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Heart Conditioning as a Healthy Strategy in Management of Cardiac Enlargement

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Abstract

Background: Remote ischemic conditioning (RIC) is widely recognized for its cardioprotective effects in the context of ischemic heart disease. Lately, it has been shown that heart conditioning can be utilized as a healthy strategy in the reversion of disease and aging. In this regard, we examine the impact of RIC on patients with cardiac enlargement.

Methods: Forty-four patients with cardiac enlargement were prospectively enrolled and randomly assigned into RIC group (n = 22) and control group (n = 22). RIC protocol is 3-min inflation/deflation of the blood pressure cuff applied in the upper arm to create transient arm ischemia. RIC treatment was performed once a day for 1 year. Left atrial and ventricular dimensions and left ventricular ejection fraction (LVEF) were all assessed in two groups.

Results: RIC was well-tolerated. After 1 year treatment, left atrial and ventricular dimensions were significantly decreased in the RIC group. Moreover, LVEF showed a significant increase, from 46.24% to 56.45% (P < 0.0001).

Conclusion: The research indicates that a year-long healthy regimen of RIC treatment may effectively reverse cardiac enlargement, thereby endorsing the broader implementation of RIC in the daily routines of these patients.

Keywords: Heart conditioning; Healthy strategy; Cardiomegaly

Introduction

Cardiomegaly is defined as the enlargement of the heart, whether through dilatation or hypertrophy, which can involve the right ventricle, left ventricle, or both, as well as the atria. This condition is commonly seen in a variety of cardiovascular disorders, including hypertension, coronary artery disease, valvular heart disease, arrhythmias, and cardiomyopathy [1, 2]. The incidence of cardiac enlargement has increased and is recognized as a pathological indicator of cardiovascular disease, which remains the leading cause of mortality worldwide.

In 1986, Murry et al were pioneers in demonstrating the phenomenon of ischemic preconditioning in canine models [3]. They found that brief, repeated occlusions of the coronary artery lasting 5 min prior to a prolonged occlusion resulted in a significant reduction in the size of myocardial infarction. Since that initial discovery, ischemic preconditioning has been extensively validated across various animal species and in human subjects [3-5]. It has been shown to confer protective benefits against post-ischemic contractile dysfunction [6], cardiac arrhythmias induced by ischemia and reperfusion [7, 8], apoptosis [9], and infarct injury [3-5]. Furthermore, ischemic preconditioning has been utilized in patients with coronary artery disease, leading to enhanced clinical outcomes during cardiac catheterization [10] and heart surgery [11].

Remote ischemic preconditioning (RIC), which involves inducing mild ischemia and subsequent reperfusion in a distant organ, has also been identified as a protective strategy for the heart. This noninvasive technique typically involves the periodic inflation of a standard blood pressure cuff to 200 mm Hg, with three to four cycles of 5 min of inflation followed by 5 min of reperfusion [12]. Researches indicate that RIC can mitigate cardiac injury and decrease the incidence of major adverse cardiovascular and cerebrovascular events in patients undergoing cardiac procedures [13-16]. Additionally, when administered daily for a duration of 28 days, RIC has been shown to improve adverse left ventricular remodeling and enhance cardiovascular function in rat models following myocardial infarction [17].

Recently, chronic RIC has emerged as a promising method for improving cardiovascular function in individuals with heart failure [18]. Furthermore, recent studies have shown that heart conditioning, similar to the heterochronic parabiosis model, can be an effective strategy for reversing both disease and aging processes [19]. In this context, heart conditioning may provide significant benefits for patients with cardiomegaly. Consequently, we aim to explore the effects of heart conditioning as a beneficial strategy for individuals experiencing cardiac enlargement.

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Materials and Methods

This study was a 1-year, single-center, randomized, controlled, prospective pilot investigation. We prospectively recruited 44 patients showing stable cardiomegaly from the outpatient services of the Department of Cardiology at Jen Ai Hospital in Taichung, Taiwan. The research protocol was approved by the Review Board and Ethics Committee of Jen-Ai Hospital, and the study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

The inclusion criteria for patients were as follows: 1) a confirmed diagnosis of cardiac enlargement by echocardiography; and 2) sinus rhythm without atrial fibrillation. To focus exclusively on the impact of RIC on cardiomegaly and to eliminate other potential influences, the exclusion criteria included: 1) more than moderate valvular heart disease; 2) recent acute coronary syndrome occurring within the last 6 months; 3) a history of atrial fibrillation, intermittent bundle branch block, or pacemaker placement; 4) peripheral arterial disease; 5) uncontrolled hypertension (systolic blood pressure exceeding 160 mm Hg or diastolic blood pressure exceeding 100 mm Hg); 6) active cancer; and 7) the presence of other serious systemic illnesses.

