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Remote Ischemic Conditioning Reduces Myocardial Infarct Size and Edema in Patients With ST-Segment Elevation Myocardial Infarction

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ABSTRACT

OBJECTIVES This study aimed to determine whether remote ischemic conditioning (RIC) initiated prior to primary percutaneous coronary intervention (PPCI) could reduce myocardial infarct (MI) size in patients presenting with ST-segment elevation myocardial infarction.

BACKGROUND RIC, using transient limb ischemia and reperfusion, can protect the heart against acute ischemia-reperfusion injury. Whether RIC can reduce MI size, assessed by cardiac magnetic resonance (CMR), is unknown.

METHODS We randomly assigned 197 ST-segment elevation myocardial infarction patients with TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 to receive RIC (4 5-min cycles of upper arm cuff inflation/deflation) or control (uninflated cuff placed on upper arm for 40 min) protocols prior to PPCI. The primary study endpoint was MI size, measured by CMR in 83 subjects on days 3 to 6 after admission.

RESULTS RIC reduced MI size by 27%, when compared with the MI size of control subjects (18.0 ± 10% [n = 40] vs. 24.5 ± 12.0% [n = 43]; p = 0.009). At 24 h, high-sensitivity troponin T was lower with RIC (2,296 ± 263 ng/l [n = 89] vs. 2,736 ± 325 ng/l [n = 84]; p = 0.037). RIC also reduced the extent of myocardial edema measured by T_2-mapping CMR (28.5 ± 9.0% vs. 35.1 ± 10.0%; p = 0.003) and lowered mean T_2 values (68.7 ± 5.8 ms vs. 73.1 ± 6.1 ms; p = 0.001), precluding the use of CMR edema imaging to correctly estimate the area at risk. Using CMR-independent coronary angiography jeopardy scores to estimate the area at risk, RIC, when compared with the control protocol, was found to significantly improve the myocardial salvage index (0.42 ± 0.29 vs. 0.28 ± 0.29; p = 0.03).

CONCLUSIONS This randomized study demonstrated that in ST-segment elevation myocardial infarction patients treated by PPCI, RIC, initiated prior to PPCI, reduced MI size, increased myocardial salvage, and reduced myocardial edema. (J Am Coll Cardiol Intv 2014;■:■-■) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AAR = area at risk

AUC = area under the curve

CMR = cardiac magnetic resonance

hsTnT = high-sensitivity troponin T

LGE = late gadolinium enhancement

LV = left ventricular

MI = myocardial infarct

MSI = myocardial salvage index

PCI = percutaneous coronary intervention

PPCI = primary percutaneous coronary intervention

RIC = remote ischemic conditioning

STEMI = ST-segment elevation myocardial infarction

STIR = short tau inversion recovery

Despite optimal myocardial reperfusion using primary percutaneous coronary intervention (PPCI), the morbidity and mortality of ST-segment elevation myocardial infarction (STEMI) patients remains substantial. One neglected therapeutic target, in these patients, is myocardial reperfusion injury, which describes myocardial injury and cell death that results, paradoxically, from reperfusing an acutely ischemic myocardium, and which contributes up to 50% of the final myocardial infarct (MI) size (1). Novel therapeutic interventions are required to protect the heart against myocardial reperfusion injury in order to reduce MI size, preserve left ventricular (LV) systolic function, and improve clinical outcomes in this patient group (2).

Remote ischemic conditioning (RIC) has emerged as a novel therapeutic intervention for protecting the heart against acute ischemia-reperfusion injury. RIC describes the endogenous cardioprotective effect elicited by applying ≥1 brief nonlethal cycle of ischemia and reperfusion to an organ or tissue remote from the heart (3,4). In the clinical setting, this can be implemented by inflating a blood pressure cuff placed on the upper arm or thigh to induce the RIC stimulus in the arm or leg (5). This noninvasive, low-cost, therapeutic intervention has been reported to be beneficial in patients undergoing coronary artery bypass graft surgery (6,7), and elective percutaneous coronary intervention (PCI) (8). More recently, RIC has been investigated in STEMI patients treated by PPCI (9,10).

Cardiac magnetic resonance (CMR) has emerged as the imaging modality of choice to assess the cardioprotective efficacy of novel therapeutic interventions in PPCI-treated STEMI patients. CMR accurately and reproducibly measures MI size (11), but more importantly, can also measure the myocardial salvage index (MSI) (12). MSI is a sensitive measure of cardioprotective efficacy, representing the proportion of the myocardium at risk of infarction "rescued" by a therapeutic intervention—this requires that the myocardium or area at risk (AAR) be quantified. The current CMR method for in vivo AAR estimation is to use T_2-weighted CMR imaging 2 to 7 days following PPCI to delineate the extent of myocardial edema (13–15). Recent studies of novel cardioprotective interventions have used MSI to demonstrate efficacy without reduction in absolute infarct size (16,17), but it has also been reported that the therapeutic intervention may itself reduce the extent of infarct-related myocardial edema (18), thereby precluding its use for calculating MSI.

Whether RIC can reduce MI size and, potentially, myocardial edema is unknown. In the current study, we use CMR to assess the cardioprotective efficacy of RIC in STEMI patients treated by PPCI.

METHODS

STUDY POPULATION. This study was approved by the UK National Research Ethics Service. Written informed consent was obtained from all participants. Patients were recruited in a consecutive manner from the Essex Cardiothoracic Centre between July 1, 2011 and April 30, 2013. Patient inclusion criteria were the following: age 18 to 80 years; presentation within 12 h of onset of chest pain, and ECG showing ST-segment elevation of ≥0.1 mV in 2 contiguous leads (≥0.2 mV in leads V_1 to V_3); pre-PCI TIMI (Thrombolysis In Myocardial Infarction) flow grade <1. Patient exclusion criteria were the following: cardiac arrest (pre- or post-PPCI procedure); cardiogenic shock; previous MI or coronary artery bypass graft surgery; significant coronary collateralization to the AAR (Rentrop grade ≥1); and any contraindication to CMR imaging.

