LEMBAR
HASIL PENILAIAN SEJAWAT SEBIDANG ATAU *PEER REVIEW*
KARYA ILMIAH : JURNAL ILMIAH*

Judul karya ilmiah (artikel) : **Exercise Training Improved Longitudinal Intrinsic Left Ventricle Function in Heart Failure with Preserved Ejection Fraction**
Jumlah Penulis : 4 orang
Status Pengusul : ~~penulis pertama~~/penulis ke 2 ~~/penulis korespondensi~~ **

Identitas Jurnal Ilmiah : a. Nama Jurnal : **International Journal of Angiology**
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g. Terindeks di Scimagojr/Thomson Reuter ISI knowledge atau di Q3**

Kategori Publikasi Jurnal Ilmiah (beri ✓pada kategori yang tepat)
☐ Jurnal Ilmiah Internasional /internasionalbereputasi.**
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Komponen Yang Dinilai	Nilai Maksimal Jurnal Ilmiah			Nilai Akhir Yang Diperoleh
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07-Juni-2020

Reviewer 1 dr Muhammad Iqbal SpJP(K)

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Total = (100%)	5,4			5
Nilai Pengusul =				5

Catatan Penilaian artikel oleh Reviewer:
Artikel ini berisikan penelitian mengenai peran latihan olah raga terhadap longitudinal strain dari ekokardiografi, penelitian ini cukup baik walau hanya sebagai kuasi eksperimental.

05-Juni-2020

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Sidhi Laksono Purwowiyoto - Exercise Training Improved Longitudinal Intrinsic Left Ventricle Function in Heart Failure with Preserved Ejection Fraction

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Exercise Training Improved Longitudinal Intrinsic Left Ventricle Function in Heart Failure with Preserved Ejection Fraction

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Abstract

Exercise improves morbidity, fatality rate, and quality of life in heart failure with low ejection fraction, but fewer data available in heart failure with preserved ejection fraction (HFPEF). The purpose of this study is to test the hypothesis that exercise training might improve the longitudinal intrinsic left ventricular (LV) function in HFPEF patients.

This quasi-experimental study had recruited 30 patients with HFPEF. Exercise training program had been performed for a month with a total of 20 times exercise sessions and evaluated every 2 weeks. Echocardiography was performed before session, second week and fourth week of exercise training. Six-minute walk tests (6MWTs) and quality-of-life variables using Minnesota living with HF scoring and the 5-item World Health Organization Well-Being Index scoring were measured before and after exercise as well. Left ventricular filling pressure, represented by the ratio of early diastolic mitral flow velocity/early diastolic annular velocity and left atrial volume index, improved during exercise. The longitudinal intrinsic LV function, represented by four-chamber longitudinal strain, augmented during exercise ($p < 0.001$). Aerobic capacity, measured by 6MWT, increased significantly ($p = 0.001$). Quality of life improved significantly during exercise ($p < 0.001$).

Exercise training was suggested to improve the longitudinal intrinsic LV function and quality of life in HFPEF. Clinical Trial Registration: ACTRN12614001042639.

Keywords

- heart failure with preserved ejection fraction
- 6-minute walk test
- four-chamber longitudinal strain
- Minnesota living with heart failure

Heart failure with preserved ejection fraction (HFPEF) has been increasing within the past 15 years and is currently estimated at 50 to 55 % of all cases of heart failure[1,2] meanwhile mortality rate remained unchanged. The mortality should emphasize the importance of public health awareness.[2] Morbidity and mortality of HFPEF are comparable with heart failure with reduced ejection fraction (HFREF). Unfortunately, treatment recommendation to reduce morbidity and mortality in HFPEF is still undetermined yet.[3] One of the clinical presentations of HFPEF is an aerobic capacity deterioration, which further leads to quality-of-life impairment.[3,4]

Exercise training (ET) has a vital role in improving the functional capacity and symptoms of both HFREF and HFPEF, patients with postcoronary artery bypass surgery, and those with high cardiovascular risk factors.[4,5] Recently, four randomized clinical studies on exercise interventions conducted in patients with HFPEF, showing that aerobic exercise for 3 to 6 months with or without resistant training was safe and effective to improve aerobic capacity, durability, and quality of life in patients with HFPEF.[6–8]

Two-dimensional speckle-tracking echocardiography (STE) is a novel technique which assesses myocardial deformation

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during the cardiac cycle.[9] The prognosis of heart failure might not reliably be measured using merely simple left ventricular (LV) EF.[9,10] Changes in longitudinal strain on STE were initially reported in HFPEF. Subclinical LV dysfunction, which can be easily detected with STE, is common in left ventricle hypertrophy and HFPEF. Studies using STE have revealed that the different causes of hypertrophy show specific deformation and myocardial motion patterns. Particularly, longitudinal deformation is impaired in the pathological state.[10] Also, the long-axis LV dysfunction may be an initial impairment in HFPEF.

