

Mechanical interventions to reduce myocardial infarct size

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Abstract

Myocardial infarction is a major cause of death and disability worldwide, and myocardial infarct size is a principal determinant of outcome. Although early and successful restoration of myocardial reperfusion after an ischemic event is the most effective strategy to reduce infarct size and improve clinical outcome, reperfusion may itself induce further myocardial damage. Mechanical interventions may limit myocardial ischemia-reperfusion injury beyond opening of the coronary artery. Several types of mechanical intervention have had cardioprotective effects in experimental studies, but few have reduced infarct size in clinical trials to a convincing degree. Remote ischemic conditioning by three or four 5-minute inflations of a blood pressure cuff interrupted by 5 minutes of reperfusion has repeatedly been shown to reduce myocardial injury in patients admitted with myocardial infarction. Similarly, intravascular cooling by infusion of cold saline has been shown to afford some protection against myocardial ischemia-reperfusion injury. Both interventions can be carried out during transport to hospital for patients with acute myocardial infarction and may provide a prognostic benefit in this group of patients. ■ *Heart Metab.* 2016;70:8-13

Keywords: ischemic preconditioning; myocardial infarction; reperfusion injury

Myocardial infarction is a leading cause of death in its acute phase, but the long-term morbidity and mortality are also alarmingly high. The frequency and severity of the most detrimental early and late consequences of a myocardial infarction—heart failure and arrhythmia—are directly related to the extent of tissue death resulting from the index infarction.

While early and successful restoration of blood flow is the most effective strategy to reduce tissue injury and improve clinical outcome, the return of oxygen-

ated blood into oxygen-deprived tissue during restoration of blood flow paradoxically induces further tissue damage by reperfusion injury, which is the tissue damage that occurs when blood supply returns to the tissue after a period of ischemia or lack of oxygen. The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than immediate restoration of normal function. Reperfusion injury may be responsible for up to 35%

Abbreviations

CHILL-MI: Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction (trial); **CONDI2/ERIC-PPCI:** Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI (trial); **PCI:** percutaneous coronary intervention; **RAPID MI-ICE:** Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention; **RIC:** remote ischemic conditioning; **STEMI:** ST-segment elevation myocardial infarction

of the final infarct size. The shorter ischemia duration achieved with today's fast transfer to acute cardiac units, acute balloon angioplasty (primary percutaneous coronary intervention [PCI]) with stent implantation, and up-to-date antithrombotic pharmacological therapy has reduced immediate mortality dramatically. Still, morbidity, in particular due to postinfarction heart failure, remains unexpectedly high. Consequently, the focus in myocardial infarction treatment has now been directed toward reducing the reperfusion injury.

The term cardioprotection refers to interventions aimed at limiting the combined ischemia-reperfusion injury. Traditionally, cardioprotective strategies have been divided into pharmacological or mechanical ones, although recent evidence suggests that there is substantial overlap in the biological effects of the two. The current article focuses on mechanical cardioprotection, which covers all nonpharmacological interventions, spanning exercise to cutaneous electrostimulation and on to cooling and various concepts of ischemic conditioning. Below, we primarily focus on modalities with extensive experimental and clinical evidence of effect (Figure 1).

Local ischemic pre- and postconditioning

The best known and most extensively investigated mechanical method to induce cardioprotection is "training" the myocardium to withstand longer-lasting ischemia by exposing it to brief and nonlethal episodes of ischemia—local ischemic preconditioning.¹ Local ischemic preconditioning has long been known to afford potent protection against ischemia-reperfusion injury, but the technique has inherent limitations, as it requires interruption of blood flow to the target organ and, thus, can be achieved only in the

operating room or during coronary angioplasty. Furthermore, in unpredictable ischemia, such as acute myocardial infarction, local ischemic preconditioning is not feasible for obvious reasons and has not found widespread clinical use.

