Remote Ischemic Conditioning

Dialogues in Cardiovascular Medicine

© 2014, Institut La Conférence Hippocrate - Servier Research Group

All rights reserved throughout the world and in all languages. No part of this publication may be reproduced, transmitted, or stored in any form or by any means, electronic, including photocopying, recording, or through an information storage and retrieval system, without the written permission of the copyright holder. Opinions expressed do not necessarily reflect the views of the publisher, editors, or editorial board. The authors, editors, and publisher cannot be held responsible for errors or for any consequences arising from the use of the information contained in this journal.
Remote Ischemic Conditioning

Editorial

Remote ischemic conditioning: bench to bedside and back again - K. Fox, R. Ferrari, R. K. Kharbanda, A. N. Redington 239

Lead Article

Remote ischemic conditioning: current knowledge and perspectives R. K. Kharbanda, A. N. Redington 241

Expert Answers to Three Key Questions

What is the role of remote ischemic conditioning for acute myocardial infarction? H. E. Bøtker, M. R. Schmidt, G. Heusch 257
What is the role of remote ischemic conditioning in surgical revascularization? - D. J. Hauserloy 266
What is the role of remote ischemic conditioning for sports medicine and rehabilitation? D. H. J. Thijssen 279

Fascinoma Cardiologica

Trails of Discovery: The complexity of endogenous mediators of vascular tone - J. D. Fitzgerald 293

Summaries of Ten Seminal Papers - H. Contractor 297

Regional ischemic ‘preconditioning’ protects remote virgin myocardium from subsequent sustained coronary occlusion K. Przyklenk and others
Myocardial protection by brief ischemia in noncardiac tissue B. C. Gho and others
Transient limb ischemia induces remote ischemic preconditioning in vivo – R. K. Kharbanda and others
Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans – M. M. Cheung and others
Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a K\textsubscript{ATP}-dependent mechanism: first demonstration of remote ischemic preconditioning – M. R. Schmidt and others
Cardiac remote ischemic preconditioning in coronary stenting (CRISP Stent) study: a prospective, randomized control trial S. P. Hoole and others
Remote ischemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial H. E. Bøtker and others
Does remote ischemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote ischemic preconditioning with postconditioning outcome trial – D. M. Hong and others
Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial – K. D. Hougaard and others
Remote ischemic conditioning enhanced the early recovery of renal function in recipients after kidney transplantation: a randomized controlled trial – J. Wu and others

Bibliography of One Hundred Key Papers 308
Editorial

Kim Fox, MD, FRCP
Roberto Ferrari, MD, PhD
Rajesh K. Kharbanda, MBChB, PhD, MRCP
Andrew N. Redington, MB, BS, MRCP, MD, FRCP

REMOTE ISCHEMIC CONDITIONING: BENCH TO BEDSIDE AND BACK AGAIN

In the first issue of Dialogues in Cardiovascular Medicine published nearly 20 years ago, the inaugural editorial described the main objectives of each issue. These were “…to choose a topic of clinical relevance, explore it in concise detail, to place it into clinical perspective, and identify pressing questions that dominate the field…” and “…to deliver to the practicing cardiologist the best overview…”

In 1997, in the second volume of the Dialogues in Cardiovascular Medicine series, the fourth issue was titled “Preconditioning.” James M. Downey and Michel V. Cohen authored the lead article “Preconditioning: what it is and how it works”, in the Expert Answers section the pressing issues at the time were addressed: Robert A. Kloner explored the evidence that preconditioning occurs in human, Garrett J. Gross addressed a second window for preconditioning and its potential for clinical exploitation, and Derek M. Yellon and Gary F. Baxter assessed the role for pharmacological exploitation of preconditioning. In the 18 years following this issue, there have been substantial advances in the field of preconditioning and its potential for clinical application. Therefore, this issue is a timely update.

WHY IS REMOTE CONDITIONING CLINICALLY RELEVANT?

Local preconditioning, for which there is extensive knowledge about the basic science, remains the most powerful method to reduce ischemia-reperfusion injury in the laboratory setting; however, there were many challenges in translation to the clinic. One important challenge was that preconditioning had to be administered before ischemia, which limited its use to elective planned situations.

In 2003, the concept of local ischemic postconditioning was described. This had the key advantage that it could be applied to patients presenting after the onset of ischemia. At this time, the treatment of patients with acute infarction was also changing with a
shift from thrombolysis to primary angioplasty. Local postconditioning by balloon occlusion of the culprit coronary artery was tested in randomized studies in patients undergoing primary angioplasty and demonstrated good biological efficacy in terms of infarct size reduction. However, despite many small proof-of-principle studies showing effects on infarct size and left ventricular function, a definitive outcome-powered study is still lacking. The ongoing DANAMI-3 trial (DANish Study of optimal Acute treatment of patients with ST-segment elevation Myocardial Infarction) will help determine whether local postconditioning has any clinical benefit.

In 2002, we described the ability to induce systemic remote conditioning by limb ischemia, rather than internal organ ischemia. This simple, cheap, and safe (to date) intervention has key advantages: (i) it can be delivered at any time during the ischemia-reperfusion event, ie, in planned elective situations or in emergency situations en route to treatment, at the time of treatment, or chronically after treatment, and (ii) it has systemic effects with the potential to induce multiorgan protection in the brain, heart, kidney, and lung, for example. These features have driven the early translation to the clinic and many large outcome studies are under way to determine the effects on myocardial infarction, stroke, and organ transplantation. The practicing cardiologist will be aware of these reports.

In this issue, we have followed the objective set out in the first editorial. Rajesh K. Kharbanda and Andrew N. Redington provide an overview of remote ischemic conditioning by describing the mechanisms, clinical areas of study, and some caveats for future considerations. Hans E. Botker, Michael R. Schmidt, and Gerd Heusch look at the role of remote conditioning in acute myocardial infarction, with a particular focus on the methodology to measure infarct size, the efficacy of treatment in early translational studies, and the potential barriers for the translation to the clinic. Derek J. Hausenloy discusses the role of remote conditioning in surgical revascularization, highlighting the complexity of studying this heterogeneous group with multiple confounders. Dick H. J. Thijsen explores the wider systemic influences of ischemic conditioning and its relationship to exercise, sports, and rehabilitation science. These papers should provide the inquisitive busy cardiologist with a thorough update on the area.

Remote conditioning is currently being tested in several large clinical studies. Its biological efficacy in human has been demonstrated, but translation to clinical efficacy is still unproven and ongoing trials will define its value. Continued research into the underlying basic science may yet help us to amplify the protection remote conditioning affords: bench to bedside and back again may be the pathway to maximize its benefits.
Remote ischemic conditioning: current knowledge and perspectives

Rajesh K. Kharbanda, MBChB, PhD, MRCP1; Andrew N. Redington, MB, BS, MRCP, MD, FRCP2

1 Oxford University Hospitals NHS Trust - UK
2 Cincinnati Children’s Hospital Medical Center - USA

WHY SHOULD A CLINICIAN BE INTERested IN CARDiAC CONDITIONING?

Coronary artery disease still accounts for the majority of mortality and morbidity in the developed world.1 Primary percutaneous coronary intervention (PPCI) is now the recommended emergency treatment for ST-segment elevation myocardial infarction (STEMI), and early angiography and revascularization are recommended in patients with other acute coronary syndromes (ACS).2 Stable advanced coronary disease may also be treated by percutaneous coronary intervention (PCI) or surgery. In all of these settings, the disease, and sometimes its treatment, leads to a degree of myocardial infarction (MI) caused by ischemia-reperfusion injury.3 Thus, even though reperfusion therapy for acute myocardial infarction (AMI) has reduced immediate mortality, later heart failure, as a consequence of MI, is now an increasing healthcare burden.4 Large-scale epidemiological evidence suggests that even a small elevation in circulating biomarkers associated with PCI or surgery confers an adverse outcome. Furthermore, the increasing prevalence of an aging population with associated comorbidities, and presenting with a more complex disease, has changed the demographics of patients, and served to focus our attention on how to further optimize outcomes in these higher-risk situations.5

The last 2 decades have seen an explosion in experimental strategies (eg, pharmacologic preconditioning) that have the potential to improve outcomes by modifying ischemia-reperfusion injury, but so far, few have translated into mainstream clinical practice. Although the profound effects of ischemic cardiac conditioning were discovered almost 30 years ago, the recent evolution of its delivery to tissues remotely represents a paradigm that has the potential to significantly improve outcomes for many forms of cardiovascular disease.
WHAT IS CARDIAC CONDITIONING?

Conditioning refers to a range of strategies that aim to limit tissue injury resulting from ischemia and reperfusion. "Conditioning" can be achieved by repeated cycles of brief periods of nonlethal ischemia followed by reperfusion, or pharmacological methods, and can be demonstrated in a wide range of cells, tissues, and organs. The most powerful "conditioning" stimulus is a series of short periods of nonlethal ischemia of the target tissue prior to the prolonged ischemia-reperfusion event. Local ischemic preconditioning was described in 1986, but it has failed to find a direct clinical application, primarily due to the difficulty in rendering the human heart ischemic. In 2003, the concept of local ischemic postconditioning was described, where reperfusion, which was interrupted by a series of short periods of ischemia, also reduced MI in animal models. This was translated rapidly to the clinical setting with the advent of PPCI to treat STEMI. Although several proof-of-principle studies have reported positive effects, there is no large outcome study, and the procedure is invasive and limited to PPCI.

Remote ischemic conditioning (RIC) describes the phenomenon of cardioprotection, which is achieved by ischemia in a distant organ. This concept was derived from the finding that ischemia in one vascular territory of the heart could induce protection in an adjacent territory. Subsequent studies showed that the protection could be transferred between organs with potent cardioprotection being demonstrable after cycles of ischemia and reperfusion to the gut or kidney in rodent models. Again, the clinical applicability of such an approach was limited, but in 2002, we described the effectiveness of intermittent limb ischemia prior to experimental MI in a porcine model (remote ischemic preconditioning [RIPC]). Limb ischemia is easily achieved using a tourniquet or blood pressure cuff, and it is clearly a simple technique that is easy to deliver clinically. Unlike local conditioning, remote conditioning can also be applied during cardiac ischemia (remote perconditioning), immediately or shortly after the onset of reperfusion, or later (remote postconditioning). The typical protocol uses a blood pressure cuff inflated to 200 mm Hg to temporarily stop the blood supply to the arm or leg for 5 minutes, followed by a 5-minute period of reperfusion, and is repeated 3 or 4 times. This can be applied in the clinical setting either in situations where a period of ischemia and reperfusion is predictable (such as planned cardiac surgery or transplantation) or during treatment for emergency ischemia-reperfusion syndromes, such as STEMI.

WHAT ARE THE MECHANISMS OF RIC?

RIC protection can be considered as a reflex with a stimulus, an afferent pathway, and an efferent pathway in 3 phases: trigger, mediator, and effector. Signal transduction from the remote organ involves the somatosensory system, the spinal cord, and the autonomic nervous system, and in addition, there is a circulating humoral factor pathway (Figure 1).

**Trigger**

Ischemia is one trigger for remote protection, but the reflex can be initiated by other peripheral stimuli, including peripheral nociception (remote preconditioning of trauma, topical capsaicin), direct peripheral nerve
stimulation, and noninvasive transcutaneous nerve stimulation and electroacupuncture. While the exact nature of the transmitter through neuronal or humoral pathways to the heart is unknown, all of these stimuli appear to result in the release of an unidentified molecule into the blood and/or in the generation of a signal through the spinal cord to activate both cardiac vagal and sympathetic efferent fibers to release cardioprotective substances.

**Mediating factor**

It has long been known that coronary effluent from a locally preconditioned heart induces cardioprotection in a naive receptor heart. The presence of a circulating cardioprotective factor after RIC was first suggested in a porcine transplant model, where RIC of the limb in a recipient pig provided cardioprotection in the transplanted and denervated donor heart. More definitive evidence came from studies in an isolated rabbit heart model, where plasma from remotely preconditioned animals was cardioprotective when perfused into an isolated naive heart. The dialysate from the plasma using a 15 kDa membrane was cardioprotective, and after processing over a C18 hydrophobic column, the eluate of small hydrophobic molecules provided potent cardioprotection. Animal studies have confirmed that RIC, which is induced by femoral nerve stimulation, transcutaneous peripheral nerve stimulation, capsaicin, or even electroacupuncture, appear to work, at least in part, via the release of cardioprotective factors into the blood.

The exact nature of the factor(s) is unknown, but several candidate molecules are of interest. A recent proteomic study identified multiple potential cardioprotective targets released into the blood after a limb RIC protocol. Recent studies have focused on stromal cell-derived factor 1α (SDF-1α) and microRNA-144. SDF-1α is a small cardioprotective chemokine acting via the receptor CXCR4. Circulating plasma levels of SDF-1α were increased in rats subjected to RIPC; however, the cardioprotection of RIPC was only partially abrogated by pretreating the animals with a specific CXCR4 inhibitor, suggesting that additional or complementary pathways contribute to the preconditioned phenotype. In another study, microRNA-144 levels were increased in mouse myocardium after RIPC, and the effect of RIC was completely abrogated by the use of a specific antagonir to microRNA-144. Interestingly, intravenous microRNA-144 was cardioprotective, both acutely and 3 days after administration. Importantly, microRNA-144 levels were increased in the plasma of mice and humans subjected to limb RIC.

**Effector**

No matter what the exact nature of the mediating factor, the downstream effects of RIC appear to recapitulate many of the known intracellular effects of local preconditioning. For example, RIC activates the reperfusion injury salvage kinase (RISK) pathway, leading to phosphorylation of inositol-triphosphate kinase, protein kinase B (AKT), extracellular-regulated kinase (ERK) 1/2, and glycogen synthase kinase 3β (GSK-3β), although variations exist between some species and models (Figure 2, page 244).
Probably as a result of inducing this prosurvival kinase-cascade, modification of mitochondrial responses plays a crucial role in the cardioprotection induced by RIC. In mouse experiments, RIC activated the nitrite-nitric oxide (NO) pathway, induced S-nitrosation of mitochondrial proteins, and reduced complex I respiration and reactive oxygen species (ROS) formation.\(^3\)\(^1\)

In rabbits with limb RIPC, blocking mitochondrial aldehyde dehydrogenase 2 (ALDH2) with cyanamide abrogated protection; in parallel experiments in humans with a functionally inactive polymorphism of this enzyme, endothelial protection by RIPC was eliminated.\(^3\)\(^2\) Better preservation of mitochondrial respiration was also seen in the right atrial tissue of patients undergoing coronary artery bypass graft (CABG) surgery with RIC, as well as demonstrating a lower incidence of postoperative atrial fibrillation.\(^3\)\(^3\)

Apart from mitochondrial function, RIC increased myocardial glycolytic flux and reduced infarct size in adult, but not neonatal, hearts.\(^3\)\(^4\),\(^3\)\(^5\)

**Systemic effects of RIC**

Unlike other forms of conditioning, RIC has pleiotropic effects beyond induction of ischemia resistance.

**Effects of RIC on platelet activation**

In healthy volunteers subjected to forearm ischemia for 20 minutes, platelet activation (measured by increased circulating monocyte-platelet aggregates) was abolished in subjects randomized to receive local conditioning prior to the ischemic insult.\(^3\)\(^6\) In patients with known obstructive coronary artery disease and in patients undergoing ablation for atrial fibrillation, RIC reduced adenosine diphosphate (ADP)-stimulated platelet aggregation.\(^3\)\(^7\)

**Effects of RIC on circulating inflammatory cells**

In human volunteers, RIC downregulated the expression of proinflammatory genes in circulating monocytes, reduced neutrophil adhesion, and suppressed phagocytosis after 10 days of RIC.\(^3\)\(^8\) In patients undergoing CABG, RIC was not associated with any difference in circulating markers of inflammation (e.g., interleukin [IL]-6, IL-8, IL-10, or tumor necrosis factor [TNF]-α levels), but there was a significant reduction in neutrophil kinin B1 and B2 receptor expression, confirming similar results previously seen in healthy human volunteers subjected to RIC.\(^3\)\(^9\),\(^4\)\(^0\)

**Effects on vascular function**

The RIC stimulus induces coronary vasodilation in animal studies\(^4\)\(^1\) and systemic vasodilation in human...
subjects.\(^2\) Sustained RIC can also improve systemic endothelial function.\(^4\) Daily repeated RIC for 7 days in healthy young subjects and in patients with AMI undergoing primary PCI was associated with improved flow-mediated dilation.\(^44,45\) Thus, RIC appears to be more biologically inclusive than classic agonist-receptor induction of conditioning (eg, pharmacologic conditioning), perhaps explaining the broader portfolio of effects that it exhibits in ischemia-reperfusion injury, and its potential additional effects to modify reperfusion injury and the more chronic responses that can occur in the weeks and months after infarction (see below).

**WHAT IS THE CLINICAL EVIDENCE THAT RIC IS EFFECTIVE IN PATIENTS?**

**Studies in cardiac surgery**

Cardiac surgery is associated with a variable degree of cardiac and multiorgan ischemia-reperfusion injury. Consequently due to the predictable timing of the ischemia-reperfusion event and the simplicity of RIC, the first clinical studies of RIC were predominantly performed in patients undergoing cardiovascular surgery, the results of which are reported, in detail, in an accompanying article.

Although a recent meta-analysis confirms the biological efficacy of RIC in reducing biomarker release, the clinical benefits remain uncertain.\(^46-49\) The results of ongoing multicenter studies powered for clinical outcomes will be reported within the next 2 to 3 years,\(^50,51\) and hopefully, will clarify the clinical utility of RIC in the cardiac surgical arena.

**Studies in elective PCI**

While periprocedural myocardial injury increases depending upon the complexity of the procedure,\(^52\) considerable debate remains about the relevance of cardiac injury that occurs at the time of PCI.\(^3,53,54\) For example, in high-risk acute coronary syndrome (ACS) patients, a small amount of myocardial injury related to PCI may confer longer-term advantages, which may not be the case in low-risk (eg, stable) patients, especially in those with significant ventricular impairment. Indeed, there is an increasing body of evidence suggesting that even relatively minor insults may have long-term adverse consequences. In a meta-analysis of 20 studies, including 15,581 patients undergoing elective PCI, Nienhuis et al reported that elevation of troponin I or T post-PCI was significantly associated with increased mortality (\(P=0.001\)).\(^55\) These results were further confirmed with a more recent meta-analysis of 22 studies with 22,353 patients. Troponin I and T levels following nonurgent PCI are indicative of all-cause mortality (\(P<0.01\)) and a combination of all-cause mortality and MI (\(P<0.01\)).\(^56\) Furthermore, Milani et al\(^57\) demonstrated that any detectable troponin release following PCI is predictive of myocardial injury and the incidence of death. In their 2,272-patient study, the incidence of death was higher in patients with troponin release compared with patients with no detectable troponin: 22.8% (>99th percentile upper reference limit [URL]), 21.4% (detectable, but <99th percentile URL), and 17.7% (non-detectable). Additionally, the combined end point of death and MI was higher in the groups with detectable troponin release as compared with the group with non-detectable troponin release (51.9% of 372 patients and 50.3% of 587 patients vs 35.6% of 1313 patients).\(^57\)

Biomarker release after PCI has been used as a surrogate end point to assess the efficacy of RIC in a series of studies,\(^58-66\) and a recent meta-analysis confirms that RIC can reduce procedural myocardial injury as assessed by troponin release.\(^67\) The clinical implications of these observations are not clear, but in one study, following patients treated with RIC at the time of elective PCI, there was a reduction in the incidence of major adverse cardiac and cerebral events (MACCE) at 3 months,\(^59\) and in a subsequent report, 6 years after the procedure.\(^60\) While encouraging, the study was underpowered, and to our knowledge, currently, no large-scale studies are being performed to test the efficacy of RIC in PCI to modify hard clinical end points (Table I, page 246).

**Studies in acute STEMI**

Acute STEMI remains the most important ischemia-reperfusion syndrome. While advances in reperfusion therapy have reduced mortality, significant myocardial damage and its adverse long-term sequelae remain a challenge. The systems for delivering care have focused on reducing symptom-reperfusion times, and refinement of antiplatelet and anticoagulant regimens, but the focus is now on methods to modify the reperfusion injury itself. Unfortunately, several trials testing adjuvant pharmacological conditioning have failed to show improvement in salvage,\(^68\) but the early trials with RIC are more encouraging.

The first proof-of-concept study demonstrating that RIC can increase myocardial salvage, investigated 333 patients undergoing primary PCI for STEMI. RIC was applied as upper arm ischemia for four 5-minute cycles with a 5 minute reperfusion, and was initiated in the am-
bulance during transportation to the primary PCI unit (perconditioning). A total of 133 patients underwent single-photon emission computed tomography (SPECT) for assessment of salvage and infarct size — RIC increased salvage by 36%. In patients with left anterior descending (LAD) territory MI and in patients with an occluded culprit artery (Thrombolysis in Myocardial Infarction [TIMI] 0-1) on admission, infarct size reduction was 44% and 31%, respectively, indicating that patients at the highest risk seem to have benefited more by RIC as an adjunctive therapy to primary PCI.69 The findings translated into improved left ventricular ejection fraction (LVEF) in LAD infarcts.70 Although not powered to evaluate clinical outcome, a follow-up of the total cohort suggested that the beneficial effect of RIC translated into a reduction in major cardiovascular events up to 4 years after the index event.71 There are now a number of positive studies testing RIC in STEMI including remote postconditioning.72 Ongoing clinical outcome studies in this area are underway and this area is discussed more fully in an accompanying article in this issue.

