

The Effects of Aerobic Exercise on Functional Capacity of Geriatric Chronic Heart Failure Patients

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Background: *Chronic heart failure, a condition predominantly affecting the elderly, is a major clinical burden and cause death in admission patients especially the elderly population. The focus of cardiac rehabilitation recently is exercise used as one of the modality of therapy designed for stable heart failure patients. Exercise is recommended as one of modality in management of heart failure to improve prognosis, increase physical activity tolerance and quality of life of heart failure patients.*

Aim: *The objective of this study is to understand is aerobic exercise program can improve functional capacity in geriatric heart failure patients.*

Methods: *The design of this study is randomized controlled trial. Twenty subjects were cardiology outpatient clinic at Dr Sardjito hospital men and women with chronic heart failure functional class I-II of NYHA age \geq 60 years and agreed to be included to the study. Subjects were divided into two group randomly, which were the exercise group (10 subjects) and the control group (10 subjects). To compare the functional capacity of both groups, t-test independent is used with condition of normal data range and Mann Whitney test is used if abnormal data range is found. The level of significance was set at $p < 0,05$ with confidence interval 95%*

Result : *Comparison of the mean increase in the six minute walk test distance between aerobic exercise group $107,9 \pm 22,153$ meters compared with the control group $21,3 \pm 16,166$ was significantly better in the aerobic exercise group ($p < 0,001$)*

Conclusion : *Aerobic exercise can improve the functional capacity of patients with chronic heart failure in the elderly.*

Keyword: *chronic heart failure, elderly, aerobic exercise, functional capacity.*

Latar Belakang. *Gagal jantung kronik merupakan kondisi yang sering muncul pada usia lanjut dan menjadi penyebab kematian tertinggi pada pasien rawat inap terutama populasi usia lanjut. Rehabilitasi jantung, fokus utamanya adalah latihan fisik untuk pasien dengan gagal jantung stabil akhir-akhir ini digunakan sebagai modalitas terapi. Latihan fisik direkomendasikan sebagai upaya penanganan gagal jantung untuk memperbaiki prognosis, meningkatkan toleransi aktivitas fisik dan kualitas hidup penderita gagal jantung*

Tujuan penelitian *Untuk mengetahui program latihan fisik aerobik dapat meningkatkan kapasitas fungsional pasien gagal jantung kronik pada usia lanjut.*

Metode. *Penelitian ini adalah uji klinik acak terkontrol. Dua puluh subyek adalah pasien rawat jalan di poliklinik jantung RSUP Dr. Sardjito laki-laki dan wanita dengan gagal jantung kronik NYHA kelas fungsional I-II berusia ≥ 60 tahun dan bersedia diikutsertakan dalam penelitian. Subyek dibagi dalam dua kelompok secara acak, yaitu kelompok latihan fisik aerobik (10 subyek) dan kelompok kontrol (10 subyek). Untuk membandingkan kapasitas fungsional (six minute walk test) pada kelompok latihan fisik aerobik dan kelompok kontrol dilakukan uji independent t-test bila sebaran datanya normal dan apabila sebarannya tidak normal digunakan uji Mann Whitney. Perbedaan dianggap bermakna bila nilai $p < 0,05$ dengan interval kepercayaan 95 %.*

Hasil penelitian. *Perbandingan rerata peningkatan jarak six minute walk test antara kelompok latihan fisik aerobik ($107,9 \pm 22,153$ meter) dibandingkan dengan kelompok kontrol ($21,3 \pm 16,166$ meter) secara signifikan lebih baik pada kelompok latihan fisik aerobik ($p < 0,001$)*

Kesimpulan. *Latihan fisik aerobik dapat meningkatkan kapasitas fungsional pasien gagal jantung kronik pada usia lanjut.*

Kata kunci : gagal jantung kronik, usia lanjut, latihan fisik aerobik, kapasitas fungsional.

Background

Chronic heart failure (CHF) is a disease that frequently arise and become the cause of death in hospitalized patients, especially the elderly¹. In the last decade shows an increased prevalence of CHF is more than 10% in the elderly population².

