

EFFECT OF CIRCUIT TRAINING ON TNF ALPHA LEVELS AND SIX MINUTES WALK TEST IN PATIENTS WITH CHRONIC HEART FAILURE

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Abstract: *Physical exercise in patients with heart failure can decrease the level of proinflammatory biomarkers and increase functional capacity. Circuit training is one of the most advantageous exercise models because it improves cardiorespiratory fitness and muscle strength. This study aimed to investigate the effect of circuit training on TNF alpha and six minutes walk test in patients with chronic heart failure in RSUP Dr. Kariadi. Twenty-six stable chronic heart failure with reduced ejection fraction patients were randomized into exercise group that received circuit training in the rehabilitation center of Kariadi Hospital for a month and control group. TNF- α levels as a inflammatory biomarker and distance of six minute walk test as a functional capacity parameter were taken before and after the exercise period. Nine-teensubjects completed the study without any significant side effects. There was no significant difference in TNF- α levels before and after treatment between treatment groups and control groups ($p=0,513$). The treatment group with circuit training showed a greater increase in distance of six minute walk test than the control group ($p=0,034$). It was concluded that circuit training in patients with chronic heart failure can increase distance of six minute walk test, but no changes in TNF alpha levels.*

Keywords: *Circuit training, TNF- α , six minute walk test*

INTRODUCTION

Heart failure was still a health problem worldwide. In Indonesia based on Riskesdas data in 2013, the prevalence of heart failure was 0.3% with 229,696 patients.¹ Data in Dr.Kariadi hospital showed heart failure as the fourth cause of inpatients with 70.9 % rehospitalization rate in 6 months .² Physical exercise is recommended to improve the functional capacity, prognosis, and life quality in patients with heart failure in addition to pharmacological regimens and device therapy³⁻⁷. From various studies, physical exercise in heart failure significantly increased functional capacity. The six minute walk test is the alternative test of functional capacity indirectly. It is easier to perform in patients with heart failure. Harris et al found patients with heart failure who followed aerobic exercise for 6 weeks have a 10% increase in 6 minute walk test.^{5,6,7}

Physical exercise also proved to acted as an anti-inflammatory. In patients with chronic heart failure, elevated levels of proinflammatory cytokines in the plasma correlate with the severity of symptoms of heart failure. TNF- α is the most studied cytokine. Studies on Left Ventricular Dysfunction, shows that in patients with symptomatic heart failure, the levels of TNF- α increase progressively.⁸ There was a significant association between elevated TNF- α and NYHA functional class. Dunlay et al found that increasing TNF- α was associated with mortality rates in patients with heart failure.⁹ Smart et al evaluated four studies about the effect of exercise on inflammatory biomarkers, whereas exercise in heart failure patients decreased levels of Tumor Necrotizing Factor alpha (TNF- α), but no significant change in the levels of interleukin-6 (IL-6).¹⁰

There is no universal provision of the type of exercise given to patients with chronic heart failure. Continuous aerobic training is the most commonly used exercise

because it is easy and simple. Interval Aerobic Training is an aerobic exercise using ergocycle or treadmill, but in practice there is a short resting phase until it reaches high intensity. High intensity exercise is considered more effective in patients with heart disease. Resistance training combines increased muscle strength and endurance have benefits in patients with heart failure. Circuit exercise was a physical exercise method that involved a series of different exercises that were performed sequentially and continuously over a cycle/circuit. The choice of specific, fast-moving exercises from one post to another was aimed to maximized the effectivity and efficiency. Some researchers suggest that circuit exercise is appropriate for heart failure patients, as it proved to improved cardiorespiratory fitness and muscle strength at the same time. Beale et al conducted a study comparing interval training with high intensity with circuit training in patients with chronic heart failure. From the results of his research it was found that circuit training increased maximum oxygen consumption and quality of life significantly, and the effectiveness of circuit training compared with high intensity interval training did not differ significantly.¹¹⁻¹⁶

This study aimed to investigated the effect of circuit exercise on TNF- α levels as proinflammatory biomarkers and 6-minutes walk test distance as functional capacity parameters in patients with chronic heart failure.

RESEARCH METHODS

This study was an unblinded, randomized controlled trial (RCT) pre-test and post-test control group design. This study had obtained Ethical Clearance approval from Medical Ethics Committee of Faculty of Medicine and Dr. Kariadi hospital Semarang No.565 / EC / FK-RSDK / IX / 2017.