<table>
<thead>
<tr>
<th>Author (year) group studied</th>
<th>Number (control/RIC)</th>
<th>RIC protocol timing</th>
<th>Primary end point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliodromitis (2006)58</td>
<td>21/20</td>
<td>Upper limb 3 IR cycles (5/5 min)</td>
<td>TnI (12, 24, 48 h post-PCI)</td>
<td>Greater increase in CK-MB and TnI with RIC</td>
</tr>
<tr>
<td>Hoole (2009)59</td>
<td>98/104</td>
<td>Upper limb 3 IR cycles (5/5 min)</td>
<td>TnI (24 h post-PCI)</td>
<td>Reduction in median TnI levels Reduction in 6-mo MACCE</td>
</tr>
<tr>
<td>Davies (2013)60 (Hoole cohort)</td>
<td>97/95</td>
<td>Upper Limb</td>
<td>MACCE at year 6</td>
<td>6-y reduction in MACCE</td>
</tr>
<tr>
<td>Ahmed (2013)61</td>
<td>72/77</td>
<td>Upper limb 3 IR cycles (5/5 min)</td>
<td>TnT 16 h post-PCI</td>
<td>Reduction in mean TnT No reduction in CK or MI</td>
</tr>
<tr>
<td>Prasad (2013)62 Elective and unstable 80% single vessel</td>
<td>48/47</td>
<td>Upper limb 3 cycles (3/3 min) Just prior to PCI</td>
<td>TnT (8, 16, 24 h post-PCI)</td>
<td>No effect on TnT levels</td>
</tr>
<tr>
<td>Luo (2013)63</td>
<td>104/101</td>
<td>Upper limb 3 IR cycles (5/5 min)</td>
<td>hsTnI 16 h post-PCI</td>
<td>Reduction in median hsTnI levels, type 4a MI</td>
</tr>
<tr>
<td>Xu (2014)64 Elective (Elderly &gt;65 +DM)</td>
<td>98/104</td>
<td>Upper limb 3 IR cycles (5/5 min)</td>
<td>hsTnI 16 h post-PCI</td>
<td>No reduction in median hsTnI or type 4a MI</td>
</tr>
<tr>
<td>Liu (2014)65</td>
<td>98/102</td>
<td>Upper Limb 3 IR cycles (5/5 min)</td>
<td>TnI 24 h post-PCI</td>
<td>Reduction in median TnI, CK, CK-MB level Reduction in 6-mo MACCE</td>
</tr>
<tr>
<td>Zografos (2014)66 Stable “ad hoc” PCI ≈1/4 multivessel</td>
<td>47/47</td>
<td>Upper limb 1 cycle IR (5/1 min) Just prior to PCI</td>
<td>TnI Increase after 24 h</td>
<td>Lower increase in TnI Reduction in type 4a MI</td>
</tr>
</tbody>
</table>

Table 1. Summary of studies in PCI investigating the effects of RIC.

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase myocardium-specific MB isoenzyme; DM, diabetes mellitus; IR, ischemia-reperfusion; MACCE, major adverse cardiac and cerebral events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIC, remote ischemia conditioning; TnI, Troponin I; TnT, Troponin T.
WHAT IS THE ROLE OF CHRONIC CONDITIONING?

An emerging concept, known as chronic conditioning, is the extended use of RIC delivered daily for weeks or months. In an experimental study of MI, RIC demonstrated a dose-dependent effect on cardiac remodeling, heart failure, and death rate in the absence of a significant additional reduction in infarct size, by daily administration for the first 28 days after the MI. This result demonstrates beneficial effects beyond modification of acute ischemic effects, presumably related to the aforementioned pleiotropic cellular effects. Ongoing translational studies are underway to test if this important observation can be reproduced in patients after STEMI. The DREAM trial (Daily REMote ischaemic conditioning following Acute Myocardial infarction) is exploring the effect of daily RIC initiated after PPCI and continued for 4 weeks in 72 STEMI patients presenting with impaired LVEF (EF<45%)—primary end point is improvement in LVEF at 4 weeks post-MI. In Canada, the CRIC-RCT trial (Chronic Remote Ischemic Conditioning to modify post-MI remodeling) is testing the effect of repeating RIC daily for 28 days on the change, from baseline, in LV end diastolic volume at 28 days by cardiac magnetic resonance imaging (MRI) in 82 STEMI patients treated by PPCI.

Other potential clinical benefits of RIC

Renoprotection
Patients with chronic kidney disease are at risk of coronary disease and at a greater risk of acute kidney injury, such as contrast-induced nephropathy, during vascular or CABG surgery. Several proof-of-concept studies have demonstrated that RIC is effective in reducing contrast-induced nephropathy in high-risk patients undergoing cardiac catheterization and after cardiac and vascular surgery. For example, in one of the earliest clinical studies of RIC, there was a significant reduction in renal impairment in patients undergoing abdominal aortic aneurysm surgery. However, a recent study failed to reproduce these benefits. Nonetheless, recent meta-analyses of clinical studies demonstrate that RIC significantly attenuates biochemical markers of acute kidney injury. Large clinical trials (eg, ERICCIN [Effect of Remote Ischemic Conditioning against Contrast-Induced Nephropathy]) are currently in progress to fully define the clinical importance of these findings.

Neuroprotection
Animal studies show that RIC can protect the brain from ischemia-reperfusion injury. In a porcine study, neurocognitive impairment after bypass surgery was significantly attenuated by RIC. However, it appears that these encouraging experimental data fail to translate to major clinical effects. In a small study of 180 patients following elective cardiac surgery with cardiopulmonary bypass, no effect of RIPC on neurocognitive dysfunction incidence and severity was observed. In another small study, there was, again, no effect of RIPC on neurocognitive dysfunction following carotid endarterectomy.

The situation may be different in reperfused stroke. Again, an experimental study suggested potent neuroprotection by both preconditioning and perconditioning. In a recent study of 443 stroke patients, the National Institutes of Health (NIH) stroke score improved in patients randomized to RIC, but penumbral salvage, final infarct size at 1 month, infarct growth from baseline to 1 month by MRI, and clinical outcome at 3 months were not different between control and RIC groups. In another study, patients with stroke resulting from intracranial stenosis were randomized to control therapy or additional chronic bilateral limb RIC twice daily for 300 days. Not only did RIC improve the rate and extent of functional recovery, but it also reduced stroke recurrence (from 26.7% to 7.9%) during the first year after the sentinel event. If reproduced in large multicenter trials, these results would clearly have a major impact on clinical management of acute stroke syndromes.

Sport and rehabilitation medicine
Adaptation to systemic hypoxia, such as during extreme sport, may have advantages for athletes. RIC has been tested in the setting of elite-level swimmers and has shown improved maximal performance. The concept that the systemic effects of RIC may be beneficial in patients with systemic hypoxia has also been suggested, and although early clinical studies are negative, further investigations are warranted. This area is discussed, in depth, in an accompanying article.

HOW SHOULD THE CLINICIAN INTERPRET THE DIFFERING RESULTS AND WHAT CLINICAL STUDIES ARE NEEDED?

There is a wide range of conditioning interventions that are very effective in an experimental laboratory, but do not realize any significant benefits when tested in randomized clinical trials. While there is a very powerful effect in experimental studies, the clinical data regarding RIC ranges from strongly positive effects to no effect in apparently similar patient groups.
This has been the subject of some debate and the wider community has not unreasonably questioned the relevance of conditioning. There are, however, a number of important considerations that should be taken into account, largely related to the heterogeneity of patients compared with the laboratory model. First, nearly all the experimental data is obtained in young, healthy male rodents or larger mammals, with a controlled and reproducible insult and a well-defined treatment protocol. In clinical studies, the effects of RIC are subject to the vagaries of clinical disease and its treatment, including duration of ischemia, location of culprit vessel and degree of occlusion, differing area at risk, presence of collaterals, and effectiveness of the intervention to achieve reperfusion. Furthermore, demonstrating additional clinical benefit from additional interventions is difficult in small MIs when the outcomes are excellent with current therapy.

In addition to the heterogeneity of the clinical syndrome, the impact of comorbidities, other diseases, and medications on the effectiveness of RIC need to be taken into account. Experimental studies suggest that age and diseases, such as hyperlipidemia, diabetes, and hypertension, raise the threshold for inducing conditioning. Pharmacological treatments also have an impact (eg, specific sulphonylureas used to treat type 2 diabetes) on conditioning responses. Conversely, insulin, metformin, some statins, angiotensin-converting enzyme inhibitors, antiplatelet agents, and opioids can, themselves, be cardioprotective and raise the threshold for an additional benefit. A number of volatile anesthetics used during cardiac surgery can also reduce the efficacy of RIC.

WHAT MIGHT THE FUTURE HOLD?

There is good evidence from experimental and clinical studies that RIC protects the heart and other organs from ischemia-reperfusion injury. Repeated brief inflation/deflation of a blood pressure cuff at the arm, leg, or both is feasible, noninvasive, and inexpensive. It is biologically effective with regard to surrogate measures of tissue injury, and so far, no adverse safety signals have been reported. However, an important number of confounders exist, and in the era of stratified medicine, the concept that therapy should be targeted to appropriate patients is evolving.

For example, specific patients may have the most to gain from RIC therapy, and in others, the use of adjuvant drugs or their genetic inheritance may limit the efficacy of RIC. For example, we have shown that human volunteers with a Glu504Lys polymorphism in ALDH2 are resistant to RIC protection against ischemia-induced endothelial dysfunction, and in these patients, RIC may be ineffective. In addition, a wider range of cardioprotection interventions may be delivered in combination to fully exploit the range of different pathways that can be activated, and these combinations may be specific to each patient.

As we gain a deeper understanding of the underlying mechanisms of RIC and conditioning, we will be better placed to harness these to optimize cardioprotection from this endogenous reflex and improve hard outcomes from major cardiovascular diseases. Acute cardiac and myocardial surgery remain important areas for future study, but the increasing recognition of pleiotropic effects of RIC beyond ischemia and reperfusion means that its application to sports and rehabilitation medicine is of key interest.

REFERENCES


Postoperative neurocognitive dysfunction in patients undergoing cardiac surgery after remote ischemic preconditioning: a double-blind randomized controlled pilot study.  

82. Walsh SR, Nouraei SA, Tang TY, Sadat U, Carpenter RH, Gaunt ME.  
Remote ischemic preconditioning for cerebral and cardiac protection during carotid endarterectomy: results from a pilot randomized clinical trial.  

Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial.  
Stroke. 2014;45:159-167.

Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis.  

85. Jean-St-Michel E, Manlhiot C, Li J, et al.  
Remote preconditioning improves maximal performance in highly trained athletes.  

86. McDonald MA, Braga JR, Li J, Manlhiot C, Ross HJ, Redington AN.  
A randomized pilot trial of remote ischemic preconditioning in heart failure with reduced ejection fraction.  

Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning.  

Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting.  

89. 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?  

The RlPOST-MI study, assessing remote ischemic perconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction.  
Remote Ischemic Conditioning

*Expert Answers to Three Key Questions*

1. What is the role of remote ischemic conditioning for acute myocardial infarction?
   
   *H. E. Bøtker, M. R. Schmidt, G. Heusch*

2. What is the role of remote ischemic conditioning in surgical revascularization?
   
   *D. J. Hausenloy*

3. What is the role of remote ischemic conditioning for sports medicine and rehabilitation?
   
   *D. H. J. Thijssen*
What is the role of remote ischemic conditioning for acute myocardial infarction?

Hans E. Bøtker, MD, PhD, FACC, FESC¹; Michael R. Schmidt, MD, PhD¹; Gerd Heusch, MD, FACC, FESC, FRCP²

¹Department of Cardiology - Aarhus University Hospital Skejby - Aarhus - DENMARK
²Institute for Pathophysiology - West German Heart and Vascular Centre Essen - University of Essen Medical School - Essen - GERMANY

Urgent revascularization and concomitant acute medical therapy of ST-segment elevation myocardial infarction have been optimized extensively over the last decade. However, postinfarction heart failure continues to carry a detrimental effect on outcome. Hence, novel therapeutic targets beyond the open coronary artery are needed to improve long-term outcomes. Conditioning the heart to resist ischemia-reperfusion injury has become a core focus in cardiovascular research. Remote ischemic conditioning, in particular, has been utilized in a number of clinical settings with promising results. Here we discuss its role in acute myocardial infarction with focus on infarct size reduction, clinical outcome, mechanisms, and a potential reduction effect in specific patient groups.

Keywords: ischemia-reperfusion injury; ischemic preconditioning; myocardial infarction; primary percutaneous intervention; remote ischemic conditioning

Address for correspondence: Prof Hans E. Bøtker, Department of Cardiology, Aarhus University Hospital Skejby, Brendstrupgaardsvej 100, DK-8200 Aarhus N, Denmark (e-mail: heb@dadlnet.dk)

Dialogues Cardiovasc Med. 2014;19:257-265

Treatment of acute ST-segment elevation myocardial infarction (STEMI) requires initiation of a chain of efforts to accomplish optimal treatment benefits and outcomes. A rapid diagnosis and direct referral to the catheterization laboratory for opening of the occluded coronary is the first major step. Implementation of telemedical electrocardiogram (ECG) recording in ambulances enables a correct on-site diagnosis and optimized transportation logistics, such that all STEMI patients are referred directly to the intervention center to reduce referral delay and mortality (Figure 1, page 258)¹. Optimization of the interventional procedure, using appropriate med-
clinical therapy, often initiated in the ambulance, and dedicated operators are the next step to secure an optimal procedural result. While we have succeeded with implementation of these steps within the last 10 to 15 years, a final element, which has gained attention because its consequences have been increasingly clear with the improvement in early mortality, is the potential effect of reperfusion injury. In experimental studies, reperfusion injury may contribute to up to 50% of the final infarct size, and hence, play a significant role for the development of heart failure after acute myocardial infarction (AMI). Indeed, while 1-year mortality has decreased, it has not decreased to the same extent as 30-day mortality. The decline in the incidence of heart failure after AMI has not reached the magnitude that we might have expected from clinical trial data and the prevalence is increasing. Survival and quality of life with heart failure following AMI remain poor and have worsened from 2007 to 2010, demonstrating that challenges still remain for the treatment of this high-risk condition after AMI (Figure 2). Therefore, the reduction in reperfusion injury can be considered the next major target for improving outcome after AMI. This review will focus on remote ischemic conditioning (RIC) as a potential modality to attenuate reperfusion injury in patients undergoing primary percutaneous coronary intervention (PPCI) for STEMI.

CONCEPTS OF ISCHEMIC CONDITIONING

Most tissues can be trained to enhance resistance against ischemic injuries by exposing them to brief periods of ischemia, i.e., ischemic preconditioning, prior to a longer lasting ischemic insult. This fascinating biological phenomenon was first described in the myocardium by Murry et al in 1986, and was later shown to be an almost universally inherent feature of mammalian tissues. Although, evidently a fundamental mode of self-preservation of mammalian species, the full biological complexity, multitude of signaling pathways involved, and protective mechanisms have remained largely covert until recently. Presumably, only a fraction of these mechanisms have been uncovered. Nevertheless, as ischemic preconditioning turned out to infer the strongest protection against ischemia-reperfusion injury hitherto discovered, immense efforts have been made to translate this intrinsic property into a clinically useful tool.

However, the technique has inherent limitations, as it requires interruption of blood flow to the target organ, and thus, it can only be achieved in the operating room or during coronary angioplasty. Furthermore, additional time for the preconditioning procedure is required before surgery or intervention. Preconditioning alone may cause complications or deterioration of organ function (e.g., emboli of atheroma) because of the intermittent aortic clamping or intermittent coronary balloon inflation. Hence, local ischemic preconditioning has not found widespread clinical use.

Two important offsprings of ischemic preconditioning have made the way for clinical applicability. First, the discovery, in experimental models, that the stimulus could be delayed until the time of reperfusion, i.e., ischemic postconditioning, and still preserve most of its protective effect, have made it theoretically possible to utilize this method in situations involving acute/unpredictable ischemia. Ischemic postconditioning can be performed by repeated brief inflations of an angioplasty balloon in the culprit lesion in the coronary artery immediately following PPCI. The underlying mechanism may involve gentle reperfusion, but also activation of intracellular cardioprotective signaling pathways identified in RIC. However, the
results of clinical trials utilizing ischemic postconditioning have been ambiguous, and the relevance of it in clinical practice remains to be clarified.

Second, and most likely with a broader clinical potential, is the concept of RIC. In 1993, Przyklenk et al reported that brief coronary artery occlusions preconditioned the myocardium not only within, but also outside, the perfusion territory. Subsequently, it was shown that this remote cardioprotection could also be achieved from other organs or tissue beds, eg, by intermittent occlusion of a mesenteric or renal artery. The potential clinical utility became apparent when Kharbanda et al demonstrated that repeated brief limb ischemia induced similar protection against myocardial ischemia-reperfusion injury. Transient leg or arm ischemia—often achieved in patients by intermittent inflation of a blood pressure cuff—has now become, by far, the most widely used method to induce RIC, and today RIC is used almost synonymously with repetitive brief limb ischemia. Due to its noninvasive nature and easy applicability, there is a widespread interest in RIC, and over the last decade, a large number of experimental and clinical studies have demonstrated a broad array of systemic effects of RIC.

From the site of the remote stimulus, through humoral and neuronal pathways, RIC activates several protective mechanisms in the target organ similar to those activated by local ischemic preconditioning. Furthermore, RIC modifies the systemic inflammatory response and prevents endothelial dysfunction and platelet activation following ischemia-reperfusion injury. In experimental studies, RIC has been shown to afford protection against ischemia-reperfusion in the liver, lung, kidney, brain, heart, as well as protecting against cardiopulmonary bypass-induced neural, pulmonary, and myocardial damage. Proof-of-principle randomized clinical trials (RCT) have shown that RIC protects against ischemia-reperfusion injury in the heart, brain, kidney, and lung.

MEASURING MYOCARDIAL INJURY IN THE CLINIC

Most clinical studies of infarct size after coronary revascularization have used indirect estimates of tissue damage, such as release of biomarkers and resolution of ST-segment elevation. These surrogate end points have predictive power in large cohorts, but their usefulness in the individual patient and small-sized study cohorts is moderate. Direct visualization of the area at risk and final infarct size to calculate the salvage index (proportion of salvaged area at risk) can be achieved by myocardial perfusion imaging using 99mTc-sestamibi single-photon emission computed tomography (SPECT). Final infarct size by SPECT correlates with histopathological estimates of infarct size. Final infarct size and salvage index are predictors of death. Once bound to viable myocardium, 99mTc-sestamibi does not redistribute, as such the area at risk can be assessed by injecting a tracer before angioplasty. The 6-hour half-life of the isotope allows subsequent SPECT imaging up to 8 hours after revascularization. SPECT

Figure 2. National trends in heart failure hospitalizations from 1998 to 2010 in the USA.
Heart failure hospitalizations after acute myocardial infarction shown as per 100-patient years (Panel A) and 1-year mortality (Panel B).
visualization includes tissue perfusion by coronary collaterals. Assessment of final infarct size by SPECT requires repeated imaging in the stable postinfarction state; however, SPECT does not distinguish between a previous and a new infarction.

Efforts to assess area at risk and final infarct size by cardiac magnetic resonance imaging (CMRI) have been increasingly used in studies of potential cardioprotective interventions due to the logistical challenges, cost, and radiation exposure.

The late gadolinium enhancement technique is validated in numerous experimental and clinical studies, and has established CMRI as the reference method for quantifying infarct size and is even superior to SPECT for detecting subendocardial infarcts due to a higher spatial resolution. In contrast, quantification of the area at risk by CMRI remains challenging not only because the optimal protocol to quantify the edema, which is thought to represent the area at risk, remains to be defined, but also because any cardioprotective intervention that reduces final infarct size also seems to reduce edema, hence potentially underestimating salvage. On the other hand, CMRI may add pathological insight as this modality allows differentiation of acute from chronic infarction since only recent infarcts contain edema. Moreover, CMRI characterizes different infarct components, such as intramyocardial hemorrhage, because different relaxation times, characterized as T1 and T2, and use of gadolinium contrast allow characterization of tissue morphology (Figure 3).

A more detailed review of modalities applicable for assessment of myocardial ischemia-reperfusion injury is given in Bøtker et al. 13

**RIC reduces infarct size in patients admitted with STEMI**

A specific quality of RIC, which is in contrast to local ischemic conditioning, is the potential application during ongoing target-organ ischemia. Experimental studies showed that RIC, applied during an evolving myocardial infarction, so-called *per*conditioning, induced cardioprotection similar to remote ischemic *pre*conditioning. 14 The broader term conditioning, which avoids specification of stimulus timing, is now frequently used.