However, by applying the local ischemic conditioning stimulus *after* the ischemic event (eg, at the time of reperfusion in primary PCI)—so-called ischemic postconditioning—most of these obstacles for clinical use are overcome. In experimental models, ischemic postconditioning inhibits ischemia-reperfusion injury almost as effectively as ischemic preconditioning.² Some clinical studies suggest that local ischemic postconditioning reduces myocardial injury in patients undergoing primary PCI for acute myocardial infarction,^{3,4} but another recently published trial could not confirm this effect.⁵ Furthermore, two large-scale trials failed to show any effect on myocardial reperfusion and clinical end points.^{6,7} These two trials each included approximately 700 patients admitted with ST-segment elevation myocardial infarction (STEMI) randomized to either standard primary PCI or primary PCI followed by postconditioning,⁶ with one of the trials including a third group with a combination

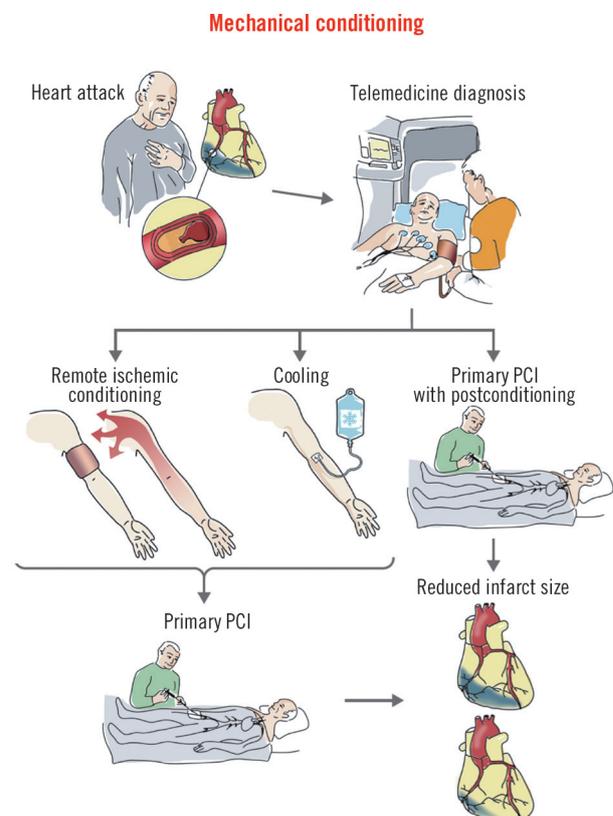


Fig. 1 Concepts of mechanical conditioning.

Abbreviations: PCI, percutaneous coronary intervention.

of remote ischemic conditioning (RIC) and postconditioning in addition to primary PCI.⁷

Remote ischemic conditioning

Based on the original groundbreaking observation of local ischemic preconditioning, the concept of conditioning the myocardium from afar (*remote* ischemic conditioning, RIC) was developed through a series of increasingly clinically applicable techniques culminating in the presently used concept of achieving organ protection by inducing brief episodes of limb ischemia⁸ with a blood-pressure cuff.

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 preconditioning. Furthermore, RIC modifies the systemic inflammatory response and prevents endothelial dysfunction⁸ and platelet activation⁹ after ischemia-reperfusion injury.

The simple and noninvasive nature of RIC has facilitated its translation into clinical use. Since the first demonstration of its effect in humans in 2002,⁸ multiple randomized clinical trials have shown that RIC affords cardioprotection in patients admitted with acute myocardial infarction treated by either primary PCI¹⁰⁻¹² or thrombolysis¹³ (*Table 1*). Moreover, a recent follow-up study by Sloth et al suggested that the reduced myocardial injury achieved by RIC treatment in the ambulance during transport to hospital of STEMI patients admitted for primary PCI may translate into improved clinical outcome.¹⁴ Although experimental evidence indicates that risk factors and comorbidity modify the efficacy of RIC, only minor attenuation by smoking and left ventricular hypertrophy has been demonstrated in the clinical use of RIC.¹⁵

To date, RIC is the most extensively investigated mechanical means to achieve cardioprotection and is the intervention showing the most consistent benefit. A large-scale clinical trial (CONDI2/ERIC-PPCI [Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI]) is currently investigating whether RIC provides clinical benefit to patients admitted with myocardial infarction.