One of the main symptoms of CHF is intolerance to physical activity, which indicated the existence of feelings tired and short of breath when doing physical activity which minimal activity though³. In addition to the efforts of treatment and use of devices, physical exercise is recommended in order to improve the handling of heart failure prognosis, increase the tolerance of physical activity and quality of life of patients with heart failure⁴.

In the elderly needed due to the complexity of the condition of a multidisciplinary approach polypharmacy, comorbidities, and quality of life can improve morbidity and mortality. Cardiac rehabilitation, the main focus is the physical exercise for patients with stable heart failure lately used as a therapeutic modality⁵.

Evidence obtained in animal studies show physical exercise is able to reduce the production of reactive oxygen species (ROS) in heart of old mice. Five months physical exercise that have been carried out in mice can stimulate mitochondrial biogenesis, preventing depletion and mitochondrial DNA mutations, increasing the oxidative capacity, restore mitochondrial morphology, and inhibiting apoptosis in pathological tissue including myocard^{6,7}.

Study the effects of physical exercise was also done in elderly with heart failure. The elderly was given physical exercise fail to repair cardiac stiffness and diastolic dysfunction, but in other studies may improve arterial elasticity, aerobic capacity and has a functional value, quality of life, and shorter hospitalization^{8,9}. Early physical exercise programme in CHF patients after hospitalization is safe to do and improve fitness and decrease the incidence of major cardiovascular event relative¹⁰.

Six minute walk test (6MWT) is a simple test to evaluate the performance of the global and integrated responses of all the systems involved during the tests performed, including cardiopulmonary system, systemic circulation, peripheral circulation, blood, neuromuscular and metabolic muscle. In this test the patients set their own pace and strength to walk according to the daily walking activity (submaximal physical exercise) and did not get the maximum capacity of physical exercise, so the test is better in describing the functional level of physical exercise for daily physical activity¹¹.

The diversity of study on Caucasian and Asian races makes the reason for the need to do research on the effects of physical exercise program on functional capacity in elderly patients with CHF in Indonesia.

The purpose of this study was to determine the aerobic exercise program can improve functional capacity of patients with chronic heart failure in the elderly.

Methods

This study is a randomized, controlled clinical trial conducted at the Cardiology Hospital performed in Dr. Sardjito began December 1, 2014 - March 2015. Subjects were outpatients men and women with chronic heart failure NYHA functional class I-II \geq 60 years old and are willing to participate in the study.

Study inclusion criteria: all outpatient heart clinic of Hospital Dr. Sardjito both men and women with chronic heart failure of New York Heart Association (NYHA) functional class I-II \geq 60 years old and are willing to participate in research, willing to follow the program of aerobic physical exercise. Exclusion criteria in this study : patients with unstable angina pectoris disease, moderate to severe aortic stenosis, chronic obstructive pulmonary disease, chronic kidney disease with eGFR $<$ 60, musculoskeletal disorders that can not follow the stages of physical exercise, stroke, severe dementia , and patients lives outside of Yogyakarta district. Criteria drop out in this study : did not follow a program of physical exercise \geq 20%, cardiovascular events occurred during the study, loss of follow-up.

The independent variable in this study is a aerobic physical exercise program. While confounding variables as factors that affect functional status were age, sex, long-suffering heart failure, levels of hemoglobin, the etiology of CHF, type of medical therapy, ejection fraction, NYHA status, comorbid diabetes mellitus, hypertension, and dyslipidemia and glomerolus filtration rate. The dependent variable is the functional status (6MWT).

Elderly outpatients with chronic heart failure in cardiac clinic of Dr. Sardjito Hospital that meet the inclusion and exclusion criteria in the study given informed consent. Recording baseline data in the form are age, gender, education, employment, levels of hemoglobin, urea, creatinine, comorbid diabetes mellitus, hypertension, dyslipidemia, NYHA functional class, long-suffering heart failure, MMSE score, the etiology of heart failure and status ejection fraction by echocardiogram, thorax X-ray examination, electrocardiography and the type of medical therapy. Randomization of samples using a computer.