The possibility of initiating cardioprotective treatment after the onset of myocardial ischemia has simplified translation of RIC into the clinical setting. In a study of 333 patients with STEMI admitted for PPCI, patients were randomized to either standard PPCI or PPCI preceded by RIC, which was commenced during ambulance transport to the hospital. RIC was conducted by 4 cycles of alternating 5-minute inflation to 200 mm Hg and 5-minute deflation using a standard upper-arm blood pressure cuff. The study showed that RIC reduced infarct size and increased myocardial salvage as measured by single-proton emission CT, in particular among patients admitted with larger anterior STEMI. 9

An echocardiographic substudy of patients with anterior infarcts showed improved left ventricular function in the intervention group. 15

In a similar study, Rentoukas et al confirmed cardioprotection by RIC in patients admitted for PPCI due...
Role of remote ischemic conditioning for acute myocardial infarction - Bøtker and others

Table 1. Clinical studies demonstrating the beneficial effect of RIC in AMI.

<table>
<thead>
<tr>
<th>Study</th>
<th>End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bøtker et al. 2010</td>
<td>Salvage index (SPECT)</td>
</tr>
<tr>
<td>Munk et al. 2010</td>
<td>LVEF at 30 d (Echoardiography and SPECT)</td>
</tr>
<tr>
<td>Rentoukas et al. 2010</td>
<td>ST-segment resolution</td>
</tr>
<tr>
<td>Crimi et al. 2013</td>
<td>CK-MB release after PCI</td>
</tr>
<tr>
<td>Prunier et al. 2014</td>
<td>CK-MB release after PCI</td>
</tr>
<tr>
<td>Sloth et al. 2014</td>
<td>MACCE at 4 y</td>
</tr>
<tr>
<td>White et al. 2014</td>
<td>Myocardial edema and infarct size (CMRI)</td>
</tr>
</tbody>
</table>

Abbreviations: AMI, acute myocardial infarction; CK-MB, creatine kinase myocardium-specific MB isoenzyme; CMRI, cardiac magnetic resonance imaging; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebral events; PCI, percutaneous coronary intervention; RIC, remote ischemic conditioning; SPECT, single-photon emission computed tomography.

...to STEMI, as troponin release was reduced and ST-segment resolution improved among RIC-treated patients. Interestingly, this study suggested that cardioprotection by RIC may be augmented by concomitant morphine administration.

RIC treatment may also have beneficial effects when initiated at the time of reperfusion. In a study of 100 patients, Crimi et al reported reduced creatine kinase myocardium-specific MB isoenzyme (CK-MB) release and reduced infarct size as measured by CMRI in RIC-treated STEMI patients, even though RIC was not commenced before the first balloon inflation (remote ischemic postconditioning). Combining local postconditioning with RIC does not seem to reduce infarct size further in the clinical setting.

Whether RIC also reduces myocardial ischemia-reperfusion injury in STEMI patients treated with thrombolysis is presently being investigated in the ERIC-LYSIS trial (Effect of Remote Ischaemic Conditioning in STEMI patients treated by thrombolysis). Until now, RIC has consistently shown beneficial effects on myocardial injury in all published trials investigating RIC in STEMI patients (Table I).

Of particular interest, the prevention of postinfarction heart failure is the emerging concept of chronic RIC. An extended use of RIC, on a daily basis, for the first 28 days after an AMI has demonstrated that RIC may modulate cardiac remodeling, heart failure, and even mortality in a dose-dependent manner. Even though this effect demonstrates beneficial effects beyond modification of acute ischemic effects, an immediate translation into improved exercise capacity in heart failure patients has not yet been demonstrated.

**RIC may improve long-term clinical outcomes**

While the published trials assessing the effect of RIC in STEMI patients have all used surrogate effect markers and have not been properly sized to measure the effect on clinical outcomes, emerging data suggest that the observed reduction in various markers of myocardial injury translates into prognostic benefit for the patients.

Recently, Sloth et al published 4-year follow-up data on our original study, which showed that major adverse cardiac and cerebral events (MACCE) occurred for 17 (13.5%) patients in the RIC-treated group compared with 32 (25.6%) patients in the control group, yielding a hazard ratio of 0.49 (95% confidence interval [95% CI], 0.27-0.89; P=0.018). Furthermore, only 5 deaths (4%) occurred in the intervention group compared with 15 (12%) in the control group, yielding a hazard ratio of 0.32 (95% CI, 0.12-0.88; P=0.027).

In similar trials investigating the long-term effect of RIC in patients undergoing elective percutaneous coronary intervention (PCI) and coronary artery bypass surgery, RIC also conferred a MACCE-free survival benefit.

**Mechanisms: how does RIC work?**

By definition, RIC is initiated by a brief ischemic stimulus. The majority of experimental and clinical data indicates that the number and duration of inflations determine the cardioprotective efficacy rather than the tissue volume exposed to intermittent short-lasting ischemia. Most frequently, 3 to 4 cycles of 5-minute ischemia of the upper arm or thigh have been used. However, growing evidence implies that transient ischemia or interruption of blood flow is not a requisite trigger for remote protection. Notably, several stimuli mimic the infarct-sparing effect of RIC, including physical exercise, peripheral nociception, direct peripheral nerve stimulation, and noninvasive transcutaneous nerve stimulation and electroacu-
puncture. Although several remote conditioning protocols have been tested in terms of arm vs leg, fewer vs more cycles, and shorter vs longer cycles, none have, so far, shown convincing superiority to the originally proposed algorithm of 4 cycles of 5-minute limb ischemia.

The organ-protective effects of RIC are partially mediated through the release of endogenous substances into the bloodstream, as plasma from RIC-treated animals and humans is cardioprotective. Moreover, the same plasma can be dialyzed and the dialysate applied to a naive, isolated heart to achieve cardioprotection equal in strength to cardioprotection in hearts from RIC-treated animals. Similarly, in a cardiac transplant model, RIC of a recipient animal reduces ischemia-reperfusion injury in the subsequently transplanted (denervated) donor heart, again suggesting the presence of a powerful humoral component to the RIC stimulus. However, cardioprotection by RIC also seems to partially rely on intact afferent neuronal signaling, and furthermore, RIC induces a range of myocardial gene expression responses associated with the stress-response and repair mechanisms.

RIC activates several pathways and mechanisms that eventually result in complex and powerful organ protection. As experimental models rarely allow for investigation of more than one or two systems, a complete understanding of the underlying protective mechanisms is still lacking. Furthermore, a wide range of animal models, conditioning protocols, and variable end points add to the confusion.

In brief, RIC is believed to induce the release of unidentified trigger substances, which may include adenosine, bradykinin, and opioids. Interestingly, recently published studies show that microRNAs may mediate and/or protect against ischemia-reperfusion injury in local, and remote, ischemic conditioning. These signaling cascades act in concert with inhibition of platelet and neutrophil activation and other anti-inflammatory effects. A variety of triggers activate sarcolemmal receptors, inducing further intracellular signal transduction by mediators that finally act on the effectors, which include mitochondria, connexins, and cytoskeletal elements.

Specific cardioprotective pathways have been identified and include the endothelial nitric oxide synthase (eNOS)-protein kinase G pathway, the reperfusion injury salvage kinase (RISK) pathway, and the survival activating factor enhancement (SAFE) pathway. These changes are associated with increased myocardial glycolytic flux and posttranslational modification of proteins by O-linked β-N-acetylglucosamine (O-GlcNAc), which seem to be involved in cardioprotection by RIC.

The pathways interact and converge on the mitochondria to modify membrane integrity by inhibiting the opening of the membrane permeability transition pore. The pore is closed during myocardial ischemia, but opens during reperfusion, causing mitochondrial swelling, loss of function, and potentially, cellular necrosis. Inhibition of the mitochondrial permeability transition pore appears to act as the dominating final effector in the cascade of events triggered by RIC. A detailed description of the known signaling pathways and effectors of RIC is beyond the scope of this article, but several more comprehensive reviews of the current mechanistic insight have been published.
Role of remote ischemic conditioning for acute myocardial infarction - Butler and others

**WILL ALL STEMI PATIENTS BENEFIT FROM RIC?**

Experimental studies using diseased animal models suggest that the effect of local ischemic conditioning may be modulated by aging, sex, and comorbidities. Although less investigated, some of these conditions may also affect the efficacy of RIC. Dialysate from RIC-treated diabetic patients induced cardioprotection in isolated rabbit hearts, unless these patients suffered from neuropathy. Davies et al found that the long-term prognostic benefit of RIC, observed in patients undergoing elective PCI, was attenuated in patients with diabetes, but no published data show a reduced effect of RIC in STEMI patients with diabetes or another comorbidity. Importantly, no adverse effects of RIC have so far been reported, and we believe that RIC can safely be applied universally to STEMI patients. Hence, trials investigating the effect of RIC in STEMI patients should not exclude patients suffering from diabetes or another comorbidity. Pharmacological therapy may also impact the cardioprotective effect of RIC. Sulphonylureas used for treatment of type 2 diabetes may attenuate the conditioning response. On the other hand, insulin, metformin, β-blockers, some statins, angiotensin-converting enzyme inhibitors, some antiplatelet agents, and opioids have inherent cardioprotective properties and may raise the threshold for an additional benefit of RIC.

**ALTERNATIVE METHODS TO ACHIEVE CARDIOPROTECTION**

Other approaches to achieve protection against myocardial ischemia-reperfusion injury have been investigated, including cooling and pharmacological conditioning. Moderate hypothermia induced prior to reperfusion reduces infarct size in animal models. A clinical pilot study suggested that patients admitted with anterior STEMI who are rapidly cooled to a body temperature below 35°C by the combination of cold saline infusion together with an endovascular cooling catheter before primary PCI developed smaller infarcts. More recently, the CHILL-MI study (Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction), using a similar cooling technique as in the initial pilot study, showed that while cooling did not have a general cardioprotective effect, it seems to reduce infarct size in patients with anterior STEMI admitted for PPCI within 4 hours of symptom onset. In addition, cooling caused a significant reduction in heart failure events. The increasing insight into the mechanisms involved in local and remote ischemic conditioning has encouraged the search for potential targets for pharmacological intervention against ischemia-reperfusion injury. While a vast number of pharmacological agents have been shown to afford cardioprotection in experimental models, most of these drugs yielded ambiguous results when tested in clinical studies. To date, the most promising pharmacological approaches for cardioprotection include cyclosporine, eventide, and metoprolol, all of which seem to consistently provide cardioprotection in the clinical setting.

However, an important limitation—and a potential explanation for the lack of success—of the majority of pharmacological conditioning, is that most agents act through a single signaling pathway in the complex and interactive system of protective mechanisms activated by ischemic conditioning and cooling.

**WHAT IS NEEDED TO INTRODUCE RIC AS A STANDARD ADJUVANT THERAPY FOR STEMI?**

RIC is one of the most promising methods to achieve cardioprotection in patients admitted with AMI. So far, the evidence suggests significant clinical benefit from RIC in patients with larger infarcts and no significant adverse effects have been reported. RIC is easily applicable, low-cost, and universally available. Thus, it may seem attractive to introduce RIC as standard adjuvant therapy in STEMI patients, but we strongly emphasize that properly sized RCTs are essential to clarify whether RIC affords clinically relevant prognostic benefits to patients. Currently, a large-sale, multinational clinical trial (COND I 2 [effect of remote ischemic COND I-tioning on clinical outcomes in ST-segment el-evation myocardial infarction pa-tients undergoing primary percutane-ous coronary intervention]) is investigating the effects of RIC in STEMI patients on clinical end points.

The full potential of RIC has not yet been explored. As RIC appears to have multiorgan protective capabili-ties, patients with cardiogenic shock, severe arrhythmias, including cardiac arrest, and threatening global ischemia of the brain, heart, liver, and kidney during organ transplantation may benefit from this novel approach.

Importantly, even if large RCTs confirm the beneficial effect of RIC, there may be obstacles before RIC may work its way into guidelines on standard therapy in STEMI patients. Paradoxically, the low-cost nature of RIC may be its worst adversary, as the lack of direct financial interest in promoting RIC’s integration into clinical practice may leave other
Role of remote ischemic conditioning for acute myocardial infarction - Bøtker and others

COMPETING INTERESTS

Annie Tollefsen, Associate Editor, was not involved in the editorial review of this article.

REFERENCES

Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction. 

2. Yellow DM, Haussenloy DJ.
Myocardial reperfusion injury. 


4. Chen J, Hsieh AF, Dharmarajan K, Masoudi FA, Krumholz HM.

5. Murry CE, Jennings RB, Reimer KA.
Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. 

Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. 

Transient limb ischemia induces remote ischemic preconditioning in vivo. 
Circulation. 2002;106:2831-2833.

Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. 

Remote ischemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomized trial. 

Remote ischemic preconditioning reduces myocardial injury after coronary artery bypass surgery with crystalloid cardioplegic arrest. 

Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. 
Stroke. 2014;45:159-167.

Protective effect of remote ischemic preconditioning in renal ischemia/reperfusion injury, in a model of thoracoabdominal aorta approach. 

13. Bøtker HE, Kaltoft AK, Pedersen SF, Kim WY.
Measuring myocardial salvage. 

Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a KATP-dependent mechanism: first demonstration of remote ischemic preconditioning. 

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. 

FINANCIAL SUPPORT

Funding. HEB was supported by the Novo Nordic Foundation, Fondation Leducq (06CVD), the Danish Research Council for Strategic Research (11-115818), and the Danish Research Council (11-108354). GH was supported by the German Research Foundation (He 1320/18-1). 3

Conflicts of interest. HEB and MRS are shareholders of CellAegis Inc, Toronto, Canada. GH serves as a consultant to Servier.
Cardioprotective role of remote ischemic peri-
conditioning in primary percutaneous coro-
nary intervention: enhancement by opioid action.

Remote ischemic post-conditioning of the lower limb during primary percutaneous coro-
nary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial.

The RIPOST-MI study, assessing remote ischemic perconditioning alone or in combi-
nation with local ischemic postconditioning in ST-segment elevation myocardial infarction.

19. clinicaltrials.gov.
Effect of Remote Ischaemic Conditioning in STEMI patients treated by thrombolySIS.

Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischemic condition-
ing as an adjunct to primary percutaneous coronary intervention.

Remote ischemic conditioning reduces myocar-
dial infarct size and edema in patients with ST-segment elevation myocardial infar-
cation.
JACC Cardiovasc Interv. 2015;8:178-188.

Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up.

Cardioprotective and prognostic effects of remote ischemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial.

MicroRNA-144 is a circulating effector of remote ischemic preconditioning.

25. Jensen RV, Zachara NE, Nielsen PH, Kimose HH, Kristiansen SB, Botker HE.
Impact of O-GlcNAc on cardioprotection by remote ischemic preconditioning in non-
diabetic and diabetic patients.

26. Kharbanda RK, Nielsen TT, Redington AN.
Translation of remote ischemic preconditioning into clinical practice.

Translating cardioprotection for patient benefit: position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology.

28. Heusch G.
Cardioprotection: chances and challenges of its translation to the clinic.

29. Schmidt MR, Redington A, Botker HE.
Remote conditioning the heart overview: translatability and mechanism.

Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction.
The CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction.

31. clinicaltrials.gov.
Effect of remote ischaemic CONDItioning on clinical outcomes in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention.
Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. For IHD patients with multivessel coronary artery disease, surgical revascularization by coronary artery bypass graft (CABG) surgery remains the treatment strategy of choice. Over the last few years, higher risk patients are undergoing CABG surgery, which increases the likelihood of complications, such as perioperative myocardial, renal, pulmonary, and cerebral injury, and results in worse short-term and long-term clinical outcomes. Therefore, novel therapeutic strategies are required to reduce multi-organ injury in this clinical setting. In this regard, the role for remote ischemic conditioning (RIC) in protecting the heart and other organs against acute ischemia-reperfusion injury and its therapeutic potential for improving clinical outcomes in patients undergoing surgical revascularization by CABG surgery will be reviewed.

**Why is there still a need to improve cardioprotection in CABG surgery?**

During CABG surgery, patients are at risk of experiencing perioperative myocardial injury (PMI), the result of which is cardiomyocyte death, leading to reduced left ventricular systolic function, and a subsequent increased risk of developing heart failure. The causes of PMI are mul-

---

**SELECTED ABBREVIATIONS AND ACRONYM S**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CBP</td>
<td>cardiopulmonary bypass</td>
</tr>
<tr>
<td>ERICCA</td>
<td>Effect of Remote Ischemic preconditioning on Clinical outcomes in patients undergoing Coronary Artery bypass graft surgery [study]</td>
</tr>
<tr>
<td>GTN</td>
<td>glyeryl trinitrate</td>
</tr>
<tr>
<td>IHD</td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td>MACE</td>
<td>major adverse cardiac events</td>
</tr>
<tr>
<td>OPCAB</td>
<td>off-pump coronary artery bypass</td>
</tr>
<tr>
<td>PMI</td>
<td>perioperative myocardial injury</td>
</tr>
<tr>
<td>RIC</td>
<td>remote ischemic conditioning</td>
</tr>
<tr>
<td>RIPCAGE</td>
<td>impact of Remote Ischemic Preconditioning preceding Coronary Artery bypass Grafting on inducing Europrotection [study]</td>
</tr>
<tr>
<td>RIPHeart</td>
<td>Remote Ischaemic Preconditioning for Heart surgery [study]</td>
</tr>
</tbody>
</table>

---

**Keywords:** cardioprotection; coronary artery bypass graft surgery; ischemia; remote ischemic conditioning; reperfusion

**Address for correspondence:**
Prof Derek J. Hausenloy, The Hatter Cardiovascular Institute, University College London, 67 Chenes Mews, London, WC1E 6HX, UK (e-mail: d.hausenloy@ucl.ac.uk)
Role of remote ischemic conditioning in surgical revascularization

During CABG surgery, the heart is subjected to global ischemic injury as the aorta is clamped and the patient is put onto CPB. As the patient is taken off CPB and the aorta is unclamped, the heart is subjected to global reperfusion injury, which compounds the myocardial ischemic injury. Reperfusion injury refers to the reperfusion-induced death of cardiomyocytes, which were viable at the end of ischemia. This occurs during reperfusion of ischemic myocardium, and causes reperfusion arrhythmias, myocardial stunning, microvascular obstruction, and cell death. Despite current strategies for cardioprotection during CABG surgery (eg, hypothermia and cardioplegia), a significant amount of PMI still occurs, resulting in worse clinical outcomes postsurgery. This is exacerbated by the fact that higher risk patients are undergoing CABG surgery due to a number of factors, including an aging population and increased prevalence of comorbidities, such as diabetes, hypertension, heart failure, and concomitant valve surgery. The result of this is an increase in perioperative myocardial, renal, pulmonary, and cerebral injury. Therefore, novel cardioprotective therapies are required to protect the heart and other organs during CABG surgery, and in this regard, RIC is a potential therapeutic option.

Effect of RIC in CABG Surgery

The ability to noninvasively induce RIC, by simply inflating and deflating a cuff placed on the arm or leg to apply cycles of brief ischemia/reperfusion (henceforth referred to as limb RIC), has facilitated the translation of RIC from being a laboratory phenomenon into the clinical arena. Surgical revascularization by CABG surgery, where the heart is subjected to acute global ischemia-reperfusion injury, was the first clinical setting in which limb RIC was investigated (Table I, page 268).

The first clinical study to investigate the effect of limb RIC in patients undergoing CABG surgery was a small underpowered pilot study by Gunaydin et al, where, in 8 patients undergoing CABG surgery, it was reported that limb RIC (two 3-minute arm cuff inflations/deflations) reduced serum lactate dehydrogenase release. This study was actually performed before limb RIC (three 5-minute cycles of arm cuff inflations/deflations) had been characterized in human volunteers by Kharbanda et al. Several years later, in 2006, Cheung et al showed that limb RIC (three 5-minute cycles of thigh cuff inflations/deflations) reduced peak Troponin I (TnI) and lowered inotropic support and airway pressures in infants and children undergoing cardiac bypass surgery for congenital heart disease. The first study to investigate limb RIC in patients undergoing surgical revascularization by CABG surgery was by our group in 2007; we demonstrated that limb RIC (three 5-minute cycles of arm cuff inflations/deflations), applied after anesthesia, but prior to surgical incision, attenuated PMI in 57 patients undergoing CABG+valve surgery as evidenced by a 43% reduction in serum cardiac enzymes (ie, 72-hour area under the curve [AUC] Troponin T [TnT]) compared with controls. Since 2007, a number of clinical studies have investigated the cardioprotective effect of limb RIC in this setting, but the results have been inconsistent (Table I). The reasons for this are many and are discussed in a later section.

The cardioprotective effects of limb RIC, in the setting of adult CABG surgery, have been subjected to several meta-analyses. For the most part, these studies have confirmed that limb RIC can protect the heart against acute ischemia-reperfusion injury during CABG surgery. This was evidenced by significant reductions in PMI, which were measured by serum cardiac enzymes (eg, creatine kinase myocardium-specific MB isoenzyme [CK-MB], TnT, and TnI) in 2008. However, in the setting of pediatric cardiac surgery, a recent meta-analysis has failed to demonstrate any cardioprotective effect with limb RIC, suggesting that the juvenile heart may not be as amenable to RIC protection. In terms of hard clinical endpoints following CABG surgery, meta-analyses have failed to report any impact with limb RIC, although this should not come as a surprise given that the analyzed clinical studies were not designed or powered to investigate the effect of limb RIC on these clinical end points.

Does Limb RIC Improve Clinical Outcomes Following CABG Surgery?

