

# Effect of Exercise Training on Heart Rate Variability in Patients with Heart Failure After Percutaneous Coronary Intervention

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## ABSTRACT

**Background:** This study aims to evaluate the effect of exercise training on heart rate variability (HRV) and to determine the correlation between parameters of HRV and the ejection fraction in patients with heart failure after percutaneous coronary intervention.

**Material and Methods:** Fifty patients with left ventricular ejection fraction  $\leq 40\%$  undergone percutaneous coronary intervention were randomly allocated in either an exercise training (ET) group or a control group. The ET group performed exercise training for 45 minutes, three times a week for seven weeks. Patients in both groups received a leaflet for daily exercising at home. HRV parameters comprising, the standard deviation of normal R-R intervals (SDNN), the square root of the mean of the squares of successive R-R intervals differences (RMSSD), the percentage of successive R-R intervals differing from more than 50 ms (PNN50), using 24-hour Holter electrocardiographic monitoring was measured.

**Results:** After the intervention, the SDNN improved in the ET group ( $P=0.002$ ), while changes in all remaining HRV indices were insignificant ( $P\geq 0.05$ ). The control group showed no significant changes in any HRV parameters ( $P\geq 0.05$ ). Changes in SDNN in the ET group were significantly different from the control group ( $P=0.003$ ). At baseline, our results revealed a significant weak correlation between ejection fraction and SDNN ( $r=0.279$ ,  $P=0.047$ ). However, ejection fraction did not correlate significantly with RMSSD and PNN50.

**Conclusion:** Exercise training is safe and feasible in post percutaneous coronary intervention patients, even in those with reduced ejection fraction. In a seven-week period, exercise training was effective in improving HRV in heart failure patients after percutaneous coronary intervention.

## Keywords

Exercise Training, Heart Failure, Percutaneous Coronary Intervention, Heart Rate Variability

## Introduction

Coronary artery disease is a major reason for the heart failure [1]. Although percutaneous coronary intervention (PCI) is an effective approach to restore myocardial perfusion, in some patients, heart failure develops even after PCI [2, 3]. Left ventricular dysfunction is associated with an increased risk of sudden cardiac death [1]. Optimal medical therapy and cardiac rehabilitation in conjunction with PCI can be beneficial in diminishing the impact of heart failure [3].

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Exercise training is well-established non-pharmacological therapy for heart failure patients [4]. Several studies have shown that the exercise can be an asset for heart failure patients, improving their functional capacity [5], quality of life [6, 7], cardiac [8] and vascular functions [9], and reducing mortality and morbidity [10].

Heart rate variability is a physiological feature that reflects the impact of the autonomic nervous system on the cardiac function. Depressed heart rate variability (HRV) has been confirmed to be a prognostic marker and is correlated with morbidity and mortality [11-13]. However, HRV is not utilized in the current clinical practice. Establishing the correlation between HRV parameters and an ejection fraction can help verify the validity of HRV as a clinical tool for evaluating the response to therapeutic interventions in patients with heart failure. Also exercise training has been reported in order to improve HRV in patients following PCI [14, 15]; however, no study has focus specifically on the impact of exercise therapy on HRV in heart failure patients after PCI.

The aim of the present study is to investigate the effect of exercise training on HRV indices and to examine the correlation between these parameters and the ejection fraction in patients with heart failure after the percutaneous coronary interventions.

## Materials and Methods

### Study Design and Participants

This randomized, controlled, parallel-group trial investigated the effect of exercise training on heart rate variability in patients with heart failure after percutaneous coronary intervention.

All patients undergone percutaneous coronary intervention and referred to the Cardiac Rehabilitation Department of Al-Zahra Heart Charity Hospital in Shiraz from October 2015 to November 2016 by their cardiologist, one month after angioplasty, were evaluated for

inclusion in this study. The inclusion criteria were age 40-70 years, left ventricular ejection fraction  $\leq 40\%$ , and New York Heart Association functional class I, II or III. Patients were excluded from the study if the following criteria were met: severe exercise intolerance, uncontrolled arrhythmia, uncontrolled angina pectoris, severe kidney or lung diseases, musculoskeletal or neuromuscular conditions preventing exercise testing or training, and signs or symptoms of ischemia [16, 17]. All participants signed an informed consent form before participating in the study. Ethics approval was obtained from the Shiraz University of Medical Sciences Ethics Committee (reference number: IR.SUMS.REC.1394113).

