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Efficacy of comprehensive remote ischemic conditioning in elderly patients with acute ST-segment elevation myocardial infarction underwent primary percutaneous coronary intervention

Yan-Ling WANG[1], Qi YANG[2], Cheng-Yan HU[1], Yan-Yan CHU[1], Zheng SUN[3], Huan ZHAO[1], Zhi LIU[1,✉]

1. Department of Cardiology, Xuanwu Hospital, Capital Medical University, Beijing, China; 2. Department of Radiology, Chaoyang Hospital, Capital Medical University, Beijing, China; 3. Department of Radiology, Xuanwu Hospital, Capital Medical University, Beijing, China

✉ Correspondence to: xwyy168@sina.com

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ABSTRACT

BACKGROUND Remote ischemic conditioning (RIC) is used to protect against myocardial injury. However, there is no adequate evidence for comprehensive RIC in elderly patients with ST-segment elevation myocardial infarction (STEMI). This study aimed to test whether comprehensive RIC, started pre-primary percutaneous coronary intervention (PPCI) and repeated daily on 1–30 days post-PPCI, can improve myocardial salvage index (SI), left ventricular ejection fraction (LVEF), Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and 6-min walk test distance (6MWD) in elderly patients with acute STEMI during 12 months follow-up.

METHODS 328 consenting elderly patients were randomized to receive standard PPCI plus comprehensive RIC (the treatment group) or standard PPCI (the control group). SI at 5–7 days after PPCI, LVEF, left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), KCCQ-CSS, 6MWD and adverse events rates were measured and assessed.

RESULTS SI was significantly higher in the treatment group [interquartile range (IQR): 0.38–0.66, $P = 0.037$]. There were no significant differences in major adverse events at 12 months. Although the differences of LVEDVI, LVESVI and LVEF between the treatment group and the control group did not reach statistical significance at 6 months and 12 months, LVEF tended to be higher, LVEDVI tended to be lower in the treatment group. The KCCQ-CSS was significantly higher in the treatment group at 1 month (IQR: 46.5–87, $P = 0.001$) and 12 months (IQR: 55–93, $P = 0.008$). There was significant difference in 6MWD between the treatment group and the control group (IQR: 258–360 *vs.* IQR: 250–345, $P = 0.002$) at 1 month and (IQR: 360–445 *vs.* IQR: 345–432, $P = 0.035$) at 12 months. A modest correlation was found between SI and LVEF ($r = 0.452$, $P < 0.01$), KCCQ-CSS ($r = 0.440$, $P < 0.01$) and 6MWD ($r = 0.384$, $P < 0.01$) respectively at 12 months.

CONCLUSIONS The comprehensive RIC can improve SI, KCCQ-CSS and 6MWD. It may be an adjunctive therapy to PPCI in elderly patients with STEMI.

Acute ST-segment elevation myocardial infarction (STEMI) is one of the most common causes of mortality and disability. Over the past decades, mortality rate of STEMI is higher among the older versus the younger. Higher age, left main coronary artery or three-vessel disease, and neurological disorders were stronger predictors of mortality and heart failure (HF) in the elderly.[1,2] Primary percutaneous coronary intervention (PPCI) is effective in opening the infarct-related artery and is the first recommended therapy for STEMI.[3] However, an increasing number of survivors are at risk of larger infarct size and ensuing left ventricular (LV) dysfunction and HF.[4] Ischemia-reperfusion injury (IRI) is believed to account for up to 40% to 50% of that.[5] New treatments are needed

to reduce IRI, increase myocardial salvage, preserve cardiac function, and reduce the incidence of HF and death.[6] At the same time, new treatments should improve the quality of life (QOL) and capacity for activities of patients with acute myocardial infarction (AMI), especially among the elderly.

