

The effect of low-intensity intradialytic aerobic exercise on heart rate variability in maintenance hemodialysis patients



Dilia Ratna Dewi¹, Damayanti Tinduh^{1*}, Andriati¹, Mochammad Thaha²,
Mohammad Fathul Qorib³, Soenarnatalina Melaniani⁴

¹Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;

²Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Universitas Airlangga Hospital, Surabaya, Indonesia;

³Department of Anatomy, Histology and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia;

⁴Department of Epidemiology, Biostatistics, Population Studies, and Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia;

*Corresponding author:
Damayanti Tinduh;
Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;
damayanti.tinduh@fk.unair.ac.id

Received: 2022-11-30

Accepted: 2022-12-29

Published: 2023-01-24

ABSTRACT

Background: End-stage renal disease (ESRD) patients undergoing maintenance HD typically adopt a sedentary lifestyle which increases cardiometabolic risk and takes many years to be clinically detectable. Heart rate variability (HRV) is a non-invasive method to assess cardiac autonomic modulation. Interventions to increase HRV, such as exercise therapy, have been examined, given the theoretical plausibility that improvements in HRV may lead to improved outcomes. This study aimed at assessing the effects of aerobic exercise during hemodialysis sessions on the HRV of patients with ESRD.

Methods: This research is a quasi-experimental study with pre and post-test randomized control group design. From the total of 20 ESRD patients undergoing maintenance HD randomly assigned to either exercise or control group, 2 subjects dropped out, leaving 18 ESRD patients. The patients in the exercise group were submitted to a low intradialytic aerobic exercise, performed during the first two hours of HD, twice weekly, for 12 weeks. At baseline and after 12 weeks, all participants underwent short-(for 5 min) term measurements of HRV. The data were analyzed in the SPSS package program.

Results: There is a significant difference in post-pre changes (Δ) SDNN between the exercise and control group, but there were no significant differences in Δ RMSSD ($p = 0.157$) and Δ LF/HF ratio ($p = 0.859$), with the large effect size for Δ SDNN (Cohen's D 1.01), medium effect size for Δ RMSSD (Cohen's D 0.70), and very small effect size for Δ LF/HF ratio (Cohen's D 0.09).

Conclusion: Twelve weeks of supervised low-intensity intradialytic aerobic exercise has modified heart rate variability in maintenance hemodialysis patients.

Keywords: end-stage renal disease, heart rate variability, intradialytic exercise, maintenance hemodialysis.

Cite This Article: Dewi, D.R., Tinduh, D., Andriati., Thaha, M., Qorib, M.F., Melaniani, S. 2023. The effect of low-intensity intradialytic aerobic exercise on heart rate variability in maintenance hemodialysis patients. *Bali Medical Journal* 12(1): 374-380. DOI: 10.15562/bmj.v12i1.3957

INTRODUCTION

End-stage renal disease (ESRD) is a rapidly increasing global health and healthcare burden.¹ Currently, about 3 million patients are receiving renal replacement therapy for ESRD worldwide out of 10 million who would qualify for renal replacement therapy (RRT); these numbers are expected to grow by 50% to 100% until 2030.² The prevalence of patients undergoing routine HD in Indonesia increased from 11,484 in 2010 to 132,142 in 2018. The proportion of patients undergoing routine HD compared to patients undergoing kidney replacement therapy with HD and CAPD in Indonesia in 2018 was 98%.³ Hemodialysis (HD) is an important and commonly used RRT for ESRD patients.⁴ More than 60% of

all patients with ESRD are treated with HD during their lifetime.⁵ ESRD patients undergoing maintenance HD typically adopt a sedentary lifestyle and spend less time being physically active than healthy adults.^{6,7} A HD session represents a long sedentary period, which often hinders the maintenance of HD patients from engaging in physical activity and, as such, dialysis treatments contribute to lower physical activity levels.^{8,9} Recent studies suggested that sedentary behavior increases cardiometabolic risk and contributes to the development of many chronic diseases.¹⁰ Cardiometabolic changes resulting from a sedentary lifestyle may take many years to be clinically detectable. For this reason, other biomarkers involved in the genesis of these dysfunctions have been more

largely studied. In this sense, heart rate variability (HRV) is a noninvasive method to assess cardiac autonomic modulation.¹¹ Among the most used indices of HRV, the standard deviation of the NN interval (SDNN) has been suggested to reflect global variability, while the root mean square of successive differences (RMSSD) has been linked to vagal activity. The low-frequency (LF)/high-frequency (HF) ratio is considered by some investigators to mirror sympathovagal balance or to reflect sympathetic modulations.¹² Changes in HRV patterns serve as health indicators since several studies have suggested that higher HRV values are associated with positive health status, whereas reduced HRV indicates poor or inadequate adaptation of the autonomic

nervous system (ANS) and is associated with increased cardiovascular risk and mortality.¹¹ It is reported that HRV is severely de-arranged in CKD patients and becomes even more pronounced in HD. In these patients, HRV is thought to cause sympathetic hyperactivity and vagal withdrawal, possibly leading to left ventricular hypertrophy and complex arrhythmias development. Various pathophysiological mechanisms underlying this effect have been proposed, including reduced arterial baroreflex function, activation of the renin-angiotensin-aldosterone system (RAAS) and renal afferents fibers, CV remodeling, altered nitric oxide (NO) bioavailability, mental stress, insulin resistance, increased endothelin production, salt retention, and activation of atrial natriuretic peptide.¹³

