Time to Give Up on Cardioprotection?
A Critical Appraisal of Clinical Studies on Ischemic Pre-, Post-, and Remote Conditioning*

Gerd Heusch, Tienush Rassaf

Abstract: The mortality from acute myocardial infarction (AMI) remains significant, and the prevalence of post-myocardial infarction heart failure is increasing. Therefore, cardioprotection beyond timely reperfusion is needed. Conditioning procedures are the most powerful cardioprotective interventions in animal experiments. However, ischemic preconditioning cannot be used to reduce infarct size in patients with AMI because its occurrence is not predictable; several studies in patients undergoing surgical coronary revascularization report reduced release of creatine kinase and troponin. Ischemic postconditioning reduces infarct size in most, but not all, studies in patients undergoing interventional reperfusion of AMI, but may require direct stenting and exclusion of patients with >6 hours of symptom onset to protect. Remote ischemic conditioning reduces infarct size in patients undergoing interventional reperfusion of AMI, elective percutaneous or surgical coronary revascularization, and other cardiovascular surgery in many, but not in all, studies. Adequate dose-finding phase II studies do not exist. There are only 2 phase III trials, both on remote ischemic conditioning in patients undergoing cardiovascular surgery, both with neutral results in terms of infarct size and clinical outcome, but also both with major problems in trial design. We discuss the difficulties in translation of cardioprotection from animal experiments and proof-of-concept trials to clinical practice. Given that most studies on ischemic postconditioning and all studies on remote ischemic preconditioning in patients with AMI reported reduced infarct size, it would be premature to give up on cardioprotection. (Circ Res. 2016;119:676-695. DOI: 10.1161/CIRCRESAHA.116.308736.)

Key Words: myocardial ischemia ■ postconditioning ■ preconditioning ■ reperfusion ■ reperfusion injury

Both the incidence of acute ST-segment–elevation myocardial infarction (STEMI) and the mortality from STEMI have decreased over the last 3 decades.1–3 However, despite the success of reperfusion therapy by primary percutaneous coronary intervention (PCI) or thrombolysis, STEMI is still of significant concern. Although door-to-balloon time for primary PCI has declined, mortality has not, possibly because of an increasing number of older and sicker patients.4,5 Also, patients who survive an acute myocardial infarction (AMI) often develop heart failure, and the prevalence of heart failure is increasing in developed countries.3,6 Infarct size is the major determinant of patients’ outcome.7–9 Clearly, timely and complete reperfusion is the most effective way to limit infarct size. However, reperfusion also adds an additional reperfusion injury on top of ischemic injury, and it, thus, contributes to infarct size.10–12 Therefore, additional interventions and treatments on top of timely reperfusion are still needed to reduce infarct size and improve the clinical outcome of patients with AMI.13–20

Apart from acute STEMI (type 1 myocardial infarction), additional cardioprotection is also sought in elective PCI with the aim to reduce periprocedural myocardial infarction (type 4a) and in surgical coronary revascularization with the aim to reduce perioperative myocardial infarction (type 5).21 In some studies, cardioprotection was also sought in major cardiovascular surgery other than coronary artery bypass grafting (CABG).

In the animal experiment, the conditioning phenomena are the most powerful cardioprotective, that is, infarct size reducing interventions. Ischemic preconditioning describes brief episodes of myocardial ischemia/reperfusion before the sustained coronary occlusion that results in infarction.22,23 Ischemic postconditioning describes brief episodes of coronary reocclusion/reperfusion in the immediate reperfusion phase after a sustained coronary occlusion that results in infarction.22,23 Remote ischemic conditioning describes brief episodes of ischemia/reperfusion of an organ or tissue remote from the heart; these episodes of distant ischemia/reperfusion can precede (preconditioning), follow (postconditioning), or occur in parallel (perconditioning) to the sustained coronary occlusion that causes the infarction.26 The most
robust end point of protection by the conditioning phenomena is a reduction of infarct size. All forms of conditioning are operative only when there is eventual reperfusion and do not protect with permanent coronary occlusion. The conditioning phenomena protect not only the myocardium but also the coronary microcirculation from ischemia/reperfusion injury.

The pathomechanisms of myocardial ischemia/reperfusion injury have been reviewed in detail elsewhere. Briefly, cell death arises from necrosis, apoptosis, necroptosis, and autophagy; ischemic injury is exacerbated by reperfusion. Cardiomyocyte calcium overload and oscillatory release/reuptake of calcium from the sarcoplasmic reticulum result in uncoordinated and excessive myofiber contractions. Digestion of sarcolemma and cytoskeleton by calpain and other enzyme activation, and the mitochondria as end-effectors. Inhibition of mitochondrial permeability transition pore opening is a key effect of all conditioning phenomena. There are also numerous attempts to use single signaling molecules of the conditioning phenomena as drugs or drug targets to achieve cardioprotection. Although the intracardiac signal transduction of the conditioning phenomena seems largely similar, the transfer factor(s) from the distant organ or tissue to the heart in remote ischemic conditioning is/are still enigmatic, but seem(s) to involve both neuronal and humoral signaling. There are obvious species differences in the signal transduction of the conditioning phenomena, and only little information is available on the signal transduction in the human heart: protein kinase C, the reperfusion injury salvage kinase pathway, and the signal transducer and activator of transcription 5 and the mitochondria seem to be involved.

The translation of cardioprotection by the conditioning phenomena and by drugs that recruit part of their signaling to the clinical arena has been difficult to date. Although there are several positive proof-of-concept studies for each of the conditioning phenomena, no phase III study has yet reported a better clinical outcome as the primary end point. With the neutral results of 2 recent phase III trial in cardiac patients, that is, ERICCA (Effect of Remote Ischemic Preconditioning on Clinical Outcomes in CABG Surgery) and RIPHeart (Remote Ischemic Preconditioning in Heart Surgery), and also a number of recent neutral trials which used drugs to recruit signaling steps of the conditioning phenomena in patients with AMI, that is, CIRCUS (Does Cyclosporine Improve Clinical Outcome in ST Segment Elevation Myocardial Infarction) and CYCLE (Cyclosporine A in Reperfused Myocardial Infarction), disappointment and frustration prevail.