All patients underwent cardiac exercise test on a treadmill test to determine whether there is ischemia, arrhythmias, hypertensive response, and risk stratification to prevent complications when performed physical exercise. All patients underwent measurement of six minute walk test at baseline and weeks 4 both in the control group and the treatment group.

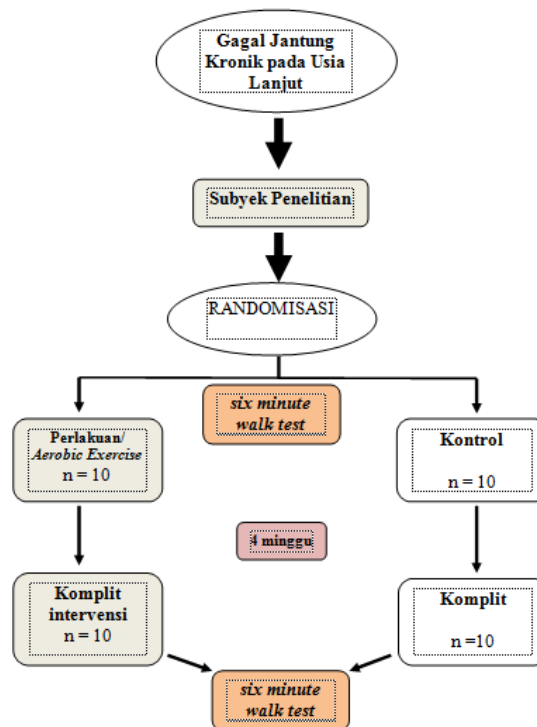
The treatment group following the cardiac rehabilitation program in the form of aerobic exercise in accordance with the functional capacity of the current measurement of the first six-minute walk test under the supervision and prescription of exercise heart specialist. Aerobic exercise is done with a frequency of 1-3 times a week for four weeks in cardiac rehabilitation Hospital Dr. Sardjito. Exercise contain heating components for 5 minutes, core exercises such as walking for 20-30 minutes and cooling for 10 minutes. Exercise is guided by a cardiac rehabilitation nurse, electrocardiography examination to monitor the heart rhythm when needed, such as when the arrhythmia arises or complaints from patients.

Exercise programme include:

- a) Type of exercises: aerobic exercise endurance types, such as walking on a treadmill without elevation or flat.
- b) The intensity of the exercise is determined by the walking distance that must be taken. In the first practice walking distance adapted to the test results mileage six minute walk test, starting from the assumption of 50-70% of the mileage for 30 minutes. Subjective complaints will always be asked by the officer who oversees. Walking mileage gradually increased according to ability, exercise heart rate and severity of the complaint.
- c) Patients also recommended exercises such as walking in home with the distance that has been determined by the instructor with a frequency of 5-7 times a week. Compliance training is done by asking subjects to fill the blank schedule of exercise daily by study subjects. Patients were also monitored over by phone to ensure that the patient exercises at home and also asked related complaints during exercise.

The control group was not included in the programme of aerobic physical exercise. During the study, the control group did daily physical activity as usual. The control group performed six minute walk test at baseline and weeks 4 as in the treatment group.

Flow of participants through each stage of the trial



Sample size estimation of 10 people in each group are considered adequate to detect the effect of aerobic exercise on the status fungsional / 6MWT. Data presented in the form of mean and standard deviations, and the analysis is done by intention to treat. To view the data distribution Shapiro-Wilk test to see the variable distribution. Variables with normal distribution hypothesis test is then performed paired t-test to compare functional capacity before and after aerobic physical exercise and test hypotheses independent t-test to compare the functional capacity of the control group and the treatment group. If the distribution is not normal it will be Mann Whitney and Wilcoxon test. For categorical data used Pearson's Chi Square. If the hypothesis is not proven then confounding variables multivariate analysis. Differences were considered significant if obtained $P < 0.05$ with a 95% confidence interval¹².