This study was conducted at Dr. Kariadi hospital Semarang in August-November 2017. The subjects of the study were stable chronic heart failure patients at Dr. Kariadi hospital Semarang who fulfilled the inclusion criteria of 40-65 years old, resides in Semarang, had the ischemic heart failure etiology based on medical data, the functional class of NYHA II - III with 20-40% left ventricular ejection fraction, had received appropriate heart failure therapy based on standardized heart failure treatment for at least 6 weeks, and no incidence of acute heart failure, congestion, worsening of symptoms of heart failure during the last 3 months. The subjects were excluded if pregnant, had kidney disease, history of malignant arrhythmias, in state of infection, had a mobility disability, BMI > 27, had a history of lung disease or with acute exacerbations of asthma, uncontrolled diabetes mellitus, uncontrolled hypertension, cancer, other inflammatory diseases or taking steroids on a regular basis, severe depression or psychosis, in the course of the study will undergo a cardiac surgical procedure or percutaneous coronary intervention, had undergone aerobic exercise program at optimal dosage routinely, or used implants such as Implantable Cardioverter Defibrillator (ICD) and Permanent Pace Maker (PPM).

Twenty six people met the study criteria and had been willing to be a research sample through approval on informed consent. After a simple randomization, 13 subjects were obtained in the treatment group and 13 subjects in the control group.

Before the treatment, the two groups performed blood samples to measure TNF- α levels, 10 cc blood sampling through peripheral venous was taken from the patient's arm. After the blood froze, it was centrifugated immediately. When the blood serum was separated, the samples frozen and stored at -200 C. Then the sample and the list of names were sent using dry ice to Prodia

laboratory, Central Jakarta. Two groups performed a 6-minutes walk test, where the subjects were asked to walk on a 15-meters straight path that had been provided for 6 minutes. The test result was the distance (in meters) that could be taken by research subjects within 6 minutes.

The treatment group was given circuit exercise protocol under supervision in the rehabilitation room of Dr. Kariadi Hospital for 1 month which consisted 12 sessions. Each session consisted 5 minutes of warming and stretching exercises, 20 minute core circuit exercise involved 6 posts, ergocycle posts, bridging, brisk walking, biceps curl, up and down stairs, and punching. Each post takes 1 minute with a break between posts for 30 seconds. Each subject has a chance to undergo two rounds. After the core exercise was done, there was cooling time for 5 minutes. At the beginning of each exercise, blood pressure, pulse, and saturation checks are performed, as well as the calculation of the exercise targets using the karvonen formula. At the interval between the exercise post, the pulse and saturation measurements are taken. After practice, subjects are invited to discuss various topics about heart failure. In the 7th session onwards, exercise loads in each post increased. The control group received standard heart medication and were advised to do walking exercises independently at home. After one month the two groups were taking blood samples of TNF- α and a 6-minute walk test again.

The data that were obtained then collected and analyzed. Normality test used Shapiro Wilk test. Hypothesis test between two groups used unpaired t-test parametric test, or Mann-Whitney non-parametric test. For pre and post data analysis, hypothesis test used paired t-test parametric test, or non-parametric test of Wilcoxon. The p value <0.05 is a significant value. Data analysis used IBM SPSS statistic version 21.

RESULTS AND DISCUSSION

Thirteen subjects from the treatment group, 3 subjects dropped out because they did not complete the exercise sessions as expected. From 13 subjects of the control group, 4 subjects dropped out because one subjects had a nucleus pulposus hernia and 3 subjects could not be contacted. No incidence of stroke, acute coronary syndrome, syncope, or acute heart failure during exercise at the hospital.

From 19 subjects who completed the study, the mean age were 57.05 ± 6.67 years

old. Total 73% of subjects were men with an average BMI 24.56 ± 2.87 kg / m². All subjects were patients with systolic heart failure with $32 \pm 6.44\%$ left ventricular ejection fraction mean. All subjects suffered from heart failure with NYHA class II classification. All subjects had routinely taken antiplatelet, beta-blocker, statin, and ACE-inhibitor or ARB medications. A comparison of the characteristics of the study subjects between the treatment group and the control group was showed in Table 1.