We attempt to critically review the available clinical studies on the conditioning phenomena for their data on infarct size and clinical outcome and then go on to discuss potential problems for translation from experimental animal to human studies and from proof-of-concept human studies to phase III trials.

### Ischemic Preconditioning

Evidence for the existence of ischemic preconditioning in the human heart was derived initially from studies in patients undergoing elective PCI, which revealed attenuated ECG changes, less lactate release, and less creatine kinase release during a second as compared with the first coronary occlusion. Less pain was the reported clinical end point. There were then several smaller proof-of-concept studies on ischemic preconditioning in patients undergoing surgical revascularization by CABG or valve surgery. All of them used biomarker release (creatine kinase and troponin) to reflect myocardial injury. The study cohorts were only small, but most of these studies revealed an infarct size reduction, that is, less injury (Figure 1).
Some of these small studies looked at short-term clinical outcome as secondary end point, and either no effect or a reduction of postoperative arrhythmias, need for inotropic support, and intensive care unit stay were reported. Preinfarction angina may or may not be a correlate of ischemic preconditioning, but because of its nature, only retrospective associative analyses are available. Reduced infarct size and better clinical outcome, no change in infarct size and clinical outcome, or even worse clinical outcome were reported.

### Ischemic Postconditioning

The vast majority of studies on ischemic postconditioning protocols in patients with acute STEMI undergoing reperfusion by primary PCI revealed a reduction of infarct size using either biomarker (creatine kinase, creatine kinase–muscle brain, and troponin) release or imaging (magnetic resonance imaging and single photon emission computed tomography) techniques, and intensive care unit stay were reported (Table 1). Preinfarction angina may or may not be a correlate of ischemic preconditioning, but because of its nature, only retrospective associative analyses are available. Reduced infarct size and better clinical outcome, no change in infarct size and clinical outcome, or even worse clinical outcome were reported.

#### Remote Ischemic Conditioning

All studies that used an ischemic perconditioning protocol of repeated arm or leg ischemia/reperfusion in patients with acute STEMI found reduced infarct size, which was significant in most of them, no matter whether reperfusion was by primary PCI or thrombolysis and no matter whether biomarker release or imaging was used to assess infarct size. A retrospective analysis of the CONDI trial (Effect of Remote Ischemic Conditioning on Clinical Outcome in
STEMI Patients Undergoing Primary PCI) revealed also a decreased major adverse cardiac and cerebrovascular events rate at 5 years113 (Table 3).

A similar pattern with infarct size reduction in the majority but not all studies (with 2 small extreme outlier studies reporting even increased infarct size by remote ischemic preconditioning114,115) emerged for elective PCI when either remote ischemic preconditioning116–123 or postconditioning124,125 was used for cardioprotection. In some of these studies, clinical outcome was reported as a secondary outcome, and it was either not different106,119,124 or improved.115,116,126

The studies in patients either undergoing exclusively CABG or CABG with additional valve surgery were heterogeneous in their result. Only 2 studies, one of them with only 4 patients per group, reported an increased infarct size with remote ischemic preconditioning.127,128 Other studies were either neutral36,38,129–138 or had significantly reduced infarct size, as reflected by reduced biomarker release37,139–149 (Figure 3). Only one study each found improved clinical outcome at short-term149 or more long-term follow-up.138 However, one study with increased infarct size also found increased need for postoperative inotropic support and increased ventilation time128 (Table 3). Also, in adult cardiac valve surgery150–155 and in pediatric cardiac surgery,103,156–161 most studies found reduced infarct size, as reflected by reduced biomarker release (Figure 3). The need for inotropic support was reduced in some studies.103,154,156 Almost all studies that reported their anesthetic regime and did not observe reduced infarct size had used propofol in one or the other regime (Figure 3). In fact, propofol—in contrast to isoflurane—has been demonstrated to specifically abrogate the protection by remote ischemic preconditioning,162 and this finding has been confirmed by further studies153,163 and by a meta-analysis.164 A recent meta-analysis concluded that remote ischemic conditioning reduced infarct size significantly, and that also all-cause mortality and major adverse cardiac and cerebrovascular events rate were significantly reduced,165 but this meta-analysis did not include the

