

# Effect of long-term remote ischemic conditioning in patients with chronic ischemic heart failure

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**Abstract** Remote ischemic conditioning (RIC) protects against acute ischemia–reperfusion injury and may also have beneficial effects in patients with stable cardiovascular disease. We investigated the effect of long-term RIC treatment in patients with chronic ischaemic heart failure (CIHF). In a parallel group study, 22 patients with compensated CIHF and 21 matched control subjects without heart failure or ischemic heart disease were evaluated by cardiac magnetic resonance imaging, cardiopulmonary exercise testing, skeletal muscle function testing, blood pressure measurement and blood sampling before and after  $28 \pm 4$  days of once daily RIC treatment. RIC was conducted as four cycles of 5 min upper arm ischemia followed by 5 min of reperfusion. RIC did not affect left ventricular ejection fraction (LVEF) or global longitudinal strain (GLS) in patients with CIHF ( $p = 0.63$  and  $p = 0.11$ ) or matched controls ( $p = 0.32$  and  $p = 0.20$ ). RIC improved GLS in the subgroup of patients with CIHF and with NT-proBNP plasma levels above the

geometric mean of 372 ng/l ( $p = 0.04$ ). RIC did not affect peak workload or oxygen uptake in either patients with CIHF ( $p = 0.26$  and  $p = 0.59$ ) or matched controls ( $p = 0.61$  and  $p = 0.10$ ). However, RIC improved skeletal muscle power in both groups ( $p = 0.02$  for both). In patients with CIHF, RIC lowered systolic blood pressure ( $p < 0.01$ ) and reduced NT-proBNP plasma levels ( $p = 0.02$ ). Our findings suggest that long-term RIC treatment does not improve LVEF but increases skeletal muscle function and reduces blood pressure and NT-proBNP in patients with compensated CIHF. This should be investigated in a randomized sham-controlled trial.

**Keywords** Ischemic heart disease · Heart failure · Remote ischemic conditioning · Ischemic preconditioning · Cardiac magnetic resonance · Cardiopulmonary exercise capacity

## Abbreviations

CIHF	Chronic ischemic heart failure
GLS	Global longitudinal strain
CMR	Cardiac magnetic resonance
LVEF	Left ventricular ejection fraction
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
NT-proBNP	N-terminal pro-brain natriuretic peptide
RIC	Remote ischemic conditioning

## Introduction

While advances in the treatment of acute myocardial infarction have translated into improved survival [33], prevention of evolving post-infarction heart failure remains a major clinical challenge with a 1-year mortality of nearly 50% [7].

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Chronic ischemic heart failure (CIHF) evolves due to loss of ventricular function from ischemic myocardial tissue injury [19] and induces a vicious cycle by activating compensatory neurohormonal and inflammatory mechanisms [20], which leads to adaptive metabolic and remodeling processes [19] and a progressive decline of cardiac function.

Remote ischemic conditioning (RIC) by alternating brief episodes of limb ischemia and reperfusion is an evolving therapeutic strategy to achieve protection against acute ischemia–reperfusion injury in the heart [18] and several other organs [34]. RIC has been shown to reduce myocardial injury in patients with ST-segment elevation myocardial infarction [6] as well as in patients undergoing elective percutaneous coronary intervention [21], which may translate into improved long-term clinical outcome [9, 36]. The majority of these studies have utilized RIC as single-occasion treatment in settings of acute ischemia–reperfusion. Recently, attention has enlarged on the potential beneficial effects of repeated RIC application and the effect of RIC in patients with stable cardiovascular conditions [18]. Experimental studies have suggested that repetitive daily RIC administration may confer additional beneficial effects through anti-remodeling processes [41, 42] and improvement of endothelial and microcirculatory function [24, 26]. Furthermore, a clinical pilot study suggests that a single application of RIC may improve exercise capacity in a fraction of patients with heart failure and reduced ejection fraction [29]. We hypothesized that long-term, repetitive RIC application has potential clinical implication for patients suffering from stable ischemic heart disease. The aim of the present study was to investigate whether daily RIC application for 4 weeks improves left ventricular function, cardiopulmonary exercise capacity, skeletal muscle function, blood pressure and serology markers of heart failure in patients with stable compensated CIHF and matched controls without heart failure or ischemic heart disease.

## Methods

### Patients

We recruited patients with compensated CIHF from the outpatient heart failure clinic at Department of Cardiology, Aarhus University Hospital, Denmark and Department of Cardiology, Viborg Region Hospital, Viborg, Denmark. At the time of study enrollment, all patients were clinically stable and on optimal heart failure treatment. Criteria for inclusion were: (I) age  $\geq 18$  years, (II) left ventricular ejection fraction (LVEF)  $\leq 45\%$ , and (III) New York Heart Association functional class I–III. Criteria for exclusion were: (I) permanent atrial fibrillation, (II) diabetes mellitus, (III) peripheral neuropathy, (IV) current dialysis treatment,

(V) contraindication to cardiac magnetic resonance (CMR) imaging examination (e.g., metal implants including implantable cardiac device and pacemaker), (VI) hospitalization for cardiovascular disease within 30 days, and (VII) strenuous exercise within 3 days prior to each study visit.

