Remote ischemic conditioning reduces myocardial infarct size in STEMI patients treated by thrombolysis

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In many developing nations where primary percutaneous coronary intervention (PPCI) is not widely available, ST-segment elevation myocardial infarction (STEMI) patients are still treated by thrombolysis (1). However, as thrombolytic therapy is less effective than PPCI at restoring blood flow in the infarct-related coronary artery, thrombolyzed STEMI patients experience larger myocardial infarcts and are more likely to develop heart failure. As such, there is an urgent need for an innovative, easily applied, and low-cost cardioprotective therapy. In this regard, the heart can be protected against MI, by simply applying cycles of brief ischemia/reperfusion to the arm or leg–a phenomenon termed remote ischemic conditioning (RIC) (2). Therefore, we hypothesized that RIC initiated on arrival at the hospital and prior to thrombolysis can reduce enzymatic MI size in STEMI patients (the ERIC-LYSIS Study: NCT02197117).

We performed a multicenter single-blinded, randomized controlled trial in the developing nation of Mauritius. The Mauritian Ministry of Health and Quality of Life provided ethical approval of the study. All patients gave informed consent before entering the study. Adult patients presenting with a STEMI were randomly assigned to receive either RIC (4 5-minutes cycles of upper-arm cuff inflation to 200 mmHg and deflation) or control (un-inflated cuff placed on the upper-arm for 40 minutes) on immediate arrival at the hospital. Exclusion criteria included contra-indications for thrombolysis; previous MI; cardiac arrest; arterio-venous shunts; and pre-existing treatment with nicorandil or glibenclamide. Thrombolysis was achieved using streptokinase at a dose of 1.5 million units over 60 minutes. The RIC or control protocols were initiated prior to and continued during thrombolysis, and did not delay the onset of reperfusion. The predefined primary endpoint was enzymatic MI size assessed by 24 hour area-under-the-curve (AUC) serum Troponin-T and CK-MB, measured at 0, 6, 12, and 24 hours.

Between March 2011 and November 2013, 519 STEMI patients were randomly assigned to receive either RIC (N = 258) or control (N = 261). The 2 groups were similar in patient characteristics. Data were available for 414 patients for AUC Troponin-T and 407 patients for AUC CK-MB. Median enzymatic MI size was 32% (24 hr AUC Troponin-T) and 19% (24 hr AUC CK-MB) smaller in patients administered RIC when compared to control patients (**Table**)

The ERIC-LYSIS study was the first to investigate the effect of RIC in STEMI patients reperfused by thrombolysis in a developing nation. We found that those patients randomized to receive RIC upon arrival at the hospital and prior to thrombolytic therapy experienced a significant reduction in enzymatic MI size when compared to control. The size of this cardioprotective effect is comparable to that observed in STEMI patients treated by PPCI, in which studies have reported 25-30% reductions in MI size measured by myocardial SPECT and cardiac MRI (3-5). The limitations of our study include the following: although tissue plasminogen activator (t-PA) is the most commonly used thrombolytic agent in developed countries, streptokinase (which costs 10-fold less than t-PA) continues to be used in developing nations; and conducting a randomized control trial in a developing nation with very limited resources was challenging and explains in part why we were only able to obtain data on enzymatic MI size.

In conclusion, we have shown that RIC reduced MI size in STEMI patients treated with thrombolysis, making this noninvasive, easily applied, low cost therapy an attractive option in developing nations where health care resources are limited and current therapy is not optimal.

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Table 1: Patient characteristics and AUC cardiac enzymes

Variable	Control (N=258)	RIC (N=261)	P-value
Male	204 (79%)	209 (80%)	
Age (years)	56 ± 11	57 ± 11	
Enzymatic MI size (ng.h/ml)			
24 hr AUC CK-MB	2,894 ± 2,306	2,378 ± 2,089	
Mean ± SD	2,381 (980, 4,690)	1,928 (780, 3,289)	0.026
Median (IQR)			
24 hr AUC Troponin-T	105.9 ± 69.5	90.0 ± 67.6	
Mean ± SD	109.0 (41.1, 162.7)	74.6 (28.5, 149.0)	0.020
Median (IQR)			

Values are expressed as number (%) and mean ± SD. SD, standard deviation; AUC, area under the curve. CI, confidence interval; IQR, inter-quartile range. *p-value from non-parametric Mann-Whitney U test for equality of distributions between control and RIC arms.