Research Article

Aerobic Exercise Training and Nontraditional Cardiovascular Risk Factors in Hemodialysis Patients: Results from a Prospective Randomized Trial

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Keywords

Left ventricular hypertrophy · Physical activity · Chronic kidney disease · Cardiovascular diseases

Abstract

Introduction: Chronic kidney disease (CKD) patients have a high incidence of cardiovascular diseases (CVD) which increases their morbidity and mortality. A sedentary lifestyle in CKD is directly linked to the onset of CVD. Physical activity can bring beneficial effects to CKD patients. **Aims:** The aim of this study was assess the impact of aerobic training on nontraditional cardiovascular risk factors in CKD patients on hemodialysis. **Materials and Methods:** This is a prospective, controlled, and randomized clinical trial with analysis of intention to treat. Thirty patients underwent an exercise treadmill test, an arterial stiffness evaluation, echocardiography and analysis of endothelial reactivity, and carotid ultrasound and laboratorial tests, including analysis of serum aldosterone. The intervention group (IG) ($n = 15$) underwent aerobic exercise during hemodialysis 3 times a week for 4 months. The control group (CG) ($n = 15$) had no intervention. All of the patients were reassessed after 4 months. **Results:** In the IG, there was a statistically significant improvement in flow-mediated vasodilation (FMV; $p = 0.002$) and a reduction in left ventricular hypertrophy ($p = 0.006$) and serum aldosterone ($p = 0.016$). There was an increase in C-reactive protein in the CG ($p = 0.002$). **Conclusion:** This

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aerobic training protocol was able to improve endothelial function with enhanced FMV and reduce left ventricular hypertrophy and serum aldosterone, which could have a positive impact on the reduction of nontraditional cardiovascular risk factors in CKD patients on hemodialysis.

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Introduction

A sedentary lifestyle is an important public health issue with increasing worldwide prevalence and it is a modifiable risk factor in chronic kidney disease (CKD). CKD patients have a lower maximal oxygen consumption (VO_2max) when compared to age-matched non-CKD individuals [1]. A lower VO_2max was associated with a higher cardiovascular risk in CKD and mortality [2].

Cardiovascular diseases (CVD) represent the major cause of death in CKD patients [3]. Endothelial dysfunction, which can precede CVD, is a prognostic marker in this population [4]. Endothelial function can be evaluated noninvasively by flow-mediated vasodilatation (FMV). There is an inverse relationship between renal failure and endothelium vasodilation response, with worse endothelial dysfunction found in CKD patients with CVD [5]. Aldosterone, present in high concentrations in CKD [6], could lead to endothelial dysfunction and increased vascular resistance and blood pressure (BP) [7–9].

Patients with a worse endothelial function also had a greater carotid intima media thickness [10]. An increased carotid intima media thickness is associated with a higher cardiovascular risk and it is a predictor of CVD in the general population as well as in CKD [11, 12].

Endothelial dysfunction and subclinical inflammation are associated [13]. There is a negative relationship between inflammation and the glomerular filtration rate [14, 15]. C-reactive protein (CRP), which is found in high concentrations in CKD, is an independent predictor of cardiovascular mortality [16–18]. Furthermore, the lower the physical fitness in CKD patients is, the higher the CRP level is [19].

The association between endothelial dysfunction and subclinical systemic inflammation status may result in increased stiffness of large arteries. The presence of arterial stiffness markers in CKD is a predictor of CVD-related morbidity and mortality [20].

All of the above mentioned factors can lead to left ventricular hypertrophy (LVH), which is highly prevalent in CKD. Moreover, LVH has an inverse relation to the glomerular filtration rate and predicts a worse prognosis and mortality in these patients [21].

There is a great body of evidence showing the benefits of physical exercise in reducing the cardiovascular risk in many chronic diseases. However, to the best of our knowledge, there is no study evaluating the effect of intradialytic aerobic exercise on the aldosterone concentration or FMV values, LVH, arterial stiffness, and CRP. Therefore, the aim of this study was to assess the effect of an intradialytic aerobic exercise program on nontraditional cardiovascular risk factors in hemodialysis (HD) patients.