<table>
<thead>
<tr>
<th>Authors</th>
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<th>Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cremer et al46</td>
<td>7/7</td>
<td>CABG</td>
<td>Infarct size (CK-MB) ↓n.s.</td>
<td>Inotropic support ↑n.s.</td>
</tr>
<tr>
<td>Jenkins et al47</td>
<td>16/17</td>
<td>CABG</td>
<td>Infarct size (TnT) ↑*</td>
<td>Atrial fibrillation ↓n.s.</td>
</tr>
<tr>
<td>Kaukoranta et al48</td>
<td>15/15</td>
<td>CABG</td>
<td>Infarct size (CK-MB) ↑n.s.</td>
<td>Postoperative complications Ø</td>
</tr>
<tr>
<td>Illes and Swoyer49</td>
<td>34/36</td>
<td>CABG</td>
<td>Infarct size (CK-MB) ↑n.s.</td>
<td>Intensive care unit stay Ø</td>
</tr>
<tr>
<td>Wu et al52</td>
<td>20/20</td>
<td>CABG</td>
<td>Infarct size (CK-MB) ↑n.s.</td>
<td>Intensive care unit stay ↓</td>
</tr>
<tr>
<td>Teoh et al53</td>
<td>10/10</td>
<td>CABG</td>
<td>Infarct size (TnT) ↓*</td>
<td>Arrhythmias Ø</td>
</tr>
<tr>
<td>Teoh et al54</td>
<td>10/10</td>
<td>CABG</td>
<td>Infarct size (TnT) ↓*</td>
<td>Arrhythmias ↓n.s.</td>
</tr>
<tr>
<td>Buyukates et al55</td>
<td>10/10</td>
<td>CABG</td>
<td>Infarct size (CK-MB) ↓*</td>
<td>Hospital stay ↓</td>
</tr>
<tr>
<td>Codispoti et al56</td>
<td>26/26</td>
<td>CABG</td>
<td>Infarct size (TnI) ↓*</td>
<td>Intensive care unit stay Ø</td>
</tr>
<tr>
<td>Ji et al57</td>
<td>20/20</td>
<td>CABG</td>
<td>Infarct size (TnI) ↓*</td>
<td>Intensive care unit stay Ø</td>
</tr>
<tr>
<td>Amr et al58</td>
<td>15/15</td>
<td>CABG</td>
<td>Infarct size (TnI) ↓*</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Jebeli et al59</td>
<td>20/20</td>
<td>CABG</td>
<td>Infarct size (CK-MB) Ø</td>
<td>Inotropic support ↑*</td>
</tr>
<tr>
<td>Forouzannia et al61</td>
<td>20/20</td>
<td>OPCABG</td>
<td>Infarct size (TnI) ↑n.s.</td>
<td>Arrhythmias ↓n.s.</td>
</tr>
<tr>
<td>Li et al62</td>
<td>20/20</td>
<td>Cardiac surgery</td>
<td>Infarct size (CK-MB) ↓*</td>
<td>Arrhythmias ↑*</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; CK-MB, creatine kinase-muscle brain; n.s., nonsignificant; OPCABG, off-pump coronary artery bypass grafting; TnI, troponin I; and TnT, troponin T. ↑ indicates increased; ↓, decreased; and Ø, unchanged.

*Significant.
2 recent larger phase III trials. Associative studies of prior peripheral limb ischemia before an AMI revealed conflicting data, with either lower or higher postinfarct mortality.

**Translation From Experimental Animal Data to the Diseased Patient’s Heart**

**Species and Model Differences in the Manifestations of Myocardial Ischemia/Reperfusion Injury and in Signal Transduction**

Obviously, there is a species issue. The hearts of fruit flies and zebrafish are far away from the human heart. Even among mammalian hearts, those of rodents are further away from human hearts than those of larger mammals, not only in terms of heart rate and anatomy, but also in their cardio-protective signaling. The pig heart closely resembles the human heart in heart rate, myocardial and coronary anatomy, but—in contrast to the human heart—the coronary circulation constricts in response to acetylcholine and does not constrict in response to α-adrenergic activation. Dogs have an extensive innate collateral circulation, different from a healthy human heart but comparable to many human hearts with longstanding coronary atherosclerosis. Primate hearts have a surprising resistance to myocardial ischemia/reperfusion injury and develop much smaller infarcts after 90 minutes coronary occlusion than, for example, pigs. Also with respect to cardioprotective signaling both the reperfusion injury salvage kinase pathway and
the survivor activating factor enhancement pathway are important for cardioprotection in rodents, but only the survivor activating factor enhancement pathway seems to be cardioprotective in pigs. Whereas in the survivor activating factor enhancement pathway the signal transducer and activator of transcription 3 is a central element, it is signal transducer and activator of transcription 5 that is activated in the human heart by remote ischemic preconditioning. Thus, there is no single species that comes closest to the human heart in all important aspects related to myocardial ischemia/reperfusion. Experimental studies often use reductionist approaches, that is, isolated subcellular organelles (eg, mitochondria), isolated cultured or fresh cardiomyocytes, or isolated hearts, and on purpose exclude the multitude of hemodynamic and neurohumoral variables that determine cardiac function in situ.

### Lack of Comorbidities and Comedications in Animal Experiments

Apart from species differences and reductionist approaches in experimental studies, experiments are usually performed in young and healthy animals, whereas patients with coronary artery disease are of advanced age, have several comorbidities, and take several medications. Aging per se attenuates cardioprotective signaling, although in 2 retrospective analyses for confounders, protection by remote ischemic preconditioning was seen in all age cohorts of patients undergoing surgical coronary revascularization and protection by remote ischemic preconditioning was seen in all age cohorts of patients undergoing surgical coronary revascularization.

