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Remote Ischemic Conditioning Improves Cardiovascular Function in Heart Failure Patients

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Abstract

Background: Recently, it has been shown that remote ischemic conditioning (RIC) can be used as a healthy regimen to reverse disease and aging. With this in mind, we are studying the consequences of RIC on cardiovascular function in heart failure patients.

Methods: Forty patients with stable heart failure were prospectively enlisted and randomly divided into RIC (n = 20) and control (n = 20) groups. The RIC protocol consists of a 3-min inflation and then deflation of the blood pressure cuff attached to the upper arm to produce transient ischemia of the arm. RIC treatment was performed once daily for 1 year. NYHA class, left ventricular ejection fraction (LVEF), left atrial and ventricular dimensions were all assessed in two groups.

Results: RIC was well tolerated. After 1 year of treatment, New York Heart Association (NYHA) class improved and LVEF showed a significant increase from 37.11% to 52.44% ($P < 0.0001$). Additionally, the dimensions of the left atrium (from 50.55 to 43.25 mm) and ventricle (from 53.04 to 50.15 mm) were significantly reduced in the RIC group.

Conclusion: This study suggests that 1 year of RIC treatment as a health strategy could improve cardiovascular function in heart failure patients, leading to its widespread use in these patients.

Keywords: Heart conditioning; Healthy strategy; Heart failure

Introduction

In 1986, Murry et al demonstrated for the first time ischemic preconditioning in dogs [1]. Short, repeated (5 min) occlusions of the coronary artery prior to subsequent persistent occlusion resulted in a reduction in infarct size. Subsequently, ischemic preconditioning has been well documented in all animal species studied as well as in humans [1-3]. It is advantageous and protects against post-ischemic contractile dysfunction [4], ischemia arrhythmias [5, 6], infarct injury [1-3] and apoptosis [7].

Ischemic preconditioning has also been studied in patients with coronary artery disease. It has ameliorated clinical outcomes in coronary artery disease patients undergoing cardiac catheterization [8] and cardiac surgery [9].

Remote ischemic conditioning (RIC) with mild ischemia and reperfusion of a distant organ also guards the heart. It is non-invasive and typically uses intermittent inflation of a standard 200 mm Hg blood pressure cuff, with three to four 5-min inflation periods separated by 5-min reperfusion periods [10]. In patients undergoing cardiac catheterization or cardiac surgery, RIC decreased heart damage and serious adverse cardiovascular and cerebrovascular events [11-14]. RIC has been shown to ameliorate adverse left ventricular remodeling and restore cardiovascular function when administered daily for 28 days in rats after myocardial infarction [15].

Myocardial ischemia is one of the common causes of heart failure. Despite advances in medical and/or device therapy for heart failure, community-level outcomes are still suboptimal [16, 17]. These unsatisfactory outcomes need additional therapies for the treatment of heart failure patients in their daily lives.

Recently, it has been shown that RIC can be used as a healthy regimen consistent with the heterochronic parabiotic model to reverse disease and aging [18]. Its mechanism is that RIC provides external pressure as stressor, which can elicit the body's compensatory mechanism, release healthy factors such as cardioprotective factors, and remove unhealthy factors such as free radicals, etc., improve extracellular fluid, and lead to cardiac reverse remodeling, that is, reversion of disease and aging [18]. In this sense, heart conditioning can benefit heart failure patients. Therefore, we are investigating the effects of cardiac conditioning as a healthy strategy on cardiovascular function in heart failure patients.

Materials and Methods

This was a 1-year single-center randomized, controlled, prospective preliminary pilot study.