This study uses the approval of biomedical research ethics committee of the Faculty of Medicine, University of Gadjah Mada and permission of the Director of Hospital Dr. Sardjito. All patients studied willingness to get sheets (informed consent) to follow this study.

Results and Discussion

Sample collection study carried out for 3 months and gained 20 subjects who meet the inclusion and exclusion criteria, consisting of 16 male subjects (80%) and 4 female subjects (20%) with a mean age 69 years old. The whole subject complete the study. Both groups had baseline characteristics did not differ significantly in terms of age, gender, body mass index, the cause of heart failure, ejection fraction, NYHA functional class status, degree of left ventricular systolic dysfunction, long-suffering heart failure, type of treatment received, the levels of hemoglobin , eGFR, comorbidity, blood sugar levels, LDL cholesterol levels, HDL cholesterol levels, triglyceride levels, and six-minute walk test early. Data on comparison of the characteristics of the two groups showed that both groups had similar characteristics. Basic data on the characteristics of the study subjects are presented in the following table :

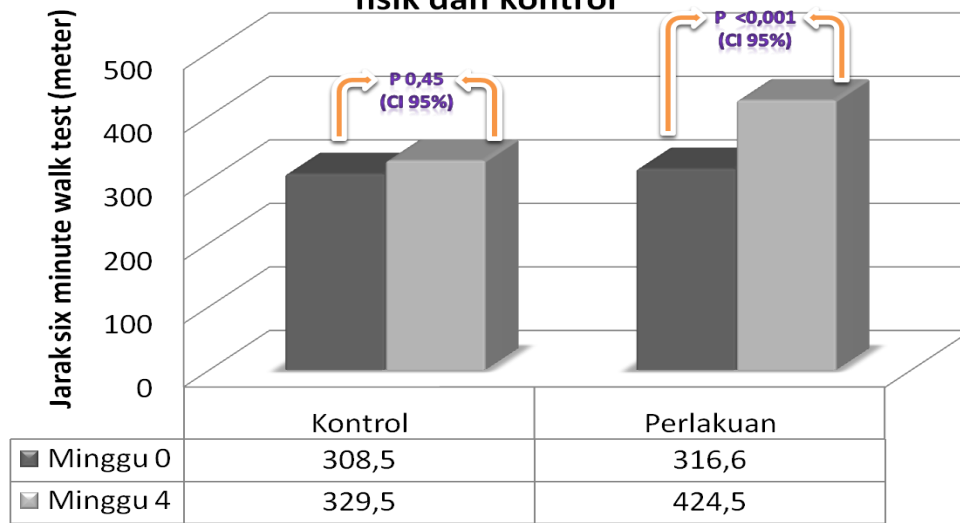
	Kelompok Kontrol (n=10)	Kelompok Latihan Fisik (n=10)	<i>p</i> value IK 95%
Rerata usia (SB) (tahun)	69 ($\pm 7,04$)	69 ($\pm 5,39$)	1,00 (ns)*
Jenis Kelamin : Laki-laki (%)	8 (80)	8 (80)	0,71
Perempuan (%)	2 (20)	2 (20)	(ns)**
Rerata IMT (SB) (kg/m ²)	22,3 ($\pm 3,76$)	23,4 ($\pm 3,24$)	0,37 (ns)*
Etiologi Gagal Jantung Kronik(%)			
Penyakit jantung koroner	5 (50)	5 (50)	1,00
Hipertensi	2 (20)	1 (10)	(ns)***
Kardiomiopati	2 (20)	3 (30)	0,53
Lain-lain	1 (10)	1 (10)	(ns)**
			0,50(ns)*
			*
			0,76
			(ns)**
Status NYHA kelas fungsional (%)			
I	7 (70)	4 (40)	0,18
II	3 (30)	6 (40)	(ns)**
Rerata ejeksi fraksi (SB) (%)	42,3 ($\pm 14,55$)	42,2 ($\pm 17,79$)	0,98 (ns)*
Derajat disfungsi sistolik ventrikel kiri (%)			0,75
- HFpEF(EF >40%)	6 (60)	3 (30)	(ns)*#
- Ringan sedang (EF 40-30%)	2 (20)	5 (50)	
- Berat (EF<30%)	2 (20)	2 (20)	
Rerata lama menderita gagal jantung (SB) (tahun)	10,1 ($\pm 1,52$)	9,2 ($\pm 1,39$)	0,18 (ns)*
Jenis terapi yang diterima pasien (%)			
<i>ACE inhibitor</i>	5 (50)	2 (20)	0,17
<i>β blocker</i>	8 (80)	8 (80)	(ns)**
<i>Angiotensin II Antagonists</i>	5 (50)	8 (80)	0,71(ns)*
Diuretik	8 (80)	7 (70)	*
			0,17
			(ns)**
			0,50