Exercise has been shown to have benefits on the potential improvements in cardiovascular outcomes, cardiorespiratory fitness, dialysis efficacy, functional capacity, health-related quality of life, and hs-CRP.¹⁴ There are three alternatives for dialysis patients, including exercise during HD, on non-dialysis days, and at home. Among the three alternatives, intradialytic exercise is the most feasible and applicable choice for HD patients: it doesn't involve any extra time for doing exercise and dialysis at the same time and leads to a lower dropout rate and greater compliance. Patients are under the supervision of doctors and machines. Any complications can be detected and treated on the spot. There is a possibility that intradialytic exercise can increase solute removal, for exercise may increase the blood flow to the muscle, and greater toxic agents can be removed by the dialyzer.¹⁵

Interventions to increase HRV, such as exercise therapy, have been examined, given the theoretical plausibility that improvements in HRV may lead to improved outcomes.¹⁶ Autonomic adaptation to aerobic exercise includes parasympathetic activity increase and sympathetic activity decrease, resulting in decreases in heart rate, blood pressure, and systemic vascular resistance. Aerobic exercise modifies heart rate control by increasing the high-frequency (parasympathetic) component of HRV and lowering the low-frequency (sympathetic)

component. Researchers have reported that a structured, low-intensity, high-frequency walking program improves autonomic function by increasing HRV in patients with peripheral artery disease.¹⁷ Only a few studies have assessed the effect of an exercise training program on cardiovascular parameters in patients with ESRD undergoing HD. This study aimed at assessing the effects of aerobic exercise during HD sessions on the HRV of patients with ESRD.

METHODS

This study was conducted in the Hemodialysis Installation, Dr. Soetomo Academic General Hospital, for 3 months, from March to June 2021. Written informed consent was obtained from all patients who agreed to be research subjects. This study was approved by the Health Research Ethics Committee of Dr. Soetomo Academic General Hospital, Surabaya, Indonesia, with ethical feasibility certificate number 0153/KEPK/II/2021.

Participants

The inclusion criteria were patients with End Stage Renal Disease and on HD for more than 3 months with an age group between 20 to 50 years of both male and female, receiving twice weekly HD, and willing to sign an informed consent and participate in the study. Patients with prior regular aerobic exercise program twice a week, unstable heart disease, severe pneumopathies, a cerebrovascular accident within the prior 6 months, persistent hyperpotassaemia before dialysis, inadequate blood pressure control (systolic blood pressure more than 180 mmHg or less than 110 mmHg), history of repeated episodes of hypoglycemia (blood glucose less than 70 mg/dl), uncontrolled hyperglycemia (random blood glucose more than 250 mg/dL), frequent large interdialytic weight gain (more than 3 kg), use antiarrhythmic drugs, cognitive impairment, hemoglobin less than 8 mg/dL, and neuromusculoskeletal disease of the lower limbs interfering with participation in the study were excluded. Subjects were considered to have dropped out when they refused to continue participating, were unable to complete

exercise based on the research protocol, were absent from the exercise program for 2 or more consecutive training or collective absences of more than 20% of the total exercise days (a maximum of 3 non-consecutive days), and hospitalization.

Study Design and Treatment

This research is a quasi-experimental study with a pre and post-test randomized control group design. The formula for determining sample size uses the same formula as the study by Masroor et al. and the minimum number of research subjects for each group is 6 people.¹⁸ This study used a consecutive sampling technique, then randomization was carried out using a lottery until the required number of subjects was fulfilled. Twenty ESRD patients undergoing maintenance HD were randomly assigned to either exercise or control group. The patients in the exercise group were submitted to a low-intensity (30-39% heart rate reserve or 11-12 Borg scale) intradialytic aerobic exercise program with a bedside cycle ergometer (Terra Fitness® brand) in a recumbent position for 30 minutes starting with a 5-minute warm-up, a 20-minute core phase, and a 5-minute cool-down phase, performed during the first two hours of HD, twice weekly, for 12 weeks. For safety reasons, heart rate, blood pressure, and oxygen saturation were monitored throughout the physical exercise session. The study was at all times under the direct supervision of the medical team; in case of any discomfort, the intervention was immediately stopped. Criteria for interruption of exercise were intense physical exhaustion, chest pain, dyspnoea, dizziness, muscle cramps, moderate or severe joint pain (Wong-Baker pain scale ≥ 4), blood pressure above 200/110 mmHg or below 110/50 mmHg, resting heart rate more than 120 beats per minute, oxygen saturation less than 90%, and body temperature above 37.5°C.