Before limb RIC can be adopted as a routine pretreatment in patients undergoing CABG surgery, it needs to be demonstrated that limb RIC can actually improve long-term major adverse cardiac events (MACE). In this regard, several clinical studies investigating the effect of limb RIC on short-term and long-term clinical outcomes (Table II, page 269) have been published. In 190 patients undergoing elective CABG surgery, our group has recently demonstrated that limb RIC (two
### Role of remote ischemic conditioning in surgical revascularization - Hausenloy

Table I. Major clinical studies of limb RIC in CABG surgery.  

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Surgical setting</th>
<th>Limb RIC protocol</th>
<th>Outcomes and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheung et al. 2006</td>
<td>37</td>
<td>Pediatric cardiac surgery for congenital heart disease</td>
<td>Four 5-min cycles of thigh cuff inflation/deflation</td>
<td>Lower TnI, reduced inotrope requirement, and lower airway resistance. First study to demonstrate beneficial effects with limb RIC.</td>
</tr>
<tr>
<td>Hausenloy et al. 2007</td>
<td>57</td>
<td>Adult CABG&lt;sup&gt;valve&lt;/sup&gt;</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>43% reduction in 72-h AUC TnT. First study to demonstrate beneficial effects with limb RIC in patients given ICCF and CBC in CABG surgery.</td>
</tr>
<tr>
<td>Thielmann et al. 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>53</td>
<td>Adult CABG&lt;sup&gt;nondiabetics&lt;/sup&gt;</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>35% reduction in 72-h AUC TnI. First study to demonstrate beneficial effects with limb RIC in patients given ICCF and CC.</td>
</tr>
<tr>
<td>Venugopal et al. 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>45</td>
<td>Adult CABG&lt;sup&gt;valve&lt;/sup&gt;</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>42% reduction in 72-h AUC TnT. First study to demonstrate beneficial effects with limb RIC in patients given CBC only.</td>
</tr>
<tr>
<td>Li et al. 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>81</td>
<td>Adult AVR/MVR</td>
<td>Three 4-min cycles of thigh cuff inflation/deflation</td>
<td>40% reduction in peak TnI in patients given isoflurane anesthesia. First study to demonstrate beneficial effects with limb RIC in valve surgery.</td>
</tr>
<tr>
<td>Ali et al. 2010&lt;sup&gt;16&lt;/sup&gt;</td>
<td>100</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>Significant reductions in CK-MB at 8, 16, 24, and 48 h.</td>
</tr>
<tr>
<td>Wagner et al. 2010&lt;sup&gt;17&lt;/sup&gt;</td>
<td>101</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflation/deflation given 18 hr prior to surgery</td>
<td>Significant reductions in TnI at 8 h. First study to demonstrate beneficial effects with delayed limb RIC.</td>
</tr>
<tr>
<td>Wu et al. 2011&lt;sup&gt;18&lt;/sup&gt;</td>
<td>75</td>
<td>Adult MVR</td>
<td>Three 5-min cycles of arm cuff + two 10-min cycles of leg cuff inflation/deflation</td>
<td>28% reduction in 4-h TnI levels and less inotrope requirements.</td>
</tr>
<tr>
<td>Kottenberg et al. 2012&lt;sup&gt;13&lt;/sup&gt;</td>
<td>64</td>
<td>Adult CABG&lt;sup&gt;nondiabetics&lt;/sup&gt;</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>50% reduction in 72-h AUC TnI in patients given isoflurane anesthesia. First study to suggest that propofol interferes with limb RIC cardioprotection.</td>
</tr>
<tr>
<td>Zografos et al. 2014&lt;sup&gt;19&lt;/sup&gt;</td>
<td>94</td>
<td>Adult CABG</td>
<td>One 5-min cycle of arm cuff inflation/deflation</td>
<td>79% reduction in peak TnI. First study to demonstrate beneficial effects with one cycle of limb RIC.</td>
</tr>
<tr>
<td><strong>Neutral studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rahman et al. 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>162</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No difference in 48-h AUC TnI. First study to report neutral effect with limb RIC.</td>
</tr>
<tr>
<td>Karuppasamy et al. 2011&lt;sup&gt;11&lt;/sup&gt;</td>
<td>53</td>
<td>Adult CABG&lt;sup&gt;aorta&lt;/sup&gt;</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No difference in 72-h AUC TnI.</td>
</tr>
<tr>
<td>Lucchini et al. 2012&lt;sup&gt;12&lt;/sup&gt;</td>
<td>56</td>
<td>Adult CABG</td>
<td>Four 5-min cycles of thigh cuff inflation/deflation</td>
<td>No difference in hsTnT.</td>
</tr>
<tr>
<td>Lomivorotov et al. 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>80</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No difference in 48-h AUC TnI or CK-MB.</td>
</tr>
<tr>
<td>Young et al. 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>96</td>
<td>Adult CABG&lt;sup&gt;valve&lt;/sup&gt;</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No difference in hsTnT.</td>
</tr>
</tbody>
</table>

**Table 1. Major clinical studies of limb RIC in CABG surgery.**  
**Abbreviations:** AVR, aortic valve replacement; AUC, area under the curve; CABG, coronary artery bypass graft; CBC, cold blood cardioplegia; CC, crystalloid cardioplegia; CK-MB, creatine kinase myocardium-specific MB isoenzyme; hs, high-sensitive; ICCF, intermittent cross-clamp fibrillation; MVR, mitral valve replacement; n, number; RIC, remote ischemic conditioning; TnI, troponin I; TnT, troponin T.
5-minute cycles of simultaneous arm and thigh cuff inflations/deflations improved short-term clinical outcomes as evidenced by a reduction in the incidence of postoperative atrial fibrillation and acute kidney injury, and a shorter stay in the intensive care unit (ICU). The prospective follow-up of a 329-patient cohort, who received limb RIC prior to CABG surgery, has suggested that RIC may improve long-term hard clinical end points. These authors found that patients randomized to receive limb RIC (three 5-minute cycles of arm cuff inflations/deflations) experienced 73% less all-cause death at 1.54 years when compared with controls (6.9% vs 1.9%). However, it is important to note that these two studies had not been prospectively powered to investigate the effect of limb RIC on clinical outcomes.

Two studies that have been prospectively designed and powered to investigate the effect of limb RIC on clinical outcomes have been recently published, but both studies showed no beneficial effects of limb RIC on clinical end points (Table II). The reasons for these neutral studies are not clear and are discussed in a later section. The ongoing large multicenter clinical trials ERICCA (Effect of Remote Ischemic preconditioning on Clinical outcomes in patients undergoing Coronary Artery bypass graft surgery) and RIPHeart (Remote Ischaemic Preconditioning for Heart surgery) have both been prospectively designed and powered to investigate the effect of limb RIC (four 5-minute arm cuff inflations/deflations) on hard clinical end points. Hopefully, these trials will provide the definitive answer concerning whether limb RIC can improve short-term and long-term clinical outcomes in patients undergoing CABG surgery.

### WHY HAVE THE RESULTS OF THE CLINICAL STUDIES BEEN MIXED?

A large number of published clinical studies have investigated the effect of limb RIC in patients undergoing CABG surgery, but the results have been inconsistent. The potential reasons for this are discussed in this section.

### Preclinical assessment of limb RIC cardioprotection

The failure to translate cardioprotective therapies, discovered in experimental studies, into clinical benefits has been extensively dis-
discussed in the literature.\textsuperscript{34-37} The use of inadequate animal models for acute myocardial ischemia-reperfusion injury may have contributed to this failure. The majority of experimental studies to assess limb RIC cardioprotection have utilized models of experimental coronary artery occlusion rather than a CPB model of ischemia-reperfusion injury. Myocardial injury, which occurs during CABG surgery, is multifactorial; therefore, more clinically relevant models for CPB-based animal myocardial ischemia-reperfusion injury\textsuperscript{38} should be used to test the cardioprotective efficacy of limb RIC.

**Heterogeneity vs homogeneity factors impacting cardioprotection**

The inconsistent effect of limb RIC in CABG patients would suggest that it might only be beneficial in certain patient populations and under specific conditions. Most of the clinical studies have selected a relatively homogenous patient population to investigate the cardioprotective efficacy of limb RIC, e.g., surgeries for CABG alone, CABG±valve, valve alone, or congenital heart disease (Table I). The neutral results of the large clinical trial by Hong et al.\textsuperscript{31} which investigated the effect of limb RIC in patients undergoing cardiac surgery for a wide range of indications (e.g., CABG alone, CABG±valve, valve alone, ascending aorta or aortic arch surgery, and congenital heart defect repair with on-pump CPB and off-pump coronary artery bypass [OPCAB]), may be explained by the heterogeneity of the patient population.

Other factors that may affect the cardioprotective efficacy of limb RIC in CABG surgery include: (i) CABG vs valve surgery. In valve surgery a significant component of the myocardial injury is due to direct handling and trauma, which may be less amenable to RIC cardioprotection when compared with CABG surgery; (ii) stable angina vs unstable angina. Patients with unstable angina may be inadvertently pre-conditioned by preceding episodes of chest pain; (iii) preexisting hypoxemia may induce a chronic pre-conditioned state in children undergoing corrective cardiac surgery for congenital heart disease, which may partly explain the neutral effects of limb RIC observed in this clinical setting\textsuperscript{39,40}, and (iv) the duration of CPB and aortic cross-clamp time. The extent of PMI sustained during CABG surgery is closely related to the duration of the acute global myocardial ischemia, which in turn is determined by the duration of CPB and aortic cross-clamp times. Limb RIC may be effective in cases where there is sufficient acute ischemia-reperfusion injury, meaning that there is something to protect against. On the other hand, when the CPB and aortic cross-clamp times are very prolonged, limb RIC may be less cardioprotective. This may explain the neutral data of the large clinical trial by Hong et al.\textsuperscript{31} in which the mean CPB and aortic cross-clamp times were about 160 and 100 minutes, respectively.

**Limb RIC protocol**

The limb RIC protocol used in most clinical studies has been poorly characterized with most studies using either three or four 5-minute cycles of arm or leg cuff inflations/deflations. The limited data would suggest that RIC may be more effective with limb RIC protocols comprising more cycles (four vs three) and using the leg, rather than the arm.\textsuperscript{41} In our recent study, we investigated the cardioprotective effects of a shorter, but more intense, limb RIC protocol comprising two 5-minute simultaneous arm and thigh cuff inflations administered prior to CABG surgery and found that this multilimb RIC protocol was beneficial for reducing PMI and improving short-term clinical outcomes.\textsuperscript{26} Most clinical studies have inflated the cuff to 200 mm Hg to induce ischemia in the arm or leg, although a few studies have inflated the cuff to 15 mm Hg above the systolic blood pressure, e.g., the large neutral study by McCrindle et al\textsuperscript{30}—whether this is sufficient to induce ischemia in the arm or leg is not known. Further work is required to optimize the limb RIC protocol to achieve maximal benefit in the shortest period of time.

Blinding to the limb RIC stimulus may influence its cardioprotective efficacy in patients undergoing CABG surgery. The majority of clinical studies has used an uninflated cuff or a simulated limb RIC protocol as the sham control, although this may have failed to adequately blind the limb RIC stimulus. A more elaborate and robust blinding protocol was used by Rahman et al\textsuperscript{8} and another study\textsuperscript{9} with the limb RIC applied to a “dummy arm” hidden beneath the surgical gowns. It has been suggested that full blinding to the limb RIC stimulus may be responsible for the smaller and statistically nonsignificant effects observed in neutral studies.\textsuperscript{42}

Timing of the limb RIC stimulus in relation to CABG surgery may also impact its cardioprotective efficacy. Most clinical studies have administered the limb RIC stimulus after anesthesia, but prior to surgical incision, whereas in some studies the limb RIC protocol was administered after surgical incision—whether this difference in timing can partly explain the neutral results is unclear.
Confounding factors

The susceptibility of the myocardium to cardioprotection may impact the efficacy of limb RIC in the setting of cardiac surgery. The results of limb RIC studies in infants and children undergoing cardiac surgery have been inconsistent. It is unclear whether this is related to the immaturity of the myocardium in terms of a postsurvival signaling pathway. At the other end of the scale, it is unclear whether increasing age, which is known to confound endogenous cardioprotection, also impacts the efficacy of limb RIC. A number of different comorbidities, such as diabetes, hyperlipidemia, and hypertension, have been shown to interfere with endogenous cardioprotective strategies including ischemic preconditioning/postconditioning. Whether the presence of these comorbidities can also interfere with limb RIC cardioprotection, and therefore, contribute to the inconsistent clinical studies, remains to be determined.

A number of different drugs, given in the perioperative period during CABG surgery, may interfere with the cardioprotective efficacy of limb RIC, such as certain anesthetics and analgesics, statin therapy, oral sulphnylureas, nicorandil, and glyeryl trinitrate (GTN). In experimental studies, it is well established that volatile anesthetics, such as isoflurane, sevoflurane, and desflurane, protect the myocardium against acute ischemia-reperfusion injury through postsurvival pathways common to ischemic preconditioning/postconditioning. Clinical studies have suggested that volatile anesthetics can reduce PMI in patients undergoing CABG surgery, although their effect on clinical outcomes is inconclusive. Therefore, the presence of volatile anesthetics might be expected to affect the cardioprotective efficacy of limb RIC in patients undergoing CABG surgery. However, despite the use of volatile anesthetics there have been both positive studies and neutral studies. To complicate the issue, it has been suggested that the intravenous anesthetic propofol (the major alternative to volatile anesthesia) may also interfere with limb RIC cardioprotection by attenuating myocardial activation of the signal transducer and activator of transcription 5 (STAT-5). Once again, despite the use of propofol anesthesia, there have been both positive studies and neutral studies. Further studies are required to unravel the interaction between different anesthetics and the cardioprotective efficacy of limb RIC.

Experimental studies have established that nitric oxide can trigger cardioprotection, and clinical studies have reported preconditioning effects of nitrates during acute myocardial ischemia-reperfusion injury. Regarding CABG surgery, a low dose of intravenous GTN may be used to control blood pressure and induce coronary vasodilatation. In a retrospective analysis of a 190-patient cohort receiving limb RIC prior to CABG surgery, we found that in patients perioperatively administered IV GTN, the magnitude of PMI was attenuated and the cardioprotective effect of limb RIC was abrogated, suggesting that IV GTN may be inherently cardioprotective during CABG surgery and that the limb RIC protocol we used was unable to add to this cardioprotective effect. In contrast, in another retrospective analysis, no effect of IV GTN therapy on limb RIC cardioprotection was noted. Interestingly, the neutral results of the clinical study by Rahman et al. may have been due to perioperative IV GTN, which was administered to all patients in the study. We are now testing, in a prospective randomized clinical trial, whether IV GTN is cardioprotective and whether it interferes with limb RIC cardioprotection in patients undergoing CABG surgery (the ERIC-GTN study [Investigation into the Role of GTN & Remote Ischemic Preconditioning | RIPC] in Cardiac Surgery).

In summary, a large number of factors have the potential to confound limb RIC cardioprotection in the setting of CABG surgery. Hopefully, the results of the ERICCA and RIPHeart randomized clinical trials will shed some light on which of these confounding factors affect limb RIC in the setting of CABG surgery.

SURROGATE MARKERS FOR ASSESSING CARDIOPROTECTIVE THERAPIES IN CABG SURGERY

The assessment of novel cardioprotective therapies, such as limb RIC, in patients undergoing CABG surgery has relied heavily upon the measurement of surrogate markers of cardioprotective efficacy, including PMI as quantified by serum cardiac enzymes. The magnitude of PMI has been shown to be associated with worse clinical outcomes post-CABG surgery. However, the use of PMI, as a surrogate marker for cardioprotection, needs to be used with caution, especially over the definition of a clinically important PMI. CABG-related myocardial infarction (type 5) has been arbitrarily defined as a rise in serum cardiac enzymes within 48 hours of surgery, to ≥10 times the upper limit of normal, as well as including either ECG changes (new left bundle branch block or T wave inversion) or imaging evidence of irreversible myocardial injury. Using this definition, the incidence of PMI can vary from 5% to 12% (using ECG criteria) to as high as 40% (using the presence of
late gadolinium enhancement on cardiac magnetic resonance imaging (MRI). It is likely that the extent of PMI, as measured by serum cardiac enzymes, is predictive of clinical outcomes post-CABG surgery. Whether the reduction in PMI by a cardioprotective therapy is actually responsible for the observed improved clinical outcomes in CABG patients has not been resolved.

The results of the ERICCA and RIFHeart trials, which are prospectively measuring both PMI and hard clinical end points, should hopefully clarify the situation and provide an idea of how robust PMI is in predicting clinical outcomes post-CABG surgery.

### Protecting Noncardiac Organs in CABG Surgery by Limb RIC

The major advantage of limb RIC as a therapeutic intervention is that it is capable of offering multi-organ protection against acute ischemia-reperfusion injury. In the setting of CABG surgery, acute ischemia-reperfusion injury can contribute to the dysfunction of vital noncardiac organs including the kidney, lungs, and brain. In this section, the potential role for limb RIC in protecting these organs against acute ischemia-reperfusion injury in the setting of CABG surgery is reviewed.

#### Renoprotection during CABG surgery

Acute kidney injury following CABG surgery may occur in up to 30% of patients with 1% to 2% requiring dialysis, and is associated with worse clinical outcomes. Limb RIC has been reported in experimental studies to protect against acute renal ischemia-reperfusion injury, and has been investigated in a number of clinical conditions in which the kidney is subjected to acute ischemia-reperfusion injury including CABG surgery. The first clinical study to investigate the renoprotective effect of limb RIC in the setting of CABG surgery was conducted by

### Table III. Major clinical studies of limb RIPC on acute kidney injury in CABG surgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Surgical setting</th>
<th>Limb RIC protocol</th>
<th>Outcomes and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venugopal et al. 2010</td>
<td>78</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflations/deflations</td>
<td>Retrospective study showing a reduction in the incidence of AKI from 25% to 11%</td>
</tr>
<tr>
<td>Thielmann et al. 2010</td>
<td>53</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflations/deflations</td>
<td>No overall difference in creatinine levels and eGFR over 72 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved postoperative peak Cr levels in RIC group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower postoperative minimum eGFR in control group</td>
</tr>
<tr>
<td>Zimmerman et al. 2011</td>
<td>120</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of thigh cuff inflations/deflations</td>
<td>Reduction from 47% to 20% in the incidence of AKI (defined as an increase in serum Cr levels by at least 0.3 mg/dL or 50% more than the baseline value within 48 h of surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in plasma NGAL at 3 h</td>
</tr>
<tr>
<td>Candilio et al. 2014</td>
<td>190</td>
<td>Adult CABG</td>
<td>Four 5-min cycles of arm cuff inflations/deflations</td>
<td>54% nonsignificant reduction in incidence of AKI</td>
</tr>
<tr>
<td><strong>Neutral studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rahman et al. 2010</td>
<td>163</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflations/deflations</td>
<td>No effect on AKI or renal biomarkers</td>
</tr>
<tr>
<td>Choi et al. 2011</td>
<td>76</td>
<td>Adult complex valve</td>
<td>Three 10-min cycles of thigh cuff inflations/deflations</td>
<td>No effect on AKI or renal biomarkers (serum creatinine, cystatin C, and NGAL)</td>
</tr>
<tr>
<td>Pedersen et al. 2012</td>
<td>103</td>
<td>Pediatric cardiac surgery for complex congenital heart disease</td>
<td>Four 5-min cycles of thigh cuff inflations/deflations</td>
<td>No effect on AKI or renal biomarkers</td>
</tr>
<tr>
<td>Gallagher et al. 2014</td>
<td>86</td>
<td>Adult CABG</td>
<td>Three 5-min cycles of arm cuff inflations/deflations</td>
<td>No effect on AKI or renal biomarkers</td>
</tr>
</tbody>
</table>

**Abbreviations:** AKI, acute kidney injury; CABG, coronary artery bypass graft; Cr, creatine; eGFR, estimated glomular filtration rate; n, number; NGAL, neutrophil gelatinase-associated lipocalin; RIC, remote ischemic conditioning; RIPC, remote ischemic preconditioning.
our research group in 2010.56 This was a retrospective analysis of 78 nondiabetic patients undergoing elective CABG±valve surgery, and it showed that limb RIC (three 5-minute cycles of arm cuff inflations/deflations) reduced the incidence of acute kidney injury by 60%. A number of clinical studies have investigated the role of limb RIC in protecting against acute kidney injury, but the results have been inconclusive (Table III).57-60 A recent meta-analysis by Haji Mohd Yasin et al,23 comprising six clinical studies, found a nonsignificant (P=0.07) benefit with limb RIC on the incidence of acute kidney injury in CABG patients.23 The results of the ongoing large multicenter ERICCA32 and RIPHeart33 trials, which are investigating the effect of limb RIC on acute kidney injury, should hopefully provide a definitive answer on whether limb RIC is renoprotective in the setting of CABG surgery.