Exercise can improve the quality of life of patients with HFPEF, but there is no evidence that it would be going through the longitudinal intrinsic LV function enhancement. So, the purpose of this study is to test the hypothesis that ET might improve the longitudinal intrinsic LV function in HFPEF patient.

Methods

Ethical Approval and Study Registration

The local Ethical Committee—Institution Review Board of Harapan Kita Hospital—National Cardiovascular Centre had approved this study. The study was a priori registered on http: www//ClinicalTrials.gov (number: ACTRN12614001042639).

Study Design and Subjects

This was a quasi-experimental and pre-post design study, consecutively recruiting 30 patients with HFPEF, namely, those who were fulfilling the 2012 ESC (European Society of Cardiology) guidelines for the diagnosis and treatment of acute and chronic HF.[11] This had been conducted in Harapan Kita Hospital—National Cardiovascular Centre of Jakarta—Indonesia, from September 2014 to January 2015. The eligibility criteria were described as follows:

Key inclusion criteria:

- Symptomatic heart failure with New York Heart Association class II–III, good LVEF (> 50%), diastolic dysfunction (> grade 1), NT-proBNP (N-terminal pro-brain natriuretic peptide) > 220 pg/mL, BNP > 200 pg/mL, global normokinetics (normal regional wall motion abnormality)
- **Minimum age:** 55 years
- **Maximum age:** 75 years
- **Gender:** both males and females

Key exclusion criteria:

- Valvular heart disease (more than moderate), pulmonary diseases (chronic obstructive pulmonary disease, moderate-to-severe asthma), acute coronary syndrome, stable angina pectoris, relevant musculoskeletal disease, symptomatic arrhythmias, blood pressure > 150/100 mm Hg. All participants had given their informed consent before study recruitment.

Exercise Intervention

All participants were enrolled in a 4-week supervised ambulatory training program. Before exercise prescription was formed, they undergo 6-minute walk tests (6MWTs) to assess the functional capacity,[12] then the exercise program was prescribed using the FITT [Frequency, Intensity, Time (duration) and Type of exercise] principle.[13] The components of the FITT principle constitute the exercise dose or quantity needed to improve aerobic capacity. Technicians who performed 6MWTs should be trained using the standard protocol before performing the test. Then, the patients exercised three to five times per week for ~90 minutes per session. Each session consisted of endurance training (cycling and walking) and was followed by relaxation. The exercise workload was individually measured by heart rate monitoring. 6MWTs, Minnesota living with heart failure questionnaire (MLWHFQ), and the 5-item World Health Organization Well-Being Index (WHO-5) questionnaire were performed before and after the supervised ambulatory training program.[14]

Echocardiography

Patients had undergone two-dimensional transthoracic echocardiography at baseline, second week and fourth week of follow-up using a commercially available system, General Electric Vivid-7 Dimension (2006-USA). Electrocardiogram-gated images were obtained in the parasternal, apical, and subcostal views with the patient lying in the left lateral decubitus position. According to the biplane Simpson's rule, LV end-diastolic volume and LV end-systolic volume in mL and EF% were defined. Interventricular septum thickness was measured (in mm) during systole. LV wall thickness was also measured (in mm). Then, left atrial (LA) volume in systole was also measured just before the mitral valve opening, using the biplane Simpson's methods, as a mean between the values recorded in apical four- and two-chamber approaches. Subsequently, LA volume was indexed for body surface area, such as left atrial volume index (LAVI) in mL/m^2.[15]