Outcomes

Baseline demographic data and clinical characteristics of the participants were obtained before the intervention. At baseline and after 12 weeks, all participants underwent short-(for 5 min) term measurements of HRV, recorded

30-60 minutes before HD. During the recording, the participants were in a sitting position and asked to remain calm during recording. The recording is done using a Polar H10 chest strap device connected to a Samsung Galaxy S20 Plus smartphone via Bluetooth using the Elite HRV application. The recording is done for 5 minutes. The raw data were exported to a computer for later analysis using Kubios HRV Standard 3.3 software. The data taken were SDNN, RMSSD, and LF/HF ratio. The exercise group was recorded before the first intradialytic exercise and the first HD after the last intradialytic exercise, while the control group was recorded before and after the 12-week observation period.

Statistical Analyses

The data were analyzed in the IBM SPSS Statistics 26. Normality analysis of the data was done with the Shapiro-Wilk test. Paired sample t-test was used for the comparison of normally distributed data within groups. An independent sample T-test was used for the comparison of normally distributed data between groups. The significance level was $p < 0.05$, and the effect sizes were also presented. A commonly used interpretation is to refer to the effect sizes as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) based on benchmarks suggested by Cohen.

RESULTS

The total subject was 20 patients who met the inclusion criteria and did not include the exclusion criteria. Subjects were randomly assigned to exercise or control groups. Each group consisted of 10 subjects. Of the 20 patients, there were 2 dropout patients (1 from the exercise group and 1 from the control group). The subject who dropped out of the exercise group was absent from 2 consecutive intradialytic exercises. He was absent from HD treatment for a week due to personal reasons, then complained of shortness of breath which required hospitalization. The complaint occurred 3 days after the last exercise session, so it was categorized as not related to exercise side effects. There were no complaints experienced by the patient during the previous exercises. The subject who dropped out of the control

group complained of shortness of breath and required hospitalization. There were 2 subjects of the exercise group who experienced complaints due to exercise, including 1 subject who complained of muscle cramps and another subject who complained of post-exercise dizziness. Dizziness and muscle cramps were also reported by 2 subjects in the control group. The subjects who complained of dizziness and muscle cramps were given management according to research protocols and were able to complete the study. Eighteen subjects completed the study. At the end of the study, data from nine subjects from the exercise group and nine subjects from the control group were analyzed.

The normality analysis results showed that all the basic characteristic data had normal distributions. The homogeneity test with parametric statistical test (independent sample T-test) showed no significant difference between the mean values of each initial characteristic of pre-intervention in the two groups, as seen in Table 1.

The values of HRV parameters of the exercise and control group can be seen in Table 2. There were no significant changes in SDNN ($p = 0.126$), RMSSD ($p = 0.171$) and LF/HF ratio ($p = 0.258$) at the exercise group with the medium effect size for SDNN and RMSSD (Cohen's D 0.568 and 0.502 respectively), and the small effect size for LF/HF ratio. There were no significant changes in SDNN ($p = 0.132$), RMSSD ($p = 0.827$), and LF/HF ratio ($p = 0.759$) in the control group over 12 weeks of observation with small effect size in SDNN, RMSSD, and LF/HF ratio (Cohen's D 0.380; 0.076; 0.106 respectively). There was no significant difference in the SDNN ($p = 0.219$), RMSSD ($p = 0.193$) and LF/HF ratio ($p = 0.754$) between groups at the end of observation. When comparing the magnitude of post-pre changes (Δ) in HRV parameters between the groups, there was a significant difference in Δ SDNN ($p = 0.034$), but there were no significant differences in Δ RMSSD ($p = 0.157$) and Δ LF/HF ratio ($p = 0.859$), with a large effect size for Δ SDNN (Cohen's D 1.01), a medium effect size for Δ RMSSD (Cohen's D 0.70), and very small effect size for Δ LF/HF ratio (Cohen's D 0.09).

DISCUSSION

Heart rate variability parameters were assessed at the baseline. The mean SDNN value of the exercise (7.21 ± 4.72 ms) and control group (8.00 ± 3.86 ms) is below the normal value (32-93 ms), according to Shaffer and Ginsberg.¹⁹ This finding is in line with the study by Seibert et al., who measured SDNN values in 28 patients undergoing HD and obtained a mean SDNN value of 13.0 ms in HD patients with diabetes mellitus and 18.0 ms in patients undergoing HD without diabetes mellitus.²⁰

The mean RMSSD value in the exercise group (7.31 ± 6.10 ms) and control (7.04 ± 4.38 ms) was also below the normal value (19-75 ms), according to Shaffer and Ginsberg.¹⁹ This finding is in line with the study by Gao et al., who measured the RMSSD value in 200 stage 5 CKD patients and obtained a mean RMSSD value of 17 (13-23) ms.²¹ Cashion et al. studied HRV in the time and frequency domain in HD patients for a period of two years. The results of his research reported that the HRV parameters decrease was associated with injury to the parasympathetic system due to structural damage to the arteries or functional changes in the autonomic nervous system secondary to uremic toxins.²²

