

A Combination of Electro-Acupuncture and Aerobic Exercise Improves Cardiovascular Function in Patients with Coronary Heart Disease

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Abstract

Objectives: The goal of this study is to determine whether a combination therapy of electro-acupuncture and aerobic exercise are effective at improving heart rate recovery and physical ability in patients with coronary heart disease (CHD). Additionally, this study aims to analyse how acupuncture improves cardiovascular function.

Methods: 108 patients diagnosed with CHD and abnormal heart rate recoveries (HRR) were recruited to the study. All subjects were randomly divided into a control group, receiving no intervention, or one of three experimental groups: aerobic exercise therapy, electro-acupuncture therapy, and a combination therapy of electro-acupuncture and aerobic exercise. Aerobic exercise was performed at an intensity of 60%-75% of maximum sports ability for 30 minutes per session. Acupoints Neiguan (PC6) and Ximen (PC4) were used for acupuncture in the electro-acupuncture experiments for 30 min sessions. Each treatment group underwent the experimental therapies five times a week for twelve weeks. For all subjects, a cardiopulmonary exercise test (CPET) was used to assess HRR and exercise ability. Heart rate variability (HRV), including low frequency (LF), high frequency (HF), a low frequency to high frequency ratio (LF/HF) and standard deviation of normal-to-normal interval (SDNN), was used to evaluate autonomic nervous function. Superoxide dismutase (SOD), nitric oxide (NO), and lipid peroxide (LOOH) in venous blood were evaluated to determine oxidative stress levels.

Results: There was no significant difference among any of the groups before treatment for any of the indices measured. After twelve weeks, the HRR in the combination therapy group was lower than any other treatment group or the control group ($p < 0.05$). The HRR in the electro-acupuncture group was lower than the aerobic exercise and the control groups ($p < 0.05$) and the HRR of the aerobic exercise group was lower than the control group ($p < 0.05$). Oxidative stress levels and heart rate variability measurements for the combination group were significantly improved over all the other groups.

Conclusions: Compared to aerobic exercise treatment or electro-acupuncture treatment alone, the combined treatment method improved heart rate recovery and exercise ability most significantly. Furthermore, the autonomic nervous function and oxidative stress level were markedly improved as well. Overall, we show that a combination therapy of electro-acupuncture and aerobic exercise can improve HRR, HRV, and oxidative stress on the heart, improving the physical ability of patients with coronary heart disease.

Keywords: Aerobic exercise; Electro-acupuncture; Coronary heart disease; Heart rate recovery; Heart rate variability; Sports ability; Alternative therapy

Introduction

Coronary heart disease (CHD) is a very common disease, affecting approximately 6.4% of Americans, and is the first and second leading causes in cardiovascular death in the United States and China respectively [1,2]. With the advancement of diagnosis and treatment technology, more patients survive the initial myocardial infarction caused by CHD, leading to an increase percentage of the population living with a disease that negatively affects their quality of life due to a decrease in physical ability, often caused by abnormal activity of the cardiac autonomic system [3]. The abnormal activity of the cardiac

autonomic system can be clinically evaluated by calculating the heart rate recovery (HRR), defined as the difference between peak heart rate and the heart rate 1 minute after exercise. An abnormal HRR, defined as a difference of less than 12 beats/min, is closely connected with reduced physical ability and is an independent risk factor that can predict coronary heart disease and, potentially, death due to cardiovascular diseases [4-6]. Increasing a patient's physical abilities as determined by heart rate recovery can significantly improve quality of life when living with cardiovascular diseases [7-9].

Current rehabilitation for patients with cardiovascular diseases typically consists of aerobic exercise therapy because functional exercise has been shown to have a vital impact on improving physical ability and quality of life [10]. Considered as an important non-pharmaceutical therapy, aerobic exercise was proven by a number of studies to improve the HRR and physical ability [11-13]. Nevertheless,

non-compliance of patients on an aerobic exercise regimen is high [14], creating a need to improve upon current therapies.

Traditional Chinese medicine acupuncture therapy has been recognized to treat many diseases including cardiovascular disease, tension headaches, and Bell's palsy [15]. Acupuncture therapy is an essential treatment method in Chinese medicine. It appears to have a positive effect on improving patients' neurological function [16] and physical ability [17]; however, the mechanism behind its efficacy is unclear and there is some controversy over which acupoints are important for improving cardiovascular health as well as the limitations to the studies on the overall benefits of acupuncture, as reported by Urroz et al. [17].

