. 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):656-662. doi:10.1161/CIRCIMAGING.110.957340.

40. Przyklenk K, Whittaker P. The Future of Remote Ischemic Conditioning: New Perspectives after ERICCA and RIPHeart. *J Cardiovasc Pharmacol Ther*. 2017;22(4):295-296. doi:10.1177/1074248417710151.

41. McLeod SL, Iansavichene A, Cheskes S. Remote ischemic perconditioning to reduce reperfusion injury during acute ST-segment-elevation myocardial infarction: A systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6(5). doi:10.1161/JAHA.117.005522.

42. Gaspar A, Lourenço AP, Pereira MÁ, et al. Randomized controlled trial of remote ischaemic conditioning in ST-elevation myocardial infarction as adjuvant to primary angioplasty (RIC-STEMI). *Basic Res Cardiol*. 2018;113(3):1-10. doi:10.1007/s00395-018-0672-3.

43. Hausenloy DJ, Kharbanda R, Rahbek Schmidt M, et al. Effect of remote ischaemic conditioning on clinical outcomes in patients presenting with an ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J*. 2015;36(29):1846-1848. http://www.ncbi.nlm.nih.gov/pubmed/26460398. Accessed September 11, 2018.

44. Weih M, Kallenberg K, Bergk A, et al. Attenuated stroke severity after prodromal TIA: a role for ischemic tolerance in the brain? *Stroke*. 1999;30(9):1851-1854. http://www.ncbi.nlm.nih.gov/pubmed/10471435. Accessed September 11, 2018.

45. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular Treatment for Acute Ischemic Stroke. *N Engl J Med*. 2013;368(10):904-913. doi:10.1056/NEJMoa1213701.

46. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. *N Engl J Med*. 2013;368(10):893-903. doi:10.1056/NEJMoa1214300.

47. Ginsberg MD. Current Status of Neuroprotection for Cerebral Ischemia: Synoptic Overview. *Stroke*. 2009;40(3, Supplement 1):S111-S114. doi:10.1161/STROKEAHA.108.528877.

48. Sitzer M, Foerch C, Neumann-Haefelin T, et al. Transient ischaemic attack preceding anterior circulation infarction is independently associated with favourable outcome. *J Neurol Neurosurg Psychiatry*. 2004;75(4):659-660. http://www.ncbi.nlm.nih.gov/pubmed/15026523. Accessed September 11, 2018.

49. Wegener S, Gottschalk B, Jovanovic V, et al. Transient Ischemic Attacks Before Ischemic Stroke: Preconditioning the Human Brain?: A Multicenter Magnetic Resonance Imaging Study. *Stroke*. 2004;35(3):616-621. doi:10.1161/01.STR.0000115767.17923.6A.

50. Connolly M, Bilgin-Freiert A, Ellingson B, et al. Peripheral vascular disease as remote ischemic preconditioning, for acute stroke. *Clin Neurol Neurosurg*. 2013;115(10):2124-2129. doi:10.1016/j.clineuro.2013.07.038.

51. Hoda MN, Siddiqui S, Herberg S, et al. Remote Ischemic Perconditioning Is Effective Alone and in Combination With Intravenous Tissue-Type Plasminogen Activator in Murine Model of Embolic Stroke. *Stroke*. 2012;43(10):2794-2799. doi:10.1161/STROKEAHA.112.660373.

52. Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: A randomized trial. *Stroke*. 2014;45(1):159-167. doi:10.1161/STROKEAHA.113.001346.

53. England TJ, Hedstrom A, O'Sullivan S, et al. RECAST (Remote Ischemic Conditioning after Stroke Trial): A Pilot Randomized Placebo Controlled Phase II Trial in Acute Ischemic Stroke. *Stroke*. 2017;48(5):1412-1415. doi:10.1161/STROKEAHA.116.016429.

54. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. *Nat Rev Neurol*. 2014;10(1):44-58. doi:10.1038/nrneurol.2013.246.

55. Geraghty JR, Testai FD. Delayed Cerebral Ischemia after Subarachnoid Hemorrhage: Beyond Vasospasm and Towards a Multifactorial Pathophysiology. *Curr Atheroscler Rep*. 2017;19(12). doi:10.1007/s11883-017-0690-x.

56. Røpcke DM, Hjortdal VE, Toft GE, Jensen MO, Kristensen SD. Remote ischemic preconditioning reduces thrombus formation in the rat. *J Thromb Haemost*. 2012;10(11):2405-2406. doi:10.1111/j.1538-7836.2012.04914.x.