The mean LF/HF ratio in the exercise group (3.36 ± 2.20) and control (3.59 ± 2.38) was within the normal value range (1.1-11.6) according to Shaffer and Ginsberg.¹⁹ This finding is in line with research by Noppakun et al., who showed a mean LF/HF ratio of 1.2 ± 0.5 in 163 ESRD patients undergoing HD.²³ Study by Kuo et al. showed a LF/HF ratio of < 2.6 in the majority of patients (70.1%) with chronic HD.²⁴ An increase in the LF/HF ratio indicates an increase in sympathetic tone. The study by Chou et al. of 326 patients with various stages of CKD revealed abnormal LF, HF, and LF/HF ratio values in 69.5%, 52.8%, and 50% of patients, respectively.²⁵

This study revealed that low-intensity intradialytic aerobic exercise for 12 weeks did not significantly improve the SDNN, RMSSD, and LF/HF ratio in the exercise group. The effect size showed that the training program in the exercise group had a moderate effect on the SDNN

Table 1. Normality and homogeneity test of the characteristics of research subjects in pre-intervention for both groups.

Characteristics	Exercise Group Means $\pm$ SD	<i>p</i> -value (Normality)	Control Group Means $\pm$ SD	<i>p</i> -value (Normality)	<i>p</i> -value (Homogeneity)
Age (year)	39.44 $\pm$ 7.07	0.518	36.44 $\pm$ 4.45	0.332	0.188
BMI (kg/m ²)	22.96 $\pm$ 4.45	0.191	22.26 $\pm$ 3.37	0.552	0.663
HD History (months)	51.56 $\pm$ 38.48	0.125	61.89 $\pm$ 33.32	0.055	0.697
Hb (mg/dL)	11.29 $\pm$ 1.55	0.116	10.02 $\pm$ 1.03	0.140	0.251
Blood glucose (mg/dL)	112.22 $\pm$ 26.43	0.136	114.89 $\pm$ 15.92	0.258	0.267
MoCA-Ina	24.89 $\pm$ 2.89	0.160	24.11 $\pm$ 3.02	0.061	0.807

Characteristics	Total (n=18)	Group		<i>p</i> -value
		Exercise (n=9)	Control (n=9)	
Gender	8M. 10F	3M. 6F	5M. 4F	0.414
Male	8 (44.4%)	3 (33.3%)	5 (55.6%)	-
Female	10 (55.6%)	6 (66.7%)	4 (44.4%)	-
BMI (kg/m ²)	22.61 $\pm$ 3.85	22.96 $\pm$ 4.45	22.26 $\pm$ 3.37	0.663
Underweight	2 (11.1%)	1 (11.1%)	1 (11.1%)	-
Normoweight	8 (44.4%)	4 (44.4%)	4 (44.4%)	-
Overweight	4 (22.2%)	2 (22.2%)	2 (22.2%)	-
Obese	4 (22.2%)	2 (22.2%)	2 (22.2%)	-
Comorbid				
Hypertension	15 (83.3%)	7 (77.8%)	8 (88.9%)	-
DM	1 (5.6%)	1 (11.1%)	0 (0%)	-
Urolithiasis	2 (11.1%)	1 (11.1%)	1 (11.1%)	-
Drugs				
Amlodipine	12 (66.7%)	6 (66.7%)	6 (66.7%)	-
Allopurinol	1 (5.6%)	0 (0%)	1 (11.1%)	-
Ca supplement	4 (22.2%)	2 (22.2%)	2 (22.2%)	-
Fe supplement	2 (11.1%)	1 (11.1%)	1 (11.1%)	-
Folic acid	4 (22.2%)	2 (22.2%)	2 (22.2%)	-
Vitamin B	2 (11.1%)	2 (22.2%)	0 (0%)	-
HD history (months)	56.72 $\pm$ 35.32	51.56 $\pm$ 38.48	61.89 $\pm$ 33.32	0.697
6-12	1 (5.6%)	1 (11.1%)	0 (0%)	-
13-36	4 (22.2%)	3 (33.3%)	1 (11.1%)	-
37-120	11 (61.1%)	4 (44.4%)	7 (77.8%)	-
>120	2 (11.1%)	1 (11.1%)	1 (11.1%)	-
HD duration (hours)				
4.5	12 (66.7%)	7 (77.8%)	5 (55.6%)	-
5	6 (33.3%)	2 (22.2%)	4 (44.4%)	-

Significant difference if *p*-value <0.05. BMI: Body Mass Index. HD: Haemodialysis. Hb: Haemoglobin. MoCA-Ina = Montreal Cognitive Assessment Indonesian version

(0.568) and RMSSD (0.502) values and a small effect on the LF/HF ratio (0.409).

The results of this study are not in line with the previous study by Kouidi et al. in 44 ESRD patients undergoing maintenance HD that showed an increase in SDNN of 58.8% and RMSSD of 68.1% in the exercise group after intervention.²⁶ This difference in results could occur because the frequency of exercise given in the previous study was 3 times a week, whereas, in this study, the exercise frequency was twice a week, the frequency of HD that is commonly practiced in Indonesia.