Tabel 1.Characteristics of the study subjects between the treatment group and the control group

Variable	Treatment group (n=10)	Control (n=9)	ρ
Age (year)	$58,5 \pm 7,4$	$55,4 \pm 5,59$	0,325 ^b
Sex, male(n,(%))	7 (70)	5 (55,6)	0,650 ^c
Body Mass Index (kg/m ²)	$23,9 \pm 3,4$	$25,2 \pm 2,2$	0,205 ^b
Historyof disease (n,(%))			
DM	3 (30)	5 (55,6)	0,370 ^c
Hypertension	7 (70)	4 (44,4)	0,370 ^c
Dyslipidemia	7 (70)	7 (77,8)	1,000 ^c
Stroke	1 (10)	2 (22,2)	0,582 ^c
Smoker (n,(%))	2 (20)	3 (33,3)	0,628 ^c
History of Revascularisation (n,(%))	6 (60)	6 (66,7)	1,000 ^c
Ejection Fraction (% biplane)	$31,3 \pm 7,1$	$32,8 \pm 5,9$	0,632 ^a
Drugs (n,(%))			
Diuretic	6 (60)	3 (33,3)	0,370 ^c
Digitalis	2 (20)	0 (0)	0,474 ^c
MRA	5 (50)	6 (66,7)	0,650 ^c
Nitrat	8 (80)	4 (44,4)	0,170 ^c
Vital signs			
Heart Rate (x/menit)	$74 \pm 7,9$	$78,7 \pm 8,8$	0,240 ^a
Systolic Blood Pressure (mmHg)	$119,7 \pm 13,5$	$128,9 \pm 15,37$	0,184 ^a
Diastolic Blood Pressure(mmHg)	$74,6 \pm 11,7$	$78,9 \pm 11,7$	0,279 ^b

variablevalue presented in mean \pm standard deviationand percentage; the value is significant if $\rho < 0,05$; ^aunpaired T tast; ^b mannwhitney test; ^c fisher's exact test; DM: Diabetes Mellitus; MRA: Mineralocorticoid Receptor Antagonist

Table 2 showed the effect of circuit exercise on TNF- α levels. There were no significant change in TNF- α levels after exercise in both groups (p treatment group = 0.139, control group = 0.138, significant

value if $p < 0.05$) there were also no significant differences in TNF- α level changes before and after treatment in both groups (p = 0,51).

Tabel 2. Comparison of TNF- α levels before and after exercise between two groups

Variable	Treatment group	Control group	ρ
TNF- α pre exercise (pg/ml)	1,42 \pm 0,32	1,61 \pm 0,45	0,595 ^b
TNF- α post exercise (pg/ml)	1,86 \pm 0,58	1,96 \pm 0,77	0,838 ^b
P	0,139 ^a	0,138 ^a	
delta TNF- α (pg/ml)	0,64 \pm 0,95	0,36 \pm 0,49	0,513 ^b

variable value presented in mean \pm standard deviation and percentage; the value is significant if $p < 0,05$.^a Wilcoxon test to assess variable difference in pairs and ^bMann whitney test to assess the difference of unpaired variables

Table 3 showed the effect of circuit exercise on of 6-minutes walk test distance. There were significant increased in distance after exercise in both groups (treatment group = 0.005, control group = 0.008; significant

value if $\rho < 0.05$). The treatment group with circuit exercise had an average distance increased significantly further than the control group ($\rho = 0.034$) after exercise.

Tabel 3. Comparison of 6MWT distance before and after exercise between two groups

Variabel	Treatment group	Control group	P
6MWT pre exercise (meters)	413,7 \pm 66,6	407,0 \pm 74,8	0,806 ^b
6MWT post exercise (meters)	482,5 \pm 73,2	442,9 \pm 61,9	0,190 ^b
P	0,005 ^a	0,008 ^a	
delta 6MWT (meters)	68,8 \pm 39,4	35,9 \pm 24,7	0,034 ^b

variable value presented in mean \pm standard deviation and percentage; the value is significant if $p < 0,05$.^a Wilcoxon test to assess variable difference in pairs and ^bMann whitney test to assess the difference of unpaired variables