**Lung protection during CABG surgery**

Acute lung injury is a common complication in patients undergoing CABG surgery, contributing to significant morbidity and mortality.61 However, there is currently no effective therapy for preventing the acute lung injury in this clinical setting, hence the need for a novel therapeutic strategy. The mechanisms underlying this form of injury are multifactorial and include acute ischemia-reperfusion injury to the lungs when patients are put onto or taken off of CPB. Importantly, prolonged CPB times and complexity of the operation have also been associated with more severe degrees of acute lung injury. The inflammatory response due to CPB, which results in the activation of blood components and vasoactive substances, induced poor alveolar oxygenation, increased pulmonary vascular resistance, and prolonged the artificial ventilation requirement. Experimental studies have reported beneficial effects of limb RIC in preventing acute lung injury.62,63 In a pioneering clinical study by Li et al,64 direct ischemic preconditioning of the heart (achieved using two 3-minute cycles of intermittent aortic cross-clamping prior to cardioplegic arrest) reduced ventilation requirements, pulmonary edema, and hemorrhage, and decreased the leukocyte count observed in lung biopsies taken 1 hour following reperfusion in patients undergoing heart valve surgery. The first clinical study to actually investigate the protective effect of limb RIC against acute lung injury in cardiac bypass surgery was by Cheung et al.6 This study was conducted in infants and children undergoing corrective cardiac surgery for congenital heart disease, and it was reported that limb RIC could lower airway resistance 6 hours postsurgery. Since then, a number of clinical studies have investigated the effect of limb RIC on acute lung injury using a variety of functional end points, but the results have been inconclusive (Table IV, page 274).65-68 With one study actually finding that limb RIC increased the need for mechanical ventilation, although this study was conducted in high-risk CABG patients.6 The reason for these mixed results is not entirely clear, but may be related to the fact that the studies were not powered to detect improvements in acute lung injury, as well as using of functional end points that may not accurately reflect the extent of acute lung injury.

**Neuroprotection during CABG surgery**

Neurocognitive dysfunction and stroke are two major neurological complications following CABG surgery, contributing to high morbidity and mortality. Two studies have investigated the effect of limb RIC on postoperative neurocognitive function in patients who underwent CABG surgery. Meybohm et al69 found, in 124 patients, that limb RIC (four 5-minute cycles of arm cuff inflations/deflations) prior to CABG surgery failed to reduce neurocognitive dysfunction at either 5 to 7 days or 3 months postsurgery. In another study of 70 patients, in the setting of OPCAB, using a similar limb RIC protocol, no effect was seen on neurocognitive dysfunction at postoperative day 7.70 The reason for these neutral results is not clear, but may be related to the fact that neurocognitive dysfunction post-CABG surgery is primarily the result of cerebral thromboembolism, hypoperfusion, and cerebral inflammation, rather than acute ischemia-reperfusion injury per se. In the experimental literature, it has been well established that limb RIC can protect the brain against acute ischemia-reperfusion injury as evidenced by reductions in cerebral infarct size.71-73 This therapeutic approach has been recently investigated in the clinical setting of acute ischemic stroke65 and poststroke.74,75 Whether limb RIC can reduce the incidence of stroke in patients undergoing CABG surgery is not currently known and remains to be investigated. In this regard, the ongoing ERICCA32 and RIPHeart33 trials, which are currently investigating the effect of limb RIC on clinical outcomes, have, as one of their end points, the incidence of stroke at 1 year. Also, the planned RIPCAGE study (impact of Remote Ischemic Preconditioning preceding Coronary Artery bypass grafting on inducing Europrotection) will investigate the effect of limb RIC (three 5-minute arm cuff inflations/deflations) on new ischemic lesions at 7 days postsurgery on brain MRI, postprocedural impairment in brain connec-
Role of remote ischemic conditioning in surgical revascularization - Hausenloy

SUMMARY AND CONCLUSIONS

Limb RIC is a noninvasive, low-cost, therapeutic intervention to protect the heart and other organs from acute ischemia-reperfusion injury in patients undergoing surgical revascularization by CABG surgery.

Limb RIC has been shown to reduce PMI (as quantified by serum cardiac enzymes) in CABG patients in proof-of-concept clinical studies and several meta-analyses. However, studies investigating limb RIC in this clinical setting have produced inconsistent results, the cause of which relates to a number of confounding factors and the complexities of CABG surgery in terms of patient selection and the conditions of surgery. Whether limb RIC can improve hard clinical end points and benefit IHD patients is currently being investigated in the large ongoing ERICCA💻 and RIPHeart💻 randomized clinical trials, and the results of these studies are eagerly anticipated and should be available in early 2015.

Acknowledgments. DJH is funded by the British Heart Foundation (grant numbers FS/10/039/28270), the Rosetrees Trust, and the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Table IV. Major clinical studies of limb RIPC on acute lung injury in CABG surgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Surgical setting</th>
<th>Limb RIC protocol</th>
<th>Outcomes and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheung et al. 2006😢</td>
<td>37</td>
<td>Pediatric cardiac surgery for congenital heart disease</td>
<td>Four 5-min cycles of thigh cuff inflation/deflation</td>
<td>Lower airway resistance at 6 h post-operation</td>
</tr>
<tr>
<td>Rahman et al. 2010😢</td>
<td>162</td>
<td>Adult CABG surgery</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No effect on ventilation time and pre-operative and postoperative PaO2/FiO2 ratios</td>
</tr>
<tr>
<td>Zhou et al. 2010😢</td>
<td>60</td>
<td>Pediatric cardiac surgery for congenital heart disease</td>
<td>Three 5-min cycles of arm cuff inflation/deflation 24 h and 1 h preoperatively</td>
<td>Better lung compliance and dynamic lung compliance</td>
</tr>
<tr>
<td>Li et al. 2010😢</td>
<td>81</td>
<td>Adult valvular heart surgery</td>
<td>Three 4-min cycles of thigh cuff inflation/deflation</td>
<td>No effect on ventilation time</td>
</tr>
<tr>
<td>Thielmann et al. 2010😢</td>
<td>53</td>
<td>Adult CABG surgery</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No effect on ventilation time</td>
</tr>
<tr>
<td>Young et al. 2012😢</td>
<td>96</td>
<td>Adult CABG surgery High risk</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>Increased ventilation time</td>
</tr>
<tr>
<td>Hong et al. 2012😢</td>
<td>70</td>
<td>Adult OPCAB surgery</td>
<td>Four 5-min cycles of thigh cuff inflation/deflation before or after anastomoses</td>
<td>No effect on PaO2/FiO2 ratio</td>
</tr>
<tr>
<td>Kim et al. 2012😢</td>
<td>54</td>
<td>Adults complex valvular heart surgery</td>
<td>Three 10-min cycles of thigh cuff inflation/deflation before or after bypass</td>
<td>No effect on PaO2/FiO2 or incidence of acute lung injury (defined as PaO2/FiO2 &lt;300 mm Hg, the detection of bilateral pulmonary infiltrates on frontal chest radiography and no clinical evidence of further elevation in the left atrial pressure)</td>
</tr>
<tr>
<td>Lomivorotov et al. 2012😢</td>
<td>80</td>
<td>Adult CABG surgery</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No effect on ventilation time</td>
</tr>
<tr>
<td>Thielmann et al. 2013😢</td>
<td>329</td>
<td>Adult CABG surgery</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>No effect on mechanical ventilation times</td>
</tr>
<tr>
<td>Jean et al. 2014😢</td>
<td>76</td>
<td>Ongoing</td>
<td>Three 5-min cycles of arm cuff inflation/deflation</td>
<td>PaO2/FiO2 ratio 24 h postsurgery Results awaited</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass graft; OPCAB, off-pump coronary artery bypass; PaO2, oxygen tension; FiO2, fraction of inspired oxygen ratio; n, number; RIC, remote ischemic conditioning; RIPC, remote ischemic preconditioning.
REFERENCES


Role of remote ischemic conditioning in surgical revascularization - Hausenloy

Remote ischemic preconditioning reduces cardiac troponin I release in cardiac surgery: a meta-analysis.

Remote preconditioning for pediatric patients undergoing congenital cardiac surgery: a meta-analysis.
Int J Cardiol. 2014;177:551-553.

Remote preconditioning and major clinical complications following adult cardiovascular surgery: systematic review and meta-analysis.

Remote ischemic preconditioning does not improve the clinical outcomes in patients undergoing coronary artery bypass grafting: a meta-analysis of randomized controlled trials.
Int J Cardiol. 2014;172:e36-e38.

Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomised controlled clinical trial.
Heart. 2015;101:185-192.

Cardioprotective and prognostic effects of remote ischemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial.

Remote ischemic preconditioning in children undergoing cardiac surgery with cardiopulmonary bypass: a single-center double-blinded randomized trial.

Does remote ischemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic Preconditioning with Postconditioning Outcome Trial.

Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery (ERICCA): rationale and study design of a multi-centre randomized double-blinded controlled clinical trial.

Remote ischemic preconditioning for heart surgery. The study design for a multi-center randomized double-blinded controlled clinical trial—the RIPHeart-Study.
Eur Heart J. 2012;33:1423-1426.


New horizons in cardioprotection: recommendations from the 2010 national heart, lung, and blood institute workshop.

Postconditioning and protection from reperfusion injury: where do we stand?

Translating cardioprotection for patient benefit: position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology.

38. Jungwirth B, de Lange F.
Animal models of cardiopulmonary bypass: development, applications, and impact.

Effect of remote ischemic preconditioning on phosphorylated protein signaling in children undergoing tetralogy of Fallot repair: a randomized controlled trial.

Remote ischemic preconditioning in cyanosed neonates undergoing cardiopulmonary bypass: a randomized controlled trial.

Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism.

42. Pilcher JM, Young P, Weatherall M, Rahman I, Bonser RS, Beasley RW.
A systematic review and meta-analysis of the cardioprotective effects of remote ischemic preconditioning in open cardiac surgery.

43. Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R.
Interaction of risk factors, comorbidities, and medications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning.

44. Muntean DM, Orduoi V, Ferrera R, Angoulvant D.
Volatile anaesthetics and cardioprotection: lessons from animal studies.


What is the role of remote ischemic conditioning for sports medicine and rehabilitation?

Dick H. J. Thijssen*1,2

1 Research Institute for Sport and Exercise Science - Liverpool John Moores University - Liverpool - UK
2 Department of Physiology - Radboud University Nijmegen Medical Centre - THE NETHERLANDS

The clinical relevance of ischemic conditioning— or more specifically here preconditioning (IPC)—likely goes far beyond the traditional research areas of cardiology and vascular surgery. For example, recent studies have explored whether application of IPC can improve exercise performance in athletes. In addition, it has been explored whether exercise has preconditioning effects and leads to protection against prolonged tissue ischemia. Furthermore, recent studies have also explored the impact of repeated IPC on the cardiovascular system since elevation in blood flow and hypoxia (induced via IPC) represent important stimuli for cardiovascular improvement. In this review, evidence is summarized for a potential role of IPC to enhance exercise performance in human and the role for repeated IPC in a rehabilitation setting to improve cardiovascular function and risk.

Keywords: cardiovascular adaptation; exercise training; rehabilitation; repeated preconditioning; sport performance

Address for correspondence:
Prof H. J. Dick Thijssen, Research Institute for Sport and Exercise Science, Tom Reilly Building, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK (e-mail: d.thijssen@ljmu.ac.uk)


In their seminal paper from 1986, Murry et al1 introduced the potential cardiovascular benefits of ischemic (pre)conditioning (IPC). They demonstrated that repeatedly occluding the left anterior descending artery for 5 minutes, interspersed with 5 minutes of reperfusion, leads to a significant reduction in infarction size compared with control animals that underwent sham interventions. Since then, IPC has been adopted in a large number of experiments that, in general, demonstrate its potential use in preventing or attenuating ischemia-induced injury in the heart and various other organ sites (eg, liver, brain, vascular endothelium, and skeletal muscle). 2-5 Despite its potency, simplicity, and noninvasive nature, IPC has not been applied frequently in areas beyond cardiology.

Application of IPC leads to a characteristic repeated exposure of short periods of hypoxia, subsequently followed by marked elevations in blood flow. Interestingly, repeated exposure to hypoxia and/or elevation in blood flow represents important characteristics of many types of exercise. The ability to resist hypoxia and/or elevated blood flow may improve exercise performance. Based on these assumptions, studies have explored the potential impact of IPC in improving exercise performance and have shown that repeated exposure to hypoxia and elevations in blood flow serve as key stimuli for vascular adaptation. As a result, repeated exposure to IPC may induce beneficial changes in vascular function and structure. In this review, evidence supporting the application of repeated IPC in sport and exercise science and rehabilitation is explored and potential future directions are summarized.

ROLE OF IPC IN SPORTS

Can IPC improve exercise performance?

The ultimate goal for athletes is to improve performance, usually by increasing fitness levels. To a large extent, maximal endurance exercise performance is determined by physiological factors that contribute to oxygen consumption. The weakest link in this chain, which goes from central (ie, lungs) to peripheral factors (ie, blood flow and mitochondria), ultimately determines the maximal ability for oxygen consumption. Previous work, largely performed in animals, has demonstrated that

SELECTED ABBREVIATIONS

EPC endothelial progenitor cell
HF heart failure
IPC ischemic preconditioning
SCI spinal cord injury
VEGF vascular endothelial growth factor
IPC increases blood supply\textsuperscript{6} and enhances resistance to prolonged ischemia. Furthermore, IPC is associated with enhanced muscle efficiency in adenosine triphosphate (ATP)-usage via ATP-sparing, improved mitochondrial function, and/or increased efficiency in the excitation-contraction coupling.\textsuperscript{4,7,8} These observations suggest that IPC may interact with factors influencing oxygen consumption, and therefore, exercise performance.

In an exploratory pilot study, we applied IPC to the lower limbs immediately prior to a maximal cycle test.\textsuperscript{9} In a group of 15 moderate-to-highly trained, healthy, young subjects, IPC was associated with a 3\% higher maximal oxygen consumption and a 1.6\% higher maximal workload (Figure 1A).\textsuperscript{9} To put these numbers into perspective, such improvements are observed after several weeks of prolonged, intensive exercise training\textsuperscript{10} or after living at high altitude and training at sea level (ie, “living high–training low” regime; a frequently adopted and accepted strategy for athletes to improve fitness levels).\textsuperscript{11}

This initial study suggested that IPC could positively affect maximal oxygen consumption. Although a higher maximal oxygen consumption is correlated with better endurance exercise performance (eg, middle-distance running),\textsuperscript{12,13} this does not necessarily mean that exercise performance improves. Therefore, in a subsequent study, we examined whether IPC, applied to both legs (four 5-minute cycles), can improve a 5000-meter competitive run. In this study, IPC was associated with an \~34 second faster finishing time (Figure 1B).\textsuperscript{14} Another important practical difference with our initial study is that the timing of the IPC-procedure was 45 minutes before the 5000-meter run, rather than immediately before the exercise event. This suggests that the benefits of IPC on exercise performance have a substantial time frame, making the IPC intervention a practical strategy that can be applied well before the exercise event or during the warm-up.

### Impact of the mode and type of exercise

To date, several research studies have explored the impact of IPC on exercise performance. When summarizing studies that have examined the impact of IPC on exercise performance (Table I),\textsuperscript{8,9,14-23} it should be acknowledged that significant heterogeneity is present between studies in the magnitude and/or direction of the effect size. This heterogeneity can be related, at least in part, to the diversity of exercise modes (eg, cycling, running, swimming), duration, (eg, sprint, en-
durance), or intensities (eg, maximal, submaximal) applied in these studies. When first reviewing the potential importance of the mode of exercise, beneficial effects of IPC on exercise performance have been reported after cycling, running, and swimming. This suggests that the mode of exercise does not determine the ability of an athlete to benefit from IPC to alter exercise performance. Duration and intensity of the exercise seem to mediate the effect of IPC on exercise performance. Studies that have explored the impact of IPC on short-duration, high-intensity sprint exercise have typically found no impact of IPC on exercise performance. For example, IPC did not alter 30-meter sprint time or peak power output during repeated 30-second all-out sprinting on a cycle ergometer. These observations are in agreement with unpublished data from our group, in which we found no impact of IPC on repeated 30-minute sprinting or repeated 15-second all-out sprinting on a cycle ergometer in elite rugby players. In contrast to high-intensity, short-duration exercise, studies exploring the impact of IPC on prolonged exercise (2 minutes up to 30 minutes) typically showed better exercise performance. Despite these marked differences between shorter vs longer exercise duration, it must be emphasized that no study has directly compared different exercise protocols within subjects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Exercise mode</th>
<th>Exercise type</th>
<th>IPC protocol</th>
<th>IPC location</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Groot et al. 2010</td>
<td>Nonathletes</td>
<td>Cycling</td>
<td>Maximal exercise test</td>
<td>Three 5-min cycles</td>
<td>2 legs</td>
<td>Workload: 1.6% increase, VO2peak: 3% increase</td>
</tr>
<tr>
<td>Jean-St-Michel et al. 2011</td>
<td>Athletes</td>
<td>Swimming</td>
<td>100 m</td>
<td>Four 5-min cycles</td>
<td>1 arm</td>
<td>Swim time: 1.1% decrease (0.7 s)</td>
</tr>
<tr>
<td>Crisafulli et al. 2011</td>
<td>Nonathletes</td>
<td>Cycling</td>
<td>Maximal exercise test</td>
<td>Three 5-min cycles</td>
<td>2 legs</td>
<td>Workload: 4% increase, VO2peak: equal</td>
</tr>
<tr>
<td>Bailey et al. 2012</td>
<td>Nonathletes</td>
<td>Running</td>
<td>5000 m</td>
<td>Four 5-min cycles</td>
<td>2 legs</td>
<td>Running time: 2.3% decrease (34 s), VO2peak: equal</td>
</tr>
<tr>
<td>Clevidece et al. 2012</td>
<td>Nonathletes</td>
<td>Cycling</td>
<td>Maximal and submaximal test</td>
<td>Three 5-min cycles</td>
<td>2 legs</td>
<td>Workload: equal, VO2peak: equal</td>
</tr>
<tr>
<td>Gibson et al. 2013</td>
<td>Nonathletes</td>
<td>Running</td>
<td>30 m sprint</td>
<td>Three 5-min cycles</td>
<td>2 legs</td>
<td>Sprint time: equal</td>
</tr>
<tr>
<td>Kjeld et al. 2014</td>
<td>Athletes</td>
<td>Rowing Swimming Swimming</td>
<td>1000 m Breath-hold duration Distance underwater</td>
<td>Four 5-min cycles</td>
<td>1 arm</td>
<td>0.4% increase (0.8 s), 21% increase (58 s), 8% increase (9 m)</td>
</tr>
<tr>
<td>Tocco et al. 2014</td>
<td>Nonathletes</td>
<td>Running</td>
<td>5000 m</td>
<td>Three 5-min cycles</td>
<td>1 arm</td>
<td>Running time: equal</td>
</tr>
<tr>
<td>Paixao et al. 2014</td>
<td>Nonathletes</td>
<td>Cycling</td>
<td>Wingate test</td>
<td>Four 5-min cycles</td>
<td>2 legs</td>
<td>Anaerobic power output: equal or decreased</td>
</tr>
<tr>
<td>Lalonde et al. 2014</td>
<td>Nonathletes</td>
<td>Cycling</td>
<td>Wingate test</td>
<td>Four 5-min cycles</td>
<td>1 arm</td>
<td>Peak power: equal</td>
</tr>
<tr>
<td>Barbosa et al. 2014</td>
<td>Nonathletes</td>
<td>Handgrip</td>
<td>Until task failure</td>
<td>Three 5-min cycles</td>
<td>2 legs</td>
<td>Time to failure: 11.2% increase</td>
</tr>
<tr>
<td>McDonald et al. 2014</td>
<td>Heart failure</td>
<td>Cycling</td>
<td>Maximal exercise test</td>
<td>Four 5-min cycles</td>
<td>1 arm</td>
<td>VO2peak: equal</td>
</tr>
<tr>
<td>Seeger, unpublished data, 2014</td>
<td>Spinal cord injury</td>
<td>Arm crank test</td>
<td>Maximal arm crank test</td>
<td>Four 5-min cycles</td>
<td>2 arms</td>
<td>Maximal workload: 4% increase, VO2peak: equal</td>
</tr>
</tbody>
</table>

Table 1. Overview of studies examining the impact of IPC on exercise performance.

Abbreviations: IPC, ischemic preconditioning; VO2peak, peak oxygen consumption.
Several studies have examined the impact of IPC on maximal workload and oxygen consumption during a maximal incremental exercise test. The impact of IPC on maximal workload and/or exercise time is somewhat conflicting because some studies have reported a 2% to 4% improvement\textsuperscript{14,15} (Seeger JP, unpublished data, 2014), while others have found no impact\textsuperscript{14,22,23}. However, a more common finding in these studies is that IPC does not alter maximal oxygen consumption at maximal or submaximal levels (Table I). This observation suggests that increments in maximal oxygen consumption or lower oxygen consumption at submaximal levels do not explain the benefits of IPC on exercise performance. It is important to acknowledge that maximal oxygen consumption does not fully explain or predict exercise performance\textsuperscript{26}. Other factors, such as a higher lactate threshold,\textsuperscript{27,28} also represent important predictors of performance. This may partly contribute to the apparent distinct findings of the effects of IPC on exercise performance vs maximal oxygen consumption.