Parameters of LV diastolic function were determined from transmitral inflow velocities using pulsed wave Doppler recordings in the apical four-chamber view. Early (E) and late peak mitral inflow velocity (A) of LV filling was calculated. Four-chamber longitudinal strain (4ChLS) was measured in the apical four-chamber (in six segments) and computed automatically generating regional data from six LV segments. For patients with sinus rhythm, analyses were performed on a single cardiac cycle, while for patients with atrial fibrillation, strain values were calculated as the average of three cardiac cycles. Two trained cardiologists for echocardiography had examined all the results.[16]

Statistical Analysis

Statistical analysis was performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, 2011). Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. Continuous variables were compared between groups using repeated analysis of variance test or Friedman test then post hoc analysis or Wilcoxon test according to the distribution of variables. Statistical significance was set at $p < 0.05$ (two-tailed), and sufficient statistical power was set at a power ≥ 0.80.

Results

The mean age of the patients was 65.3 ± 6.2 years old, and male gender was more prominent (56.7%). All subjects

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suffered hypertension (100%) followed by diabetes mellitus (40%) and atrial fibrillation (16.7%). They were treated mostly by β-blockers (80%), calcium channel blocker (53.3%), angiotensin receptor blocker (53.3%), and diuretics (20%). Some diabetics patients were treated with oral anti-diabetic (40%) and angiotensin-converting enzyme inhibitor (26.7%). The other medications were anticoagulants (16.7%), mineralocorticoid receptor antagonist (13.3%), and digoxin (3.3%). All patients' characteristics are presented in ►**Table 1**.

LV function characterized by EF measured before study, second week and fourth week after ET, was not increased significantly ($p = 0.29$; and ►**Fig. 1**). Otherwise, LV filling pressure represented by early diastolic mitral flow velocity/early diastolic annular velocity (E/e') ratio, LAVI, and the longitudinal intrinsic LV function (4ChLS) improved significantly ($p < 0.001$) as summarized in ►**Figs. 2**, **3**, **4**. The interobserver variabilities as the coefficient variations for EF, E/e' ratio, and LAVI consecutively were 8.6, 9.5, and 9.8%.

The significant changes of echocardiographic measurement were translated to improved functional capacity after exercise, as shown in ►**Table 2**. The 6MWTs increased significantly from 367.5 (188–454) m to 437.0 (215–589) ($p < 0.001$l in ►**Table 2**). Further, this was followed by

Table 1 Baseline characteristic of demographic and clinical ($n = 30$)

Variable	$n = 30$
Age (year), mean (SD)	65.3 ± 6.2
Sex, *n* (%)	
Male	17 (56.7)
Female	13 (43.3)
Comorbidities, *n* (%)	
Diabetes mellitus	12 (40)
Atrial fibrillation	5 (16.7)
Hypertension	30 (100)
Blood pressure (mm Hg)	
Systolic, mean (SD)	126.17 ± 15.51
Diastolic, median (SD)	85 ± 5.5
Treatment, *n* (%)	
Beta blocker	24 (80)
ACE inhibitor	8 (26.7)
ARB	16 (53.3)
MRA	4 (13.3)
Diuretics	6 (20)
CCB	16 (53.3)
Digoxin	1 (3.3)
Anticoagulant	5 (16.7)
OAD	12 (40)

Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; OAD, oral anti-diabetics; SD, standard deviation.

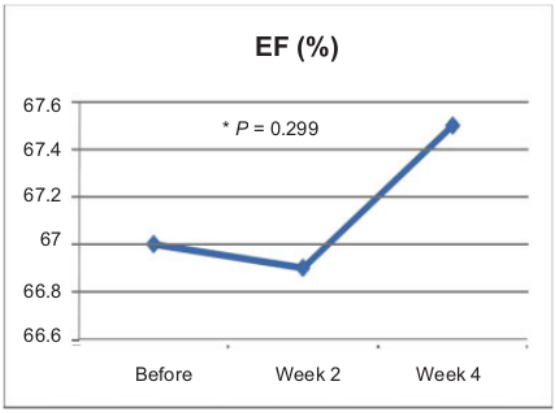

Fig. 1 The ejection fraction (EF) difference before, second week, and fourth week after exercise training. *p value = 0.299 before the study and fourth week after exercise training.