Characteristic	Aerobic Exercise (n=29)	Electro-Acupuncture (n=27)	Combination Therapy (n=30)	Control (n=26)
Age (years)	61.4 ± 8.9	63.0 ± 9.1	63.1 ± 8.8	62.3 ± 8.7
Gender (male/female)	17/12	17/10	19/11	16/10
Time since CHD diagnosis (month)	20.6 ± 9.3	19.2 ± 8.0	20.5 ± 9.1	21.1 ± 9.2
Gensini grade	11 (37.9%)	9 (33.3%)	10 (33.3%)	9 (34.6%)
BMI (kg/m ²)	25.42 ± 3.92	24.87 ± 4.01	25.36 ± 3.95	24.63 ± 3.91
After PCI	11 (37.9%)	9 (33.3%)	10 (33.3%)	9 (34.6%)
After CABG	2 (6.9%)	2 (7.4%)	2 (6.7%)	2 (7.7%)
Smoke	15 (51.7%)	13 (48.1%)	14 (46.7%)	12 (46.2%)
Hypertension	21 (72.4%)	20 (74.1%)	21 (70.0%)	20 (76.9%)
Diabetes	10 (34.5%)	8 (29.6%)	9 (30.0%)	8 (30.8%)
Hyperlipidemia	11 (37.9%)	10 (37.0%)	11 (36.7%)	10 (38.5%)
Prescriptions				
β-blocker	24 (82.8%)	22 (81.5%)	23 (76.7%)	22 (84.6%)
Antiplatelets	28 (96.6%)	27 (100%)	29 (96.7%)	25 (96.2%)
Statins	29 (100%)	27 (100%)	30 (100%)	26 (100%)
Nitrates	10 (34.5%)	7 (25.9%)	11 (36.7%)	8 (30.8%)
ACEI/ARB	27 (93.1%)	25 (92.6%)	28 (93.3%)	24 (92.3%)

Table 1: Patient characteristics. PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker.

Both acupuncture therapy and aerobic exercise therapy have been proven to be beneficial to patients with cardiovascular diseases such as coronary heart disease; however, a combination of these two therapies has not been objectively studied. This study was designed compare the effect of single aerobic exercise, single electro-acupuncture therapy and electro-acupuncture therapy combined with aerobic exercise on patients' HRR and sports ability. The goal of this study is to determine whether electro-acupuncture combined with aerobic exercise is more

beneficial than individual therapies in improving cardiovascular function.

Methods

Subjects

This study was approved by the Nanjing Jiangning Hospital Ethics Committee and all patients provided their informed consent. CHD patients with at least one main coronary vessel with stenosis >50% as determined via coronary angiography, were recruited from September 2013 to September 2014 at the cardiac rehabilitation center in Nanjing Jiangning Hospital. The following criteria excluded patients from the trial:

- patient had uncontrolled severe arrhythmia, hypertension or diabetes
- patient had severe heart failure (NYHA Class IV)
- patient had a pacemaker, a complete left bundle branch block, or a heart transplant
- patient had a musculoskeletal or neurological disease that prevented compliance with evaluation and/or treatment
- patient had an electrolyte disturbance due to disease and was using digitalis
- patient had a pulmonary disease such as chronic bronchitis or chronic obstructive pulmonary disease (COPD), which would affect respiratory function
- patient used calcium ion antagonists or β-blockers which would affect heart rate and could not stop taking the medicine for at least 2 days before performing heart rate variability test
- Patient was using antioxidants like Vitamin C and Vitamin E less than 1 month before undergoing venous blood collection.

Overall, 112 subjects with an abnormal HRR were enrolled in the study. Subjects were randomly divided into an aerobic exercise group (n=29), an electro-acupuncture group (=27), an electro-acupuncture combined with aerobic exercise group (=30) and a control group (=26). There was one case of severe angina in the aerobic exercise group during treatment. Additionally, 2 combination therapy subjects did not complete the entire study. Finally, 1 control subject did not participate in the post therapy analysis, making a total of 108 subjects that completed this study.

Cardiopulmonary exercise test (CPET)

To measure HRR and heart rate variability (HRV), a CPET system (K4b2, COSMED) was used to conduct a symptom limited exercise test. Subjects sat on the ergometer with an electrocardiograph (Holter-TECH 8000, GP/DMasia), blood pressure monitor and CPET face mask attached. A 3 to 5-minute non-load warm-up was performed. The test began with a 5W loading and was increased by 15W every minute with a speed of 50-60 rpm. Testing was stopped if subject experienced any of the following: chest pain, weakness, dyspnea, dizziness, giddiness, pallor, a declined ST interval of >2 mm, an increased ST interval ≥ 1 mm, frequent ventricular tachycardia, atrial fibrillation, or a systolic blood pressure >220 mmHg during exercise. Short-time HRV software was used for analysis. A Fast Fourier transformation (FFT) method was adopted for frequency analysis with low frequency (LF) defined as 0.04-0.15Hz and high frequency (HF) defined as 0.15-0.40 Hz.