Rerata Kadar Hemoglobin (SB) (g/dL)	12,9 (±1,07)	13,1 (±1,66)	(ns)** 0,76 (ns)*
Rerata <i>eGFR</i> (SD) (mL/min/1,73m ²)	86.6 (±3,00)	69.4 (±2,59)	0,15 (ns)*
Komorbid (%)			
DM	2 (20)	2 (20)	0,43
Hipertensi	4 (40)	5 (50)	(ns)**
Dislipidemia	4 (40)	2 (20)	0,50 (ns)** 0,31 (ns)**
TD Sistolik (SB) (mmHg)	131,7 (±17,67)	122,6(±12,8 2)	0,206 (ns)*
TD Diastolik (SB) (mmHg)	73,5 (±5,79)	67,4 (±7,321)	0,054 (ns)*
Gula darah puasa (SB) (mg/dL)	97,6 (±14,214)	99,20 (±14,566)	0,806 (ns)*
Gula darah 2 Jam Post Pandrial (SB) (mg/dL)	134,9 (±15,154)	133 (±22,813)	0,829 (ns)*
Kholesterol LDL (SB) (mg/dL)	110,7 (±32,414)	109,50(±36, 701)	0,939 (ns)*
Kholesterol HDL (SB) (mg/dL)	41,80 (±7,208)	42,5 (±6,86) 122,6	0,827 (ns)*
Trigliserida (SB) (mg/dL)	134,1 (±88,14)	(±36,32)	0,194 (ns)*
<i>Six minute walk test</i> (SB) (meter)	308,50 ±44,35	316,60 ±38,630	0,67 (ns)*

SB= Simpangan Baku, IMT= Indeks Massa Tubuh, NYHA= *New York Heart Association*, HFpEF= *Heart Failure with preserved ejection fraction*, EF= Ejeksi Fraksi, ACE = *Angiotensin Converting Enzyme*, *eGFR*=*Estimated Glomerular Filtration Rate*, lama menderita gagal jantung dinyatakan dalam tahun, * uji Independent T Test, ** uji Fisher Exact Test, *** uji Chi Square, *# uji Kolmogorov Smirnov, ns= *Non Significant*

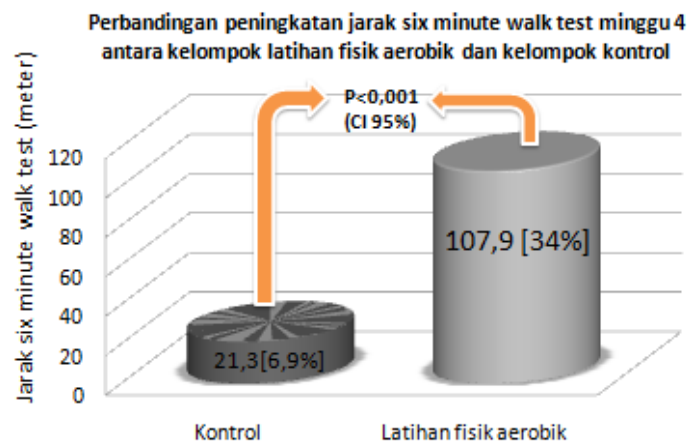
The mean six-minute walk test distance, aerobic exercise group obtained at baseline 316.6 ± 38.630 meters, at 4 weeks of aerobic physical exercise group increased distance reached 424.5 ± 49.858 meters (p <0.001). The control group gained a mean baseline six-minute walk test distance of 308.50 ± 44.35 meters, at 4 weeks the control group had increased distance reached 329.5 ± 44.175 meters (p = 0.45).