### Table 2. Clinical Outcome in Studies on Ischemic Postconditioning

<table>
<thead>
<tr>
<th>Authors</th>
<th>Acronym</th>
<th>Placebo/Intervention</th>
<th>Scenario</th>
<th>Primary End Point</th>
<th>Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lonborg et al</td>
<td>43/43</td>
<td>STEMI</td>
<td>Myocardial salvage at 3 mo (MRI)</td>
<td>↑</td>
<td>No. of patients developing heart failure at 3 mo</td>
</tr>
<tr>
<td>Tarantini et al</td>
<td>38/37</td>
<td>STEMI</td>
<td>Infarct size (MRI)</td>
<td>↑</td>
<td>MACE over 6 mo</td>
</tr>
<tr>
<td>Hahn et al</td>
<td>350/350</td>
<td>STEMI</td>
<td>ST-segment−resolution</td>
<td>Ø</td>
<td>MACE over 1 mo</td>
</tr>
<tr>
<td>Limalanathan et al</td>
<td>119/113</td>
<td>STEMI</td>
<td>Infarct size (MRI)</td>
<td>Ø</td>
<td>Mortality at 4 mo</td>
</tr>
<tr>
<td>Luz et al</td>
<td>44/43</td>
<td>STEMI</td>
<td>Infarct size (TnI)</td>
<td>↑</td>
<td>New myocardial infarction or cardiac death at 14 mo</td>
</tr>
<tr>
<td>Eitel et al</td>
<td>168/181</td>
<td>STEMI</td>
<td>Myocardial salvage within 3 days (MRI)</td>
<td>↑</td>
<td>Combined death, reinfarction, new heart failure within 6 mo</td>
</tr>
<tr>
<td>Durdu et al</td>
<td>40/39</td>
<td>CABG</td>
<td>Infarct size (CK-MB)</td>
<td>↑</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Luo et al</td>
<td>25/25</td>
<td>Valve surgery</td>
<td>Infarct size (CK-MB)</td>
<td>↑</td>
<td>Intensive care unit stay</td>
</tr>
<tr>
<td>Luo et al</td>
<td>20/20</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (TnI)</td>
<td>↓</td>
<td>Intensive care unit stay</td>
</tr>
<tr>
<td>Luo et al</td>
<td>20/20</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (TnI)</td>
<td>↓</td>
<td>Hospital stay</td>
</tr>
<tr>
<td>Li et al</td>
<td>51/48</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (TnI)</td>
<td>↓</td>
<td>Intensive care unit stay</td>
</tr>
<tr>
<td>Ji et al</td>
<td>39/41</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (TnI)</td>
<td>↓</td>
<td>Hospital stay</td>
</tr>
<tr>
<td>Luo et al</td>
<td>20/20</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (TnI)</td>
<td>↓</td>
<td>Intensive care unit stay</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CK-MB, creatine kinase–muscle brain; MRI, magnetic resonance imaging; n.s., nonsignificant; STEMI, ST-segment–elevation myocardial infarction; TnI, troponin I; and TnT, troponin T. ↑ indicates increased; ↓ decreased; and Ø, unchanged.

*Significant.
### Remote ischemic conditioning

#### Authors
- Betker (2010)
- Munk et al. (2010)
- Rentournas (2010)
- Crimi (2013)
- Prunier (2014)
- Eitel (2015)
- White (2015)
- Iliodromitis (2006)
- Hoole (2009)
- Ghaemian (2012)
- Ahmed (2013)
- Carrasco-Chinchilla (2013)
- Luo (2013)
- Prasad (2013)
- Lavi (2014)
- Xu (2014)
- Zografos (2014)
- Lanza (2015)

#### Scenario
- STEMI
- elective PCI

#### Protocol
- con 4 x 5/5 min A
- post 3 x 5/5 min L
- late pre 3 x 5/5 min A
- pre 3 x 5/5 min A
- pre 3 x 5/5 min L
- pre 1 x 5/1 min A
- pre 3 x 5/5 min A

#### Method
- SPECT
- TnI
- CK-MB
- MRI
- hsTnI
- hscTnI
- PLA/RIC
- PLA/RIC
- PLA/RIC

#### Acronym
- CONDI
- RIPS-T-MI
- LIPSIA CONDITIONING
- ERIC-LYSIS
- ERICCA
- RIPHEART
- REMOTE IMPACT

#### Placebo
- p<0.05
- p<0.05
- p<0.05

#### Figure 3. (Continued)
Cardiac surgery

Protocol
pre 3 x 5/5 min A
pre 3 x 5/5 min L
pre 3 x 5/5 min L
pre 3 x 5/5 min A
pre 3 x 5/5 min L
pre 3 x 5/5 min A
pre 4 x 5/5 min L
late+pre 3 x 5/5 min A
pre 3 x 5/5 min L
pre 4 x 5/5 min L
pre 4 x 5/5 min L
pre 4 x 5/5 min L
pre 4 x 5/5 min L

Method
TnI
TnI
TnI
TnI
TnI
TnI
TnI
CK-MB
TnI
TnI
TnI
TnI
TnI
TnI

Authors
Li (2010)
Wu (2011)
Wu (2011)
Xie (2012)
Bautin (2014)
Hu (2016)
Pinaud (2016)
Cheung (2006)
Zhou (2010)
Luo (2011)
Lee (2012)
Pavione (2012)
Jones (2013)
Pepe (2013)

Figure 3 Continued. Forest plot of clinical studies on remote ischemic conditioning with infarct size as end point. The zero represents the mean value, and the gray bars represent the standard error of the mean for the placebo group. Closed squares represent significantly reduced infarct size (means±SEM), and open squares represent nonsignificant changes. A indicates arm; CABG, coronary artery bypass grafting; ch., children; CK-MB, creatine kinase–muscle brain; hs-TnI, high-sensitivity troponin I; L, leg; MRI, magnetic resonance imaging; n.a., not available; P, propofol; per, perconditioning; post, postconditioning; pre, preconditioning; PCI, percutaneous coronary intervention; PLA, placebo group; RIC, remote ischemic conditioning group; SPECT, single photon emission computed tomography; TnI, troponin I; and TnT, troponin T.