EXPERIMENTAL PROTOCOL. In order to protect the heart against myocardial reperfusion injury, the therapeutic intervention has to be initiated prior to myocardial reperfusion. As such, patients were randomly assigned to either RIC or control protocols on arrival in hospital, and the allocated treatment was initiated prior to PPCI. A computer-generated randomization sequence was used. Sequentially numbered, sealed envelopes were opened after consent had been obtained, and these contained the study group assignment. Randomization, treatment allocation, and delivery of RIC were all performed by an unblinded investigator who was not involved with data collection or analysis. The PPCI operator, catheter laboratory and coronary care unit staff, the investigator collecting and analyzing the data, and the investigators analyzing the coronary angiograms and CMR scans were all blinded to the treatment allocation.

In patients randomized to the RIC treatment arm, a standard blood pressure cuff was placed on the upper arm and inflated to 200 mm Hg and left inflated at this pressure for 5 min. The cuff was then completely deflated and left for 5 min. This cycle was repeated 4 times, so that the total duration of the intervention was 40 min. If the patient's systolic blood pressure was >185 mm Hg, the cuffs were inflated to 15 mm Hg above that level. For radially performed PPCI, the RIC

protocol was performed on the contralateral arm. In patients randomized to the control treatment arm, a standard blood pressure cuff was placed on the upper arm and left uninflated for 40 min. The delivery of the RIC or control protocols did not delay the onset of PPCI (i.e., no delay in door-to-balloon time). If required, the protocols were continued and overlapped with the PPCI procedure.

Patients underwent PPCI according to local practice. The randomization affected no other aspect of treatment—specifically, the choice of adjunctive PPCI management was left entirely at the discretion of the blinded PPCI operator (thrombectomy, antiplatelet agents, and antithrombotic therapy). Blood samples were taken for high-sensitivity troponin T (hsTnT) at time 0 (prior to PPCI), 6, 12, and 24 h post-PPCI. A CMR scan was performed on days 3 to 6 post-PPCI.

STUDY ENDPOINTS. The pre-defined primary study endpoint was MI size measured by CMR and expressed as a percent of the LV mass. Secondary study endpoints included: MI size measured by peak levels of hsTnT and 24-h area-under-the-curve (AUC) hsTnT; MSI (defined as the AAR minus the MI size as a proportion of the AAR); the presence of microvascular obstruction on late gadolinium enhancement (LGE)