Perubahan jarak six Minute Walk Test kelompok latihan fisik dan kontrol



Changes in the six minute walk test distance of the treatment group and the control group at baseline and week 4

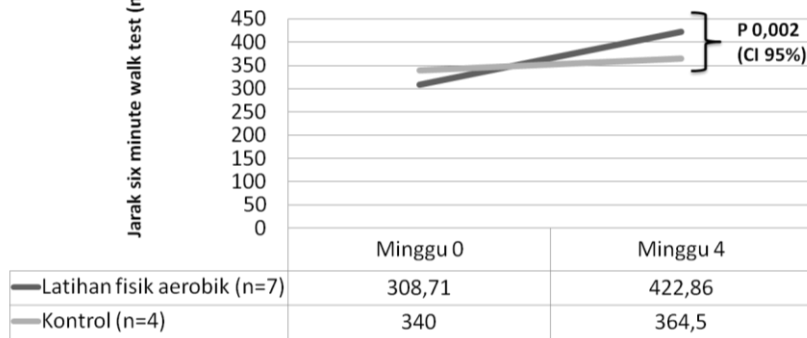
The treatment group after aerobic physical exercise has increased six-minute walk test distance significantly by 34% with a mean increase in the distance of 107.9 ± 22.153 meters ($p < 0.001$). Comparison of the average increase in the six minute walk test distance between aerobic exercise group 107.9 ± 22.153 meters compared with the control group 21.3 ± 16.166 was significantly better in the aerobic exercise group ($p < 0.001$).



Comparison of the average increase in the six minute walk test distance of 4 weeks between aerobic exercise group and the control group

Patients with heart failure with reduced ejection fraction (HFrEF) in this study, 11 samples, 7 patients included in the aerobic exercise group and 4 patients included in the control group. Patients with HFrEF after analysis found that trained group increased significantly distance of 308.71 meters 422.86 meter baseline be compared with a control group of 340 meters at baseline became 364.5 meters ($p 0.002$).

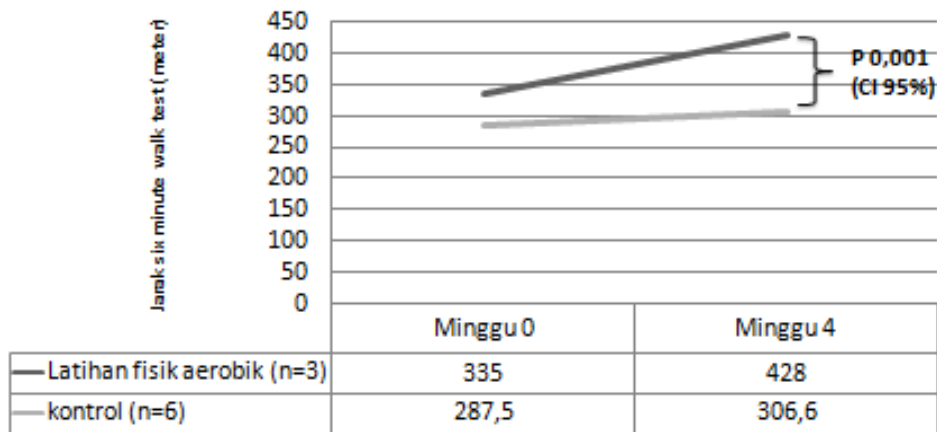
Perbandingan rerata peningkatan jarak six minute walk test pada pasien dengan penurunan ejeksi fraksi ventrikel kiri (ejeksi fraksi $\leq 40\%$)



Comparison of the increase within a six minute walk test in patients with decreased left ventricular ejection fraction (ejection fraction $\leq 40\%$)

Patients with heart failure with preserved ejection fraction (HFpEF) in this study also has benefit with aerobic exercise. Patients with HFpEF obtained 9 samples, three patients entered the aerobic exercise group and 6 patients included in the control group. Patients with HFpEF after analysis found that trained group experienced a significant increase in the distance of 335 meters at baseline became 428.33 meters compared with the control group at baseline became 287.5 meters 306.6 meters (p 0.001).