**Who can benefit from IPC**

**Athletes vs nonathletes**

An obvious question that arises is whether IPC improves exercise performance for everybody, from the untrained to the elite athlete. Most studies have included moderate-to-highly trained, amateur-level athletes. Some insight was provided by two studies that included national and international elite athletes. Jean-St-Michel et al included elite Canadian swimmers from competitive swimming teams at national and international levels.\textsuperscript{8} When a 100-meter maximal competitive swimming test (using their preferred style) was preceded by IPC, subjects demonstrated a significant 0.70-second improvement in their competitive swim time (95% confidence interval [95% CI], 0.01-1.35 seconds). In a subanalysis, they observed a comparable benefit of IPC on swim time between national-level and international-level swimmers.\textsuperscript{8} In a more recent study, elite national and international free divers and rowers were included.\textsuperscript{16} Elite free divers showed that IPC improved breath-hold duration (+21%) and the distance covered for swimming underwater (+8%). Furthermore, in the elite rowers, IPC significantly improved a 1000-meter rowing ergometry time trial by 0.8 seconds.\textsuperscript{16} Although direct comparisons between elite and nonelite athletes are lacking, these cross-sectional data suggest that the effects of IPC are not simply restricted to a single athletic or nonathletic group.

**Remote IPC**

The cardioprotective effects of IPC in preventing tissue injury are also present in remote areas, which is commonly referred to as remote IPC.\textsuperscript{29} A similar phenomenon may be evident using IPC to improve exercise performance, as IPC can be applied to active (ie, legs during running) or nonactive limbs (ie, legs during arm crank). Barbosa et al examined the impact of IPC applied to the legs on handgrip exercise performance and reported an 11% improvement in a handgrip exercise test until task failure.\textsuperscript{21} While this observation suggests the presence of a remote effect of IPC on performance, McDonald et al found no impact of IPC applied to the arms on maximal workload during an incremental cycle exercise test.\textsuperscript{22} We have also examined arm crank exercise performance in individuals with spinal cord injuries (SCI), where exercise was preceded by IPC on the arm (ie, IPC), IPC on the legs (ie, remote IPC), and a control condition. While IPC resulted in a 4% improvement in exercise time compared with the control condition, such effects were not observed during remote IPC (Seeger JP, unpublished data, 2014). Although more research work is necessary in this area, IPC seems to have a larger effect than remote IPC on exercise performance.

**Clinical groups**

A logical extension from work in this field in nonathletic or athletic healthy subjects is whether IPC affects performance in clinical groups. McDonald et al examined the impact of IPC in patients with heart failure (HF).\textsuperscript{22} In line with some,\textsuperscript{14,23} but not all,\textsuperscript{9,15} studies, IPC did not alter maximal workload and/or maximal oxygen consumption in HF patients. The authors explored their observation further and used dialysate from the HF patient (from blood samples obtained after IPC or sham) to examine the protective effect of IPC in a mouse heart Langendorff model of infarction.

Intriguingly, infarct size was similar between dialysate from IPC or sham, suggesting that IPC in HF was unable to prevent ischemic cardiac injury, which is in line with the findings on exercise performance. Reduced efficacy of IPC in HF has been described previously in animal and human studies\textsuperscript{30-32}.

We have recently explored the impact of IPC on improving arm crank exercise performance in individuals with SCI (a clinical group at increased cardiovascular risk) and found that IPC significantly improved maximal workload and enhanced exercise time in individuals with SCI (Seeger JP, unpublished data, 2014). Finally, a previous study in patients with intermittent claudication found that the IPC (applied to the arms) prolonged the walking distance before patients first experienced symp-
 Nonetheless, it should be taken into consideration that a part of these effects were attributable to familiarization effects and that the total walking distance did not significantly improve.33

**Mechanisms**

**Lactate accumulation**

Several studies that examined the impact of IPC on exercise performance have reported data on submaximal or maximal oxygen consumption, with the majority reporting no impact of IPC on maximal or submaximal oxygen consumption (Table 1). An alternative explanation for the effects of IPC on exercise performance relates to the removal and/or production of lactate, especially since the lactate threshold has a strong predictive capacity for endurance-type exercise34,35 (ie, the type of exercise that seems to yield the largest effect size from IPC). To explore this hypothesis, the magnitude of lactate accumulation was determined at multiple submaximal exercise levels, which were preceded by IPC or a sham condition.14 Interestingly, IPC resulted in an attenuated increase in blood lactate (Figure 2) These lower blood lactate concentrations at a given workload were associated with improved endurance exercise economy, even in highly trained athletes.35,36

A potential explanation for these observations may relate to a faster removal and/or lower production of lactate. IPC has been suggested to improve vascular function, leading to an increase in blood flow that may facilitate blood lactate removal and/or enhance O2 supply. Secondly, previous studies in animals and humans indicate that IPC enhances mitochondrial capacity.6,37 most likely via ATP-sensitive potassium (KATP) channels located on the inner membrane.6 These effects of IPC on mitochondria are significant observations since increases in mitochondrial capacity contribute to improvements in endurance exercise performance.38 An alternative explanation, although not mutually exclusive, relates to a reduction in muscle lactate production after IPC. Animal studies have shown that IPC can enhance muscle efficiency in ATP-usage via ATP-sparing, augment mitochondrial function, or increase efficiency of the excitation-contraction coupling4,7,8 Such changes in the metabolic chain may lead to a smaller production of lactate.

**Vascular protection**

High-intensity, strenuous exercise is associated with immediate vascular injury, leading to a decrease in vascular function.39 A reduction in the function of blood vessels may be detrimental for exercise performance,40 and may also be associated with a lower blood flow to the exercising limb.41 Several previous studies have established that IPC can prevent vascular injury after prolonged periods of ischemia42-44 or prevent cardiac damage in clinical groups.45-47 Similarly, we explored whether IPC could prevent the reduction in vascular function typically observed after strenuous exercise.48 We found that the decline in brachial artery endothelial function after strenuous exercise was completely prevented when exercise was preceded by IPC (Figure 3, page 284). Although speculative, prevention of impaired vascular function and blood-flow response during strenuous exercise by IPC may contribute to enhanced exercise performance.

**Future directions**

The current research literature suggests that IPC can be beneficial to exercise performance in healthy persons. While direct comparisons are lacking, these effects have currently been described in various types of exercise (eg, cycling, rowing, running, swimming) and in a range of
moderate-to-highly trained athletes, including those at national and international competitive levels. These remarkable effects of IPC are supported by some initial mechanistic studies showing that IPC attenuates blood lactate accumulation during submaximal exercise and prevents vascular dysfunction after strenuous running exercise.

Future studies are necessary to establish and explore the potential effect of IPC on exercise performance further. More specifically, these studies should focus upon the direct comparison between different exercise modes (eg, sprint, strength, endurance), intensities (eg, high, moderate, low), and duration (eg, short, medium, long). Further areas of research are related to the practical performance or application of IPC. This relates to the optimal timing of IPC prior to an exercise event, identification of clinical groups that benefit from IPC, the frequency in which IPC can be applied, whether IPC has a role in exercise training or prior to single exercise events only, and the potential underlying mechanisms to understand and benefit further from IPC.

ROLE OF IPC IN REHABILITATION

Repeated remote IPC: a question of dose?

Previous work from animals and humans has demonstrated that repeated exposure to elevations in blood flow or shear stress represents an important stimulus for vascular adaptations in function and structure. In addition, repeated exposure to short periods of hypoxia or ischemia may also contribute to cardiovascular adaptations. Importantly, repeated elevations in blood flow or shear stress and hypoxia represent key characteristics of IPC. Therefore, it was hypothesized that repeated IPC might induce vascular adaptations.

Over a few years, a small number of studies have explored the potential impact of repeated exposure of IPC on the vascular system. One of the first teams to explore this question was Kimura et al; they examined the impact of 28 days of daily IPC on forearm resistance artery endothelial function. Using local infusion of vasoactive substances, they demonstrated that repeated exposure to IPC improved resistance artery endothelial function through increases in nitric oxide production. Furthermore, they demonstrated that daily IPC was associated with an elevation in circulating endothelial progenitor cells (EPCs) and plasma levels of vascular endothelial growth factor (VEGF). These changes in EPCs and VEGF were hypothesized to contribute to changes in vascular function after repeated IPC.

Recently, we also found that 7 days of repeated IPC could improve brachial artery endothelial function. An important observation was that a comparable increase in endothelial function was present remotely in the contralateral arm (ie, the arm that did not directly receive the IPC stimulus). Furthermore, we repeated the assessments of bilateral endothelial function 7 days after the 7-day intervention to ensure that our postintervention measurements were not influenced by the late phase of protection (see below for definitions of phases). The bilateral improvement in brachial artery endothelial function remained 7 days post-IPC intervention. We also explored the impact of repeated IPC on skin perfusion and found an increase in baseline skin perfusion in both arms after the 7-day
IPC intervention. The observation of local and remote adaptations suggests that vascular adaptations after repeated IPC cannot be simply explained by the repeated elevations in blood flow, shear stress rate, and hypoxia. Although speculative, investigating circulating factors, such as the elevations in EPCs and VEGF may contribute to these observations. Therefore, future research is warranted.

IPC leads to an “early” phase of protection, which develops within minutes and lasts 2 to 3 hours, and a “late” phase of protection, which begins 12 to 24 hours after IPC and lasts $\approx$ 3 days. Both phases have protective effects, but also seem to work through distinct pathways. When repeated rounds of IPC are timed well (24 to 72 hours between subsequent rounds), tissues may be exposed to the “early” and “late” phases of protection at the same time. Therefore, repeated IPC may contribute to the vascular adaptations after repeated IPC. Given the relatively long duration of the “late” phase of protection, we explored whether less frequent, and arguably more practical, exposure to repeated IPC is sufficient to induce vascular adaptation. We found that receiving 3 IPC cycles/week for 8 weeks resulted in a significant improvement in brachial artery endothelial function.

The ability of repeated IPC to alter the vasculature raises the question about its potential clinical impact, especially since improvements in vascular function and structure have been linked to reduced cerebrovascular and cardiovascular risk. A recent study provided some interesting insight into this question. Meng et al evaluated the effects of 300-day repeated IPC (twice daily) on stroke recurrence and cerebral perfusion in patients with symptomatic, atherosclerotic, intracranial, arterial stenosis (Figure 5, page 286). Interestingly, lower stroke recurrence was found in the IPC group at 90 and 300 days (5.0% and 7.8%, respectively) compared with the control group (23.3% and 26.7%, respectively). The group receiving repeated IPC also demonstrated a significantly shorter time to recovery and improved cerebral perfusion.

Repeated IPC may also be associated with potentially detrimental effects, such as frequent exposure to IPC (or “hyperconditioning”), and has been linked to a potential reduction in the efficacy of IPC and/or collagen injury induction. In contrast, a previous animal study found comparable protective effects of a single vs repeated IPC against cardiac ischemia-reperfusion injury in

---

**Figure 4.** Brachial artery FMD before and after a 7-day daily IPC treatment.

Brachial artery FMD (%; Panel A) and resting (baseline) forearm CVC (Panel B) before (pre), after (post), and 8 days after (post+8) the 7-day daily IPC intervention in the IPC-treated (open circles) and contralateral arm (ie, remote IPC; solid circles) of healthy volunteers (n=13). Error bars represent SE. *Post hoc significantly different from day 0.

Abbreviations: CVC, cutaneous vascular conductance; FMD, flow-mediated dilation; IPC, ischemic preconditioning; RIPC, remote ischemic preconditioning; SE, standard error.

Another study, in pigs, also found preserved efficacy of IPC against ischemic injury with repeated IPC. Despite preservation of the effect size between single vs repeated IPC, both studies used microarray gene expression analysis to highlight that the underlying mechanisms for the protective effects of a single episode and repeated IPC are radically different. A recent study, in humans, found that 7 days of daily IPC did not alter the protective effects of IPC to prevent endothelial ischemia-reperfusion injury. Although these data suggest that repeated IPC does not impair or alter the benefits of a single IPC, the potential presence of detrimental effects should be further explored and kept in mind when repeatedly applying IPC.

Exercise training represents a potent strategy to reduce the risk of future cardiovascular events in asymptomatic individuals and those with a preexisting disease. Performance of regular exercise training is also associated with a smaller infarct size, subsequently leading to better prognosis after an infarct. Although changes in traditional cardiovascular risk factors explain some of the cardioprotective effects of training in coronary heart disease, a substantial proportion of the benefit remains unexplained. Exercise may exert “preconditioning” effects on the arterial wall, leading to protection against potentially harmful stimuli, and subsequently, prevention of cardiovascular events and progression of cardiovascular disease. Preliminary evidence from animal and human studies for this novel hypothesis is summarized below.

Animal studies revealed that exercise training reduces cardiovascular injury associated with prolonged and potentially lethal ischemia. Evidence from cross-sectional studies in humans suggests that regular exercise attenuates endothelial ischemia-reperfusion injury. To understand the effects of exercise training better, the role of myocardial K(ATP) channels have been examined for exercise-induced protection from ischemia-reperfusion injury. Hearts of 12-week trained or sedentary rats were exposed to 1 to 2 hours of ischemia-reperfusion with, or without, mitochondrial or sarcolemmal K(ATP) channel blockade. Exercise training was associated with a smaller infarct size, while sarcolemmal, but not mitochondrial, K(ATP) blockade completely prevented the training-induced cardioprotection. A role for sar-
Ischemic conditioning in sports and rehabilitation

Recent studies have provided evidence that repeated IPC potentially improves vascular function, the long-term effects of repeated IPC on cardiovascular adaptations and cardiovascular health are currently less clear. If these initial findings can be replicated in individuals with cardiovascular risk or disease and if repeated IPC translates to long-term protection against cardiovascular events, the clinical relevance of repeated IPC would be increased. Therefore, well-designed, longitudinal, randomized, controlled trials are necessary to understand the potential health effects of repeated IPC better. Studies in humans are necessary to more fully understand the preconditioning effects of acute and chronic exercise, as such, mechanisms may contribute to the largely unexplained cardioprotective effects of exercise training. More insight into the effects of exercise may contribute to improved exercise prescription guidelines, but may also contribute to an increased understanding of the impact of IPC on the protection from cardiovascular events. Finally, research should also focus on the potential risks of repeated IPC and the practical limitations of applying IPC.

**CONCLUSIONS**

Research in the area of IPC has received significant scientific attention and is currently an established area of research in cardiology. Indeed, many papers were published on applying IPC in various patients groups, including papers from multicenter, clinical trials that were published in the world’s leading scientific journals. Only recently has IPC entered the area of sport science and rehabilitation research. IPC is in its infancy in this research area, highlighted by the large number of questions that currently remain unanswered. Nonetheless, some remarkable effects have been described that have potential beyond the areas of sport science and rehabilitation. The impact of IPC on exercise performance may have the potential to enhance the effects of exercise training (or a single, competitive exercise bout) in healthy individuals and in other groups as well. Furthermore, the ability to mediate vascular adaptations through repeated exposure to IPC may represent a novel strategy to improve the cardiovascular system and possibly even cardiovascular risk/progression. Although many questions are currently unanswered, the initial studies in the area of sport science and rehabilitation described in this review warrant further investigation to explore the potential use of IPC in this field.

**Future directions**

Although initial studies have provided evidence that repeated IPC potentially improves vascular function, the long-term effects of repeated IPC on cardiovascular adaptations and cardiovascular health are currently less clear. If these initial findings can be replicated in individuals with cardiovascular risk or disease and if repeated IPC translates to long-term protection against cardiovascular events, the clinical relevance of repeated IPC would be increased. Therefore, well-designed, longitudinal, randomized, controlled trials are necessary to understand the potential health effects of repeated IPC better. Studies in humans are necessary to more fully understand the preconditioning effects of acute and chronic exercise, as such, mechanisms may contribute to the largely unexplained cardioprotective effects of exercise training. More insight into the effects of exercise may contribute to improved exercise prescription guidelines, but may also contribute to an increased understanding of the impact of IPC on the protection from cardiovascular events. Finally, research should also focus on the potential risks of repeated IPC and the practical limitations of applying IPC.

**Acknowledgments.** Dr Helen Jones and Prof Tim Cable are acknowledged for their support, practical help, assistance, and performance of a substantial portion of the work on repeated IPC. Furthermore, Mr Joost Seeger is acknowledged for the significant amount of work on IPC and exercise performance. Their contributions have been vital for the work and hypotheses presented in this review.
REFERENCES

1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. 


_Human Genomics_. 2003;5:35:480-487.


6. Riksen NP, Smits P, Rongen GA. Ischemic preconditioning: from molecular characterization to clinical application—part I. 

7. Lawson CS, Downey JM. Preconditioning: state of the art myocardial protection. 


19. Paixao RC, da Mota GR, Marocolo M. Acute effect of ischemic preconditioning is detrimental to anaerobic performance in cyclists. 

20. Lalonde F, Curnier D. Can anaerobic performance be improved by remote ischemic preconditioning? 


23. Clevidence MW, Mowery RE, Kushnich MR. The effects of ischemic preconditioning on aerobic and anaerobic variables associated with submaximal cycling performance. 

The acute effect of ischemic preconditioning on repeated high-intensity exercise performance of elite rugby players.
Presented at: 16th annual Congress of the ECSS; July 6-9, 2011; Liverpool, UK.
Energetics of running in top-level marathon runners from Kenya.
27. Farrell PA, Wilmore JH, Coyle EF, Billing JE, Costill DL.
Plasma lactate accumulation and distance running performance.
Treadmill velocity best predicts 5000-m run performance.
Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion.
Circulation. 1993;87:893-899.
30. Ferdinandy P, Schulz R, Baxter GF.
Interaction of cardiovascular risk factors with myocardial ischemia-reperfusion injury, preconditioning, and postconditioning.
Aging attenuates the protective effect of ischemic preconditioning against endothelial ischemia-reperfusion injury in humans.
32. Seeger JP, Benda NM, Riksen NP, et al.
Heart failure is associated with exaggerated endothelial ischemia-reperfusion injury and attenuated effect of ischemic preconditioning.
Remote ischemic preconditioning in patients with intermittent claudication.
34. Coyle EF, Coggan AR, Hopper MK, Walters TJ.
Determinants of endurance in well-trained cyclists.
35. Lucia H, Hoyos J, Perez M, Santalla A, Earnest CP, Chicharro JL.
Which laboratory variable is related with time-trial performance time in the Tour de France?
36. Lorenzo S, Minson CT, Babb TG, Halliwell JR.
37. Yellon DM, Hausenloy DJ.
Myocardial reperfusion injury.
Determinants of time trial performance and maximal incremental exercise in highly trained endurance athletes.
39. Dawson EA, Birk GK, Cable NT, Thijssen DH, Green DJ.
OP-PM04 Health: effect of acute exercise intensity on brachial artery endothelial function in humans.
Presented at: 16th annual Congress of the ECSS; July 6-9, 2011; Liverpool, UK.
40. Green DJ, Maiorana A, O'Driscoll G, Taylor R.
Effect of exercise training on endothelium-derived nitric oxide function in humans.
41. Brunnekreef J, Benda N, Schreuder TH, Hopman M, Thijssen D.
Impaired endothelial function and blood flow in repetitive strain injury.
Ischemic preconditioning prevents endothelial injury and systemic neutrophil activation during ischemia-reperfusion in humans in vivo.
43. Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, MacAllister RJ.
Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans; role of the autonomic nervous system.
44. Loukogeorgakis SP, Williams R, Panagiotidou AT, et al.
Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism.
Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans.
Remote ischemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial.
Cardioprotective and prognostic effects of remote ischemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial.
48. Dawson EA, Green DJ, Cable NT, Thijssen DH.
Effects of acute exercise on flow-mediated dilation in healthy humans.
49. Langille BL, O'Donnell F.
Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent.

Role of vascular endothelium in exercise-induced dilation of large epicardial coronary arteries in conscious dogs.

51. Tinken TM, Thijssen DH, Hopkins N, Dawson EA, Cable NT, Green DJ.
Shear stress mediates endothelial adaptations to exercise training in humans.

52. Laughlin MH, Newcomer SC, Bender SB.
Importance of hemodynamic forces as signals for exercise-induced changes in endothelial cell phenotype.

53. Newcomer SC, Thijssen DH, Green DJ.
Effects of exercise on endothelium and endothelial smooth muscle cross talk: role of exercise-induced hemodynamics.

Replication of ischemic preconditioning augments endothelium-dependent vasodilation in humans: role of endothelium-derived nitric oxide and endothelial progenitor cells.

55. Jones H, Hopkins N, Bailey TG, Green DJ, Cable NT, Thijssen DH.
Seven-day remote ischemic preconditioning improves local and systemic endothelial function and microcirculation in healthy humans.

Impact of eight weeks of repeated ischemic preconditioning on brachial artery and cutaneous microcirculatory function in healthy males.

57. Ras RT, Streppel MT, Draijer R, Zock PL.
Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis.

58. Green DJ, Jones H, Thijssen D, Cable NT, Atkinson G.
Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter?

59. Inaba Y, Chen JA, Bergmann SR.

60. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M.
Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis.

Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis.

62. Whittaker P, Przyklenk K.
From ischemic conditioning to ‘hyperconditioning’: clinical phenomenon and basic science opportunity.

63. Depre C, Park JY, Shen YT, et al.
Molecular mechanisms mediating preconditioning following chronic ischemia differ from those in classical second window.

64. Shen YT, Depre C, Yan L, et al.
Repetitive ischemia by coronary stenosis induces a novel window of ischemic preconditioning.