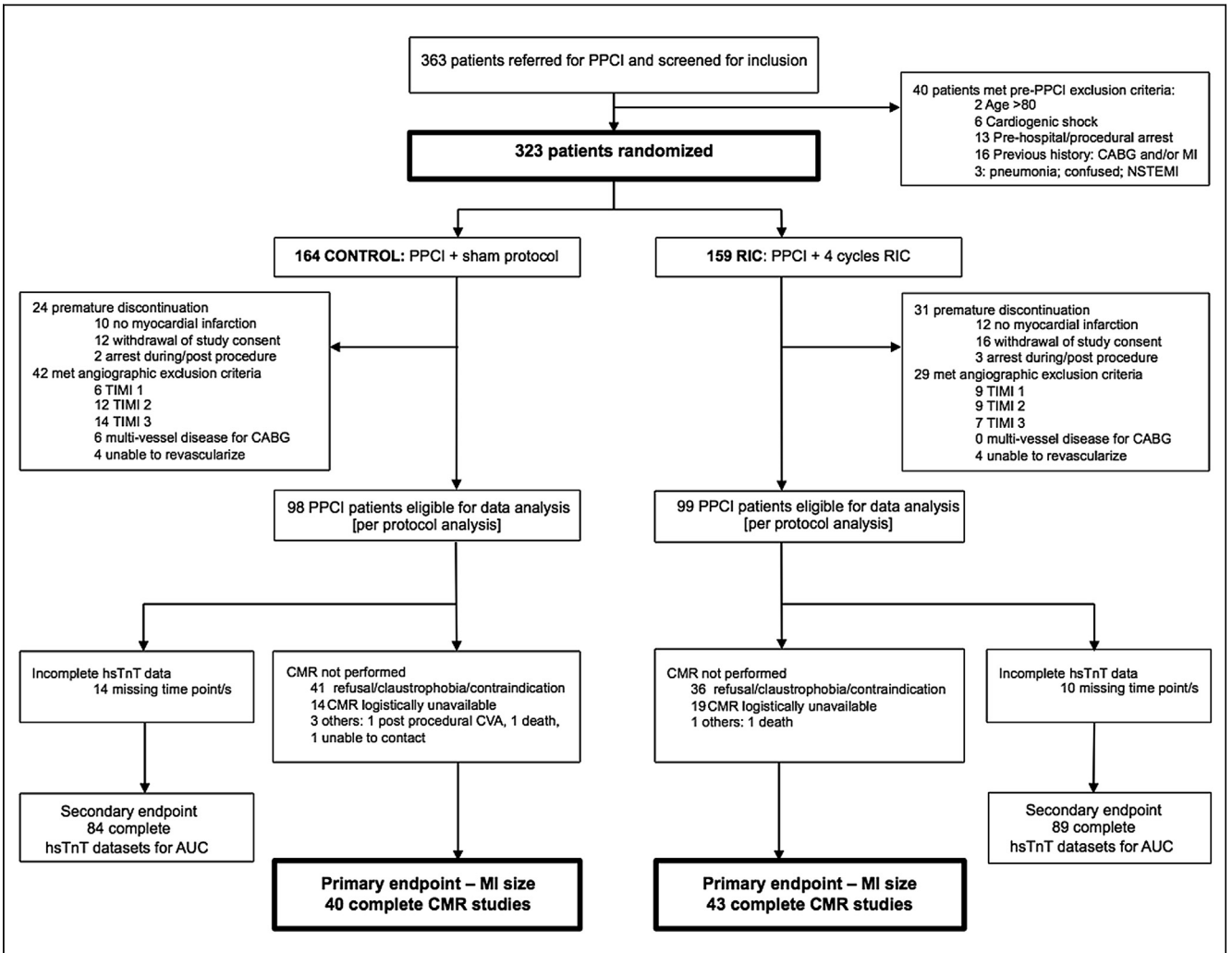

FIGURE 1 Study Profile

The flow chart shows how patients were randomized to the control group and remote ischemic conditioning (RIC) protocols and the primary and secondary endpoints of the study. AUC = area under the curve; CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance; CVA = cardiovascular accident; hsTnT = high-sensitivity troponin T; MI = myocardial infarct; NSTEMI = non-ST-segment elevation myocardial infarction; PPCI = primary percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

imaging; absolute and indexed LV volumes and ejection fraction.

High-Sensitivity Troponin T. This was measured quantitatively by a 1-step enzyme immunoassay on the basis of electro-chemiluminescence technology (Elecsys 2010, Roche, Switzerland). This assay can allow detection of concentrations <1.0 ng/l. These assays measure the upper reference limit with a coefficient of variation <10%. The threshold level of ≥14.0 ng/l indicates significant myocardial necrosis.

CMR Imaging of Myocardial Infarct Size and Myocardial Edema. All CMR imaging studies were performed on a 1.5-T MAGNETOM Avanto scanner (Siemens Healthcare, Erlangen, Germany) 3 to 6 days after admission for PPCI using a standard acute myocardial infarction protocol (19). LV volumes and mass measurements were calculated conventionally using dedicated software (CMR tools, Cardiovascular Imaging Solutions, London, United Kingdom), with papillary muscles considered as part of the LV myocardium. MI size was assessed by LGE CMR imaging 10 min after the injection of gadolinium (0.1 mmol/kg at 3 ml/s; Dotarem, Guerbet, France) with standard segmented "fast low angle single shot" inversion recovery gradient-echo sequence. The extent of myocardial edema (i.e., the AAR) corresponded to the area of increased T_2 values on native (pre-contrast), parametric T_2-mapping CMR imaging, when compared with the remote noninfarcted myocardium (20,21). A full stack of matched short-axis slices, 10 mm apart, was acquired of both LGE and T_2 maps to cover the LV from base to apex.

All CMR images were analyzed blinded to the treatment allocation and clinical details of each patient. Analysis of MI size and extent of myocardial edema was performed using an in-house macro written in ImageJ (National Institutes of Health, Bethesda, Maryland) (22). After manual tracing of the epicardial and endocardial borders, the areas of MI were quantified on LGE images using the semi-automated Otsu detection method, as previously validated by Vermes et al. (23) and further validated by our group as it gave the lowest inter- and intra-observer variability when compared with 9 other techniques (S. White, January 2014; unpublished data). Subendocardial zones of "dark" hypoenhancement (microvascular obstruction ± intramyocardial hemorrhage) within the area of hyperenhancement, were included in the infarct area. MI size equaled the total area of LGE expressed as a percent of the total area of LV myocardium. The mass of the MI (in grams of tissue) was calculated as Σ(total LGE area [cm^2] × slice thickness [cm] × myocardium-specific density [1.05 g/cm^3], and then indexed to the body surface area.

T_2-mapping CMR (20,21) was used to measure the extent of myocardial edema, as this sequence has been reported to be less susceptible to the imaging artefacts associated with traditional black-blood T_2-weighted CMR sequences, in particular, short tau inversion recovery (STIR) (21). The area of myocardial edema was quantified in the same way as for LGE, using the same semiautomated Otsu detection method (23) in LGE-matched slices (S. White, January 2014; unpublished data). Myocardial edema was assessed further—extrapolation of work by Higgins et al. (24) showing a linear relationship between T_2 values and percent of tissue water, might be inferred—by manually drawing regions of interest of the same size within: 1) the AAR, on T_2 maps, avoiding the presence of a central core of low T_2 values corresponding to microvascular obstruction ± intramyocardial hemorrhage; and 2) the remote myocardium, as previously described (18), to obtain mean T_2 values. Our methodology differed slightly from that by Thuny et al. (18) in that the whole of the AAR, and remote myocardium, was sampled (5 slice estimates per subject). Furthermore, the derivation of a signal intensity ratio was not required as absolute T_2 values are provided by the map.

CORONARY ANGIOGRAPHIC ANALYSIS. In order to provide an additional CMR-independent measure of

TABLE 1 Baseline Patient Characteristics and Treatments

	Patients With CMR		Per-Protocol Patients	
	Control Group (n = 40)	RIC Group (n = 43)	Control Group (n = 98)	RIC Group (n = 99)
Age, yrs	60 ± 11	57 ± 10	61 ± 10	58 ± 10
Male/female	30/10	37/6	76/22	81/18
BMI, kg/m^2	29.2 ± 4.6	28.8 ± 4.4	27.9 ± 4.4	28.7 ± 4.7
Smoking	21 (52)	20 (47)	53 (54)	47 (47)
Hypertension	12 (30)	8 (19)	30 (31)	22 (22)
Dyslipidemia	13 (33)	10 (23)	29 (30)	27 (27)
Medically treated diabetes	5 (13)	1 (2)	9 (9)	4 (4)
Family history of CAD	6 (15)	10 (23)	15 (15)	20 (20)
Pre-infarct angina	4 (10)	5 (12)	11 (11)	11 (11)
Duration of ischemia, min	189 (131, 290)	183 (129, 278)	183 (131, 283)	185 (131, 288)
Time from RIC to reperfusion, min	N/A	17.5 (13, 23)	N/A	16.0 (15, 19)
Treatment at time of PPCI				
Thrombectomy as first procedural device	32 (80)	35 (81)	74 (76)	84 (85)
Aspirin	40 (100)	43 (100)	98 (100)	99 (100)
Clopidogrel	35 (88)	34 (79)	74 (76)	69 (70)
Prasugrel	5 (12)	9 (21)	24 (24)	30 (30)
Abciximab	7 (18)	4 (9)	13 (13)	13 (13)
Bivalirudin	27 (68)	23 (53)	57 (58)	51 (51)

Values are mean ± SD, median (interquartile range), n, or n (%).

