The future of remote ischaemic conditioning is high-risk (patients)!

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For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), the treatment priority for limiting myocardial infarct (MI) size and preventing the onset of heart failure (HF), is timely myocardial reperfusion by primary percutaneous coronary intervention (PPCI). Despite a decline in mortality, the number of STEMI patients going onto develop post-infarct HF is on the rise. As such, there remains an urgent need to discover novel therapeutic interventions, which can be applied as an adjunct to PPCI to reduce MI size, and prevent post-infarct adverse left ventricular (LV) remodelling.

In this regard, remote ischaemic conditioning (RIC), an endogenous cardioprotective phenomenon in which brief cycles of ischaemia and reperfusion applied to an organ or tissue (including the arm or leg) remote from the heart, has been shown to reduce MI size in animal models of acute myocardial ischaemia/reperfusion injury (IRI).[17;26;28;29] The ability to deliver the cardioprotective RIC stimulus by simply inflating and deflating a pneumatic cuff placed on the upper arm or thigh, to induce three to four cycles of brief ischaemia and reperfusion (each of 5 min duration), has facilitated the testing of limb RIC in the clinical setting, making it an attractive low-cost and non-invasive treatment strategy for potentially improving clinical outcomes in STEMI patients.[4] Several small clinical studies,[3;6;33] but not all,[32] have reported that limb RIC, comprising three to four-5 min cycles of limb ischaemia and reperfusion, applied prior to, or immediately after PPCI, improved myocardial salvage and/or reduced MI size in STEMI patients (quantified by cardiac biomarkers, myocardial SPECT or cardiac MRI). Furthermore, one follow-up study,[30] and a single prospective study[10] have suggested that RIC may also improve clinical outcomes in STEMI. Despite these promising studies, the large multi-national, multi-centre, phase 3 randomised controlled CONDI-2/ERIC-PPCI trial, failed to demonstrate any beneficial effects of limb RIC on clinical outcomes (rates of cardiac death and HF hospitalisation at 12 months: 8.6% in control vs 9.4% with RIC) in STEMI patients treated by PPCI.[14] This failure to observe a benefical effect of limb RIC on clinical outcomes in STEMI patients, highlights the challenges and obstacles facing the translation of cardioprotective interventions for patient benefit.[12;15] The specific reasons for the failure to translate limb RIC into the clinical setting for patient benefit are not clear, although

several potential explanations have been discussed in recent commentaries.[5;13;15;16;18;19]

Potential reasons include: (1) the use of animal models of acute myocardial ischaemia/reperfusion injury which do not adequately represent the typical STEMI patient[2;22]; (2) the limb RIC protocol itself, which has not been optimised for maximal cardioprotection, in terms of the duration of the limb ischemia and reperfusion cycles, whether limb tissue mass makes a difference (i.e. RIC of arm versus leg), and the number of cycles. One experimental study in mice[20] has shown that two and five min (but not 10 min) of hindlimb ischemia induced cardioprotection, four and six limb RIC cycles were equally efficacious with no additional benefit with eight cycles, and one and two hindlimb RIC were equally cardioprotective. However, in another study in rats, two hindlimb RIC was shown to be more cardioprotective than single hindlimb RIC, suggesting that limb tissue mass may be important.[23] In this regard, the only clinical study to show a beneficial effect of limb RIC on clinical outcomes used limb RIC of the leg.[10] Further clinical studies are needed to determine the optimum limb RIC protocol for cardioprotection; (3) the presence of co-morbidities (such as diabetes, age, hyperlipidaemia), which may confound cardioprotection, although the evidence for this has been mainly observed in animal studies,[9] rather than clinical cardioprotection studies.[21] Furthermore, pre-specified subgroup analyses of the CONDI-2/ERIC-PPCI trial did not show any benefit with limb RIC in younger or non-diabetic patients;[14] and (4) the use of limb RIC alone as a cardioprotective intervention, an approach which may be less effective at targeting acute myocardial IRI, than a multi-intervention and multi-targeted approach such as combining limb RIC with ischaemic postconditioning.[7;8]

Another major reason for the failure of limb RIC to improve clinical outcomes in STEMI patients optimally treated by PPCI may be the *low-risk* population that was recruited in the CONDI-2/ERIC-PPCI trial as evidenced by the following:[11;18] (1) The low cardiac mortality rate of 2.7% at 12 months; (2) 96% of patients presented without symptoms or signs of heart failure (Killip Class I); (3) The median acute MI size assessed by cardiac MRI in the first week following PPCI in a 176 patient substudy of the CONDI-2/ERIC-PPCI trial, was relatively small,

with a median MI size of 17% of left ventricular mass; (4) The total acute myocardial ischaemia time was short with a median symptom onset to PPCI time of only 3 hours; and finally (5) The prevalence of cardiovascular risk factors was relatively low with 40% of patients having a history of hypertension, and 10% having medically treated diabetes.