### Randomization and Masking

After the baseline assessment and before the start of treatment protocols, the 50 patients were randomly allocated in either an exercise training (ET) group or a control group. A biostatistician generated the random allocation sequence using the permuted block randomization method. The random allocation sequence was implemented by a nurse who was unaware of the study hypothesis and intervention. All participants, referring physicians, research assistants and outcome assessors were blinded to a group assignment. All data were gathered independently by personnel blinded to the study aims, and analyzed by an analyst who was unaware of treatment allocation.

### Measurements

#### Exercise Testing

In order to predict peak  $VO_2$ , a supervised graded exercise test to record volitional fatigue or symptoms was conducted on a treadmill using Bruce protocol at baseline. The test was done in nonfasting conditions and under medication. A 12-lead ECG was recorded continuously, and blood pressure was measured with an arm cuff every 3 min.

#### Heart Rate Variability

Heart rate variability was recorded with a

24-hour Holter electrocardiographic monitor with three leads at a sampling rate of 250 Hz (Click Holter, Cardioline, Milan, Italy) before and after the seven-week intervention period. HRV parameters were obtained from Cardioline Holter software. The ECG recordings were examined by a specialist who was blinded to the participant group allocation. All ectopic beats, noisy data and artefacts were filtered out prior to calculating HRV parameters, and only the normal R-R intervals over a period of at least 15 hours of signal were analyzed. The time domain parameters considered in this study were the standard deviation of normal R-R intervals (SDNN), the square root of the mean of the squares of successive R-R intervals differences (RMSSD), the percentage of successive R-R intervals differing by more than 50 ms (PNN50).

### Interventions

The patients were randomly allocated to one of two groups: ET or control. All patients in exercise group received training three times a week for seven weeks. Training sessions were supervised by an experienced physiotherapist and a nurse. Electrocardiogram and heart rate were monitored with telemetric monitoring, and blood pressure was measured at the beginning and at the end of each session. Each training session started with warm-up for 5 minutes and ended with 5 minutes of cool-down consisting of light aerobic exercise. Patients in both groups received a leaflet for daily exercising at home. Briefly, the exercises included ten types of active exercises in trunk, upper and lower limbs. The patient was asked to do each exercise for 10 repetitions. Each exercise session at home lasted 15-20 minutes.

#### ET Protocol

The patients performed exercise training for a total of 45 minutes at 40% to 70% peak  $VO_2$  predicted with a supervised graded exercise test on a treadmill with the Bruce protocol. Exercise training consisted of exercise on a cycle ergometer for 20 minutes, an arm er-

gometer for 10 minutes and a treadmill for 15 minutes. At the beginning, training intensity was set at 40% peak  $VO_2$ , and then increased progressively to 70% peak  $VO_2$  [18, 19]. As training intensity increased, the patients' heart rate, rate of perceived exertion (Borg scale) and cardiac symptoms were also considered.

#### Control Protocol

Patients in the control group received a leaflet for daily exercising at home as explained above.

### Statistical Analysis

According to the previous studies, the sample size was determined to be 25 patients in each group, when  $\alpha=0.05$  and  $\beta=0.2$  by the NCSS (PASS) 2007 software. All analyses were done with SPSS software, v. 16 on an intention-to-treat principle. Normality of the data distribution was checked with the Shapiro–Wilk test. We used descriptive statistics including mean  $\pm$  SD for quantitative variables and the frequency (percentage) for qualitative variables to summarize the participants' baseline characteristics. Chi square test was used to compare qualitative variables among our three groups. We used the Spearman's bivariate correlation test to determine the correlation between the ejection fraction and HRV parameters. Paired t-tests and Wilcoxon signed rank tests were used for within-group comparisons for variables with normal and abnormal (PNN50) distribution, respectively. For each participant, the change in values from baseline was calculated at seven weeks (post intervention). Between-group comparisons were tested with independent t-test and the Mann-Whitney test, and  $P<0.05$  was considered significant for all tests.