BMI = body mass index; CAD = coronary artery disease; CMR = cardiac magnetic resonance; N/A = not applicable; PPCI = primary percutaneous coronary intervention; RIC = remote ischemic conditioning.

the AAR, coronary angiograms were analyzed by 2 independent investigators blinded to the treatment allocation using the BARI (Bypass Angioplasty Revascularization Investigation) trial (25) and modified APPROACH (Assessment on the Prevention of Progression by Rosiblitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History) trial (26) angiographic scores. The AAR values determined by these 2 techniques were then used to estimate the MSI: combining CMR-derived infarct size (LGE, % LV) with the score (%LV) as previously described (27,28) and calculated as detailed earlier.

SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS. The primary endpoint of the study was MI size as measured by LGE CMR. In order to detect a 25% reduction in MI size (10-g infarct mass) from an infarct mass of 40 ±14 g (29) with 90% power, and at the 0.05 2-sided significance level, we would require a sample size of 42 per group, which equates to a total of 84 patients. Because of the need to commence the RIC protocol before reperfusion, randomization had to occur prior to PPCI, but also before a definitive decision could be made as to whether the patient had met specific inclusion criteria (e.g., TIMI flow grade 0). Therefore, it was expected that a large number of patients would be randomized and then later excluded from the study.

Continuous data were reported as mean ± SD (for data approximately normally distributed) or median and interquartile range (for non-normally distributed data). Categorical data were reported as frequencies and percents. Categorical variables were compared with the chi-square test or Fisher exact test in the case of small cell sizes. Similarly, the unpaired Student *t* test was used to compare continuous variables between 2 independent groups, ensuring first that the data was approximately normally distributed for the unadjusted analysis. Covariate-adjusted analyses were performed using multivariable logistic regression for continuous outcome variables. The assumptions of the linear regression models were assessed using residual analysis. Difference in medians was compared with the Wilcoxon-Mann-Whitney test. The standard error of medians and confidence intervals of the difference in hsTnT medians were calculated using the bootstrap method (30). The statistical analysis was conducted using SPSS (version 20, SPSS Inc., IBM, Armonk, New York) and Stata (version 12, Stata Corporation, College Station, Texas). All tests were 2-sided. A p value of <0.05 was considered statistically significant.

RESULTS

Three hundred and sixty-three patients with suspected STEMI were screened for study eligibility. Of these, 323 patients were randomized to receive either RIC or control protocols on immediate arrival at the PPCI center and proceeded to coronary angiography to confirm the diagnosis of STEMI and to exclude patients with pre-PPCI TIMI flow grade >0 (**Figure 1**): 1) 164 of these patients were

TABLE 2 Angiographic Findings (Per-Protocol Analysis)

	Per-Protocol Analysis							
	Patients With CMR				CMR Not Performed			
	Control Group	RIC Group	Difference (95% CI)	p Value	Control Group	RIC Group	Difference (95% CI)	p Value
Angiographic findings	40	43			58	56		
Infarct-related artery								
LAD	17 (43)	17 (40)			25 (43)	26 (46)		
CX	4 (10)	6 (14)			10 (17)	5 (9)		
RCA	19 (47)	20 (47)			23 (40)	25 (45)		
TIMI flow grade after PPCI								
3	39 (97.5)	34 (79)	N/A	0.03	54 (93)	50 (89)	N/A	0.70
2	1 (2.5)	9 (21)	N/A		4 (7)	6 (11)	N/A	
AAR by angiographic score, %LV								
BARI score	31.8 ± 7	29.4 ± 6	2.4 (-0.3 to 5.2)	0.09	29.6 ± 7	29.2 ± 7	0.4 (-2.2 to 3.1)	0.76
APPROACH score	32.8 ± 8	30.3 ± 7	2.5 (-0.8 to 5.9)	0.14	30.1 ± 7	29.8 ± 7	0.3 (-2.5 to 3.1)	0.83

Values are mean ± SD, n, or n (%) unless otherwise stated.

AAR = area at risk; APPROACH = Assessment on the Prevention of Progression by Rosiblitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History; BARI = Bypass Angioplasty Revascularization Investigation; CI = confidence interval; CX = circumflex artery; LAD = left anterior descending artery; %LV = percent of left ventricle; RCA = right coronary artery; TIMI Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

randomized to the control group, of whom 98 patients were eligible for per-protocol analysis, with 84 patients being included in the analysis for hsTnT levels, and of those 84 patients, 40 patients were analyzed for CMR outcomes; 2) 159 of these patients were randomized to the RIC group, of whom 99 patients were eligible for the per-protocol analysis, with 89 patients finally being analyzed for hsTnT levels, and of those 89 patients, 43 patients were analyzed for CMR outcomes. There were no major differences in the baseline patient characteristics and treatments between the 2 study arms (Tables 1 and 2). In the majority of patients, the RIC or control protocols overlapped with the beginning of the PPCI procedure, and blinding of the PPCI operator was maintained as the protocol was continued underneath the sterile drapes. There were no reported adverse outcomes with RIC. Representative CMR images from 3 different study patients are shown in Figure 2.