57. Smithason S, Moore SK, Provencio JJ. Low-Dose Lipopolysaccharide Injection Prior to Subarachnoid Hemorrhage Modulates Delayed Deterioration Associated with Vasospasm in Subarachnoid Hemorrhage. In: *Cerebral Vasospasm: Neurovascular Events After Subarachnoid Hemorrhage*. Vol 115. Vienna: Springer Vienna; 2013:253-258. doi:10.1007/978-3-7091-1192-5_45.

58. Vellimana AK, Milner E, Azad TD, et al. Endothelial Nitric Oxide Synthase Mediates Endogenous Protection Against Subarachnoid Hemorrhage-Induced Cerebral Vasospasm. *Stroke*. 2011;42(3):776-782. doi:10.1161/STROKEAHA.110.607200.

59. Gonzalez NR, Connolly M, Dusick JR, Bhakta H, Vespa P. Phase i clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2014;75(5):590-598. doi:10.1227/NEU.0000000000000514.

60. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: A phase Ib study of safety and feasibility. *Stroke*. 2011;42(5):1387-1391. doi:10.1161/STROKEAHA.110.605840.

61. Laiwalla AN, Ooi YC, Liou R, Gonzalez NR. Matched Cohort Analysis of the Effects of Limb Remote Ischemic Conditioning in Patients with Aneurysmal Subarachnoid Hemorrhage. *Transl Stroke Res*. 2016;7(1):42-48. doi:10.1007/s12975-015-0437-3.

62. Pandit V, Khan M, Zakaria ER, et al. Continuous remote ischemic conditioning attenuates cognitive and motor deficits from moderate traumatic brain injury. *J Trauma Acute Care Surg*. 2018;85(1):48-53. doi:10.1097/TA.0000000000001835.

63. Sandweiss AJ, Azim A, Ibraheem K, et al. Remote ischemic conditioning preserves cognition and motor coordination in a mouse model of traumatic brain injury. *J Trauma Acute Care Surg*. 2017;83(6):1074-1081. doi:10.1097/TA.0000000000001626.

64. Joseph B, Pandit V, Zangbar B, et al. Secondary brain injury in trauma patients: The effects of remote ischemic conditioning. *J Trauma Acute Care Surg*. 2015;78(4):698-705. doi:10.1097/TA.0000000000000584.

65. Segal N, Matsuura T, Caldwell E, et al. Ischemic postconditioning at the initiation of cardiopulmonary resuscitation facilitates functional cardiac and cerebral recovery after prolonged untreated ventricular fibrillation. *Resuscitation*. 2012;83(11):1397-1403. doi:10.1016/j.resuscitation.2012.04.005.

66. Yannopoulos D, Segal N, Matsuura T, et al. Ischemic post-conditioning and vasodilator therapy during standard cardiopulmonary resuscitation to reduce cardiac and brain injury after prolonged untreated ventricular fibrillation. *Resuscitation*. 2013;84(8):1143-1149. doi:10.1016/j.resuscitation.2013.01.024.

67. Albrecht M, Meybohm P, Broch O, et al. Evaluation of remote ischaemic post-conditioning in a pig model of cardiac arrest: A pilot study. *Resuscitation*. 2015;93:89-95. doi:10.1016/j.resuscitation.2015.05.019.

68. Dong H-L, Zhang Y, Su B-X, et al. Limb Remote Ischemic Preconditioning Protects the Spinal Cord from Ischemia–Reperfusion Injury. *Anesthesiology*. 2010;112(4):881-891. doi:10.1097/ALN.0b013e3181d0486d.

69. Huang H, Zhang L, Wang Y, et al. Effect of ischemic post-conditioning on spinal cord ischemic-reperfusion injury in rabbits. *Can J Anesth Can d'anesthésie*. 2007;54(1):42-48. doi:10.1007/BF03021898.

70. Jiang X, Ai C, Shi E, Nakajima Y, Ma H. Neuroprotection against Spinal Cord Ischemia–Reperfusion Injury Induced by Different Ischemic Postconditioning Methods. *Anesthesiology*. 2009;111(6):1197-1205. doi:10.1097/ALN.0b013e3181bf1d93.

71. Johnsen J, Pryds K, Salman R, Løfgren B, Kristiansen SB, Bøtker HE. The remote ischemic preconditioning algorithm: effect of number of cycles, cycle duration and effector organ mass on efficacy of protection. *Basic Res Cardiol*. 2016;111(2):1-10. doi:10.1007/s00395-016-0529-6.