Subjects and Methods

This is a prospective, controlled, and randomized clinical trial in maintenance HD at the Clinics Hospital of Botucatu Medical School, Universidade Estadual Paulista (UNESP), Botucatu, São Paulo, Brazil. The enrolled patients were randomized into the following 2 groups: a control group (CG) followed without any training intervention for 4 months and an intervention group (IG) submitted to intradialytic aerobic physical training 3 times a week for 4 months. Both groups were submitted to an initial evaluation at baseline and a reevaluation after 4 months. All assessments were performed by blinded observers for each test. This study was

approved by the local ethical research committee and all of the patients signed a consent form. The present study occurred in concomitance with “Influence of Intradialytic Aerobic Training in Cerebral Blood Flow and Cognitive Function in Patients with Chronic Kidney Disease: A Pilot Randomized Controlled Trial” [22]; the same randomization of patients and exercise protocol were used, but different goals and variables were studied.

Patients older than 18 years and in maintenance HD for at least 3 months, on stable medication, and who did not present contraindications for physical exercises were included. Exclusion criteria were: patients who were already physically active, a previous diagnosis of coronary artery disease or a positive treadmill exercise test for coronary arterial disease, a previous stroke, cancer, liver failure, infection in activity, BP above 160×100 mm Hg at a treadmill test, and inclusion in another concurrent trial.

Physical activity was assessed using the short version of the International Physical Activity Questionnaire (IPAQ). This questionnaire classifies patients as very active, active, irregularly active, or sedentary [23].

VO_2max and resting and maximal heart rates (HR_{max}) were assessed by a treadmill exercise test using the Bruce protocol. All of the patients underwent this test without a stop in their usual medication [24].

Transthoracic Doppler echocardiography was performed with a Vivid I ultrasound machine (General Electric Company, Milwaukee, WI, USA). The following measurements were obtained: interventricular septum, posterior wall, left atrial volume in diastole, and left ventricular diameters during systole and diastole. The left ventricular mass (LVM) was calculated from those data using the Devereux formula and indexed for height to 2.7 (LVMI). Using the same equipment, carotid artery intima media thickness and brachial vascular reactivity were measured in the nonfistula arm [25, 26]. Pulse wave velocity, central BP, and the augmentation index were assessed to measure arterial stiffness with a SphygmoCor CPV (Atcor Medical, USA).

The following laboratory tests were analyzed: serum potassium, creatinine, glycaemia, TGP, bicarbonate, urea, calcium, phosphorus, hemoglobin, ferritin, serum iron, percentage of transferrin, albumin, parathyroid hormone, total cholesterol and fractions, triglycerides, CRP, aldosterone, and Kt/V.

The exercise program was performed during HD session 3 times a week, during the first 2 hours of the session, with a cycloergometer adapted to the HD chair. The aerobic training lasted 30 min without interruption, at between 65 and 75% of the HR_{max} , controlled by a Polar FS2c® heart rate monitor and with a Borg scale score around 13. The load imposed on the cycloergometer was progressively increased according to the performance of each patient.

Statistical Analysis

Data were presented as means $\pm$ SD or percentages. Categorical variables were compared at baseline by Fisher's exact test. Baseline continuous variables were compared using Student's *t* test or the Mann-Whitney U test depending on the distribution. For parametrical distribution variables, comparisons between groups, moments, and the interaction between groups and moments were performed using two-way analysis of variance for repeated measurements. For the other variables, comparisons were performed by design in repeated measures considering the effects of group, moment, and group $\times$ moment interactions using a generalized linear model with a γ distribution, followed by the multiple comparison test of Wald. The frequency with which a reduction or increase in each variable occurred was assessed between the 2 groups by Fisher's exact test. $p < 0.05$ was considered statistically significant. The statistical software used for data analysis was Sigma Stat 3.5.

Results

Clinical data of all of the patients are shown in Table 1, as are comparisons between CG and IG. Thirty patients were evaluated (mean age 58 ± 16.3 years, 15 males, mean BMI 25.3 ± 5.08). After the first evaluation 2 patients were excluded from the IG and 3 from the CG; the reasons for exclusion of these patients were, respectively: renal transplantation, bowel cancer, and abandonment. Fifteen patients were allocated to each group. Clinical baseline data were homogeneous between groups and there was no change in the reevaluation.