Remote ischemic conditioning (RIC) is an approach, in which brief episodes of ischemia distant from the heart are used to protect against myocardial injury.[7] At the onset of reperfusion with PPCI, RIC has been shown to reduce the final infarct size assessed by gated single-photon emission computed tomography, decrease the extent of LV dysfunction as well as diminish major adverse cardiac and cerebral events.[8] However, it should be noted that not all studies have been positive.[9] Maybe, the use of biochemical biomarkers of myocardial injury may compromise the possibility to reproduce minor changes in infarct size than by imaging modalities for quantification of infarct size and myocardial salvage.[10]

Recent experimental animal studies have demonstrated that in addition to its acute effect, repeated bouts of daily RIC applied after myocardial infarction (MI) for weeks may bring a dose-dependent improvement in LV remodelling.[11] But, Vanezis, *et al.*[12] have shown that daily RIC starting on third day and continued for four weeks following successful PPCI for STEMI did not improve LV ejection fraction (LVEF) as assessed by cardiovascular magnetic resonance (CMR) and Kansas City Cardiomyopathy Questionnaire after four months when compared with a matched control group. Daily RIC was only started on third day post-PPCI in that study, which might be too late to observe any beneficial effects.

China is entering an aging society and there is no adequate evidence for comprehensive RIC in elderly patients with STEMI. So, the aim of this study was to test whether comprehensive RIC, started pre-PPCI and repeated daily on 1–30 days post-PPCI, as an adjunctive therapy in elderly patients with STEMI can improve salvage index (SI), LVEF, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and 6-min walk test distance (6MWD) during long-term follow-up.

METHODS

Study Population

This prospective, single-centre randomised controlled trial was conducted at Xuanwu Hospital of Capital Medical University, Beijing, China from September 2016 to December 2019. This research protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University (D2014044) in Beijing, China. Every participant signed an informed consent after agreeing with the trial. The age of participants ranged from 60 years to 85 years. All participants presented within 12 h of symptom onset. The inclusion criteria were as follows: (1) chest pain more than 30 min; (2) new ST-segment elevation in at least two contiguous leads ≥ 0.1 mV or new left bundle branch block in electrocardiogram; and (3) serum cardiac troponin I (TnI) ≥ 0.02 ng/mL. The exclusion criteria were as follows: (1) previous MI, coronary artery bypass grafting, PCI, thrombolytic therapy within previous 30 days; (2) cardiogenic shock; (3) evidence of lower-limb ischemia precluding use of RIC, contraindications to CMR; (4) severe hepatic or renal insufficiency; (5) life expectancy < 12 months due to noncardiac disease; and (6) unable to walk because of noncardiac limitations.

Randomization and Protocols for Comprehensive RIC

A computer-generated randomization schedule was used to randomly assign participants in a 1:1 ratio to standard PPCI (the control group), or standard PPCI plus comprehensive RIC (the treatment group). After randomization, comprehensive RIC were started immediately before PPCI and repeated daily for 30 days after PPCI. RIC consisted of four cycles of alternating 5-min inflation and 5-min deflation by two standard upper-arm blood pressure cuffs to 200 mmHg of an auto-control RIC training device (Patent Number: ZL201410834305.2). Before PPCI, the first RIC was begun immediately after randomization. If four cycles of RIC had not been fully completed, the cuff would be adjusted to unilateral upper-arm in case of radial access during PPCI. After PPCI, RIC was performed once daily on 1–30 days. The control participants did not undergo any RIC interventions. The study personnel taught each participant and family members of the treatment group how to operate the device and send a RIC alert message by WeChat after discharge. Participants were required to hand in the device's record list to the investigators at their follow-up.

PPCI and Standard Therapy

All patients would receive standard-of-care therapy according to institutional guidelines. PPCI was performed via a radial arterial approach (femoral access, if necessary). All patients received aspirin 300 mg (followed by 100 mg once daily, indefinitely) and clopidogrel 600 mg (followed by 75 mg once daily for ≥ 12 months) or ticagrelor 180 mg (followed by 90 mg twice daily for ≥ 12 months) and were anticoagulated with a heparin bolus (70–100 U/kg) before PPCI. The PCI strategy was at the discretion of the treating interventional cardiologist according to conventional practice. All other medication was given at the discretion of the attending physician according to the guidelines. Venous blood samples were obtained and TnI would be measured every 6 h within 24 h of admission.