Peak power (PP), was measured at the maximum exercise load the subject could tolerate during the CPET measurement. The CPET manifold measured the uptake of oxygen by the subject during the exercise. This was used to measure the VO_{2peak} at the maximum exercise load. The CPET was also used to determine the anaerobic threshold (AT), defined as the point of transformation from aerobic to anaerobic exercise, by measuring the rate of ventilation and marking

when it increases disproportionately to the increase in VO_2 , also known as the V-slope method. HRV was measured via a low frequency index (LF) between 0.04-0.15 Hz, a high frequency index (HF) between 0.15 and 0.40 Hz, a low frequency and high frequency ratio (LF/HF) and a normal standard deviation of normal-to-normal interval (SDNN) before therapies began and after 12 weeks of treatment.

Group	HRR1 (beats)		PP (W)		VO_{2peak} (ml/kg/min)		AT (mL/kg/min)	
	Before	After	Before	After	Before	After	Before	After
Aerobic Exercise (n=28)	6.12 ± 2.07	10.13 ± 2.56 ^d	84.21 ± 15.76	96.35 ± 16.38 ^d	13.95 ± 3.57	17.89 ± 3.45	10.25 ± 2.15	12.89 ± 3.37
Electro-Acupuncture (n=27)	6.28 ± 2.16	10.97 ± 1.98 ^d	80.68 ± 16.04	82.78 ± 17.38 ^a	14.68 ± 6.40	15.05 ± 6.58	10.39 ± 2.79	12.47 ± 3.68
Combination Therapy (n=28)	7.02 ± 3.09	13.42 ± 2.89 ^{bcd}	82.10 ± 14.57	102 ± 17.09 ^{cd}	15.07 ± 3.53	18.98 ± 3.42 ^{cd}	10.37 ± 2.35	13.57 ± 2.59
Control (n=25)	7.18 ± 2.11	8.14 ± 3.02	81.36 ± 15.26	82.21 ± 16.83	13.87 ± 2.97	14.58 ± 5.80	11.01 ± 2.04	12.12 ± 2.96

Table 2: Comparison of HRR1 and exercise capabilities after treatment (x ± SD). ^aAerobic exercise vs. Electro-acupuncture; ^bAerobic exercise vs. Combination therapy; ^cElectro-acupuncture vs. Combination therapy; ^dControl vs. experimental group; p<0.05.

Oxidative stress assessment

A small aliquot of blood was collected from the subjects before and 12 weeks after therapy to assess levels of superoxide dismutase (SOD), nitric oxide (NO) and lipid hydroperoxidase (LOOH) present in the plasma. The xanthine oxidase method was used to assess SOD concentration. Spectrophotometry was used to assess NO and LOOH concentration.

Aerobic exercise

Subjects performed 30 minutes of ergometric exercise. The intensity of the exercise was adjusted for each subject according to the exercise load a subject could handle to reach their maximum heart rate (HR_{max}) by setting the training intensity at 60-70% of the individual's heart rate reserve. Exercise began at an intensity of 60% and was increased by 5% intervals based on subject's ability to a maximum of 70%. If subject could not endure the full high intensity program, the subject performed an intermittent exercise program with a 1-5 minute rest interval between each exercise period and the exercise time was increased to 60 minutes to adjust for the rest intervals. Subjects performed the aerobic exercise 5 times a week for 12 weeks.

Electro-acupuncture

Patients lay in a supine position and bilateral Neiguan (PC6) and Ximen (PC4) acupoints were selected. Acupoints were sterilized using iodine-alcohol. Sterile, 40mm needles were directly inserted to a depth of between 0.5 cun (approximately 16.67 mm) and 1 cun (approximately 33.33 mm) using a mild reinforcing and attenuating method with a frequency about 100 times/min. Electro-acupuncture therapeutic equipment (Huatuo Brand SDZ-II) with two connector wires were connected to the needles. Dilatational wave and stimulation

at intensity of 2-4 mA for 30 minutes was used based on the subject's tolerance. Subjects underwent electro-acupuncture therapy 5 times a week for 12 weeks. Subjects in the combination therapy group underwent electro-acupuncture 1 hour after the aerobic exercise therapy.