There was no statistically significant difference regarding alterations of VO_2max between groups or moments (IG at baseline: 29.2 ± 9.16 , IG after the intervention:

Table 1. Comparison between baseline clinical and demographic data groups

	IG (n = 15)	CG (n = 15)	p
Males	7 (46.7)	8 (53.3)	0.72
Age, years	50±17.2	58±15.0	0.09
BMI	25.7±3.58	26.7±4.6	0.55
VO ₂ max, mL/kg/min	28.6±5.64	23.0±10.0	0.18
Hemodialysis vintage, months	26.0±14.58	21.0±27.1	0.32
Education, years of study	5.7±3.58	4.7±3.98	0.43
Smoking	5 (33.3)	3 (20.0)	0.50
Diabetes mellitus	3 (20.0)	6 (40.0)	0.16
Hypertension	13 (86.7)	12 (80.0)	0.94
Baseline disease			
Hypertension	6 (40.0)	5 (33.3)	
Diabetic nephropathy	3 (20.0)	5 (33.3)	
Glomerulopathies	4 (26.6)	4 (26.6)	0.34
Others	2 (13.4)	1 (6.7)	
IPAQ			
Sedentary/other	7 (46.7)/8 (53.3)	8 (53.3)/7 (46.7)	0.73

Values are presented as means ± SD or numbers (%).

Table 2. Comparison of laboratory data at baseline and after intradialytic aerobic exercise

	IG		CG		p ^a	p ^b	p ^c
	baseline (n = 15)	after exercise (n = 15)	baseline (n = 15)	after exercise (n = 15)			
Aldosterone, ng/dL	36.9±23.57	23.6±18.79	25.0±14.13	26.3±11.81	0.509	0.444	0.016
Serum creatinine, mg/dL	8.7±2.27	9.1±2.06	9.7±3.17	9.9±2.38	0.319	0.268	0.926
Serum urea, mg/dL	110±18.4	109±29.6	111±28.6	118±22.1	0.469	0.350	0.123
Potassium, mmol/L	4.9±0.76	5.3±1.04	4.9±0.66	5.3±0.37	0.880	0.020	0.801
Bicarbonate, mEq/L	21±2.2	22±2.0	21±2.2	21±2.3	0.851	0.737	0.895
Glycemia, mg/dL	112±36.5	946±26.7	104±28.5	112±12.8	0.458	0.676	0.730
CRP, mg/dL	0.7±0.33	0.6±0.20	1.2±0.97	1.5±0.89	0.002	0.830	0.133
Kt/V	1.4±0.21	1.4±0.22	1.5±0.12	1.4±0.15	0.722	0.325	0.677
Albumin, g/dL	3.9±0.34	3.9±0.25	3.8±0.45	3.9±0.36	0.657	0.248	0.416
Calcium, mg/dL	8.9±0.91	8.8±1.33	9.0±0.83	9.0±0.56	0.573	0.981	0.917
Phosphorus, mg/dL	4.9±0.79	5.6±1.24	5.7±1.11	5.7±1.85	0.325	0.411	0.135
PTH, pg/mL	475±309.1	477±406.6	304±282.3	351±269.0	0.144	0.558	0.599
Hemoglobin, g/dL	11.4±1.32	12.3±1.43	12.0±1.79	12.2±1.16	0.517	0.398	0.199
Ferritin, ng/mL	801.6±900.86	643.4±534.13	867.7±588.60	926.4±645.20	0.468	0.784	0.317
Serum iron, µg/dL	75.9±30.35	67.9±39.33	66.0±22.94	92.3±39.82	0.425	0.282	0.066
Transferrin, %	38.4±22.84	31.7±22.97	35.5±11.55	44.1±18.16	0.434	0.838	0.105
Cholesterol, mg/dL	155.5±31.83	147.6±32.44	141.8±40.29	138.0±40.40	0.345	0.179	0.450
LDL, mg/dL	79.6±26.19	73.3±25.87	65.1±38.31	62.9±34.82	0.238	0.323	0.481
HDL, mg/dL	46.3±17.18	46.1±20.37	39.7±13.0	42.2±12.06	0.333	0.506	0.462
Triglycerides, mg/dL	146.6±58.50	137.9±51.27	184.0±89.66	161.6±56.07	0.157	0.205	0.582

Data are expressed as means ± SD. BIC, bicarbonate; PTH, parathyroid hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein. ^a Comparison between groups. ^b Comparison between moments. ^c Interaction between groups and moments.