The exercise intensity given in a previous study by Kouidi et al. is low to moderate intensity with a Borg scale of 11-13 for effort.²⁶ Another study by Yeh et al. used the Borg scale of 12-14 for effort.²⁷ Research by Storer et al. gave moderate intensity at a 50% peak work rate. However, all of the participants could not tolerate the intensity, so it was reduced to a low intensity, 30% of the peak work rate, which was increased progressively according to the patient's tolerance.²⁸ Whereas in this study, the intensity of the exercise given was a low-intensity exercise with a Borg scale of 11-12 for effort. The determination

of exercise intensity was considered that this was the first intradialytic exercise study at Dr. Soetomo, and there is no data regarding the condition of maintenance HD patients, so the exercise program is given at a low intensity. Recommendations from the American College of Sports Medicine (ACSM) for people with CKD are initially given a low to the moderate-intensity exercise program and gradually increase over time based on individual tolerance.²⁹

Exercise duration in the study by Kouidi et al. was 60 to 90 minutes for each exercise session (depending on the ability

Table 2. Changes in heart rate variability parameters in exercise and control groups.

HRV Parameters	Exercise group (n=9)			Control group (n=9)		
	Pre	Post	Post-pre changes	Pre	Post	Post-pre changes
SDNN (ms)	7.21 ± 4.72	9.62 ± 6.18	2.41 ± 4.24	8.00 ± 3.86	6.66 ± 3.16	-1.34 ± 2.39
RMSSD (ms)	7.31 ± 6.10	12.26 ± 11.47	4.95 ± 9.86	7.04 ± 4.38	6.75 ± 3.98	-0.29 ± 3.83
LF/HF ratio	3.36 ± 2.20	2.72 ± 2.54	-0.65 ± 1.59	3.59 ± 2.38	3.19 ± 3.68	-0.40 ± 3.76

Values are presented as mean ± SD. *Significant if *p*-value < 0.05. SDNN: standard deviation of the NN interval. RMSSD: root means square of the successive differences. LF/HF: low frequency / high frequency.

of each patient).²⁶ In this study, exercises were given with a duration of 30 minutes per session for all research subjects. The recommended duration of aerobic exercise from the ACSM for individuals with CKD is 20–60 minutes of continuous activity. If this amount cannot be tolerated, 3–5 minutes of intermittent exercise is recommended aiming to build up to 20–60 minutes.^{29,30}

The type of exercise provided in the study by Kouidi et al. consisted of cycling sessions with specific devices that were adjusted to each patient's bed, strengthening and flexibility exercises for lower limbs using therabands and weights on the limbs.²⁶ The type of exercise given in this study was aerobic exercise using a cycle ergometer. Exercise, especially aerobic exercise, causes an increase in vagal tone at rest and a decrease in sympathetic tone in healthy subjects as well as in patients with CKD, heart disease, type 2 diabetes, and other diseases.³⁰

The period of exercise is also a determining factor. Where in the study by Kouidi et al., exercises were conducted for 12 months, whereas in this study, exercises were only given for 12 weeks.²⁸ Researchers suggest that these findings may be related to the training period. Overall, the disparities in the result caused by the intensity and duration of the exercise have been known as the dose-response phenomenon.³² The choice of the 12 weeks exercise period of this study was due to the benefits observed in a previous protocol developed at the Universidade Federal de Juiz de Fora, Minas Gerais, Brazil. One such study assessed the effects of 12 weeks of intradialytic aerobic exercise in 14 patients with CKD. After the exercise period, a decrease in blood pressure was observed, an increase in quality of life was assessed using the SF-

36 questionnaire, an increase in functional capacity was assessed using a six-minute walking test, improvement in anemia and adequacy of dialysis.³² Study by Albinet et al. in 24 sedentary elderly participants who were trained with aerobic exercise for 12 weeks showed a significant increase in SDNN, RMSSD, and HF power scores.³³ Taken together, the results of the study confirm a direct association between brief aerobic exercise and vagal-mediated HRV parameters in the elderly. The choice of the training period is also considered with the conditions of the COVID-19 pandemic that hit Indonesia, especially in Surabaya. So to minimize the risk of COVID-19 transmission, 12 weeks is the ideal choice to provide exercise to patients with End Stage Kidney Disease undergoing maintenance HD.

Research by Kouidi et al. was also performed on patients without a history of diabetes mellitus,²⁶ whereas this study did not exclude patients with Diabetes Mellitus. Shah et al. found evidence of cardiac autonomic dysfunction and a worse HRV index in subjects with type 2 DM compared to controls.³⁴ HRV is independently related to prior glycemic control over time. Hemodialysis patients with diabetes are thought to be the cause of further damage to the autonomic nervous system due to diabetic and uremic neuropathy.³⁵

Heart Rate Variability is affected by the treatment of kidney failure with dialysis. The beneficial effect of HD on HRV is most pronounced during the first day of the interdialysis period. The study by Tong and Hou with a similar population also contradicts these results, where the LF/HF ratio decreased during the 3 hours of the HD procedure and returned to pre-dialysis levels 2 hours after dialysis.³⁶ In the study by Ranpuria et al.,

HRV parameters after dialysis increased compared to pre-dialysis values and lasted up to 24 hours after dialysis in the non-diabetic group.³⁵ Researchers believe that the HRV value of the control group did not change significantly because the HRV measurement was carried out shortly before HD or 68–92 hours from the previous HD, so there was no effect of HD on HRV.