As control group, we recruited subjects without heart failure and ischemic heart disease matched on age and gender. Ischemic heart disease was ruled out based on cardiac  $^{82}\text{Rb}$  rubidium positron emission tomography/computed tomography imaging or coronary angiography. Matched control subjects were recruited from Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark, Department of Cardiology, Viborg Region Hospital, Viborg, Denmark and Department of Nuclear Medicine, Aarhus University Hospital, Aarhus, Denmark. Criteria for inclusion were: (I) age  $\geq 18$  years, and (II) LVEF  $> 45\%$ . Criteria for exclusion were similar as for patients with CIHF.

Due to a pre-specified sub-study analysis evaluating the effect of RIC on platelet function and fibrinolysis [31], all participants were instructed in avoidance of non-steroidal anti-inflammatory drugs for at least 7 days prior to study initiation and during the entire study period. In addition, participants in the control group were instructed in pausing, if relevant, aspirin treatment for at least 5 days prior to each study visit. From ethical considerations, the latter was not applied for patients with CIHF.

### Design

We conducted a prospective, outcome-assessor blinded, parallel group study based on paired observations before and after study intervention. All participants underwent two study visits with  $28 \pm 4$  days apart. The  $\pm 4$ -day variation was allowed for logistical reasons. At each study visit, participants underwent blood sampling, CMR examination, and leg extension power and cardiopulmonary exercise testing. In addition, patients with CIHF were asked to fulfill a Minnesota Living with Heart Failure Questionnaire (MLWHFQ). The technical staff and participants were blinded to baseline data at the follow-up visit, and similar instructions were given at both study visits. Outcomes were measured consecutively and analyzed following study completion.

In between study visits, participants were instructed in application of RIC once daily. RIC was conducted on the same arm throughout the entire study period as 4 cycles of 5-min upper arm ischemia followed by 5 min of reperfusion using the commercially available automatic AutoRIC device (CellAegis Devices Inc., Toronto, Canada). All participants were instructed in fulfilling a checklist to assess for RIC application compliance, and to follow normal routine with no alteration in medication intake, physical activity or dietary habits.

## Cardiac magnetic resonance imaging

All CMR examinations were performed with a Philips Achieva dStream 1.5 T scanner (Philips Healthcare, Best, The Netherlands) with a 60-cm bore or a Siemens Skyra 3T scanner (Siemens Healthcare, Erlangen, Germany) with a 70-cm bore depending on the body size of the person investigated. Similar, anterior and posterior coil or a single-element anterior coil combined with a posterior coil array was used depending on the body size of the person investigated. The same CMR scanner and coils were used at both study visits. Cine-CMR examinations were conducted electrocardiogram-triggered and performed during breath-hold, and forward stroke volume was measured by velocity-encoded phase contrast measurement in the ascending aorta as previously described [16].

All CMR examinations were conducted blinded to the participants and observers in regard to study data, and data analysis was done outcome-assessor blinded in regard to both clinical and study data. The software system Segment (Medviso AB, Lund, Sweden) was used for CMR data analysis [17]. Data for LVEF and left ventricular end-diastolic volume were derived from short-axis views on which the epi- and endocardial border were automatically traced during end-diastole and end-systole. Manual correction was done in case of obvious misalignment of the cardiac contour. The slice containing > 50% visible myocardium circumference constituted the basal slice. Myocardial trabeculae were included as part of the myocardium and papillary muscles as part of the cavity. LVEF was calculated as  $[(\text{end-diastolic volume} - \text{end-systolic volume}) / \text{end-diastolic volume}] \times 100\%$ . Additional feature tracking cine-CMR data analyses were done for evaluation of peak global longitudinal strain (GLS). Data for GLS were derived from two- and four-chamber views on which the epi- and endocardial border was outlined in the end-diastole. Subsequently, an automatic computation was triggered in which the applied software algorithm automatically outlined the border throughout the cardiac cycle. The tracking contour was visually validated.

## Cardiopulmonary exercise testing

Evaluation of peak cardiopulmonary exercise capacity was done using a staged exercise ergometer bicycle test (Lode Corival Ergometer, Groningen, The Netherlands) by experienced physiotherapists with exercise data collected breath-by-breath using the commercially available software Jaeger MasterScreen CPX System (CareFusion, San Diego, USA) and JLAB software package (Jefferson Lab, Newport News, USA). Prior to each test, body mass and height were measured, and the gas-analyzing system was calibrated with a defined gas mixture. All participants underwent an identical

staged test protocol starting at 25 W and with increments of 2.5 W every 10 s. Test duration of 8–12 min was targeted to ensure steady state and to prevent prematurely test ending due to muscle fatigue. Endpoints of cardiopulmonary exercise testing were peak workload (W/kg) and peak oxygen consumption (ml/kg/min).