Patients included in the study were randomly assigned into the control and RIC groups. In the control group (n = 22), patients received standard medical treatment. In the RIC group (n = 22), patients underwent 1 year of RIC therapy in conjunction with standard medical treatment. All patients received standard medical therapy by the cardiologists, which included beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), diuretics, digoxin, antiplatelet, and nitrates. All medications were required to be continued in unchanged dosage for the duration of the study. 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 utilized. A standard blood pressure cuff was placed on the upper arm of each participant and inflated to a pressure of 200 mm Hg for 3 min, after which the cuff was automatically deflated. Patients performed the RIC treatment independently at home once daily. A physician confirmed the correct operation of the RIC by the patients during the initial week.

Transthoracic echocardiography was performed using the Acuson SC2000 (Siemens Inc., Germany) following standard protocols. M-mode echocardiography was used to measure the left atrial dimension (LA) as well as the left ventricular dimensions during end diastole (LVDd) and systole (LVSd). Additionally, the dimensions of the interventricular septum (IVS) and posterior wall (PW) were also measured. Left ventricular end-diastolic and systolic volumes were calculated using Simpson's method and indexed to body surface area. The left ventricular ejection fraction (LVEF) was then determined. The average of three measurements was taken for all variables. All echocardiograms were interpreted by the same physician, who was blinded to the other information of each patient. Echocardiograms were conducted both prior to and following a 1-year period.

Data are expressed as mean (SEM), or number. Categorical variables were analyzed using the Chi-square test. The mean values of clinical characteristics were compared between the control and RIC groups utilizing the Student's *t*-test. Additionally, the Student's *t*-test was used to compare mean values from baseline to final evaluation for both the control and RIC groups. A P-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The mean age of patients was 67.46 ± 2.52 and 67.68 ± 2.57 years in the control and RIC groups, respectively (P = 0.95). The mean LA, LVDd, and LVSd in the control group were 47.17 ± 1.4, 53.16 ± 2.24, and 39.36 ± 2.81 mm, respectively. The mean LA, LVDd, and LVSd in the RIC group were 50.27 ± 1.59, 49.3 ± 1.67, and 35.46 ± 1.92 mm, respectively (P = 0.14, 0.11, and 0.13, respectively). The mean IVS and PW in the control group were 11.67 ± 0.43 and 10.45 ± 0.37 mm, respectively. The mean IVS and PW in the RIC group were 10.87 ± 0.38 and 10 ± 0.32 mm, respectively (P = 0.32 and 0.12, respectively). The mean LVEF was 45.19±3.67% and 46.24±3.25% in the control and RIC groups, respectively (P = 0.64). There was no significant difference in the baseline patient characteristics between the control and RIC groups, as shown in Table 1.

Changes in heart dimension in the control and RIC groups

As depicted in Table 2, LA, LVDd, and LVSd were not different between the baseline and final evaluation in the control group, but were decreased significantly in the RIC group, respectively. IVS and PW were not different between the baseline and final evaluation in the control and RIC groups, respectively. Moreover, patients in the RIC group showed greater decrease in LA, LVDd, and LVSd compared with those in the control group (P = 0.002, 0.01, and 0.02), respectively. Furthermore, ejection fraction was significantly decreased between the baseline and final evaluation in the control group (45.19±3.67% to 41.53±4%, P = 0.01), but was increased significantly between the baseline and final evaluation in the RIC group (46.24±3.25% to 56.45±2.59%, P < 0.0001).

After 1 year, systolic blood pressures in the control and RIC groups were 133.41 ± 2.68 and 134 ± 2.86 mm Hg, respectively (P = 0.89). 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 ± 1.79 and 79.41 ± 1.97 mm Hg, respectively (P = 0.48). There is no significant difference between the control and RIC groups, and before and after 1 year, respectively.

Discussion

Ischemic preconditioning was first discovered by Murry et al in 1986 [3]. RIC, which includes brief episodes of ischemia

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

	Control (n = 22)	RIC (n = 22)	P value
Age, years	67.46 ± 2.52	67.68 ± 2.57	0.95
Male/female	12/10	10/12	0.55
BMI (kg/m^2)	25.36 ± 0.74	25.68 ± 0.8	0.78
Heart rate (bpm)	73.55 ± 1.83	71.68 ± 1.99	0.26
Systolic blood pressure (mm Hg)	133.41 ± 2.68	134 ± 2.86	0.89
Diastolic blood pressure (mm Hg)	81 ± 1.79	79.41 ± 1.97	0.48
Echocardiography			
LA (mm)	47.17 ± 1.4	50.27 ± 1.59	0.14
LVDd (mm)	53.16 ± 2.24	49.3 ± 1.67	0.11
LVSd (mm)	39.36 ± 2.81	35.46 ± 1.92	0.13
LVEF (%)	45.19 ± 3.67	46.24 ± 3.25	0.64
Past medical illness			
Hypertension	22	22	1
Coronary artery disease	22	22	1
Heart failure	13	14	0.9
Diabetes mellitus	8	7	0.84
Cardiac medications			
Beta-blockers	22	22	1
ACE inhibitors or ARBs	22	22	1
Diuretics	10	12	0.55
Digoxin	5	5	1
Antiplatelets	22	22	1
Nitrates	22	22	1

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

followed by reperfusion of a distant organ, also provides protective benefits to the heart. The adaptation of the heart to a preconditioned state through short, transient episodes of physiological myocardial ischemia represents a significant advancement in the field of heart protection.