72. Yamanaka T, Kawai Y, Miyoshi T, et al. Remote ischemic preconditioning reduces contrast-induced acute kidney injury in patients with ST-elevation myocardial infarction:

A randomized controlled trial. *Int J Cardiol*. 2015;178:136-141. doi:10.1016/j.ijcard.2014.10.135.

73. Verouhis D, Sörensson P, Gourine A, et al. Effect of remote ischemic conditioning on infarct size in patients with anterior ST-elevation myocardial infarction. *Am Heart J*. 2016;181:66-73. doi:10.1016/j.ahj.2016.08.004.

74. Ong ME ng H, Anantharaman V. Out-of-hospital cardiac arrest: manual or mechanical CPR? *Lancet*. 2015;385(9972):920-922. doi:10.1016/S0140-6736(14)61941-3.

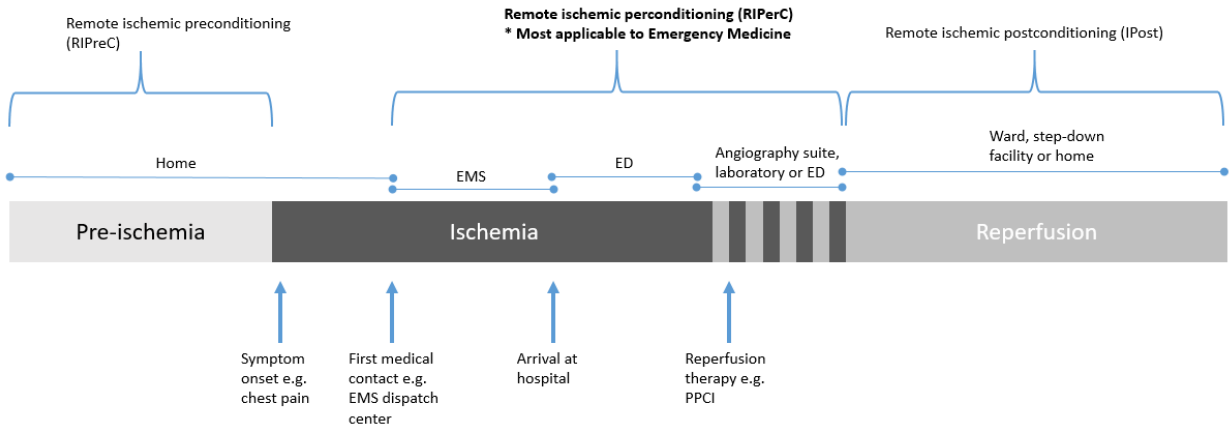
75. Liu Z, Zhao L, Hong D, Gao J. Remote ischaemic preconditioning reduces myocardial ischaemic reperfusion injury in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Acta Cardiol*. 71(5):596-603. doi:10.2143/AC.71.5.3167504.

76. Martin-Gill C, Wayne M, Guyette FX, Olafiranye O, Toma C. Feasibility of Remote Ischemic Peri-conditioning during Air Medical Transport of STEMI Patients. *Prehospital Emerg Care*. 2016;20(1):82-89. doi:10.3109/10903127.2015.1056894.

77. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology*. 2012;79(18):1853-1861. doi:10.1212/WNL.0b013e318271f76a.

78. Bøtker HE, Hausenloy D, Andreadou I, et al. *Practical Guidelines for Rigor and Reproducibility in Preclinical and Clinical Studies on Cardioprotection*. Vol 113. Springer Berlin Heidelberg; 2018. doi:10.1007/s00395-018-0696-8.

Fig 1. Time windows for remote ischemic conditioning in acute ischemic conditions (such a ST-elevation myocardial infarction, ischemic stroke with large-vessel occlusion), in relation to typical emergency care system processes



EMS: Emergency Medical Services; ED: Emergency Department; PPCI: primary percutaneous coronary intervention

Fig 2. Inter-organ protection against acute ischemia-reperfusion injury: known effector organs, target organs and mechanisms

