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ORIGINAL ARTICLE

Effects of Remote Ischaemic Conditioning on Heart Rate Variability and Cardiac Function in Patients With Mild Ischaemic Heart Failure

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Q4 **Background** Cardioprotective effects of remote ischaemic conditioning (RIC) in the setting of ischaemic heart disease have been shown recently. But the effects of RIC on heart rate variability (HRV) and cardiac function in patients with stable ischaemic heart failure (IHF) are still unknown.

Methods Q5 Fifty patients with stable IHF were enrolled and randomly divided into RIC group and control group. Remote ischaemic conditioning treatment was performed twice a day for six weeks. A RIC protocol consisted of 4 × 5 min inflation/deflation of the blood pressure cuff applied in the upper arm to create intermittent arm ischaemia. B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), 24-hour ambulatory electrocardiogram, and six-minute walk distance (6MWD) were all assessed in two groups.

Results Q6 Forty-seven patients completed the study. Remote ischaemic conditioning was well-tolerated by patients in the RIC group after six weeks treatment and LVEF showed a significant increase, from 39.2% to 43.4% ($p < 0.001$), as well as decreased BNP, increased 6MWD and HRV, but this was not observed in the control group. In addition, the patients treated with RIC also showed improved NYHA class, LVEF, 6MWD, BNP level and HRV compared to control group.

Conclusions This study suggests that a six-week course of RIC treatment could improve cardiac function and HRV in patients with mild and stable IHF, supporting widespread use of RIC in the daily lives of these patients.

Keywords Remote ischaemic conditioning • Heart rate variability • Heart failure • Ischaemic heart disease

Introduction

Q7 Ischaemic heart disease is a major cause of mortality and morbidity worldwide [1]. Survival of patients with acute myocardial infarction (AMI) has largely improved in the past decades due to the advances in, and application of, modern medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). However, the resultant ventricular dysfunction and ischaemic heart failure (IHF) have significantly increased and present, now, as a major medical problem, which substantially affects quality of life and has become a major determinant for reduced life expectancy in subjects post AMI [1]. Despite advances in drug and/or device therapy for chronic IHF with reduced left ventricular ejection fraction (LVEF), outcomes at the community level remain suboptimal [2,3]. These

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unsatisfactory results warrant investigation of further therapeutic strategies to treat heart failure patients in their daily lives. A traditional way to develop new treatments is to block the mechanisms that are known to be associated with poor survival. It is now recognised that autonomic dysfunction is one such mechanism producing poor outcomes. Abnormality of heart rate variability (HRV) is a way of measuring autonomic imbalance and has repeatedly been shown to be significantly associated with the degree of left ventricular dysfunction, progression, and prognosis of the patients with heart failure disease [4,5]. Medications that improve HRV are promising therapeutically as they also usually improve mortality [6–8].

Remote ischaemic conditioning (RIC), induced by repeated short-lasting ischaemia in a distant tissue – largely achieved by intermittent interruption of circulation in a limb – has recently emerged as a noninvasive and promising adjunctive therapy to avoid organ damage, thereby improving the outcomes of well-established therapies [9]. Remote ischaemic conditioning has been shown to reduce adverse left ventricular remodelling and improve cardiac function in rats after myocardial infarction (MI), when delivered daily for 28 days [10]. In proof-of-principle randomised clinical trials (RCTs) based on surrogate end-points such as biomarkers and imaging, RIC has been shown to protect against ischaemia-reperfusion injury in the heart, brain, kidney, and lung [9]. Especially, a number of clinical studies have confirmed the positive cardioprotective effects of RIC in the setting of acute myocardial injury including myocardial infarction [11], cardiac [12] and non-cardiac surgery [13] and percutaneous coronary intervention (PCI) [14]. However, the effects of RIC on stable IHF are still unclear. In addition, although the mechanisms of beneficial effects by RIC were not well established, recent data highlight that activation of autonomic reflex pathways contributes to powerful innate mechanisms of cardioprotection underlying the RIC phenomena. It was reported that bilateral cervical vagotomy, surgical denervation of the ischaemic limbs by sectioning the sciatic and femoral nerves, or permanent functional depletion of sensory nerves induced by neonatal systemic capsaicin (neurotoxin, the active component of chilli peppers) treatment effectively abolishes RIC cardioprotection [15,16].Therefore, we could hypothesise that RIC may bring beneficial effects to IHF by regulating cardiac autonomic function, since cardiac autonomic derangement is evident in most patients with IHF [17,18]. This study aimed to investigate the effects of six-week RIC treatment on heart rate variability and cardiac function in patients with stable IHF.

Methods

Ethics Statement

The protocol was approved by the ethics committee of Zhongda Hospital, Southeast University (Nanjing, China). Before entering the study, the subjects provided a full, informed, written consent.

Study Population

Fifty patients with stable ischaemic heart failure were recruited in this study from the outpatients in the Department of Cardiology, Zhongda Hospital, Southeast University, Nanjing, China. Patients enrolled fulfilled the following criteria: (1) an established diagnosis of systolic heart failure for at least three months, which was based on the Framingham criteria [19]; (2) history of myocardial infarction or coronary artery disease confirmed by angiography; (3) LVEF <50% at transthoracic echocardiography; (4) New York Heart Association (NYHA) functional classification of I–II; (5) walking without assistance; (6) sinus rhythm without atrial fibrillation; (7) taking angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and β-blocker for at least three months without dose titration unless there was a contraindication or patient was intolerant. The exclusion criteria were as follows: (1) more than moderate valvular heart disease; (2) recent (within six months) acute coronary syndromes; (3) history of atrial fibrillation, intermittent bundle branch block, or pacemaker implantation; (4) peripheral arterial disease; (5) uncontrolled hypertension (systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg); (6) active cancer; and (7) the presence of other serious systemic diseases.

Study Design

Patients included in the study were randomly divided into two groups: 1) Control group (n = 25), in which patients received standard medical therapy; 2) RIC group (n = 25), in which patients received six weeks' RIC treatment along with standard medical therapy. All heart failure medications were required to be continued in unchanged dosage for the duration of the study, and all examinations were performed before and after the six-week course of RIC treatment.

In each RIC treatment, a BP cuff was applied to the upper arm of each patient, first to measure BP in the left arm, then immediately thereafter the BP cuff was inflated to a pressure of 20 mmHg greater than the patient's systolic BP, it was then left inflated for five minutes, after which the cuff was deflated. Five minutes later, the cuff was inflated again as before, and a RIC-protocol was applied consisting of 4 × 5 min inflation/deflation of the cuff. Remote ischaemic conditioning treatment was repeated each morning and evening by the patients themselves. A physician (CL) confirmed that the subjects operated the RIC procedure correctly in the first week. After the first week of participation in monitored sessions, the patients performed the same protocol for three days per week under direct supervision of the physician in the hospital as before and four days at their home.

Blood samples were collected in test tubes containing EDTA at baseline and after six weeks of treatment with patients in the supine position for at least 30 minutes. The plasma was separated from blood cells by centrifugation and frozen at − 80 °C. Plasma concentrations of b-type natriuretic peptide (BNP) were measured using a specific

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