## Leg extension power rig testing

Evaluation of skeletal muscle function was assessed as leg extension power using the leg extensor power rig (Medical Engineering Unit, Nottingham University, Nottingham, UK) by experienced physiotherapists. The leg extension power test has been described elsewhere in detail [5]. Briefly, we conducted the test on dominant leg and the same leg was used at both study visits. While sitting in an upright position with arms folded across the chest, participants were verbally instructed in extension the leg as quickly and powerful as possible against a foot pedal with applied weight. Verbal encouragement was given to ensure maximal performance. Measurements were repeated every 30 s until the test was followed by two tests with similar or less power, or a maximum of ten pushes were reached. Endpoint was peak leg extension power (W/kg).

## Minnesota Living with Heart Failure Quality-of-Life Questionnaire

The impact of CIHF on quality of life was measured using the MLWHFQ, which is a standardized self-assessment measuring instrument for evaluating the therapeutic response to a given intervention in patients with heart failure [37] and allows for a comprehensive evaluation of the disease-specific quality of life in response to treatment.

All patients with CIHF were given similar instructions for filling out the questionnaire at both study visits. Fulfilling of the questionnaire was done unsupervised from any person involved in the study.

## Blood samples

At the beginning of each study visit, blood samples were drawn from the cubital vein and collected in vials containing anticoagulants. Blood for N-terminal pro-brain natriuretic peptide (NT-proBNP) measurements underwent routine analysis at the Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark.

## Blood pressure

Resting blood pressure and heart rate were measured on the same arm on both study visits. Following a resting

period of 5 min, the blood pressure and heart rate was measured twice and mean value was calculated.

## Statistics

Unpaired data were tested for normal distribution and equality of variance, and paired data were tested for normal distribution and equality and normality of distribution prior to statistical analysis. Logarithm transformation was performed when appropriate. Categorical variables were compared using  $\chi^2$  test or Fisher's exact test. Paired continuous variables were analyzed using paired Student's *t* test for parametric data or Wilcoxon signed-rank test for non-parametric data despite logarithm transformation, and unpaired continuous variables using unpaired Student's *t* test. We performed additional simple and multiple linear regression analyses to test for relationship between responses of long-term RIC treatment on cardiovascular endpoints.

Statistical analyses were conducted using STATA/SE 13 (StataCorp, College Station, USA). Data are presented as number (%), or mean  $\pm$  standard deviation [95% confidence interval (CI)] for parametric data, geometric mean (95% CI) for logarithm transformed data or median (interquartile range) for non-parametric data. Statistical significance was set as two-sided *p* value of  $< 0.05$ .

The primary study endpoint was change in LVEF. The coefficient of variability of LVEF using CMR imaging has been found to be 7% in patients with heart failure [14]. To be able to detect clinical relevant changes based on the impact of angiotensin-converting enzyme inhibitors and beta-blockers on LVEF in chronic heart failure studies [10, 13], power calculations revealed that 20 patients with CIHF were needed to detect an absolute change in LVEF of 3% with a power of 90% at a two-sided significance level of 5%.

## Ethics

Data were collected according to the study protocol at the Department of Cardiology and Centre of Research in Rehabilitation (CORIR), Aarhus University Hospital, Aarhus, Denmark, The MR Centre, Aarhus University, Aarhus, Denmark, and Department of Cardiology, Viborg Region Hospital, Viborg, Denmark. The study was carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association, and was approved by The Central Denmark Region Committees on Health Research Ethics and The Danish Data Protection Agency. The study was registered with clinicaltrials.gov (Identifier: NCT02248441). All participants gave written informed consent prior to inclusion.

## Results

A total of 22 patients with CIHF and 21 matched control subjects were included in the study (Fig. 1). Descriptive baseline characteristics are shown in Table 1.

### Cardiac magnetic resonance imaging

Data for CMR were available for all patients with CIHF and for 20 matched control subjects and are shown in Table 2. Overall, RIC did not affect LVEF or GLS in patients with CIHF ( $p = 0.63$  and  $p = 0.11$ ) or matched control subjects ( $p = 0.32$  and  $p = 0.20$ ). While RIC improved GLS in the subgroup of patients with CIHF and NT-proBNP plasma levels above the geometric mean of 372 ng/l ( $p = 0.04$ ), we found no relationship between baseline GLS and the response of long-term RIC treatment on GLS in a simple linear regression analysis ( $p = 0.39$ ). In the same subgroup of patients, we found no relationship between the responses of long-term RIC treatment on cardiovascular endpoints, i.e., GLS, peak oxygen uptake, systolic blood pressure and NT-proBNP, in multiple linear regression analyses ( $p = \text{NS}$  for all).