RIC Reduced MI Size in STEMI Patients. Compared with the control patients, STEMI patients who were administered RIC prior to PPCI had a reduction in MI size (measured by CMR and expressed as a percent of the LV) of 27% ($p = 0.009$) (Figure 3A). Furthermore, we found that the RIC, when compared with the control group, protocol reduced absolute MI mass ($p = 0.029$) (Table 3). Finally, the RIC, when compared with the control group, protocol also significantly reduced plasma levels of hsTnT at 24 h ($p = 0.037$) (Figure 3B and Table 3) and resulted in a nonsignificant reduction in total 24-h AUC hsTnT ($p = 0.09$) (Figure 3B; Table 3). In a multivariable analysis adjusting for the effects of baseline variables (age, sex, body mass index, smoking, hypertension, dyslipidemia, diabetes, family history of coronary artery disease, pre-infarct angina, ischemia time, BARI score, APPROACH score) the reduction in MI size remained statistically significant ($p = 0.025$).

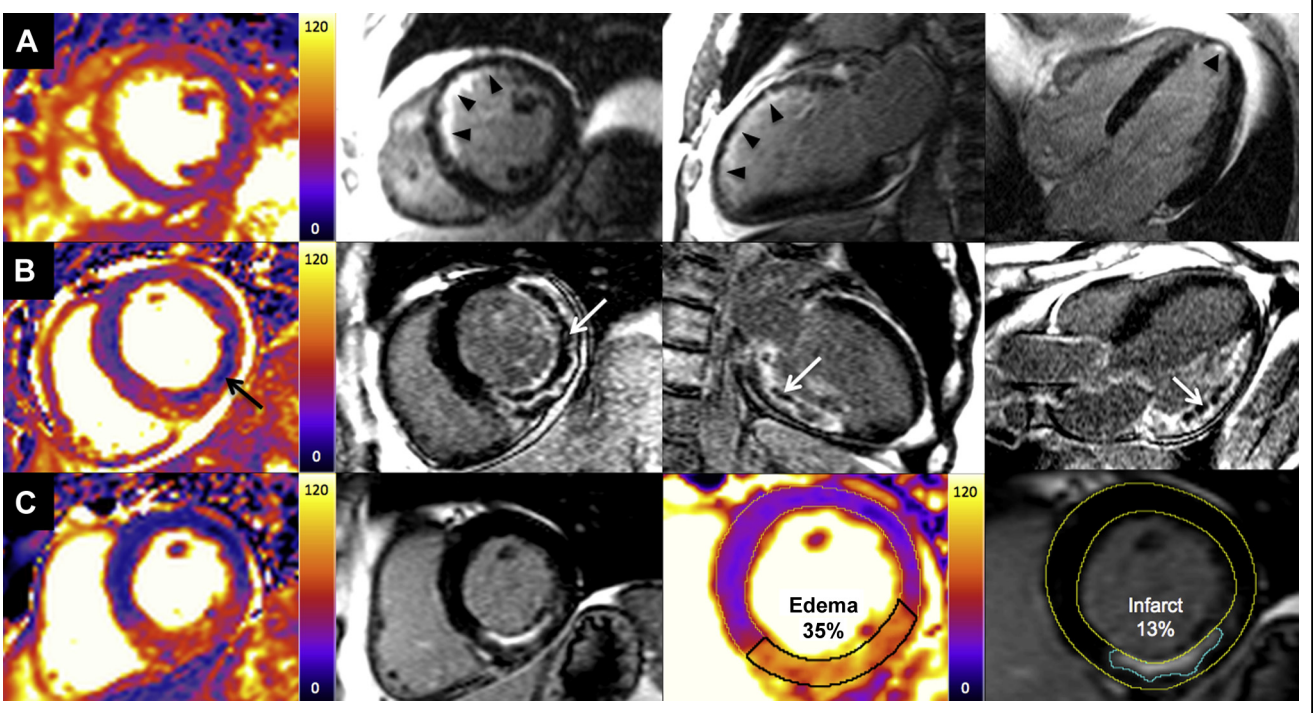

FIGURE 2 Representative CMR Images From 3 Patients

(A to C) Color parametric T2 maps depict the area of myocardial edema (**orange-yellow area**, short-axis view) and late gadolinium enhancement to assess myocardial infarct size in the short-axis view, and then long axis-views. The third and fourth images of **row C** illustrate how the areas of edema (increased T2 values) and infarct (late gadolinium enhancement) expressed as percentage of the LV were segmented in ImageJ. Patient **A**: Subendocardial myocardial infarction (with good salvage) in the left anterior descending coronary artery territory affecting the anteroseptum **(small black arrowheads)**. Patient **B**: Transmural myocardial infarction (with minimal salvage) in a dominant circumflex coronary artery territory, accompanied by microvascular obstruction **(dark hypointense core, long white arrows)**, and significant intramyocardial hemorrhage on the T2 map **(purple core, long black arrow)**. Patient **C**: Myocardial infarction in the inferior wall of the right coronary artery territory. CMR = cardiac magnetic resonance.