As such, we believe there remains the potential for limb RIC to improve clinical outcomes in *higher-risk* STEMI patients in low- and middle-income developing countries in sub-Saharan Africa, where PPCI is not widely available and STEMI patients are still treated by thrombolysis. As thrombolytic therapy is less effective than PPCI at restoring blood flow in the infarct-related coronary artery, STEMI patients treated by thrombolysis experience larger myocardial infarcts, are more likely to develop heart failure, and are at increased risk of death. The prevalence of ischaemic heart disease and related mortality rates are predicted to rise by 70% in African men and 74% in women by 2030.[25] Therefore, given the rising burden of acute coronary syndromes in sub-Saharan Africa,[24] there is an urgent need for an easily applied, low-cost treatment strategy that has the ability to reduce MI size and prevent HF in *higher-risk* STEMI patients in the region. As such, we believe there remains the potential for limb RIC to improve clinical outcomes in *higher-risk* STEMI patients in low- and middle-income developing countries in sub-Saharan Africa.

There are a number of potential reasons why STEMI patients from these countries may be at increased risk of experiencing worse clinical outcomes when compared to *low-risk* patients in Europe or the United States of America and these include: (1) Inadequate access to hospital facilities, especially in rural areas, resulting in prolonged transfer times to facilities where thrombolytic treatment can be delivered, thereby increasing the total acute myocardial ischaemia time.[1] In this regard, it has been shown that the cardioprotective effect of limb RIC in STEMI may increase with the duration of ischaemia;[27] (2) The increased prevalence of cardiovascular risk factors[1] such as hypertension (present in upto 60% of patients) and diabetes (present in upto 40% of patients), which in many people remains undiagnosed and untreated; (3) Streptokinase thrombolysis is still widely used across the continent to treat STEMI, even though it is less effective at restoring coronary blood flow, than tissue

plasminogen activator; and (4) Suboptimal use and compliance with secondary preventative therapy (anti-platelet therapy, beta-blockers, renin-angiotensin blockers and statins) for improving clinical outcomes post-STEMI with one study showing that only 56% of patients were discharged on Guideline-directed discharge medical therapy;[1] and (5) Delayed presentation to the hospital is common with nearly 70% of patients presenting after 6 hours of chest pain onset resulting in increased total acute myocardial ischaemia times.[31] Clinical studies have reported high in-patient mortality rates in STEMI patients in developing countries in sub-Saharan Africa ranging from 15 to 21%, confirming the *higher-risk* population in these developing countries.[1;31]

The safety, feasibility, and cardioprotective efficacy of limb RIC in STEMI patients treated by streptokinase thrombolysis has already been demonstrated in the previously published Phase 2 multi-centre randomised clinical ERIC-LYSIS trial in the multi-ethnic developing sub-Saharan African country of Mauritius.[34] In that study, we found that limb RIC (comprising four-5 min inflations of deflations of a pneumatic cuff placed on the upper arm), initiated prior to thrombolysis, reduced MI size as measured by serum cardiac biomarkers with a 32% reduction in 24-hours area-under-the-curve (AUC) Troponin-T, and a 19% reduction in 24-hours AUC CK-MB, when compared to sham.[34] Whether limb RIC can improve clinical outcomes (cardiac death and HF hospitalisation) in *higher-risk* STEMI patients treated by thrombolysis is not known, and needs to be tested in a suitably powered multi-center, multi-country Phase 3 clinical study.

In summary, limb RIC failed to improve clinical outcomes in a *low-risk* group of STEMI patients optimally treated by PPCI, and recruited in developed countries in Europe as part of the CONDI-2/ERIC-PPCI trial. It is likely that the low-cost and non-invasive intervention of limb RIC will have greater utility, and be more efficacious in *higher-risk* STEMI patients in developing nations where PPCI is not widely available, and patients are still treated by thrombolysis.

Conflict of interest statement:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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