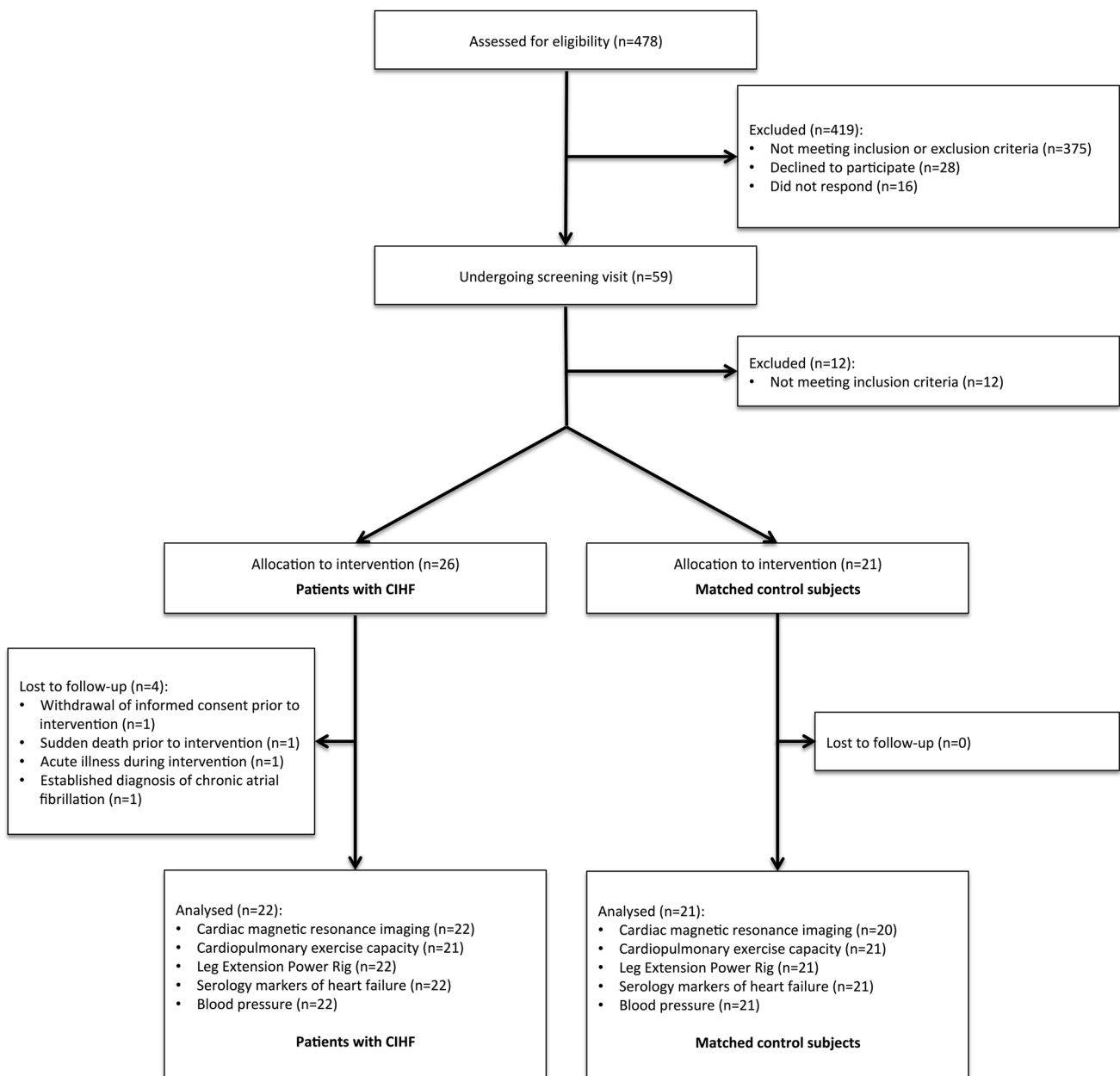
### Cardiopulmonary exercise capacity and skeletal muscle function

Data for cardiopulmonary exercise testing were available for 21 patients with CIHF and for all matched control subjects (Table 2). Twenty (95%) patients with CIHF achieved a respiratory exchange ratio  $\geq 1.10$  at both study visits and hence representative data for the true cardiopulmonary exercise capacity. Similarly, in matched control subjects, 19 (90%) achieved a respiratory exchange ratio  $\geq 1.10$  at both study visits. Long-term RIC treatment did not affect peak cardiopulmonary exercise capacity in patients with CIHF or matched control subjects.

Skeletal muscle function data were available for all patients with CIHF and matched control subjects. Long-term RIC treatment increased skeletal muscle power in patients with CIHF ( $2.3 \pm 0.8$  W/kg vs.  $2.5 \pm 0.8$  W/kg following long-term RIC treatment; 95% CI 0.02–0.21,  $p = 0.02$ ), equivalent to a 9% increase. Similarly, long-term RIC treatment increased skeletal muscle power in matched control subjects ( $2.4 \pm 0.8$  W/kg vs.  $2.6 \pm 0.8$  W/kg following long-term RIC treatment; 95% CI 0.04–0.38,  $p = 0.02$ ), equivalent to an 8% increase.

### Disease-related quality of life

Data for MLWHFQ score were available for all patients with CIHF. Long-term RIC treatment improved self-assessed disease-related quality-of-life borderline significantly



**Fig. 1** CONSORT flow diagram on eligibility, inclusion and follow-up. See text for details. *CIHF* chronic ischemic heart failure

( $15 \pm 10$  points vs.  $12 \pm 9$  points following long-term RIC treatment; 95% CI  $-5.42$  to  $0.24$ ,  $p = 0.07$ ).