### Results

We screened 205 patients, 152 of whom were excluded because they did not meet the eligibility criteria, and three patients declined participation. Fifty patients were randomized to each of the two groups. Three participants

withdrew from the study because of loss of interest and severe knee pain. Participants completed the study without any serious adverse events. Premature ventricular contractions were recorded in two patients. One patient in ET group experienced severe hypotension during two consecutive training sessions which were normalized after exercise discontinuation. Another patient in ET group had the respiratory problem that was not related to exercise training and had to be hospitalized for three days. These last two patients resumed training after one week.

Our results showed no statistically significant differences between groups at baseline for demographic and clinical characteristics (Table 1). There were also no significant differences between groups for heart rate variability parameters at baseline ( $P \geq 0.05$ ).

Changes in parameters after the intervention in both groups are presented in Table 2. After seven weeks of exercise training, SDNN increased after the intervention in the ET group ( $P=0.002$ ), while changes in RMSSD and PNN50 were not significant in training group ( $P \geq 0.05$ ). The control group showed no significant changes in any heart rate variability parameter ( $P \geq 0.05$ ). The results of independent t-test revealed statistically significant differences between the two groups with respect to the mean change values in SDNN ( $P=0.003$ ). There were no significant differences amongst groups regarding changes in remaining outcomes ( $P \geq 0.05$ , Table 3).

Our results demonstrated a significant correlation between the ejection fraction and SDNN at baseline ( $r = 0.279$ ,  $P=0.047$ ). However, ejection fraction did not correlate significantly with RMSSD and PNN50 ( $P=0.246$  and  $P=0.505$ , respectively).

## Discussion

To the best of our knowledge, the present study is the first to investigate the effect of exercise training on HRV in heart failure patients after percutaneous coronary intervention. All

**Table 1:** Baseline demographic and clinical characteristics of participants.

	exercise training (n=25)	Control (n=25)	P-value
<b>Age(year)</b>	57.64(7.85)	57.32(9.41)	0.897
<b>Weight(Kg)</b>	72.64(10.21)	70.28(14.60)	0.511
<b>Height(Cm)</b>	164.72(7.55)	163.68(11.16)	0.702
<b>BMI(Kg/m<sup>2</sup>)</b>	26.71(2.91)	26.10(3.86)	0.530
<b>Male/female</b>	18/7	16/9	0.544
<b>NYHA I/II/III</b>	9/11/5	11/10/4	0.870
<b>LVEF (%)</b>	33.80(6.17)	35.00(5.59)	0.475
<b>Drug therapy</b>			
<b>ACE-I (%)</b>	32	32	1.000
<b>Aspirin (%)</b>	100	100	NA
<b>Plavix (%)</b>	100	100	NA
<b>ARBs (%)</b>	36	32	0.765
<b>CCBs (%)</b>	12	8	1.000
<b>Diuretics (%)</b>	48	40	0.569
<b>Statins (%)</b>	88	92	1.000
<b>Nitrates (%)</b>	88	84	1.000
<b>Digoxin (%)</b>	16	0	0.110
<b>Comorbidity</b>			
<b>Diabetes (%)</b>	16	20	1.000
<b>Hypertension (%)</b>	36	20	0.345

Data are presented as the mean (SD) or number of patients or percentages. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitors; NA, not applicable; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

participants completed the study without any serious adverse events, and they admitted that exercise protocols were safe and well tolerated. The main finding of our study was that exercise training was effective only in increasing SDNN in training group. No significant changes in HRV parameters were seen in the control group. A significant difference was seen only for SDNN between the ET and control groups.

Several studies reported improvements in HRV indices in the time domain after exercise training [14, 20-22]. Our results were similar

**Table 2:** Within-group comparisons for parameters of heart rate variability.

	Exercise training (n=25)			Control (n=25)		
	Pre	Post	P value	Pre	post	P value
<b>SDNN(ms)</b>	99.27(33.04)	130.96(57.76)	0.002	117.67(40.59)	117.69(40.71)	0.998
<b>RMSSD(ms)</b>	31.45(13.19)	36.26(18.97)	0.079	32.75(11.76)	30.67(14.11)	0.460
<b>PNN50 (%)</b>	6.90(7.40)	6.42(7.84)	0.986	8.22(7.04)	7.30(6.23)	0.715

Data are presented as the mean (SD). SDNN, standard deviation of normal R-R intervals; RMSSD, square root of the mean of the squares of successive R-R intervals differences; PNN50, percentages of differences between adjacent R-R intervals that are greater than 50 millisecond.