Statistics analysis

GraphPad Prism 6.0 software (GraphPad Software, La Jolla, California) was used to perform the statistical analysis of the data. A one-way ANOVA was used to determine if there was statistical difference between the means of the groups for each measurement. Multiple comparisons using a Holm-Sidak correction was performed to compare each group. Statistical significance was set at p<0.05.

Results

Overall, there was no statistical difference in any of the groups based on subject characteristics or drugs prescribed that may affect the outcome of the results (Table 1).

Prior to treatment, there was no significant difference in HRR, PP, VO_{2peak} , AT, HRV (LF, HF, LF/HF, and SDNN) and oxidative stress levels (SOD, NO, and LOOH) among the four groups. However, Table 2 indicates that after 12 weeks of treatment, the HRR of the combination therapy group was improved over the individual therapy groups and the control group (p<0.05). Table 2 also indicates the exercise ability of the subjects in regards to VO_{2peak} and PP increased after the combination therapy. Although there was a small improvement in physical ability in the combination therapy group over the aerobic exercise group, the difference was not statistically significant.

Group	LF (Hz)		HF (Hz)		LF/HF		SDNN (ms)	
	Before	After	Before	After	Before	After	Before	After
Aerobic Exercise (n=28)	612.6 ± 148.2	579.3 ± 164.3	112.6 ± 5.7	157.8 ± 8.9 ^d	4.51 ± 2.45	2.97 ± 1.87	65.7 ± 6.74	70.7 ± 7.31
Electro-Acupuncture (n=27)	609.9 ± 152.3	560.4 ± 173.4	109.7 ± 8.9	177.9 ± 5.9 ^{ad}	4.39 ± 1.55	2.28 ± 1.56	63.5 ± 6.08	76.8 ± 6.45 ^{ad}
Combination Therapy (n=28)	611.5 ± 149.6	551.4 ± 163.9	111.8 ± 3.2	179.5 ± 7.7 ^{bd}	4.32 ± 1.67	2.37 ± 1.66	63.7 ± 5.67	77.8 ± 5.43 ^{bd}
Control (n=25)	611.7 ± 139.8	609.8 ± 149.7	110.3 ± 3.3	119.3 ± 5.9	4.22 ± 1.08	3.97 ± 1.35	64.8 ± 5.77	67.9 ± 7.03

Table 3: Comparison of HRV after treatment (x ± SD). ^aAerobic exercise vs. Electro-acupuncture; ^bAerobic exercise vs. Combination therapy; ^cElectro-acupuncture vs. Combination therapy; ^dControl vs. experimental group; p<0.05.

To measure the heart rate variability and consequently autonomic nervous function, the LF, HF, ratio of LF to HF, and SDNN were compared in Table 3. Combination therapy and electro-acupuncture caused a significant improvement in the HF and SDNN measurements over the control group. Most importantly, electro-acupuncture increased HF and SDNN more than the aerobic exercise group (p<0.05). There was no change in the LF and LF/HF measurements between any of the groups.

Table 4 shows that combination therapy improved the oxidative stress indices SOD and LOOH over the other experimental groups and the control group (p<0.05). Additionally, the SOD and LOOH concentrations of the aerobic exercise group were significantly higher than the control group after the intervention. Electro-acupuncture caused an increase in SOD concentrations over the control group (p<0.05); however, it was not statistically different from the aerobic exercise group. None of the groups caused a significant change in the concentration of NO.

Discussion

Currently, common therapies for patients with CHD are mainly pharmaceutical interventions with recommendations for establishing a

healthier lifestyle by including exercise and maintaining a healthy diet. Unfortunately, many patients are non-compliant with this recommendation, creating a need for a more effective alternative therapy for CHD. In an effort to determine whether a combination of aerobic exercise and electro-acupuncture could improve conditions for patients with CHD, we analysed exercise ability in terms of PP, VO_{2peak} and AT. We also measured HRR because it has been shown to be an effective indicator of abnormal cardiac autonomic control caused by CHD. Gharacholou et al. demonstrated that abnormal HRR was altered by diastolic insufficiency after symptom limited exercise [18]. Additionally, Bubnova et al. demonstrated that after a year of exercise, patients with CHD had improved HRR and physical ability, improving their quality of life [19]. Here, we show that a combination therapy of exercise and electro-acupuncture is able to improve a patient's PP and VO_{2peak}, greatly increasing their ability for physical activities like climbing stairs or even participating in sports. This study demonstrated in Table 2 that, at minimum, participating in alternative medicine like electro-acupuncture can improve a patient's HRR; however acupuncture alone cannot improve exercise ability.