### Serology markers of heart failure

Data for NT-proBNP were available for all patients with CIHF and matched control subjects. Long-term RIC treatment decreased plasma levels of NT-proBNP in patients with CIHF [ $372$  (95% CI  $256$ – $540$ ) ng/l vs.  $315$  (95% CI  $224$ – $443$ ) ng/l following long-term RIC treatment,  $p = 0.02$ ]. In contrast, long-term RIC treatment did not affect plasma

levels of NT-proBNP in matched control subjects [ $67$  (95% CI  $50$ – $88$ ) ng/l vs.  $71$  (95% CI  $50$ – $100$ ) ng/l following long-term RIC treatment,  $p = 0.53$ ].

### Blood pressure

Data for resting blood pressure were available for all patients with CIHF and matched control subjects (Table 2). Among patients with CIHF, long-term RIC treatment decreased systolic blood pressure and non-statistically significantly diastolic blood pressure ( $p < 0.01$  and  $p = 0.19$ ). Similar, long-term

**Table 1** Baseline characteristics

	Patients with CIHF ( <i>n</i> = 22)	Matched control subjects ( <i>n</i> = 21)	<i>p</i> value
Male	20 (91%)	17 (81%)	0.41
Age (years)	66 ± 9.7	63.1 ± 6.3	0.21
Body mass index (kg/m <sup>2</sup> )	31 ± 6.0	27 ± 4.2	0.01
New York Heart Association class			–
I	10 (45%)	–	
II	12 (55%)	–	
III	0 (0%)	–	
Smoking			0.28
Never	6 (27%)	10 (48%)	
Former	11 (50%)	9 (43%)	
Current	5 (23%)	2 (10%)	
Previous acute myocardial infarction	19 (86%)	–	–
Coronary revascularization			–
Percutaneous coronary intervention	18 (82%)	–	
Coronary artery by-pass grafting	4 (18%)	–	
In current treatment for			
Stable angina pectoris	2 (9%)	0 (0%)	0.49
Hypertension	12 (55%)	5 (24%)	0.06
Paroxysmal atrial fibrillation	3 (14%)	0 (0%)	0.23
Chronic obstructive pulmonary disease	2 (9%)	1 (5%)	1.00
Kidney disease	0 (0%)	0 (0%)	–
Systemic inflammatory/immunologic disease	0 (0%)	0 (0%)	–
In current treatment with			
Antiplatelet therapy	22 (100%)	8 (38%)	< 0.001
Anticoagulant therapy	3 (14%)	0 (0%)	0.23
Statins	21 (95%)	8 (38%)	< 0.001
Beta-blockers	18 (82%)	1 (5%)	< 0.001
Angiotensin-converting enzyme inhibitors	15 (68%)	2 (10%)	< 0.001
Angiotensin II receptor blockers	5 (23%)	2 (10%)	0.41
Calcium channel blockers	1 (5%)	1 (5%)	1.00
Diuretics	13 (59%)	3 (14%)	< 0.01

Data are expressed as mean ± standard deviation or number (%)

CIHF chronic ischemic heart failure

RIC treatment tended to decrease systolic blood pressure and diastolic blood pressure in matched control subjects ( $p = 0.09$  and  $p = 0.10$ ).

#### Effect modification by baseline N-terminal pro-brain natriuretic peptide plasma level on outcome

Patients with CIHF were grouped according to the geometric mean of 372 ng/l of baseline NT-proBNP plasma levels (Table 3). We found no effect by long-term RIC treatment on LVEF or peak cardiopulmonary exercise capacity irrespective of baseline NT-proBNP plasma levels. The beneficial effect of long-term RIC treatment on NT-proBNP plasma levels was restricted to patients with CIHF and baseline NT-proBNP plasma levels above the geometric mean ( $p = 0.03$ ).

Among these patient, long-term RIC treatment improved GLS ( $p = 0.04$ ). In contrast, the beneficial effect of long-term RIC treatment on skeletal muscle power was restricted to patients with baseline NT-proBNP plasma levels below the geometric mean ( $p < 0.001$ ).

#### Discussion

The main findings of the present study were that although long-term RIC treatment did not affect LVEF per se in patients with CIHF, long-term RIC treatment reduced NT-proBNP plasma levels and systolic blood pressure, and improved left ventricular function in terms of GLS in patients with highest NT-proBNP plasma levels. Moreover,

**Table 2** Effect of long-term remote ischemic conditioning on cardiac magnetic resonance imaging, cardiopulmonary exercise capacity and hemodynamic variables