65. Luca MC, Lumi A, McLaughlin K, Gori T, Parker JD.
Daily ischemic preconditioning provides sustained protection from ischemia-reperfusion induced endothelial dysfunction: a human study.

Relative intensity of physical activity and risk of coronary heart disease.

67. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT.
Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy.

68. Mora S, Cook N, Buring JE, Ridker PM, Lee IM.
Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms.

Exercise reduces infarct volume and facilitates neurobehavioral recovery: results from a systematic review and meta-analysis of exercise in experimental models of focal ischemia.

70. McElroy CL, Gissen SA, Fishbein MC.
Exercise-induced reduction in myocardial infarct size after coronary artery occlusion in the rat.

71. Bowles DK, Farrar RP, Starnes JW.
Exercise training improves cardiac function after ischemia in the isolated, working rat heart.

72. Brown DA, Jew KN, Sparagna GC, Musch TI, Moore RL.
Exercise training preserves coronary flow and reduces infarct size after ischemia-reperfusion in rat heart.

73. Peng FL, Guo YJ, Mo WB, Xu SM, Liao HP.
Cardioprotective effects mitochondrial ATP-sensitive potassium channel in exercise conditioning.
Cardioprotection afforded by chronic exercise is mediated by the sarcolemmal, and not the mitochondrial, isoform of the KATP channel in the rat.

Endothelial ischemia-reperfusion injury in humans: association with age and habitual exercise.

Habitual resistance exercise and endothelial ischemia-reperfusion injury in young adults.

77. Michelsen MM, Stottrup NB, Schmidt MR, et al.
Exercise-induced cardioprotection is mediated by a bloodborne, transferable factor.

Interval exercise, but not endurance exercise, prevents endothelial ischemia-reperfusion injury in healthy subjects.

79. de Vries WR, Bernards NT, de Rooij MH, Koppeschaar HP.
Dynamic exercise discloses different time-related responses in stress hormones.

80. de Meirleir K, Naaktgeboren N, Van Steirteghem A, Gorus F, Olbrecht J, Block P.
Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise.

81. Schwarz L, Kindermann W.
Changes in beta-endorphin levels in response to aerobic and anaerobic exercise.
**HISTORICAL STUDIES ON VASCULAR TONE MECHANISMS**

The control of blood vessel tone has been a subject of scientific research for at least 2 centuries. A major focus has been the effects of sympathetic tone on blood flow to voluntary muscles in different animal species. Claude Bernard observed a marked rise in blood pressure in the horse after ablation of the cervical sympathetic nerves. In the 1930s, studies on blood flow in subjects who fainted showed an increase in forearm blood flow, suggesting a substantial decrease in vascular tone mediated by sympathetic vasodilation nerve fibers. Infusion of adrenaline (10 µg/min) caused a transient, but distinct, dilatation followed by a moderate increase in blood flow.

There are numerous reports of other studies exploring the physiology and pharmacology of smooth muscle control in different organs. A major area of interest has been the mechanisms involved in catecholamine-mediated changes on smooth muscle tone (Figure 1). In the context of this Dialogue in Cardiovascular Medicine's symposium regarding myocardial preconditioning mechanisms and possible mediators, the unsolved question is "what are the endogenous mediators involved in cardiac preconditioning, especially remote preconditioning?" A more specific topic might be whether nitric oxide could be a potential candidate for this role.

The biochemical pathways controlling the formation and levels of intracellular nitric oxide have been described in the literature, including the discovery of endothelial-derived relaxing factor (EDRF). Experimental preconditioning in either rats or dogs results in a considerable 20% reduction in the size of the subsequent myocardial infarction once the coronary artery is irreversibly obstructed. The possible endogenous mediators of this beneficial outcome have challenged scientists in this field since the phenomenon was first described.

**DISCOVERY OF ENDOTHelial-DERIVED RELAXING FACTOR**

While evaluating the potential role of nitric oxide in remote preconditioning, it is important to describe the evolution of studies on vascular tone in the coronary vessels. One of the themes in these essays has been the importance of serendipity in scientific research. Thus, in the mid-1970s, Furchgott was performing a range of experiments on smooth muscle and attempting to analyze the receptors possibly involved in mediating tone in isolated aortic vessels.
vessel smooth muscle from rabbits. For instance, his group showed that tracheal smooth muscle contains both β1- and β2-adrenergic receptors. Initial studies of the rabbit aortic smooth muscle were designed to see if the rabbit aorta also contained β1-adrenergic receptors, in addition to β2-adrenergic receptors, as an analogy with tracheal smooth muscle. They also studied the effect of acetylcholine in this aortic ring preparation.

In his Nobel lecture on December 8, 1998, Furchgott describes the results of the initial experiments (Figure 2).

However, in the very first experiment of this planned series in May 1978, my technician did not follow my directions correctly: early in the experiment before blocking the α-adrenergic receptor with dibenamine, he tested carbacol for its contracting activity before rather than after (as prescribed in the directions) washout of a previous test dose of norepinephrine. The response to carbacol was not a contraction, but a partial relaxation of the norepinephrine-induced contraction.

The unexpected relaxation of the rabbit aorta in vitro by muscarinic agonists was very exciting because the effect was in accord with the potent vasodilating action of these agonists in vivo. The challenge was to determine why had his group failed to observe cholinergic-induced relaxation of aortic preparations in the past, and why had it now become manifest? One difference in experimental design from the previous work had been that the rabbit thoracic aorta was the transverse ring rather than the helical strip, which had been used in earlier experiments with muscarinic agonists. Unexpectedly, only the aortic rings responded with relaxation to these muscarinic agonists, while the aortic strips responded with contraction. He showed that rubbing the intimal surface of the aorta eliminated the relaxing response to cholinergic agonists. When care was taken not to rub the intimal surface of the ring, then excellent relaxation could be induced. There was a complete loss of the relaxation response to acetylcholine when aortic endothelial cells were completely removed by preincubation with collagenase.

Subsequent studies demonstrated that cholinergic agonists stimulated the release of a diffusible relaxing substance from endothelial cells, which was termed EDRF. Numerous ensuing studies seeking other endothelium-dependent relaxing agents soon identified several, including ATP and ADP, bradykinin, substance P, histamine, thrombin, serotonin, and vasopressin. Some of these agents had species-dependent relaxation responses. For example, histamine produced EDRF in the rat, but not the rabbit, while bradykinin was active only in isolated canine and human arteries. In the context of potential mediators of remote preconditioning, it was observed that isolated canine coronary arteries were relaxed by noradrenaline via α2-adrenoreceptors in an EDRF manner, but this kind of relaxation could not be shown in canine systemic arteries. Similarly, serotonin relaxed canine coronary arteries, but not systemic arteries. Furchgott believed that EDRF might be mediated by short-lived hydroperoxides or free radicals, or alternatively, these effects could occur by stimulating the G cyclase in vascular smooth muscle to lead to an increase in cGMP. This latter hypothesis was subsequently shown to be correct by several independent groups who were also anxious to identify the nature of EDRF.

In London, Greglewsky et al published a paper in Nature showing that superoxide was involved in EDRF breakdown. At the same time, Furchgott presented a paper at a symposium claiming that EDRF was nitric oxide. By coincidence, Ignarro, presented a paper at the same symposium, also claiming that EDRF was nitric oxide, which was based on studies conducted on isolated bovine pulmonary vessels. However, this 1986 symposium was only published in 1988. During the 2 intervening years, three other groups confirmed, in different experiments, that EDRF had the same characteristics as nitric oxide. The findings that a gas could act as a mediator of smooth muscle tone was clearly in sharp contrast to the classical neurotransmitters.
The endothelial cell plays a central role in modulating coronary vessel tone. The early EDRF studies identified a number of endogenous factors that could activate EDRF and presumably generate nitric oxide. Transient occlusion (15 min) of either a coronary vessel or other remote artery, repeated four times, causes a reduction in experimental infarction from 27% to 7%. Is nitric oxide the endogenous mediator?

A recent report by Rassaf et al\(^{17}\) demonstrated that there is bioactive transport of nitric oxide in humans. Furthermore, in mice where the endothelial nitric oxide synthase (eNOS) enzyme had been genetically deleted (eNOS\(^{-/-}\)) to reduce nitric oxide formation, the protective effect of preconditioning was abolished. A model proposed by Rassaf et al suggests that ischemia generates vasodilatation by metabolites and that increased flow and shear forces on the endothelium activates eNOS, thereby generating nitric oxide, which is then oxidized to nitrite and transported to the ischemic heart. This mechanism has yet to be shown clinically.

It seems that there is still much to learn about the biochemical and physiological role of nitric oxide (Figure 3).\(^{18}\) There are now three forms of nitric oxide synthase, that is, neuronal NOS (nNOS or NOS-1), inducible NOS (iNOS or NOS-2), and eNOS (NOS-3). They are widely distributed throughout the body, and the contribution of nitric oxide to physiology and disease remains to be further elucidated.\(^{17}\)

**COMMENTARY**

Of the four major groups studying EDRF and nitric oxide, the importance of three of the research leaders was recognized by awarding them the Nobel Prize in 1998. Robert Furchgott (1916-2009) was an outstanding cardiovascular physiologist and pharmacologist who had been committed to science from his adolescent years. He achieved international recognition and he was awarded numerous prizes for his work.

Louis Ignarro (1941-) is the son of Italian immigrants. He obtained a PhD in pharmacology at the University of
Wisconsin, Madison, WI and joined the Geigy pharmaceutical company in the US in 1968, heading the anti-inflammatory projects. He also studied cyclic GMP, which was a newly identified nucleotide. He subsequently returned to academic life at the University of Tulane, New Orleans, LA, as an assistant professor, where he continued to work on cyclic GMP. In the early 1980s, his group worked on the role of nitric oxide in cellular functions and showed that EDRF was, in fact, nitric oxide.

Ferid Murad (1936-) is the son of Albanian immigrants who had a modest economic background. He graduated from DePauw University, Greencastle, IN in biology (Figure 4, page 295). He then joined the new MD-PhD program in Western Reserve University. He started research on nucleotides, including cGMP, which he continued to study after joining the National Institute of Health as a clinical associate. He was subsequently appointed Chief of Medicine at Stanford University, Stanford, CA from 1981 until 1988. Then, he joined the Abbott pharmaceutical company running research and development projects with 1500 scientists plus staff. He left Abbott in 1993 to set up the biotech company Molecular Genetics Corporation. In 1997, he rejoined academia by setting up an integrated medicine and clinical pharmacology group at the University of Texas, Houston, TX.

These brief biographies illustrate, yet again, the “Trails of Discovery” themes that involve a serious commitment to important scientific research, the contribution of serendipity to the success of those with prepared minds, and the importance of differences in culture in various scientific and industrial institutions. It is noteworthy that two of the three Nobel Laureates spent time in research departments of pharmaceutical companies.

REFERENCES


   Paris, France: Bailliere; 1876.


Remote Ischemic Conditioning

Summaries of Ten Seminal Papers

Hussain Contractor, MBChB, MRCP, DPhil

Department of Cardiology - University Hospital of South Manchester - Southmoor Road - Wythenshawe Manchester M23 9LT - UK (hussain.contractor@nhs.net)


1. Regional ischemic ‘preconditioning’ protects remote virgin myocardium from subsequent sustained coronary occlusion
   K. Przyklenk and others. Circulation. 1993

2. Myocardial protection by brief ischemia in noncardiac tissue
   B. C. Gho and others. Circulation. 1996

3. Transient limb ischemia induces remote ischemic preconditioning in vivo

4. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery…
   M. M. Cheung and others. J Am Coll Cardiol. 2006

5. Intermittent peripheral tissue ischemia during coronary ischemia reduces myocardial infarction through a KATP-dependent mechanism…

6. Cardiac remote ischemic preconditioning in coronary stenting (CRISP stent) study: a prospective, randomized control trial
   S. P. Hoole and others. Circulation. 2009

7. 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
   H. E. Botker and others. Lancet. 2010

8. Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery?…
   D. M. Hong and others. Eur Heart J. 2014

9. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial
   K. D. Hougaard and others. Stroke. 2014

10. Remote ischemic conditioning enhanced the early recovery of renal function in recipients after kidney transplantation…

Selection of seminal papers by Hussain Contractor, MBChB, MRCP, DPhil
University Hospital of South Manchester - Manchester - UK

Highlights of the years by Sherri Smith, PhD
Publications office
Within a few years of the initial description of preconditioning, several independent groups had gone on to confirm that preconditioning, induced by brief periods of ischemia and reperfusion, prior to a prolonged ischemic episode, was a reproducible and robust effect, limiting myocardial infarction size. Until this stage, preconditioning had only been investigated on a "local" level with the preconditioning stimulus delivered to the same vascular bed as the subsequent index ischemia. In a truly seminal step forward, Przyklenk et al investigated whether preconditioning may have more widespread effects with cardioprotection in territories remote from the coronary run-off in which the stimulus was applied.

Using a surgical canine model, both the left anterior descending and circumflex arteries were exposed prior to the application of a preconditioning stimulus in the circumflex territory consisting of four 5-minute cycles of ischemia and reperfusion. The left anterior descending artery was then occluded for 1 hour, and subsequent infarct size and area at risk was measured histologically by means of an in vivo blue dye that stained the area at risk, followed by incubation in triphenyltetrazolium chloride to assess the area of myonecrosis. Hemodynamic and regional wall motion data were collected and the collateral blood supply was measured by means of radioactive microspheres.

The results convincingly and compellingly established that a preconditioning stimulus in the circumflex territory markedly reduced infarct size in the left anterior descending territory, demonstrating, for the first time, the phenomenon of "preconditioning at a distance," or as it is now known, remote preconditioning. Infarct size was reduced from 16±5% in the area at risk in controls to 6±2% in studies where remote preconditioning had taken place (P<0.05), a reduction of over 60%, which is comparable with the results seen in studies on local preconditioning. Although there was a trend toward improved hemodynamics in the preconditioned group, this failed to reach statistical significance.

Seven years after the first description of ischemic preconditioning, this study represented a stellar leap forward in the field of cytoprotective biology, demonstrating a remote effect of what was previously considered a local occurrence of an interesting, but seemingly nonutilizable, phenomenon. This study acts as the direct progenitor of the subsequent rich literature on preconditioning over the intervening 20 years, and it would lead to a host of clinically important and relevant discoveries.

The Czech Republic and Slovakia separate in the so-called Velvet Divorce; the Braer Storm, the most intense extratropical cyclone on record for the northern Atlantic Ocean, occurs in January; and the largest waterborne disease outbreak in documented US history, known as the Milwaukee Cryptosporidiosis outbreak, occurs in Milwaukee, WI.
An apparent pertinent question following the initial description of preconditioning in territories remote from the arterial supply was whether remote preconditioning only applied on an "intra"organ basis or whether the same phenomenon could be detected on a systemic basis with "inter"organ transmission of protection.

Utilizing a surgical Wistar rat model, the authors used myocardial infarct size, determined as a percentage of the area at risk, as the key outcome measure, ascertained histologically as in previous studies. In a complicated protocol involving classic preconditioning with cycles of coronary artery occlusion as the stimulus and cycles of mesenteric or renal artery occlusion as the remote preconditioning stimulus in groups with normothermia and hypothermia, the authors established the first firm basis of true remote preconditioning with "transmission" of preconditioning between organs.

A brief period of mesenteric artery occlusion was effective in protecting the myocardium in both normothermic and hypothermic conditions. Interestingly, renal artery ischemia was only effective in providing protection in hypothermic conditions, attesting to a complex system with differing effects in different vascular beds, which possibly pertains to the amount of ischemic tissue involved and the concept of a threshold effect, which is needed to trigger the preconditioning stimulus.

Having established mesenteric ischemia as a robust stimulus, the study went on to explore, in more detail, potential mechanisms by which the stimulus may be protective using the nondepolarizing ganglionic blocker, hexamethonium. Purporting a potential neurogenic pathway, hexamethonium was shown to abolish the protective effect of mesenteric ischemia on myocardial infarct size, but had no effect on either the protection seen with classic local preconditioning by coronary occlusion or myocardial infarct size per se. Extending their experimental protocol, the effects of permanent mesenteric artery occlusion were also investigated with prolonged ischemia in this remote bed, but failed to illicit cardioprotection. Implying that reperfusion is a key driver in the preconditioning stimulus, the authors speculated that the release of substances during the reperfusion phase, such as free radicals or cytokines, may be an active stimuli in the transmission of the preconditioning signal.

Describing a true systemic effect of a preconditioning stimulus, this important study remains, to this day, as an important contributor to our understanding of the biological basis and extent of preconditioning, delineating a neural mechanism as part of the preconditioning signal, and attesting to the highly complex biology of this phenomenon.

Steffi Graf wins her 19th Grand Slam title by defeating Arantxa Sánchez Vicario in the longest ever women's final at the French Open; the Nintendo 64 video game system is released in Japan; and Göran Kropp, a Swedish adventurer and mountaineer, reaches Mount Everest's summit alone, without oxygen, after having bicycled there from Sweden.
Remote preconditioning of cardiac tissue induced by episodes of brief ischemia in other tissues or organs was now firmly established in experimental models; therefore, interest turned to potential clinically relevant means of eliciting this cardioprotective response and perhaps more importantly whether similar mechanisms were at play in the more complex physiology of humans.

Using two separate experimental models, the authors utilized limb ischemia as a stimulus to protect the myocardium, and as a potential clinically viable and accessible vascular bed in which to perform cyclic episodes of ischemia and reperfusion without generating clinical harm or instability. In the first experimental model, preconditioning was stimulated in Landrace pigs by tourniquet occlusion of a hind limb, followed by an elegant closed-chest model using minimally invasive balloon angioplasty occlusion of the left anterior descending artery as the index ischemic event. Infarct size was measured as a percentage of the area at risk, which was histologically determined, and comparisons were made with a sham-intervention group. Hemodynamic measures of ventricular function were recorded with a pressure-volume loop catheter. Myocardial infarct size was significantly reduced by limb preconditioning with a decrease in mean infarct size from $53\pm8\%$ to $26\pm9\%$ ($P<0.05$). Parameters of ventricular performance, such as the time constant of ventricular relaxation (tau), were also improved by the intervention.

In a second protocol, the authors expanded this data to an experimental human model of ischemia-reperfusion injury. The authors utilized strain-gauge plethysmography to measure forearm blood flow responses to acetylcholine. Contralateral limb ischemia was used as the preconditioning stimulus with endothelial response, both before and after ischemia-reperfusion, as the primary end point. In this important study, the authors demonstrated that remote preconditioning by limb ischemia in humans elicits a similar physiological response, providing robust protection against prolonged episodes of ischemia as evidenced by the dramatic preservation of endothelial responsiveness, which is otherwise lost after extended periods of limb ischemia. In a translational first, this study demonstrates a clinically relevant and acceptable mechanical limb stimulus that is able to provide significant protection against prolonged ischemia. This work would directly form the foundation for future studies into the mechanisms of human preconditioning and the basis of multiple clinical studies into the applicability and relevance of preconditioning in human ischemia-reperfusion syndromes.

Clozapine is the first drug approved by the Food and Drug Administration for reducing the risk of suicidal behavior; the Golden Jubilee of UK’s Queen Elizabeth II occurs on the 50th anniversary of King George VI’s death in 1952; and Mt Stromboli, a volcano on a small island in the Tyrrhenian Sea, off the north coast of Sicily, erupts for the first time in 17 years.
Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans


J Am Coll Cardiol. 2006;47:2277-2282

The reproducible effects of remote preconditioning were now well established in animal models and were in the early translation to human physiology. Therefore, attention turned to the clinical applicability of this stimulus within the setting of cardiac surgery: providing a predictable and potentially deleterious episode of prolonged ischemia and reperfusion, which appeared ripe for modification by preconditioning.

While classic, direct preconditioning had already been demonstrated in patients undergoing coronary artery bypass grafting, clinical reluctance to induce repeated episodes of myocardial ischemia in patients with an already tenuous blood supply limited its potential for use. Remote preconditioning, achieved using a noninvasive blood pressure cuff, induced limb ischemia, and bypassed the risks of arrhythmia, myocardial dysfunction, and low cardiac output. This was a more benign and acceptable intervention with an extremely low potential for harm.

In this single-center study of 37 children undergoing cardiac surgery to repair a variety of congenital heart defects, 17 children were randomized to the remote preconditioning group and 20 to the control group. Children in the intervention arm underwent four 5-minute cycles of lower-limb ischemia induced by inflation of a blood pressure cuff, and study investigators were blinded to participant group allocations. Due to the increasing data on the systemic effects from preconditioning stimuli, a wide variety of parameters were measured, including indices of ventilation, myocardial injury, and recovery, as well as identifying systemic inflammatory response markers.

Remote preconditioning was shown to have a number of salutary effects, including reductions in myocardial injury as measured by troponin I release ($P<0.04$), reductions in postoperative inotropic requirements, which suggests an improved recovery in myocardial performance and vascular tone, and finally, a reduction in airway resistance ($P=0.009$) associated with the remote preconditioning stimulus.