Perbandingan rerata peningkatan jarak six minute walk test pada pasien dengan HFpEF(ejeksi fraksi $\geq 40\%$)



Comparison of the increase within a six minute walk test in patients with HFpEF (ejection fraction $\geq 40\%$)

Results of this study showed aerobic physical exercise program is able to improve the functional capacity of patients with chronic heart failure in the elderly. Functional capacity measured by the six-minute walk test which is one of the submaximal exercise test, easy to do, inexpensive, safe and able to reflect the day-to-day functional capacity. Improvements six minute walk distance in the group of aerobic exercise in 4 weeks (range indicated by improvement of 34% in the treatment group) according to the functional performance is a consequence of an increase daily activity.

In the past, physical exercise is avoidable and not recommended in patients with chronic heart failure because it was feared cause worsening of the clinical condition. Patients are encouraged to bed rest and not to do activities that cause complaints¹³. The new concept regarding the treatment of chronic heart failure actually considers a long bed rest in patients with heart failure will increase deconditioning thus worsening clinical condition of patients with heart failure due to negative changes in skeletal muscle as atrophy, changes in skeletal muscle fiber types, decreasing the function of peripheral vascular dilatation, and a vicious circle that will continue to worsen the clinical condition of patients with heart failure¹⁴.

There are similarities aspects of the pathophysiology of heart failure patients with deconditioning due to bed rest, namely the peripheral hemodynamic changes, changes in autonomic control, functional capacity, changes in skeletal muscle, as well as the psychological aspects¹⁵. However, the changes caused by bed rest and that heart failure is reversible with physical exercise programme through increased cardiac output and other changes include improving aerobic, neurohumoral, autonomic, skeletal muscle, ventilation and hemoreology¹⁶.

The study also showed 11 patients with heart failure with decreased ejection fraction even in patients with severe decrease in ejection fraction may gain in aerobic physical exercise programme. A prospective study shows evidence that physical exercise can restore the left ventricular remodeling process with improved ejection fraction of 30% to 35% in four weeks in subjects age diverse population with ischemic heart disorders and cardiomyopathy¹⁷. Mechanisms that could explain the improvement in the patient's ejection fraction heart failure, some authors interpret the effect of physical exercise can reduce the burden of afterload by lowering blood pressure at rest so that they can improve endothelial function.

Heart failure patients with ejection fraction $\geq 40\%$ or called HFpEF in this study also benefit with aerobic physical exercise program. Intolerance of physical activity in patients with HFpEF caused by the stretching of the heart muscle stiffness and decreased maximal VO₂ resulting in a decrease in cardiac output resulting in a failure to improve the end-diastolic volume and stroke volume through frank starling mechanism¹⁸. Physical exercise program is able to improve heart rate, skeletal muscle perfusion and functional capacity in elderly patients with HFpEF¹⁸. Other studies have shown an improvement in left ventricular diastolic function and remodeling of heart muscle repair after aerobic physical exercise in patients with HFpEF¹⁹.

During physical exercise runs in this study did not found any of the subjects who experienced worsening heart failure or complications occur. In the group with very low ejection fraction did not occur cardiovascular events (major adverse cardiac event) during the aerobic physical exercise program.

Clinical application of the results of this study encourage us to recommend aerobic exercise program for patients with heart failure, especially in the elderly. However, not all patients with chronic heart failure given the advanced age appropriate for prescribing physical exercise in general, physical exercise program is tailored to the needs of each patient. With such an important part of cardiovascular rehabilitation for patients with heart failure, especially the elderly.

