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EDITORIAL

Remote ischaemic conditioning modulates platelet reactivity: the need to optimize the therapy is more important than ever before

Sandrine Lecour *

Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Anzio road, 7925 Observatory, Cape Town, South Africa

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This editorial refers to 'Effect of remote ischaemic conditioning on platelet reactivity and endogenous fibrinolysis in ST-elevation myocardial infarction: a substudy of the CONDI-2/ERIC-PPCI randomized controlled trial' by D.A. Gorog *et al.*, pp. 623–634.

More than 25 years after its discovery in the preclinical setting, remote ischaemic conditioning has shown convincing potential to limit reperfusion injuries in the setting of acute myocardial infarction in both preclinical and small proof of concept clinical studies. Sadly, the clinical translation of this inexpensive and simple therapy, consisting of short and repeated bouts of ischaemia–reperfusion episodes performed remotely to the heart (usually in the limb by inflation/deflation of a blood pressure cuff), has proved to be challenging.

Although the outcome of the largest clinical trial testing the benefit of remote ischaemic conditioning in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI trial) was disappointing, lessons can certainly be learnt from this study.[1] This multicentre, randomized, placebo-controlled clinical trial conducted in Europe (mainly Denmark and UK) included over 5400 patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI). Regrettably, remote ischaemic conditioning, performed during ambulance transfer or at the arrival in hospital, failed to reduce infarct size, to reduce cardiac mortality and to limit rehospitalization for heart failure at 1 year. Multiple explanations for the lack of benefit of remote ischaemic conditioning in this trial have been suggested, including the fact that the patients recruited in this trial already received state-of-the-art management/therapy (with low mortality rate, small infarct size, and small rehospitalization rate even in the control group), thus making it challenging to demonstrate any further benefits from remote ischaemic conditioning in this category of patients.[2] However, this large trial and subsequent sub-studies of the trial bring valuable information and new knowledge that are critical to further optimize future translation of remote ischaemic conditioning in the clinical setting.

In this regard, Gorog *et al.*[3] explored the effect of remote ischaemic conditioning on thrombotic status in a sub-study of the CONDI-2/ERIC-PPCI trial. Traditionally, most of the benefits of remote ischaemic conditioning against reperfusion injury have been attributed to the activation of prosurvival signalling pathways such as the RISK and SAFE pathways to rescue the cardiomyocytes.[4] However, there has been mounting evidence in both preclinical and clinical studies suggesting that targeting the survival of the myocardium is not the only benefit of remote ischaemic conditioning, with modulation of the microcirculation, the endothelial function, and the platelet activation/aggregation process observed following ischaemic conditioning.[5] The data from Gorog *et al.* strongly suggest that remote ischaemic conditioning is associated with a reduction in platelet reactivity, as observed with a longer *in vitro* thrombosis occlusion time at 48 h in patients receiving remote ischaemic conditioning. This association was lost at 6–8 weeks, thus supporting the suggestion that protection with remote ischaemic conditioning may not have a long-lasting effect on thrombosis activity and that chronic, rather than acute, remote ischaemic conditioning may be a more appropriate strategy to limit platelet reactivity in STEMI patients. Unfortunately, this effect was not associated with any benefit for the patient. However, this is not entirely surprising considering the low-risk profile of the patients. This result, however, strengthens the hypothesis that patients with high-risk profile, in particular, patients with high risk of stent thrombosis, may benefit from the modulation of platelet reactivity after remote ischaemic conditioning.

This study strongly suggests that remote ischaemic conditioning has the potential to confer benefits in STEMI patients but it reminds us that optimization of the therapy is critical before it can translate to the clinical setting. Indeed, the following five points (see *Figure 1*) need to be carefully addressed:

(1) Which patient is likely to benefit from remote ischaemic conditioning? *High-risk* patients with potentially a larger infarct and a higher probability of major adverse cardiac events, patients from high-income countries living away from a PCI centre or patients from low-to-middle-income countries with no adequate health care system or suboptimal pharmacological and reperfusion therapies, are more likely to benefit from remote ischaemic conditioning.[2,6] As an example, patients that benefit from optimal therapy will receive the platelet $P2Y_{12}$-receptor antagonists which have been described to confer cardioprotection via

*Corresponding author. Tel: +27 214066278, E-mail: sandrine.lecour@uct.ac.za

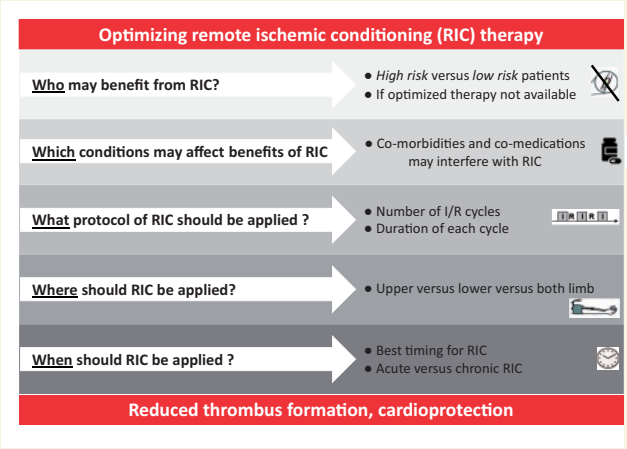

Figure 1 Some of the key points that need to be optimized to facilitate clinical translation of RIC in the setting of acute myocardial infarction. RIC, remote ischaemic conditioning.

mechanisms similar to remote ischaemic conditioning.[5] If remote ischaemic conditioning may not add further benefit in patients already treated with $P2Y_{12}$ receptor antagonists (as was the case in the present study), it may still benefit patients who are not given the opportunity to receive the platelet $P2Y_{12}$ inhibitors (as is often the case in patients from low- to middle-income countries).[6,7]

(2) Which conditions may affect the benefits of remote ischaemic conditioning? Multiple preclinical studies suggest that confounders such as co-morbidities and co-medications may limit the cardioprotective properties of ischaemic conditioning but convincing clinical data are still missing.[8]

(3) What protocol of remote ischaemic conditioning should be used? Unfortunately, the number of cycles of ischaemia–reperfusion and the duration of each cycle to maximize the protection have been poorly studied in both experimental and clinical settings.[9]

(4) Where should remote ischaemic conditioning be performed? Most clinical studies have performed the remote ischaemic conditioning protocol in the upper limb while experimental studies (in rodents and pigs) have often performed the remote ischaemic conditioning protocol in the hindlimb. There is scant information as to whether remote ischaemic conditioning may exert better cardioprotective properties if performed in the lower limb, the upper limb or possibly in both limbs at the same time.[9]

(5) When should remote ischaemic conditioning be performed? Although the current study did not see any difference between patients who received remote ischaemic conditioning during ambulance transfer compared to those who received the therapy at the arrival in hospital, the timing when remote ischaemic conditioning needs to be performed to confer maximal protection has hardly been studied in both preclinical and clinical studies.[9]

Although remote ischaemic conditioning has the potential benefit to promote cell survival and limit thrombotic activity in STEMI patients, it is unlikely to successfully translate in the clinical setting before the five questions listed above (Who-Which-What-When-Where) have been critically answered and taken into consideration in future clinical studies.

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