While most subsequent studies have concentrated on adult surgery and have, to date, produced mixed results, this initial, carefully performed and controlled study demonstrated multiple beneficial effects from preconditioning in children in the perioperative period and continues to guide current investigators who are attempting to translate early data into applicable human paradigms.
Even though the benefits of remote preconditioning had been demonstrated in a number of conditions of predictable, iatrogenic ischemia-reperfusion injury, the majority of the morbidity and mortality related to these common syndromes comes from unpredictable episodes, such as myocardial infarction and stroke.

By its very nature, in the majority of cases, preconditioning, under these conditions, is not applicable without any warning or herald symptoms to presage the application of a preconditioning stimulus prior to the full-blown onset of an ischemic insult. While the phenomenon of postconditioning may present an answer to a number of these concerns, clinical reluctance in obstructing a recently restored blood supply in an ischemic and unstable tissue is understandable, limiting the widespread adoption of this technique.

Instead, in this experimental study, the concept of remote perconditioning was explored by utilizing the balloon angioplasty model of myocardial infarction in Landrace pigs. Due to the utilization of a distant vascular bed or tissue than the region undergoing the ischemic insult in generating the signal, a remote conditioning stimulus could potentially be delivered at the same time that the index ischemic event is taking place, opening the door for its use during the presentation of a number of ischemic syndromes.

A total of 20 animals were randomized to either intervention or sham groups, and the perconditioning stimulus was commenced at the onset of ischemia with four 5-minute cycles of ischemia and reperfusion of the hind limb. Once more, the primary end point was myocardial infarct size as a percentage of the area at risk and measured using histology. Hemodynamic data was accrued with the use of pressure-volume loop catheters. To further characterize potential mechanisms of the stimulus, a number of animals in further experiments were pretreated with the K⁺-dependent K<sub>ATP</sub> channel inhibitor glibenclamide.

The results demonstrated impressive reductions in a number of deleterious cardiac indices including infarct size (60%±5% in controls vs 38%±5% in the intervention group; P=0.004), degree of LV contracture, change in ejection fraction, and change in the time constant of diastolic relaxation (tau), which all favored the perconditioning group. Furthermore, the number of ventricular arrhythmias requiring cardioversion during the reperfusion period was significantly reduced. These effects were abolished by the addition of glibenclamide, thereby, providing strong supportive evidence for the K<sub>ATP</sub> channel as a key mediator in the perconditioning pathway.

With this initial demonstration of a remote conditioning stimulus being able to influence ischemia-reperfusion even when delivered after the onset of ischemia, the application and relevance of cytoprotection in myocardial infarction syndromes was suddenly magnified. This study provided the rationale and context for future developments in the clinical research of cardioprotection and greatly galvanized ongoing interest in the field.

---

Gianfranco Ferré, an Italian-born fashion designer who was also known as “the architect of fashion,” dies at age 63; a 16th-century trading ship is excavated near the shores of Drogheda, Ireland; and the award-winning Canadian indie-rock band Rheostatics performs their last concert.
Cardiac remote ischemic preconditioning in coronary stenting (CRISP stent) study: a prospective, randomized control trial


Circulation. 2009;119:820-827

Nearly 40% of percutaneous coronary intervention (PCI) procedures remain elective in patients with symptomatic, but otherwise stable coronary artery disease. Of these procedures, approximately one-third will have a detectable troponin rise signifying myocyte necrosis, secondary to ischemia, induced by the procedure. While the majority of these troponin increases are small, a number of studies have suggested that they are not benign and are associated with subsequent cardiovascular events.

Data from a number of studies now suggest that remote preconditioning could be elicited in humans and provide cytoprotection in several clinically predictable episodes of iatrogenic ischemia and reperfusion, including pediatric and adult cardiac surgery and aortic aneurysm repair. Therefore, the aims of this study were to ascertain whether remote preconditioning could reduce the troponin release associated with elective PCI.

A total of 242 patients were recruited and randomly allocated in a 1:1 fashion to a preconditioning protocol of three 5-minute cycles of upper-limb ischemia interspersed with reperfusion or a sham procedure, which was delivered approximately 1 hour prior to their angioplasty procedure. The primary outcome was troponin I release at 24 hours with a number of secondary outcomes, including rates of major adverse cardiovascular events (MACE) at 6 months.

The results demonstrated a benefit for remote preconditioning with a significant reduction in overall troponin I (TnI) release (0.06 vs 0.16 ng/mL, \(P = 0.04\)) and a much greater proportion of patients with no detectable troponin leak at all (48% vs 29%, \(P < 0.005\)). Interestingly, patients in the preconditioning group also experienced significantly less chest pain and ischemic ECG changes than in the control group, and quite remarkably, 6-month MACE rates showed a highly significant reduction in the preconditioned group (hazard ratio [HR], 0.28; 95% confidence interval [95% CI], 0.12-0.85; \(P = 0.018\)).

This relatively small, well-conducted study demonstrated the ability of remote preconditioning to improve outcomes and a patient’s experience in an extremely common and overall low-risk procedure. This cheap, safe, easy-to- implement, and well-tolerated preconditioning stimulus significantly reduced periprocedural troponin release, and in agreement with the data, it appeared to improve longer-term outcomes with respect to MACE.

The replication of this data in future studies will be important for adoption of preconditioning as a routine procedure in the management of these patients, further reducing risks and increasing long-term benefits.

Cargo ship MV Maersk Alabama is captured by Somali pirates, making it the first successful pirate seizure of a ship registered under the American flag since the 1820s; the typhoon Ketsana begins to cause record amounts of rainfall in Manila, Philippines, leading to the declaration of a “state of calamity” in 25 provinces; and Ekaterina Maximova, an internationally known Soviet-Russian ballerina, dies at age 70.
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;375:727-734

Despite the demonstration of postconditioning, a potential mechanism to reduce reperfusion injury in acute ischemic syndromes, a general reluctance to induce further episodes of ischemia in an already stunned and rhythmically unstable myocardium had limited its adoption. A potentially safer and clinically acceptable mode to reduce infarct size was the recently described remote perconditioning, with the stimulus delivered in the remote site of a limb after onset of the index ischemia, but prior to reperfusion.

In this single-center study, patients presenting with chest pain and an initial ECG (conducted by the paramedics) showing evidence of ST-segment elevation myocardial infarction, necessitating primary percutaneous coronary intervention (PCI), were recruited. Participants were randomized during transport to the PCI center either to remote perconditioning, involving four 5-minute cycles of ischemia interspersed with reperfusion of the upper limb, or a sham procedure. PCI operators and other hospital staff were blinded to study allocation. Prior to mechanical reperfusion, the area at risk was estimated by means of Technetium-sestamibi–gated single photon emission CT (SPECT), with all patients undergoing primary PCI and stent implantation as per normal practice. Final infarct size was measured at 30 days by means of a repeat SPECT study. The primary end point was myocardial salvage index with secondary end points including final infarct size, ST-segment elevation resolution, and troponin T (TnT) concentrations.

Due to a number of exclusions and the 24-hour unavailability of SPECT scanning, 73 and 69 patients from the conditioning and control groups, respectively, completed follow-up with salvage index. The study demonstrated a significant improvement in salvage index in the intervention group (0.75 vs 0.55; P=0.035); the greatest benefit was seen in patients with completely occluded arteries at presentation (thrombolysis in myocardial infarction [TIMI], 0 flow) and those with LAD territory infarcts, which carry the highest overall risk of mortality.

This important study demonstrates the utility of intrinsic conditioning mechanisms in reducing infarct size in episodes of unpredictable ischemia, which carry a high societal burden in terms of morbidity and mortality, as well as placing a huge drain on healthcare system resources. With a strong correlation between infarct size and subsequent outcomes in myocardial infarction, future clinically powered studies are warranted to assess this simple, safe, and well-tolerated intervention for its ability to improve prognosis and reduce morbidity.
A number of initial, small-scale studies demonstrating that remote preconditioning was effective in reducing surrogate end points, such as myocardial troponin release in cardiac surgery patients, subsequent, and generally larger, studies have not always replicated these findings and generated doubt about the clinical utility of conditioning in these settings to further improve already excellent clinical outcomes. Appropriately sized and powered clinical studies were warranted in this regard, to answer these vital questions.

This study enrolled 1280 adult patients undergoing elective cardiac surgery for heterogeneous reasons, including bypass grafting, valve repair or replacement, and aortic and congenital surgery. Participants were randomized to a protocol of both remote preconditioning followed by remote postconditioning at the completion of the intervention, or a sham procedure involving attachment, but non-inflation, of a blood pressure cuff to the upper limb. The primary end point was a wide-ranging composite of major adverse events including myocardial infarction, arrhythmia, stroke, renal failure, multiorgan failure, and death.

The results of this large, rigorously conducted study were neutral with the rate of the composite end point being 38% in the intervention group and 38.1% in the control group ($P=0.998$). Multiple other secondary end points were also neutral, including length of intensive care unit stay (2 days vs 2 days, $P=0.475$), median length of overall hospital stay (9 days vs 9 days, $P=0.89$), and multiple clinical parameters, such as inotropic requirements, ventilation times, use of mechanical ventricular assist devices, and transfusion requirements.

Translation of the early promise of relatively small-scale, clinical preconditioning studies to larger, appropriately powered clinical trials has remained elusive. Approaching the 30-year anniversary since the first description of myocardial protection by preconditioning, there are still no widely accepted or recommended indications for its use in specific patient groups. Whether a deeper understanding of the cellular and subcellular mechanisms of conditioning will allow us to predictably and powerfully enhance cytoprotection remains a topic of debate. However, until large-scale studies are able to demonstrate clinically meaningful benefits from this intervention, the adoption of conditioning as a routine part of global clinical practice will remain elusive.

**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;35:176-183
Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial


Stroke. 2014;45:159-167

Stroke pathophysiology and natural history shares a commonality with myocardial infarction, and in its turn, is a very clinically important ischemic syndrome whose healthcare costs, in terms of both morbidity and mortality, imbue a high societal burden. While most conditioning work has centered on myocardial ischemia-reperfusion injury, conditioning itself appears to be a systemic phenomenon with an increasing body of literature demonstrating protection in a number of organs including the brain.

Therefore, stroke would seem to be an important and potentially modifiable disease to target for conditioning. In this early clinical study, a perconditioning protocol similar to that previously described for myocardial infarction was used in patients presenting with acute neurology, which was thought to be secondary to a stroke. Patients were randomly allocated to perconditioning or control (ie, no preconditioning) groups. Four 5-minute cycles of upper-limb ischemia-reperfusion were delivered during the ambulance transfer to the stroke center, where patients then underwent baseline MRI scanning to confirm evidence of an acute ischemic stroke prior to thrombolysis by recombinant tissue plasminogen activator (rTPA). The primary outcome measure was ischemic penumbral salvage with a number of secondary outcomes, including final infarct size and functional recovery status at 3 months.

Out of a total of 443 patients randomized during initial ambulance transfer, 24% were found to have a nonstroke diagnosis, while other patients were excluded from the final follow-up cohorts due to self-resolving transient ischemic attacks (TIA) or evidence of an intracranial hemorrhage on neuroimaging, making them unsuitable for thrombolysis. In total, 91 patients completed follow-up as per protocol in the conditioning group, with 80 receiving standard therapy without conditioning in the control group.

Overall, there was no significant difference in the primary end point between the two groups, as they had similar penumbral salvage levels, final infarct size, and infarct growth over time. Interestingly, however, patients in the conditioning group had lower National Institutes of Health Stroke Scale scores on initial hospital assessment and higher rates of TIA than the control group, as well as having a tendency toward smaller perfusion defects and milder diffusion weighted-imaging changes on their initial studies, although neither of these parameters reached significance. While speculative, these changes may suggest that conditioning is not only acting on the reperfusion phase of injury, but also in limiting the initial ischemic injury, as less patients in the intervention group required reperfusion therapy on arrival than in the controls. Using modeling to determine the effect of conditioning on tissue infarct risk, there was a highly significant difference between the intervention and control groups (P=0.0003) as pertains to infarct risk.

The results of this small, initial study hold some promise for future clinical gains in stroke treatment, where even minor changes may result in huge functional gains in quality of life for patients and caregivers.
Remote ischemic conditioning enhanced the early recovery of renal function in recipients after kidney transplantation: a randomized controlled trial


J Surg Res. 2014;188:303-308

Organ transplantation represents one of the most remarkable advances in the whole of human medicine and provides patients with nearly indescribable benefits in terms of quality of life and functional status. Transplant medicine is now globally well established with ever-increasing demands for organ donation leading to increasing work on how to utilize organs that are more marginal without compromising donor outcomes. One possible, and increasingly common, venue is to utilize organs from donors who have already suffered cardiac death in patients due to receive a renal transplant. Due to the inevitably prolonged ischemic time associated with a nonbeating heart donation, concerns remain about problems with delayed graft function, acute rejection episodes, problems with chronic fibrosis, and eventual graft loss, all of which have been associated with the initial ischemic injury experienced by the organ.

In this study on 48 kidneys transplanted from 24 nonbeating heart donors into 48 recipients, one individual from each paired donation was randomized to a preconditioning protocol consisting of three 5-minute cycles of ischemia and reperfusion achieved by cross-clamping the exposed external iliac artery during the transplant procedure or a control group. The primary outcome measures were indices of graft function and evidence of acute rejection as evidenced by renal biopsy and clinical criteria.

In patients randomized to ischemic conditioning, serum creatinine was consistently lower, estimated glomerular filtration rate (eGFR) consistently higher ($P<0.01$ for both), and urinary neutrophil gelatinase–associated lipocalin (NGAL) levels consistently lower ($P<0.05$) during the first week after transplantation, attesting to an improvement in graft function as compared with controls. No significant episodes of acute rejection were experienced during the study and there were no significant differences found on routine biopsy samples. There were no safety concerns associated with the conditioning protocol and no difference in postoperative adverse events between the two groups.

This promising proof-of-concept study suggests improvement in graft function associated with ischemic conditioning in the recipients of renal transplants. Whether this small, initial gain will translate into long-term improvements in graft survival remains unclear, and this will require long-term follow-up and much larger patient numbers.

As with so many initial studies, ischemic conditioning appears to display promising early effects in attenuating ischemia-reperfusion injury with surrogate markers of patient health, demonstrating favorable profiles in the intervention group. However, for the paradigm of conditioning as a whole, the real questions about patient outcomes and tangible clinical benefits remain unanswered. Now, the primary challenge and goal for the community of physicians and researchers who have devoted such time and resources in pursuit of this most enticing of interventions is to find answers to these questions.

The most severe Ebola virus epidemic in West Africa occurs, infecting over 23 000 people and killing at least 9000 people; a tiny fragment of zircon dating back 4.4 billion years is confirmed to be the oldest known piece of Earth’s crust; and the Catholic Church simultaneously canonizes Pope Saint John XXIII and Pope John Paul II
Remote Ischemic Conditioning

Bibliography of One Hundred Key Papers

selected by Rajesh K. Kharbanda, MBChB, PhD, MRCP¹;
Andrew N. Redington, MB, BS, MRCP, MD, FRCP²

¹Oxford University Hospitals NHS Trust - Department of Cardiology - Oxford - UK
²Cincinnati Children’s Hospital - Medical Center - Cincinnati - USA
(e-mail: rajesh.kharbanda@ouh.nhs.uk)

Effect of remote ischemic preconditioning on serum troponin T level following elective percutaneous coronary intervention.

Ali N, Rizwi F, Iqbal A, Rashid A.
Induced remote ischemic pre-conditioning on ischemia-reperfusion injury in patients undergoing coronary artery bypass.

Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial.

Bailey TG, Birk GK, Cable NT, et al.
Remote ischemic preconditioning prevents reduction in brachial artery flow-mediated dilation after strenuous exercise.

Barbosa TC, Machado AC, Braz ID, et al.
Remote ischemic preconditioning delays fatigue development during handgrip exercise.

Basalay M, Barsukeyevich V, Mastitskaya S, et al.
Remote ischaemic pre- and delayed postconditioning—similar degree of cardioprotection but distinct mechanisms.

Remote ischemia conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial.

Effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomised controlled clinical trial.
Heart. 2015;101:185-192.

Cheung MM, Kharbanda RK, Konstantinov IE, et al.
Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans.

Effect of remote ischemic preconditioning on renal dysfunction after complex valvular heart surgery: a randomized controlled trial.


<table>
<thead>
<tr>
<th>Bibliography of One Hundred Key Papers</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clinics (Sao Paulo).</em> 2013;68:495-499.</td>
</tr>
<tr>
<td><strong>Saxena P, Shaw OM, Misso NL, et al.</strong></td>
</tr>
<tr>
<td><strong>Schmidt MR, Smerup M, Konstantinov IE, et al.</strong></td>
</tr>
<tr>
<td><strong>Schmidt MR, Stottrup NB, Contractor H, et al.</strong></td>
</tr>
<tr>
<td><strong>Schmidt MR, Stottrup NB, Michelsen MM, et al.</strong></td>
</tr>
<tr>
<td><strong>Shimizu M, Tropak M, Diaz RJ, et al.</strong></td>
</tr>
<tr>
<td><strong>Sloth AD, Schmidt MR, Munk K, et al; CONDI Investigators.</strong></td>
</tr>
<tr>
<td><em>Eur Heart J.</em> 2014;35:168-175.</td>
</tr>
<tr>
<td><strong>Stazi A, Scalone G, Laurito M, et al.</strong></td>
</tr>
<tr>
<td><em>Circulation.</em> 2014;129:11-17.</td>
</tr>
<tr>
<td><strong>Tamareille S, Mateus V, Ghaboura N, et al.</strong></td>
</tr>
<tr>
<td><em>Basic Res Cardiol.</em> 2011;106:1329-1339.</td>
</tr>
<tr>
<td>Author(s)</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Authors</td>
</tr>
<tr>
<td>----------------------------------------------</td>
</tr>
</tbody>
</table>
Remote Ischemic Conditioning

Aims & Scope
Dialogues in Cardiovascular Medicine is a peer-reviewed, quarterly journal for cardiologists and physicians with an interest in cardiology. In order to promote in-depth understanding of the current body of knowledge on a specific area of cardiovascular medicine, each issue aims to provide a comprehensive analysis of a single topic. The Lead Article explores each topic in concise detail. Three pressing questions that dominate the field are identified and given personal replies by undisputed authorities in the Expert Answers section. The Summaries of Ten Seminal Papers put the topic into historical perspective. The Fascinomata Cardiologica section takes a thought-provoking and at times unconventional approach to cardiology from a variety of vantage points. Finally, a selected Bibliography of One Hundred Key Papers is available for those readers who wish to undertake a more exhaustive investigation of the topic. Dialogues offers unique coverage of the state of the art in clinical cardiology. The journal is selected for medical libraries and is a part of the continuing medical education program of several major international cardiological societies.

Volume 19 - Number 4

Dialogues in Cardiovascular Medicine

Published 4 times a year by:
Institut La Conférence Hippocrate (AICHI)
50 rue Carnot
92284 Suresnes Cedex
FRANCE
Tel: +33 (0)1 55 72 60 00
Fax: +33 (0)1 55 72 68 88
Permissions
Tel: +33 (0)1 55 72 61 17
Fax: +33 (0)1 55 72 35 04
E-mail: david.mason@fr.netgrs.com

Editorial Offices
Roberto Ferrari
(Academic Assistant: Mrs Juliette Verri)
Azienda Ospedaliero - Universitaria di Ferrara
Ospedale di Cone - 2/C3 - Via Aldo Moro 8
44124 Cone (Ferrara) - ITALY
Tel: +39 (0)53 2 23 9882 / Fax: +39 (0)53 2 23 7841
E-mail: fri@unife.it

Kim Fox
(Academic Assistant: Ms Deborah Curcher)
National Heart and Lung Institute
Institute of Cardiovascular Medicine and Science
Royal Brompton Hospital
London SW7 2AZ - UK
Tel: +44 (0)20 7351 8626
E-mail: D.Curcher@rbht.nhs.uk

Publication Director / Directeur de la Publication
Laurence Allès, Pharm D
Suresnes, FRANCE
Tel: +33 (0)1 55 72 68 89
Fax: +33 (0)1 55 72 60 01
E-mail: david.mason@fr.netgrs.com

www.dialogues-cvm.org

Indexed in: EBSCO, Scopus, PASCAL/EMBASE

Forthcoming Issue
Acute Heart Failure: the Heart Failure Patient’s Journey—the Vulnerable Phase

Dialogues in Cardiovascular Medicine is a peer-reviewed, quarterly journal for cardiologists and physicians with an interest in cardiology. In order to promote in-depth understanding of the current body of knowledge on a specific area of cardiovascular medicine, each issue aims to provide a comprehensive analysis of a single topic. The Lead Article explores each topic in concise detail. Three pressing questions that dominate the field are identified and given personal replies by undisputed authorities in the Expert Answers section. The Summaries of Ten Seminal Papers put the topic into historical perspective. The Fascinomata Cardiologica section takes a thought-provoking and at times unconventional approach to cardiology from a variety of vantage points. Finally, a selected Bibliography of One Hundred Key Papers is available for those readers who wish to undertake a more exhaustive investigation of the topic. Dialogues offers unique coverage of the state of the art in clinical cardiology. The journal is selected for medical libraries and is a part of the continuing medical education program of several major international cardiological societies.

Indexed in: EBSCO, Scopus, PASCAL/EMBASE

Subscriptions
Orders can be placed directly with the publisher

www.dialogues-cvm.org