Ventricular remodeling involves changes in the geometry, structure, and function of the heart. It plays a crucial role in heart failure, correlating with a decline in ejection fraction, disease progression, and overall clinical outcomes [20]. The primary goal of heart failure treatment is to prevent or reverse the remodeling process. One study defines reverse remodeling as a greater than 15% increase in LVEF, or a minimum 10% in-

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

	Control (n = 22)			RIC (n = 22)			P value*
	Baseline	Final	P value	Baseline	Final	P value	
LA (mm)	47.17 ± 1.4	47.86 ± 1.55	0.61	50.27 ± 1.59	41.64 ± 1.11	0.0001	0.002
LVDd (mm)	53.16 ± 2.24	55.2 ± 2.53	0.17	49.3 ± 1.67	46.41 ± 1.38	0.05	0.01
LVSd (mm)	39.36 ± 2.81	41.6 ± 3.45	0.07	35.46 ± 1.92	31.18 ± 1.53	0.004	0.02
IVS (mm)	11.67 ± 0.43	10.92 ± 0.42	0.73	10.87 ± 0.38	11.26 ± 0.32	0.32	0.47
PW (mm)	10.45 ± 0.37	9.89 ± 0.31	0.18	10 ± 0.32	10.46 ± 0.23	0.12	0.13
LVEF (%)	45.19 ± 3.67	41.53 ± 4	0.01	46.24 ± 3.25	56.45 ± 2.59	< 0.0001	0.0002

Data are presented as number or mean (SEM). *Compared the differences from basal to final evaluation of RIC group with those of control group. Student's *t*-test was used, as appropriate. IVS: interventricular septum; LA: left atrial dimension; LVDd: left ventricular end diastolic dimension; LVEF: left ventricular ejection fraction; LVSd: left ventricular end systolic dimension; PW: posterior wall; RIC: remote ischemic conditioning.

crease in LVEF accompanied by improvements in left ventricular end-systolic parameters over a year [21]. Another study shows that reductions in both end-systolic and end-diastolic volumes are linked to reverse remodeling [22]. In our current study, significant improvements were observed in the RIC group, including an increase in ejection fraction and reductions in left atrial, left ventricular diastolic, and systolic diameters. We hypothesize that RIC acts as a stressor to the heart, triggering compensatory mechanisms that release healthy factors like cardioprotective agents and eliminate unhealthy factors such as free radicals. This advantageous cycle leads to reversion of disease, akin to the heterochronic parabiotic model, as evidenced by the reverse remodeling and cardiac enlargement improvement in this study [20].

Remodeling is a complex process that involves structural, functional, electrical, and metabolic changes. Our study focused on the macroscopic changes occurring in the left heart chamber. Various cardiovascular disorders can affect the structure and function of the left heart, leading to its gradual enlargement. Patients who experience complete left-sided reverse remodeling of both the left atrium and left ventricle have a significantly lower risk of heart failure or mortality compared to those with only partial or minimal left-sided reverse remodeling [22].

Heart conditioning is a highly appealing approach to achieving cardioprotection due to its safety and practicality. RIC protocols utilize ischemia and reperfusion of the limbs rather than direct coronary intervention. Consequently, the existence of conditioning effects in humans could significantly encourage the development of methods or strategies aimed at maintaining a continuously conditioned and protected physiological state, ideally on a regular and indefinite basis. In this investigation, RIC was administered over an extended period of 1 year as a healthy regimen. The results clearly demonstrated that heart conditioning, as a healthy strategy, leads to a notable reduction in heart size among patients suffering from cardiac enlargement.

Given that RIC was executed simply through the inflation of a blood pressure cuff, a method that patients could easily perform themselves, the results of this study suggest that RIC may serve as a self-care treatment option for cardiomegaly in both inpatient and home-care settings. Furthermore, patients showed high compliance with the simple RIC procedure, which involved inflating a blood pressure cuff, as they only needed to perform it once a time and once a day for their health benefits.

Overall, this study underscores that heart conditioning, as a healthy strategy, is a valuable, safe, and effective adjunctive treatment for patients with cardiac enlargement, potentially influencing cardiac reverse remodeling, recovery, and overall quality of life.

Study limitation

Limitations of this study include its relatively small sample size, due to the long-term intervention protocol. The daily application of RIC over the course of 1 year as a health strategy has not been previously documented. Consequently, this research serves as a preliminary pilot study. Nevertheless, the statistical analysis revealed a P-value of less than 0.0001, indicating a highly significant and positive outcome. To validate these findings and investigate additional clinical outcomes, further randomized controlled trials with a larger patient population are necessary.

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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

DWC Lee and WWH Lee collected clinical data, performed statistical analysis, drafted and reviewed the manuscript. AYS Lee conceptualized this study, collected clinical data, performed statistical analysis, drafted, reviewed 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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