	Baseline	Following long-term RIC	95% CI	<i>p</i> value
<b>Patients with CIHF</b>				
Magnetic resonance imaging variables				
LV ejection fraction (%)	44 ± 9.7	44 ± 9.2	− 0.9 to 0.6	0.63
LV end-diastolic volume (ml)	223 ± 61.1	220 ± 63.4	− 10.0 to 4.1	0.39
GLS-strain rate (%)	− 8.9 ± 2.2	− 9.5 ± 2.5	− 1.2 to 0.1	0.11
Cardiopulmonary exercise capacity variables				
Peak workload (W/kg)	1.6 ± 0.31	1.6 ± 0.33	− 0.02 to 0.1	0.26
Peak oxygen uptake (ml/kg/min)	19.9 (95% CI 18.3 to 21.6)	20.1 (95% CI 18.5 to 21.9)		0.59
Hemodynamic variables				
Systolic blood pressure (mmHg)	130 ± 14.2	124 ± 16.8	− 10.0 to − 2.7	<0.01
Diastolic blood pressure (mmHg)	77 ± 7.9	75 ± 9.5	− 5.4 to 1.1	0.19
Heart rate (bpm)	68 ± 10.4	67 ± 7.7	− 3.9 to 2.1	0.56
<b>Matched control subjects</b>				
Magnetic resonance imaging variables				
LV ejection fraction (%)	71 ± 5.2	71 ± 5.3	− 0.2 to 0.4	0.32
LV end-diastolic volume (ml)	148 ± 32.9	147 ± 32.9	− 3.4 to 1.6	0.46
GLS-strain rate (%)	− 14.1 ± 1.5	− 14.6 ± 1.4	− 1.1 to 0.2	0.20
Cardiopulmonary exercise capacity variables				
Peak workload (W/kg)	2.3 ± 0.5	2.2 ± 0.5	− 0.1 to 0.04	0.61
Peak oxygen uptake (ml/kg/min)	28.2 ± 5.8	27.1 ± 5.4	− 2.3 to 0.2	0.10
Hemodynamic variables				
Systolic blood pressure (mmHg)	145 ± 15.2	140 ± 13.7	− 9.3 to 0.7	0.09
Diastolic blood pressure (mmHg)	88 ± 12.1	85 ± 11.2	− 5.9 to 0.6	0.10
Heart rate (bpm)	71 (65–83)	69 (63–81)		0.25

Data are expressed as mean ± standard deviation, geometric mean (95% CI) or median (interquartile range)

CIHF chronic ischemic heart failure, RIC remote ischemic conditioning, LV left ventricular, GLS global longitudinal strain, bpm beats per minute

long-term RIC treatment improved skeletal muscle power in both patients with CIHF and matched control subjects without heart failure and ischemic heart disease. These findings suggest that RIC may not only improve myocardial contractile function in most severely compromised patients with CIHF but also add a general improvement of skeletal muscular function even in a compensated state of heart failure.

Previous findings indicate that repetitive application of RIC does not result in tachyphylaxis of the cardioprotective from RIC against subsequent acute *I/R* injury in terms of infarct size reduction [32]. In addition, experimental proof-of-principle studies have demonstrated that long-term, repetitive application of RIC following the acute phase of a myocardial infarction confers myocardial anti-remodeling effects [41, 42] and may improve survival [41]. Under stable conditions, Jones et al. demonstrated that repetitive daily RIC administration for 7 days improve peripheral endothelial and microcirculatory function assessed by non-invasive ultrasound-derived flow-mediated vasodilation and laser Doppler flowmetry-derived cutaneous vascular conductance,

respectively [24]. More recently, the same authors demonstrated that improvement of endothelial function could be maintained for several weeks with three times per week application of RIC [25]. In addition, twice daily RIC application for 7 days enhanced echocardiography-assessed coronary flow reserve derived from coronary blood flow velocities [26], which may reflect improvement of the coronary microcirculatory in response to RIC. We extended previous findings by demonstrating that long-term RIC application for 4 weeks seems to have beneficial hemodynamic effects by decreasing systolic blood pressure, and hence, afterload, and to improve myocardial contractile function in those patients with compensated CIHF, who have the most extensive elevated NT-proBNP levels. Endogenously derived substances assumed causally involved in cardioprotection by RIC are vasodilative by nature, e.g., adenosine, nitric oxide and bradykinin [18]. Release of such substances in connection to RIC application may explain the blood pressure-lowering effect from RIC as demonstrated in the present study.

**Table 3** Effect of long-term remote ischemic conditioning categorized in patients with chronic ischemic heart failure and baseline NT-proBNP plasma levels > 372 or ≤ 372 ng/l