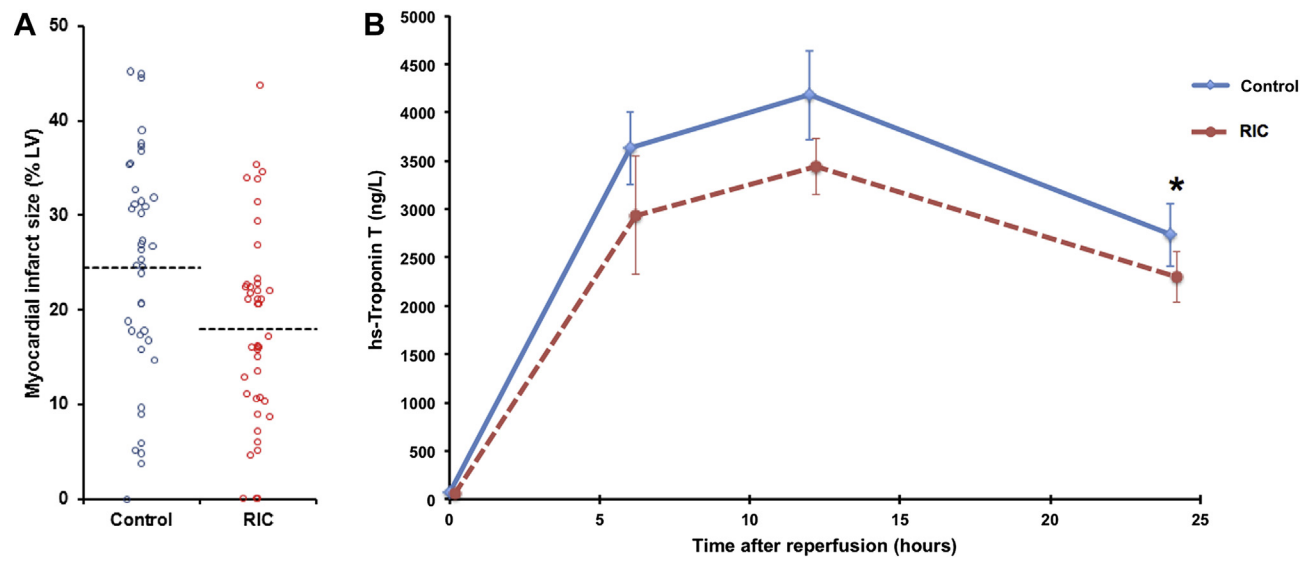

FIGURE 3 **MI Size of RIC Versus Control Patients**

(A) Patients randomized to remote ischemic conditioning (RIC), when compared to control patients, sustained a significantly smaller myocardial infarct (MI) size (percent of left ventricle, %LV), as measured by late gadolinium enhancement cardiac magnetic resonance: 18.0 ± 10% **(red)** versus 24.5 ± 12.0% **(blue);** p = 0.009. Individual values are plotted for all cardiac magnetic resonance subjects. **Dashed line** is the mean. **(B)** Patients randomized to RIC **(dashed line),** when compared to control patients **(solid line),** sustained a smaller MI size (area-under-the-curve high-sensitivity [hs] troponin T) (p = 0.09) and was significantly smaller at 24 h. *p = 0.037. The data was skewed, and the bootstrap method used to calculate standard error of medians. Values are median ± SEM.

RIC Reduced Myocardial Edema in STEMI Patients. With RIC, the extent of myocardial edema delineated by T_2-mapping CMR was reduced by 19% compared with that of the control patients (p = 0.003) (Figure 4A, Table 3). As expected, within the AAR, when compared to the remote myocardium, there was a significant increase in mean T_2 values in both RIC (p ≤ 0.0001) (Figure 4B, Table 3) and control patients (p < 0.0001) (Figure 4B). However, the RIC, when compared with the control, protocol also resulted in a modest but significant reduction in mean T_2 values within the AAR (p = 0.001) (Figure 4B). There was no reduction in mean T_2 values within the remote myocardium between the RIC and control groups (p = 0.633) (Figure 4B, Table 3). In a multivariable analysis that adjusted for the effects of baseline variables (age, sex, body mass index, smoking, hypertension, dyslipidemia, diabetes, family history of coronary artery disease, pre-infarct angina, ischemia time, BARI score, APPROACH score), the reduction in edema extent remained statistically significant (p = 0.003).

RIC Improved Myocardial Salvage in STEMI Patients. Because RIC was found to reduce the extent of myocardial edema, this precluded its use as a measure of the AAR and its validity to calculate MSI. However, using CMR-independent angiographic jeopardy scores (BARI and APPROACH) to estimate the AAR (Table 2), we found that the MSI was increased by >50% with the RIC, when compared with the control, protocol (p = 0.03) (Table 3).

DISCUSSION

This study shows that RIC saves the myocardium from infarction in STEMI patients treated by PPCI. It reduced MI size by 27% (both absolute in terms of grams of myocardial tissue and as a percent of the LV) and increased the MSI by >50%. There was also a significant reduction (19%) in hsTnT levels at 24 h in RIC-treated patients and a reduction in total 24-h AUC hsTnT. Unexpectedly, when compared with the control protocol, RIC reduced the extent of myocardial edema, precluding the use of this CMR technique to measure the AAR in the presence of RIC. The intervention—4 arm cuff inflations and deflations of a standard blood pressure cuff—is simple, low-cost, and does not delay the onset of PPCI. The barriers for the delivery of such a therapeutic intervention across a healthcare system would be low.

The actual mechanism through which RIC protects the myocardium from acute ischemia-reperfusion