We prospectively recruit 40 Chinese patients with stable heart failure from the outpatients in the Department of Cardiology, Jen-Ai Hospital, Taichung, Taiwan. This study was ap-

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proved by the Ethic Committee of Jen-Ai Hospital. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Patients recruited fulfilled the following criteria: 1) an established diagnosis of systolic heart failure for at least 3 months, which was based on the symptoms and signs of heart failure and the Framingham criteria [19]; etiology of heart failure was hypertension, diabetes mellitus and coronary artery disease; 2) left ventricular ejection fraction (LVEF) less than 40% at transthoracic echocardiography; 3) New York Heart Association (NYHA) functional classification greater than or equal to II; 4) sinus rhythm without atrial fibrillation. The exclusion criteria were as follows: 1) recent (within 6 months) acute coronary syndrome; 2) more than moderate valvular heart disease; 3) history of intermittent bundle branch block, atrial fibrillation, or pacemaker implantation; 4) uncontrolled hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg); 5) peripheral arterial disease; 6) active cancer; and 7) the presence of other serious systemic diseases.

Patients enlisted in the study were randomly divided into the control and RIC groups. In the control group (n = 20), patients received standard medical therapy. In the RIC group (n = 20), patients received 1 year's RIC treatment along with standard medical therapy. All examinations were performed before and after the 1-year course of RIC treatment.

In each RIC treatment, an automated healthy sphygmomanometer (Urion Co., China) was used. A standard blood pressure cuff was applied to the upper arm of each patient, and inflated to a pressure of 200 mm Hg for 3 min, after which the cuff was deflated automatically. RIC treatment was performed by the patients themselves once every day at home. A physician assured that the patients performed the RIC correctly in the first week.

Transthoracic echocardiography was performed using Acuson SC2000 (Siemens Inc., Germany) in the standard manner. Left ventricular end-diastolic and systolic volumes were obtained using the Simpson's method and indexed by body surface area. LVEF was then calculated. Left atrial dimension (LA) and left ventricular dimension during end diastole (LVDd) and systole (LVSd) were also assessed with echocardiography. The mean of three measurements was used for all variables. All echocardiogram were interpreted by the same physician, who was blinded to the other information of each patient.

Data were presented as mean (SEM), or number. Categorical variables were evaluated using the χ^2 test. Average values of clinical characteristics were compared between the control and RIC groups by Student's *t*-test. Similarly, Student's *t*-test was used, respectively, to compare mean values between baseline and final evaluation for the control and RIC groups. A probability value of P < 0.05 was considered significant.

Results

Baseline characteristics

The mean age of patients was 68.4 ± 2.77 and 65.8 ±2.35 years in the control and RIC groups, respectively. The NYHA class distribution was 3.15 ± 0.15 in the control group and 3.25 ± 0.12 in the RIC group, respectively. The mean LVEF was 33.23±0.15% and 37.11±1.72% in the control and RIC groups, respectively. Furthermore, the mean LA, LVDd and LVSd in the control group were 46.69 ± 2.21, 59.08 ± 2.81 and 47.14 ± 3.24 mm, respectively. The mean LA, LVDd and LVSd in the RIC group were 51.08 ± 2.5, 51.69 ± 2.28 and 38.77 ± 2.62 mm, respectively. There was no significant difference in the baseline patient characteristics between the control and RIC groups, as shown in Table 1.

Changes in cardiovascular function in the control and RIC groups

As shown in Table 2, the NYHA class was improved in the RIC group (P < 0.0001). LVEF was decreased between the baseline and final evaluation in the control group (P < 0.05). However, LVEF was improved highly significantly from 37.11% to 52.44% in the RIC group. Furthermore, patients in the RIC group showed greater improvement in LVEF compared with those in the control group (P < 0.0001).

As depicted in Table 2, LA and LVDd were not different between the baseline and final evaluation in the control group, but were decreased significantly in the RIC group (P < 0.01), respectively. Moreover, LVSd was significantly increased in the control group (P < 0.05), but significantly decreased in the RIC group (P < 0.05). Furthermore, patients in the RIC group showed greater decrease in left atrial and ventricular dimensions compared with those in the control group (P = 0.03, 0.02 and 0.001), respectively.