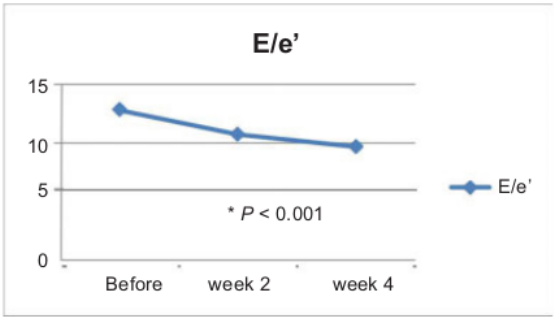

Fig. 2 E/e' difference before second week and fourth week after exercise training. *p value < 0.001 before the study and fourth week after exercise training. E, early diastolic mitral flow velocity; e', early diastolic annular velocity.

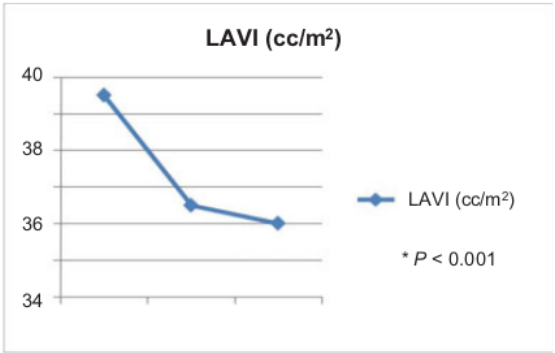

Fig. 3 LAVI difference before second week and fourth week after exercise training. *p value < 0.001 before the study and fourth week after exercise training. LAVI, left atrial volume index.

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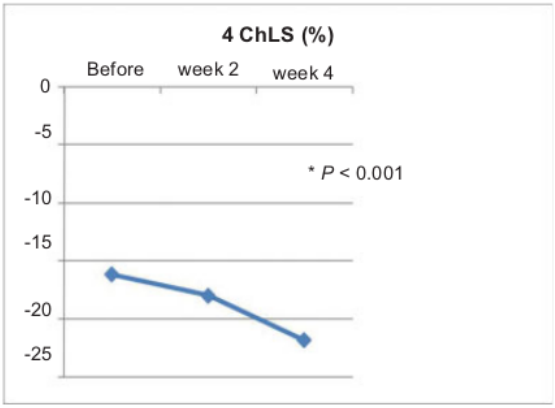

Fig. 4 4ChLS difference before second week and fourth week after exercise training. *p value < 0.001 before the study and fourth week after exercise training. 4ChLS, four-chamber longitudinal strain.

Table 2 Quality of life and 6MWTs before and after exercise training

Variables	Questionnaire scoring	p Value
MLWHFQ		< 0.001
Before	64.23 ± 13.20	
After	35 ± 16.80	
WHO-5		< 0.001
Before	10.50 ± 4.20	
After	19.47 ± 2.09	
Variables	**Distance**	**p Value**
6MWTs (meter)		< 0.001
Before	367.5 (188–454)	
After	437.0 (215–589)	

Abbreviations: MLWHFQ, Minnesota living with heart failure questionnaire; WHO, World Health Organization; 6MWTs, six minutes walking test.

improved the quality of life, as assessed by MLWHF and WHO-5 questionnaire[14] (MLWHFQ; $p < 0.001$ and WHO-5; $p < 0.001$ in ►**Table 2**).

Discussion

In this study, ET suggested to improve the longitudinal intrinsic LV function; then it was additionally translated by the increased 6MWTs and better quality of life measured by MLWHF and WHO-5 questionnaire. To the best of our knowledge, this is the first study that tested the effect of ET on longitudinal intrinsic LV function assessed by STE. Additionally, a meta-analysis studied the effect of ET on diastolic dysfunction and demonstrated a significant improvement in E/e' ratio in the exercise group than controls.[17] Further study revealed that exercise-induced reduction in E/e' ratio was associated with a 38% gain in VO2-max and 50% improvement in physical functioning score.[18]

LAVI is known to reflect the severity of increased LA filling pressure caused by LV diastolic dysfunction. LAVI was markedly higher in patients with than those without cardiac events ($p < 0.01$). The Kaplan–Meier analysis showed that there was a stepwise increase in the risk of cardiac events with each increment of LAVI category, and LAVI >53.3 mL/m^2 correlated with the highest risk of cardiac events.[19] According, the benefit of ET in this particular study is supposed to be associated with atrial reverse remodeling and improved longitudinal intrinsic LV diastolic function.