CMR and Echocardiography

Imaging with CMR were performed at 5–7 days after PPCI using a 3.0T magnetic resonance imaging (MRI) scanner (Magnetom Verio; Siemens Healthcare, Erlangen, Germany). A gadolinium-based contrast agent of 0.2 mmol/kg (Magnevist, Bayer Healthcare, Germany) was administered. Cine MRI images was acquired using a retrospectively electrocardiogram-gated, steady-state free precession cine MRI technique in short-axis and long-axis views of the heart. T2-weighted cardiac MRI was performed by short inversion time inversion recovery dark blood technique with single slice breath-hold acquisition and inversion recovery preparation. The amount of area at risk, myocardial salvage and final infarct size were acquired and expressed as a percentage of the LV mass volume. SI was calculated as: myocardial salvage/area at risk (Figure 1).[13] Quantitative CMR image analysis was performed using a commercial software (CVI42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada).

Echocardiography was performed within 24 h of PPCI, and repeated 6 months, 12 months after intervention. LVEF, LV end-diastolic volume index (LVEDVI) and LV end-systolic volume index (LVESVI) were analyzed by individuals who were blinded to all clinical and angiographic data, using a commercially available ultrasound system (Vivid 7, GE Healthcare, Horten, Norway). LVEF was assessed by the modified biplane Simpson rule.

Study Endpoints

All patients alive were followed up for up to 12 months after discharge and would be required to return for clinic visits at 1 month, 6 months, and 12 months, respectively. In addition, the standardized protocol also included telephone contacts and the recording of recurrent cardiac events.

The primary endpoints were LVEF at 12 months and SI at 5–7 days after PPCI. The secondary endpoints were major adverse events at 12 months, KCCQ-CSS and 6MWD at 1 month and 12 months. Major

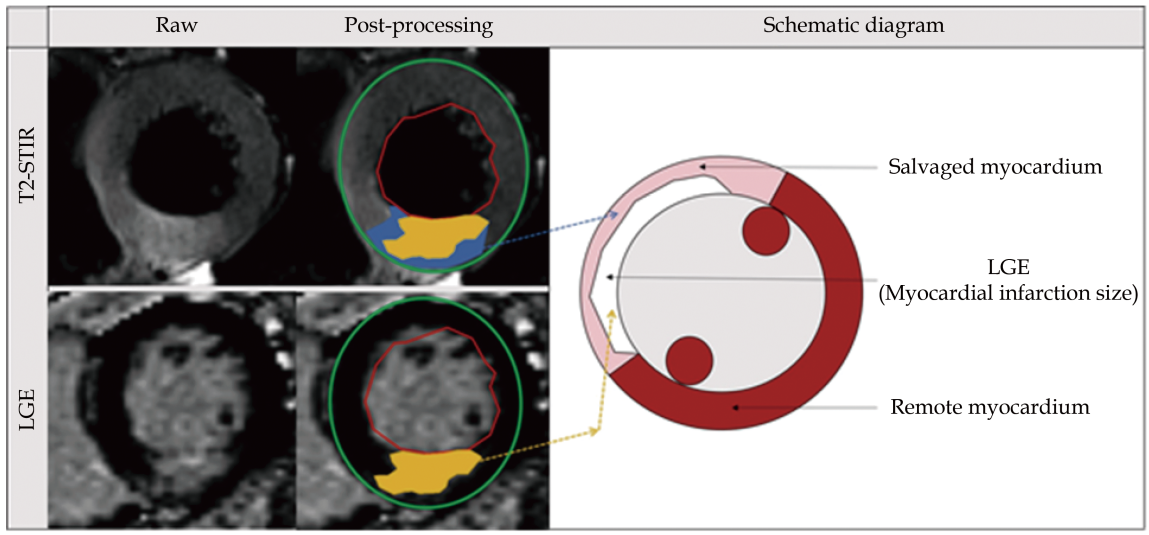

Figure 1 Cardiovascular magnetic resonance images of area at risk, myocardial salvage and final infarct size. LGE: late gadolinium enhancement.

adverse events included cardiac death, hospital readmissions with HF, unstable angina, recurrent infarction, and ischemic stroke/transient ischemic attack. The medical notes were then reviewed to confirm the details and the cause of death. The KCCQ-CSS captures physical limitation and total symptom scores of HF scaled from 0 to 100, with higher scores indicating better Health-Related Quality of Life. The 6MWD was carried out as follows: after resting seated for 10 min, patients were instructed to walk as fast and as long as possible, in a 30 m obstacle-free corridor for 6 min. The total distance was measured, rounding to the nearest meter.