Cooling

Moderate hypothermia induced prior to reperfusion may reduce infarct size in animal models.¹⁶ Important

prerequisites include a systemic rather than regional hypothermia and a target core temperature below 35°C achieved before onset of reperfusion.¹⁷ A clinical pilot study has suggested that patients admitted with anterior STEMI and 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 develop smaller infarcts.¹⁸

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 an overall cardioprotective effect, it seems to reduce infarct size in patients with anterior STEMI admitted for primary PCI within 4 hours of symptom onset. In addition, cooling caused a significant reduction in heart failure events.¹⁹ Possible explanations for an overall lack of cardioprotective effect in the CHILL-MI study are a borderline statistical power and that cooling below 35°C was not achieved in all patients. Consequently, recent studies have targeted optimizing methods for fast and reliable temperature reduction.

Even with the currently applied methods, cooling may be beneficial, as a prespecified pooled analysis of another cooling study—RAPID MI-ICE (Rapid Intravascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention)—and CHILL-MI indicated a reduction in myocardial infarct size and a reduction in heart failure with endovascular cooling in patients admitted with STEMI for primary PCI, predominantly in patients with a large area of myocardium at risk.²⁰

Exercise

Several preclinical and clinical studies have shown that exercise induces cardioprotection. Its relevance is limited in the setting of acute myocardial infarction. It is of interest, however, that mechanisms between RIC and exercise are overlapping. Both RIC and exercise induce dialyzable, bloodborne protection that can be abrogated by opioid receptor blockade (naloxone).²¹ Of note, RIC may also increase exercise capacity as shown in highly trained athletes, a concept that may have relevance in patients with post-infarction heart failure.²²

Effects of mechanical interventions on myocardial metabolism

The metabolic changes occurring in the myocardium during and after acute ischemia are described in a separate article in the current issue of *Heart and Metabolism*. Worth mentioning here is the interesting

observation that mechanical cardioprotection interventions seem at least in part to exert their cardioprotective effects by activating intracellular signaling pathways, including the endothelial nitric oxide synthase (eNOS)-related system—which is recruited immediately by adenosine, bradykinin, and opioids—the reperfusion injury salvage kinase (RISK) pathway, and

Remote ischemic conditioning

Study	No. of patients (control/RIC)	RIC regimen	End point	Outcome
Bøtker et al, ¹⁰ 2010	69/73	Upper limb 4 cycles I/R (5/5 min)	Salvage index (SPECT)	20% increase in salvage index
Munk et al, ²³ 2010	110/108	Upper limb 4 cycles I/R (5/5 min)	LVEF at 30 days	5% increase in LVEF in anterior infarcts
Rentoukas et al, ²⁴ 2010	30/33	Upper limb 3 cycles I/R (5/5 min)	ST-segment resolution	20% increase in proportion of patients achieving full ST-segment resolution
Crimi et al, ²⁵ 2013	50/50	Lower limb 3 cycles I/R (5/5 min)	CK-MB (AUC 72 h after PCI)	20% reduction in CK-MB release
Prunier et al, ¹² 2014	17/18	Upper limb 4 cycles I/R (5/5 min)	CK-MB (AUC 72 h after PCI)	31% reduction in CK-MB release
Sloth et al, ¹⁴ 2014	167/166	Upper limb 4 cycles I/R (5/5 min)	MACCE at 4 y	12% reduction in MACCE
Yellon et al, ¹³ 2015	260/260	Upper limb 4 cycles I/R (5/5 min)	TnT (AUC 24 h after PCI)	17% reduction in TnT release
Eitel et al, ⁷ 2015	232/232	Upper limb 3 cycles I/R (5/5 min) + local postC	Salvage index (MRI)	23% increase in salvage index
White et al, ²⁶ 2015	40/43	Upper limb 4 cycles I/R (5/5 min)	Myocardial edema (MRI)	27% reduction in myocardial edema

Ischemic postconditioning

Study	No. of patients (control/postC)	PostC regimen	End point	Outcome
Staat et al, ³ 2005	14/16	60 s x 4	CK (AUC 72 h)	36% decrease in CK
Sörensson et al, ²⁷ 2010	38/38	60 s x 4	CK (AUC 72 h)	No statistically significant effect
Lønborg et al, ⁴ 2010	59/59	30 s x 4	Infarct size (MRI)	31% increase in salvage ratio
Freixa et al, ⁵ 2012	40/38	60 s x 4	Infarct size (MRI)	No statistically significant effect
Hahn et al, ⁶ 2013	350/350	60 s x 4	ST-segment resolution	No statistically significant effect