After 1 year, systolic blood pressures in the control and RIC groups were 133.4 ± 2.68 and 134 ± 2.86 mm Hg, respectively. There is no significant difference between the control and RIC groups, and before and after 1 year, respectively. Moreover, after 1 year, diastolic blood pressures in the control and RIC groups were 81 ± 1.7 and 79.4 ± 1.9 mm Hg, respectively. There is no significant difference between the control and RIC groups, and before and after 1 year, respectively.

Discussion

This study showed that a 1-year RIC treatment as a healthy strategy improved cardiovascular function in heart failure patients without side effects, substantiating the common use of RIC in the daily lives of these patients. The results are compatible to those of Chen et al [20]. They reported that 6 weeks of RIC treatment improved heart function in patients with mild ischemic heart failure, leading to increases in LVEF (from 39.2% to 43.4%) and heart rate variability (from 861.8 to 893 ms), and decrease in B-type natriuretic peptide (from 68.8 to 55.2 pg/mL). Moreover, chronic RIC for 7 to 28 days has been shown in experimental and clinical studies to confer protective and beneficial effects on post-infarct cardiac remodeling and chronic heart failure [21].

The NYHA functional class is a simple method of quan-

Table 1. Baseline Characteristics of Patients in the Control and RIC Groups

	Control (n = 20)	RIC (n = 20)	P value
Age, years	68.4 ± 2.77	65.8 ± 2.35	0.55
Male/female	10/10	9/11	0.25
NYHA class	3.15 ± 0.15	3.25 ± 0.12	0.61
BMI (kg/m^2)	24.74 ± 0.78	24.93 ± 0.87	0.38
Heart rate (bpm)	70.15 ± 1.64	68.65 ± 1.74	0.3
Systolic blood pressure (mm Hg)	137.25 ± 2.68	135.75 ± 3.41	0.39
Diastolic blood pressure (mm Hg)	79.1 ± 2.01	80.45 ± 2.02	0.3
Echocardiography			
LA (mm)	47.85 ± 1.71	50.55 ± 1.94	0.31
LVDd (mm)	58.74 ± 1.86	53.04 ± 1.79	0.07
LVSd (mm)	47.4 ± 2.24	39.96 ± 1.84	0.06
LVEF (%)	33.23 ± 1.76	37.11 ± 1.72	0.09
Past medical illness			
Hypertension	20	20	1
Coronary artery disease	20	20	1
Diabetes mellitus	13	13	1
Cardiac medications			
Beta-blockers	20	20	1
ACE inhibitors or ARBs	20	20	1
Diuretics	16	17	0.55
Digoxin	12	12	1
Antiplatelets	20	20	1
Nitrates	20	20	1

Data are presented as number or mean (SEM). Student's *t*-test or χ^2 test, as appropriate. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; NYHA: New York Heart Association; LA: left atrial dimension; LVDd: left ventricular end diastolic dimension; LVSd: left ventricular end systolic dimension; LVEF: left ventricular ejection fraction; RIC: remote ischemic conditioning.

tifying functional performance based on medical history and has good prognostic value for heart failure patients [22], which was significantly improved by the RIC in this study. There was also clinical improvement in patients' signs and symptoms.

LVEF, the important marker of systolic heart function, was also significantly elevated in heart failure patients in the RIC group.

Ventricular remodeling refers to alteration in the geometry, structure, and function of the heart. This is the main process of heart failure and correlates with diminished ejection fraction, disease progression, and clinical outcomes [23]. The notion of stopping or reversing the progression of remodeling is an important goal in the treatment of heart failure. In one study, reverse remodeling was defined as an increase in LVEF

Table 2. Changes in Cardiovascular Function of Patients at Baseline and at Final Evaluation in the Control and RIC Groups