Statistical Analysis

The primary endpoint was LVEF after AMI at 12 months. As reported changes in LVEF after MI,[14] an absolute difference in LVEF of 5% between the treatment group and the control group is regarded as a clinically relevant improvement. A sample of 75 patients at least in each group was needed for an alpha level 0.05% and 80% power using a two-sided test. To allow for a drop-out rate of 20% and to expand the sample size, 328 patients were recruited eventually.

Continuous variables were expressed as mean ± SD or median (interquartile range, IQR) and compared by use of the independent Student's *t*-test or the Mann-Whitney *U* test when appropriate. Categorical variables were expressed as counts (percentages) and compared by the Pearson's chi-squared test or the Fisher's exact probability test. The Kaplan-Meier method was used for cumulative event-free survival analysis, and the log-rank test for assessing the statistical differences between the curves. Pearson correlation analysis was applied to evaluate the relationship among SI, KCCQ-CSS and 6MWD. Two-sided *P*-value < 0.05 were considered statistically significant. All statistical analyses were performed with SPSS 21.0 (SPSS Inc., IBM, Armonk, NY, USA).

RESULTS

The Baseline Characteristics

We assessed 652 patients with STEMI for eligibility at arrival to the emergency department of Xuanwu Hospital of Capital Medical University, Beijing, China. After screening by inclusion criteria and exclusion criteria, a total of 328 consenting elderly patients were randomized to receive either standard PPCI (the control group, 163 patients), or standard PPCI plus comprehensive RIC (the treatment group, 165 patients). Participants in the treatment group and the control group were well matched in terms of baseline characteristics and demographics (Table 1). There were no significant differences between the treatment group and the control group in baseline levels of systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin, alanine transaminase, serum creatinine and low-density lipoprotein cholesterol. Discharge medication was very similar between the treatment group and the control group with high use of optimal medical therapy.

Comprehensive RIC and PPCI Procedure

Apart from mild pain in the treated time and temporary spots, the repeated daily RIC procedure was well tolerated by all of participants. Infarct-related artery and vessels with clinically significant disease, TIMI flow pre-PCI and symptom-to-balloon time were similar between the treatment group and the control group; the frequencies comparison of TIMI flow grade III post-PCI, thrombus evacuation, stenting and intra-aortic balloon pump between the treatment group and the control group were not statistically significant. There was no significant difference in medications of peri-PCI between the treatment group and the control group with high use of optimal medical therapy (Table 2).

Outcomes of CMR

Although there were no differences in area at risk (percentage of LV), myocardial salvage (percentage of LV) and infarct size (percentage of LV) between the treatment group and the control group, the median SI was significantly higher in the treatment group (0.55, IQR: 0.38–0.66) than in the control group (0.50, IQR: 0.36–0.60) ($P = 0.037$) at 5–7 days after PPCI (Table 3).

Peak TnI and Echocardiography

There was no difference in peak TnI between the

Table 1 Periprocedural demographic and clinical data of patients randomized to the treatment group and the control group.

Variables	Control group (n = 163)	Treatment group (n = 165)	P-value
Demographics			
Age, yrs	67.94 ± 5.48	68.84 ± 5.42	0.140
Male	129 (79.1%)	130 (78.8%)	0.937
Risk factors			
Diabetes mellitus	53 (32.5%)	52 (31.5%)	0.846
Hypertension	95 (58.3%)	86 (52.1%)	0.262
Dyslipidemia	51 (31.3%)	50 (30.3%)	0.847
Previous stroke	24 (14.7%)	20 (12.1%)	0.489
Current smokers	103 (63.2%)	102 (61.8%)	0.797
Body mass index, kg/m^2	25.08 ± 5.19	25.43 ± 4.25	0.505
Clinical details			
Systolic blood pressure, mmHg	111.13 ± 16.93	112.53 ± 18.78	0.478
Diastolic blood pressure, mmHg	63.06 ± 10.01	62.53 ± 9.97	0.633
Heart rates, beats/min	69.83 ± 16.50	67.96 ± 15.05	0.286
Hemoglobin, g/L	124.10 ± 15.27	123.10 ± 14.35	0.541
Alanine transaminase, IU/L	40.74 ± 25.71	42.12 ± 28.54	0.645
Serum creatinine, μmol/L	78.87 ± 34.16	79.91 ± 59.50	0.85
Low-density lipoprotein cholesterol, mmol/L	2.76 ± 0.92	2.77 ± 0.89	0.94