Cooling

Study	No. of patients (control/cooling)	Cooling regimen	End point	Outcome
Dixon et al, ²⁸ 2002	21/21	Endovascular cooling	Infarct size (MRI)	No statistically significant effect
Erlinge et al, ¹⁹ 2014	59/61	IV cold saline	Infarct size (MRI)	No statistically significant effect
Erlinge et al, ²⁰ 2015	69/71	IV cold saline	Infarct size (MRI)	15% reduction in infarct size / area at risk
Nichol et al, ²⁹ 2015	26/28	Peritoneal cold saline	Infarct size (MRI)	No statistically significant effect

Table 1 Major studies of the effect of mechanical conditioning in patients with acute myocardial infarction admitted for primary percutaneous coronary intervention.

Abbreviations: AUC, area under the curve; CK-MB, creatine kinase MB; I/R, ischemia/reperfusion; IV, intravenous; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; postC, postconditioning; RIC, remote ischemic conditioning; SPECT, single-photon emission computed tomography; TnT, troponin T.

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the survivor activating factor enhancement (SAFE) pathway. These pathways ultimately converge at the mitochondrial level to modify mitochondrial function. Some evidence suggests that a temporary downregulation of mitochondrial function during initial reperfusion—including not only reduced respiration, but also reduced glycolytic flux—is associated with a subsequently improved mitochondrial respiration and a reduced reactive oxygen species formation. However, the exact interplay between modification of cytosol signaling pathways and simultaneous changes in mitochondrial function has yet to be integrated into a comprehensive scheme. Similarly, the causal relation to metabolic changes associated with mechanically induced cardioprotection is unknown. After the initial activation of anaerobic glycolysis with lactate production, persistent ischemia inhibits both glycolysis and glycogenolysis. Conditioning strategies accentuate this inhibition and also enhance postischemic glycogen resynthesis. A cardioprotective effect of the inhibited glycolysis by local ischemic preconditioning of hearts has been attributed to a reduction in ischemic tissue acidosis. Our previous finding that inhibition of the malate-aspartate shuttle reduces myocardial lactate accumulation during ischemia and tracer-estimated glycolytic flux during reperfusion to the same extent as classical ischemic preconditioning uncovers a potential underlying metabolic mechanism of cardioprotection that is also in accordance with an initial downregulation of mitochondrial function during initial reperfusion.³⁰

Conclusion

A wide array of mechanical interventions to reduce myocardial infarct size have shown consistent effects in experimental models, but so far only cooling and remote ischemic conditioning have shown convincing reduction in infarct size in a clinical setting. Currently, large trials are underway to elucidate the effect of RIC and cooling on clinical outcome in patients admitted with myocardial infarction. ■