Remote ischemic conditioning

in all age cohorts of patients with acute STEMI undergoing primary PCI. However, patients with coronary artery disease have also been exposed to risk factors and comorbidities that increase the sensitivity to myocardial ischemia/reperfusion injury and attenuate cardioprotective signaling, such as hypertension, hypercholesterolemia and diabetes mellitus. Patients with coronary artery disease have endothelial dysfunction. The endothelium, however, is important in mediating the cardioprotective effect of remote ischemic conditioning. The diseased coronary circulation with atherosclerotic plaques in the epicardial arteries and microvascular dysfunction is more susceptible to myocardial ischemia/reperfusion and possibly contributes to such injury, but may also have triggered the development of a collateral circulation which may protect from myocardial ischemia/reperfusion injury. Most of the above studies have not taken age or the confounding risk factors and comorbidities into consideration, although some of them excluded patients with diabetes mellitus or with an angiographically visible collateral circulation. However, in a recent retrospective analysis for confounders, risk factors and diabetes mellitus did not interfere with protection by remote ischemic preconditioning in patients with AMI. Apart from and in addition to comorbidities, medications are significant confounders of cardioprotection, either because they induce cardioprotection per se and leave less room for protection by a conditioning intervention or because they interfere with the signal transduction of a conditioning intervention. Statins not only reduce myocardial ischemia/reperfusion injury per se, but may—with chronic use—also interfere with cardioprotective signaling. However, in a recent retrospective analysis for confounders, statin use even facilitated protection by remote ischemic perconditioning in patients with AMI. The same may be true for β-blockade, specifically for metoprolol, but β-blockade may also abrogate the protection by conditioning interventions. Calcium antagonist pretreatment is associated with cardioprotection, but calcium antagonists seem not to interfere with conditioning. In antidiabetic treatment, there are the sulfonylureas that interfere with cardioprotective signaling because they inhibit ATP-dependent potassium channel activation, whereas some glitazones and the glucagon-like peptide 1 analog exenatide, and some dipeptidyl peptidase 4 inhibitors protect per se. Only high-dose aspirin that blocks both cyclooxygenase 1 and 2 seems to interfere with cardioprotection. While a patient with coronary artery disease who suffers an AMI or undergoes a cardiovascular intervention will likely have one or more of the above drugs on board, nitrates, opioids, and purinergic receptor 2Y12 (P2Y12) antagonists would be administered acutely to induce coronary vasodilation and control blood pressure, to reduce pain, and to inhibit platelet aggregation. Although chronic nitrate use and nitrate tolerance abrogate protection by conditioning interventions, the acute use
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<th>Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bøtker et al106 and Sloth et al113</td>
<td>CONDI</td>
<td>69/73 STEMI</td>
<td></td>
<td>Myocardial salvage ↑*</td>
<td>MACE at 30 days Ø</td>
</tr>
<tr>
<td>Hoole et al116 and Davies et al126</td>
<td>CRISP</td>
<td>98/104 Elective PCI</td>
<td></td>
<td>Infarct size (TnI) ↓*</td>
<td>MACCE at 6 mo ↓*</td>
</tr>
<tr>
<td>Ghaemian et al115</td>
<td>Stent</td>
<td>40/40 Elective PCI</td>
<td></td>
<td>Infarct size (TnT) ↑*</td>
<td>Chest pain ↓*</td>
</tr>
<tr>
<td>Carrasco-Chinchilla et al124</td>
<td></td>
<td>118/114 Elective PCI</td>
<td></td>
<td>Infarct size (CK-MB) ↓*</td>
<td>MACCE at 1 y Ø</td>
</tr>
<tr>
<td>Praed et al118</td>
<td></td>
<td>48/47 Elective PCI</td>
<td></td>
<td>Infarct size (TnT) ↑↓*</td>
<td>Composite of death, infarction, revascularization Ø</td>
</tr>
<tr>
<td>Liu et al129</td>
<td></td>
<td>102/98 Elective PCI</td>
<td></td>
<td>Infarct size (CK-MB) ↓*</td>
<td>Composite of death, hospital admission with UA/ACS, infarction, heart failure, stroke at 6 mo ↓*</td>
</tr>
<tr>
<td>Rahman et al120</td>
<td></td>
<td>82/80 CABG</td>
<td></td>
<td>Infarct size (TnT) ↑↓*</td>
<td>Mortality 30 days Ø</td>
</tr>
<tr>
<td>Karuppasamy et al121</td>
<td></td>
<td>27/27 CABG</td>
<td></td>
<td>Infarct size (TnI) Ø</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Hong et al141</td>
<td></td>
<td>35/35 RIC+RIPost</td>
<td></td>
<td>Infarct size (TnI) ↓*</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Lomivorotov et al132</td>
<td></td>
<td>40/40 CABG</td>
<td></td>
<td>Infarct size (TnI) Ø</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Lucchinetti et al133</td>
<td></td>
<td>28/27 CABG</td>
<td></td>
<td>Infarct size (hsTnT AUC) ↑↓*</td>
<td>Postoperative complications Ø</td>
</tr>
<tr>
<td>Saxena et al140</td>
<td></td>
<td>15/15 CABG</td>
<td></td>
<td>Infarct size (TnI) ↑*</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Ahmad et al134</td>
<td></td>
<td>32/35 CABG</td>
<td></td>
<td>Infarct size (CK-MB) Ø</td>
<td>Postoperative complications Ø</td>
</tr>
<tr>
<td>Slagsvold et al136</td>
<td></td>
<td>30/30 CABG</td>
<td></td>
<td>Infarct size (TnT) ↑↓*</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Choi et al146</td>
<td></td>
<td>38/80 CABG+cardiac surgery</td>
<td></td>
<td>Acute kidney injury Ø</td>
<td>Infarct size (CK-MB) ↓*</td>
</tr>
<tr>
<td>Young et al128</td>
<td></td>
<td>48/48 CABG+cardiac surgery</td>
<td></td>
<td>Infarct size (hsTnT) ↑↓*</td>
<td>Ventilation time ↑*</td>
</tr>
<tr>
<td>Meybohm et al135</td>
<td></td>
<td>90/90 CABG+cardiac surgery</td>
<td></td>
<td>Neurocognitive dysfunction Ø</td>
<td>Intensive care unit stay ↓*</td>
</tr>
<tr>
<td>Thielmann et al144</td>
<td></td>
<td>167/162 CABG+cardiac surgery</td>
<td></td>
<td>Infarct size (TnI) ↑*</td>
<td>Hospital stay j.n.s.</td>
</tr>
<tr>
<td>Cabrera-Fuentes et al138</td>
<td></td>
<td>6/6 CABG+cardiac surgery</td>
<td></td>
<td>Infarct size (TnI) ↑↓*</td>
<td>Mortality over 4 y ↓*</td>
</tr>
</tbody>
</table>

(Continued)
of nitrates during surgical coronary revascularization does not interfere with protection by remote ischemia preconditioning.219 Opioids are triggering molecules in ischemic preconditioning and remote postconditioning, 108,220–222 but there is no unequivocal evidence that acute opioid treatment reduces infarct size in patients (for review see Kleinbongard and Heusch30). A particular problem for the translation of cardioprotection by conditioning strategies may be the increasing use of novel and more potent P2Y12 antagonists which—Independently from their platelet inhibitory action—recruit signal transduction steps of conditioning223 and reduce infarct size per se.224–226

In conclusion, a multitude of potential reasons (species differences, reductionist models, aging, comorbidities, and comedications) and their combination easily explain why data from experimental animals cannot be readily translated to use in patients having an AMI or undergoing a cardiovascular intervention.