In this study, TNF- α levels did not change significantly after 1 month of circuit exercise. Previous studies had reported changes in levels of TNF- α in patients with heart failure who performed physical exercise. Adamopoulos et al studied 24 patients with chronic heart failure who were given a 12-week physical exercise program. There was a significant decrease in TNF- α (p < 0.001).¹¹ Smart et al combined four studies and found that out of 106 patients involved there was a significant decrease in TNF- α (P = 0.020).¹⁰ However, other studies confirmed

that there was no significant change in TNF- α levels but changes occurred in other cytokines; local muscular TNF- α ¹⁸, sTNFR1 and sTNFR2 (P = 0.010 and P = 0.020).¹⁹

Decreased levels of TNF- α in patients with heart failure who did physical exercise proved the role of physical exercise as anti-inflammatory. But how the exact mechanism was not fully understood yet. Chronic exercises were showed to improved inflammatory status or provide protection against current inflammation.²⁰ Several factors were presumed as the etiology: a shift

in monocyte phenotype and decreased immune cell production, local adaptation of immune function, and adaptation of intracellular ROS formation. Several studies indicated the adaptation in regulation of cytokine released from immune cells in response to regular exercise.²¹ However, how and how long the adaptation process depends on the type, duration, and intensity of exercise performed.²⁰

No significant change in TNF- α levels in this study possibly because of relatively short exercise times compared to previous studies. According to Gielen, anti-inflammatory effect emerged over a long period of time.¹⁸ This was consistent with the results of study conducted by Smart, where TNF- α changes were related to exercise duration ($r = 0.21$).¹⁰ There were no further studies about how long exercise took, what kind of exercise model, as well as the right intensity to adapt the exercise process to obtain anti-inflammatory effects.²¹

Changes in TNF- α level also more prevalent in patients with moderate-severe heart failure.¹¹ In this study the study subjects were all patients with NYHA II heart failure with a higher left ventricular ejection fraction score ($31.3 + 7.1\%$ in the treatment group and $32.8 + 5.9\%$ in the control group) compared with the study of Adamopoulos et al (NYHA II and III heart failure with left ventricular ejection fraction $23.2 + 1.2\%$).¹¹ Several studies mentioned that regular exercise did not give a significant result in serum cytokine levels in patients with mild heart failure.¹⁸

This study also intended to determine the effect of circuit exercise on 6-minute walk test distance in patients with chronic heart failure. The 6-minute walk test is one of the alternatives to test the functional capacity indirectly that was easier performed in patients with heart failure.²² A 6-minute walk could be well tolerated by the patient, and reflected the daily activities more accurately than other measures.²³ The 6-minute walk

test was functional capacity measuring instrument with 0.96 alpha reliability coefficient.²³

In this study, there was an average increase of 6-minute walk test distance in chronic heart failure patients who did circuit exercise in hospital compared to control group ($p = 0,034$). This study supported the results of previous research conducted by Beale et al that compared high intensity interval exercise with circuit exercise in patients with chronic heart failure. The results showed the functional capacity of patients who performed circuit exercise significantly increased than patients with high intensity interval exercise.¹² In addition, Harris et al said that patients with heart failure who followed aerobic exercise for 6 weeks experienced a 10% increase in 6-minute walk test and the duration of the exercise.²⁴ While Oka and Sanders who examined the effects of aerobic exercise at home for 12 weeks, found an increase in a 6-minute walk test, increased nutritional intake, a 17% reduction in body mass index and a 9% reduction in body weight.²⁵

The mechanisms responsible for the enhancement of functional capacity in patients with heart failure who did exercise were still unclear. Some authors attributed it to increased oxygen extraction in the peripheral and increased cardiac output which also increased oxygen delivery.²⁶ Another study suggested that physical exercise could improve total peripheral vascular resistance significantly and peripheral perfusion in patients with chronic heart failure through reduction of sympathetic overdrive.²⁷ While other theories suggested that physical exercise was capable of improving endothelial dysfunction in trained extremities, by enhancement of nitric oxide (NO) synthesis locally. Where with these improvements will improve peripheral perfusion in patients with heart failure.²⁷

Some of the limitations experienced by author in this study was the subject of this study were patients with NYHA II heart failure with left ventricular ejection fraction higher than in previous studies. In addition, the duration of exercise is relatively shorter than other studies. The control group did not have the same quality and quantity of exercise in terms of frequency, intensity, type and duration of exercise. Another limitation is the cytokine examined in this study only TNF- α , so it had not shown the effect of physical exercise on proinflammatory cytokine levels thoroughly.

CONCLUSION

Circuit training in patients with chronic heart failure can increase distance of six minute walk test, but no changes in TNF alpha.

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