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REFERENCES

1. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res.* 2015;116:674-699.
2. Zhao ZQ, Corvera JS, Halkos ME, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol.* 2003;285:H579-H588.
3. Staat P, Rioufol G, Piot C, et al. Postconditioning the human heart. *Circulation.* 2005;112:2143-2148.
4. Lønborg J, Kelbaek H, Vejstrup N, et al. Cardioprotective effects of ischemic postconditioning in patients treated with primary percutaneous coronary intervention, evaluated by magnetic resonance. *Circ Cardiovasc Interv.* 2010;3:34-41.
5. Freixa X, Bellera N, Ortiz-Perez JT, et al. Ischaemic postconditioning revisited: lack of effects on infarct size following primary percutaneous coronary intervention. *Eur Heart J.* 2012;33:103-112.
6. Hahn JY, Song YB, Kim EK, et al. Ischemic postconditioning during primary percutaneous coronary intervention: the effects of postconditioning on myocardial reperfusion in patients with ST-segment elevation myocardial infarction (POST) randomized trial. *Circulation.* 2013;128:1889-1896.
7. Eitel I, Stiermaier T, Rommel KP, et al. Cardioprotection by combined intrahospital remote ischaemic preconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial. *Eur Heart J.* 2015;36:3049-3057.
8. Kharbanda RK, Mortensen UM, White PA, et al. Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation.* 2002;106:2881-2883.
9. Pedersen CM, Cruden NL, Schmidt MR, et al. Remote ischemic preconditioning prevents systemic platelet activation associated with ischemia-reperfusion injury in humans. *J Thromb Haemost.* 2011;9:404-407.
10. Botker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010;375:727-734.
11. White SK, Frohlich GM, Sado DM, et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv.* 2015;8(1 pt B):178-188.
12. Prunier F, Angoulvant D, Saint Etienne C, et al. The RIPOST-MI study, assessing remote ischemic preconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction. *Basic Res Cardiol.* 2014;109:400.
13. Yellon DM, Ackbarkhan AK, Balgobin V, et al. Remote ischemic conditioning reduces myocardial infarct size in STEMI patients treated by thrombolysis. *J Am Coll Cardiol.* 2015;65:2764-2765.
14. Sloth AD, Schmidt MR, Munk K, et al. Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *Eur Heart J.* 2014;35:168-175.
15. Sloth AD, Schmidt MR, Munk K, et al. Impact of cardiovascular risk factors and medication use on the efficacy of remote ischaemic conditioning: post hoc subgroup analysis of a randomised controlled trial. *BMJ Open.* 2015;5:e006923.
16. Dave RH, Hale SL, Kloner RA. Hypothermic, closed circuit pericardioperfusion: a potential cardioprotective technique in acute regional ischemia. *J Am Coll Cardiol.* 1998;31:1667-1671.
17. Maeng M, Mortensen UM, Kristensen J, Kristiansen SB, Andersen HR. Hypothermia during reperfusion does not reduce myocardial infarct size in pigs. *Basic Res Cardiol.* 2006;101:61-68.
18. Gotberg M, Olivecrona GK, Koul S, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circ*

- Cardiovasc Interv.* 2010;3:400-407.
19. Erlinge D, Gotberg M, Lang I, et al. 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. *J Am Coll Cardiol.* 2014;63:1857-1865.
 20. Erlinge D, Gotberg M, Noc M, et al. Therapeutic hypothermia for the treatment of acute myocardial infarction-combined analysis of the RAPID MI-ICE and the CHILL-MI trials. *Ther Hypothermia Temp Manag.* 2015;5:77-84.
 21. Michelsen MM, Støttrup NB, Schmidt MR, et al. Exercise-induced cardioprotection is mediated by a bloodborne, transferable factor. *Basic Res Cardiol.* 2012;107:260.
 22. Jean-St-Michel E, Manlhiot C, Li J, et al. Remote preconditioning improves maximal performance in highly trained athletes. *Med Sci Sports Exerc.* 2011;43:1280-1286.
 23. Munk K, Andersen NH, Schmidt MR, et al. Remote ischemic conditioning in patients with myocardial infarction treated with primary angioplasty: impact on left ventricular function assessed by comprehensive echocardiography and gated single-photon emission CT. *Circ Cardiovasc Imaging.* 2010;3:656-662.
 24. Rentoukas I, Giannopoulos G, Kaoukis A, et al. Cardioprotective role of remote ischemic preconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv.* 2010;3:49-55.
 25. Crimi G, Pica S, Raineri C, et al. Remote ischemic preconditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc Interv.* 2013;6:1055-1063.
 26. White SK, Frohlich GM, Sado DM, et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv.* 2015;8:178-188.
 27. Sörensson P, Saleh N, Bouvier F, et al. Effect of postconditioning on infarct size in patients with ST elevation myocardial infarction. *Heart.* 2010;96:1710-1715.
 28. Dixon SR, Whitbourn RJ, Dae MW, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol.* 2002;40:1928-1934.
 29. Nichol G, Strickland W, Shavelle D, et al. Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment elevation myocardial infarction. *Circ Cardiovasc Interv.* 2015;8:e001965.
 30. Støttrup NB, Løfgren B, Birkler RD, et al. Inhibition of the malate-aspartate shuttle by pre-ischaemic aminooxyacetate loading of the heart induces cardioprotection. *Cardiovasc Res.* 2010;88:257-266.