### Table 3. Continued

<table>
<thead>
<tr>
<th>Authors</th>
<th>Acronym</th>
<th>Placebo/Intervention</th>
<th>Scenario</th>
<th>Primary End Point</th>
<th>Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candilio et al149</td>
<td>89/89</td>
<td>CABG+cardiac surgery</td>
<td>Infarct size (hsTnT AUC) ↓*</td>
<td>Composite of death, infarction, stroke, or revascularization at 6 wk n.s.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensive care unit stay ↓*</td>
<td>Atrial fibrillation ↓*</td>
</tr>
<tr>
<td>Gallagher et al137</td>
<td>43/43</td>
<td>CABG+cardiac surgery</td>
<td>Infarct size (TnT) ↑n.s.</td>
<td>Mortality at 30 days Ø</td>
<td>Inotropic support ↓*</td>
</tr>
<tr>
<td>Haussenloy et al227</td>
<td>801/811</td>
<td>CABG+cardiac surgery</td>
<td>MACCE within 12 mo ↓n.s.</td>
<td>hscTnl AUC ↓*</td>
<td></td>
</tr>
<tr>
<td>Meybohm et al150</td>
<td>693/692</td>
<td>CABG+cardiac surgery</td>
<td>Composite death, infarction, stroke, acute renal failure Ø</td>
<td>TnT at 6 h ↓n.s.</td>
<td></td>
</tr>
<tr>
<td>Walsh et al158</td>
<td>127/124</td>
<td>CABG+cardiac surgery</td>
<td>Infarct size (CK-MB) ↑n.s.</td>
<td>Mortality at 6 mo ↑n.s.</td>
<td>MACCE at 6 mo Ø</td>
</tr>
<tr>
<td>Li et al150</td>
<td>27/26</td>
<td>Cardiac surgery</td>
<td>Infarct size (Tnl) ↓n.s.</td>
<td>Intensive care unit stay Ø</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Hu et al154</td>
<td>100/101</td>
<td>Cardiac surgery</td>
<td>Infarct size (Tnl) ↓*</td>
<td>Intensive care unit stay Ø</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Pinaud et al155</td>
<td>49/50</td>
<td>Cardiac surgery</td>
<td>Infarct size (Tnl) ↑n.s.</td>
<td>Intensive care unit stay Ø</td>
<td>Ventilation time Ø</td>
</tr>
<tr>
<td>Cheung et al156</td>
<td>20/17</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (Tnl) ↓*</td>
<td>Inotropic support ↓*</td>
<td></td>
</tr>
<tr>
<td>Luo et al157</td>
<td>20/20</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (Tnl) ↓*</td>
<td>Inotropic support ↓*</td>
<td></td>
</tr>
<tr>
<td>Pavione et al159</td>
<td>10/12</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (Tnl) ↑n.s.</td>
<td>Intensive care unit stay Ø</td>
<td>Hospital stay Ø</td>
</tr>
<tr>
<td>Pepe et al161</td>
<td>20/20</td>
<td>Cardiac surgery/children</td>
<td>Infarct size (Tnl) ↓n.s.</td>
<td>Intensive care unit stay ↓n.s.</td>
<td>Hospital stay Ø</td>
</tr>
</tbody>
</table>
Translation From Proof-of-Concept Studies to Larger Trials With Clinical Outcome as End Point

Prerequisites to Demonstrate Effective Cardioprotection

The size of the area at risk and of the impending infarction is of major importance for the impact of any cardioprotective intervention on clinical outcome. Miura and Miki\textsuperscript{227} carefully reviewed clinical studies on infarct size limitation and concluded that for a meaningful reduction of mortality and post-myocardial infarction, heart failure infarct size had to be reduced to <20\% of the left ventricle. To achieve that in the quartile of patients with the most severe myocardial infarction and an area at risk between 28.5\% and 53\% of the left ventricle, the cardioprotective intervention would need to reduce infarct size from 75\% to <40\% of the area at risk. Several subsequent consensus papers\textsuperscript{3,19,228} agreed that patients with a large area at risk, notably those with an anterior infarction, would have the greatest benefit from cardioprotection and that trials with clinical outcome as end point should, therefore, focus only on these patients. For effective cardioprotection by ischemic postconditioning to become apparent, the coronary blood flow at admission must be of TIMI (Thrombolysis in Myocardial Infarction) grade 0 to 1, whereas with some spontaneous thrombolysis (TIMI 2–3), no further infarct size reduction is achieved,\textsuperscript{192} possibly as a result of preexisting protection by gentle reperfusion in both the placebo and the intervention groups.\textsuperscript{229} For that same reason, that is, to avoid partial preexisting reperfusion before opening of the culprit coronary occlusion primary PCI, patients with angiographically visible collaterals were excluded in the proof-of-concept studies on ischemic postconditioning.\textsuperscript{73,110,192} Finally, for effective cardioprotection to become apparent and clinically meaningful, there must be sufficient salvageable myocardium left, and the time from symptom onset to interventional reperfusion should be no longer than 2 to 4 hours.\textsuperscript{19,230,231} On the contrary, with a short duration of ischemia, all ischemic myocardium may be rescued by reperfusion per se, and an additional cardioprotection may be difficult to demonstrate.\textsuperscript{20,179,231} Also, with a short duration of ischemia, ischemic postconditioning may even add to myocardial injury.\textsuperscript{232}