Data are presented as means ± SD or n (%).

treatment group and the control group (median: 21.0 ng/mL *vs.* 21.2 ng/mL, IQR: 5.4–37.7 *vs.* IQR: 8.1–50.0, P = 0.215) after PPCI. Median baseline LVEF was not significantly different between the treatment group (46.0%, IQR: 41.0–57.0) and the control group (47.0%, IQR: 40.0–56.0) (P = 0.635). The baseline LVEDVI and LVESVI were also similar between the treatment group and the control group. Similarly, there were no significant differences in LVEDVI, LVESVI and LVEF between the treatment group and the control group at 6 months and 12 months during the follow-up period.

Although differences did not reach statistically significant, LVEF tended to be higher, and LVEDVI tended to be lower in the treatment group at 12 months.

Follow-up Information at 12 Months

Follow-up information was available for all 328 randomized patients at 12 months, with no patients lost to follow-up. There were 30 adverse events (9.1%) at 12 months after PPCI. There was no significant difference in major adverse events between the treatment group (one cardiac death, five hospital readmissions with HF, four unstable angina, three recurrent infarction, and one ischemic stroke/transient ischemic attack) and the control group (two cardiac deaths, seven hospital readmissions with HF, four unstable angina, two recurrent infarction, and one ischemic stroke/transient ischemic attack). Kaplan-Meier curves of adverse event-free survival proved the above result (χ^2 = 0.165, P = 0.685 by log-rank test; Figure 2).

KCCQ-CSS and 6MWD at 1 Month and 12 Months

The KCCQ-CSS was significantly higher in the treatment group at 1 month (IQR: 46.5–87, P = 0.001) and 12 months (IQR: 55–93, P = 0.008). There was also significant difference in 6MWD between the treatment group and the control group (IQR: 258–360 *vs.* IQR: 250–345, P = 0.002) at 1 month and (IQR: 360–445 *vs.* IQR: 345–432, P = 0.035) at 12 months (Table 3).

The Correlation Between SI and LVEF, KCCQ-CSS and 6MWD at 12 Months

A modest correlation was found between SI and LVEF (r = 0.452, P < 0.01), KCCQ-CSS (r = 0.440, P < 0.01) and 6MWD (r = 0.384, P < 0.01) respectively at 12 months (Table 4).

Table 2 Angiographic and periprocedural data of patients randomized to the treatment group and the control group.

Variable	Control group (n = 163)	Treatment group (n = 165)	P-value
Infarct-related artery			
Left anterior descending artery	75 (46.0%)	79 (47.9%)	0.989
Right coronary artery	61 (37.4%)	59 (35.8%)	
Circumflex coronary artery	25 (15.3%)	25 (15.2%)	
Not identifiable	2 (1.2%)	2 (1.2%)	
Vessels with clinically significant disease			
0	2 (1.2%)	2 (1.2%)	0.978
1	93 (57.1%)	97 (58.8%)	
2	23 (14.1%)	24 (14.5%)	
3	45 (27.6%)	42 (25.5%)	
TIMI flow pre-PCI			
0	116 (71.2%)	127 (77.0%)	0.214
I	20 (12.3%)	15 (9.1%)	
II	16 (9.8%)	8 (4.8%)	
III	11 (6.7%)	15 (9.1%)	
Thrombus evacuation	34 (20.9%)	44 (26.7%)	0.217
Symptom-to-balloon time, min	356 (267–462)*	345 (256–456)*	0.308
Stenting of culprit lesion	149 (91.4%)	152 (92.1%)	0.815
Intra-aortic balloon pump	10 (6.1%)	14 (8.5%)	0.414
TIMI flow post-PCI			
0	4 (2.5%)	3 (1.8%)	0.948
I	5 (3.1%)	5 (3.0%)	
II	15 (9.2%)	13 (7.9%)	
III	139 (85.3%)	144 (87.3%)	
Medications of peri-PCI			
Aspirin	163 (100%)	165 (100%)	1.0
Clopidogrel	151 (92.6%)	156 (94.5%)	0.480
Ticagrelor	12 (7.4%)	9 (5.5%)	0.480
Heparin	163 (100%)	165 (100%)	1.0
Abciximab	52 (31.9%)	41 (24.8%)	0.156
Angiotensin-converting enzyme inhibitors/ Angiotensin II receptor blockers	138 (84.7%)	144 (87.3%)	0.496
Beta-blocker	126 (77.3%)	139 (84.2%)	0.111
Statin	155 (95.1%)	162 (98.2%)	0.120
Diuretic	20 (12.3%)	15 (9.1%)	0.351

Data are presented as n (%). *Presented as median (interquartile range). PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction.