Table 3. Comparison of the IG and the CG before and after intradialytic aerobic exercise in relation to the echocardiographic data and arterial stiffness

	IG		CG		p^a	p^b	p^c
	baseline ($n = 14$)	after ($n = 14$)	baseline ($n = 14$)	after ($n = 14$)			
LV diastole, mm	44.5±4.85	44.9±5.42	44.8±4.39	44.9±4.60	0.922	0.443	0.741
LV systole, mm	28.9±5.47	29.2±6.56	26.7±3.27	26.6±3.23	0.200	0.862	0.388
IS, mm	12.2±2.08	11.8±2.15	12.5±1.92	12.3±2.09	0.649	0.007	0.317
PW, mm	11.9±1.78	11.2±1.69	12.5±1.92	12.3±1.90	0.223	0.002	0.069
LA volume, mL	46.4±17.59	47.2±18.88	37.8±12.48	37.9±11.96	0.136	0.420	0.501
Mass, g	221±60.0	208±53.6	234±57.2	230±59.6	0.412	0.007	0.168
LVMI, g/m ^{2.7}	62.3±18.26	58.7±17.01	65.7±16.94	64.5±17.38	0.492	0.006	0.163
Left CIMT, mm	0.65±0.200	0.64±0.180	0.72±0.170	0.71±0.180	0.327	0.334	0.909
Right CIMT, mm	0.68±0.180	0.68±0.180	0.68±0.180	0.69±0.180	0.961	0.597	0.781
FMV ^d , %	6.8±7.41	9.0±9.36	6.9±8.03	4.9±3.59	0.991	0.054	0.002
Femoral PWV, m/s	8.5±2.86	8.1±3.13	10.3±3.80	10.1±3.49	0.309	0.132	0.305
Augmentation index, %	21.7±15.06	25.5±12.89	27.2±5.5	31.9±13.07	0.060	0.671	0.243

Data expressed as means ± SD. ^a Comparison between groups. ^b Comparison between moments. ^c Interaction between groups and moments. IS, interventricular septum; PW, posterior wall; LA, left atrium; CIMT, carotid intima media thickness. ^d Data analyzed by gamma distribution.

31.3 ± 8.36; CG at baseline: 23.3 ± 10.74, CG after the intervention: 24.6 ± 10.77; $p = 0.638$). There was no statistically significant difference in total treadmill test time, walked distance, or maximum metabolic equivalent of task (MET) ($p = 0.610$, $p = 0.507$, and $p = 0.623$, respectively).

The laboratory data of both groups at baseline and after the exercise protocol are shown in Table 2. Aldosterone resulted in a statistically significant reduction in IG after the intervention. Potassium presented a statistically significant difference between moments, with an increase in both groups. CRP was higher in the CG than in the IG at the post training moment. Other laboratory variables did not present significant differences between groups, moments, or interactions between groups and moments.

Echocardiographic variables at baseline were homogeneous. IG presented a statistical difference in relation to baseline values, with a reduction in interventricular septum size and the posterior wall in diastole ($p = 0.007$ and $p = 0.002$, respectively). There was a reduction in LVMI and an increase in reactive hyperemia. FMV increased in the IG ($p = 0.002$). In relation to arterial stiffness and BP variables, there were no significant differences between groups, moments, or interactions. Data are expressed in Table 3.

Discussion

A sedentary lifestyle is associated with mortality in HD patients [27]. Almost 35% of HD patients exercise insufficiently or do not perform any exercise, which is associated with vascular and cardiac disease development [2]. Many medicinal treatments have been studied to improve the quality of life of HD patients but, despite high investments, there has been no improvement in the survival of these patients. Considering the relative low cost and good applicability of the HD sessions in routine practice, performing intradialytic exercises seems an attractive adjuvant therapy in CKD. Even simple protocols for performing only 15 min of intradialytic metabolic exercise has been shown to have a positive impact in CKD patients

(e.g., improved HD performance) [28]. Therefore, KDIGO (2013) recommends the practice of regular physical exercise for CKD patients [29].