Cardioprotection in Cardiovascular Surgery

Studies on conditioning in patients undergoing cardiovascular surgery are done for 2 different purposes: (1) to identify novel protective strategies for patients at high cardiovascular risk, and (2) to identify novel protective strategies for all patients having myocardial ischemia/reperfusion, notably myocardial infarction. The surgical setting with ischemic cardioplegic arrest then serves as a controlled scenario of myocardial ischemia/reperfusion. For patients at cardiac risk, volatile rather than intravenous anesthesia is recommended,\textsuperscript{233,234} and a background cardioprotection by volatile anesthesia per se and also by use of opioids\textsuperscript{235} must be taken into consideration. Also, cardiovascular surgery entails not only myocardial injury by ischemia/reperfusion but also by surgical trauma, which is also reflected in biomarker release. Peripheral trauma at the stimulus site can elicit a remote conditioning response much like peripheral ischemia/reperfusion,\textsuperscript{235,236} but the conditioning response does not protect from traumatic injury at the target organ. Because conditioning interventions protect only from ischemia/reperfusion injury but not from trauma, the traumatic component of injury dilutes the cardioprotective effects of conditioning. Protection by remote ischemic preconditioning\textsuperscript{219} and also protection by cyclosporine A\textsuperscript{237} become only apparent by reduced troponin release after CABG when cardiopulmonary bypass times are longer. Although further studies on protection of patients at high risk for ischemic events when undergoing cardiovascular surgery are certainly warranted, the setting of cardiovascular surgery is not well suited to resolve the fundamental question whether conditioning procedures can provide clinical benefit for patients with AMI. The myocardial injury from cardiovascular surgery is usually minor, and the protective management is good, whereas a large infarct size reduction is needed to improve outcome and prognosis in patients with AMI.\textsuperscript{227} Also, there are too many variables in a cardiosurgical setting that may dilute a cardioprotective effect of conditioning (anesthetic regime, surgical approach, cardioplegia/preservation technique, etc).

Lack of Phase II Studies

For none of the conditioning studies an adequate dose-finding phase II study exists. A few studies revealed that a stronger stimulus or the combination of 2 conditioning phenomena\textsuperscript{96} resulted in greater protection, as expected. However, a truly optimal stimulus has never been defined, and this is not a trivial issue. The optimal stimulus may depend on the patient cohort under study, that is, a stronger stimulus may be necessary to induce protection in, for example, diabetics.\textsuperscript{238} On the contrary, a stimulus can be too strong and protection be lost\textsuperscript{239–241} or even a state of hyperconditioning be induced with increased myocardial injury.\textsuperscript{232,242}

Current State of Translation for Ischemic Preconditioning

Because the occurrence of an AMI cannot be predicted, ischemic preconditioning cannot be used clinically to reduce infarct size. Therefore, attention has been shifted to ischemic postconditioning and remote ischemic conditioning. Also for cardiovascular surgery where ischemic preconditioning could possibly be used, remote ischemic conditioning is more attractive because it is equally protective as local ischemic conditioning and avoids the risks associated with coronary manipulation.

Current State of Translation for Ischemic Postconditioning

Studies with clinical outcome as the primary end point do not exist for ischemic pre- and postconditioning, and the patient cohorts of most studies reporting secondary clinical outcome data were small. The 3 trials on ischemic postconditioning with the largest patient cohorts were neutral with respect to infarct size and clinical outcome.\textsuperscript{30,34,96} With respect to the above criteria to identify a cardioprotective intervention, a straightforward explanation emerges: different from the original proof-of-concept studies of Ovize and
collaborators,73 either the time from symptom onset was longer, that is, within 12 hr90,96 rather than 6 hours, or no direct stenting was used.90,94 As outlined earlier, little protection is expected after 12 hours of coronary occlusion.19,20,230,231 Direct stenting avoids coronary microembolization and further myocardial injury by manipulation of the culprit coronary lesions,243 which may obscure the otherwise protective effect of ischemic postconditioning.796 The results of the phase III trial DANAMI 3-iPOST (Danish Study of Optimal Acute Treatment of Patients With ST-Segment–Elevation Myocardial Infarction–Ischemic Postconditioning) have not yet been published, but only presented orally at the meeting of the American College of Cardiology 2016 in Chicago. The primary end point of all-cause mortality and hospitalization for heart failure was not significantly reduced, but left ventricular ejection fraction was improved by ischemic postconditioning at 18 months follow-up. However, DANAMI 3-iPOST has several limitations: (1) no direct stenting, see above, (2) inclusion of patients with symptom onset within 12 hours before reperfusion, see above, (3) a weaker stimulus, that is, 4 cycles of 30 s reocclusion/30 s reperfusion rather than 4 cycles of 1 minute reocclusion/1 minute reperfusion in the positive proof-of-concept trials by Ovize and collaborators, and (4) a much lower event rate than assumed in the power analysis, such that the end point was analyzed after >2 rather than at 1 year, which obviously with increasing temporal distance from the intervention dilutes its potentially protective effect.

The reasons why the 2 larger phase III trials that attempted to postcondition the reperfused myocardium pharmacologically with cyclosporine A (a drug that inhibits mitochondrial permeability transition pore opening) have failed to see protection have been discussed in detail.20,244 Reasons include recruitment of patients long after symptom onset, use of different solvents, lack of direct stenting, and the increasing use of P2Y12 antagonists which protect per se.