Group	SOD (NU/ml)		NO (µmol/L)		LOOH (µmol/L)	
	Before	After	Before	After	Before	After
Aerobic Exercise (n=28)	62.3 ± 23.5	210.2 ± 43.8 ^d	376.1 ± 206.4	478.3 ± 276.5	0.89 ± 0.11	0.52 ± 0.13 ^d
Electro-Acupuncture (n=27)	63.7 ± 21.7	223.2 ± 33.5 ^d	375.6 ± 189.5	489.3 ± 298.7	0.79 ± 0.13	0.64 ± 0.23
Combination Therapy (n=28)	61.4 ± 22.9	320.1 ± 23.6 ^{bcd}	362.4 ± 177.6	498.4 ± 301.6	0.78 ± 0.21	0.49 ± 0.21 ^{cd}
Control (n=25)	60.3 ± 21.9	108.1 ± 21.7	359.7 ± 159.9	370.3 ± 311.7	0.79 ± 0.23	0.77 ± 0.24

Table 4: Comparison of oxidative stress after treatment (x ± SD). ^aAerobic exercise vs. Electro-acupuncture; ^bAerobic exercise vs. Combination therapy; ^cElectro-acupuncture vs. Combination therapy; ^dControl vs. experimental group; p<0.05.

In an effort to identify how acupuncture affects the body, Jones et al. applied acupuncture-transcutaneous electrical nerve stimulation (Acu-TENS) on Neiguan (PC6) and showed that HRR was increased compared to the control group [20]; however, there was no significant difference of oxygen consumption between two groups, similar to our result in Table 2. Also similar to Table 2, Kristen et al. concluded that

acupuncture has no impact on VO_{2peak} [21], suggesting that electro-acupuncture is involved in some other pathway for improving cardiovascular function. Additionally, by assessing HRV, a number of studies have confirmed the effect of acupuncture on adjusting autonomic nervous function through a decrease in the activity of the sympathetic nerve, an increase the activity of parasympathetic nerve

and an improvement in the coordination of autonomic nerve system [22,23]. We can conclude that electro-acupuncture affects the parasympathetic nervous system by observing a significant increase in HF measurements in subjects receiving electro-acupuncture or combination therapy. Additionally, in Table 3, the SDNN of the combined therapy group as well as the electro-acupuncture therapy group were improved over the control group, indicating an improvement in the electrophysiology, suggesting an improvement in autonomic nervous function of the patients' hearts in these groups. In addition to improving the autonomic function of the heart, several studies have also shown an improvement in oxidative stress levels after acupuncture therapy [24].

An increase of oxidative stress levels participates in the mechanism of coronary artery impairment and is the reason for the increase of risk of cardiovascular disease for patients [25]. Danieli et al. [26] also found that the oxidative stress levels decreased after 12-week aerobic exercise by assessing the concentrations of SOD, NO, and LOOH in the plasma of patients before and after treatment. Liu et al. [27] found that acupuncture can reduce the rats' oxidative stress level by assessing SOD in hippocampus of rats with brain infarction. In addition, Wang et al. applied electro-acupuncture on rats with Parkinson Disease and came to the conclusion that acupuncture has an anti-oxidative stress function [28]. Our study indicates that although aerobic exercise and electro-acupuncture can increase concentrations of anti-oxidative indicators like SOD and reduce the concentration of LOOH, the two therapies together produce an additive effect (Table 4). This additive effect of the combination therapy is important for improving the physical ability of patients with CHD.

Overall, we show that a combination of both aerobic exercise and electro-acupuncture has an additive effect in improving all measured indices including: HRR, oxidative stress, and HRV. This conclusion is particularly important for clinicians working with patients with CHD. Performing a combination of both acupuncture and aerobic exercise can improve both the health of a patient and their ability to participate in regular physical activities. There were some limitations to this study, such as the relatively short course period of only 12 weeks and no direct assessment of an improvement on the quality of life of the patients. Future research should focus on exploring other possible mechanisms for the synergistic effect of the combination therapy as well as whether patients with other cardiovascular diseases could also benefit from a combination of acupuncture and aerobic exercise.

Conclusion

This study demonstrates that electro-acupuncture combined with aerobic exercise can markedly improve HRR, the exercise ability of CHD patients, and is significantly better than either therapy alone. This combined therapy shows a synergistic effect of electro-acupuncture and sports rehabilitation in reducing oxidative stress, a common cause of many cardiovascular diseases including CHD. This convenient, effective, and cheap therapy combines Chinese and Western medicine and is easy to promote in a clinical setting. Also, by suggesting a combination therapy, even if a patient is non-compliant with one aspect of the recommendation, either aerobic exercise or electro-acupuncture alone will create an improvement on the patient's overall health.

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