Several studies have shown functional improvements and an improved quality of life, but few studies have evaluated the impact of physical training on cardiovascular outcomes. Studies have shown LVH regression in nephrectomized rats and in non-CKD patients [30, 31]. In HD patients, Momeni et al. [32] observed an increase in the LV ejection fraction, improvement of diastolic function, and a reduction of the right ventricle size, with no alterations in LVH.

The present study showed that, concurrently with the reduction of LVH, there was a decrease in aldosterone levels in trained individuals. Aldosterone blockade can decrease LVM in HD patients [33]. Aerobic training can decrease aldosterone in heart failure in obese individuals [34, 35].

This aldosterone decrease after physical exercise was not found in healthy individuals. In a systematic review, Goessler et al. [36] evaluated the effect of physical exercise for at least 4 weeks on variables of the renin-angiotensin-aldosterone system [36]. Three studies evaluated aldosterone and no effect after the training protocol was found.

FMV was increased after our aerobic exercise protocol in trained individuals. A similar finding was reported by Currie et al. [37] in coronary patients and by Birk et al. [38] in healthy individuals with acute exercise in both trials.

The literature presents divergent results about endothelial function after protocols with longer durations. Van Craenenbroeck et al. [39] submitted 48 CKD patients to moderate home aerobic exercise for 3 months. As a result, they found an increase in VO_2max and quality of life, but there was no improvement in FMV or pulse wave velocity. Liao et al. [40] showed that 30 min of intradialytic aerobic cycling could improve the endothelial function in 20 CKD patients, represented by an increase in endothelial progenitor cells and a significant reduction of the inflammation, with lower CRP and interleukin-6, after a 3-month protocol [40].

In our study, CRP was high in both groups at baseline, with constant chronic inflammation in HD patients, as already reported [41, 42]. After the exercise protocol, CRP levels were higher in the CG than in the IG. This fact may be related to a possible protective effect of exercise, with a reduced progression of the inflammatory state in patients submitted to physical exercise. Moraes et al. [43] also showed a change in the inflammatory status of HD patients, with a CRP reduction after 6 months of resistance exercises during HD [43]. In agreement with this, Groussard et al. [44] demonstrated an improvement in the inflammatory status of CKD patients submitted to intradialytic cycling training, with concomitant improvement of physical fitness and the lipid profile and a reduction of triglycerides. In contrast, this result was not observed with aerobic exercise in stage 3 CKD patients [45, 46].

The increase in the estimated VO_2max was expected as a result of improvement in physical fitness; however, it was not observed in the present study. This fact could be justified by the exercise intensity imposed, which was not enough for cardiovascular conditioning, even though the load used was based on recommendations from the Brazilian guidelines for cardiopulmonary and metabolic rehabilitation [47]. Despite this, the intensity used was able to show other benefits in IG patients.

The number of patients is a limitation of this study, although it was sufficient to reach the proposed sample calculation. Even with the intention of increasing the sample size of the protocol, patients had difficulty adhering to the program because of the initial assessments and revaluations which were performed on interdialytic days (i.e., a period during which the subject did not need to come to the hospital). Moreover, many patients were afraid of the tests that would be performed. The study design (i.e., a prospective, controlled and randomized trial) and the blindness of evaluators regarding the group and moment of evaluation are strengths of the current study.

Conclusion

The present intradialytic aerobic training protocol was able to improve endothelial function through FMV, reduce LVH and serum aldosterone, and, possibly, prevent the progression of an inflammatory status. On the other hand, there was no change in arterial stiffness markers or in central and peripheral BP values. This protocol had a positive impact on the reduction of nontraditional cardiovascular risk factors in HD patients.

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Statement of Ethics

Written informed consent was obtained from all subjects. This study was approved by the Ethics Research Committee (number 4408/2012). The authors declare that they have no potential conflicts of interest to disclose.

Disclosure Statement

The authors declare that they have no potential conflicts of interest to disclose.

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