TABLE 3 Study Outcomes

	Control Group	RIC Group	Difference (95% CI)	p Value
CMR findings	40	43		
Infarct size, %LV	24.5 ± 12	18.0 ± 10	6.5 (1.7–11.3)	0.009
Absolute infarct mass, g	26.0 ± 17	18.8 ± 12	7.2 (0.7–13.7)	0.029
Indexed infarct mass, g/m^2	12.9 ± 8	9.4 ± 6	3.5 (0.4–6.6)	0.026
T_2 extent of edema, %LV	35.1 ± 10	28.5 ± 9	6.6 (2.4–10.9)	0.003
Mean T_2 value, ms				
Remote myocardium	50.1 ± 2.0	49.9 ± 2.5	0.2 (-0.8 to 1.2)	0.633
Infarct zone	73.1 ± 6.1	68.7 ± 5.8	4.32 (1.7–6.9)	0.001
Myocardial salvage index				
Using CMR to estimate AAR	0.26 (0.15, 0.42)	0.35 (0.16, 0.57)	-0.07 (-0.17, to 0.03)	0.171
Using BARI to estimate AAR	0.27 ± 0.30	0.41 ± 0.28	-0.14 (-0.27 to -0.02)	0.028
Using APPROACH to estimate AAR	0.28 ± 0.29	0.42 ± 0.29	-0.14 (-0.27 to -0.01)	0.031
MVO	22 (55)	20 (47)		0.440
Left ventricular volumes and mass				
LVEDV, ml	152.2 ± 31	154.9 ± 31	-2.8 (-16.5 to 10.9)	0.687
LVESV, ml	65.7 ± 27	65.3 ± 24	0.4 (-10.8 to 11.5)	0.947
SV, ml	86.5 ± 16	89.6 ± 17	-3.2 (-10.3 to 3.9)	0.379
EF, %	57.9 ± 10	59.0 ± 10	-1.1 (-5.4 to 3.2)	0.603
Mass, g	165.0 ± 36	163.0 ± 37	2 (-13.9 to 17.8)	0.805
Indexed left ventricular volumes and mass				
LVEDVI, ml/m^2	76.1 ± 13	77.2 ± 13	-1.1 (-7.0 to 4.8)	0.712
LVESVI, ml/m^2	32.8 ± 12	32.5 ± 12	0.2 (-5.0 to 5.5)	0.936
SVI, ml/m^2	43.3 ± 7	44.6 ± 7	-1.3 (-4.4 to 1.8)	0.403
Mass-I, g/m^2	82.1 ± 13	80.8 ± 13	1.3 (-4.4 to 7.0)	0.651
hs troponin T, ng/l	84	89		
0 h	72 (26, 206)	65 (23, 115)	-7 (-43 to 26)	0.128
6 h	3,632 (1,000, 7,612)	2,937 (1,077, 6,598)	-695 (-2,154 to 758)	0.386
12 h	4,178 (1,867, 6,598)	3,443 (1,475, 5,950.5)	-735 (-1,747 to 382)	0.288
24 h	2,736 (1,427, 4,873)	2,296 (981, 4,008)	-440 (-1,201 to 396)	0.037
Total 24-h AUC	87,566 (34,992, 133,640)	65,244 (26,841, 111,600)	-22,322 (-47,844 to 10,248)	0.088

Values are mean ± SD, median (interquartile range), n, or n (%) unless otherwise stated.

AUC = area under the curve; EF = ejection fraction; hs = high sensitivity; LVEDV = left ventricular end-diastolic volume; LVEDVI = left ventricular end-diastolic volume index; LVESV = left ventricular end-systolic volume; LVESVI = left ventricular end-systolic volume index; Mass-I = mass index; MVO = microvascular obstruction; SV = stroke volume; SVI = stroke volume index; other abbreviations as in Tables 1 and 2.

currently remains unclear, although it has been suggested that a neurohormonal pathway conveys the cardioprotective signal from the remotely conditioned arm to the heart (4). The current paradigm suggests that an as yet unidentified humoral factor produced in response to the remote conditioning stimulus, which then conveys the protective signal to the heart, where known cardioprotective pathways are then activated (4). Interestingly, it appears that an intact neural pathway to the limb is required for the production of the humoral factor (31,32). Whatever the putative mechanism, RIC has been previously reported to protect the heart against acute ischemia-reperfusion injury in a number of different clinical settings including coronary artery bypass graft surgery (6,7), and elective PCI (8,33). More recently, 2 pioneering clinical studies have investigated the effect of RIC in STEMI patients treated by PPCI (9,10,34). In a small trial of 33 STEMI patients per group, Rentoukas et al. (9) failed to demonstrate any benefit with an abbreviated RIC protocol (3 4-min cycles of upper arm cuff inflation/deflation) in terms of ST-segment resolution and peak troponin I levels. In a larger study comprising 142 STEMI patients, Bøtker et al. (10) reported that RIC using the standard protocol (4 5-min cycles of upper arm cuff inflation/deflation) delivered in the ambulance, while transferring to the PPCI center, improved myocardial salvage assessed by single-photon emission computed tomography analysis 1 week post-PPCI. However, there was no reduction in absolute MI size seen in that study (10). Furthermore, although follow-up of this cohort seemed to suggest long-term benefit, the primary composite endpoint of major adverse cardiac and cerebrovascular event was driven by noncardiac mortality (35).