Conclusions and Recommendations

Aerobic exercise can improve the functional capacity of patients with chronic heart failure in the elderly. Results of this study encourage us to recommend aerobic exercise program for patients with heart failure, especially in the elderly. Future studies should prescribing and monitoring of physical exercise can be done three times a week in the hospital so that the

monitoring and dose adjustment of physical exercise can be carried out more intensively. Necessary checks maximal oxygen capacity (VO₂max) to prove the improvement of functional capacity is the effect of aerobic capacity improvement. Variable smoking should be included in the baseline characteristics of the patients.

Reference

1. Croft JB, Giles WH, Pollard RA et al. 1999. Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. *Arch Intern Med*; 159:505–510.
2. Gibbs LM, Addington-Hall J, Gibbs JS. 1998. Dying from heart failure: lessons from palliative care. Many patients would benefit from palliative care at the end of their lives. *BMJ*; 317:961–962.
3. Goldberg LR, Turner B, Wilim S. 2010. In The Clinic: Heart Failure. *Annals Int Med.*: ITC6-1-14
4. McKelvie RS. 2008. Exercise training in patients with heart failure: clinical outcomes, safety, and indications. *Heart Fail Rev.*; 13:3-11
5. Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD. 2003. Exercise and heart failure. A statement from the American Heart Association committee on exercise, rehabilitation, and prevention. *Circulation*; 107:1210 –25.
6. Judge S, Jang YM, Smith A, Selman C, Phillips T, Speakman JR, Hagen T, Leeuwenburgh C. 2005. Exercise by lifelong voluntary wheel running reduces subsarcolemmal and interfibrillar mitochondrial hydrogen peroxide production in the heart. *Am J Physiol Regul Integr Comp Physiol*; 289:R1564–R1572.
7. Safdar A, Bourgeois JM, Ogborn DI, Little JP, Hettinga BP, Akhtar M, Thompson JE, Melov S, Mocellin NJ, Kujoth GC, Prolla TA, Tar nopolsky MA. 2011. Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtdna mutator mice. *Proc Natl Acad Sci U S A.*; 108:4135– 4140.
8. Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, Palmer D, Levine BD. 2010. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation.*; 122:1797–1805.
9. Austin J, Williams R, Ross L, Moseley L, Hutchison S. 2005. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *Eur J Heart Fail*; 7:411–417.
10. Basuni R. 2012. Keamanan dan manfaat program latihan fisik dini pada penderita pasca rawat gagal jantung. *Desertasi program studi doktor fakultas kedokteran universitas indonesia*. Universitas Indonesia
11. Crapo, R.O., Richard Casaburi, Allan L. Coates, Paul L. Enright., Neil R. MacIntyre, Roy T. McKay, Douglas Johnson, Jack S. Wanger, R. Jorge Zeballos, 2002. ATS Statement: Guidelines for the Six Minute Walk Test. *Am J Respir Crit Care Med* vol 166. pp 111-117.
12. Dahlan, M.S. *Besar Sampel dalam Penelitian Kedokteran dan Kesehatan*. Arkans 2006. Jakarta, 26-34
13. Keteyian S.J., Kraus W.E., 2008. Introduction : exercise in patients with chronic heart failure. *Heart Fail Rev*, 13: 1-2
14. Perk J., Mathes P., Gohlke H., Monpere C., Hellemans I., McGee H., et al., 2007. Exercise training in heart failure. *Cardiovascular prevention and rehabilitation*. London: Springer-Verlag; p. 142-155

15. Evans W.J., Lambert C.P., 2007. Physiological basic of fatigue. *Am J Phys Med Rehabil*; 86 (Suppl): S29-S46
16. Rees K., Taylor R.S., Singh S., Coats A.J., 2004. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev*: CD 003331
17. Hambrecht R., Gielen S., Linke A., Fiehn E., Yu J., Walther C., *et al.* 2000. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomised trial. *JAMA*;283:3095–3101.
18. Haykowsky M., Kitzman D., 2012. Exercise physiology in heart failure and preserved ejection fraction. *Heart Failure Clin* 10; 445-452
19. Edelmann F., Gelbrich G., Dungan H., Frohling S., Wachter R., Stahrenberg R., *et al.* 2011. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in diastolic heart failure) pilot study. *J Am Coll Cardiol* 18; 58(17): 1780-91.