DISCUSSION

The principal finding from this prospective randomized trial testing the cardioprotective effect of comprehensive RIC is clinically feasible and effective in increasing SI, KCCQ-CSS and 6MWD in the elderly patients with STEMI.

In our study, the myocardial SI assessed by CMR was significantly higher in the treatment group at 5–7 days after AMI, although there were no differences in area at risk, infarct size and peak TnI between

Table 3 Peak TnI, echocardiography, cardiovascular magnetic resonance data, KCCQ-CSS and 6MWD of patients randomized to the treatment group and the control group.

Variable	Control group (n = 163)	Treatment group (n = 165)	P-value
Within 24 h after PPCI			
Peak TnI, ng/mL	21.2 (8.1–50.0)	21.0 (5.4–37.7)	0.215
LVEDVI, mL/m^2	81.2 (70.5–96.0)	80.9 (73.9–90.2)	0.180
LVESVI, mL/m^2	45.0 (34.4–59.9)	44.8 (36.0–54.1)	0.183
LVEF, %	47.0 (40.0–56.0)	46.0 (41.0–57.0)	0.635
5–7 days after PPCI			
Salvage index	0.50 (0.36–0.60)	0.55 (0.38–0.66)	0.037
Area at risk, percentage of LV	25.3% (17.3–35.7)	26.4% (18.0–37.2)	0.779
Myocardial salvage, percentage of LV	12.30% (6.91–16.70)	13.55% (7.0–20.01)	0.187
Infarct size, percentage of LV	11.6% (7.1–20.3)	10.4% (7.0–18.6)	0.246
1 month after PPCI			
KCCQ-CSS	70 (39–82)	81 (46.5–87)	0.001
6MWD, m	303 (250–345)	335 (258–360)	0.002
6 months after PPCI			
LVEDVI, mL/m^2	84.6 (73.9–98.4)	81.3 (72.0–92.1)	0.091
LVESVI, mL/m^2	49.6 (38.9–61.0)	47.5 (33.9–55.2)	0.061
LVEF, %	49.0 (42.0–57.8)	50.6 (43.0–58.0)	0.146
12 months after PPCI			
LVEDVI, mL/m^2	88.3 (77.4–104.1)	86.0 (73.9–97.6)	0.065
LVESVI, mL/m^2	48.3 (37.4–64.1)	47.0 (30.0–68.0)	0.107
LVEF, %	51.0 (44.0–58.5)	53.0 (45.0–58.7)	0.117
KCCQ-CSS	76 (46–89)	86 (55–93)	0.008
6MWD, m	403 (345–432)	425 (360–445)	0.035

Data are presented as median (interquartile range). KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LV: left ventricular; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index; PPCI: primary percutaneous coronary intervention; TnI: troponin I; 6MWD: 6-min walk test distance.

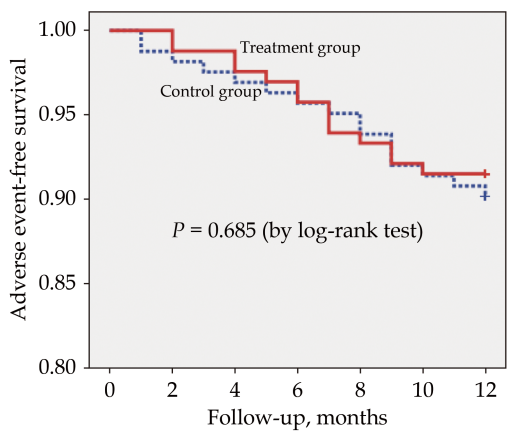

Figure 2 Kaplan-Meier curves of adverse events at 12 months between the treatment group and the control group.