The results of this study showed that the mean SDNN and RMSSD values in the exercise group were higher than those in the control group. In contrast, the LF/HF ratio in the exercise group was lower than in the control group after 12 weeks of observation. Based on the statistical analysis, this difference is not significant. This result is in line with the study by Reboredo et al., which stated that there was no significant difference in the HRV of CKD patients undergoing maintenance HD after 12 weeks of intradialytic aerobic exercise with the control group.³²

O'Neal et al. study on 1,175 participants to determine the normative range of HRV measurements and validate the significance of HRV measurements on 6,332 participants. The results of this study determined an abnormal SDNN value of 6.1 ms and borderline abnormal of 8.2 ms, while an abnormal RMSSD value of 6.0 ms and borderline abnormal of 8.0 ms. Abnormal and borderline abnormal values for SDNN and RMSSD are associated with an increased risk of cardiovascular disease events and all-cause mortality, as well as confirming the prognostic significance of the proposed values.³⁷ In this study, there was an increase in the mean SDNN and RMSSD values in the exercise group from the abnormal normative range (7.21 ms and 7.31 ms) to the borderline abnormal (9.62 ms and 12.26 ms), while the mean SDNN and RMSSD values in the control

group remained within the abnormal normative range.

The mean SDNN and RMSSD values in the exercise group increased, while those in the control group decreased. There is a significant difference in Δ SDNN between the exercise and control group by calculating the magnitude of Cohen's D effect, which shows a large effect (1.01). There was no significant difference in Δ RMSSD between the exercise and control groups by calculating the magnitude of the Cohen's D effect, which showed a moderate effect (0.70). The mean LF/HF ratio decreased in the exercise and control groups without any significant difference with a very small Cohen's D effect size (0.09). These results indicate that low-intensity intradialytic aerobic exercise has a significant effect on increasing the SDNN value. Increasing the RMSSD value with a moderate effect and decreasing the LF/HF ratio with a small effect.

Previous research by Headley and Violan emphasized that an exercise program during HD can reduce uremia and improve the quality of life for this population.³⁸ Similar results were verified by a study by Parsons et al. with aerobic exercise using a cycle ergometer for 15 minutes in the first 3 hours of HD, three times a week for 8 weeks.³⁹

This study has several weaknesses, including uncontrolled confounding variables such as gender, BMI, diabetes mellitus, coronary artery disease, hypercholesterolemia, sleep patterns, stress, and physical activity on interdialytic days, which can affect HRV variables in this study. In addition, the investigators have not blinded to the exercise intervention, and the intervention was of relatively short duration and thus could not examine the long-term effects of exercise on HRV.

CONCLUSION

Twelve weeks of supervised low-intensity intradialytic aerobic exercise has modified heart rate variability in maintenance hemodialysis patients.

ETHICAL CLEARANCE

This study was approved by the Health Research Ethics Committee of Dr. Soetomo Academic General Hospital.

Surabaya Indonesia with ethical feasibility certificate number 0153/KEPK/II/2021.

FUNDING

This research did not receive any specific grant from funding agencies in public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

AUTHOR CONTRIBUTION

All authors have contributed equally from the conceptual framework, data acquisition, and data analysis until the study results are reported through publication.

ACKNOWLEDGMENTS

We would like to express our deepest gratitude to the heads of the institution, board members, and staff of Dr. Soetomo General Academic Hospital and Universitas Airlangga for their cooperation and encouragement. We are also immensely grateful to all the participants participating in this study.

REFERENCES

- Thurlow JS, Joshi M, Yan G, et al. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy. *Am J Nephrol*. 2021;52(2):98-107. doi:10.1159/000514550.
- Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. *Circulation*. 2021;143(11):1157-1172. doi:10.1161/CIRCULATIONAHA.120.050686.
- Indonesian Renal Registry. 11th Report of Indonesian Renal Registry. Perkumpulan Nefrologi Indonesia. 2018. p1-46.
- Huang JC, Kuo IC, Tsai YC, et al. Heart Rate Variability Predicts Major Adverse Cardiovascular Events and Hospitalization in Maintenance Hemodialysis Patients. *Kidney Blood Press Res*. 2017;42(1):76-88. doi:10.1159/000469716.
- Jamshidpour B, Bahrpeyma F, Khatami MR. The effect of aerobic and resistance exercise training on the health related quality of life, physical function, and muscle strength among hemodialysis patients with Type 2 diabetes. *J Bodyw Mov Ther*. 2020;24(2):98-103. doi:10.1016/j.jbmt.2019.10.003.
- Broers NJH, Martens RJH, Cornelis T, et al. Physical Activity in End-Stage Renal Disease