LV EF is a crucial echocardiographic parameter in clinical decision of cardiac patients. Particularly in those with HFPEF, it has been questioned whether EF is an accurate and reliable parameter to characterize LV performance.[20] LV global longitudinal strain had demonstrated the limitations of EF in many clinical settings. In primary severe mitral regurgitation, the increased volume overload might induce changes in the extracellular matrix, which is reflected by reduced LV global longitudinal strain, despite preserved EF.[21] Additionally, in patients with severe secondary mitral regurgitation, speckle-tracking global longitudinal strain shows more deteriorated LV systolic function than LVEF.[22] Moreover, strain rate imaging is accurate in detecting increased the LV stiffness in HFPEF, but it is not superior to already established tissue Doppler imaging analysis including E/e' ratio in patients with an only mild degree of disease.[23]

This study revealed that although ET might improve the longitudinal intrinsic LV function, it did not affect global EF. Anyway, the advantages of longitudinal intrinsic LV function over EF in assessing LV systolic function had been demonstrated more in several studies.[24,25]

Conventionally, the longitudinal intrinsic LV function is expressed as a negative value because it represents the shortening of the myocardium relative to the original length. The more negative the value is, the better the LV systolic functions are. Therefore, any value of the longitudinal intrinsic LV function less negative than –20% might be considered pathological.[26] This was shown in this study that initial 4ChLS of –16.30 % improved to –21.86 % after 4-week ET.

In HFPEF, peripheral muscle dysfunction is another critical mechanism contributing to exercise intolerance (i.e., breathlessness and fatigue). The diaphragm of HFPEF rats demonstrated ($p < 0.05$) a fiber type shift from fast-to-slow twitch, fiber atrophy, a decreased pro-oxidative but increased antioxidant capacity, reduced proteasome activation, impaired in situ mitochondrial respiration, and in vitro muscle weakness and increased fatigability. ET, however, prevented mitochondrial and functional impairments in both diaphragm and soleus muscles.[27] Also, ET reduced the plasma levels of tumor necrosis factor-alpha and interleukin-6 (IL-6) and increased the plasma levels of IL-10. Consequently, aerobic ET program improved the inflammatory profile and cardiac function and attenuated cardiac remodeling in chronic heart failure.[28]

Chronic illness, such as heart failure, is not only life threatening to patients but it will also lead to severe depression. Approximately 14% of heart failure patients are suffering from high levels of psychological distress. WHO-5 can help to

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monitor the emotional well-being of patients as part of the clinical practice, thus enhancing the likelihood of recognizing depression.[29] The WHO-5 is a short, self-administered questionnaire covering five positively worded items, which are related to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), general interests (being interested in things) and becomes a reliable measure of emotional functioning. It is accurate in identifying depression as compared with clinical diagnosis.[29]

This study might seem to improve the well-being index as summarized in ►**Table 2**. This is consistent with the study which showed that the improvement in exercise capacity with ET was associated with a decrease in depression, anxiety, emotional status, and an increase in quality of life in patients with heart failure.[30,31]

Additionally, another study demonstrated that participation in a 12-week aerobic interval-training program resulted in significant improvements in several measures of quality of life in patients with ischemic HF with an implantable cardioverter defibrillator. At follow-up, there was a significantly less sedentary activity in the aerobic interval training group.[32] In contrast, Smart et al proved that ET in patients with HFPEF did not change the quality of life and depression scores assessed by MLWH and Hare-Davis score, although the 16-week exercise program had increased the VO_2-max.[33]

The 6MWTs was developed by the American Thoracic Society for the assessment of the functional capacity and exercise tolerance in those with the pulmonary, cardiovascular disease.[12] It is a simple and easily performed test that does not require high technology and provides objective data on the exercise tolerance. This study showed that ET significantly improved the 6MWTs results in HFPEF.

The limitation of this study was a quasi-experimental study, in which it did not have any control group, but it was representing the daily clinical practice in our hospital. So, the conclusions derived from this study are only "hypothesis-generating" manner. Confounder also could not wholly be omitted, so we tried to confirm by measuring the functional capacity and quality-of-life variables.

Conclusion

ET program was suggested to improve the longitudinal intrinsic LV function, functional capacity, and quality of life in HFPEF patients.

Conflict of Interest
None.

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