	Control (n = 20)			RIC (n = 20)			P value*
	Baseline	Final	P value	Baseline	Final	P value	
NYHA class	3.15 ± 0.15	2.95 ± 0.2	0.3	3.25 ± 0.12	1.2 ± 0.09	< 0.0001	< 0.0001
LA (mm)	47.85 ± 1.71	48.35 ± 1.92	0.75	50.55 ± 1.94	43.25 ± 1.35	0.31	0.03
LVDd (mm)	58.74 ± 1.86	58.95 ± 2.79	0.91	53.04 ± 1.79	50.15 ± 1.62	0.07	0.02
LVSd (mm)	47.4 ± 2.24	49.7 ± 3.02	0.05	39.96 ± 1.84	35.65 ± 1.69	0.02	0.001
LVEF (%)	33.23 ± 1.76	29.39 ± 2.17	0.02	37.11 ± 1.72	52.44 ± 2.27	< 0.0001	< 0.0001

Data are presented as number or mean (SEM). Student's *t*-test or χ^2 test, as appropriate. NYHA: New York Heart Association; LA: left atrial dimension; LVDd: left ventricular end diastolic dimension; LVSd: left ventricular end systolic dimension; LVEF: left ventricular ejection fraction; RIC: remote ischemic conditioning. *Compared the differences from basal to final evaluation of RIC group with those of control group.

of more than 15% or an increase in LVEF of more than 10% plus an improvement in end-systolic parameters of the left ventricle for 1 year [24].

Another study suggested that a decrease in end-systolic and end-diastolic volume correlates with reverse remodeling [25]. In the present study, significant improvements were observed, including an increase in ejection fraction, decreased left atrium, and left ventricular diastolic and systolic diameter in the RIC group.

We hypothesize that RIC is stress on the heart that triggers compensatory mechanisms that release healthy factors such as cardioprotective factors and eliminate unhealthy factors such as free radicals [18]. This beneficial cycle results in reversion of disease, consistent with the heterochronic parabiotic model, as demonstrated by reverse remodeling and improvement in heart failure in this study [18].

RIC with brief ischemia and reperfusion of a distant organ also guards the myocardium. This shift of the heart to a preconditioned state with short and transient physiological myocardial ischemia is considered an important advance in this area of myocardial protection.

RIC is the most interesting method of inducing cardioprotection because it is both safe and easy to perform. RIC protocols use ischemia and reperfusion of the arm or leg instead of coronary manipulation. Therefore, evidence that conditioning exists in humans can render an important impetus for the investigation of modalities or strategies to keep the body in a continuously conditioned and protected state. In this study, RIC was conducted as a healthy strategy over a relatively long period of time of 1 year. The results clearly showed that heart conditioning, as a healthy strategy, significantly improved cardiovascular function in heart failure patients through the reverse remodeling process, indicating the reversion of disease.

Since the RIC was performed only simply, with inflation of blood pressure cuff, which could be performed by the patients themselves at home, the present study indicates that RIC can be used as a self-care heart failure treatment for inpatients and home-care patients. Moreover, patients have good compliance because they merely performed RIC once a time and once a day, for the sake of health.

Conclusion

Overall, this study shows that heart conditioning as a health strategy is a valuable, safe, and effective adjunctive treatment for patients suffering from heart failure that could impact cardiac remodeling and recovery, as well as quality of life.

Study limitations

One of the restrictions of this study is the relatively small sample size due to the long-term intervention protocol. Daily use of RIC for 1 year as a healthy strategy has never been reported. Therefore, this is a preliminary pilot study. However, according to statistical analysis, a P-value of less than 0.0001 in the results of this pilot study is highly significant and positive, which supports the conclusion of this analysis. Further randomized controlled trials with more patients enrolled are needed to confirm these findings and investigate further clinical outcomes.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

All patients completed a written informed consent.

Author Contributions

MY Shyu collected clinical data, performed statistical analysis, drafting and review the manuscript. AYS Lee conceptualized this study, collected clinical data, performed statistical analysis, drafting, review and edited the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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