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Reducing myocardial infarct size by remote ischemic conditioning

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Abstract

Ischemic heart disease is the leading cause of death and morbidity in the world, and ST-segment elevation myocardial infarction (STEMI) remains associated with a significant mortality rate and complications noted at 1-year follow-up, despite prompt coronary reperfusion achieved with either thrombolysis or primary percutaneous coronary intervention (PPCI). It is therefore clear that novel cardioprotective strategies are required to improve clinical outcomes in these subjects; in this regard, remote ischemic conditioning (RIC), a phenomenon by which brief episodes of transient limb ischemia-reperfusion are able to protect a distant or "remote" organ or tissue from a sustained period of ischemia, has been demonstrated as a promising low-cost therapeutic strategy in order to reduce myocardial injury and improve clinical outcomes in these patients. In the current article, we provide an updated review of randomized clinical trials investigating the effects of RIC in patients presenting with STEMI. ■ *Heart Metab*. 2016;70:36-39

Keywords: cardioprotection; myocardial infarction; remote ischemic conditioning

Background

Following an ST-segment elevation myocardial infarction (STEMI), timely restoration of blood flow with primary percutaneous coronary intervention (PPCI) or thrombolysis is the most effective strategy for reducing myocardial infarct (MI) size, heart failure (HF), ventricular arrhythmias, and mortality. Despite a significant reduction in case fatality in the last three decades, the mortality rate post-STEMI remains as high as 2.5%-10%, with an overall estimated rate of 10% of in-hospital HF or shock, 6%-7% of reinfarction at 1 year, 1.8% of in-hospital major bleeding, and 1.8%-2% stroke at 1 year.[1] Crucially, restoration of coronary perfusion has been demonstrated to paradoxically induce myocardial damage, and this phenomenon, termed myocardial ischemia-reperfusion injury (IRI), has been demonstrated to account for up to 50% of the final MI size in animal studies[2]; therefore, novel cardioprotective strategies are required to reduce IRI after MI and to improve patient outcomes. Numerous strategies that have been investigated—including pharmacological agents, mechanical cardioprotection, and endovascular cooling—have not demonstrated a significant benefit. However, one promising approach consists of enhancing the innate mechanisms of cardioprotection from IRI by "conditioning" the heart before, during, or after the ischemic insult. Remote ischemic conditioning (RIC) offers the advantage of applying the conditioning stimulus to a "remote" or distant organ/tissue, such as the limb, thereby obviating the

Abbreviations

AUC: area under the curve; **CK-MB:** creatine kinase–MB; **ERIC-PPCI:** Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI (trial); **HF:** heart failure; **IRI:** ischemia-reperfusion injury; **LV:** left ventricular; **MI:** myocardial infarct; **PPCI:** primary percutaneous coronary intervention; **RIC:** remote ischemic conditioning; **STEMI:** ST-segment elevation myocardial infarction

need to invasively intervene on the heart in order to achieve cardioprotection.[3] In the current review, we will focus on the main studies evaluating the effects of RIC in the setting of STEMI treated with PPCI or thrombolysis and will discuss the ongoing multicenter study, the results of which should ultimately provide a conclusive answer about the potential beneficial impact of RIC on clinical outcomes.

RIC and PPCI

The application of RIC in patients presenting with STEMI represents the closest translation of experimental models to the clinical scenario: acute and complete coronary occlusion in the context of STEMI resembles the direct coronary artery ligature in animal studies, and typically, STEMI subjects have no preexisting comorbidities and are on no regular medications, similarly to the preclinical settings.

Rentoukas et al[4] evaluated the effects of RIC in the setting of STEMI and found that the rate of full ST-segment resolution was highest in patients receiving RIC (three 4-minute cycles of transient upper-arm ischemia-reperfusion beginning 10 minutes before the estimated time of the first balloon inflation) or RIC plus morphine, compared with PPCI alone; there was no significant difference between the two conditioned groups. Additionally, subjects receiving RIC plus morphine presented the lowest troponin-I peak and the highest degree of ST-segment return to baseline.