- Patients: The Effects of Starting Dialysis in the First 6 Months after the Transition Period. *Nephron*. 2017;137(1):47-56. doi:10.1159/000476072.
- Tentori F, Elder SJ, Thumma J, et al. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. *Nephrol Dial Transplant*. 2010;25(9):3050-3062. doi:10.1093/ndt/gfq138.
- da Costa Rosa CS, Nishimoto DY, Freitas Júnior IF, Ciolac EG, Monteiro HL. Factors Associated With Levels of Physical Activity in Chronic Kidney Disease Patients Undergoing Hemodialysis: The Role of Dialysis Versus Nondialysis Day. *J Phys Act Health*. 2017;14(9):726-732. doi:10.1123/jpah.2016-0715.
- Gomes EP, Reboredo MM, Carvalho EV, et al. Physical Activity in Hemodialysis Patients Measured by Triaxial Accelerometer. *Biomed Res Int*. 2015;2015:645645. doi:10.1155/2015/645645.
- Volaklis K, Mamadjanov T, Meisinger C. Sedentary behavior and kidney function in adults: a narrative review. *Wien Klin Wochenschr*. 2021;133(3-4):144-152. doi:10.1007/s00508-020-01673-2.
- Marques A, Santos T, Martins J, Matos MG, Valeiro MG. The association between physical activity and chronic diseases in European adults. *Eur J Sport Sci*. 2018;18(1):140-149. doi:10.1080/17461391.2017.1400109.
- Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93(5):1043-1065.
- Mitsiou M, Dimitros E, Roumeliotis S, Liakopoulos V, Kouidi E, Deligiannis A. Effects of a Combined Intradialytic Exercise Training Program and Music on Cardiac Autonomic Nervous System Activity in Hemodialysis Patients. *Life (Basel)*. 2022;12(8):1276. Published 2022 Aug 20. doi:10.3390/life12081276.
- Aisyah V, Subagyo, and Subadi I. Effect of Aerobic Exercise on Brain-derived Neurotrophic Factor (BDNF) Serum Level in Stroke Subjects with Cognitive Function Impairment. *SPMRJ*. 2020;2(2):42-48. doi:10.20473/spmrj.v2i2.17669.
- Sheng K, Zhang P, Chen L, Cheng J, Wu C, Chen J. Intradialytic exercise in hemodialysis patients: a systematic review and meta-analysis. *Am J Nephrol*. 2014;40(5):478-490. doi:10.1159/000368722.
- Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. *Can J Cardiol*. 2010;26(6):303-312. doi:10.1016/s0828-282x(10)70395-0.
- Brenner IKM, Brown CA, Hains SJM, Tranmer J, Zelt DT, Brown PM. Low-Intensity Exercise Training Increases Heart Rate Variability in Patients With Peripheral Artery Disease. *Biol Res Nurs*. 2020;22(1):24-33. doi:10.1177/1099800419884642.

