Effect of remote ischemic conditioning on infarct size in patients with anterior ST-elevation myocardial infarction

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Background Previous studies indicate that remote ischemic conditioning performed before percutaneous coronary intervention (PCI) reduces infarct size in patients with ST-elevation myocardial infarction (STEMI). It remains unclear whether remote conditioning affords protection when performed in adjunct to primary PCI. We aimed to study whether remote ischemic per-postconditioning (RIperpostC) initiated after admission to the catheterization laboratory attenuates myocardial infarct size in patients with anterior STEMI.

Methods In this prospective multicenter trial 93 patients with anterior STEMI were randomized to RIperpostC or sham procedure as adjunct to primary PCI. RIperpostC was started on arrival in the catheterization laboratory by 5-minute cycles of inflation and deflation of a blood pressure cuff around the left thigh and continued throughout the PCI procedure. Infarct size and myocardium at risk were determined by cardiac magnetic resonance at day 4 to 7. The primary outcome was myocardial salvage index.

Results There was no significant difference in myocardial salvage index between the RIperpostC and control group (median 48.5% and interquartile range 30.9%-60.8% vs 49.2% [42.1%-58.8%]). Neither did absolute infarct size in relation to left ventricular myocardial volume differ significantly (RIperpostC 20.6% [14.1%-31.7%] vs control 17.9% [13.4%-25.0%]). The RIperpostC group had larger myocardial area at risk than the control group (43.1% (35.4%-49.7%) vs 37.0% (30.8%-44.1%) of the left ventricle, $P = .03$). Peak value and area under the curve for troponin T did not differ significantly between the study groups.

Conclusions RIperpostC initiated after admission to the catheterization laboratory in patients with anterior STEMI did not confer protection against reperfusion injury. (Am Heart J 2016;181:66-73.)

The strategy for modern treatment of ST-elevation myocardial infarction (STEMI) is rapid reperfusion of the occluded artery by primary percutaneous coronary intervention (PCI) and anti-thrombotic therapy, which has led to considerably improved prognosis.[1] Reperfusion is not only of benefit by relieving ischemia, but is also associated with morphological and functional myocardial changes that significantly contribute to tissue damage known as reperfusion injury.[2] This is a complex series of events involving oxidative stress and inflammatory processes leading to endothelial dysfunction, cardiac arrhythmias, myocardial contractile dysfunction and cardiomyocyte death. Animal studies suggest that about 50% of the final infarct size develops as a result of the reperfusion injury.[3] Thus, further substantial therapeutic gains can be achieved by developing novel treatment strategies that prevent reperfusion injury.

The concept of inducing protection against reperfusion injury by preconditioning the heart through brief repetitive cycles of local ischemia was described by Murry et al[4] Recent clinical studies applying the conditioning stimulus in tissue distant from the heart—remote ischemic conditioning—have shown encouraging results.[5-8] Remote ischemic conditioning of the upper

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arm during the ambulance transport to primary PCI reduces infarct size in relation to the myocardium at risk (MaR) in patients with STEMI with particular benefit among patients with anterior STEMI.[5] In a subsequent study investigating the effect of remote ischemic conditioning starting at reperfusion, a reduction in creatine kinase–myocardial-band (CK-MB) levels was demonstrated but it did not reduce infarct size determined by cardiac magnetic resonance (CMR) imaging among patients randomized to remote ischemic conditioning.[7] White et al found that remote ischemic conditioning performed during late ischemia and early reperfusion reduced absolute infarct size and area of edema but did not affect myocardial salvage index (MSI).[8] Thus, the efficacy of remote ischemic conditioning to reduce infarct size when the intervention is started after admission to the catheterization laboratory remains elusive. Therefore, the present trial was designed to determine if remote ischemic conditioning performed during late ischemia and early reperfusion (remote ischemic per-postconditioning - RIperpostC) reduces infarct size in patients presenting with anterior STEMI. To this end we used a validated CMR method for the determination of infarct size and MaR.[9]