the treatment group and the control group. Our results are consistent with the study by Bøtker, *et al.*,[8] in the proof-of-concept study, the per-RIC stimulus was administered during ambulance transfer to PPCI, resulting in a significant increase in myocardial salvage by 36% measured by myocardial perfusion imaging. Rapid admission and acute interventional treatment combined with modern antithrombotic pharmacologic therapy frequently establish complete reperfusion and acutely stabilize the patient, which may be major factors in determining area at risk, infarct size and peak TnI and which may be the dominant course of no differences in above three indicators between the treatment group and the control group in our study.[15,16] The increasing of myocardial SI represents the decreasing of microvascular obstruction, another clinically detectable marker of microvascular injury, correlates with LV remodelling and function in long-term post-AMI.[17–19]

Table 4 Correlation between salvage index and LVEF, KCCQ-CSS and 6MWD.

Variable	Salvage index	*P*-value
LVEF, 12 months	$r = 0.452$	< 0.01
KCCQ-CS	$r = 0.440$	< 0.01
6MWD	$r = 0.384$	< 0.01

KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF: left ventricular ejection fraction; 6MWD: 6-min walk test distance.

However, the reperfusion itself further increases to the damage in the myocardium compromising the long-term outcome.[20] RIC is a cardioprotective tool which has shown promise in preclinical and clinical trials in the context of acute ischemia.[21] In addition, in a rat model of acute MI, Wei, *et al.*[11] observed a dose-dependent improvement in LV remodelling as well as survival to 84 days in the treatment group given RIC for 28 days compared with the control group given RIC only at the time of MI. This suggests that repeated daily RIC post-MI may provide distinct and separate benefits, especially on LV remodelling and function.[22]

While, in our study, there were no significant differences in LVEDVI, LVESVI and LVEF between the treatment group and the control group. PPCI and modern pharmacologic therapy for AMI including antithrombotic, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blocker and statins play an important role in preventing cardiac remodelling and protecting cardiac function. Benefits of repeated daily RIC may be covered up by these clinical standard treatments. Although differences did not reach statistically significant, LVEF tended to be higher, and LVEDVI tended to be lower in the treatment group. So, it still showed the benefits on LV remodelling and function of repeated daily RIC. In the preclinical study by Wei, *et al.*,[11] these beneficial changes were accompanied by positive modulation of key remodelling processes, such as a reduction in oxidative stress, attenuation of the expression of genes associated with fibrosis and hypertrophy, and blunting of the inflammatory response with reduced levels of neutrophil and macrophage infiltration in the myocardium. These effects are beyond of a single RIC application at the time of MI.

In our study, SI correlated moderately well with LVEF, KCCQ-CSS and 6MWD. Exercise capacity and QOL are important aspects of the patient journey that could be ameliorated by novel therapeutics in patients with AMI. For this reason, recent the United States Food and Drug Administration guidance states that improvement in QOL and exercise capacity (without a favorable effect on hard endpoints) are valid for approving drugs for HF, suggesting that they should be used more commonly as important endpoints in HF clinical trials.[23] In our study, increased SI helped with QOL and exercise capacity improvement. It is well-established that the coronary microvasculature may also contribute to the IRI despite successful revascularization.[24] Repeated daily RIC continues to minimize microvascular damage and protects myocardial function during long-term follow-up after MI.[25]

Because acute remodelling begins very early post-infarct, comprehensive RIC should be done early. This is a way to attenuate a number of the upstream mechanisms that can lead to maladaptive remodelling and HF.[12,26] Maybe, that is a reason of null outcome in some studies. These studies also support the theory that to reap the maximum benefits from repeated daily RIC post-MI in terms of remodelling, treatment should be instigated early in the acute phase.[12,27]

LIMITATIONS

There are several limitations that must be noted. Firstly, CMR examination was performed just once for each patient due to acceptability of patients and fund. Secondly, the sample size is still relatively small, and the current study may be not powered for subgroup analyses. Last but not least, time of symptom-to-balloon was relatively long (about 5 h), which might weaken the protective effect of comprehensive RIC. Future studies should focus on geriatric patients with elevated Killip class, in whom cardiac death and risk of HF are high, leaving room for improved clinical outcome.

CONCLUSIONS

In conclusion, the comprehensive RIC can improve SI, KCCQ-CSS and 6MWD, it may be an adjunctive therapy to PPCI in elderly patients with STEMI.

ACKNOWLEDGMENTS

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