	Baseline	Following long-term RIC	95% CI	<i>p</i> value
Patients with CIHF and baseline NT-proBNP plasma level > 372 ng/l ( <i>n</i> = 10)				
Magnetic resonance imaging variables				
LV ejection fraction (%)	41 ± 9.4	42 ± 9.2	− 0.3 to 0.6	0.44
LV end-diastolic volume (ml)	218 ± 72.2	220 ± 69.8	− 3.9 to 7.4	0.50
GLS-strain rate (%)	− 8.6 ± 2.8	− 9.8 ± 2.7	− 2.3 to − 0.1	0.04
Cardiopulmonary exercise capacity variables				
Peak workload (W/kg) <sup>a</sup>	1.7 ± 0.3	1.7 ± 0.3	− 0.1 to 0.1	0.70
Peak oxygen uptake (ml/kg/min) <sup>a</sup>	20.3 (95% CI 17.4 to 23.8)	20.9 (95% CI 17.6 to 25.0)		0.36
Hemodynamic variables				
Systolic blood pressure (mmHg)	133 ± 11.8	127 ± 15.4	− 13.0 to − 0.3	0.04
Diastolic blood pressure (mmHg)	78 ± 8.6	74 ± 8.2	− 8.2 to 1.7	0.17
Heart rate (bpm)	67 ± 10.8	66 ± 8.3	− 5.0 to 2.5	0.47
Skeletal muscle power (W/kg)	2.4 ± 0.8	2.4 ± 0.8	− 0.2 to 0.2	0.82
Disease-related quality of life (MLWHFQ point)	10 ± 6.6	8 ± 6.0	− 6.5 to 1.3	0.16
NT-proBNP (ng/l)	778 (95% CI 510.9 to 1186.0)	621 (95% CI 437.3 to 881.7)		0.03
Patients with CIHF and baseline NT-proBNP plasma level ≤ 372 ng/l ( <i>n</i> = 12)				
Magnetic resonance imaging variables				
LV ejection fraction (%)	46 ± 9.9	45 ± 9.2	− 1.8 to 0.9	0.47
LV end-diastolic volume (ml)	227 ± 53.2	220 ± 60.8	− 19.5 to 5.7	0.25
GLS-strain rate (%)	− 9.2 ± 1.7	− 9.2 ± 2.3	− 0.7 to 0.8	0.90
Cardiopulmonary exercise capacity variables				
Peak workload (W/kg)	1.5 ± 0.3	1.6 ± 0.3	− 0.03 to 0.1	0.25
Peak oxygen uptake (ml/kg/min)	19.6 (95% CI 17.6 to 21.8)	19.5 (95% CI 17.7 to 21.4)		0.82
Hemodynamic variables				
Systolic blood pressure (mmHg)	127 ± 15.8	121 ± 18.1	− 11.3 to − 0.9	0.03
Diastolic blood pressure (mmHg)	77 ± 7.7	76 ± 10.8	− 6.3 to 3.8	0.61
Heart rate (bpm)	69 ± 10.5	68 ± 7.3	− 5.7 to 4.6	0.82
Skeletal muscle power (W/kg)	2.3 ± 0.8	2.5 ± 0.8	0.1 to 0.3	<0.001
Disease-related quality of life (MLWHFQ point)	18 ± 10.5	16 ± 9.3	− 7.2 to 2.1	0.25
NT-proBNP (ng/l)	201 (95% CI 156.0 to 259.1)	179 (95% CI 138.1 to 230.8)		0.26

Data are expressed as mean ± standard deviation or geometric mean with 95% CI

NT-proBNP N-terminal pro-brain natriuretic peptide, CIHF chronic ischemic heart failure, RIC remote ischemic conditioning, LV left ventricular, GLS global longitudinal strain, bpm beats per minute, MLWHFQ Minnesota Living With Heart Failure Questionnaire

<sup>a</sup>Data on peak workload and peak oxygen uptake were available for nine patients with CIHF and baseline NT-proBNP plasma level > 372 ng/l

NT-proBNP is a cardiac polypeptide secreted from the ventricles in response to ventricular volume expansion and pressure overload [15]. It is a frequently used surrogate marker in clinical trials on patients with heart failure, as increasing levels are associated with worse outcome in patients with heart failure [28]. In addition, meta-analysis has demonstrated that brain natriuretic peptide-guided heart failure treatment lowers mortality in patients with heart failure and reduced LVEF [11]. In the present study, the decrease in NT-proBNP, therefore, likely indicates a beneficial effect of RIC, and the finding is consistent with a recent published study evaluating the effect of RIC in patients with mild ischemic heart failure [8]. Of importance, we

demonstrated an increase in GLS measured by CMR in the subgroup with the highest levels of NT-proBNP. Traditionally, LVEF has been used to estimate systolic function and is a predictor of prognosis as well as pivotal in the planning of treatment in patients with heart failure. However, GLS is increasingly used and importantly has been demonstrated to be a superior predictor of prognosis compared to LVEF [38]. In addition, GLS is associated with wall stress and correlates well with NT-proBNP in patients with chronic heart failure [12]. The underlying reason for the changes in both NT-proBNP and GLS is likely related and may be due to alleviation in myocardial wall stress caused by reduction in afterload, as demonstrated by the decrease in blood



pressure. Our findings suggest that the effect of RIC on myocardial contractile function may be of particular benefit in the most severely compromised heart failure patients even though they were clinically compensated and on optimal heart failure treatment. In contrast, RIC increased skeletal muscle power only in the subgroup of patients with the lowest levels of NT-proBNP. Thus, patients with CIHF irrespectively of NT-proBNP levels seem to benefit from long-term RIC treatment although partly in terms of different clinical endpoints. Intriguingly, our findings suggest that RIC may improve quality of life in both patients with normal and elevated NT-proBNP levels.

In heart failure, increased sympathetic activity correlates with a poor prognosis and is a target of established anticongestive treatment [40]. Recently, it was shown that 6 weeks of RIC improves cardiac dysautonomia evaluated by heart rate variability in patients with heart failure [8]. The finding supports that repeated RIC increases the parasympathetic nervous system and promotes withdrawal of sympathetic nervous activity, and hence, rebalances the cardiac dysautonomia that evolves in heart failure. These effects of RIC may be the cause of the observed reduction in NT-proBNP plasma levels. However, this remains speculative, as we did not evaluate heart rate variability in the present study.