Bøtker and colleagues[5] demonstrated that in patients with evolving STEMI, RIC—comprising four 5-minute cycles of upper-arm ischemia-reperfusion during transport to hospital and before PPCI—improved the myocardial salvage index at 30 days; no difference was found in final infarct size, troponin-T concentrations, ST-segment resolution, death, reinfarction, left ventricular (LV) function, and hospital admission for HF within 30 days. Subsequently, the same group[6] showed that a similar conditioning stimulus was also able to reduce the rate of major adverse cardiovascular and cerebral events (MACCE)—a composite end point of all-cause mortality, nonfatal MI, readmission for HF, and stroke/transient ischemic attack—for a median follow-up of 3.8 years.

Munk et al[7] failed to demonstrate that LV function could be improved by a similar RIC stimulus, although the majority of patients presented a small-to-moderate area at risk, thus small differences in LV function changes may not have been detected on echocardiography. However, importantly, in a subgroup of high-risk patients—for which the study was not adequately powered—RIC improved LV function at 30 days.

In addition, Manchurov et al[8] showed improved endothelial function up to 1 week post-PPCI, and more recently, Crimi and colleagues[9] found that a standard conditioning stimulus reduced total creatine kinase (CK)-MB release and improved T2-weighted edema volumes and ST-segment elevation resolution in patients with an occluded left anterior descending artery.

In a large cohort of 323 STEMI patients, our group demonstrated that four 5-minute cycles of upper-arm ischemia-reperfusion reduced infarct size (measured by cardiac magnetic resonance) 6 days after admission, total troponin-T release at 24 hours, and myocardial edema, and improved myocardial salvage.[10]

Intriguingly, there was no difference in CK-MB area under the curve (AUC) in patients receiving PPCI alone, PPCI plus RIC (three 5-minute cycles of upper-arm ischemia-reperfusion), or PPCI plus RIC and local ischemic conditioning, although positive effects were identified in the RIC and RIC plus local ischemic group when infarct size was corrected for the area at risk.[11] More recently, it has been demonstrated that used in addition to PPCI, three 5-minute cycles of upper-arm ischemia-reperfusion significantly reduced contrast-induced acute kidney injury,[12] and combined RIC and local postconditioning improved the myocardial salvage index at 3 days, though there was no difference in infarct size, microvascular obstruction, and clinical outcomes at 6 months.[13]

RIC and thrombolysis

A recently published multicenter, single-blinded trial[14] evaluated the effects of RIC in STEMI patients treated

by thrombolysis with streptokinase. This trial, conducted in Mauritius, is particularly relevant for those areas where PPCI service has limited availability. Preconditioned subjects (four 5-minute cycles of upper-arm ischemia-reperfusion, initiated before and continued during thrombolysis) sustained significantly less myocardial IRI than controls (troponin-T AUC was 32% lower and CK-MB AUC was 19% lower), thereby showing for the first time that RIC could be beneficial in this therapeutic context also and that it provides similar cardioprotective effects to those obtained in the setting of RIC-PPCI.

Conclusions

In the current review, we have briefly evaluated the application of RIC in the context of STEMI, where emergency coronary reperfusion was achieved with PPCI or thrombolysis. Crucially, all of the above-mentioned studies used surrogate biomarkers of myocardial IRI (such as troponin or CK-MB), microvascular reperfusion, LV function, and acute kidney injury as their primary end points and did not include clinical outcomes among their objectives or were not adequately powered to detect significant differences in clinical outcomes. Two large multicenter studies recently completed in the United Kingdom[15] and Germany[16] demonstrated no significant beneficial effect of RIC on clinical outcomes in patients undergoing elective coronary artery bypass grafting (CABG) with or without valve surgery. This could be explained by the relatively small additional cardioprotection provided by RIC to patients already receiving optimized medical therapy with more advanced surgical and anesthetic techniques and by the potential interference of intravenous anesthetics with RIC effects; crucially, the level of myocardial IRI during cardiac surgery is significantly inferior to that observed in reperfused STEMI patients, and myocardial IRI in cardiac surgery is secondary to multiple factors, with ischemia-reperfusion being one of these. It is therefore conceivable that RIC might provide more significant beneficial effects than cardiac surgery in STEMI patients: currently, a large multicenter randomized controlled trial is being conducted in the United Kingdom, Denmark, and Spain (ERIC-PPCI, NCT02342522 [Effect of Remote Ischemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI]) in order to investigate whether RIC, given with four 5-minute cycles of upper-arm ischemia-reperfusion, reduces the combined primary end point of cardiac death and hospitalization at 12 months post-PPCI. This study is expected to provide a conclusive answer to whether RIC has a beneficial impact on major cardiac events in STEMI patients. ■

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