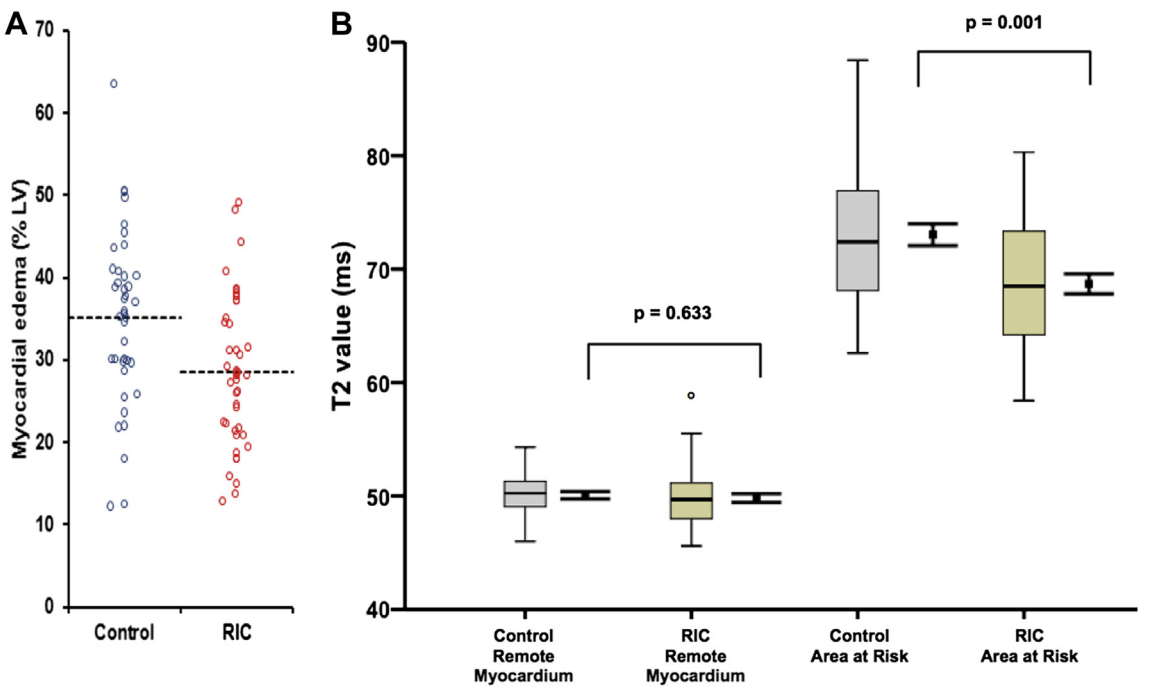

FIGURE 4 Reduction in Myocardial Edema and T2 Values in RIC Versus Control Patients

(A) In patients randomized to remote ischemic conditioning (RIC), the extent of myocardial edema delineated by quantitative T_2-mapping cardiac magnetic resonance (percent of the left ventricle, %LV) was significantly reduced when compared with that of control patients: 28.5 ± 9.0% **(red)** versus 35.1 ± 10.0% **(blue);** p = 0.003. Individual values are plotted for all cardiac magnetic resonance subjects. **Dashed line** is the mean. **(B)** Graph shows that in patients randomized to RIC, mean T_2 values in the area at risk assessed by quantitative T_2-mapping cardiac magnetic resonance were significantly reduced when compared with that of control patients (p = 0.001). However, there was no significant difference in mean T_2 values in the remote, noninfarcted myocardium between RIC and control patients (p = 0.633). Values are mean ± SEM **(error bars)** and median with IQR **(box plot)**. The **circle** (°) represents 1 outlying patient.

The reason for the positive effect of RIC in our study in terms of MI size reduction may relate to a number of factors: 1) we delivered the standard RIC protocol on arrival at the PPCI center; 2) we only selected STEMI patients with complete occlusion in the infarct-related artery (pre-PPCI TIMI flow grade 0), as these patients were less likely to have spontaneously reperfused and therefore most likely to benefit from RIC; and 3) we used CMR to measure the MI size reduction, which would be expected to be more sensitive than either serum cardiac enzymes and/or single-photon emission computed tomography analysis (36).

The ability to assess the cardioprotective efficacy of a novel therapeutic intervention in STEMI patients treated by PPCI, can be optimized by measuring MSI. The MSI offers a more sensitive measure of cardioprotective efficacy in cases where absolute MI size reduction is not detectable between the therapeutic intervention and control, because it "normalizes" for the differences in the AAR that exist between STEMI patients. T_2-weighted CMR is a histologically validated, noninvasive, imaging technique for retrospectively measuring the AAR (13–15), but it has evoked controversy, and traditional sequences (e.g., black-blood STIR) are recognized to have limitations (37,38). Newer sequences have improved on this (39,40). We chose to use T_2-mapping CMR in this study for the following reasons: there is evidence to support that it is more robust when compared with traditional STIR imaging (21); it has recently been histologically validated (41); and it provides a data output map that is quantitative.

We found that RIC not only reduced the extent of myocardial edema, but it also lowered T_2 values within the AAR. Similarly, Thuny et al. (18) found that ischemic post-conditioning, another "mechanical" therapeutic intervention for reducing myocardial reperfusion injury in STEMI patients, also reduced myocardial edema and the signal hyperintensity, which was delineated by traditional STIR T_2-weighted CMR imaging. These findings suggest that for these specific interventions, CMR edema imaging should not be used to measure the AAR and calculate MSI,

and other measures of AAR should be considered (e.g., single-photon emission computed tomography or angiographic jeopardy scores (25–28)).

In contrast, other therapeutic interventions for preventing acute ischemia-reperfusion injury in PPCI-treated STEMI patients—exenatide (17); therapeutic hypothermia (16); metoprolol (42)—have improved myocardial salvage without affecting the extent of myocardial edema delineated by T_2-weighted CMR. This suggests that whether the therapeutic intervention affects myocardial edema may be specific to the therapy under investigation. Further work is needed to better understand the pathophysiology of myocardial edema in the setting of a reperfused MI.

STUDY LIMITATIONS. A large number of patients were randomized but were not included in the final CMR analysis (**Figure 1**). The main reasons for this included: 1) patient randomization took place prior to coronary angiography, before a definitive diagnosis of STEMI could be confirmed; and 2) a proportion of randomized patients had pre-PCI TIMI flow grade >0 and were thus excluded. Despite achieving a significant reduction in the primary study endpoint, we found only a trend to reduction in hsTnT. We believe that the study was underpowered for this secondary endpoint and recruitment was designed to detect MI size by a more sensitive method (CMR). This has also been seen in similar, yet positive studies (10).

CONCLUSIONS

In this randomized study, we have demonstrated that RIC delivered on arrival in-hospital can reduce MI size assessed by CMR, in STEMI patients treated by PPCI. Importantly, RIC was also found to reduce the extent of myocardial edema, thereby precluding its use to measure the AAR and calculate the MSI for this therapeutic intervention. A large multicenter randomized controlled clinical trial is now needed to investigate whether the reduction in MI size we observed will result in improved clinical outcomes in STEMI patients treated by PPCI.

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