18. Masroor S, Bhati P, Verma S, Khan M, Hussain ME. Heart Rate Variability following Combined Aerobic and Resistance Training in Sedentary Hypertensive Women: A Randomised Control Trial. *Indian Heart J.* 2018;70 Suppl 3(Suppl 3):S28-S35. doi:[10.1016/j.ihj.2018.03.005](https://doi.org/10.1016/j.ihj.2018.03.005).
19. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health.* 2017;5:258. doi:[10.3389/fpubh.2017.00258](https://doi.org/10.3389/fpubh.2017.00258).
20. Seibert E, Zohles K, Ulrich C, et al. Association between autonomic nervous dysfunction and cellular inflammation in end-stage renal disease. *BMC Cardiovasc Disord.* 2016;16(1):210. Published 2016 Nov 3. doi:[10.1186/s12872-016-0385-1](https://doi.org/10.1186/s12872-016-0385-1).
21. Gao X, Wang J, Huang H, et al. Nomogram Model Based on Clinical Risk Factors and Heart Rate Variability for Predicting All-Cause Mortality in Stage 5 CKD Patients. *Front Genet.* 2022;13:872920. Published 2022 May 16. doi:[10.3389/fgene.2022.872920](https://doi.org/10.3389/fgene.2022.872920).
22. Cashion AK, Holmes SL, Arheart KL, Acchiardo SR, Hathaway DK. Heart rate variability and mortality in patients with end stage renal disease. *Nephrol Nurs J.* 2005;32(2):173-184.
23. Noppakun K, Putchagarn P, Phrommintikul A, Wongcharoen W. Effects of interdialytic interval on heart rate variability in chronic hemodialysis patients: a cross-sectional study. *Sci Rep.* 2021;11(1):20944. Published 2021 Oct 22. doi:[10.1038/s41598-021-00093-0](https://doi.org/10.1038/s41598-021-00093-0).
24. Kuo G, Chen SW, Huang JY, et al. Short-term heart rate variability as a predictor of long-term survival in patients with chronic hemodialysis: A prospective cohort study. *J Formos Med Assoc.* 2018;117(12):1058-1064. doi:[10.1016/j.jfma.2018.09.006](https://doi.org/10.1016/j.jfma.2018.09.006).
25. Chou YH, Huang WL, Chang CH, et al. Heart rate variability as a predictor of rapid renal function deterioration in chronic kidney disease patients. *Nephrology (Carlton).* 2019;24(8):806-813. doi:[10.1111/nep.13514](https://doi.org/10.1111/nep.13514).
26. Kouidi E, Karagiannis V, Grekas D, et al. Depression, heart rate variability, and exercise training in dialysis patients. *Eur J Cardiovasc Prev Rehabil.* 2010;17(2):160-167. doi:[10.1097/HJR.0b013e32833188c4](https://doi.org/10.1097/HJR.0b013e32833188c4).
27. Yeh ML, Wang MH, Hsu CC, Liu YM. Twelve-week intradialytic cycling exercise improves physical functional performance with gain in muscle strength and endurance: a randomized controlled trial. *Clin Rehabil.* 2020;34(7):916-926. doi:[10.1177/0269215520921923](https://doi.org/10.1177/0269215520921923).
28. Storer TW, Casaburi R, Sawelson S, Kopple JD. Endurance exercise training during haemodialysis improves strength, power, fatigability and physical performance in maintenance haemodialysis patients. *Nephrol Dial Transplant.* 2005;20(7):1429-1437. doi:[10.1093/ndt/gfh784](https://doi.org/10.1093/ndt/gfh784).
29. Ferguson B. ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. J Can Chiropr Assoc. 2014;58(3):328.
30. Deligiannis A, D'Alessandro C, Cupisti A. Exercise training in dialysis patients: impact on cardiovascular and skeletal muscle health. *Clin Kidney J.* 2021;14(Suppl 2):ii25-ii33. Published 2021 Jan 11. doi:[10.1093/ckj/sfaa273](https://doi.org/10.1093/ckj/sfaa273).
31. Gde Agung Mahendra ID, Subadi I, Wardhani IL, Satyawati R, Alit Pawana IP, Melaniani S. Effects of Otago Exercise Program on serum Interleukin-6 level in older women. *Ann Med Surg (Lond).* 2022;78:103733. Published 2022 May 7. doi:[10.1016/j.amsu.2022.103733](https://doi.org/10.1016/j.amsu.2022.103733).
32. Reboredo Mde M, Pinheiro Bdo V, Neder JA, et al. Effects of aerobic training during hemodialysis on heart rate variability and left ventricular function in end-stage renal disease patients. *J Bras Nefrol.* 2010;32(4):367-373.
33. Albinet CT, Boucard G, Bouquet CA, Audiffren M. Increased heart rate variability and executive performance after aerobic training in the elderly. *Eur J Appl Physiol.* 2010;109(4):617-624. doi:[10.1007/s00421-010-1393-y](https://doi.org/10.1007/s00421-010-1393-y).
34. Shah AS, El Ghormli L, Vajravelu ME, et al. Heart Rate Variability and Cardiac Autonomic Dysfunction: Prevalence, Risk Factors, and Relationship to Arterial Stiffness in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. *Diabetes Care.* 2019;42(11):2143-2150. doi:[10.2337/dc19-0993](https://doi.org/10.2337/dc19-0993).
35. Ranpuria R, Hall M, Chan CT, Unruh M. Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. *Nephrol Dial Transplant.* 2008;23(2):444-449. doi:[10.1093/ndt/gfm634](https://doi.org/10.1093/ndt/gfm634).
36. Tong Y, -Q, Hou H, -M: Alteration of Heart Rate Variability Parameters in Nondiabetic Hemodialysis Patients. *Am J Nephrol* 2007;27:63-69. doi: [10.1159/000099013](https://doi.org/10.1159/000099013).
37. O'Neal WT, Chen LY, Nazarian S, Soliman EZ. Reference ranges for short-term heart rate variability measures in individuals free of cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *J Electrocardiol.* 2016;49(5):686-690. doi:[10.1016/j.jelectrocard.2016.06.008](https://doi.org/10.1016/j.jelectrocard.2016.06.008).
38. Headley S, Germain M, Mailloux P, et al. Resistance training improves strength and functional measures in patients with end-stage renal disease [published correction appears in *Am J Kidney Dis.* 2008 Dec;52(6):1204. Nindl, Bradley [corrected to Nindl, Bradley C]]. *Am J Kidney Dis.* 2002;40(2):355-364. doi:[10.1053/ajkd.2002.34520](https://doi.org/10.1053/ajkd.2002.34520).
39. Parsons TL, Toffelmire EB, King-VanVlack CE. Exercise training during hemodialysis improves dialysis efficacy and physical performance. *Arch Phys Med Rehabil.* 2006;87(5):680-687. doi:[10.1016/j.apmr.2005.12.044](https://doi.org/10.1016/j.apmr.2005.12.044).



This work is licensed under a Creative Commons Attribution