Methods

Study group

Between July 2013 and May 2015 patients with signs and symptoms of anterior STEMI were eligible for participation. Enrolling centers were Karolinska University Hospital, Södersjukhuset and Danderyd University Hospital, in Stockholm, Sweden. Inclusion criteria were chest pain indicating myocardial ischemia with a duration >30 minutes and <6 hours, ST-elevation >0.1 mV (>0.2 mV in V2-V3) in two contiguous leads (V1-V6) and age over 18 years. Exclusion criteria were previous myocardial infarction, left bundle branch block, previous coronary artery bypass grafting, cardiac arrest, severe claudication, atrial fibrillation, treatment with glibenclamide or cyclosporine on admission, any condition that may interfere with the possibility for the patient to comply with the study protocol or PCI not performed during the index event. Informed oral consent was sufficient for entering the study, but was complemented by written consent within 24 hours. The study was performed according to the Declaration of Helsinki,[10] and was approved by the regional ethics committee in Stockholm. The clinical trial registration no. was NCT02021760 (clinicaltrials.gov). The study was supported by a grant from the Swedish Research Council for "Knowledge gaps in clinical medicine" 521–2011-404, Swedish Research Council grant 10,857, the Swedish Heart and Lung Foundation, Stockholm County Council ALF grant and Karolinska Institutet/Stockholm County Council Strategic Cardiovascular Programme. The present trial was performed without any relationships to industry. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study design and procedures

The primary objective was to test the hypothesis that RIperpostC reduces infarct size in relation to MaR in patients with anterior STEMI as determined by CMR on days 4 to 7. The study was performed as a multicenter prospective randomized study with blinded evaluation. Eligible patients were transferred directly to the catheterization laboratory and were randomized in a 1:1 manner to RIperpostC or sham as adjunct to primary PCI. Computer-generated randomization was performed in blocks of eight and kept in sealed envelopes at the participating centers. RIperpostC was started immediately after randomization using a blood pressure cuff around the left thigh. The cuff was connected to an automated device (PeriVasc Cuff Unit, EBIDA, Göteborg, Sweden) programmed to inflate to 200 mmHg (or 20 mmHg above systolic blood pressure if systolic blood pressure was above 180 mmHg) for 5 minutes followed by deflation for 5 minutes in repeated cycles in patients randomized to RIperpostC,. At least one cycle had to be completed before reperfusion (defined as first balloon inflation). RIperpostC was continued throughout the angiography and PCI procedures with 4 cycles performed after reperfusion (Figure 1). In patient randomized to sham, the blood pressure cuff was applied but not inflated.

PCI was performed according to local guidelines. Patients received double antiplatelet therapy with aspirin (300-500 mg) and any of ticagrelor (180 mg) or clopidogrel (600 mg) in the ambulance or immediately on arrival to the catheterization laboratory. Further medication including the choice of heparin, bivalirudin and glycoprotein IIb/IIIa-inhibitor, the use of thrombus aspiration, direct stenting and type of stent was at the discretion of the treating PCI operator according to clinical indication.

CMR imaging

CMR was performed at Karolinska University Hospital 4 to 7 days after the PCI using a 1.5 T Siemens Magnetom Aera scanner (Siemens Healthcare, Erlangen, Germany). Electrocardiogram-gated images were acquired during repeated breath-holds. A gadolinium-based contrast agent (Gd-DTPA, 0.2 mmol/kg, Dotarem, Guerbet, France) was administered. Initial scout images were acquired and the short axis was localized. Early contrast-enhanced steady state free precession and late gadolinium-enhanced (LGE) images were obtained in 12-14 short axis views (8 mm thickness, 2 mm gap) and in the 2-3-4 chamber views for the determination of MaR and infarct size, respectively. LGE images were acquired 15 to 20 minutes after contrast injection using an inversion recovery gradient echo