During the progression of heart failure a decrease in muscle function is observed and overt cardiac cachexia may develop [23]. Such changes correlate with a poor prognosis and are related to a low-grade inflammation and release of pro-inflammatory cytokines [1]. Hence, approaches to circumvent this maleficent process or even reverse it are warranted. In the present study, we were able to demonstrate an increase in muscle power following RIC treatment using the leg extensor power rig testing, which has been found to correlate with functional performance and risk for mobility limitations in elderly persons [4]. The increase in muscle power from RIC may be due to the previous mentioned effect on the autonomic nervous system, anti-inflammatory effect of RIC [27, 32, 35] and partly by activation in nitric oxide pathways and improvement in metabolism by attenuation of adenosine triphosphate depletion [22]. Our findings are consistent with those from a previous study on short-term RIC application in healthy volunteers [39]. Importantly, we extended previous findings by demonstrating that the effect of RIC on skeletal muscle strength is likely caused by direct effects on the skeletal musculature that do not presuppose cardiac effects. However, this remains speculative and needs to be further investigated.

Despite an increase in muscle power in the present study and recent observed effect of RIC on 6-min walking testing and cardiopulmonary exercise testing [8], we were not able to find any effect on cardiopulmonary exercise capacity in the present study. The latter is in agreement with recent observations on young healthy volunteers [3], and with

previous findings by McDonald and colleagues on the acute effects of a single application of RIC in patients with heart failure [29]. However, in the present study, the patients may be restricted by joint pain, leg fatigue or other factors limiting the value of exercise testing [2]. On the other hand, the study by McDonald and colleagues suggests that a fraction of patients with heart failure may be preconditioned *per se* and thus have no additional effect from RIC on exercise capacity [29].

### Limitations

The present study is based on paired observations before and after intervention and not a randomized controlled design. Thus, we cannot exclude bias from potential non-RIC-related effects. In particular, this might be relevant when evaluating skeletal muscle function and self-assessed disease-specific quality of life. In addition, the study design did not allow exploration of any causal relations of the effect of long-term RIC treatment. Consequently, the study should be considered exploratory, and our results need to be further investigated in a randomized sham-controlled study and causality should be sought. Patients were treated for 4 weeks but the treatment time may have been too short to induce cardiac remodeling effects and left ventricular function improvements in terms of LVEF changes. Treatment with angiotensin-converting enzyme inhibitor or a beta-blocker induces cardiac remodeling after approximately 3 months of treatment [10, 13]. Nevertheless, the present study was able to demonstrate signs of improvements in heart failure in terms of reduced NT-proBNP and increased GLS. Even so, we found no relation between responses from long-term RIC treatment on GLS, peak oxygen uptake, systolic blood pressure or NT-proBNP plasma levels by multivariate analyses. However, due to sample size, results from multivariate analyses should be interpreted with caution.

We recruited patients with CIHF in NYHA class I–II only. Consequently, the results of the present study do not apply on patients with CIHF and more advanced heart failure, which may also benefit from long-term RIC treatment. In addition, we acknowledge that normal LVEF is by definition  $> 50\%$  according to the present European guidelines [30]. However, due to the large variance of echocardiography-derived LVEF assessment, we decided on a cut-off inclusion criterion at  $LVEF \leq 45\%$  to avoid the risk of including patients with  $LVEF > 50\%$ .

RIC compliance is an important potential confounder in this study. Participants were continuously reminded of RIC application throughout the entire study period and fulfilled a checklist hereof, implying excellent RIC compliance. While we have no documentation of the true RIC compliance, potential lack of compliance cannot explain the observed beneficial effects of long-term RIC treatment. For

GLS analysis using feature tracking cine-CMR evaluation we relied only on two- and four-chamber views. Including three-chamber views might have allowed for a more comprehensive assessment of GLS. Twenty-four-hour blood pressure monitoring would have enabled a more comprehensive evaluation of the effect of long-term RIC treatment on blood pressure. We did not assess for any persistent effect from RIC treatment on blood pressure. Finally, we did not assess if the included patients or control subjects were already pre-conditioned and whether this could explain the lack of effect of long-term RIC treatment on myocardial contractile function and exercise capacity as observed in the present study.

## Conclusion

Our findings suggest that long-term RIC treatment does not improve LVEF but increases skeletal muscle function and reduces blood pressure and NT-proBNP in patients with compensated CIHF. The clinical implications of our exploratory study should be further investigated in a randomized sham-controlled trial.

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**Author contributions** KP, RRN, HEB, and MRS designed the experiments. KP did the data analysis and drafting of the manuscript. All authors participated in data acquisition and critical revision of the manuscript.

## Compliance with ethical standards

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**Conflict of interest** HEB and MRS are shareholders in CellAegis Devices Inc. KP, RRN, AJ, MSH, SR, JR, WYK, and AKP declare that they have no conflict of interest.

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