**Current State of Translation for Remote Ischemic Conditioning**

There are only 2 trials on remote ischemic conditioning with clinical outcome as end point, that is, ERICCA and RIPHeart, both in patients undergoing cardiovascular surgery and both with a neutral outcome,37,38 in contrast to several prior139,148 and concomitantly49 smaller proof-of-concept studies in patients undergoing cardiovascular surgery. The potential reasons for this discrepancy have been discussed in detail.245-248 Importantly, both ERICCA and RIPHeart not only failed to find benefit from remote ischemic conditioning on mortality, myocardial infarction, and stroke at hospital discharge38 or after 12 months,37 but they also failed to see an acute benefit in terms of a reduction of troponin release, such that from the lack of an acute protection, no better clinical outcome was to be expected. The most likely reason for the failure to see protection in terms of troponin release and clinical outcome is the use of propofol anesthesia in 90% of ERICCA patients and all patients per-protocol in RIPHeart. Propofol is known to abrogate protection by remote ischemic conditioning, which is seen with volatile anesthesia,153,162-164 and volatile anesthesia is the recommended anesthesia for patients at cardiac risk.233,234 As seen from Figure 3, the only study with a significant increase of infarct size128 and all neutral studies where information on the anesthetic regime is available,186,188,130-133,135-138,150,155 had used propofol anesthesia, which, therefore, appears as the major denominator of all neutral/negative studies on remote ischemic conditioning in cardiovascular surgery.14 Specifically, Lucchini et al135 who claim that isoflurane induces cardioprotection per se and leaves no room for additional protection by remote ischemic conditioning used propofol for induction of anesthesia such that it is possible that, in fact, propofol abrogated protection by remote ischemic conditioning also in their study. A second problem with ERICCA and RIPHeart is the inclusion of many patients who not only underwent CABG but also more traumatic valve surgery such that the troponin release may reflect myocardial injury by ischemia/reperfusion and by trauma. However, remote ischemic preconditioning protects only from ischemia/reperfusion injury and not from traumatic injury at the target organ, and the protective effect on ischemia/reperfusion injury is then diluted. The discrepancy of the completed troponin data subset (significant reduction by remote ischemic preconditioning) and the extrapolated total cohort troponin data raises concern about the protocol adherence in the different participating ERICCA centers,37 whereas a contemporary study in the lead author’s institution also reported reduced troponin T and better short-term clinical outcome (less atrial fibrillation, kidney injury, and intensive care unit study).149

**Conclusions and Perspectives**

The majority of small proof-of-concept studies on ischemic pre-, post-, and remote ischemic conditioning are positive. Notably, all studies on remote ischemic conditioning in patients with STEMI reported an infant size reduction (Figure 3). However, not only were patient cohorts often small, but also surrogate end points (notably, infarct size) rather than clinical end points were assessed, and the positive results might reflect publication bias. The 3 studies on ischemic postconditioning with larger cohorts were neutral, but the observed lack of infarct size reduction may be the result of lack of direct stenting and of inclusion of patients with symptom onset within as long as 12 hours before reperfusion. Unfortunately, adequate dose-finding phase II studies do not exist at all. Currently, there are only 2 phase III studies in the entire conditioning field, both on remote ischemic preconditioning in cardiovascular surgery, both with neutral results, and both with major problems (use of propofol, mixture of traumatic and ischemia/reperfusion injury). Of note, both phase III studies explicitly reported no safety concerns. With this background, we think it would be premature to abandon conditioning and cardioprotective interventions. Importantly, there is still a need for further reduction of mortality and morbidity from AMI and also for better protection of patients at cardiac risk when they undergo major cardiovascular surgery. Of course, phase III trials with robust clinical outcome data are needed to prove cardioprotection by conditioning. However, although we appreciate the difficulties of recruiting patients for a phase III trial, we—at least
at this point—discourage an all-comer approach. In times of personalized medicine and to identify the ideal patient population and setup, it seems entirely appropriate to focus on patients with a larger anterior myocardial infarction who are reperfused within 6 hours from symptom onset and who are likely to have clinical benefit from the conditioning intervention. For all other patients with AMI, it is good enough that there are no safety concerns for conditioning interventions. Also, if it turns out that indeed direct stenting is a prerequisite for ischemic postconditioning to protect, whenever the coronary anatomy and interventional procedure permits, direct stenting should be kept in mind. Likewise, if protection by remote ischemic preconditioning during cardiovascular surgery requires the use of volatile anesthesia rather than propofol, why not use volatile anesthesia? As discussed in detail earlier, most of the studies performed to date are heterogeneous: use of (1) different clinical entities with different clinical protocols (CABG, CABG+valve surgery, cardiac surgery in children, STEMI, PCI), (2) different inclusion/exclusion criteria even for the same clinical entity and protocol, (3) different conditioning algorithms, and (4) different methods to measure infarct size (troponin I, troponin T, creatine kinase–muscle brain, single photon emission computed tomography, magnetic resonance imaging) have all contributed to the current uncertainty on the efficacy of conditioning procedures in clinical practice. It is most disconcerting that there are several consensus papers that highlight these problems with the existing studies on cardioprotection and make detailed recommendations on how an ideal study should be conducted, but then some of the authors of such consensus papers go on to publish studies that do not adhere to these recommendations.

Against the prevailing disappointment and frustration in the field of cardioprotection, we still see a future for cardioprotection in a more personalized medicine, and we encourage adequate more focused phase III studies. The ongoing CONDI 2/ERIC-PPCI study (Effect of Remote Ischemic Conditioning on Clinical Outcome in STEMI Patients Undergoing Primary PCI/Effect of Remote Ischemic Conditioning on Clinical Outcome in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) on remote ischemic preconditioning in patients with STEMI will possibly give us an answer, although again patients with symptom onset within as long as 12 hours before reperfusion, who are unlikely to have benefit, are included. In conclusion, it is not yet time to give up on cardioprotection by conditioning interventions.

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**Disclosures**

None.

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