**Table 3:** Between-group comparisons for changes in parameters of heart rate variability.

	Exercise training (n=25)	Control (n=25)	P value
<b>SDNN(ms)</b>	31.68(44.43)	0.01(25.49)	0.003
<b>RMSSD(ms)</b>	4.81(13.13)	-2.08(13.86)	0.077
<b>PNN50 (%)</b>	-0.48(6.05)	-0.91(6.24)	0.992

Data are presented as the mean (SD). SDNN, standard deviation of normal R-R intervals; RMSSD, square root of the mean of the squares of successive R-R intervals differences; PNN50, percentages of differences between adjacent R-R intervals that are greater than 50 millisecond.

to those reported by Larsen et al. [21], who demonstrated a significant increase only in the SDNN index, whereas the changes in RMSSD and PNN50 were not statistically significant. Another publication demonstrated that a high-intensity interval exercise program was effective in increasing the SDNN and RMSSD indices in patients following PCI for angina pectoris [14]. One hypothesis for the contrasting results of clinical trials to study the effects of exercise in patients with the cardiovascular disease is the different types and intensities of training. In addition, the difference between the population characteristics might account for the dissimilarity between our results and those reported in the mentioned study.

The RMSSD and PNN50 indices reflect vagal modulation, whereas SDNN is an index of total HRV modulated by low-frequency cyclical alterations. These low frequency changes reflect thermoregulatory and peripheral chemoregulatory mechanisms, and variations in activity of the renin-angiotensin system. Therefore, the depressed SDNN in heart failure patients mirrors the summed effect of abnormalities in sympathetic, parasympathetic, chemoreceptor and renin-angiotensin function, and also reflects changes in respiratory pattern and physical inactivity [23]. Improvements in SDNN after exercise training may signal the normalization of these processes; small improvement in multiple mechanisms can cause a significant increase in SDNN [21]. Since, SDNN measurement provides prognostic information about morbidity and mortality in heart failure patients [23], an increased SDNN index indicates a valuable effect of the exercise training. The mechanisms by which exercise training improves HRV are not well understood. Two potential mediators have been considered to play a role in improving cardiac vagal modulation: nitric oxide and angiotensin II. Nitric oxide is thought to increase cardiac vagal control and to inhibit sympathetic influence indirectly, while angiotensin II is known to inhibit cardiac vagal tone. Exercise training has been demonstrated to increase nitric oxide bioavailability and to suppress angiotensin II [24-26]



The ejection fraction correlated significantly only with one of the time domain parameters (SDNN). Similarly, a weak correlation between SDNN and the ejection fraction in patients after myocardial infarction was reported by Kleiger et al [27]. All parameters of cardiac function mirror the balance between the sympathetic and parasympathetic influences on the heart. There is an increase of sympathetic activity and a decrease in the vagal tone in heart failure leading to a reduction in SDNN, which appears early in cardiac dysfunction. This may explain the relationship between the ejection fraction, as a cardiac function parameter, and SDNN [28]. In the present study, the SDNN index is not strongly related to the ejection fraction. Modulation of the SDNN index by multiple factors including sympathetic, parasympathetic, neuroendocrine, and renin-angiotensin functions may be the reasons of this weak relationship [23]. Measurement of SDNN in combination with other measurements might be a useful tool to assess the clinical condition of patients with heart failure. However, it remains unclear whether the improvement in SDNN is associated with the improvement in the ejection fraction in this group of patient. Our study was not designed to assess the ejection fraction, thus we were unable to examine the correlation between changes in SDNN and the ejection fraction.

The current study has several limitations. The first, we did not obtain follow-up data. The second, since this study included only patients with systolic heart failure, our results may not be applicable to individuals with diastolic heart failure. We suggest additional researches with larger group sizes and the follow-up assessment to determine whether the positive effects of exercise training are maintained with time.

## Conclusion

The present study demonstrated that exercise training is safe and feasible in post percutaneous coronary intervention patients, even in

those with the reduced ejection fraction. Heart failure patients after percutaneous coronary intervention can achieve a significant improvement of heart rate variability from a short-term exercise training program (seven weeks). Furthermore, one of the sensitive HRV indices, SDNN, and left ventricular ejection fraction are correlated weakly in these patients.

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## Conflict of Interest

None

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