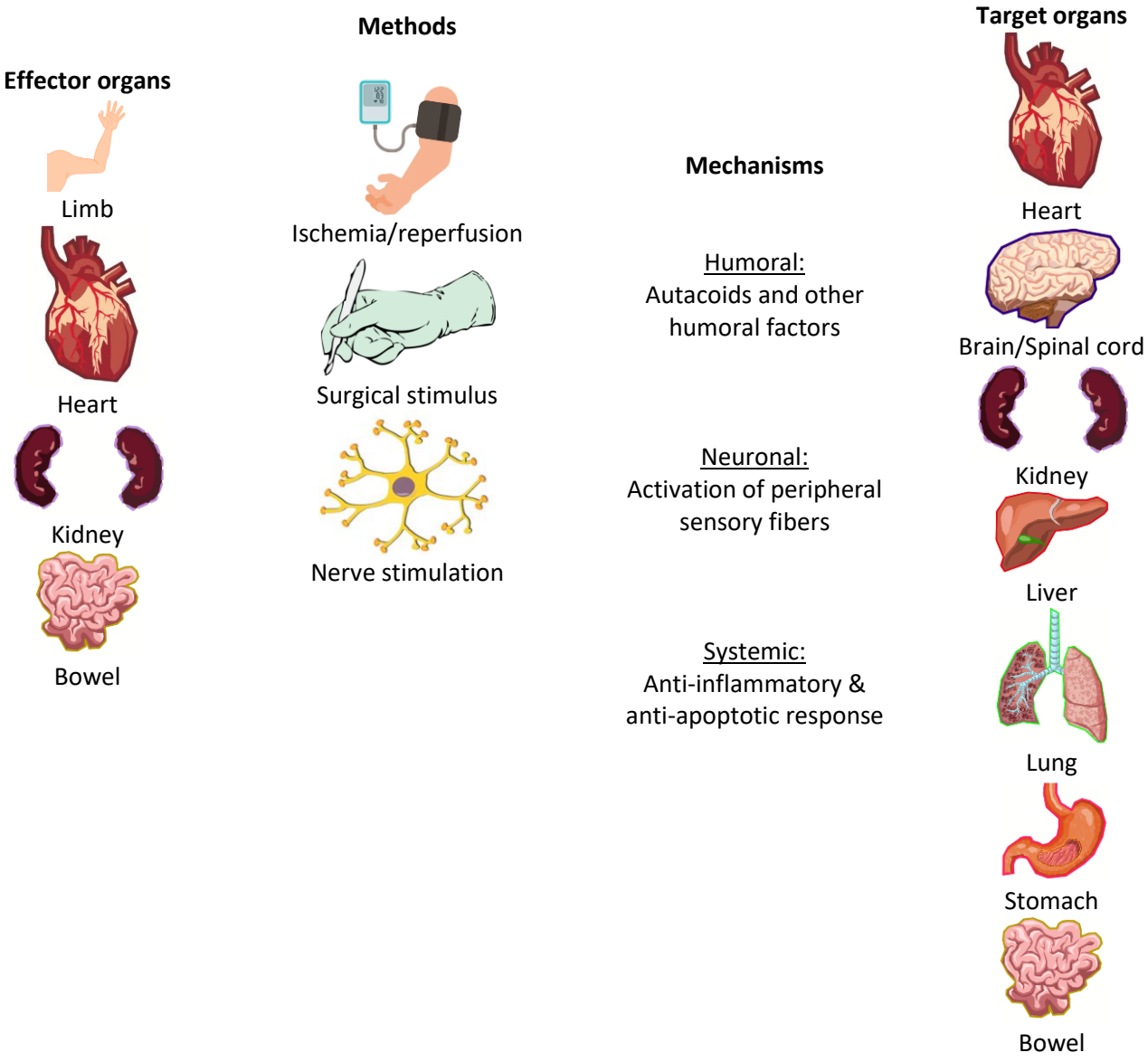


Table 1. Summary of data available for translation of potential applications of remote ischemic conditioning for acute organ protection in Emergency Medicine

	ST-elevation myocardial infarction	**Acute ischemic stroke**	**Aneurysmal Subarachnoid hemorrhage**	**Cardiac arrest**	**Traumatic brain injury**
Mechanistic data	+	+	+/-	+/-	+/-
Pre-clinical data	+	+	+	+	+
Potential issues over safety	-	-	-	--	-
Proof-of-concept human data	++	++	+	--	+
Clinical data	++, *	+, *	+, *	--, *	+
Meta-analysis data	+	+	--	--	--

Mechanism of cardioprotection known: +, well-studied; +/-, not clear

Pre-clinical data: +, consistent protection

Potential issues over safety: -, no known safety issues; -- not available

Proof-of-concept human data: ++, several positive studies; +, only one positive study; --, not available

Clinical data: ++, several positive studies; +, only one positive study; --, not available; *, ongoing studies

Meta-analysis data: +, positive data; --, not available